1,3-Dipolar Cycloadditions: Click Chemistry for a New Synthesis of 5-Substituted Tetrazoles and Applications in Organocatalysis

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Par

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IMPRIMATUR POUR LA THESE

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Neuchâtel, le 21 septembre 2007

Le doyen :
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UNIVERSITE DE NEUCHATEL
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Abbreviations

Symbol	Entity
Abs.	Absorbance
Ac	Acetyl
AcOH	Acetic acid
Al.	Aliphatic
Ar.	Aromatic
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
BOM	1-Benzyloxymethyl
br	Broad signal
BuOH	Butanol
*t*Bu	*tert*-Butyl
calc.	Calculated
Cbz	Benzyloxycarbonyl
Cq	Quaternary carbon
1D, 2D, 3D	One-, two-, three-dimensional
d	Doublet (NMR)
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DMF	Dimethylformammide
DMSO	Dimethylsulfoxyde
dr	Diastomeric ratio
ee	Enantiomeric excess
EtOAc	Ethyl acetate
FT-IR	Fourier Transform Infrared (Spectroscopy)
HPLC	High Performance Liquid Chromatography
HR-MS	High Resolution Mass Spectroscopy
IR	Infrared (Spectroscopy)
J	Coupling constant
m	Multiplet (NMR) Medium (IR)
M_A	Mass of the acid (MS)
M_B	Mass of the base (MS)
mp	Melting point
MS	Mass Spectroscopy
NMR	Nuclear Magnetic Resonance
Pd/C	Palladium on charcoal
Ph	Phenyl
PMB	*p*-Methoxy benzyl
PTC	Phase Transfer Catalysis

q	Quartet (NMR)
R_f	Retention factor
r.t.	Room temperature
s	Singlet (NMR) Strong (IR)
sep	Septet (NMR)
t	Triplet (NMR)
TBAF	Tetrabuthylammonium fluoride
TBDMS	*t*Butyl dimethyl silyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofurane
TLC	Thin Layer Chromatography
TMS	Trimethylsilane
Tr	Trityl
Ts	Tosyl
TS	Transition State
UV	Ultraviolet Spectroscopy
vibr.	Vibration (IR)
w	Weak (IR)

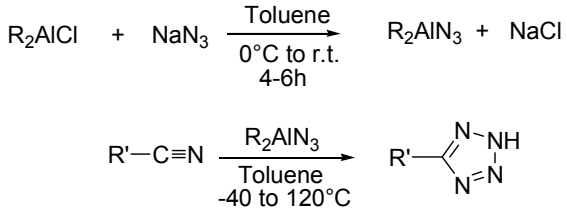
Entity	**Symbol**	**Unit**
Calculated density in g/cm^3	D_c	
Final structure agreement factors	R1, wR2	
Length	Å	Angstrom
Molecular Weigh	MW	g/mol
Number of molecules per unit cell	Z	
Optical rotation	$[\alpha]_D^{25}$	°
Pressure	bar	Bar
Temperature	T	° C
Time	t	min h
Unit-cell angles	α, β, γ	°
Unit-cell lengths	a, b, c	Å
Volume	L	Liter
Unit-cell volume	V	Å^3
Vibration frequency	$\tilde{\nu}$	cm^{-1}
	λ	nm
Wave number	cm^{-1}	Wave number

Keywords

Tetrazole, Sartans, Nitriles, Dialkylaluminum azide, Cycloaddition, Alkylation, Methylation, Organocatalysis, Enamine

Summary

Tetrazoles are a class of heterocycles with a wide range of applications in medicinal chemistry and in material sciences [1]. However a versatile method to synthesize tetrazoles through safe protocols is still highly desirable. Indeed each of the general known procedures uses either toxic metals, expensive reagents, harsh reaction conditions and may lead to the formation of dangerous hydrazoic acid or explosive sublimates. We report herein the discovery and development of a novel efficient process for transforming a wide variety of nitriles into the corresponding tetrazoles in high yield, using a simple and safe protocol. It has been found that the organoaluminum azides are effective reagents for the direct conversion of nitriles to tetrazoles (Scheme 1) [141,142].



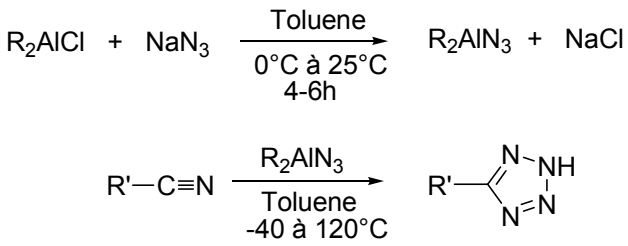
Scheme 1. Novel synthesis of tetrazole rings

The organic soluble dialkylaluminum azides are prepared in a short time (4-6 h, r.t.) from the corresponding cheap dialkylaluminum chlorides. The cycloaddition occurs under mild conditions, and it is possible to synthesize a broad range of tetrazole derivatives with a high selectivity. This methodology can be applied to the synthesis of the pyrrolidine tetrazole, a versatile alternative of proline in organocatalysis. A variety of new catalysts based on pyrrolidine tetrazole skeleton are therefore efficiently prepared and tested [142].

Resumé

Les besoins récents en chimie organique de synthèse appliquée focalisent les efforts des chercheurs au développement de nouvelles voies efficaces et versatiles pour la préparation de molécules bioactives, en prenant en comptes en particulier les critères économiques et environnementaux. Nous avons développé une méthode novatrice et écologique pour la préparation de tetrazoles [141,142]. Ce groupe fonctionnel trouve des applications dans des domaines variés allant des matériaux aux explosifs, et est d'un intérêt tout particulier en chimie médicinale [1].

Cette importance a conduit au développement de diverses méthodes de préparation des tétrazoles, toutes présentant cependant des désavantages majeurs comme l'utilisation de réactifs toxiques ou explosifs, entre autres. La méthode alternative que nous avons développée permet la formation de tétrazoles à partir de nitriles en utilisant des azides de dialkylaluminium, qui possèdent l'avantage d'être des réactifs bon marché et non toxiques et permettent la préparation d'une large variété de tétrazoles de façon très efficace, adaptable à l'échelle industrielle (Scheme 1).



Scheme 1. Nouvelle méthodologie de formation de tétrazole

Nous avons ensuite appliqué cette méthodologie à l'organocatalyse [142], c'est-à-dire à la préparation et l'étude de molécules organiques ayant la faculté de catalyser des transformations chimiques très sélectives, procédé particulièrement attractif d'un point de vu environnemental et économique en constant développement.

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Chapter 5 Experimental part

Synthesis is the one in which the target molecule is prepared from readily available starting materials in one simple, safe environmentally acceptable, and resource-effective operation that proceeds quickly and in quantitative yields

P. A. Wender [1]

[1] P. A. Wender, Introduction: Frontiers in Organic Synthesis, *Chem. Rev.* **1996**, *96(1)*, 1-2 (editorial)

Chapter 1.
The 5-Substituted Tetrazoles

Tetrazoles are a class of heterocycles with a wide range of applications which are currently receiving considerable attention[1,] therefore the literature on tetrazole is expanding rapidly. This functional group has a role in coordination chemistry as a ligand,[2,3,4] as well as in various materials sciences applications including photography and specialty explosives [5]. Extensive work has also been carried out in the field of medicinal chemistry, where tetrazoles are frequently used as metabolically stable surrogates for carboxylic acids [6,7,8].

Less appreciated, but of enormous potential, are the many useful transformations that make tetrazoles versatile intermediates en route to substituted tetrazoles and especially to other 5-ring heterocycles *via* Huisgen rearrangement [9,10]. The prime reason for the scarcity of practical applications for these sophisticated tetrazole-based reactions is the lack of appealing synthetic routes to the key intermediates 5-substituted tetrazoles.
Tetrazoles readily tolerate a wide range of chemical environments [1] and new uses for this unique family of heterocycles continue to emerge in both materials science, and pharmaceutical applications.

1.1. The 5-Substituted Tetrazole

5-Substituted tetrazoles that contain a free N-H bond are frequently referred to as tetrazolic acids and exist in two tautomeric forms (Figure 1) [1, 11,12].

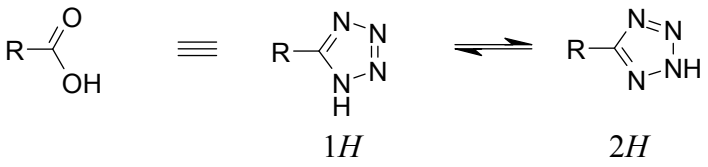


Figure 1. Tetrazolic acids are bioisosteres of carboxylic acids

The tautomerism is a rapid process in solution and individual tautomers can not be detected even at low temperature. The corresponding dipole moments are 5.63 D for the 1*H*-tautomer and 2.19 D for the 2*H*-form [1]. In the gas phase, the 2*H*-tautomer tends to be the dominant form, while in solution the 1*H*-tautomer is favored because of solvation effects.

Tetrazoles can be regarded as nitrogen analogues of carboxylic acids. The free N-H bond of tetrazoles makes them acidic molecules and both the aliphatic and aromatic heterocycles have pK_a values similar to the corresponding carboxylic acids (4.5-4.9 vs 4.2-4.4, respectively) due to the ability of the moiety to stabilize a negative charge by electron delocalization [1].

Tetrazole nitrogens have a considerable amount of local electron density, which consequently leads to a wide range of stable metallic and molecular complexes [13]. Furthermore, the tetrazole ring possesses a strong electron-withdrawing inductive effect (-I) which surpasses the weak mesomeric effect (+ M), therefore, the ring is a deactivating group [1].

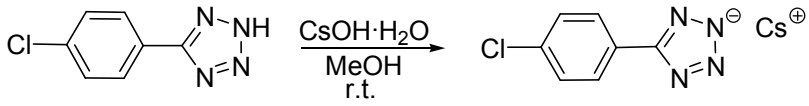
1.1.1. Chemical & Physical Properties

1.1.1.1. Aromaticity

The tetrazole ring is a 6π-azapyrrole-type system [1,11]. Reactivity of 5-substituted tetrazoles permits them to be classified as aromatic compounds [1,14]. In tetrazoles, two of the six π-electrons required by the Hückel rule are provided by the lone pair of one nitrogen while the remaining four π-electrons are provided by the other four atoms of the ring.

1.1.1.2. Tetrazolate anions: acidity

5-Substituted tetrazoles display an acidity comparable with the corresponding carboxylic acids [1,15]. One difference between the tetrazole ring and the carboxylic acid group is the annular tautomerism of the tetrazoles. Substituents at C-5 have effects similar to those for carboxylic acids, while in general, 5-aryltetrazoles are stronger acids. The increased acidity is ascribed to an enhanced resonance stabilization in the 5-phenyltetrazole anion relative to benzoate [1b]. The tetrazolate anions are easily generated with metal hydroxides and are stable in hot alcoholic and aqueous solutions (Figure 2) [16,1]



1 **2**

Figure 2. Example of a metal tetrazolate salt

1.1.1.3. Solubility

5-Substituted tetrazoles are generally soluble in polar organic solvents such as ethyl acetate and DMSO, but under basic conditions they can be easily extracted into the water phase as a salt, like the carboxylic acid. Very polar tetrazole derivatives such as pyridine-tetrazoles **103**, **104** and **105** or pyrrolidine tetrazoles **113** are soluble in water therefore the extraction from water can be problematic.

1.1.2. Application of Tetrazole Derivatives

Tetrazoles are an increasingly popular functionality with wide ranging application. They have found use in coordination chemistry [16,17] and in various materials sciences applications including photography [1,18], specialty explosives [5], information recording systems [19] and agricultural composition [20]. In addition extensive work has been carried out in the field of medicinal chemistry [1,9].

1.1.2.1. Application in medicinal chemistry

1.1.2.1.1. *cis*-Amide bond mimic

Marshall *et al.* [21] have proposed a new use for the tetrazole ring as a *cis*-amide bond mimic within a peptide chain and this structural motif can be used to pre-organise the amide bonds of peptides, enzyme substrates and inhibitors into a *cis*-conformation [21,22,23]. Incorporation of tetrazole dipeptide analogues into biologically active peptides such as somatostatin and bradykinin has been demonstrated (Figure 3) [24].

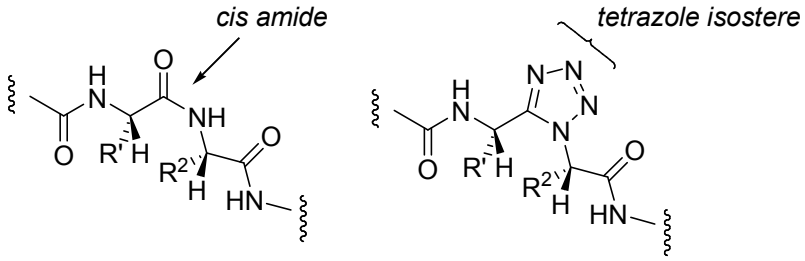
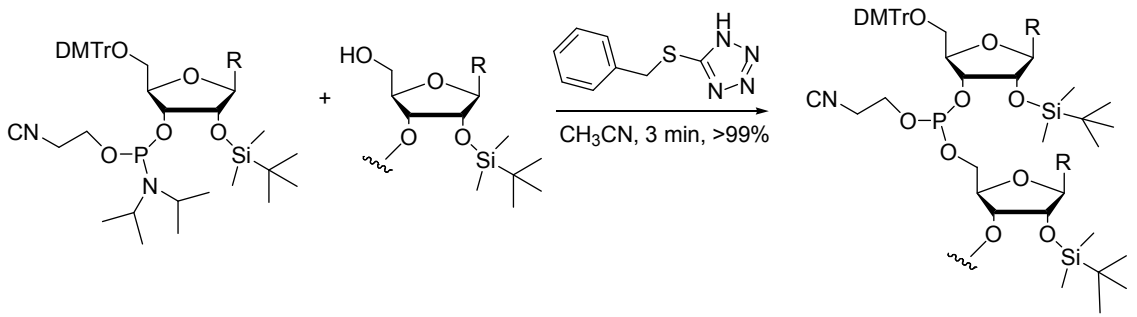


Figure 3. The tetrazole ring as a *cis*-amide bond mimic

1.1.2.1.2. DNA, RNA synthesis

5-Alkylthiotetrazoles, specifically 5-benzylthiotetrazole and 5-ethylthiotetrazole, are a powerful activators for DNA and RNA synthesis (Scheme 1) [25,26,27]. The presence of the thio group makes the tetrazole ring more acidic than the corresponding 5-alkytetrazoles [28]; this improves its ability to act as an activator. In addition, the solubility with biologically active compounds, where reactions are carried out in acetonitrile, is also enhanced. Comparison of 5-(benzylmercapto)-tetrazole to other activators revealed the following order in coupling yield of 2'-*O*-TBDMS phosphoramidites: 5-

(benzylmercapto)-tetrazole > 5-(ethylmercapto)-tetrazole > 4,5-dicyanoimidazole > 1*H*-tetrazole [25].

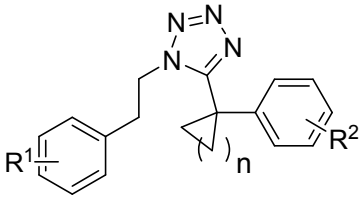


Scheme 1. RNA phosphoramidite coupling reaction with 5-(mercapto)-1*H*-tetrazole activation

1.1.2.2. Pharmaceutical properties

Tetrazole itself does not exhibit pharmacological activity ; however, many of its derivatives possess interesting biological activities and they are frequently used as metabolically stable surrogates for carboxylic acids, while tetrazoles generally offer a more favourable pharmacokinetic profile [1,29,30,31,32].

Like their carboxylic acid analogues, tetrazoles exhibit a planar structure. However, Hansch has shown that anionic tetrazoles are almost 10 times more lipophilic than the corresponding carboxylate,[33] which is an important factor in allowing the molecule to pass through cell membranes. Hydrogen bonding capability of tetrazolic anions with receptor recognition sites is a key interaction for enhanced binding affinity [34]. In addition, in the design of drug molecules, one advantage of tetrazoles over carboxylic acids is that they are resistant to many biological metabolic degradation pathways [35]. Tetrazole derivatives have been investigated in areas as diverse as anti-arrhythmic agents (**3**) [36], anti-diabetic agents [32f,37], anti-cholesterol agents [1b], antifungal agents [38], anti-allergic agents (**5**) [29,39,40], neurodegenerative diseases (**6-9**) [1,29,41] among others [8]. Some examples are given in Figures 4-7.



3

n= 0, 1, 2, 3, 4
R^1= *p*-MeO-, *p*-Me-, *p*-F-
R^2= *p*-Cl-, -O-Me-

Figure 4. Anti-arrhythmic agents [36]

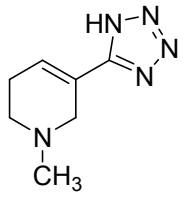


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Figure 5. Muscarinic agonist [42]

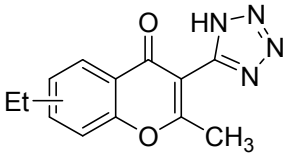

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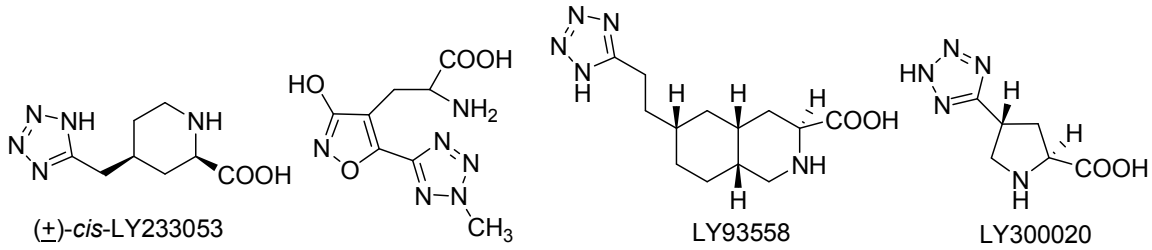
Figure 6. Anti-allergenics



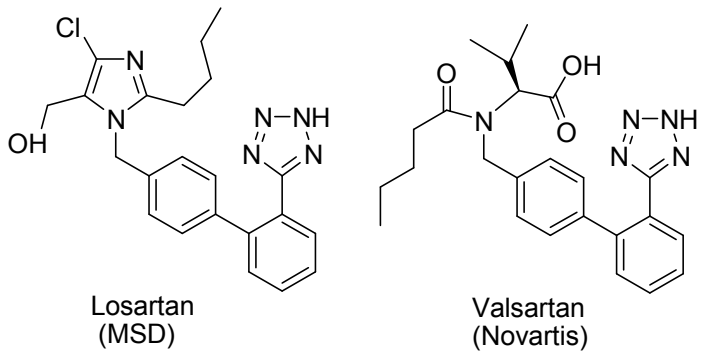
(±)-*cis*-LY233053 LY93558 LY300020

6 **7** **8** **9**

Figure 7. Tetrazole derivatives with central nervous system activity

1.1.2.2.1. Cardiovascular activity

The 5-(4'-methyl-1,1'-biphenyl-2-yl)-tetrazole subunit has been used as a carboxylic acid mimic in the class of so called sartan derivatives (Figure 8). Angiotensin II (AII) is the octapeptide responsible for the peripheral effects of the rennin-angiotensin system [43,44,45,46,47] which include the regulation of blood pressure and volume homeostasis. Lorsartan was the first nonpeptide angiotensin receptor antagonist to appear on the market [41,42,44,48] followed by Valsartan (Figure 8). The 5-(4'-methyl-1,1'-biphenyl-2-yl)-1*H*-tetrazole subunit has become ubiquitous in the most potent and bioavailable antagonists disclosed to date [31].



Losartan (MSD) Valsartan (Novartis)

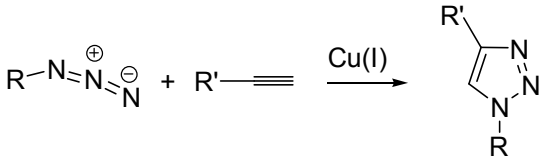
Figure 8. Sartans

1.1.3. Synthesis of Tetrazoles

5-Substituted tetrazoles are usually obtained by the addition of azide ion to organic nitriles and many methods are reported in the literature [1,8,49,50,51]. Unfortunately, each of those protocols suffers from some disadvantages: the use of both toxic metals and expensive reagents, drastic reaction conditions, water sensitivity and possible presence of dangerous hydrazoic acid or other explosive sublimates.

The Huisgen 1,3-dipolar cycloaddition

The Huisgen 1,3-dipolar cycloaddition is the reaction of alkynes to azides to form 1,4-disubsituted-1,2,3-triazoles (Scheme 2)[9]. A notable variant of the Huisgen cycloaddition is the copper (I) catalyzed variant, in which organic azides and terminal alkynes are united to afford 1,4-regioisomers of 1,2,3-triazoles as sole products [52]. Huisgen was the first to understand the scope of this organic reaction. This cycloaddition is considered *the cream of the crop* of "click chemistry". The azide and alkyne functional groups are largely inert towards biological molecules and aqueous environments, which allows the use of the Huisgen 1,3-dipolar cycloaddition in target guided synthesis [53] and activity-based protein profiling [54]. The resulting triazole has similarities to the ubiquitous amide moiety found in nature, but unlike amides, is not susceptible to cleavage.



Scheme 2. Huisgen 1,3-dipolar cycloaddition of alkynes to azides

1.1.3.1. Synthesis of tetrazoles from nitriles with azides

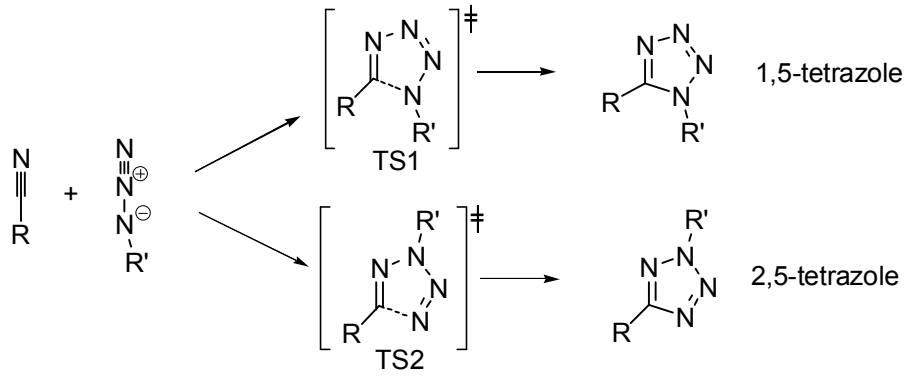
Tetrazoles are generally prepared by the reaction of a hydrazoic acid source with a nitrile, in an inert solvent at high temperatures. They fall into three main categories: those that make use of tin or silicon azides, those that use strong Lewis acids [55,56] and those that are run in acidic media [57]. The few methods that seek to avoid hydrazoic acid liberation during the reaction by avoiding acidic conditions, require a very large excess of sodium azide [58]. In addition, all of the known methods use organic solvents, in particular, dipolar

aprotic solvents such as DMF. This is one of the solvent classes that process chemists would rather not use.

The mechanism of the reaction of azide salts to nitriles is different for different azide species [59,60,61] and several possible reaction pathways can be envisioned [62,63,64].

Neutral cycloaddition

A [2+3] cycloaddition is the most likely pathway for the bimolecular addition of non-ionic azides to nitriles [61]. In concerted cycloadditions, two different isomers of tetrazole, the 1,5- and the 2,5-disubstituted, can be formed. Generally the TS1 is the preferred transition state using electron-withdrawing substituents R (Scheme 3).



Scheme 3. Neutral cycloaddition

Anionic mechanism

In reactions where NaN_3 is added to nitriles in aprotic organic solvents, such as dimethylformammide (DMF), it has been found that yields are generally lower and higher temperature are required [57,62]. In theses cases, there are two possible mechanisms,[61] either a direct [2+3] cycloaddition or a two step-mechanism sequence wherein the azide first nucleophilically attacks the nitrile, followed by ring closure. In this context, Sharpless *et al.* have calculated the barriers of cycloaddition of the azide anion to nitrile [61]. As in the case of the neutral [2+3] cycloadditions, the barrier for anionic [2+3] cycloaddition decreases with increasing electron-withdrawing potential of the substituent on the nitrile. The geometry of the transition state of anionic reactions is more asymmetric than for neutral reactions. The $C_{nitrile}$-N_{azide} distance is significantly shorter than the $N_{nitrile}$-N_{azide} distance. The difference grows with the electron-withdrawing potential of the substituent and for very strong electron-withdrawing groups like RSO_2, an intermediate such as that shown in Figure 9 could be found. Despite the

existence of this intermediate for the strongly activated nitriles, the $\Delta G^{\neq}$ of the transition state for the ring closing turns out to be identical to the $\Delta G^{\neq}$ for concerted [2+3] transition state. The two pathways have therefore essentially the same rate [61].

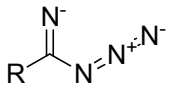
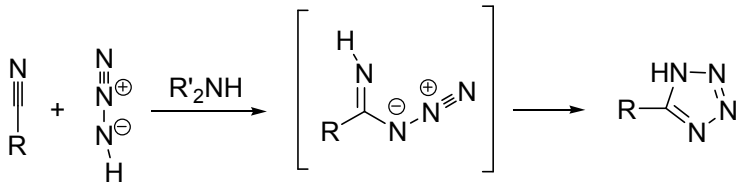


Figure 9.

Proton involvement

Koldobskii *et al.*[65] showed that protic ammonium salts of azide are competent dipoles; tetrabutylammonium azide does not work. When a proton is available, the nitrile is activated and the reaction is supposed to proceed *via* an intermediate instead of a direct [2+3] dipolar cycloaddition (Scheme 4) [61].



Scheme 4.

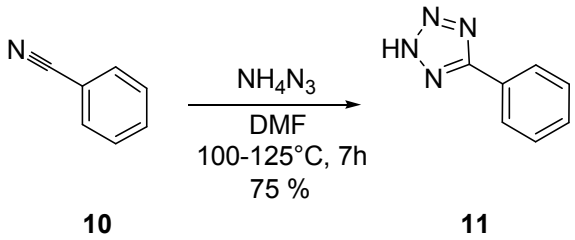
1.1.3.1.1. Hydrazoic acid

The acid –catalysed cycloaddition between hydrazoic acid and nitriles has long been one of the main routes to 5-substituted tetrazoles [8,66]. The first method to appear in the literature was the reaction of hydrazoic acid (HN_3) with organic cyanides in 1932 [67]. This process is generally thought to occur by a concerted 1,3-dipolar cycloaddition mechanism, in which the nitrile acts as the dipolarophile toward the azide, which serves as the 1,3-dipolar species in the cycloaddition. Protonation of the tetrazolium anion upon workup provides the tetrazolic acid. In literature a two-step mechanism has also been reported [68]. However this standard procedure needs the direct addition of a large excess of dangerous and harmful hydrazoic acid. Hydrazoic acid itself is poisonous, extremely explosive, and has a low boiling point (37 °C). Not many organic solvents are stable at the high temperatures that are necessary for this cycloaddition (sometimes as high as 130 °C), and for this reason DMF is most commonly used for this purpose [1,29].

1.1.3.1.2. Metal salt methods using sodium azide

1.1.3.1.2.1. Ammonium and trialkyl ammonium azides

The reaction of nitriles with the ammonium and trialkyl ammonium azides in organic solvents such as dimethylformamide, has been found fifteen years ago by Lofquist and Finnegan [62] to be a general method to give good yields of 5-substituted tetrazoles. The reactive azide species is prepared *in situ* by reaction of sodium azide and the appropriate ammonium or trialkyl ammonium chloride (Scheme 5). The proposed mechanism involves a nucleophilic attack of azide ion on the carbon of the nitrile group, followed by ring closure of the imino azide to form the tetrazole ring [62]. Electronegative substitution on the nitrile enhances the rate of the reaction. The solubility of the azide salt also influences the rate of reaction. The ammonium azides are soluble in dimethylformamide.

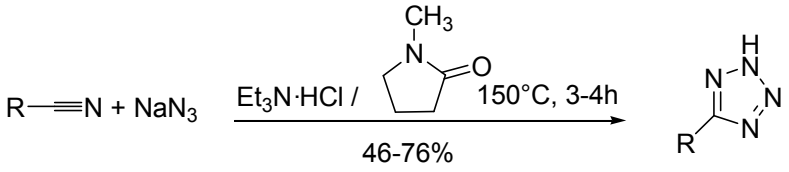


10 **11**

Scheme 5. Synthesis of 5-phenyltetrazole with ammonium azide

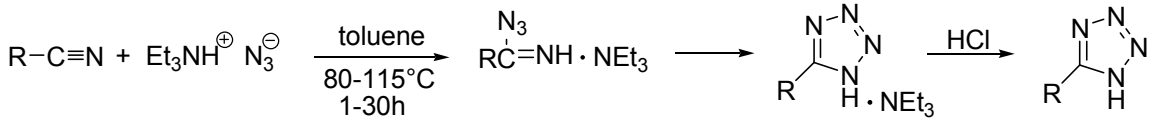
This methodology is not appropriate for the preparation of 5-thiosubstituted tetrazoles because they easily undergo irreversible decomposition to hydrazoic acid and thiocyanate at or near their melting points, which are, in several cases, quite close to the reflux temperature of DMF [69]; therefore using high temperature is not advisable in these cases. In addition this protocol for the synthesis of tetrazole rings is accompanied by the sublimation of explosive NH_4N_3 [70]. The sublimation of explosive NH_4N_3 also occurs when other aprotic solvents instead of the DMF are used for the reaction.

Bernstein and Vacek showed that a combination of sodium azide and triethylammonium chloride is an useful alternative to synthesize tetrazoles when *N*-methylpyrrolidinone is used as a solvent instead of the DMF (shorter reaction times) (Scheme 6) [71]. DMF under heating and basic conditions partially decomposes and forms free nucleophilic amines which may react with starting nitriles which contain certain functional grups [71]. An alternative to eliminate the amine sources was found to be the use of 1-methyl-2-pyrrolidinone as solvent.



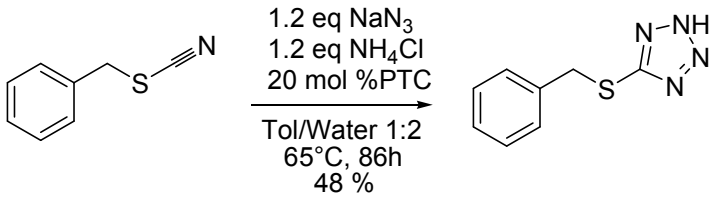
Scheme 6. Preparation of 5-substituted tetrazoles

Koguro *et al*., reported a variant by using triethyl amine hydrochloride in toluene [72]. In this procedure, the authors proposed that the intermediate complex [$Et_3N{\cdot}HN_3$] is first ionized as Et_3NH^+ and N_3^-, then, each of these react with the triple bond of the nitrile group to produce **14** (Scheme 7). When an aromatic solvent such as toluene is used, both the cation and the anion are not solvated, and the reaction thus proceeds smoothly.



Scheme 7. Synthesis of tetrazoles with triethylammonium azide

LeBlanc and Jursic recently reported a simple alternative for the method using sodium azide and ammonium chloride in DMF, by working under phase transfer conditions (PTC) (Scheme 8) [73]. Hexadecyltrimethylammoniumbromide was found to be the most useful catalyst. The ratio of water and toluene as well as the reaction temperature are important factors to obtain satisfactory yields. This methodology can be a good alternative to the simple use of sodium azide and amonium chloride [69] for the preparation of 5-alkylthio and 5-arylthiotetrazoles, which are activators for RNA and DNA synthesis. However this procedure requires long reaction times, which makes an application in an industrial scale up improbable.

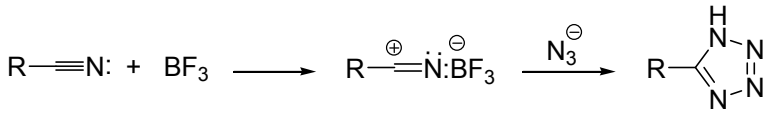


Scheme 8. Synthesis of tetrazoles using PTC conditions

1.1.3.1.2.2. NaN_3 in the presence of Lewis acid

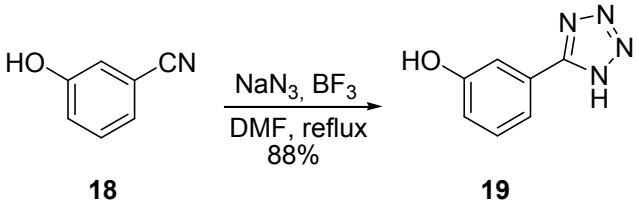
Finnegan and Lofquist reported in 1958 the study of the tetrazole formation in the presence of Lewis acids [62]. The proposed mechanism involves a nucleophilic attack of the

azide ion on the carbon of nitrile group, followed by ring closure of the imino azide to form the tetrazole ring. Conditions which enhance or favour a δ^+ charge on the nitrile carbon, such as the cordination of a Lewis acid, increase the rate of the reaction (Scheme 9).



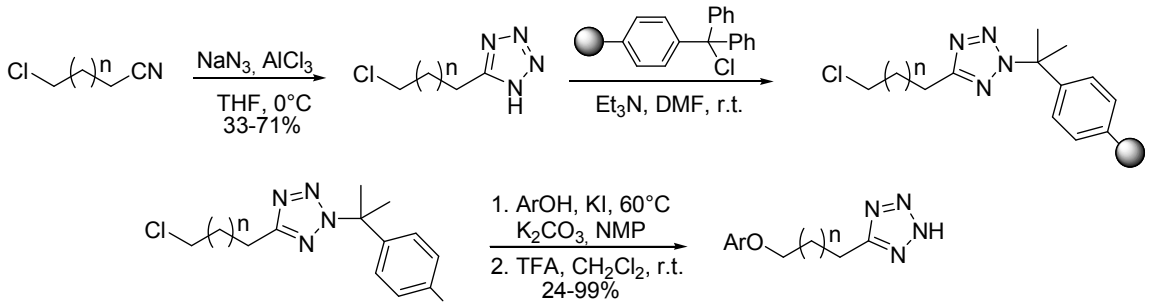
Scheme 9. Tetrazole formation in the presence of Lewis acid

Nearly four decades later Shechter *et al.* reported the preparation of a few simple 5-(hydroxy-phenyl)tetrazoles by the addition of aryl nitriles with sodium azide in the presence of boron trifluoride (Scheme 10) [74].



Scheme 10. Preparation of tetrazoles with NaN_3 in the presence of BF_3 as Lewis acid

Recently the use of aluminum chloride as a Lewis acid catalyst for the generation of aliphatic tetrazoles with a relatively low yield has been reported [75]. The crude was protected as a resin-bound trityl derivatives, which was subjected to alkylation followed by cleavage from the solid support to generate the desired tetrazole derivatives (Scheme 11).



Scheme 11. Tetrazole ring formation with NaN_3 in the presence of $AlCl_3$ as Lewis acid

1.1.3.1.3. Sharpless methodology: The Click Chemistry approach

The Click Chemistry

The term "Click Chemistry" was introduced by K. Barry Sharpless *et al.* in 2001 [76,77]. "Click chemistry" is a modular approach that uses only practical and reliable

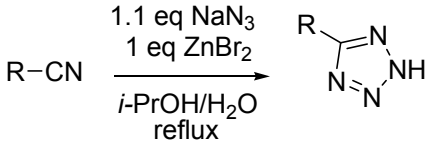
reactions with readily available reagents. In several instances water is the ideal reaction solvent, providing the best yields and highest rates. Reaction work-up and purification uses benign solvents and avoids chromatography.

One of the "click approaches" is the copper-(I)-catalyzed 1,2,3-triazole formation from azides and terminal acetylenes as a particularly powerful linking reaction, due to its high degree of reliability and complete specificity of the reactants.

Synthesis of tetrazole rings

Sharpless *et al*. have reported a simple protocol for transforming a wide variety of nitriles into the corresponding 1*H*-tetrazoles, by using NaN_3 in the presence of Zn(II) salts in aqueous conditions (Scheme 12) [61,63,78,79]. This procedure shows a good level of generality, however, in the case of sterically hindered aromatic or alkyl inactivated nitriles, high temperatures (140 - 170 °C) are required. They have not been able to achieve significant conversions of aromatic nitriles bearing an sp^3-hybridized substituent in the *ortho* position [63].

When the reaction is run at a concentration of 1 M in sodium azide and 1 M of $ZnBr_2$ a small amount of hydrazoic acid in the headspace above the reaction mixture is liberated [78]. Even at 100 °C, release of hydrazoic acid is minimal. The exact role of zinc is not yet clear [78]. The mechanism of the reaction has been controversial, with evidence supporting both a two-step mechanism and a concerted [2+3] cycloaddition [61].



Scheme 12. Tetrazole ring formation with the Sharpless methodology

The chief competing reaction is hydrolysis of the nitrile to primary amide; therefore with electron-poor nitriles, lowering the amount of zinc avoids significant formation of the amide byproduct. Other zinc salts such perchlorate and triflate also work; Zinc bromide is the best compromise between cost, selectivity and reactivity.

1.1.3.1.4. Tin- and silicon-mediated methods

Some of the newer methods for the preparation of 5-substituted tetrazoles involve the reaction of alkyl- or arylnitriles with safer organic soluble azides such as trialkyltin azide or trimethylsilylazide [29,1,80].

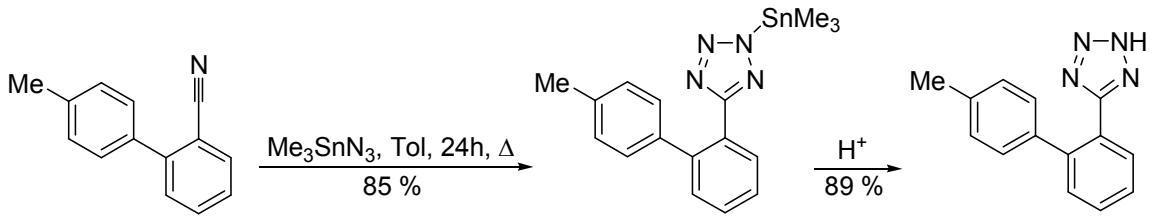
1.1.3.1.4.1. Trialkyltin azides

Methods for the tetrazole formation from organic-soluble reagents trimethylstannyl[81] or tri-*n*-butylstannyl azides [48,82] are more commonly utilized in larger scale than the sodium azide / ammonium salt protocols.

Duncia and Carini,[44] of DuPont, looking for a good alternative method to synthesize sartans (Section 1.1.2.2.1.)[83] and using the biphenylnitrile **20** as a model system, discovered that both trimethyl- and *n*-butyltin azides react forming the trialkltin-tetrazole adducts. However, removal and disposal of stoichiometric (highly toxic) residual organotin at the end of the reaction is a major drawback of this methodology [48].

Trialkyltin azide is typically prepared *in situ* from trialkyl chloride (volatile and toxic) and sodium azide, and has been shown to be effective in the synthesis of 5-substituted tetrazoles. Better yields are generally obtained compared to silicon-based azide reagents.

The treatment of the starting nitrile **20** with trimethyl- or tri-*n*-butyltin azide [48] in toluene or xylene at refluxing gives the corresponding tetrazole. The insoluble tin-tetrazole adduct **21** precipitates and when the reaction is finished, the product is simply filtered and dried. Subsequent acid hydrolysis yields the desired tetrazole (Scheme 13).



Scheme 13. Synthesis of sartans precursor using trimethyltin azide

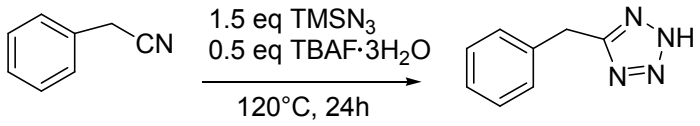
Higher temperature and/or longer reaction time are required using tri-*n*-butyltin reagent because of the more bulky character. An alternative to remove the tributyltin moiety, is to substitute the tin group with a trityl protecting group.

1.1.3.1.4.2. Trimethylsilyl azide

Trimethylsilyl azide has been reported to react with nitriles to give 5-substituted tetrazoles [84]. It is an attractive azide source due to its stability and relatively high boiling point (105 °C). However, benzonitrile reacts with only very low conversion and *ortho*-substituted benzontriles fail to undergo the reaction.

$TMSN_3$ under solvent free conditions

Pizzo *et al.* recently reported the use of $TMSN_3$ in solvent free conditions [85]. Catalytic amount of tetrabutylammonium fluoride (TBAF) is used for the anionic activation of the silicon-nitrogen bond [86]. The use of TBAF has the advantage to activate the azide nucleophile and deprotects the *N*-silylated products. This catalytic system is relatively efficient and a wide range of tetrazoles are obtained in 1 to 48 hours at 85 to 120 °C (Scheme 14).

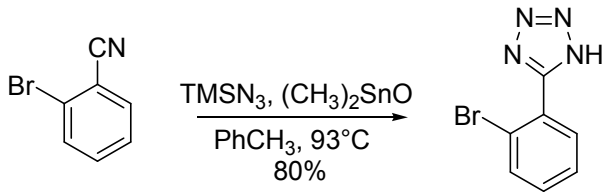


23 **24**

Scheme 14. Synthesis of tetrazoles with $TMSN_3$ in the presence of TBAF

$TMSN_3$ in the presence of dibutyltin oxide as catalyst

The use of trimethlsilyl azide in the presence of a catalytic amount of dibutyltin oxide to convert nitriles into tetrazoles has been developed (Scheme 15) [43,87,88].

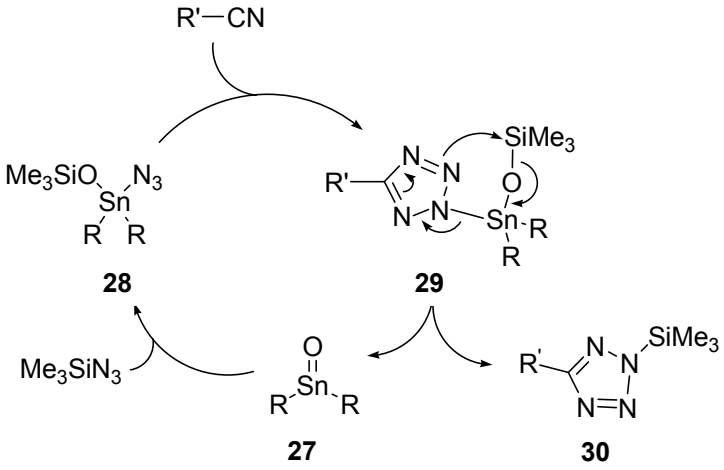


25 **26**

Scheme 15. Synthesis of tetrazoles with $TMSN_3$ in the presence of dibutyltin oxide as catalyst

In the general procedure the nitrile is treated in toluene at high temperature for 24 to 72 hours, with 2 equivalents of trimethylsilyl azide and 0.1 equivalent of dibutyltin oxide to provide the desired tetrazole. However in some cases, full conversion is obtained using in total 1 equiv of tin reagent ad 5 equiv of $(TMS)N_3$ at 100 °C (Scheme 15).

The catalytic cycle involves the formation *in situ* of the dialkyl(*O*-trimethylsilyl)-azidostannylhydrin **28** which reacts with the nitrile to give the *N*-(dialkyl-(trimethylsloxy)stannyl)tetrazole **29** (Scheme 16). The intermediate *N*-(dialkyl (trimethylsoloxy)stanyl)tetrazole **29** breaks down into the *N*-(trimethylsilyl)tetrazole **30** and the dialkyltin oxide **27** that carries on the catalytic cycle (Scheme 16) [43].



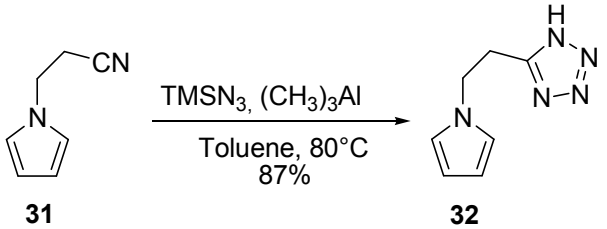
Scheme 16.

The trimethylsilyl azide as the azide source greatly reduces the hazard posed by *in situ* generation of hydrazoic acid and eliminates the possibility of the exposure to the toxic trialkyltin chloride used for the preparation of trialkyltin azide. However, at least two equivalents of trimethylsilyl azide are required for the reaction to run to completion and it is still difficult to separate the desired product from the stannane compounds. In addition the stannane compounds used in these reactions are generally highly toxic and require additional treatment of the waste water.

$TMSN_3$ in the presence of trimethyl aluminium

A method using trimethylsilyl azide was recently described by Lilly chemists Huff and Staszak,[55] who showed that an equimolar mixture of trimethylaluminum and trimethylsilyl azide in hot toluene is an efficient combination to prepare 5-substituted tetrazoles (Scheme 17). However, highly hindered nitriles resulted in poor conversion and the results are similar to those obtained using nBu$_3$SnN$_3$.

Roeder and Dehnicke [89] reported that trimethylaluminum when treated with trimethylsilyl azide forms a 1 to 1 complex at temperatures below 120 °C which reacts to give $(Me_2AlN_3)_3$ only at higher temperature. Therefore, it is likely that trimethylaluminum simply acts as a Lewis acid under these reactions and does not form $(Me_2AlN_3)_2$.

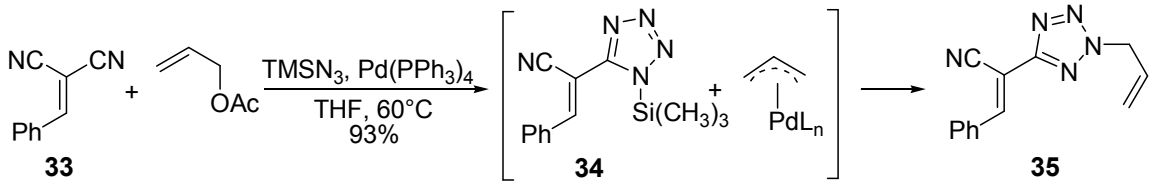


31 32

Scheme 17. Synthesis of tetrazoles with $TMSN_3$ in the presence of Me_3Al

$TMSN_3$ in the presence of $Pd(PPh_3)_4$: Yamamoto methodology

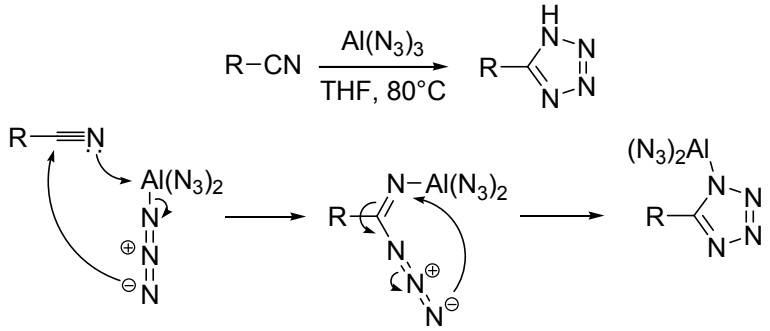
Yamamoto *et al*. reported the synthesis of 2-allyltetrazoles starting from cyano compounds *via* the palladium-catalyzed three-components coupling reaction [90]. The *N*-silyl tetrazole **34**, derived from the cycloaddition reacts *in situ* with the π-allylpalladium species to provide the *N*-allylated product **34** (Scheme 18).



Scheme 18. Preparation of 2,5-disubstituted tetrazoles

1.1.3.1.5. Aluminum azide

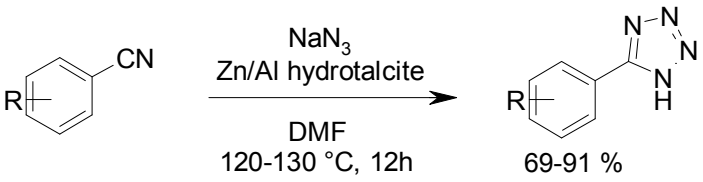
Aluminum azides have already been reported by Wiberg and Michaud in a 1957 German patent [91]. The $Al(N_3)_3$ can be prepared by treatment of $AlCl_3$ with 3 equivalents of NaN_3 in THF at reflux [91,92]. However, using aluminum azide for the preparation of tetrazoles, two moles of HN_3 are formed for every mole of product during the acidic quench of the reaction. The mechanism proposed proceeds through intramolecular delivery of N_3^- from $Al(N_3)_3$ complexed with the nitrile (Scheme 19).



Scheme 19. Proposed mechanism fort the tetrazole formation with $Al(N_3)_3$

1.1.3.1.6. Synthesis of 5-substituted tetrazoles using Zn/Al hydrotalcite catalyst

Katam and *et al.* reported an alternative methods to prepare tetrazole rings using Zn/Al hydrotalcite as heterogeneous catalyst [93] (Scheme 20). The anionic [Zn-Al-Cl], with [Zn]/[Al] ratio of 3 to 1, is synthesized by co-precipitation at pH 9. This methodology requires relative high temperature and long reaction times in DMF, with the use of Zn which requires additional treatment of the waste water.



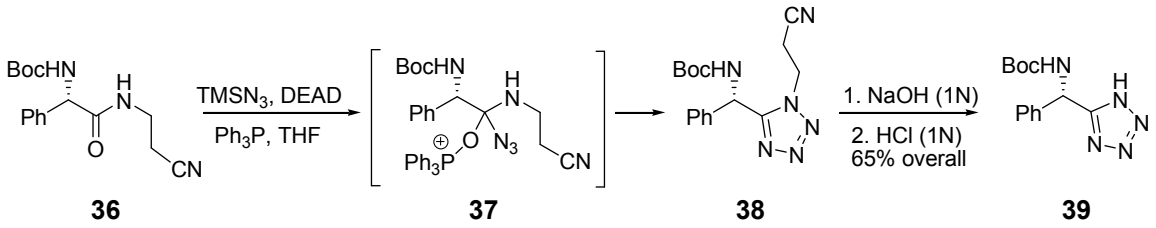
Scheme 20. Zn/Al hydrotalcite catalyzed synthesis of 5-substituted-tetrazoles

1.1.3.2. Synthesis of tetrazoles with other methods

Several reports have appeared which make use of precursors other than nitriles to prepare 5-substituted-1*H*-tetrazoles. A short overview of these methods are given herein.

1.1.3.2.1. From *N*-(cyanoethyl)amides

N-(Cyanoethyl)amides **36** reacts with trimethylsilyl azide to provide 1*N*-protected tetrazole **38** (Scheme 21). Removal of the *N*-cyanoethyl moiety of **38** with aqueous sodium hydroxide, followed by acidification, led to the free tetrazole **39** in relative good overall yield (Scheme 21) [8].

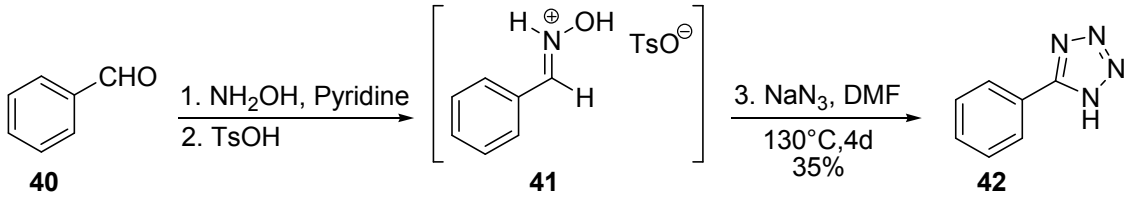


36 **37** **38** **39**

Scheme 21.

1.1.3.2.2. From oxime salts

An useful process for the preparation of 5-substituted-tetrazoles is the reaction of oxime salt **41** with sodium azide developed by Antonowa and Hauptmann [94]. In this procedure, benzaldehyde **40** may be directly transformed into the corresponding aryl tetrazole **42** (Scheme 22).

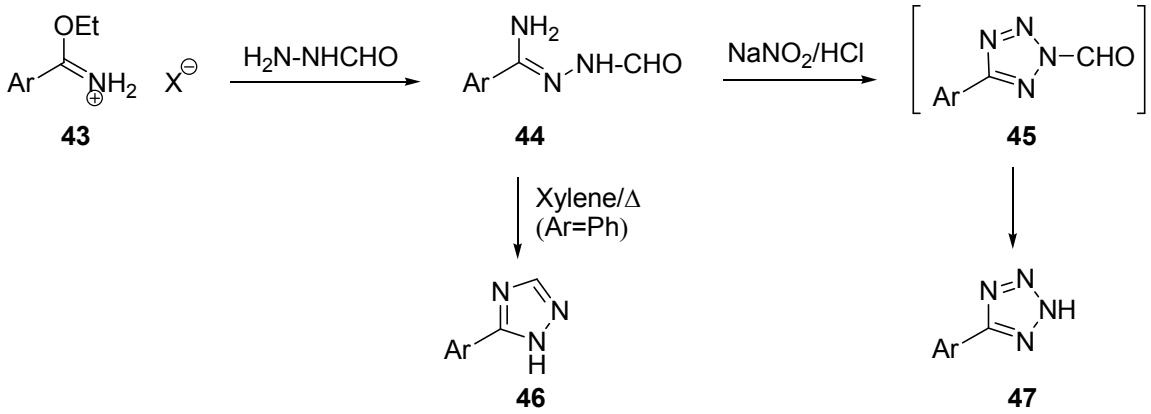


40 **41** **42**

Scheme 22. Synthesis of tetrazoles from oxime salts

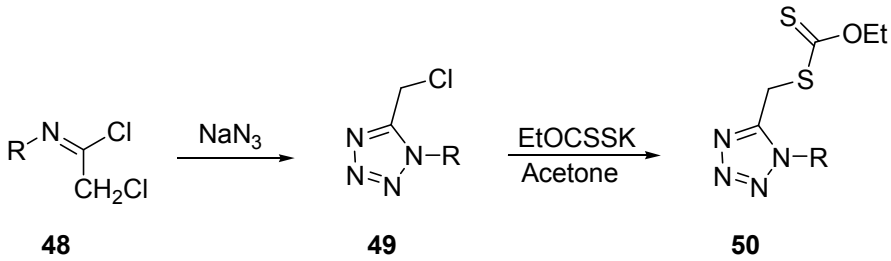
1.1.3.2.3. From imidate salt and imidoyl chlorides

Zard *et al.* proposed an alternative method to prepare 5-substituted tetrazoles from imidate salts which does not involve azides [95]. The reaction of imidates **43** with *N*-formyl hydrazine is known to give 1,2,4-triazoles *via* the intermediate *N*-formyl amidrazones **44**. However, by working at low temperature (0 °C) the triazole formation can be avoided and indeed, in the presence of sodium nitrite and diluted HCl, the desired tetrazole **47** can be isolated in good yields (Scheme 23). The triazole **46** can be isolated only upon heating in xylene.



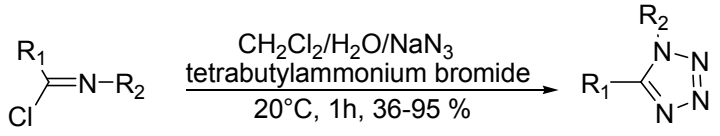
Scheme 23.

Few years later, Zard [96] proposed a method to prepare disubstituted tetrazoles. The reaction of imidoyl chloride **48** with sodium azide provides the 5-chloro methyl tetrazole **49** which is then treated with potassium *O*-ethyl xanthate in acetone to give the corresponding tetrazole xanthates **50** (Scheme 24).



Scheme 24.

Koldobskii *et al.* proposed the synthesis of 1,5-disubstituted tetrazoles under phase-transfer conditions from imidoyl chlorides by treatment with sodium azide (Scheme 25)[97].



Scheme 25. Synthesis of tetrazoles from imidoyl chlorides

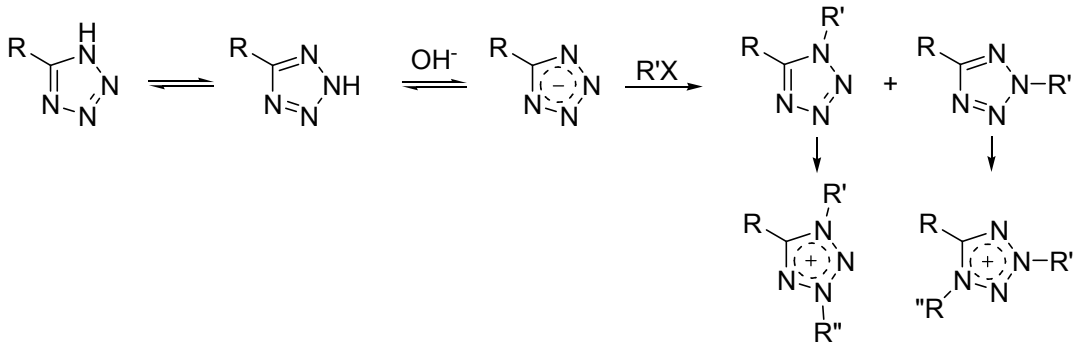
1.1.4. Reactivity of Tetrazoles

Reactivity of 5-substituted tetrazoles permits to classify them as aromatic compounds. The ring undergoes electrophilic substitution, is stable toward oxidation and, in general, the tetrazole ring remains unchanged during reduction of susceptible substituents [1].

1.1.4.1. Reaction with electrophiles

Peculiarities of the π-electron system of the tetrazole ring is the availability of lone pairs of the nitrogens which allow these heteroatoms to be attacked by various electrophilic reagents [1,98]. Aside from the variety of alkyl substituents, many other groups can be introduced including acyl, imidoyl, silyl, phosphoryl, sulfonyl, aryl, vinyl and amino functions [98].

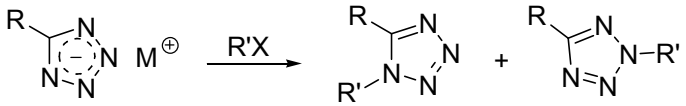
The most common nucleophile type reactions at the tetrazole nitrogens arise from the acidity of the ring N-H bond (Section 1.1.1.2.). The tetrazolic acids form stable anions when treated with bases and are more reactive than neutral tetrazoles towards electrophiles and alkylating agents (Scheme 26) [98]. The product is a mixture of 1*N*- and 2*N*-alkyl isomers, the relative proportions of which depend upon the conditions of the alkylation, the steric requirements of the alkylating agent and the influence of the 5-substituent. In general, electron-donating substituents at C-5 tend to favor 2*N*-alkylation. A more exhaustive discussion of this topic is given in Chapter 2.



Scheme 26. Reactions with electrophiles

1.1.4.1.1. Alkylation of tetrazolate anion salts

Metal salts of 5-substituted tetrazoles undergo to alkylation on heating with alkyl halides in a wide range of solvents. The products are a mixture of 5-substituted 1*N*- and 2*N*-alkyl tetrazoles (Scheme 27) [1].



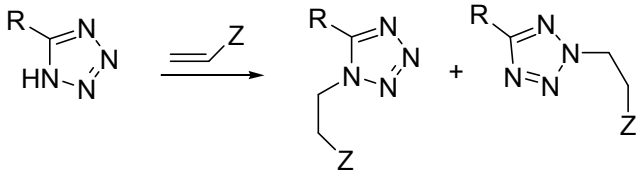
Scheme 27. Alkylation to tetrazoles to form a mixture of 1,5- and 2,5-disubstitted tetrazoles

1.1.4.1.2. Acylation and alkylation of neutral tetrazoles

There are a variety of electrophilic substitutions on 5-substituted tetrazoles with reagents such as hydrazonoyl halides, electron-deficient vinyl systems and acyl halides [49]. These reactions are carried out in the presence of excess Et_3N used to promote loss of halide or hydrogen halide (generating nitrilimines or nitrile oxides) and involve the tetrazolate anion as the reactive tetrazole species [1].

Michael reaction

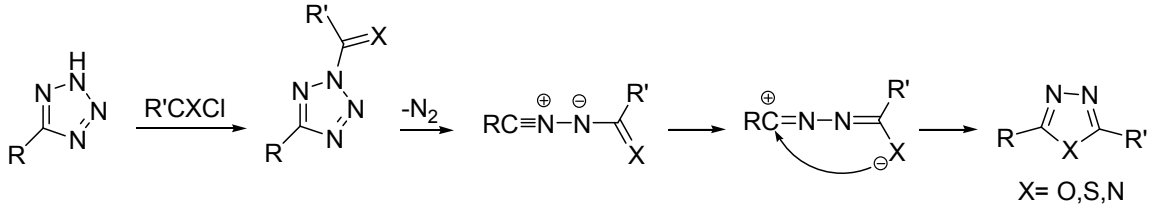
The Michael reactions of 5-substituted tetrazoles with electron-deficient vinyl systems give the 2-alkylated products in yields of about 50-80 % [1] (Scheme 28).



Scheme 28. Michael reactions of 5-substituted tetrazoles

Acylation

Electrophiles such as acyl halides and imidoyl halides attack the 5-substituted tetrazole ring at the N2-position which can give after thermal decomposition the Huisgen product (Scheme 29).



Scheme 29. Acylation of tetrazoles followed by thermal decomposition and Huisgen reaction

1.1.5. The Chemistry of the Cyano Group

1.1.5.1. Introduction

Nitriles are very important intermediates in synthetic organic chemistry [99,100]. They are also of considerable industrial importance as integral part of dyes, herbicides, natural products, agrochemicals and new biological active agents.

1.1.5.1.1. History

Hydrogen cyanide was discovered in 1782 by Carl Scheele, who was investigating the dye Prussian Blue or Berliner Blau, as it was known in the German-speaking world. Mixing the dye with an acid and heating gave him a flammable gas that dissolved well in water, producing an acidic solution. Logically enough, he called his discovery Berlin Blausäure (Prussic acid). Scheele's death in 1786 is sometimes attributed to accidental poisoning by hydrogen cyanide. J. L. Gay-Lussac was the first to prepare the pure acid in 1811 and Friedrich Wöhler and Justus von Liebig were the first to prepare the first nitriles benzoyl cyanide and benzonitrile in 1832.

1.1.5.2. Chemical & Physical properties

The chemical and physical properties of nitriles are in this section briefly discussed. The cyanide ion CN^- is isoelectronic with carbon monoxide and dinitrogen and, because of the highly electronegative nitrogen, the C≡N bond is highly polar, resulting in high molecular dipole moments [99]. Nitriles, therefore, have strong permanent dipole-dipole attractions as well as van der Waals dispersion forces between the molecules. Hence, nitriles have higher boiling points than would otherwise be expected from their molecular weights. Alkane-nitriles with α-hydrogens typically have pK_a ~ 25, but the acidity increases if more than one cyano group is present as seen in the case of the malononitrile (pK_a 11.0).

Nitriles are important laboratory and industrial solvents because of their characteristic physical properties. The common solvent acetonitrile can be taken as an example. It has a high boiling point for a two-carbon system (bp 81.6 °C/760 Torr), due to the above mentioned large dipole moment (3.9 D) leading to intermolecular association.

On account of their σ-donating, π-accepting and potential π-donating properties, nitriles act as ligands in coordination and organometallic compounds, besides the cyanide anion (Figure 10).

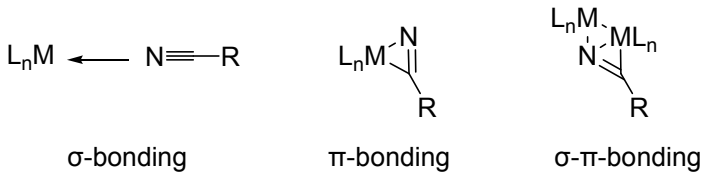


Figure 10. Ligand binding models of nitriles

The ability of the cyano group to act as a ligand has been exploited to form liquid – crystalline metal complexes. These are found to have enhance electronic polarizabilities[101] (Figure 11).

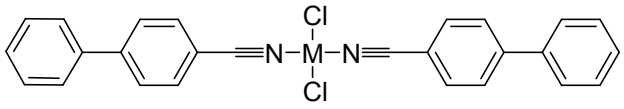
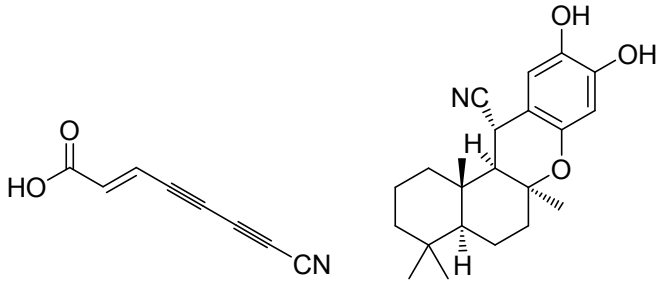


Figure 11. Metal-complex liquid crystals with nitrile ligands

1.1.5.3. Biological activity

Although nitriles (organic cyanides) have sometimes been stigmatized as poisonous, compared to simple cyanide salts such as sodium and potassium cyanide, they are ordinarily much less toxic. The parent compound, hydrogen cyanide can cause rapid death in humans due to metabolic asphyxiation. Death can occur within seconds or minutes of the inhalation of high concentrations of hydrogen cyanide gas. A recent study reports an estimated LC(50) in humans of 270 ppm for a 6-8 minutes exposure [102].

Organic compounds possessing a cyano group occur in nature, including compound **51**, which has antibiotic activity and compound **52** which is an antiviral agent isolated from a *Verongida* sponge (Figure 12).



51 **52**

Figure 12. Naturally occurring compounds containing a cyano group

Compounds containing a cyano group have applications in medicinal chemistry and some of them are also available on the market. A selection of drugs is given in Figure 13.

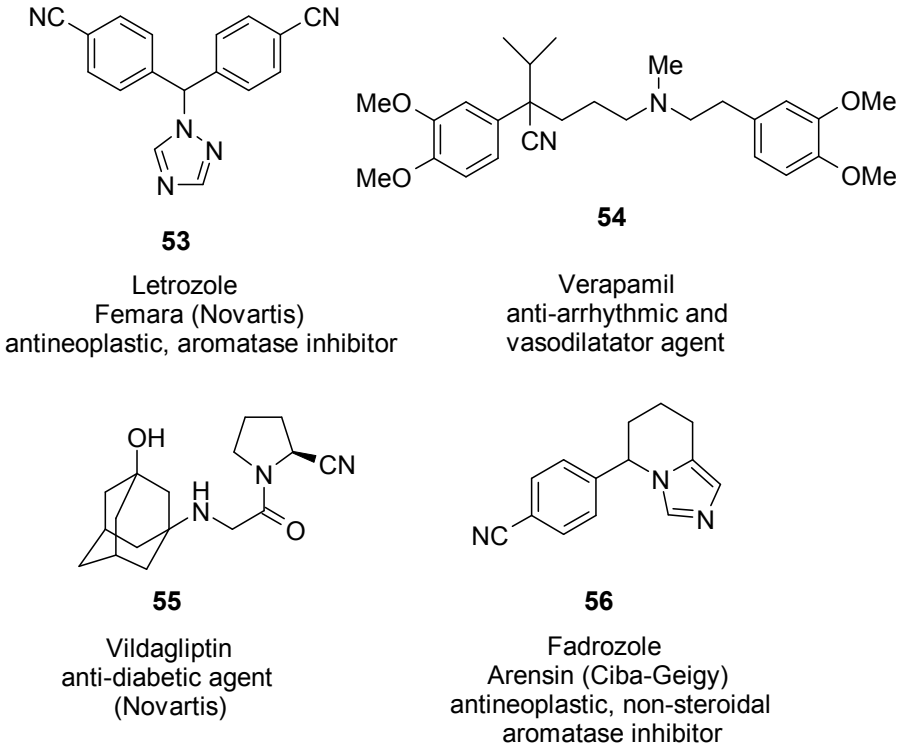


Figure 13. Selected cyano-substituted pharmaceuticals

1.1.5.4. Preparation of nitriles

The development of new methods for the synthesis of nitriles is important in organic synthesis, since nitriles are useful as intermediates for the preparation of amines, tetrazoles and other functional groups. The synthetic methods for the preparation of nitriles can be related mainly to four reaction type: addition, substitution, elimination and conversion of other nitriles [103,104].

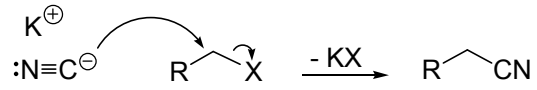
1.1.5.4.1. Preparation of nitriles by addition of hydrogen cyanide

Several methods for the preparation of nitriles by addition of hydrogen cyanide to unsaturated compounds have been developed [104a] including the addition of HCN in the presence of dicobalt octacarbonyl,[105] nickel catalysts,[106] and palladium catalysts [107].

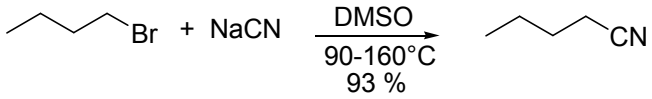
1.1.5.4.2. Preparation of alkyl nitriles by substitution

One of the most general methods for the synthesis of nitriles is a direct nucleophilic substitution of alkyl halides with inorganic cyanides [104a] (Scheme 30). The classical

conditions involve heating a halide with a cyanide salt in aqueous alcohol solution or in aprotic polar solvents such as DMSO (Kolbe nitrile synthesis) (Scheme 31) [108]. In analogy, the use of metal thiocyanates such as KSCN in a nucleophilic substitution with organic halides is a general procedure to introduce the thiocyanate group into a molecule [109].



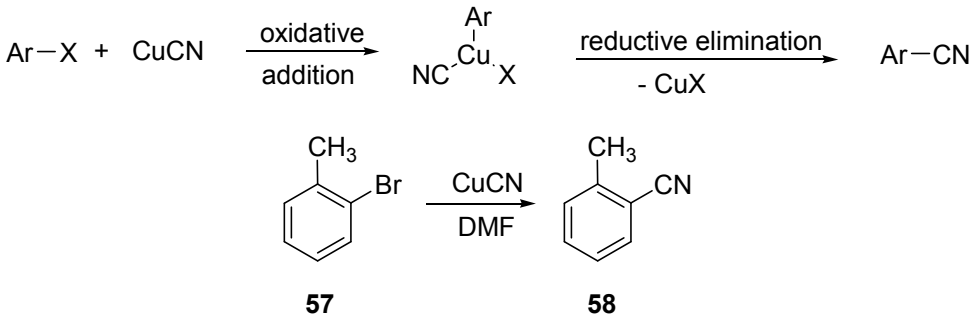
Scheme 30. Mechanism of the Kolbe nitrile synthesis



Scheme 31. Synthesis of nitriles

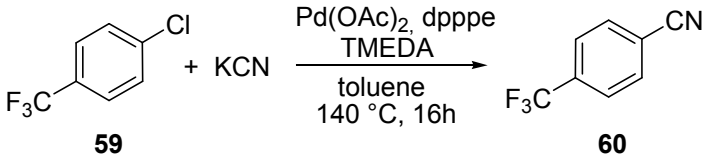
1.1.5.4.3. Preparation of aryl nitriles

Aryl nitriles can be prepared by the cyanation of aryl halides with an excess of copper(I) cyanide in a polar high-boiling solvent such as DMF [110], nitrobenzene, or pyridine at reflux temperature (Rosenmund-von Braun Reaction) [111]. The mechanism probably involves the formation of a Cu(III) species through oxidative addition of the aryl halide at the Cu(I). Subsequent reductive elimination then leads to the product (Scheme 32).



Scheme 32. Synthesis of aryl nitriles catalyzed by copper salts

Recently alternative procedures for the synthesis of aryl nitriles are reported, including the use of less toxic cyanide source such as $K_4[Fe(CN)_6]$ [112], or palladium catalysis (Scheme 33) [113].



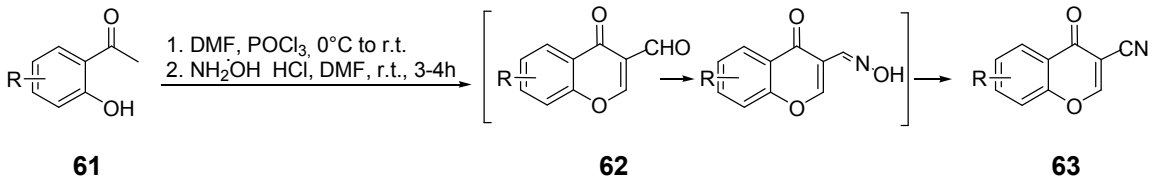
Scheme 33. Cyanation of aryl chlorides

1.1.5.4.3.1. Preparation of nitriles by dehydration

In the last 40 years, a number of efficient methods have been developed for the dehydration of oximes and amides to nitriles and the search for better reagents is still on going [104,114,115].

Numerous reagents such as Burgess reagent,[116] PPh_3 / CCl_4,[117] trifluoroacetic or acetic anhydride and anhydrous pyridine,[118,119] alkyl cyanoformates,[120] aluminum iodite,[121] silica gel,[122] tetrachloropyridine,[123] phthalic anhydride,[124] etc.[125] have been developed. In addition Vilsmeier reagent, Propsal, cyanurchloride and *N*,*N'*-carbonyl-diimidazole (DCI) are some examples which find an industrial application.

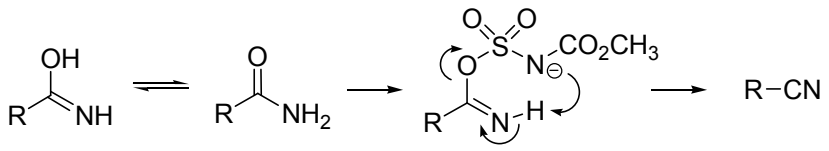
The usefulness of this synthetic approach to nitriles, directly from aldehydes, is demonstrated in the one-pot synthesis of carbonitrile derivative **63** from 2-hydroxyacetophenone **61**. Compounds **61** are first subjected to the Vilsmeier-Haack reaction to form aldehyde **62** *in situ*. Treatment of this mixture with hydroxylamine hydrochloride provides the desired nitriles **63** (Scheme 34) [126].



61 **62** **63**

Scheme 34. One-pot synthesis of 4-oxo-4*H*-1-benzopyran-3-carbonitriles

A further method for the preparation of nitriles from primary amides utilizes the methyl (carboxysulfamoyl) triethylammonium hydroxide inner salt (Burgess reagent) [127,128]. The mechanism of the reaction involves formation of the sulfonate ester from the enolate form of the amide followed by *syn* elimination (Scheme 35).

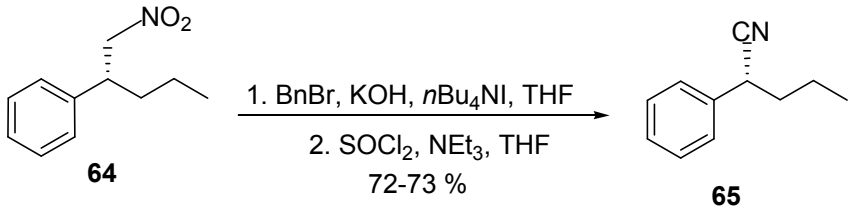


Scheme 35. Conversion of primary amides into nitriles by using the Burgess reagent

1.1.5.4.4. Preparation of nitriles from nitroalkanes

Carreira *et al.* reported a convenient protocol for the synthesis of optically active aldoximes and nitriles starting from chiral nitroalkanes [129]. The treatment of the starting nitro-compounds with benzyl bromide, KOH and nBu$_4$NI followed by addition of $SOCl_2$

leads directly to nitriles in relative good yields without loss of optical activity (Scheme 36).

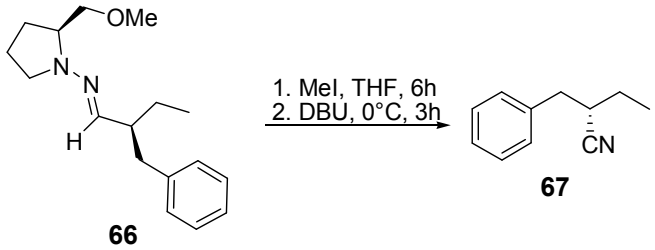


Scheme 36. Transformation of optically active nitroalkanes into nitriles in a one-pot procedure

1.1.5.4.5. Preparation of nitriles from hydrazones

Several procedure has been developed for the preparation of nitriles from hydrazones, including oxidative cleavage of dimethylhydrazone of aldehydes with magnesium monoperoxyphthalate hexahydrate (MMPP) [104b,130] and microwave-assisted solvent-free oxidative cleavage using oxone with wet alumina [131].

A convenient procedure to form nitriles under mildly basic conditions is the treatment of dimethylhydrazones with excess of methyl iodide followed by reaction with DBU (Scheme 37)[132].



Scheme 37. Synthesis of nitriles from hydrazone of aldehydes

1.1.5.5. Reactivity of nitriles

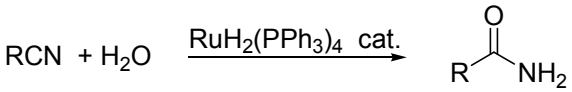
The importance of nitriles as intermediates in organic synthesis is well established [100,104a]. However nitriles are relatively unreactive in comparison to other unsaturated organo-nitrogen compounds. A classic example is acetonitrile, commonly employed as a solvent in a variety of reactions. The low reactivity of nitriles is attributed to the low basicity of the *sp*-hybridised nitrogen atom.

Nitriles typically undergo nucleophilic additions and the chemistry of the nitrile functional group, C≡N, is very similar to that of the carbonyl, C=O of aldehydes and ketones.

1.1.5.5.1. Hydration of nitriles to form primary amides

Nitriles can be converted to the corresponding primary amides. Several methods has been developed including the application enzymatic reactions [133a], catalytic hydration with manganese dioxide on silica gel,[133b] alkaline solution of peroxide, microwave irradiation with sodium perborate tetrahydrate in a mixture of water/ethanol [134].

Nitriles are activated by low-valent ruthenium complexes and undergo reactions with nucleophiles under neutral conditions (Scheme 38) [104a,135].



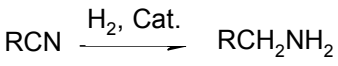
Scheme 38. Catalytic hydration of nitriles under neutral conditions

1.1.5.5.2. Hydrolysis of nitriles to carboxylic acids

Carboxylic acids can be prepared by hydrolysis of nitriles. The reaction requires strong acid (*e.g.* H_2SO_4) or strong base (*e.g.* NaOH) and heat.

1.1.5.5.3. Reduction of nitriles to primary amines

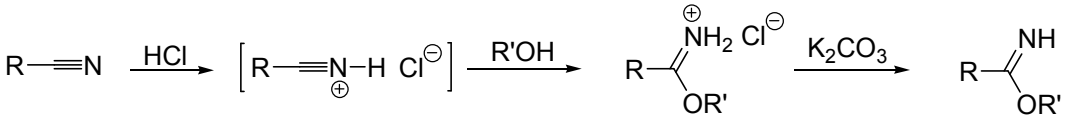
Nitriles can be converted to the corresponding primary amines by hydrogenation. Several catalysts can be used including Rh-AlO_3 in ammonia ethanol [136], nickel catalysts such as Raney Nickel, Ni-Al-NaOH, palladium catalysts, BH_3, $NaBH_4/AlCl_3$, $LiAlH_4$ among others (Scheme 39) [104a].



Scheme 39. Reduction of nitriles to amines

1.1.5.5.4. Pinner reaction

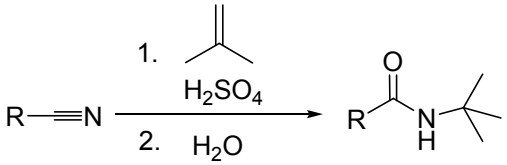
The Pinner reaction is the partial solvolysis of a nitrile to yield an iminoether. Treatment of the nitrile with gaseous HCl in a mixture of anhydrous chloroform and an alcohol produces the imino ether hydrochloride. These salts are known as Pinner salts and may react further with various nucleophiles (Scheme 40) [137].



Scheme 40. Synthesis of imino ethers

1.1.5.5.5. Ritter reaction

Nitriles are converted to the corrsponding *N*-alkyl amides *via* the Ritter reaction using various alkylating reagents, for example, strong acid and isobutylene [138] (Scheme 41). Tertiary alcohols, such as *tert*-butyl acetate [139,140], react with nitriles in the presence of strong acids to form amides *via* a carbocation.



Scheme 41. Ritter reaction

1.2. Application of Click Chemistry for a new Synthesis of 5-Substituted Tetrazoles from Organoaluminum Azides and Nitriles. Results and Discussion

Recently tetrazole derivatives have attracted much attention for the use as starting materials in fine chemicals (Section 1.1). However, a versatile method for synthesizing tetrazoles through a safe and simple manipulation has not been developed.

In the course of our investigation into an alternative synthesis of sartan derivatives (Figure 14), it became of interest to find an alternative safe process for the preparation of tetrazoles on an industrial scale.

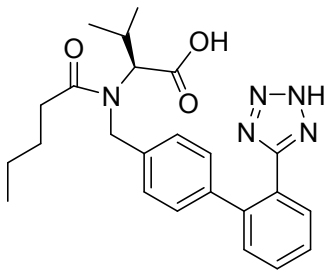
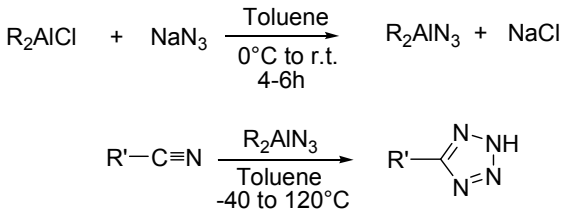


Figure 14. Valsartan (Novartis)

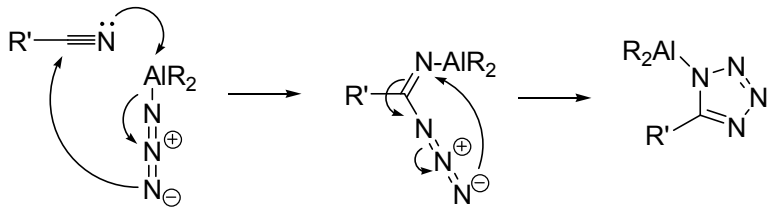
We report here the discovery and development of a novel process for the efficient transformation of a wide variety of nitriles into the corresponding tetrazoles using dialkylaluminum azide. We have found that organic aluminum compounds are effective azide sources for the direct conversion of nitriles to tetrazoles (Scheme 42) [141,142].



Scheme 42. [2+3] Cycloaddition route to tetrazoles

Dialkylaluminum azides can be prepared rapidly (Scheme 42) by the addition of an equimolecular amount of dialkylaluminum chloride to sodium azide in an aprotic organic

solvent such as toluene, xylene or hexane [143,144]. The alkyl residue (R) can be branched (isobutyl-) or linear (methyl- or ethyl-) [141,142]. During the cycloaddition no by-products are formed and the desired tetrazole is produced in high yield. The product can easily be isolated in excellent purity with a simple work up proedure. Although the mechanism is not yet understood, we suggest that the aluminum acts as a Lewis acid, activating the nitrile to azide addition (Scheme 43).



Scheme 43. Proposed two-step mechanism for the formation of tetrazoles

1.2.1. Dialkylaluminum azides

1.2.1.1. Introduction

1.2.1.1.1. The dialkylaluminum azide

The structures of the diethylaluminum and dimethylaluminum azides in solution were already investigated in the 1960s and determined as a trimer $(R_2AlN_3)_3$ which form a planar six-member ring with symmetry D_{3h} (Figure 15) [145].

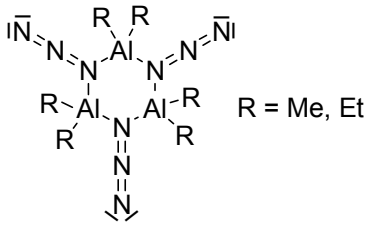


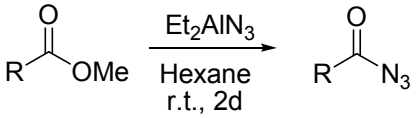
Figure 15. Trimeric form in solution of dialkylaluminum azide

1.2.1.1.2. The reactions of the diethylaluminum azide

Diethylaluminum azide is already known as an activated azide donor for the conversion of esters to acylazides [143], ring opening of epoxyalcohols [146] and triazole formation from α'-amino-α,β-unsaturated ketones [147], but has never been employed in the synthesis of tetrazoles.

Conversion of esters to acylazides

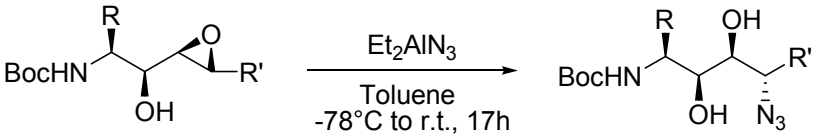
Rawal and *et al.* reported a one-pot procedure for the conversion of esters to acyl azides using diethylaluminum azide which combine into one reagent the nucleophilic azide unit with a highly oxophilic species [143]. The reaction is carried out at room temperature using two equivalents of diethylaluminum azide to form the desired acylazide with 60 - 77 % of yield (Scheme 44).



Scheme 44. One-pot procedure for the synthesis of acyl azides

Ring opening of epoxyalcohols

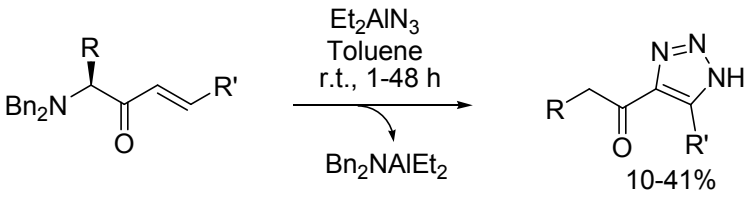
Benedetti *et al.* reported the reaction of 2,3-epoxyalcohols with diethylaluminum azide to give 3-azido-1,2-diols under mild condition (Scheme 45) [146a].
The reaction is highly selective, leading to the formation of the corresponding azido diols with inversion of configuration at C-3.



Scheme 45. Ring opening of 2,3-epoxyalcohols with Et_2AlN_3

Triazole formation from α'-amino-α,β-unsaturated ketones

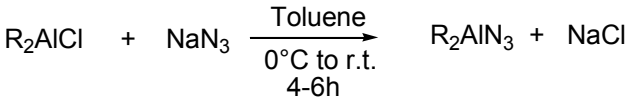
A few years later, Benedetti *et al.* reported the preparation of triazoles from α'-amino-α,β-unsaturated ketones using diethylaluminum azide (Scheme 46) [147].



Scheme 46. Triazole formation from α'-amino-α,β-unsaturated ketones with Et_2AlN_3

1.2.1.2. Diethylaluminum azide formation

Dialkylaluminum azides can be prepared in a short time by addition of an equimolecular amount of dialkylaluminum chloride to sodium azide in an aprotic organic solvent such as toluene, xylene or hexane. According to literature procedures, [143] we have prepared a variety of dialkylaluminum azides where the alkyl residue is branched (isobutyl-) or linear (methyl- or ethyl-) (Scheme 47) [141,142].



Scheme 47. Preparation of dialkylaluminum azides

1.2.1.2.1. FT-IR Study

The formation of Et_2AlN_3 from diethylaluminum chloride and sodium azide was followed by FT-IR spectroscopy (Scheme 48, Figures 16-18). A clear solution of diethylaluminum chloride (3.7 ml, 2.7 M in xylene) was treated, at room temperature, with sodium azide (0.65 g) in one portion and the IR spectra measured every two minutes for a period of 24 hours. During the course of the reaction, the temperature was also monitored internally.

$$Et_2AlCl + NaN_3 \xrightarrow[r.t.]{Xylene} Et_2AlN_3 + NaCl$$

Scheme 48. Formation of diethylaluminum azide

The temperature increased during the first 15 minutes, from 25 to 34 °C and then decreased again to 25 °C. After the addition of sodium azide, the IR spectra showed immediately a strong signal at 2138 cm^{-1}, typical of azides, $\nu_{asim}(N_3)$, which increased during the time (Figure 17). The sodium azide is almost not soluble in a solvent such as xylene and is not detected by IR, that means that this band at 2138 cm^{-1} corresponds to the formation of diethylaluminum azide in solution. An other typical azide band appears at 1223 cm^{-1}, but this signal decreased within 6-7 hours and a new signal at 1269 cm^{-1} appeared, which corresponds to the symmetry valence $\nu_{sim}(N_3)$ [145b]. In conclusion, from the FT-IR pictures seams that the diethylaluminum azide is immediately formed, but the equilibrium in solution, may be between the monomeric and the trimeric forms, is stabilized within 6 – 7 hours (Figures 17, 18).

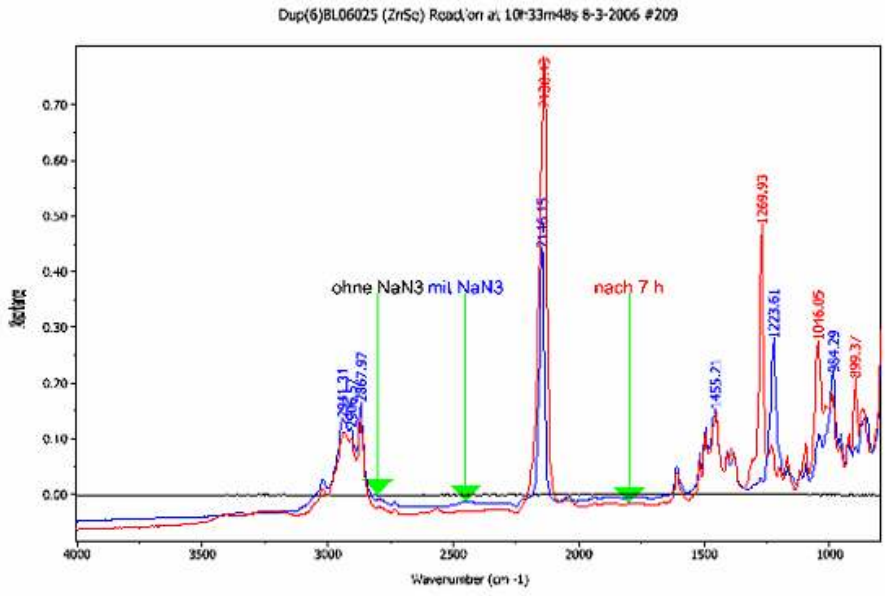


Figure 16. Proceeding of the reaction

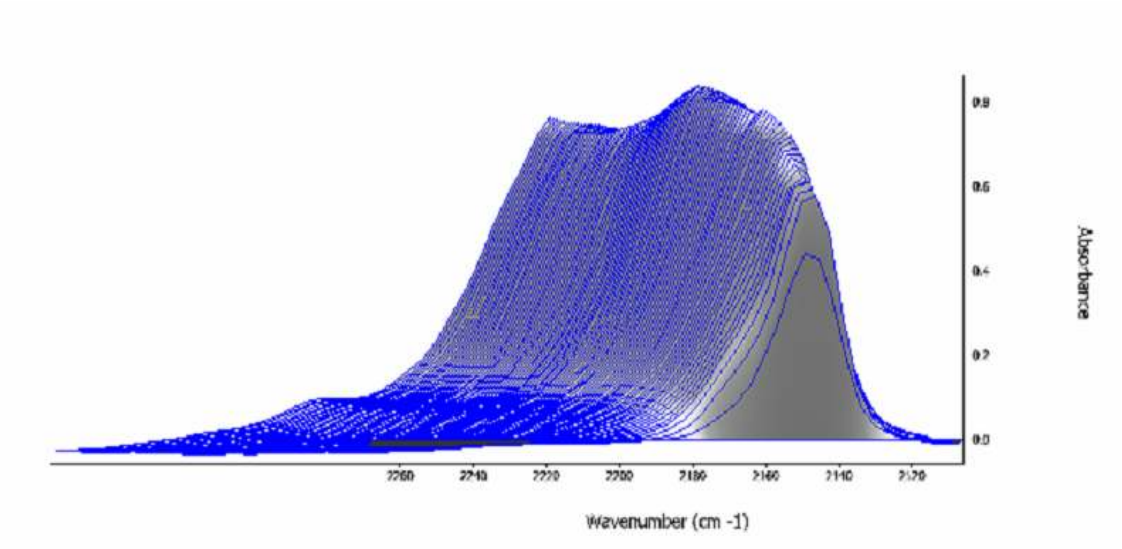


Figure 17. Signal at 2138 cm^{-1} (3D picture)

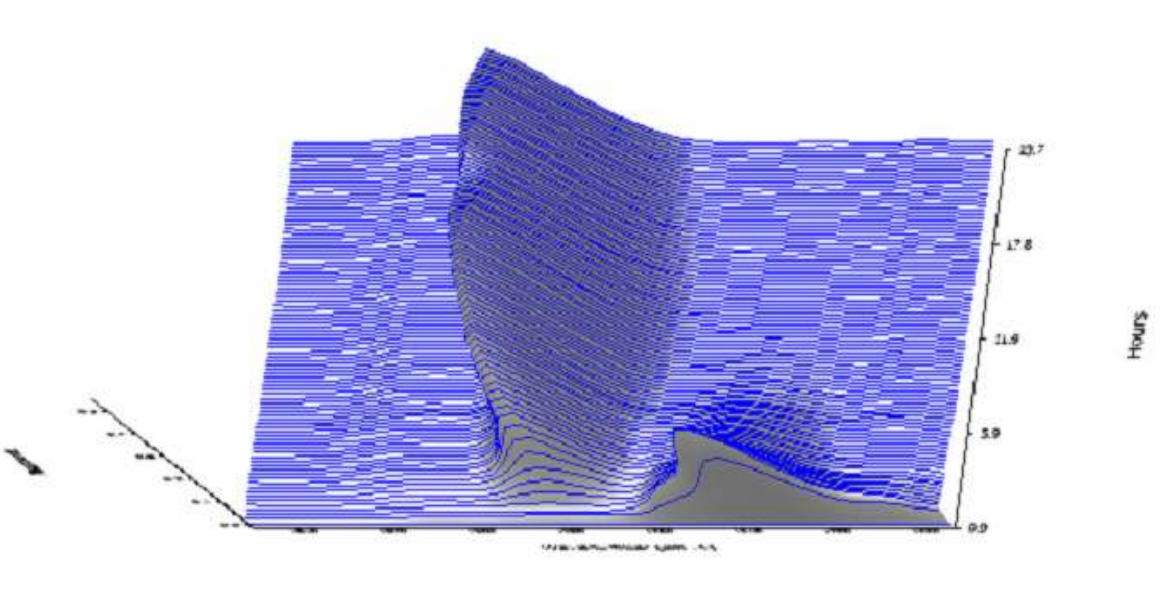


Figure 18. Decrease of signal at 1223 cm^{-1}, increase of signal at 1269 cm^{-1} (3D picture)

1.2.1.2.2. Differential scanning calorimetry (DSC)

The thermal behaviors of diethylaluminum and tributyltin azides are indicated by the DSC thermographs shown in Figure 19 and 20 respectively. All calorimetric scans were performed with the Mettler Toledo 821 calorimeter.

The diethylaluminum azide, warmed at 4 °C/min, starts an exothermic decomposition at 220 °C, with the maximum peak at 278 °C, and an onset of the decomposition in the range of 230-260 °C (Figure 19). In the case of dibutyltin azide, under the same conditions (4 °C/min) the exothermic decomposition starts at 180 °C with the maximum

peak at 288 °C and an onset of the decomposition in the range of 230-280 °C (Figure 20). Of note, the DSC of diethylaluminm azide is better compared to that of tributyltin azide in terms of safety margins. The isothermal DSC was also measured at 150 °C for 12 hours and the diethylaluminum azide shows is stable under these conditions.

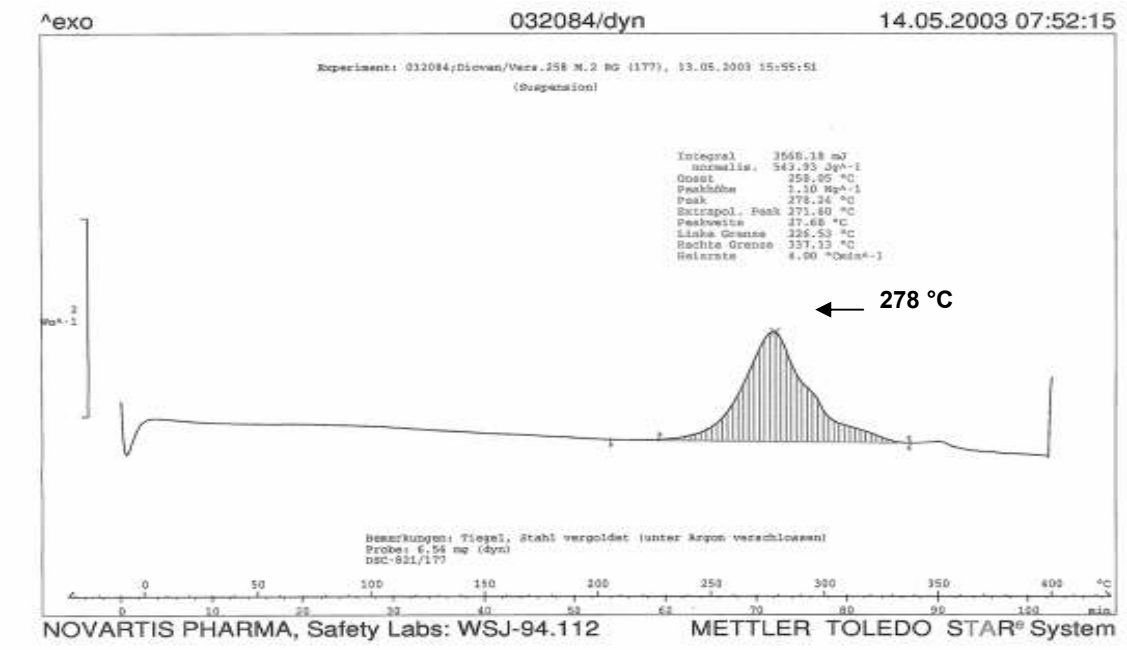


Figure 19. Dynamic DSC of Et_2AlN_3

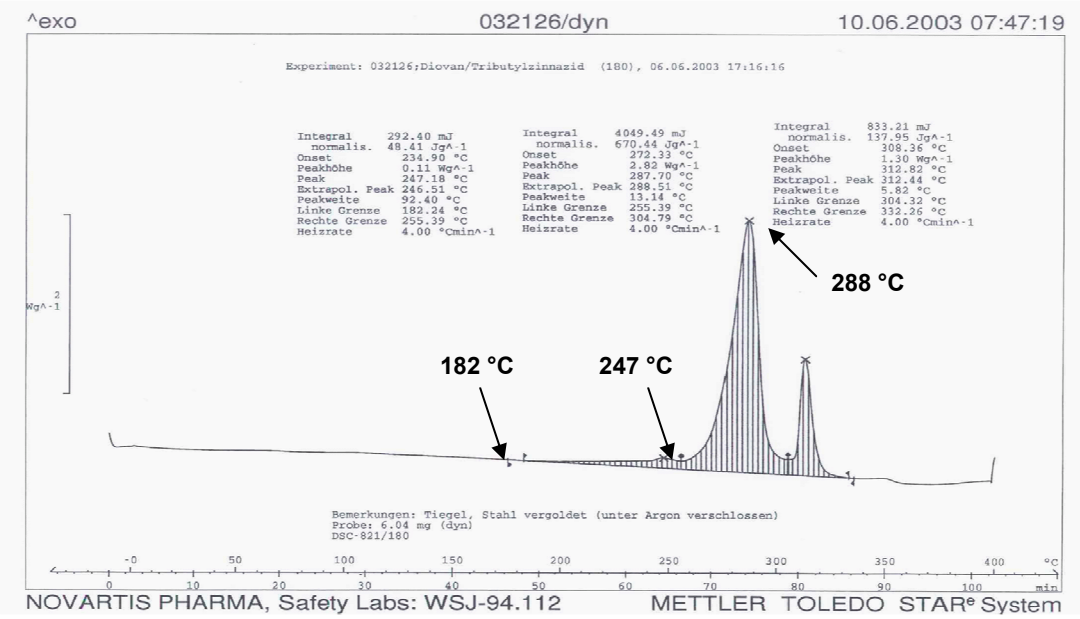


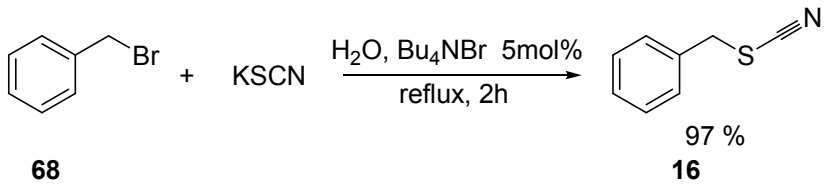
Figure 20. Dynamic DSC of *n*-Bu_3SnN_3

1.2.2. Synthesis of Starting Materials

1.2.2.1. Alkyl thiocyanates

Alkyl thiocyanates are important synthetic intermediates for the preparation of sulfur-containing organic compounds. For introduction of a thiocyanate group into an organic molecule, the most general route is the use of metal thiocyanates such as KSCN in a nucleophilic substitution with organic halides (Section 1.1.5.4.2.) [109]. Nucleophilic substitutions are frequently carried out in two phases system using phase transfer catalysis (PTC) [148] to facilitate the reaction between the organic reactant in the organic phase and the nucleophile in the aqueous phase as an inorganic salt.

Synthesis of benzylthiocyanate (16) [109]

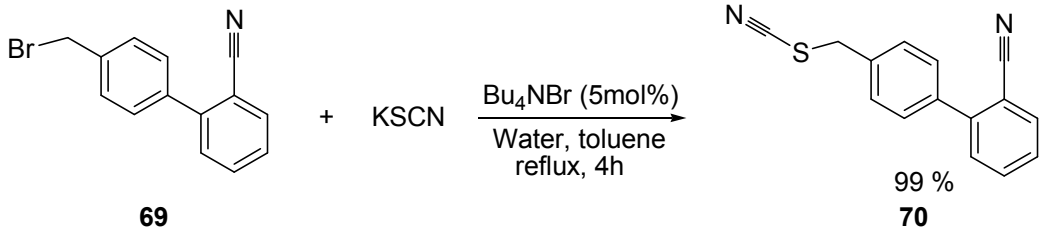


Scheme 49. Synthesis of benzylthiocyanate

The synthesis of benzylhiocyanate **16** is carried out at 100 °C with benzylbromide and two equivalents of aqueous potassium thiocynate in the presence of catalytic amount of tetrabutylammonium bromide as phase transfer catalyst (5 mol %) (Scheme 49). The reaction is stirred for two hours and the product is isolated by extraction with ethyl acetate. The crude product is purificated by bulb-to-bulb distillation to give the product as a yellow crystalline material in good yield (Experimental part, Section 5.1).

Synthesis of 4'-thiocyanato methyl-biphenyl-2-carbonitrile (70) [109]

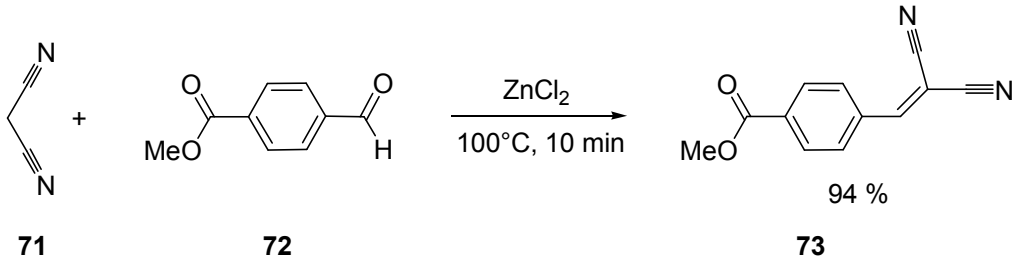
The 4'-thiocyanato methyl-biphenyl-2-carbonitrile **70** is prepared by following the same procedure used for **16** under PTC conditions.



Scheme 50. Synthesis of 4'-thiocyanato methyl-biphenyl-2-carbonitrile

1.2.2.2. Synthesis of nitrile derivatives from malononitrile

Synthesis of 4-(2,2-dicyanoethenyl)- benzoic acid methyl ester (73)



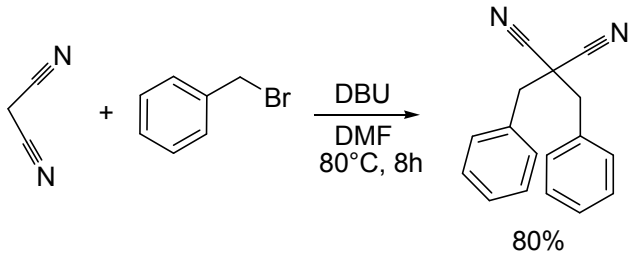
71 **72** **73**

Scheme 51. Synthesis of 4-(2,2-dicyanoethenyl)- benzoic acid methyl ester

Following the procedure reported by Venkataratnam [149] the preparation of 4-(2,2-dicyanoethenyl)-benzoic acid methyl ester **73** is carried out in the presence of zinc chloride as catalyst under solvent free conditions. An equimolar amount of malononitrile and methyl-4-formylbenzoate, in the presence of zinc chloride (10 mol %) is warmed at 100 °C for 15 minutes. The resulting heterogenic mixture is cooled to room temperature, washed with aqueous methanol (5 % solution) and filtered to give the pure desired product **73** as a yellow crystalline material in very good yield.

2,2-Dibenzyl-malonitrile (74)

For symmetric compounds, malononitrile undergoes dialkylation readily by treating with an appropriate alkylating agent [150]. The treatment of malononitrile with 2.4 equivalents of DBU and benzyl bromide in DMF at 80 °C for 8 hours (Scheme 52), followed by a simple work up procedure, affords the desired 2,2-dibenzyl-malonitrile **74** with 80 % of yield.

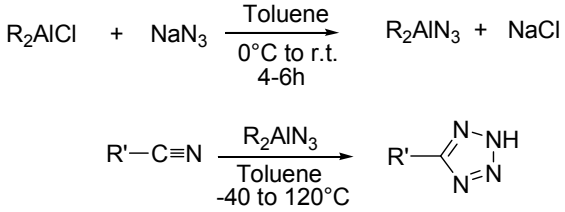


71 **68** **74**

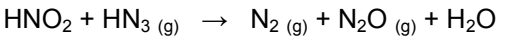
Scheme 52. Synthesis of 2,2-dibenzyl-malonitrile

1.2.3. Synthesis of Tetrazoles with Dialkylaluminum Azides

A wide variety of nitrile derivatives in the presence of different functional groups are efficiently converted into the corresponding tetrazoles using dialkylaluminum azide under mild conditions [141,142]. The reaction temperature depends on the reactivity of the substrates and can be selected from a range of -40 °C to 120 °C (Scheme 53). The rate of the 1,3-cycloaddition generally increases with increase in the electron-withdrawing characteristics of the substituent R' in the nitrile. The dialkylaluminum azide is prepared *in situ* by mixing, under argon or nitrogen in anhydrous conditions, equimolecular amounts of dialkylaluminum azide in solution (in hexane, xylene or toluene) and solid sodium azide at 0 °C (Experimental Part, Chapter 5.1). During the reaction a suspension of NaCl is formed. The starting nitrile is then added to the azide mixture at room temperature. In the case of reactive substrate such as cyanopyridines and cyanopyrazines low temperatures are required. The reactions are followed by HPLC and TLC and generally when the analysis show > 98 % conversion, the mixture is cooled to 0 °C and the excess of dialkylaluminum azide used (1 – 3 equivalents) is safely destroyed by quenching with sodium hydroxide and sodium nitrite, followed by acidification with hydrochloric acid, which destroys the hydrazoic acid formed (Scheme 54).



Scheme 53. [2+3] Cycloaddition route to tetrazoles



Scheme 54. Safe removal of hydrazoic acid during the work-up

Acidification (pH ≤ 2) removes the aluminum salts which are water soluble. Basic extraction of the tetrazole derivative separates the starting nitrile into the organic phase and then re-acidification affords the pure product.

All the reaction conditions herein described are not optimized because our scope was first prove the compatibility and the application of the dialkylaluminum azide as an azide

source which reacts with a wide variety of starting nitriles in the presence of different functional groups to give the corresponding tetrazole derivative.

1.2.3.1. Synthesis of tetrazoles in the presence of sulfonyl, thio, thiocyano functional groups

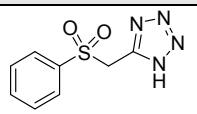
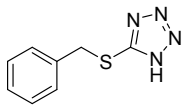
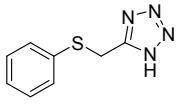
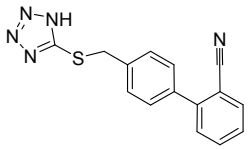
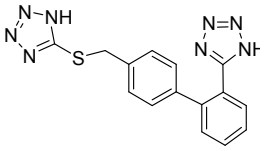
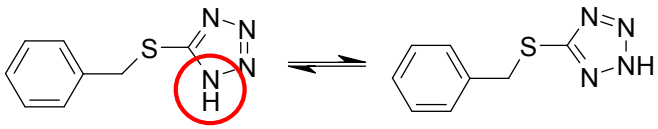
Entry	T [°C]	Time [h]	Product	Yield [%]
1[a,b]	55	3	 **75**	76*
2[a]	45	4.5	 **17**	46
[b]	60	1		40
3[a]	55	24	 **76**	83*
4[c]	r.t.	24	 **77**	87
5[c]	110	72	 **78**	93

Table 1. Synthesis of 5-substituted tetrazoles.
Notes: * Isolated yield after crystallization; [a] Et_2AlN_3 (2.5 M in toluene); [b] *i*-Bu_2AlN_3 (1.8 M in toluene); [c] Et_2AlN_3 (2.7 M in xylene).

Tetrazole derivatives in the presence of sulfonyl, thio, thiocyano functional groups are synthesized in good yields under mild reaction conditions (Table 1). The 5-phenylsulfonylmethyl-tetrazole **75** is prepared in good yield with 1.4 equivalents of Et_2AlN_3 and the reaction mixture stirred for 3 hours at 55 °C (Table 1; entry 1). The same experiment is done using *i*-Bu_2AlN_3 to obtain the same yield. 5-Benzylthio-tetrazole **17** is prepared using 1.4 equivalents of Et_2AlN_3 at 45 °C for 4 and half hours (Table 1; entry 2). The desired product **17** is obtained in only 40-50 % yield because of the formation of benzyl isothiocyanate derivated from the rearrangement of the starting thiocyanate [151]. The same result is obtained dropping the substrate in three portions into the azide mixture

over a period of one hour, and a comparable yield is obtained using *i*BuAlN$_3$ as azide source at 60 °C for 1 hour. Interesting to mention that the X-ray structure shows that compound **17** crystallized only in the 1*H*-tautomeric form (Figures 21, 22)(See X-ray discussion, Chapter 4).



1*H*-Tautomer 2*H*-Tautomer

Figure 21. Tautomeric equilibrium of **46** in solution

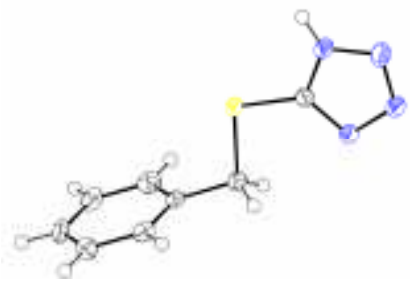


Figure 22. Structure of 5-(benzylthio)-*1H*-tetrazole **17** in the crystal with thermal ellipsoids drawn at 50 % probability level

Phenylsulfanylmethyl-tetrazole **76** is obtained in very good yield using 1.4 equivalents of Et_2AlN_3 at 55 °C for 30 hours (Table 1; entry 3). The mono- and bis-tetrazoles, respectively **77** and **78**, can be selectively obtained depending on the reaction conditions (Table 1; entries 4, 5). The mono-tetrazole **77** is obtained with complete regioselectivity in good yield using 1.5 equivalents of Et_2AlN_3 at room temperature in 24 hours. Trace of byproduct derivated from the rearrangement of the starting material, is also observed in this case [151]. The *bis*-tetrazole **78** is obtained using 2.8 equivalents of Et_2AlN_3 starting from **77**. The mixture is stirred for 3 days from 90 to 110 °C giving the desired product in excellent yield (Table 1).

1.2.3.2. Synthesis of tetrazoles in the presence of double bonds

The reaction of benzylidenemalonitrile with Et_2AlN_3 gives the corresponding tetrazoles **79** or **80** in good yield under mild conditions (Table 2). To obtain the mono-tetrazole derivative **79**, the reaction is stirred for 6 hours at 40 °C with 2 equivalents of Et_2AlN_3 (Table 2; entry 6). The desired tetrazole **79** is obtained in very good yield but with a purity of 91 % (HPLC) with the partial formation of the *bis*-tetrazole derivative (Table 2; entry 7). Tetrazole **80** is obtained by treatment of the starting nitrile with 3 equivalents of Et_2AlN_3 at 65 °C for 24 hours, yielding the desired pure *bis*-tetrazole derivative in good yield. It is interesting to mention that under these conditions the

starting benzylidenemalonitrile gives only the tetrazole derivatives **79** and **80** without any conjugate addition of the ethyl residue to the double bond which undergoes in the case of Et_2AlCl in toluene at -40 °C [152]. The five membered nitrogen-containing heterocycles are traditional centers for energetic materials [5], for this reason the thermal behavior of compound **80**, with contains geminal *bis*-tetrazoles in the structure, was measured with a Mettler Toledo 821 calorimeter. The dynamic DSC (heating 4 °C/min) shows the thermal stability, under this condition, of **80** until 190 °C. However, at 203 °C a small endothermic peak, attributed to the melting point, is followed by a strong exothermic decomposition with maximum at 205 °C, with a measured enthalpy of -1302 kJ Kg^{-1} and this energy corresponds to an adiabatic temperature of *ca* 868 °C.

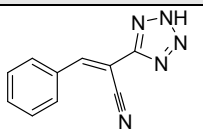
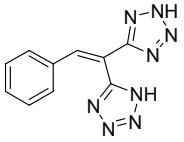
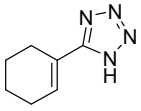
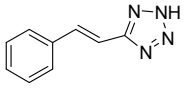
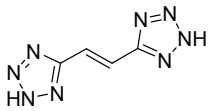
Entry	T [°C]	Time [h]	Product	Yield [%]
6[a]	40	6	 **79**	97
7[b]	65	24	 **80**	75
8[a]	90	20	 **81**	65**
9[b]	60	18	 **82**	97*
10[b]	r.t.	2	 **83**	71

Table 2. Synthesis of 5-substituted tetrazoles.
Notes:* Yield after extractions and crystallization; ** Yield after direct crystallization of the crude; [a] Et_2AlN_3 (2.5 M in toluene), [b] Et_2AlN_3 (2.7 M in xylene)

Alpha,*beta*-unsaturated vinyl nitriles are relatively good substrates, however cyclohexene-1-carbonitrile requires, a higher temperature (Table 2; entries 8, 9). The reaction is carried out using 1.4 equivalents of Et_2AlN_3 at 90 °C for 24 hours to give the desired 5-(1-cyclohene-1-yl)-tetrazole **81** in good yield. The reaction does not undergo at

T < 50 °C and at 75 °C the reaction requires longer reaction time (36 hours) to give the desired product with the same yield. Cinnamonitrile gives the desired 5-styryl-tetrazole **82** in very good yield using 1.3 equivalents of Et_2AlN_3 at 50-70 °C for 18 hours. The reaction proceed very well without the formation of any byproducts. Fumaronitrile provides the corresponding tetrazole **83** after two hours at room temperature (Table 2; entry 10).

1.2.3.3. Synthesis of tetrazoles from alkyl nitriles

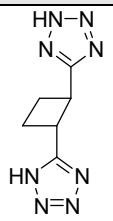
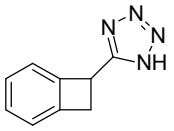
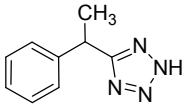
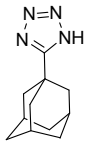
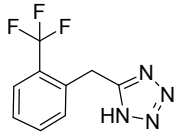
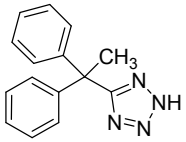
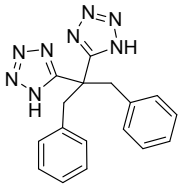
Entry	T [°C]	Time [h]	Product	Yield [%]
11[a]	90	30	 **84**	60*
12[a]	70	49	 **85**	64**
13[b]	60	24	 **86**	81
14[c]	100	3 d	 **87**	82
15[c]	65	17	 **88**	80
16[b]	85- 120	18	 **89**	45
17[b]	75	18	 **90**	87

Table 3. Synthesis of 5-alkylsubstituted tetrazoles.
Notes:*Yield after extractions and crystallization; **Yield after direct crystallization of the crude;[a] Et_2AlN_3 (1.8 M in toluene), [b] Et_2AlN_3 (2.7 M in xylene), [c] Et_2AlN_3 (in toluene 2.5 M)

Inactivated and sterically hindered alkyl nitriles require relatively high temperature and longer reaction time (Table 3). The *trans*-cyclobutane-1,2-di-tetrazole **84** (Table 3; entry 11), is synthesized from the corresponding dinitrile using 1.33 equivalents of Et_2AlN_3 at 90 °C for 30 hours in relative good yield. Excess of Et_2AlN_3 does not influence the rate of the reacion. The tetrazole **85** is obtained under similar conditions using 1.5 equivalents of Et_2AlN_3 at 70 °C for 49 hours (Table 3; entry 12). Sterically

hindered nitriles such as 2-phenyl-propionitrile provides the corresponding tetrazole **86** in good yield with 1.33 equivalents of Et_2AlN_3 at 60 °C for 24 hours and more bulky 2,2-diphenylpropionitrile require higher temperature to give the corresponding tetrazole **89** (Table 3; entries 13, 16). The inactivated 1-adamantenecarbonitrile requires longer reaction times and provides the corresponding tetrazole **87** with an excess of Et_2AlN_3 (2.23 equivalents) at 90-110 °C for three days (Table 3; entry 14). The 5-(2-trifluoromethyl)-benzyl-tetrazole **88** is prepared in good yield using 1.5 equivalents of Et_2AlN_3 or Me_2AlN_3 at 65 °C for 17 hours (Table 3; entry 15). Geminal di-nitriles such as 2,2-dibenzyl-malonitrile require mild reaction conditions. The *bis*-tetrazole **90** is prepared at 75 °C for 18 hours using 1.6 equivalents of Et_2AlN_3 for each nitrile group (Table 3; entry 17).

1.2.3.4. Synthesis of tetrazoles from aromatic nitriles

Aromatic nitriles are suitable substrates for this methodology (Table 4). Simple benzonitrile requires 1.1 to 1.3 equivalents of Et_2AlN_3 at 80 °C for 24 hours yielding the desired tetrazole **1** in excellent yield (Table 4; entry 18). The corresponding 1,2-dicyanobenzene requires shorter reaction times and provides the bis-tetrazole **91** in good yield using 1.4 equivalents of Et_2AlN_3 at 90 °C for only 3 hours (Table 4; entry 19). The 4-cyanophenylacetonitrile requires longer reaction time compared to 1,2-dicyanobenzene and the reaction is carried out with an excess of Et_2AlN_3 (2.1 equivalents) at 75 °C for 24 hours to give the desired *bis*-tetrazole **93** in good yield (Table 4; entry 21). Aromatic nitro-nitriles such as the 4-nitrobenzonitrile are very reactive and the nitro-group may react with the Et_2AlN_3 instead of the cyano group. In this case the reaction is very exothermic with gas evolution even at 0 °C and only 15 % of the desired tetrazole **94** is isolated under these conditions (Table 4; entry 22). At a given temperature some hetero-substituted aromatic nitriles require shorter reaction times than benzonitrile, for example 2-hydroxybenzonitrile is converted to the corresponding tetrazole **95** in two hours at 80 °C instead twenty-four hours (Table 4; entry 23). The hydroxyl group is rotected in situ with triethylaluminum (Section 1.2.3.5.). *Para*-substituted halogen benzonitriles undergo the cycloaddition (Table 4; entries 28, 29). The 5-(4-chloro-phenyl)-tetrazole **2** is obtained in very good yield using 1.57 equivalents of Et_2AlN_3 at 90 °C for 24 hours and the 5-(4-fluoro-phenyl)-tetrazole **99** using 1.5 equivalents of Et_2AlN_3 at 130 °C for 15 hours.

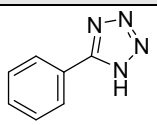
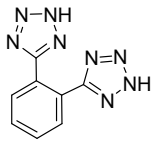
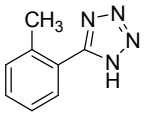
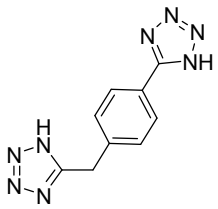
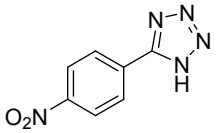
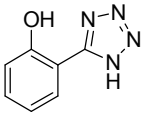
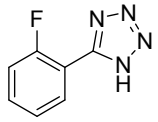
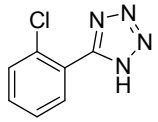
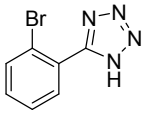
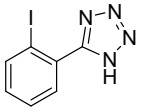
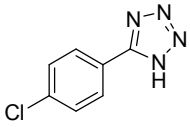
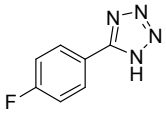
Entry	T [°C]	Time [h]	Product	Yield [%]
18[a]	80	24	 **42**	99*
19[a]	90	3	 **91**	75
20[a]	80	25	 **92**	83
21[a]	75	24	 **93**	95
22[a]	0	0.16	 **94**	15
23[a]	80 r.t.	2.5 4	 **95**	97
24[b]	90 55	7 39	 **95**	95
25[a]	50	27	 **97**	95
26[a,c]	50	30	 **26**	71
27[a]	50	3d	 **98**	85
28[d]	90	24	 **1**	97
29[b]	130	15	 **99**	88*

Table 4. Synthesis of 5-arylsubstituted tetrazoles.

Notes: * Yield after extractions and crystallization; [a] Et_2AlN_3 (2.7 M in xylene),[b] Et_2AlN_3 (1.8 M in toluene), [c] Me_2AlN_3 (1 M in hexane/toluene), [d] Et_2AlN_3 (2.5 M in toluene)

The reaction proceeds well in the case of *ortho*-substituted aryl nitriles where steric hindrance might be anticipated to reduce yield (Table 4; entries 20, 23, 25-27). In comparison with the methodology proposed by Sharpless [63,78,79] we have been able to achive conversion of aromatic nitriles bearing an sp^3-hybridized substituent in *ortho* position (Table 4; entry 20) at relative high temperature and long reaction time.

5-*Ortho*-methylphenyl-tetrazole **92** is prepared in good yield using one equivalent of Et_2AlN_3 at 80 °C for 25 hours (Table 4; entry 20). *Ortho*-halogen substituted aromatic nitriles (Table 4; entries 24-27) reach to completion at 50 °C within approxymately 30 hours of reaction. The reactivities of each *o*-halogen benzonitrile was checked by parallel

reactions at 50 °C mixing equimolar amounts of *o*-fluoro and *o*-bromobenzonitrile, equimolar amounts of *o*-fluoro and *o*-chlorobenzonitrile and finally equimolar amounts of *o*-fluoro and *o*-iodobenzonitrile and following the respective conversions by HPLC. *Ortho*-fluoro, -chloro and –bromobenzonitrile have comparable reactivity, but *o*-iodobenzonitrile provides complete conversion after three days. An approximate explanation can be given looking the steric hinderance of iodine in *o*-position and the relative electronic effect in the aromatic ring attached to the nitrile (Figures 23, 24). The *ortho*-halogen influences the electronic properties of the aromatic ring and indirectly the activation of the nitrile group though the cycloaddition. The molecules were built and optimized using Syayl software (Tripos) (Figure 23). The charges were calculated using Gasteiger-Marsili method and the electrostatic potential was mapped with Molcad on the Connoly surface of each molecule (Figure 24). Corey–Pauling–Koltun (CPK) models are the simplest type of representation of the surface of small molecules. In these space-filling models, the atoms are represented as spheres whose radii are proportional to the atom's van der Waals radius (Figure 23). Figure 24 shows the effect in the aromatic ring of the presence of halogen atoms compared to the simple benzonitrile. In the case of *o*-iodobenzonitrile, the aromatic ring is probably more electron-rich because of the major mesomeric effect of iodo compared to the halogens series (Figure 24). The total surface of the simple benzonitrile and *o*-fluorobenzonitrile are comparable (respectively 114.8 $Å^2$ and 118.8 $Å^2$) as well as the total van der Waals surface of *o*-bromo and *o*-chlorobenzonitrile (respectively 128.4 $Å^2$ and 132.8 $Å^2$). The van der Waals surface of *o*-iodobenzonitrile is bigger compared to the above mentioned series (141.5 $Å^2$) because of the bigger size of the iodine atom (Figure 23).

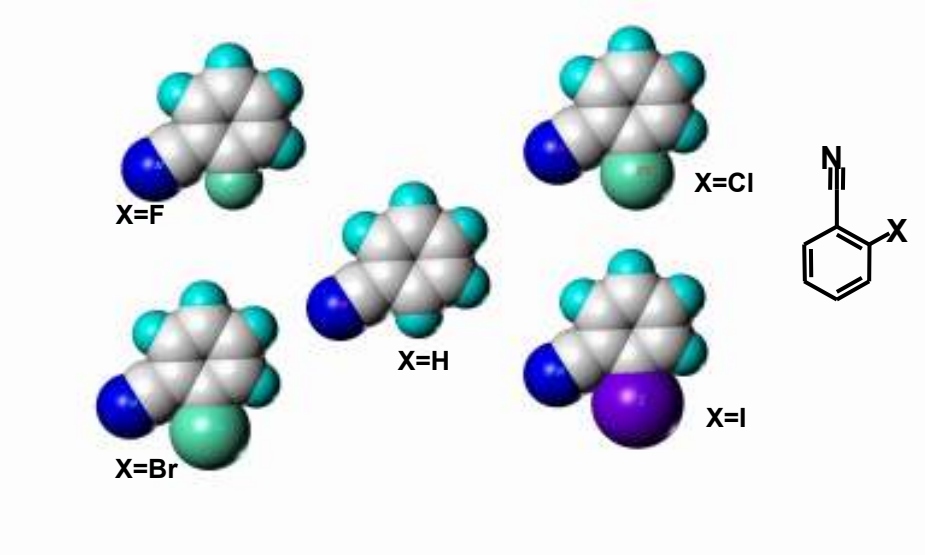


Figure 23. 3D Representation of CPK model of *ortho*-halogenbenzonitriles and benzonitrile

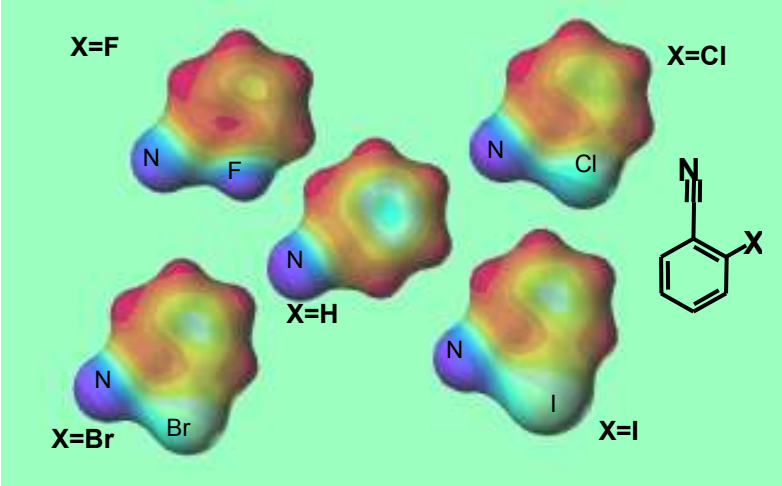
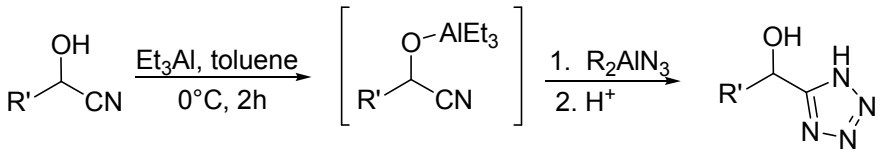


Figure 24. 3D Representation of electrostatic potential on van der Waals surface for *ortho*-halogenbenzonitriles and benzonitril

1.2.3.5. Synthesis of tetrazoles in the presence of hydroxy group

Alkyl and aryl nitriles with an *alpha*-hydroxyl group react at a lower temperature, although it is necessary to protect the hydroxyl group with triethyl aluminum, which is removed during the conventional workup procedure (Table 4; entry 23; Table 7; entries 30-33). The protection of the hydroxyl group is done *in situ* mixing 1.2 equivalents of triethyl aluminum in toluene with the starting hydroxy nitrile derivative at 0 °C and stirring the resulting mixture for two hours (Scheme 55).



Scheme 55. Protection *in situ* of the hydroxyl group and cycloaddition

Tetrazole **100** is synthesized in relative good yield using 1.3 equivalents of diethylaluminum azide from 0 °C to room temperature in 24 hours (Table 5; entry 30). The reaction was done only once without any optimization for safety reasons because of the risk of HCN formation from the starting nitrile. Mandelonitrile and *R*-mandelonitrile provide the corresponding tetrazoles **101** and **102** in very good yield using 1.5 equivalents of Et_2AlN_3 at 40 - 45 °C in around one hour (Table 5; entries 31, 32).

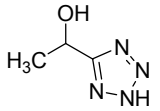
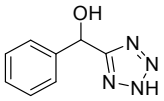
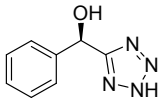
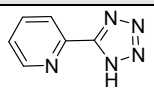
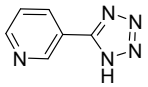
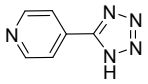
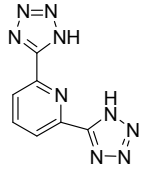
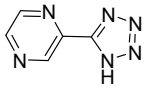
Entry	T [°C]	Time [h]	Product	Yield [%]
30[a]	0 to r.t.	24	 **100**	65
31[a]	45	1.3	 **101**	82*
32[a]	40	1	 **102**	99

Table 5. Synthesis of 5-substituted tetrazoles.
Notes:* Yield after crystallization; [a] Et_2AlN_3 (2.7 M in xylene)

1.2.3.6. Synthesis of 5-substituted heteroaromatic tetrazoles

Heteroaromatic nitriles such as pyridinecarbonitriles and cyanopyrazine give the corresponding tetrazoles in a few hours at low temperature with good yields (Table 6; entries 33-37) ; they require shorter reaction times and lower reaction temperature than benzonitrile (Table 4; entry 18). The main problem of these substrates is the high hydrophilicity of the corresponding product which makes difficult the purification with the common extraction procedure. In all these cases the reaction mixture is quenched with HCl (2 M), the pH adjusted with potassium carbonate to isoelectric point at 6.5, the aqueous phase is then saturated with solid NaCl and the product extracted with ethyl acetate ; some of the product can be lost in the aqueous phase. *Ortho*-, *meta*- and *para*-cyanopyridine have similar reactivity and give the corresponding tetrazole derivative, respectively **103**, **104**, **105** using 1.3 equivalents of Et_2AlN_3 at 0 °C for 3 hours (Table 6; entries 33-35). The 2,6-pyridinedicarbonitrile gives the desired tetrazole **106** (Table 6; entry 36) using 3 equivalents of Et_2AlN_3 at 0 °C for one hour and is more reactive that the analogue 1,2 dicyanobenzene (Table 4; entry 19). The pyrazinecarbonitrile is too reactive with Et_2AlN_3 (reaction very exothermic) and the use of *i*-Bu_2AlN_3 is more appropriate (Table 6; entry 37). The reaction undergoes with stoichiometric amount of azide from –40 to 0°C in three hours to give the desired product **107** in good yield.

Entry	T [°C]	Time [h]	Product	Yield [%]
33[a]	0 to r.t.	3	 **103**	67
34[a]	0 to r.t.	3	 **104**	78*
35[a]	0 to r.t.	3	 **105**	95*
36[a]	0	1	 **106**	84
37[b]	-40 to 0	3	 **107**	64*

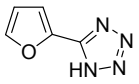
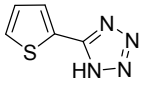
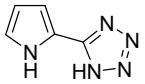
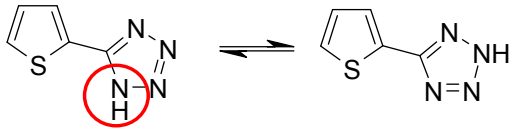
Entry	T [°C]	Time [h]	Product	Yield [%]
38[a]	55	12	 **108**	87
39[a]	55	12	 **109**	81*
40[a]	0 to r.t.	24	 **110**	82

Table 6. Synthesis of heteroaromatic tetrazoles

Notes:* Yield after crystallization; [a] Et_2AlN_3 (2.7 M in xylene); [b] *i*-Bu_2AlN_3 (1.8 M in toluene)

2-Furanonitrile, 2-thiophenecarbonitrile and pyrrole-2-carbonitrile have similar reactivity (Table 6; entries 38 - 40). 2-Furanonitrile and 2-thiophene-carbonitrile give the corresponding tetrazole, respectively **108** and **109**, in good yield using 1.2 equivalents of Et_2AlN_3 at 55 °C for 12 hours and the purification was done using the conventional work-up procedure (Table 6; entries 38, 39). The pyrrole-2-carbonitrile is converted into the corresponding tetrazole **110** using an excess of Et_2AlN_3 (2.3 equivalents) because of the presence of the NH in the pyrrole ring and the reaction is carried out from 0 °C to room temperature in 24 hours (Table 6; entry 40). X-Ray structure analysis of **108**, which contains an heteroatom near the tetrazole ring, shows that this compound crystallized exclusively in the *1H*-tautomeric form as in the case of compound **17** (See X-ray discussion, Chapter 4)(Scheme 56, Figure 25).



1*H*-Tautomer 2*H*-Tautomer

Scheme 56. Tautomeric equilibrium of **109** in solution

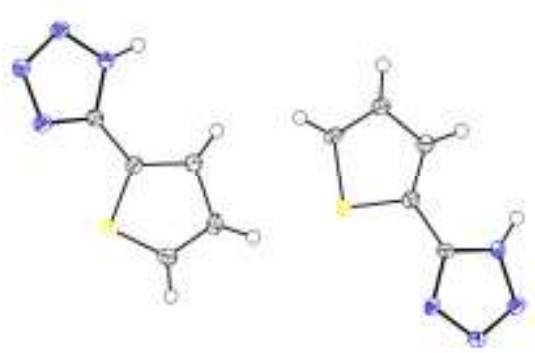
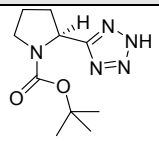
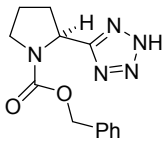
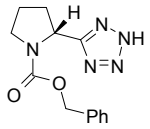
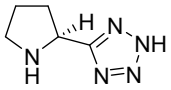
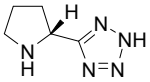


Figure 25. Structure of 5-thiophen-2-yl-*1H*-tetrazole **109** in the crystal with thermal ellipsoids drawn at 50 % probability level

1.2.3.7. Synthesis of tetrazoles in the presence of amides, amines, esters and ethers

Nitriles containing amido, ester and ether functional groups require mild reaction conditions (Table 7). Both enantiomers of 2-tetrazol-pyrrolidine-1-carboxylic acid benzyl ester **112** and **113** (Table 7, entries 42, 43) are prepared for the first time under very mild conditions in 9 hours at 55 °C in high yield [142]. The preparation of the (*R*)-enantiomer **113** was also increased to 1.5 kg with very good reproducibility. The cycloaddition proceeds well using 1.3 - 1.5 equivalents of Et_2AlN_3 or Me_2AlN_3 [142]. The Boc analogue **111** is formed under the same reaction conditions (Table 7; entry 41),[142] but the necessary acidic work-up partially cleaves the Boc group giving the unprotected pyrrolidine tetrazole **114**. To avoid the cleavage of the Boc-group, the reaction mixture was directly quenched with a solution of $KHSO_4$ (10 %) at pH 5, but afforded 57 % of the desired product. The aqueous phase after the work-up is evaporated and stirred 4 hours in ethanol, filtered and delivered 25 % of the unprotected pyrrolidine tetrazole **114**. The tetrazoles **112** and **113** are of interest because they are the precursors of the tetrazol-5-yl pyrrolidine **114** and **115** respectively, which are interesting alternative to proline [153] as an organocatalyst for a variety of reactions including: aldol reactions,[154,155] Mannich reactions,[156,157] Diels-Alder reactions [158,159] and Michael additions [160].

Entry	T [°C]	Time [h]	Product	Yield [%]
41[a,b]	40	30	 **111**	57
42[a,c,d]	50	9	 **112**	96
43[c]	55	9	 **113**	95
44[e] [f] [g]	r.t. 55-85 50	4 18 16	 **114**	94* 99 81
45[e]	r.t.	4	 **115**	97 94*

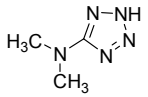
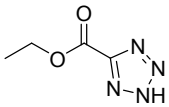
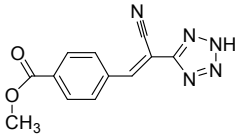
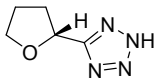
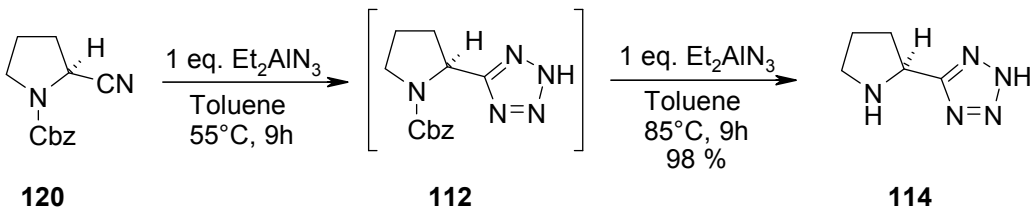
Entry	T [°C]	Time [h]	Product	Yield [%]
46[c]	r.t.	2	 **116**	71
47[a]	r.t.	1	 **117**	94
48[c]	r.t.	72	 **118**	54*
49[h]	40	3	 **119**	92

Table 7.

Notes: * Yield after crystallization; [a] Et_2AlN_3 (2.5 M in toluene); [b] *i*-Bu_2AlN_3 (1.8 M in toluene); [c] Et_2AlN_3 (2.7 M in xylene); [d] Me_2AlN_3 (1 M in hexane); [e] H_2, Pd/C 10 % in EtOH; [f] excess Et_2AlN_3 (2.5 M in toluene or 2.7 M in xylene); [g] i) Et_2AlN_3 (2.7 M in xylene) for 8h at 50 °C, ii) HCl (6M) for 8 h at r.t.; [h] Et_2AlN_3 (1.8 M in toluene)

The pyrrolidine tetrazole in both enantiomeric forms, can be directly obtained in a one-pot reaction from the starting nitrile with an excess of dialkylaluminum azide to provide first the cycloaddition (T ≤ 55 °C) and then the cleavage reaction (T ≥ 65 °C) (Scheme 57) [142]. Although purity of **114** obtained under these conditions is high according to NMR, but broad peaks by IR suggests the presence of some water soluble inorganic materials that are difficult to remove.



Scheme 57. One pot reaction for the preparation of 1*H*-tetrazol-5-yl

We were the first to solve the X-ray structure of the 2(*R*)-tetrazol-5-yl-pyrrolidine. According to X-ray analysis, the compound **115** crystallized as hydrate and is existing in zwitterionic form (Figure 26; See X-ray discussion, Chapter 4).

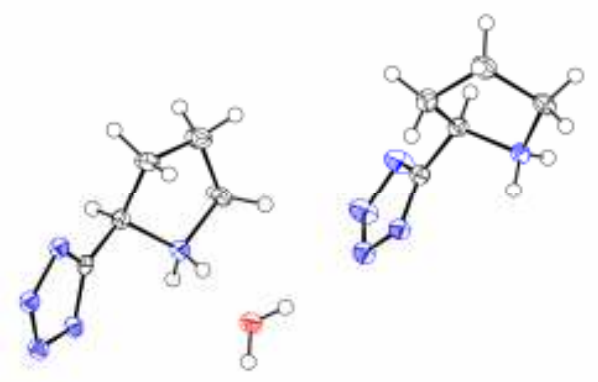


Figure 26. Structure of 2(*R*)-tetrazol-5-yl-pyrrolidine **115** in the crystal with thermal ellipsoids drawn at 50 % probability level

Because of the possible application in organocatalysis, the thermal behavior was measured for tetrazoles **112** and **114** (Figures 27-30). All calorimetric scans were performed with a Mettler Toledo 821 calorimeter. The dynamic DSC (heating 4 °C/min) shows the relative thermal stability of **112** until 200 °C (Figure 27). A peak at 86 °C, with a measured endothermy of 74 $kJkg^{-1}$, is attributed to the melting point. The exothermic decomposition starts at 254 °C with an measured enthalpy of –391 $kJKg^{-1}$and this energy correspond to an adiabatic temperature of *ca* 260 °C (Figure 27). The (*S*)-2-(tetrazol-5-yl)-pyrrolidine **114** is thermally stable until 260 °C (Figure 29). A small endothermic peak at 168 °C is attributed to the melting point, with a measured endothermy of 25 $kJkg^{-1}$ and is followed by an highly spontaneous exothermic decomposition with maximum at 275 °C, with a measured enthalpy of -1182 $kJkg^{-1}$ which corresponds to an adiabatic temperature of *ca* 290 °C (Figure 29). The isothermal DSC was also measured at 90 °C for 12 hours and both compounds **112** and **114** showed to be stable under these conditions (Figures 28, 30).

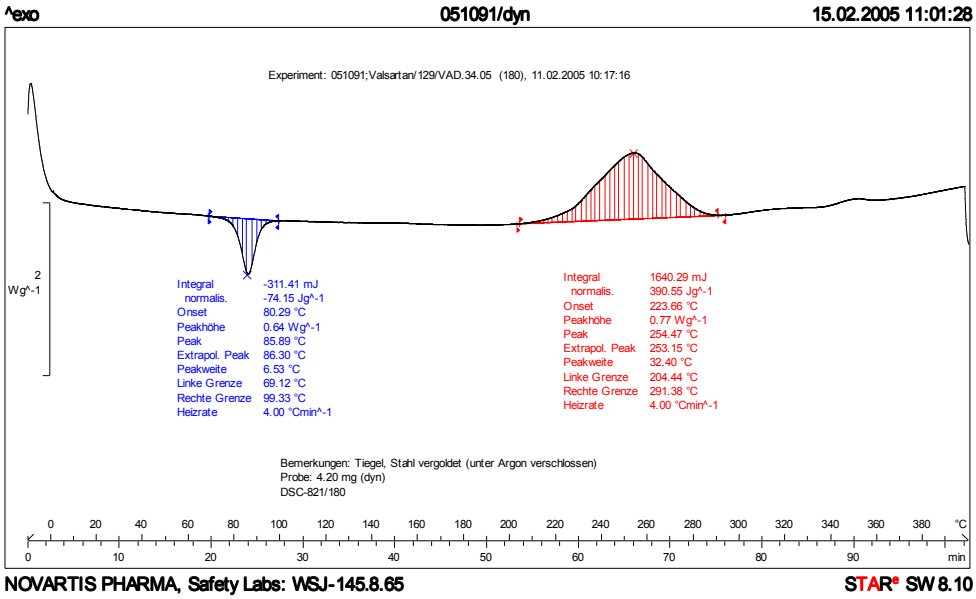


Figure 27. Differential scanning calorimetry (DSC) for (*S*)-2-(tetrazol-5-yl)-pyrrolidine-1-carboxylic acid benzyl ester **112**

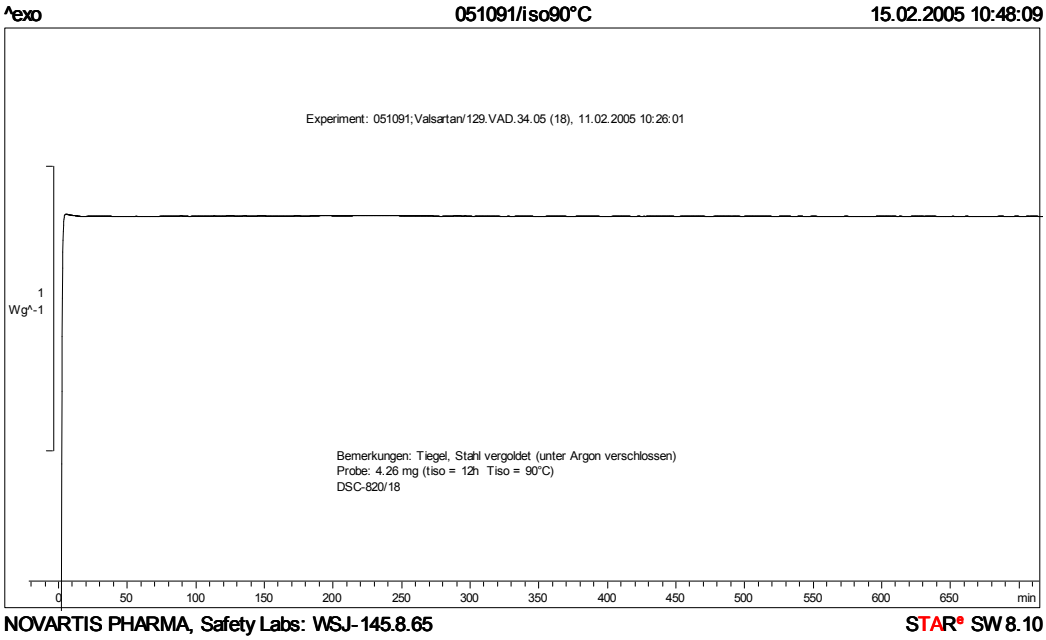


Figure 28. Isothermic differential scanning calorimetry (DSC) at 90 °C for 12 hours for (*S*)-2-(tetrazol-5-yl)-pyrrolidine-1-carboxylic acid benzyl ester **112**

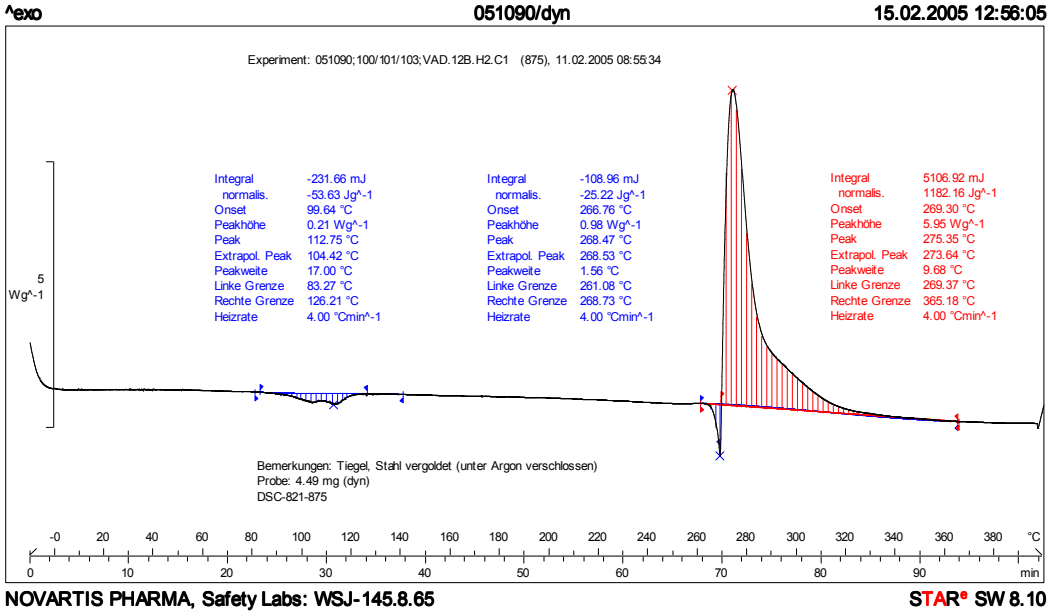


Figure 29. Differential scanning calorimetry (DSC) for (*S*)-2-(tetrazol-5-yl)-pyrrolidine **114**

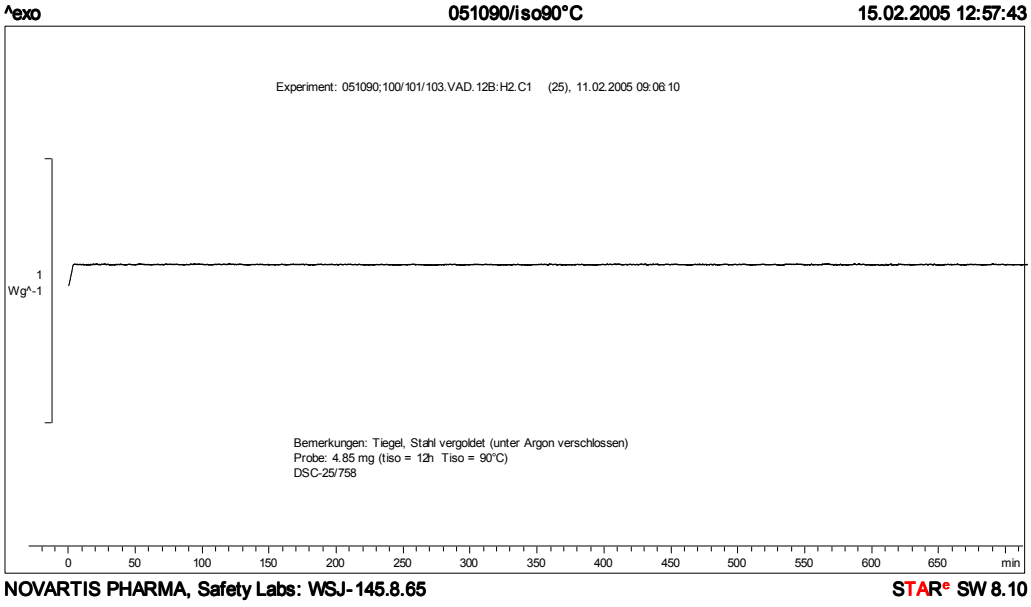
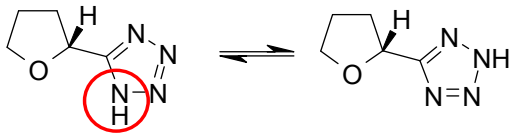


Figure 30. Isothermic differential scanning calorimetry (DSC) at 90 °C for 12 hours for (*S*)-2-(tetrazol-5-yl)-pyrrolidine **114**

Dimethylcyanide provides the corresponding tetrazole **116** in good yield using 1.5 equivalents of Et_2AlN_3 at room temperature for 2 hours (Table 7; entry 46). The ester groups are stable at room temperature in the presence of dialkylaluminum azides (Table 7; entries 47, 48). For example, ethyl-tetrazole-5-carboxylate **117** (Table 7; entry 47) is efficiently prepared using 1.3 equivalents of Et_2AlN_3 at room temperature in one hours and the mono-tetrazole **118** is prepared using 1.6 equivalents of Et_2AlN_3 at room temperature for 3 days (Table 7; entry 48). In this case the reaction was stopped before the complete conversion to be able to isolate only the mono-tetrazole derivative.

2(*R*)-Cyano-tetrahydrofurane is efficiently converted into the corresponding tetrazole **119** using 1.3 equivalents of Et_2AlN_3 at 40 °C for 3 hours (Table 6; entry 49). The (*R*)-5-(tetrahydro-furan-2-yl)-tetrazole **119**, similarly to **46** and **109**, crystallized exclusively in the 1*H*-tautomeric form (Scheme 58, Figure 31; See X-ray discussion, Chapter 4).



1*H*-Tautomer 2*H*-Tautomer

Scheme 58. Tautomeric equilibrium of **119** in solution

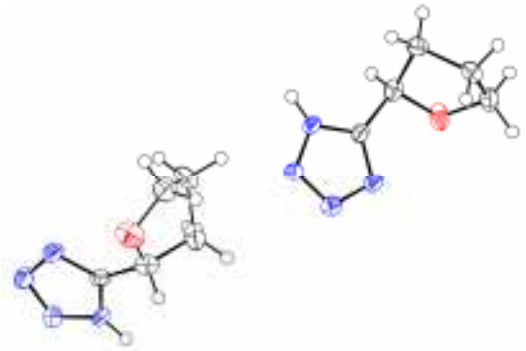
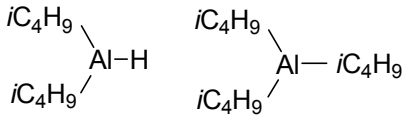


Figure 31. Structure of (*R*)-5-(tetrahydro-furan-2-yl)-1*H*-tetrazole **119** in the crystal with thermal ellipsoids drawn at 50 % probability level

1.2.3.8. Synthesis of tetrazoles in the presence of carbonyl groups

In analogy with DIBAH and TIBA [161] (Figure 32), aldehyde and ketone functional groups are reduced to the corresponding alcohols with Et_2AlN_3 (Table 8; entries 50-52).



DIBAH TIBA

Figure 32.

The mechanism may involve a hydride shift from the β-carbon on the residue of the diethylaluminum azide to the carbonyl group (Scheme 59) with the formation of one molecule of ethylene which derives from the organoaluminum.

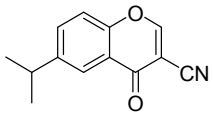
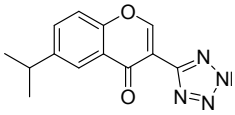
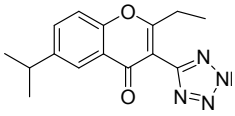
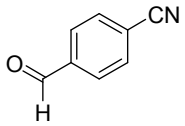
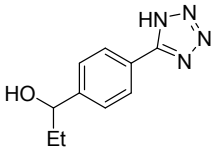
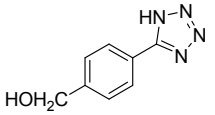
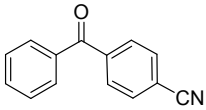
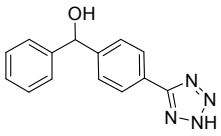
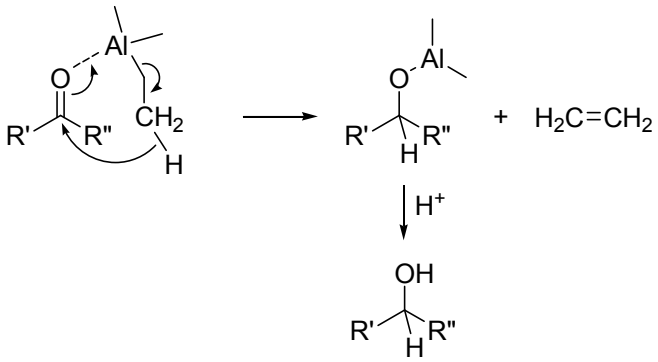
Entry	Starting material	T [°C]	Time [h]	Product	Yield [%]
50[a,b]	 **121**	r.t.	24	 **122**	57*
				 **123**	37*
51[b]	 **124**	50	24	 **125**	36**
				 **126**	50*
52[b]	 **127**	r.t.	14	 **128**	38

Table 8.

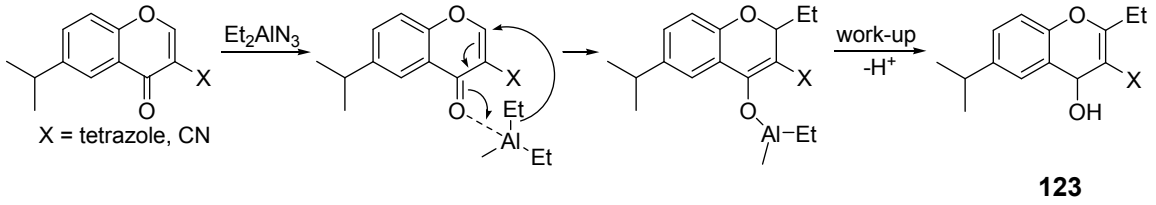
Notes: * Yield after chromatography; ** Yield after extractions and crystallization; [a] Et_2AlN_3 (2.5 M in toluene), [b] Et_2AlN_3 (2.7 M in xylene)



Scheme 59. Proposed mechanism for the carbonyl reduction with Et_2AlN_3

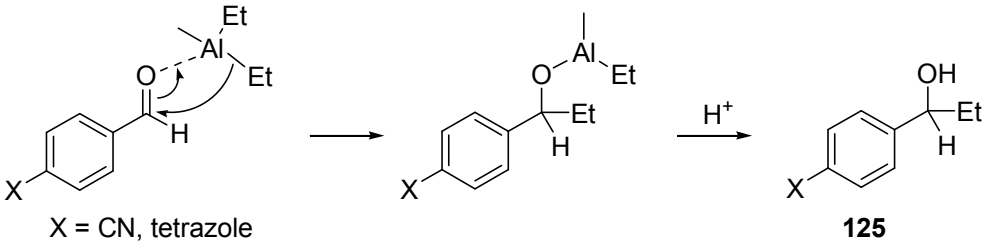
The treatment of 6-isopropyl-4-oxo-4*H*-chromene-3-carbonitrile with 2.8 equivalents of Et_2AlN_3 at room temperature for 24 hours gives a mixture of tetrazoles **122** and **123** in very good yield (95 %) in ratio ca 3:2 (Table 8; entry 50). The two tetrazole derivatives are then isolated by chromatography. The α-β-unsaturated bond in the 6-isopropyl-4-oxo-4*H*-chromene-3-carbonitrile could be activated by the coordination of the aluminum species with the carbonyl group and the alkyl residue of the dialkylaluminum azide may migrate to the β-position of the double bond. The system then, probably during the work-up, restabilizes the aromaticity by oxidation (Scheme 60).

The tetrazole ring may be already formed or can be formed simultaneously to the alkyl migration.



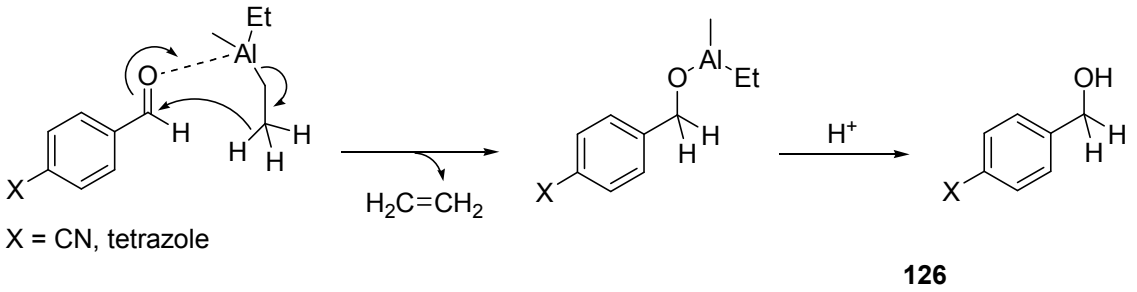
Scheme 60. Proposed mechanism for the formation of **123**

The 4-cyanobenzaldehyde reacts with 3 equivalents of Et_2AlN_3 to give a mixture of tetrazole **125** and **126** in good yield (85 %) in ratio ca 2:1 (Table 8; entry 51). The reaction probably proceed *via* an alkoxyaluminum intermediate which undergoes the ethyl migration [162] or hydride shift to give respectively **125** (Scheme 61) and **126** (Scheme 62). The tetrazole ring may be already formed or can be formed simultaneously to the alkyl or the hydride migration.



Scheme 61. Proposed mechanism for the formation of **125**

The product **126** is formed by the hydride shift from the β-carbon on the alkyl residue of the diethylaluminum azide to the carbonyl group (Scheme 62) with the formation of one molecule of ethylene which derives from the alkylaluminum residue.



Scheme 62. Proposed mechanism for the formation of **126**

According to Scheme 105, the tetrazole **128** could be also formed by the migration of the hydride group to the carbonyl (Table 8; entry 52).

1.2.3.9. Synthesis of triazoles

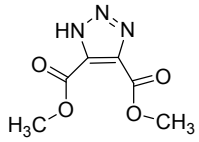
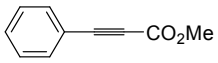
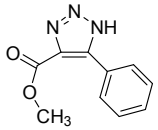
Entry	Starting material	T [°C]	Time [h]	Product	Yield [%]
53[a]	MeO_2C—≡—CO_2Me **129**	-50 to 0	5	 **130**	72
54[b]	 **131**	r.t.	72	 **132**	57

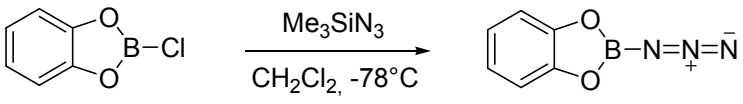
Table 9. Synthesis of triazoles. [a] Et_2AlN_3 (1.8 M in toluene), [b] Et_2AlN_3 (2.7 M in xylene)

We only started to investigate the triazoles formation using dialkylaluminum azides with alkynes. First experiments show that the cycloaddition occurs under mild conditions (Table 9). For example triazole **130** is prepared in a relative good yield with equimolecular amount of Et_2AlN_3 starting at – 50 °C and warming the reaction mixture to 0 °C in five hours (Table 9; entry 53). Methyl phenylpropiolate requires longer reaction time compared to but-2-ynedioic acid methyl ester and triazole **132** is prepared in good yield in three days at room temperature (Table 9; entry 54).

1.2.3.10. Synthesis of alternative azides

During the course of the studies, we have investigated the [1,3,2]-benzodioxaborole-2-azido **134** and the diisopropoxyde aluminum azide **139** as novel azide sources for the synthesis f tetrazoles, but, unfortunately without any success. Boron azides were already reported in the 1960s [163,164] but never used for the preparation of tetrazole rings.

1.2.3.10.1. [1,3,2] Benzodioxaborole-2-azido (134)



133 **134**

Scheme 63. Synthesis of [1,3,2]-benzodioxaborole-2-azido **134**

The [1,3,2]-benzodioxaborole-2-azido **134** is prepared following the procedure reported by Klapötke and co-workers [165]. *Beta*-chloro- or bromo-catecholborane dissolved in dichloromethane is treated, at -78°C, with 1.5 equivalents of trimethylsilylazide. The resulting solution is gradually warmed to room temperature and stirred for two hours. The solvent and the excess of trimethylsilylazide are removed by evaporation to give the product as a white crystalline material, which is hydrolyzed after few minutes.

The reaction was furthermore followed by FT-IR spectroscopy and the spectra measured every two minutes for a period of 20 hours. The temperature was also monitored internally (Figures 33, 34). The trimethylsilylazide has a characteristic absorption band caused by asymmetric stretching vibration of the azide group at 2138 cm^{-1}. After the addition of β-chloro-catecholborane this peak decreases and a new strong absorption band appears at 2169 cm^{-1}, characteristic of the stretching vibration of the boron-azide group $\nu(B\text{-}N_3)$. The desired [1,3,2]-benzodioxaborole-2-azido **134** hydrolyzed after crystallization, while we tried to prepare *in situ* 1.5 equivalents of **134** and use it toward cycloaddition for the synthesis of tetrazoles. Unfortunately, no tetrazoles are isolated using reactive starting nitriles under different reaction conditions (Scheme 66, Table 10). In some cases (Table 10; entries 1, 3), 4 % of desired product is detected by HPLC but probably because of the cycloaddion with the trimethylsilyl azide species.

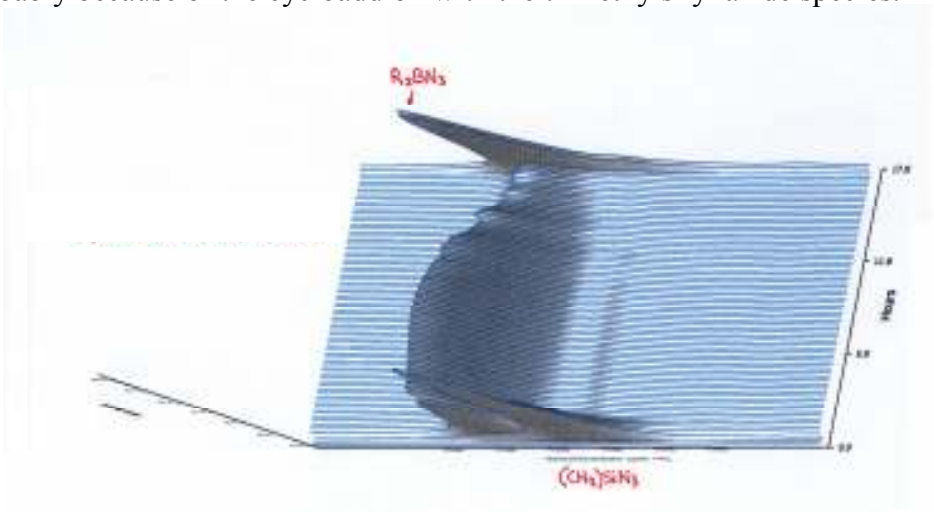


Figure 33. Decrease of signal at 2138 (s, $\nu(Si\text{-}N_3)$), increase of signal at 2169 (s, $\nu(B\text{-}N_3)$) cm^{-1} (3D picture)

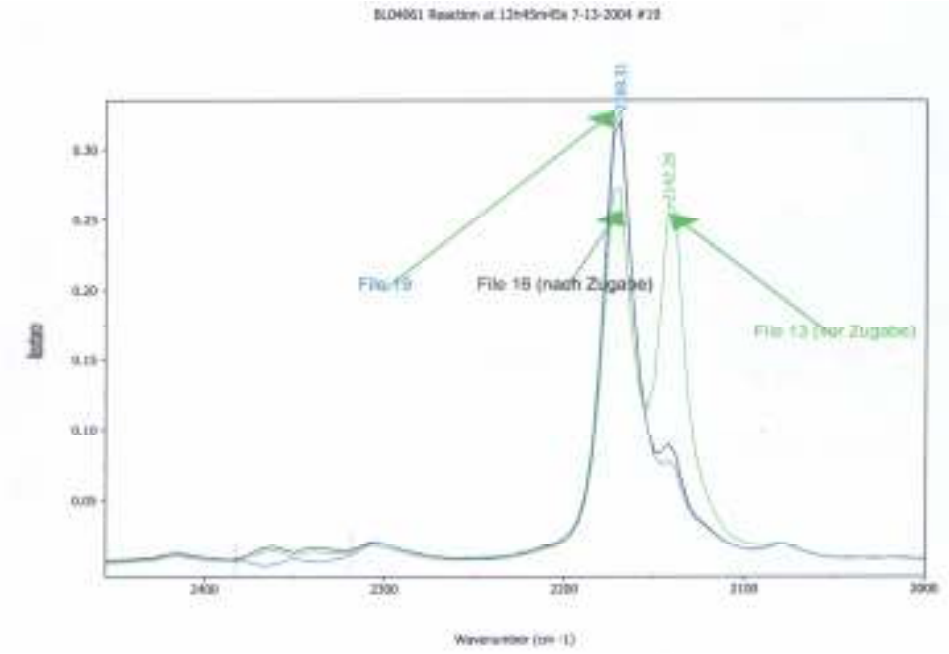
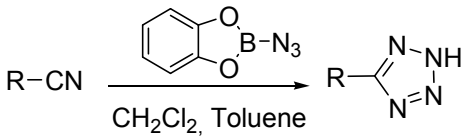


Figure 34. Decrease of signal at 2138 (s, $\nu(Si\text{-}N_3)$), increase of signal at 2169 (s, $\nu(B\text{-}N_3)$) cm^{-1}



Scheme 64. Synthesis of tetrazoles with [1,3,2]-benzodioxaborole-2-azido

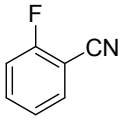
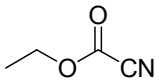
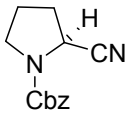
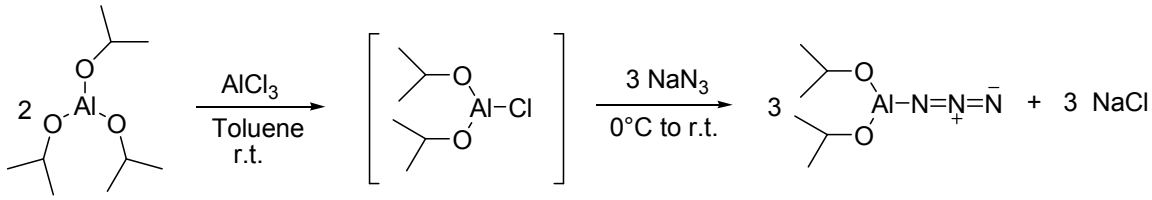
Entry	Starting material	T [°C]	Time [h]	Conversion [%]
1[a]	 **135**	50	24	0
		120	60	4
2[a]	 **136**	55	27	0
3[a]	 **120**	r.t. to 55	48	4

Table 10. Synthesis of tetrazoles with [1,3,2]-benzodioxaborole-2-azido [a] conversion by HPLC

1.2.3.10.2. Diisopropoxyde aluminum azide (139)

We tried to prepare and isolate the diisopropoxyaluminum azide from the reaction of diisopropoxyaluminum chloride prepared *in situ* with sodium azide (Scheme 65). A solution of 2 equivalents of aluminum isopropoxyde in toluene is treated, at 0 °C, with

aluminum chloride, warmed at room temperature and stirred over the night. The resulting solution is cooled at 0 °C and treated with 3 equivalents of sodium azide, than gradually warmed at room temperature and stirred over the night. The resulting heterogeneous mixture is centrifuged to obtain two solid layers and an upper solution which are checked separately by IR without detect any characteristic stretching vibration of an organoaluminum-azide group around 2150 cm^{-1}.



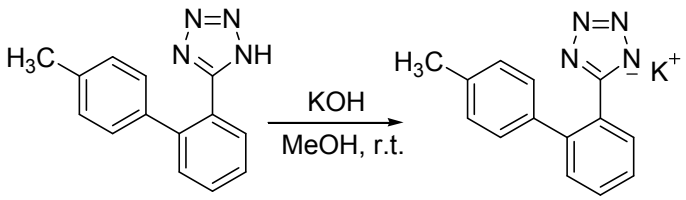
137 **138** **139**

Scheme 65. Synthesis of disopropoxyde aluminum azide

1.2.3.11. Tetrazolate salts and nucleophilic substitution

Neutralization of tetrazolic acids with metal hydroxides give stable metal tetrazolate salts (Section 1.1.1.2.) [1,16] which are reactive toward nucleophilic substitution.

1.2.3.11.1. 5-(4'-Methyl-biphenyl-2-yl)-tetrazole potassium salt (140)



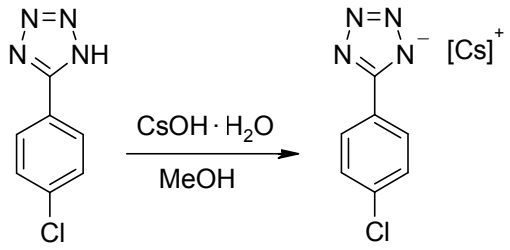
22 **140**

Scheme 66. Preparation of 5-(4'-methyl-biphenyl-2-yl)-1*H*-tetrazole potassium salt **140**

5-(4'-Methyl-biphenyl-2-yl)-tetrazole, dissolved in methanol, is treated with equimolar amounts of potassium hydroxide and stirred at room temperature for two hours. The solvent is removed to give the desired tetrazolate salt in quantitative yield.

1.2.3.11.2. 5-(4-Chloro-phenyl)-tetrazole cesium salt (2)

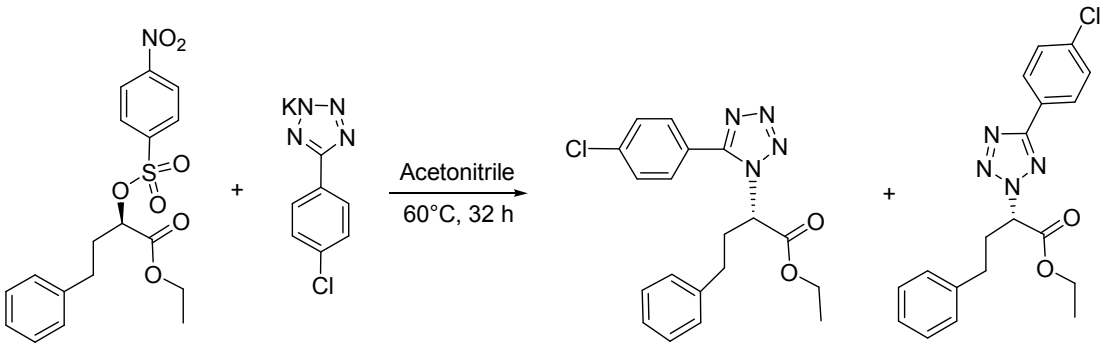
The 4-chloro-phenyl-tetrazole **1**, dissolved in methanol, is treated with equimolar amounts of cesium hydroxide monohydrate and stirred at room temperature for one hour. The solvent is removed to give the desired tetrazolate derivative in quantitative yield.



1 **2**

Scheme 67. Preparation of 5-(4-chloro-phenyl)-tetrazole cesium salt **2**

1.2.3.11.3. Nucleophilic substitution with tetrazoles



*N*1-Isomer
13.5 %

*N*2-Isomer
81 %

141 **142** **143** **219**

Scheme 68. Synthesis of (*S*)-2-[5-(4-chloro-phenyl)-tetrazol-1-yl]-4-phenyl-buthyric acid ethyl ester **143** and (*S*)-2-[5-(4-chloro-phenyl)-tetrazol-2-yl]-4-phenyl-buthyric acid ethyl ester **219**

The 5-(4-chloro-phenyl)-tetrazole potassium salt is prepared by treating the 1.3 equivalents of 4-chlorophenyltetrazole **1** with equimolar amounts of potassium hydroxide in methanol at room temperature for one hour. The solvent is removed and the resulting crystalline material added, at room temperature, to a solution of (*R*)-2-(nitro-benzenesulfonyloxy)-4-phenyl-butyric acid ethyl ester **141** in acetonitrile. The resulting mixture is stirred 32 hours at 60 °C. The product is extracted with ethyl acetate and potassium carbonate to remove the excess of tetrazole into the aqueous phase and then chromatographed (elution system hexane / ethyl acetate 9:1) to give the two regioisomers in good yield with a ratio N1- and N2- of 1 to 6. The reaction is not further investigated and should follow an S_N2 mechanism.

1.3. The 5-Substituted Tetrazoles: Conclusions

The first reported method to synthesize tetrazoles was the reaction of hydrazoic acid (HN_3) with organic cyanides in 1932 [67]. However, this procedure has not found practical application on account of the high toxicity, explosive nature and low boiling point (37 °C) of hydrazoic acid. Currently, 5-substituted tetrazoles are usually obtained by the addition of azide salts to nitriles (typically at 100-150 °C) (Section 1.1.3.). Unfortunately, all of these protocols have disadvantages including: the use of toxic metals, expensive reagents, harsh reaction conditions, water sensitivity and the presence of dangerous hydrazoic acid. Methods that seek to avoid hydrazoic acid liberation during the reaction by avoiding acidic conditions require a large excess of sodium azide as well as long reaction times. In addition, the majority of methods use dipolar aprotic solvents such as DMF. One of the most common methods involves the use of sodium azide in the presence of ammonium chloride or tertiary ammonium hydrochloride to form *in situ* ammonium azide species (Section 1.1.3.1.2.1.). The reaction is accompanied by the sublimation of explosive NH_4N_3, which also occurs when aprotic solvents instead of DMF are used for the reaction [166]. Trimethylsilyl- and trialkyltin- azide are alternative general reagents (Section 1.1.3.1.4.). In some cases, full conversion can only be obtained with a large excess of azide and harsh reaction conditions. The major drawback of this method is the difficult removal of highly toxic residual organotin at the end of the reaction [167]. Huff proposed a procedure in 1993 using equimolar amounts of trimethylsilyl azide activated by triethylaluminum in toluene, but highly hindered nitriles resulted in poor conversion (Section 1.1.3.1.4.2.). The Sharpless approach utilizing zinc catalysis in aqueous conditions is an improvement over previous methods (Section 1.1.3.1.3.), but still requires the tedious removal of zinc salts from the final product and additional waste water treatments. Moreover, the reaction rates at 100 ° C are often insufficient for bulk intermediates and the process requires higher temperature and longer reaction time.

The application of dialklaluminum azide for the synthesis of 5-substituted tetrazoles is a new efficient process and offers several advantages over many of the previously published procedures, including a reduced environmental impact resulting from the

elimination of toxic waste [141,142]. The use of dialkylaluminum azides as an azide source greatly reduces the hazard posed by *in situ* generation of hydrazoic acid and avoids ammonium- and alkylammonium- azide formation. The reaction is suitable for use on a large scale as special care is not required when recycling waste water because aluminum is a non-toxic metal compared to tin organo metallics. As dialkylaluminum chlorides are available in large quantities and are relatively inexpensive (they are produced for use in Ziegler-Natta catalysis) the reaction is also economically attractive. Dialkylaluminum azides are prepared in a short time (4-8 h, r.t.), are soluble in organic solvents, are cheap and non-toxic. The cycloaddition occurs under mild conditions and it is possible to synthesize a broad variety of tetrazole derivatives in the presence of different functional groups including halogens, –sulfonyl, -thioethers, alkenes, esters, and ethers [168]. Because of the low pK_a of 1*H*-tetrazoles (~3-5) and their highly crystalline nature, a simple work up procedure is usually sufficient to provide the pure tetrazoles. In addition we can confirm that the general procedure described herein is applicable to a wider range of substrates leading to the corresponding tetrazoles in good yields. The high reactivity, low costs and the eco-compatibility due to the aluminum make this novel process particularly attractive and, in addition, is applicable for large scale preparation. Therefore the discovery and the development of this new methodology for the preparation of tetrazoles is significant with respect to safety, economy, ecology, diversity of substrates.

Chapter 2.
Alkylation of Tetrazole Ring

2.1. Alkylation of Tetrazole Ring: Introduction

The tetrazole itself is an aromatic nucleus, which may exist in two tautomeric forms (Figure 35)[1] (See Section 1.1.).

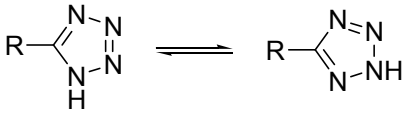
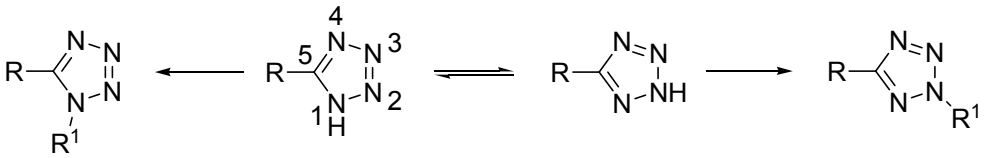


Figure 35. Tautomeric forms of 5-substituted tetrazoles

Replacement of the tautomeric ring hydrogen leads to two possible type of disubstituted tetrazoles, namely the 1,5- and the 2,5-disubstituted tetrazoles, respectively the 1*N* and 2*N*-alkylated (Scheme 69). The transformation of 5-substituted tetrazoles to *N*-substituted tetrazoles is fundamentally important for the preparative chemistry of tetrazoles.



Scheme 69. Structure and numbering of disubstiuted tetrazoles

2.1.1. Chemical and Physical Proprieties of Disubstituted Tetrazoles

2.1.1.1. Physical properties

N-Unsubstituted tetrazoles are generally white solids where the hydrogen in the tetrazole ring provides intermolecular hydrogen bonding which influences the melting point. *N*-Unsubstituted tetrazoles tend to be moderately high-melting solids due to these intermolecular hydrogen bonding. Replacement of the ring NH hydrogen by a methyl causes in 1,5- and 2,5-disubstituted tetrazoles a low-melting point except where the 5-substituent itself is capable of forming hydrogen bonds (*e.g.*, OH or NH) [1]. In molecules where hydrogen bonding is not possible, for example in the *N*-methyl disubstituted tetrazole series, the more polar 1,5-disubstituted form (high dipole moment) usually has a higher melting point or boiling point than the corresponding 2,5-disubstituted isomer (lower dipole moment) (Figure 36). In general 1,5-disubstituted tetrazoles have a dipolar moment in the range of 5.0-5.90 D and the corresponding 2,5-derivatives have values of 2.4-2.7 D [1].

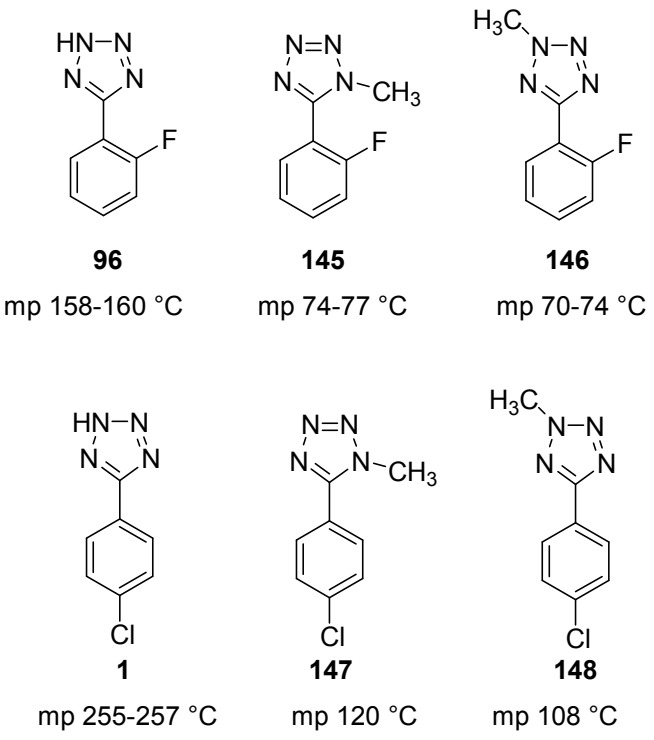


Figure 36. Examples of melting points of tetrazole series

2.1.1.2. Solubility and chromatography

The solubility of tetrazoles is strongly influenced by the effect of carbon or nitrogen substituents on the charge distribution in the ring. In general, 2,5-disubstituted tetrazole, with low dipole moments, tend to be soluble in apolar organic solvents [1]. The different dipole moments usually ensure excellent separation of regio-isomers on silica gel columns with normal elution systems such as hexane / ethyl acetate 5:1.

2.1.1.3. Nuclear magnetic resonance spectroscopy

NMR spectroscopy is particularly useful for determing the sustitution pattern in tetrazoles. ^{13}C-NMR shifts of the tetrazole C-5 is sensitive to the bonding pattern in the ring and allows a distinction of isomers. The chemical shift for 2,5-disubstituted tetrazoles are generally 10 ppm deshielded than for the corresponding 1,5-disubstituted isomers (Figure 37, see Experimental Part, Section 4.2) [1,169].

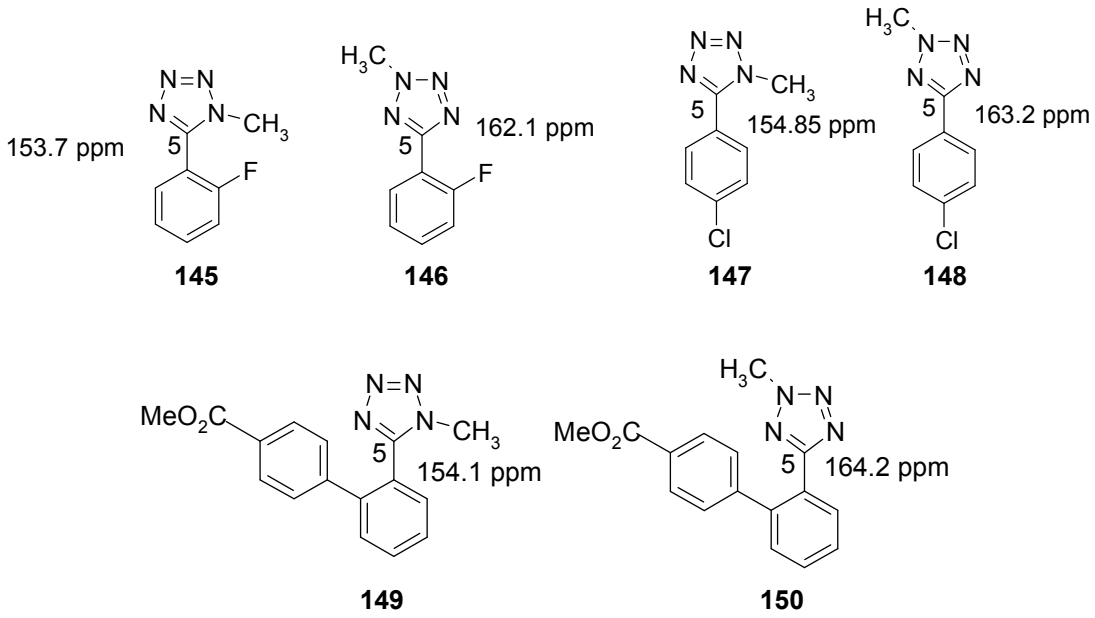


Figure 37. ^{13}C-NMR shifts of the C-5 in 1,5- and 2,5-disubstituted tetrazoles

The chemical shifts of carbon atoms in nitrogen heterocycles are generally governed by the number and location of nearby nitrogen atoms. The electron densities may be the main factors in determining chemical shifts. Tetrazole exhibited abnormal ^{13}C shielding but showed ^{1}H shift in agreement with the π-electron densities.

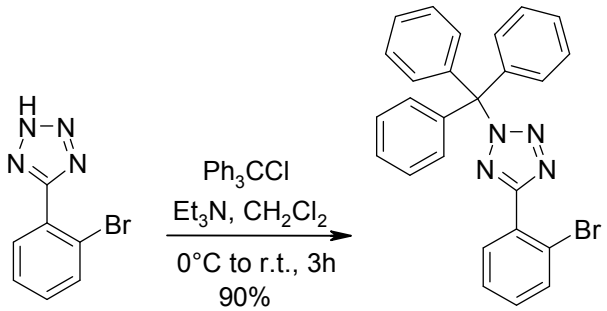
2.1.2. Alkylation of Tetrazole Ring with Alkyl Halides

Alkylation of 5-substituted tetrazoles is one of the most useful routes for the preparation of *N*-substituted derivatives due to the availability of various starting tetrazoles, alkylating agents and to the simplicity of the process [32a,98,170]. At the present time, introduction of an appropriate *N*-substituent into an already existing tetrazole cycle is the most common synthetic pathway to disubstituted tetrazoles (Section 1.1.4).

In almost all the cases alkylation of 5-substituted tetrazoles with alkyl halides give rise to mixtures of isomeric 1,5- and 2,5-disubstituted tetrazoles [1,171] (Section 2.1). The position of substitution has been found to be sensitive to the steric requirements of the alkylating agent and to the C-5 substituent of tetrazole [98,172]. We report here some example of recent reported literatures for the alkylation of 5-substituted tetrazoles.

2.1.2.1. Alkylation of tetrazoles

Triphenylmethyl (trityl) group is one common protecting group for tetrazole rings [173]. It is demonstrated that the alkylation of tetrazoles with triphenylchloromethane provides exclusively the N2-derivatives (Scheme 70) [32a]. The reaction is usually carried out in the presence of base and it is presumable that tritylation of 5-substituted tetrazoles follows S_N1 mechanism.



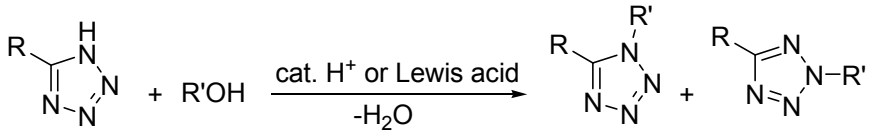
26 **151**

Scheme 70. Preparation of *N*-trityl-tetrazoles

2.1.2.2. Alkylation of tetrazoles with alcohols

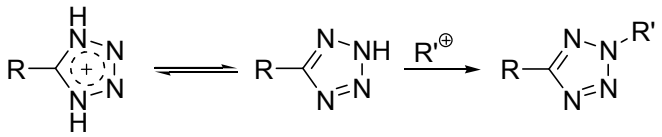
The alkylation of tetrazoles with alcohols can be performed under a variety of conditions [170]. Alcohols readily generate carbenium cations in the presence of acidic

catalysts and react with *N*-unsubstituted tetrazoles yielding mixtures of 1N- and 2N-regioisomers. The reaction can be carried out in neutral organic solvents (dichloromethane, acetonitrile, chloroform) in the presence of catalytic amounts of sulphuric or a Lewis acid (Scheme 71).



Scheme 71.

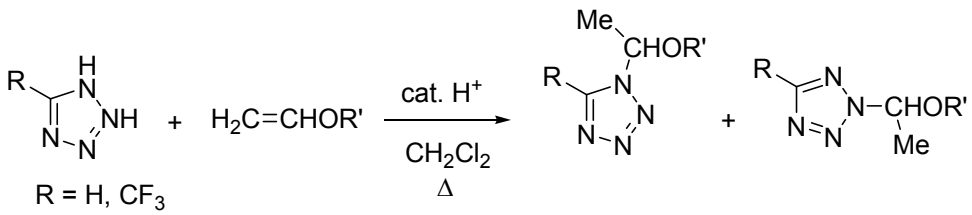
Formation of 2*N*-alkyl derivatives as the sole products has been reported for the reaction of 5-substituted tetrazoles with secondary and tertiary aliphatic alcohols such as *tert*-butyl alcohol in sulphuric acid media (Scheme 72) [98,174,175,176]. The reaction proceed at room temperature in high yields in relative short time (1-3 hours). In this acidic conditions the tetrazoles is partailly protonated to form the symmetrical 1H,4H-tetrazolium cation, in the latter, only the atoms N2 and N3 are accessible for electrophilic attack whereas both N1 and N4 are blocked by the attached protons.



Scheme 72.

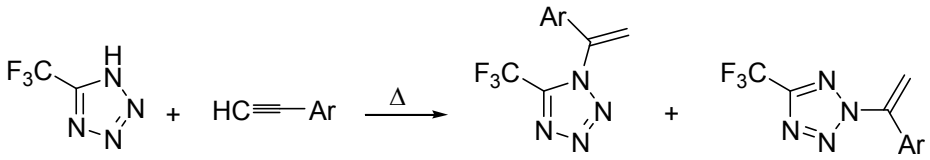
2.1.2.3. Alkylation of tetrazoles by addition of C-C multiple bonds

N-Unsbstituted tetrazoles react with vinyl ethers in acidic-catalyzed conditions. The tetrazole forms a bond with the α-carbon atom of the vinyl moiety (Scheme 73). The *N*2-alkylated tetrazole is the predominantly formed products.



Scheme 73. Addition onto C=C bonds

Addition onto the triple bonds in aryl acetilenes yields α-substituted *N*-vinyltetrazoles, but so far, only 5-trifluoromethyltetrazoles has been reported as 5-substituted starting material (Scheme 74).

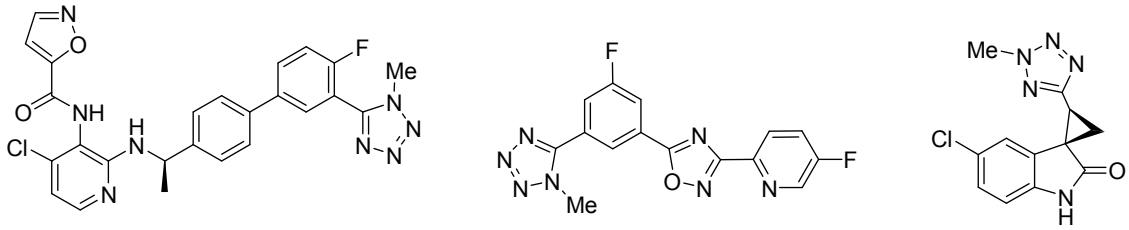


152 **153** **154**

Scheme 74. Addition onto C≡C bonds

2.1.3. Methylation of Tetrazole Ring

In the last years a wide variety of *N*-methyl-tetrazole derivatives has been reported from pharmaceutical companies as compounds with biological activities. In medicinal chemistry they can find application in the treatment of pain and inflammation **155** [177], obesity **156** [178], HIV **157** [179], diabete [180], as anticancer [181] and antimicrobial agents [182]. More than 600 patent applications including *N*-methyl-tetrazole derivatives were published in the last ten years from pharmaceutical and agricultural companies and some example is shown in Scheme 77.



155 **156** **157**

Scheme 75. *N*-Methyl tetrazoles with biological activity

2.1.3.1. Methylation with dimethyl sulfate

Dimethyl sulphate [183] is a well known methylating agent for amines, phenols, alcohols, thiols and tetrazoles [184,185]. Typically, one methyl is removed more quickly than the other methyl group. The mechanism that typically occurs with dimethyl sulfate is an S_N2 reaction.

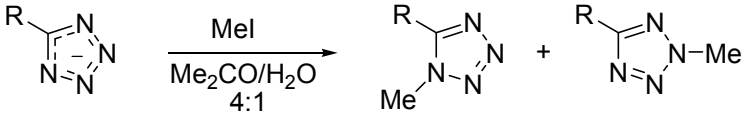
Dimethyl sulfate is carcinogenic and toxic [186]. The toxicity of dimethyl sulfate is so extreme that some consider it a potential chemical weapon while is absorbed through the skin, mucous membranes and gastrointestinal tract. Since dimethyl sulfate is very toxic, other methylating reagents are often used. However, it is sometimes more appropriate to use dimethyl sulfate due to the effectiveness and affordability.

2.1.3.2. Methylation with methyl iodide

Methyl iodide is an excellent reagent for S_N2 substitution reactions and is a well known reagent used for methylation, like dimethyl sulfate, but is less hazardous and more

expensive. Methyl iodide is a liquid with low boiling point (42.5 °C) and there are some disadvantages to its use such as its toxic profile [187]. The substance can be absorbed into the body by inhalation of its vapor, by ingestion and through the skin. It is irritating to the eyes, the skin and the respiratory tract and may cause effects on the central nervous system.

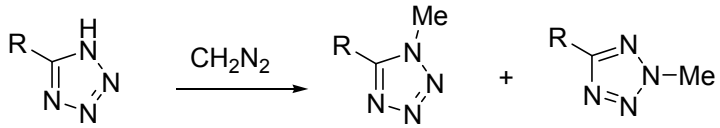
Methylation of tetrazoles is normally carried out on the tetrazolate anion generated *in situ* by dissolution in an equimolar quantity of aqueous sodium hydroxide, with stoichiometric methyl iodide in acetone followed by heating at reflux for 3 to 18 hours (Scheme 76),[188,189] or in ethanol-water (1:1) under reflux for 12 hours [12,190] or with NaH in THF [191] among others.



Scheme 76. Methylation of tetrazole rings with MeI

2.1.3.3. Methylation with diazomethane

Diazomethane is a well known methylating agent for carboxylic acids [2,192]. It react with 5-substituted tetrazoles to yield the corresponding disubstituted derivatives, 1- and 2*N*-methyltetrazoles, in ratio close to that observed for alkylation of the respective tetrazolates with dimethylsulfate or methyl iodide [98] (Scheme 77).



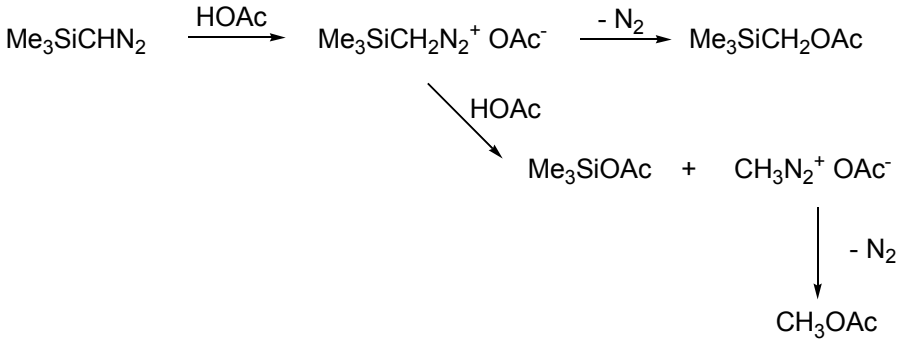
Scheme 77. Methylation of tetrazole ring with CH_2N_2

A plausible explanation for such similarity is that the first stage of the process is a fast proton transfer from the NH-acidic heterocycles to a diazomethane molecule. Then, at the rate limiting step, the tetrazolate anion and protonated diazomethane form an ion pair [98].

The methylation of tetrazoles with diazomethane has the tendency to be currently rarely used because of its highly toxic and explosive nature. In addition, polyethylene may form as a byproduct of diazomethylation [193].

2.1.3.4. Methylation with trimethylsilyldiazomethane

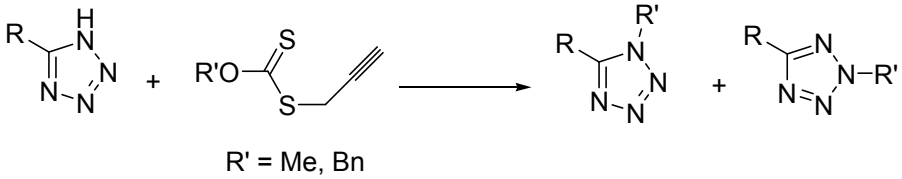
Trimethylsilyldiazomethane, [194] a greenish yellow liquid, is stable thermally and can be distilled at atmospheric pressure, is commercially available and is a safer alternative for diazomethane as methylatig agent. However the industrial use of this methylating agent is limitated by cost and by the fact that it forms numerous artifacts complicating spectra interpretation. Thus a reaction of this diazoalkane with water-free acetic acid in benzene at room temperature gave not only the expected trimethylsilylmethyl acetate but also methyl acetate and trimethylsilyl acetate (Scheme 78) [195].



Scheme 78.

2.1.3.5. *O*-Alkyl-*S*-propargyl xanthates (dithiocarbonates)

Zard *et al.* reported recently esterification reagents capable of reacting with NH-acids as well [196] to methylate and benzylate 5-substituted tetrazoles (Scheme 79). The methylation gives a 1 to 7 mixture of 1N- and 2N-substituted tetrazoles respectively, whereas the only reaction product detected in the benzylation is the corresponding 2-alkyl derivatives.

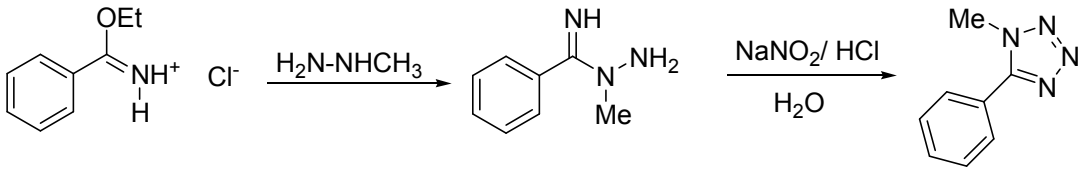


R' = Me, Bn

Scheme 79. Alkylation of tetrazoles with dithiocarbonates

2.1.3.6. Synthesis of methyl-tetrazoles from imidates

In an extension work of Zard [96], reaction of imidate hydrochloride salt with methyl hydrazine gives compound **159** which could be treated with sodium nitrite in diluted hydrochloric acid to give the 1*N*-methyl-5-phenyltetrazole in good yield. This approach is complementary to the direct methylation of the free tetrazole ring which leads to a mixture of isomers where the 2N-isomer dominates (Scheme 82).



158 **159** **160**

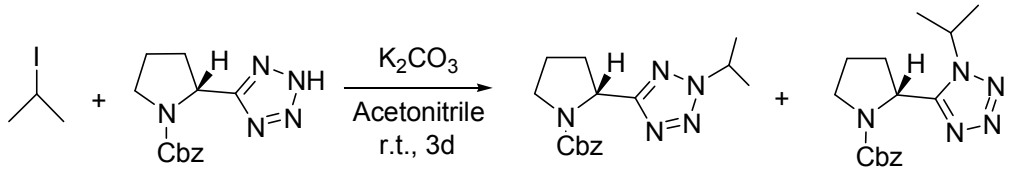
Scheme 80. Synthesis of 1*N*-methyl-5-phenyltetrazoles from imidates

2.2. Alkylation of Tetrazole Ring: Results and Discussion

In the course of our investigation towards the protection or alkylation of the tetrazole moiety, we prepared a variety of *N*-alkylated tetrazoles including *tert*-butyl- (See Chapter 3), benzyl-, trytil- and methylated derivatives. According to published data for numerous 1,5- and 2,5-disubstituted tetrazoles, the 1,5-regioismer are generally more polar, they have a higher melting point and the position of the C-5 signal in their ^{13}C NMR differs considerably: it is located at about δ 150 ppm and 160 ppm, respectively for the 1,5- and the 2,5-regioisomer (Section 2.1.1.). Therefore, the regioisomers can be distinguished with a high reliability and, generally, they can be isolated in good yields by simple chromatography on silica gel.

Preparation of *N*-isopropyl-tetrazole rings

The (*R*)-2-(tetrazol-5-yl)-pyrrolidine-1-carboxylic acid benzyl ester **113** is efficiently alkylated at room temperature in acetonitrile under basic conditions using 2 equivalents of 2-iodopropane (Scheme 83) [142]. The two regioisomers are isolated by chromatography (elution system: hexane / ethylacetate 3:1).



64% 28%

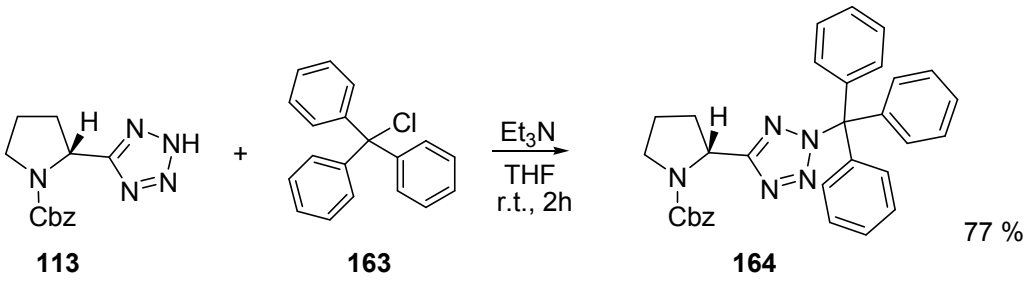
113 **161** **162**

Scheme 81. Synthesis of (*R*)-2-(isopropyl-tetrazole-5-yl)-pyrrolidine-1-carboxylic acid benzyl esters **161** and **162**

Tritylation of tetrazole ring

The (*R*)-2-(tetrazol-5-yl)-pyrrolidine-1-carboxylic acid benzyl ester **113** is also efficiently converted into the corresponding trityl derivative using 1.1. equivalent of chlorotriphenylmethane in the presence of triethylamine in THF at room temperature for 2 hours (Scheme 84). The triphenylmethyl (trityl) is a common protecting group for the

tetrazoles [173]. According to published data, the alkylation of **113** with triphenylchloromethane provides exclusively the 2N-derivatives **164** for steric reasons [32a] and the tritylation presumably follows a S_N1 mechanism.

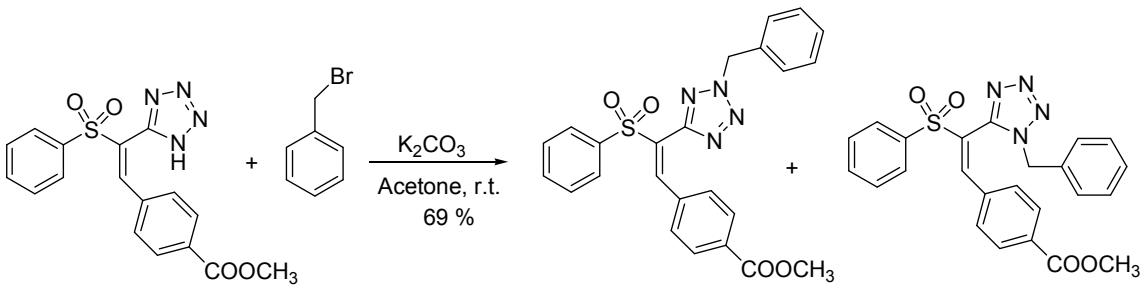


113 **163** **164**

Scheme 82. Synthesis of (*R*)-2-(2-trityl-2*H*-tetrazol-5-yl)-pyrrolidine-1-carboxylic acid benzyl ester **164**

Benzylation of tetrazole rings

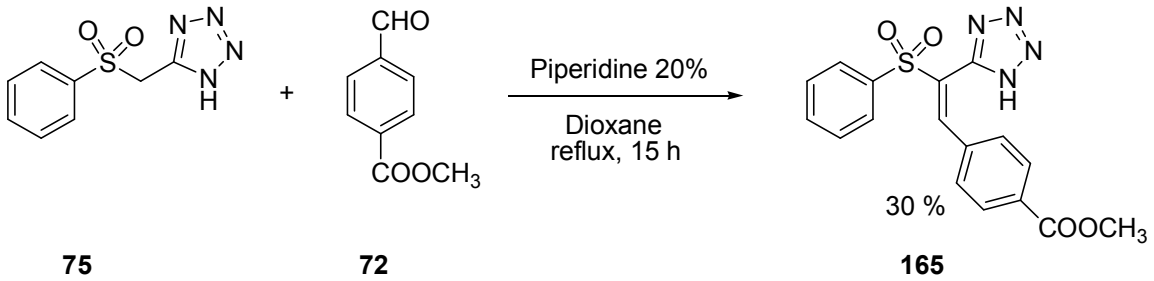
Tetrazole rings are readily converted into the *N*-benzyl derivative at room temperature using 1.2 equivalents of benzyl bromide in acetone under basic conditions. The 4-[2-benzenesulfonyl-2-(benzyl-tetrazol-5-yl)-vinyl]-benzoic acid methyl ester **166** and **167** are obtained in ratio 1 to 1 (Scheme 83). The two regioisomers have a similar polarity and their separation is very difficult by chromatography on silica gel.



165 **68** **166** **167**

Scheme 83. Synthesis of 4-[2-benzenesulfonyl-2-(benzyl-tetrazol-5-yl)-vinyl]-benzoic acid methyl ester **166** and **167**

The starting 4-[2-benzensulfonyl-2-(tetrazol-5-yl)-vinyl]-benzoic acid methyl ester **165** is obtained *via* Knovenagel reaction between the tetrazole **75** and methyl-4-formylbenzoate in the presence of 20 % of piperidine in dioxane at reflux for 15 hours yielding only 30 % of the desired Knovenagel product **165** (Scheme 84).



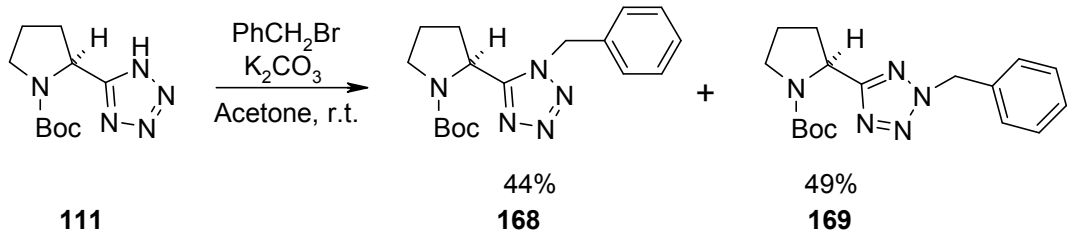
Scheme 84. Knovenagel reaction for the synthesis of 4-[2-benzensulfonyl-2-(tetrazol-5-yl)-vinyl]-benzoic acid methyl ester **165**

To improve the yield of this reaction, different reaction parameters were tested but dioxane as solvent in the presence of piperidine was found to be the best condition (Table 11).

Entry	Aldehyde [equiv]	Solvent	Catalyst	T [°C]	Time [h]	Yield [%]
1	1	*i*-BuOH	β-alanine	100	12	6.5
2	1	pyridine	piperidine	125	18	18
3	1	dioxane	piperidine	reflux	15	30
4	1.5	dioxane	piperidine	reflux	15	20

Table 11. Screening of reaction conditions for the synthesis of 4-[2-benzensulfonyl-2-(tetrazol-5-yl)-vinyl]-benzoic acid methyl ester **165**

The 2-(tetrazol-5-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester **111** was readily converted into the corresponding *N*-benzylated derivatives **168**, **169** under the same conditions as **165** (Scheme 85). Fortunately, in this case, the two regioisomers are efficiently separated by chromatography on silica gel (elution system: hexane/ethyl acetate 3:1)



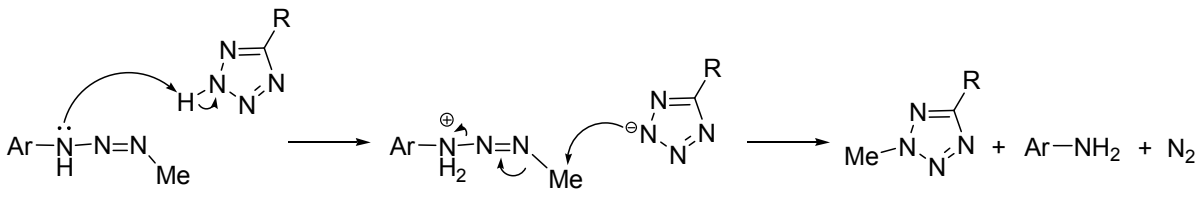
Scheme 85. Synthesis of (*S*)-*tert*-butyl-2-(benzyl-tetrazol-5-yl)-pyrrolidine-1-carboxylate **168** and **169**

2.2.1. Novel Methylation of Tetrazole Rings using 1-Methyl-3-*p*-tolyltriazene as Methylating Agent

Methylation of tetrazole rings is normally carried out by using iodomethane, diazomethane, dimethylsulfate or trimethylsilyldiazomethane (Section 2.1). All these methodologies suffer from several disadvantages such as the high toxic profile and thermal instability of the methylating agent, possible presence of byproducts and toxic water waste. Therefore, a new and safe methodology for the methylation of tetrazole rings is highly desirable. We have found that the 1-methyl-3-*p*-tolyltriazene is an efficient and safer methylating agent for tetrazole ring and overcome the above mentioned disadvantages. 1-Alkyl-3-*p*-tolyltriazenes [197,198,199] are commercially available or can be easily prepared [4,200,201]. The 1-methyl-3-*p*-tolyltriazene is a well known alkylating agent used for the methylation of carboxylic acids,[193,202] but it was never used for the methylation of tetrazole rings.

The methylation of tetrazole rings proceeds nearly quantitatively in an aprotic solvent such as dichloromethane at room temperature in a short time and with a wide variety of 5-substituted tetrazoles in the presence of different functional groups such as halogens, double bonds, protecting groups (Boc and Cbz), thio and sulfanyl. The reaction can be easily monitored by TLC (typical elution system: ethyl acetate / hexane 1:4) or by HPLC. The ratio of the 1,5- and 2,5-regioisomers is between 1:1 to 1:4 depending on the nature of the substituent in position C-5 and the isomers are easily separated by simple chromatography on silica gel.

Although the mechanism is not well understood, we suggest that the pathway for the carboxylic acids [265,202] can be extended to 5-substituted tetrazoles. The tetrazole ring is deprotonated and the resulting tetrazolate attacks the methyl group in a nucleophiic substitution S_N2 to form the desired *N*-methyl-tetrazole derivative, aniline and nitrogen (Scheme **86**).



Scheme 86. Proposed mechanism for the methylation of *N*-unsubstituted tetrazoles with methyl-aryl-triazene

2.2.1.1. 1-Methyl-3-*p*-tolyltriazene

Alkyl-aryl-triazenes exist as a tautomeric mixture of forms **170** and **171** (Figure 38) and are already known as methylating agent for carboxylic acids [203].

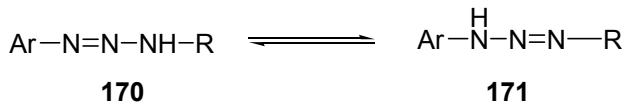


Figure 38. Tautomeric forms of alkyl-aryl-triezenes

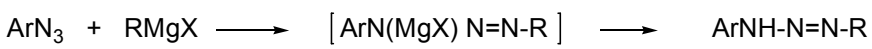
The IR spectra of monoalkyltriazenes generally show two NH stretching vibration bands, one at 3480 – 3440 cm^{-1}, assigned to tautomer **170** and the other near 3338 cm^{-1} assigned to tautomer **171** [201]. From the temperature dependence of the intensity ratio of the IR bands, ΔH of the tautomeric equilibrium is estimated to be 0.3 kcal mol^{-1}. ^{1}H NMR spectrum of 3-methyl-1-*p*-tolyltriazene, measured in dichloromethane at –65 °C or in chloroform at -55 °C, exhibits only one resonance, a doublet for the *N*-methyl protons, indicating that only tautomer **170** is detectable under these conditions. However, tautomer **171** of the same *p*-tolyltriazene has been detected in chloroform by ^{13}C NMR spectroscopy [204] and the failure to detect the ^{1}H NMR signals of the form **171** has been ascribed to low intensities of these signals which may well be considerably broadened.

2.2.1.1.1. Preparation of 1-methyl-3-*p*-tolyltriazene

The 1-methyl-3-*p*-tolyltriazene can be easily prepared from the corresponding diazonium [6,200,201] salt or *via* the Grignard method [200,201a].

2.2.1.1.1.1. Preparation *via* Grignard

The formation of monoalkyltriazene by the reaction of a Grignard reagent with an aryl azide was already reported by Dimroth in 1903 (Scheme 87)[199,201a].

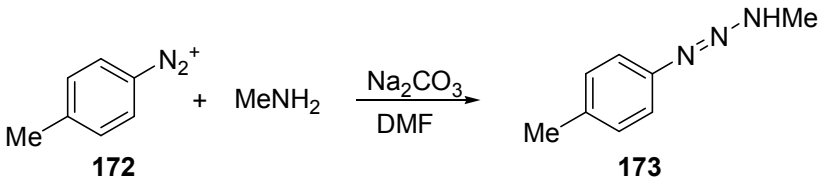


Scheme 87. Synthesis of monoalkyl-triazene *via* Grignard reaction

This methodology can not be used when the aryl group contains substituents which may react with the Gignard reagent such as CO_2R and CN functional groups. In the majority of such instances the diazonium coupling method described below, is a practical alternative.

2.2.1.1.1.2. Preparation *via* diazonium coupling

The monoalkyl-aryltriazenes can be easily prepared with the *N*-coupling of an aryl diazonium salts with primary amines in the presence of sodium carbonate in DMF (Scheme 88) [200,201a].



172 **173**

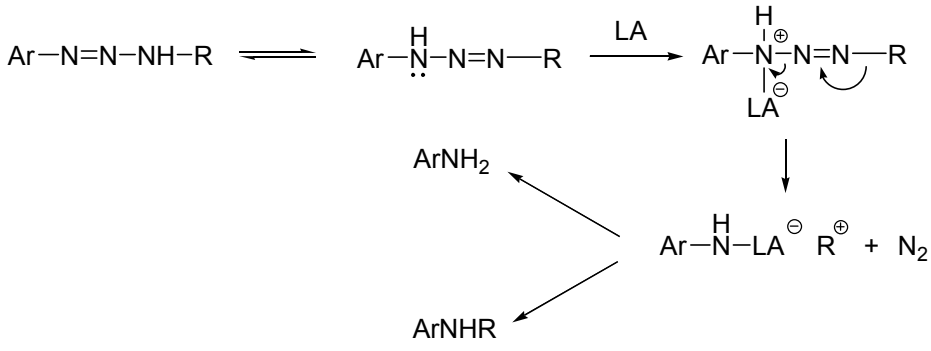
Scheme 88. Synthesis of 1-methyl-3-*p*-tolyltriazene *via* diazonium salt

2.2.1.1.2. Reactions of 1-alkyl-aryltriazene

Synthetic applications of monoalkyltriazenes include esterification, deamination of primary amines and the ability to act as bridging agents in coordination chemistry, although one could look upon this property as an extension of their nucleophilic character [201a].

2.2.1.1.2.1.Reaction with acids

Alkyl-aryltriazenes decompose when in contact with acids; consequently, purification by standard chromatographic methods is not always possible [201a]. For instance the reaction of 1-phenyl-3-alkyltriazenes with aluminum trihalides affords *N*-alkylanilines, with nitrogen evolution (Scheme 89).

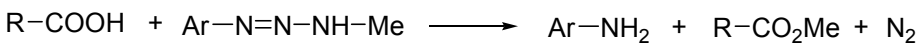


Scheme 89. Degradation of monoalkyl-aryl-triazenes

2.2.1.1.2.2. Methylation of carboxylic acids

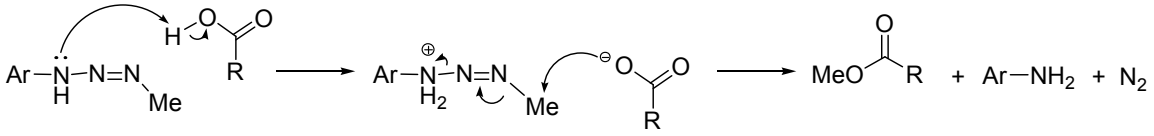
1-Alkyl-3-aryltriazenes are known alkylating agent of carboxylic acids because of its facility to release the alkyl fragment [193,201c,]. The reaction of carboxylic acids with 1-

methyl-3-*p*-tolyltriazene, in particular with polymethacrylic acids, is already known for several years (Scheme 90) [193,200-202].



Scheme 90. Methylation of carboxylic acids with 1-methyl-3-*p*-tolyltriazene

The proposed mechanism for the methylation of carboxylic acids with 1-methyl-aryltriazene follows a nucleophilic substutution S_N2 to give the desired methyl-ester, aniline and nitrogen [201a,202] (Scheme 91).

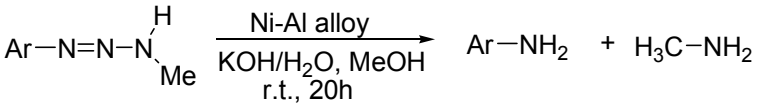


Scheme 91. Proposed mechanism for the methylation of carboxylic acids with methyl-aryltriazene

Contrary to diazomethane, 1-methyl-3-*p*-tolyltriazene can be purchased and safely stored on the shelf to be used as needed and the formation of polyethylene contamination is eliminated.

2.2.1.1.2.3. Reduction to anilines and primary amines

The alkyl-aryltriazene can also be reduced to aniline and primary amine by using nickel/aluminum alloy in base [205]. The compound is reduced under mild conditions dissolving the triazene in water or alcohol with potassium hydroxide and treating with nickel/aluminum alloy at room temperature for twenty hours (Scheme 92).

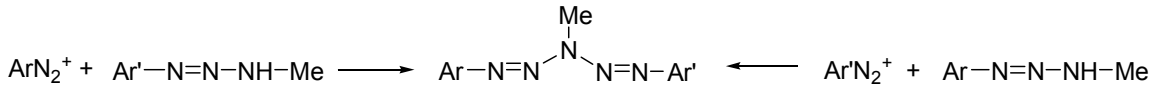


Scheme 92. Reduction of 1-methyl-aryltriazene with Ni/Al alloy

2.1.1.1.2.2. Nucleophilic attack

The nucleophilic character of monoalkyl-aryltriazenes is at once evident from the fact that formation of penta-azadienes often accompanies triazene formation during *N*-diazo coupling. Dimroth [199] showed that the same unsymmetrical penta-azadiene arises

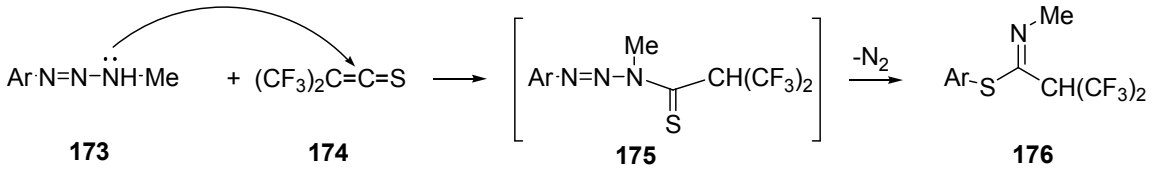
from two different coupling reactions of diazonium salt with 1-methyl-3-aryltriazene (Scheme 93).



Scheme 93. Formation of penta-azadiene

Significantly, diazo-coupling occurs at the N-atom adjacent to the methyl, not the aryl group. The greater nucleophilicity of N-3 is also evident during acetylation with acetic anhydride, which affords 3-acyl derivatives [199a,201a].

Reaction of 1-methyl-3-*p*-tolyltriazene **173** with thioketene **174** affords the *S*-aryl thioimide **176** *via* the thioacylated triazene **155** (Scheme 94).



Scheme 94. Reaction of 1-methyl-3-*p*-tolyltriazene with thioketenes

2.2.1.1.2.5. Complex formation

The nucleophilic character of triazenes leads to the formation of triazenido-metal bonds, which offer a variety of bonding arrangements in transition metal complexes [201a]. Three fundamental coordination modes have been identified: 1) monodentate, with Pt and Pd (typical for dialkyltriazenes), 2) bidentate, with Rh and Co, 3) triazenido-group as a bridging ligand between two metal atoms, which can also be bonded to each other, with Ag, Rh, Ir and Hg (Figure 39) [201a].

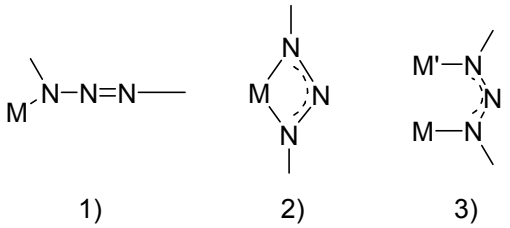
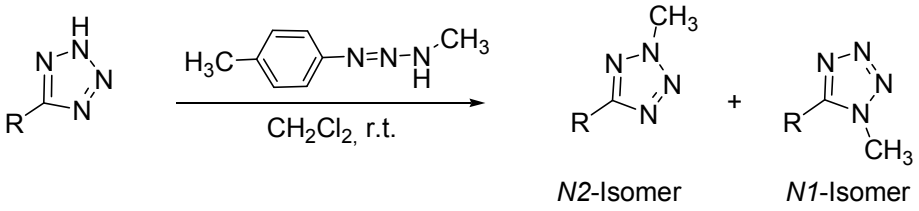


Figure 39. Modes of complexation of triazenes

2.2.1.2. Methylation of tetrazole rings with 1-methyl-3-*p*-tolyltriazene

A series of tetrazoles with different functional groups at the C-5 position are converted into the corresponding *N*-methyl derivatives in good yield under mild conditions. All the *N*-methyl tetrazoles, with exception of **147** and **148**, are unknown compounds. The reactions are achieved by dissolving the tetrazole derivative in dichloromethane and treating with 1.25-1.5 equivalents of 1-methyl-3-*p*-tolyltriazene from 0 °C to room temperature (Scheme 95).



Scheme 95. Methylation of the tetrazole ring

When HPLC and TLC analysis show ≥ 98 % conversion (usually after 20 minutes – 2 hours), the reaction mixture is cooled at 0 °C and treated with HCl (2 M) to quench the excess of 1-methyl-3-*p*-tolyltriazene which decomposes to aniline, *N*-methyl-aniline and nitrogen (Sectition 5.2.4.). The desired *N*-methyl-tetrazole is extracted with dichloromethane into the organic phase. The two regioisomers are then isolated by chromatography on silica gel (typical elution system: hexane/ethyl acetate 4:1) to yield the two pure N1- and N2-isomers in ratio between 1:1 to 1:4, depending on the nature of the substituent in position C-5 (Table 12).
All the reaction conditions herein described are not optimized because our first goal was to prove the applicability of 1-methyl-3-*p*-tolyltriazene as a versatile methylating agent for tetrazole rings.

According with published data, the N1-regioisomer is more polar compared to the *N*2 and this is confirmed by the melting point and the HPLC analysis (Table 13). The position of the C-5 signal in their ^{13}C NMR differs considerably: it is located at about δ 150 ppm for the N1-isomer and 160 ppm for the N2-isomer. Therefore, isomeric 1,5- and 2,5-disubstituted tetrazoles can be distinguished with a high reliability (Introduction, Section 2.1).

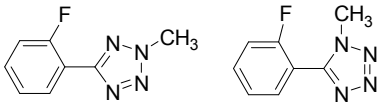
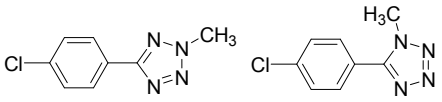
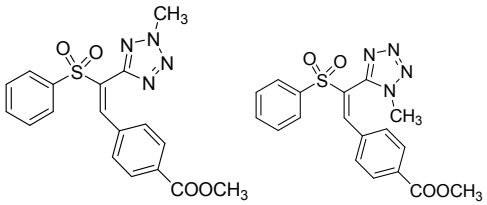
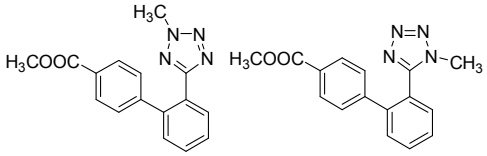
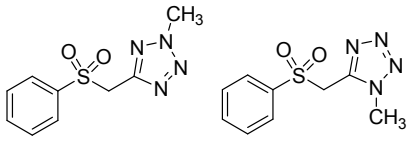
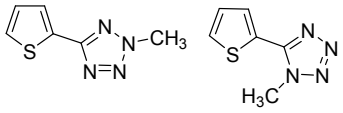
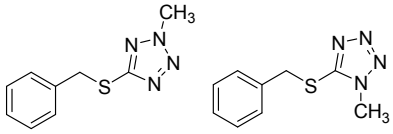
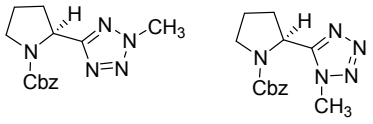
Entry	Time [h]	Product	*N*2/*N*1-Isomer[b] [%]	Yield[c] [%] *N*2	*N*1
1[a]	2	 **146** **145**	71/29	58	12
2[a]	2	 **148** **147**	75/25	44	13
3[a]	0.2	 **177** **178**	57/43	66	14
4[a]	4	 **150** **149**	73/27	53	17
5[a]	0.3	 **179** **180**	52/48	38	36
6[a]	2	 **181** **182**	66/34	55	42
7[a]	1	 **183** **184**	52/48	53	32
8[a]	1.5	 **185** **186**	75/25	61	31

Table 12. Synthesis of *N*-methyl-substituted tetrazoles.

Notes: [a] reaction performed at r.t.; [b] *N*2/*N*1 ratio based on HPLC of the crude; [c] isolated yield after chromatography

Product	HPLC	^{1}H NMR (CH_3-N) [ppm]	^{13}C NMR (C-5) [ppm]	mp [°C]
146	8.90	4.45	162.1	70-74
145	6.37	4.03	153.7	74-77
148	8.21	4.41	163.2	108
147	5.61	4.15	153.2	120
177	9.54	4.40	156.9	156-158
178	9.35	3.83	147.8	158-160
150	14.03	3.86	164.2	-
149	12.02	3.56	154.1	117-120
179	4.62	4.33	156.1	137-139
180	4.55	4.12	146.5	182-184
181	5.75	4.40	160.2	84-85
182	3.37	4.20	149.4	110-111
183	7.90	4.33	162.4	-
184	6.54	3.84	153.1	-
185	8.03	4.27, 4.30	167.7, 167.9*	-
186	7.08	3.81, 4.10	156.3, 156.7*	-

Table 13. Physical properties of *N*-methyl-substituted tetrazoles.

* Rotamers

Aromatic tetrazole derivatives in the presence of halogens are suitable substrates for methylation with 1-methyl-3-*p*-tolyltriazene (Table 12; entries 1, 2). The reaction is carried out at room temperature in 2 hours using 1.5 equivalents of 1-methyl-3-*p*-tolyltriazene (Table 12; entries 1, 2). The halogen position on the aromatic ring does not influence the final ratio of N1- and N2-regioisomer which is around 1 to 2. Starting tetrazole derivative which contain aromatic rings, conjugated double bond and sulphonyl moiety undergoes the methylation in a very short time (15 minutes) affording the desired *N*-methylated tetrazole **178** and **177** in good yield with a regioselectivity N1 and N2 of 1 to 4 (Table 12; entry 3). The X-ray structure of **177** was solved and used as additional reference to distinguish in all the cases the 1,5- and 2,5-disubstituted tetrazole isomers (see X-ray discussion, Chapter 4) (Figure 40).

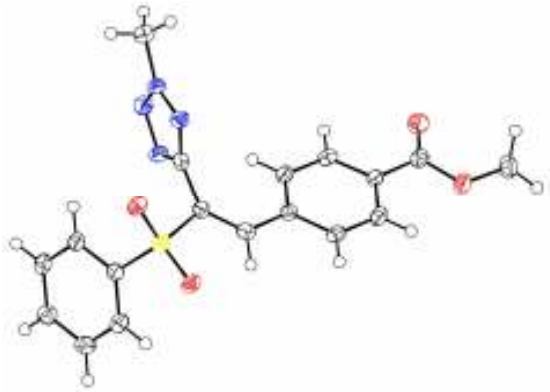
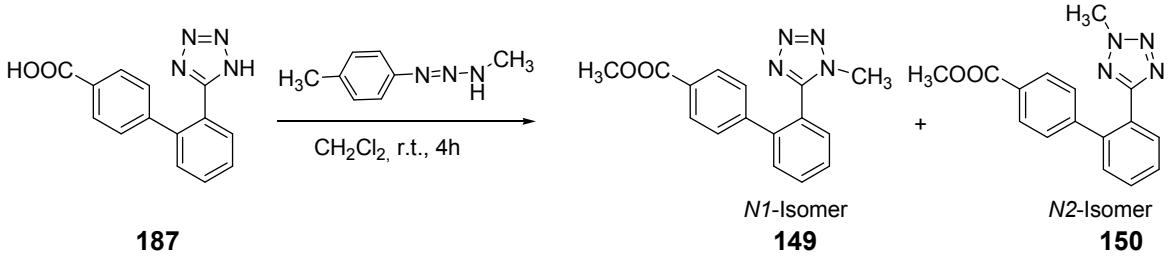


Figure 40. Structure of 4-[2-benzene-sulphonyl-2-(2-methyl-2*H*-tetrazol-5-yl)-vinyl]-benzoic acid methyl ester **177** in the crystal with thermal ellipsoids drawn at 50 % probability level

In the case of 2'-(tetrazol-5-yl)-biphenyl-4-carboxylic acid **187**, the tetrazole ring and the carboxylic acid moieties are simultaneously methylated in good yields using 1-methyl-3-*p*-tolyltriazene at room temperature in 4 hours (Table 12; entry 4) (Scheme 96).

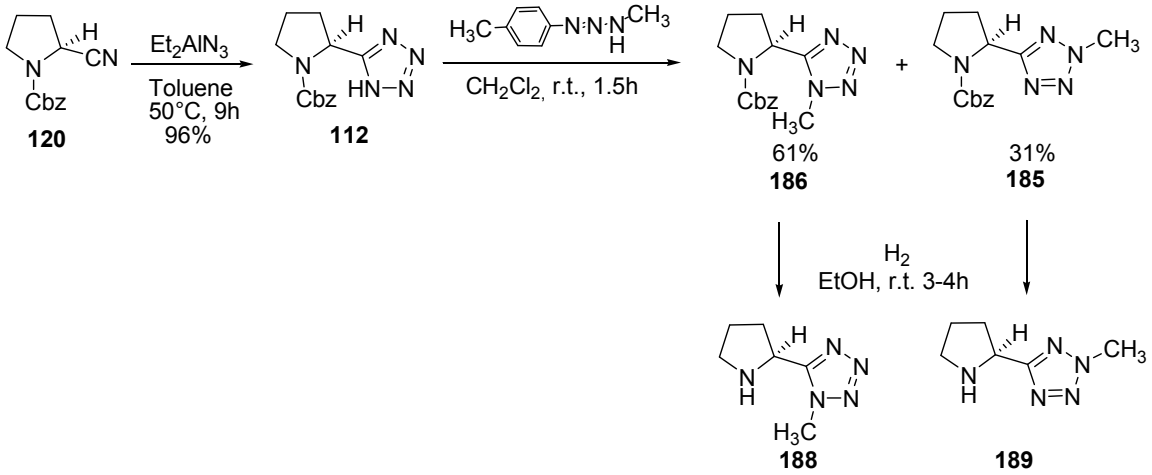


187 **149** **150**

Scheme 96. Synthesis of 4-[1-ethylidene-2-(methyl-terazol-5-yl)-penta-2,4-dienyl]-benzoic acid methyl ester **149** and **150**

The regioselectivity is lower in the case of sulfur containing tetrazole derivatives (Table 12; entries 5-7), between 1 to 1 (Table 12; entry 5) up to ca 2 to 3 (Table 12; entry 7) with the 2*N*-methylated tetrazole as the major regio-isomer. 5-Phenylsulfonylmethyl-tetrazole **75** undergoes the methylation using 1.4 equivalents of 1-methyl-3-*p*-tolyltriazene at room temperature for 20 minutes (Table 12; entry 5). The 5-thiophen-2-yl-tetrazole **109** provides the corresponding *N*-methyl-tetrazoles **181** and **182** in high yield using 1.5 equivalents of 1-methyl-3-*p*-tolyltriazene at room temperature for 2 hours (Table 12; entry 6). The 5-benzylsulfanyl-*N*-methyl-tetrazoles **181** and **182** are obtained in 2 hours in good yield using 1.5 equivalents of 1-methyl-3-*p*-tolyltriazene with a slight higher regioselectivity compared to **75** and **17** (Table 12; entries 5-7).

The (*S*)-2-(tetrazol-5-yl)-pyrrolidine-1-carboxylic acid benzyl ester **112** is methylated in very good yield using 1.5 equivalents of 1-methyl-3-*p*-tolyltriazene at room temperature for 1.5 hours, with a regioselectivity N1 and N2 of 1 to 2 (Table 12; entry 8) [205]. The resulting (*S*)-2-(methyl-tetrazol-5-yl)-pyrrolidine-1-carboxylic acid benzyl esters **185**, **186** can be considered as precursors of a novel class of *N*-alkylated-tetrazole-pyrrolidine organocatalysts [142] (Organocalysis; Chapter 3) which could be prepared from the cleavage of the Cbz protecting group, as shown in Scheme 99.



120 **112** **186** **185** **188** **189**

Scheme 97. Proposed synthesis of novel organocatalysts

2.3. Alkylation of Tetrazole Rings: Conclusions

The introduction of an appropriate *N*-substituent into an already existing tetrazole cycle is the most common synthetic pathway to disubstituted tetrazoles (Section 1.1.4), due to the availability of various starting tetrazoles, alkylating agents and the simplicity of the process [32a,98,170]. These transformations are fundamentally important therefore in the last years a wide range of *N*-alkyl-tetrazole derivatives has been reported from pharmaceutical companies as compounds which present biological activities [177-181]. Although the disubstituted tetrazoles attract interest, the preparation methods for these compounds are not sufficiently developed [37a]. Within last decades not a single new approach was advanced for building up a tetrazole ring with substituents in position *N*-1 or *N*-2, especially for methylated tetrazole rings.

We have prepared a wide variety of *N*-alkylated tetrazoles, including *N*-isopropyl, -*tert*-butyl (See Chapter 3), -trytil, -benzyl and methyl tetrazoles. According to published data for numerous 1,5- and 2,5-disubstituted tetrazoles, we were able to isolate and distinguish with high reliability the two regioisomers. In almost all the cases, alkylation of 5-substituted tetrazoles with alkylating agents give rise to mixtures of isomeric 1,5- and 2,5-disubstituted tetrazoles [1,171] (Section 2.1). The position of substitution has been found to be sensitive to the steric requirements of the alkylating agent and to the C-5 substituent of tetrazole [98,172]. A significant instance are the trytilation and the *tert*-butylation of tetrazole rings which provide exclusively the N2-regiosiomer.

The general protocols for the methylation of tetrazole rings suffer from several disadvantages such as the high toxic profile of the methylating agent, toxic water waste and possible presence of byproducts (Section 2.1.3.). Typical examples of methylating agents used for tetrazoles are methyl iodide, dimethylsulfate and diazomethane. We have found that the 1-methyl-3-*p*-tolyltriazene is a valuable, safe and efficient alternative for the methylation of tetrazole rings, with possible application for large scale process. The 1-methyl-3-*p*-tolyltriazene is a well known alkylating agent used for the methylation of carboxylic acids [193,202], but never used for the methylation of tetrazoles. The reaction occurs rapidly (20 min to 4 hours) at room temperature. A simple work-up procedure gives the mixture of 1-5 and 2-5-methyl-tetrazole derivatives which are generally

separated by chromatography on silica gel. Contrary to other methylating agents, 1-methyl-3-*p*-tolyltriazene can be purchased and safely stored on the shelf to be used as needed. The possibility of polyethylene contamination typical in the case of diazomethane is eliminated because of the reagent's stability. The high reactivity, low cost and safe storage of 1-methyl-3-*p*-tolyltriazene make this novel process particularly attractive with possible application in an industrial scale. In addition, other alkyl-aryltriazenes could be tested and used to introduce different alkyl residues in the tetrazole moiety thanks to their high reactivity as an alkyl fragment-donor and their availability.

Chapter 3.
Organocatalysis

Until a few years ago, it was generally accepted that transition metal complexes and enzymes were the two main classes of very efficient asymmetric catalysts. Synthetic chemists have scarcely used small organic molecules as catalysts throughout the last century, even though some of the very first asymmetric catalysts were purely organic molecules. By contrast chemists have focused on transition metal catalysts. A change in perception occurred during the last few years when several reports confirmed that relatively simple organic molecules can be highly effective and remarkably enantioselective catalysts of a variety of fundamentally important transformations [206]. This rediscovery has initiated an explosive growth of research activities in organocatalysis both in industry and in academia. As realization grows that organic molecules not only have a "green" advantage but also can be very efficient catalysts, asymmetric organocatalysis may begin to catch up with the spectacular advancements of enantioselective transition metal catalysis.

Asymmetric catalysis represents still one of the major challenges in modern organic chemistry. Besides the well-established asymmetric metal-complex-catalyzed syntheses and biocatalysis, the use of "pure" organic catalysts turned out to be an additional efficient tool for the synthesis of chiral building blocks.

3.1. Organocatalysis: introduction

Between the extremes of transition metal catalysis and the enzymatic transformations, a third approach to the catalytic production of enantiomerically pure organic compounds has emerged: organocatalysis [207]. Organocatalysis is the acceleration of chemical reaction with substoichiometric amount of an organic compound. Organocatalysts are purely "organic molecules" composed of mainly C, H, O, N, S and P atoms to accelerate chemical reactions. Organocatalysts have several advantages including inertness toward moisture and oxygen, availability, low cost and low toxicity, which confers a huge direct benefit in the production of pharmaceutical intermediates when compared with transition metal catalysts.

During the last few years the asymmetric catalysis of carbonyl transformations *via* iminium ion and enamine intermediates using chiral amines as organocatalysts has grown most remarkably. The first publications from the groups of MacMillan, List, Denmark, and Jacobsen among others paved the way in the years 1990s. These reports introduced highly enantioselective transformations that rivaled the metal-catalyzed reactions in both yields and selectivity. Once this foundation was laid, mounting interest in organocatalysis was reflected in a rapid increase in publications on this topic from a growing number of research groups.

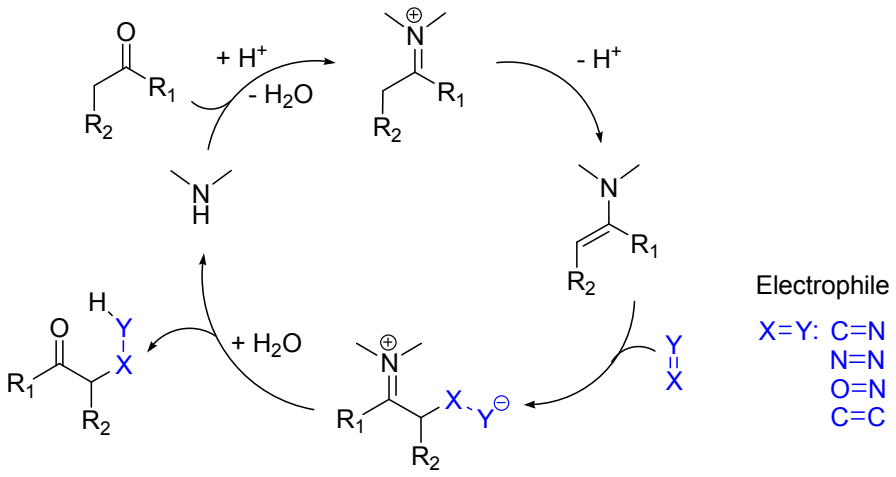
3.1.1. Catalysts and Mechanism: The Enamine and Iminium Catalysis

The majority of organocatalysts are Lewis bases which initiate the catalytic cycle *via* nucleophilic addition to the substrate [208]. Two different approaches can be envisaged for organocatalyzed reaction [209,210,211] (Scheme 98).

Scheme 98. Enamine and iminium organocatlysys approach

3.1.1.1. Enamine catalysis

The first mechanism involves the catalytic formation of an enamine intermediate with the chiral amine, generally a chiral pyrrolidine derivative. The enamine, which is generated from carbonyl compound *via* iminium ion formation, reacts with an electrophile to give an α-modified iminium ion which gives, upon hydrolysis, the α-modified carbonyl compound [153e,212] (Scheme 99). Examples of enamine catalysis are proline-catalyzed aldol reactions, Mannich reactions and Michael additions among others[207].



Scheme 99. Enamine catalysis

3.1.1.2. Iminium catalysis

The second approach is based on a chiral iminium ion from an unsaturated carbonyl and the chiral amine. The active species is an iminium ion formed by reversible reaction of a chiral amine with an α,β-carbonyl substrate (Scheme 98). Example of iminium catalysis is the MacMillan's enantioselective Diels-Alder reaction [213].

3.1.1.3. Organocatalysts

Whereas many metal centers are good Lewis acids, organic catalysts tend to react as heteroatom-centered Lewis bases. Novel, previously unexplored catalysts classes are emerging. For example, asymmetric catalysis by Brønsted acid is a recent addition to the field of organocatalysis. Moreover, the design and use of synergetic systems and bifunctional catalysts, which have two distinct functionalities (e.g. a Lewis base and a Brønsted acid) within the same molecule, is becoming more and more common [207]. A selection of typical organocatalysts is shown in Figure 41. Proline **193**, a chiral-pool compound which catalyzes reactions by iminium ion or enamine pathway, is a prototypical example which promotes aldol and related reactions [210,214]. The same is true for cinchona alkaloids [215] **190** and **191**. Amino acid derived organocatalysts such as the oxazolidinone **192** introduced by MacMillan *et al*. [213] or the thiourea **199** introduced by Jacobsen *et al.* have enabled excellent enantioselectivity in *e.g*., Diels-Alder reactions of α,β-unsaturated aldehydes (oxazolidinone **192**) or hydrocyanation of imines [216] (thiourea **199**). Diamine catalysts such as **195** and **197** introduced respectively by Alexakis [209,217] and Barbas [218] are versatile organocatalysts for Michael additions as well as tetrazole analogues of proline-derivatives **114** [219] and **197** [153g,160a].

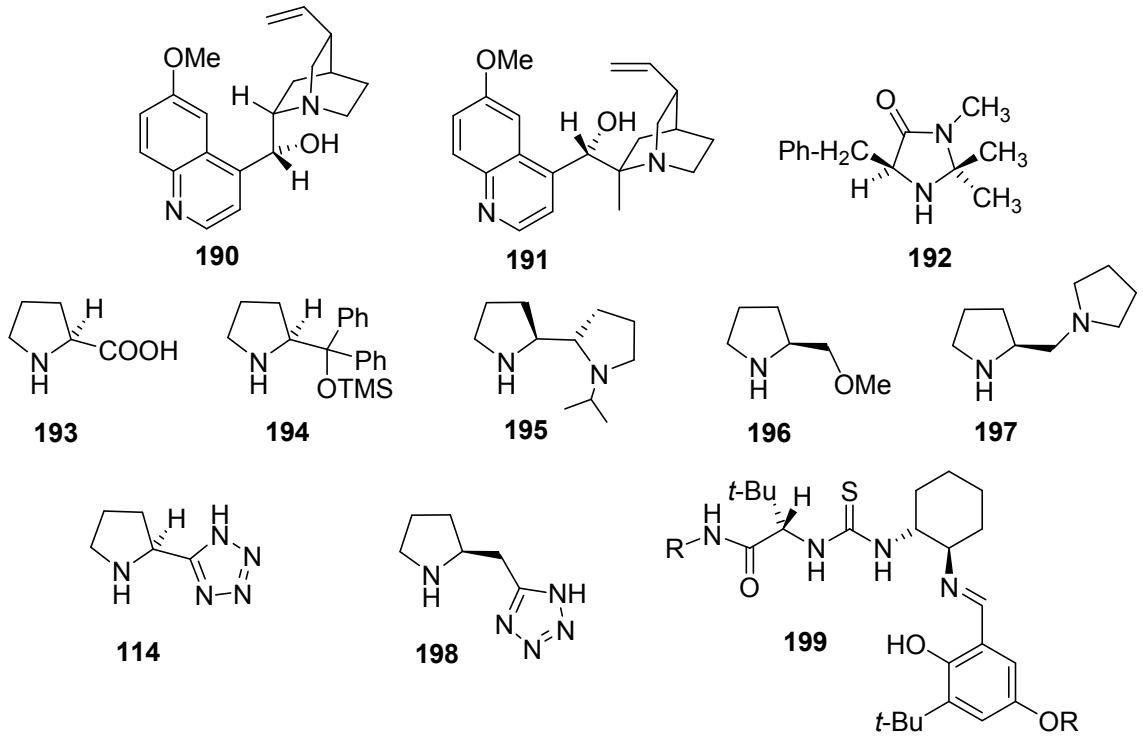
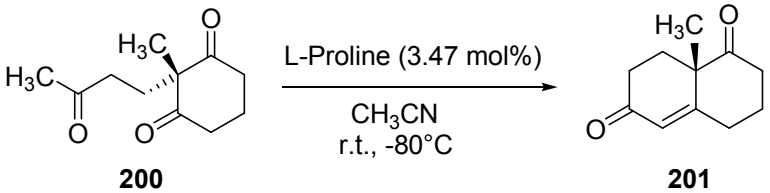


Figure 41. Selection of organocatalysts

3.1.1.4. Proline

3.1.1.4.1. History

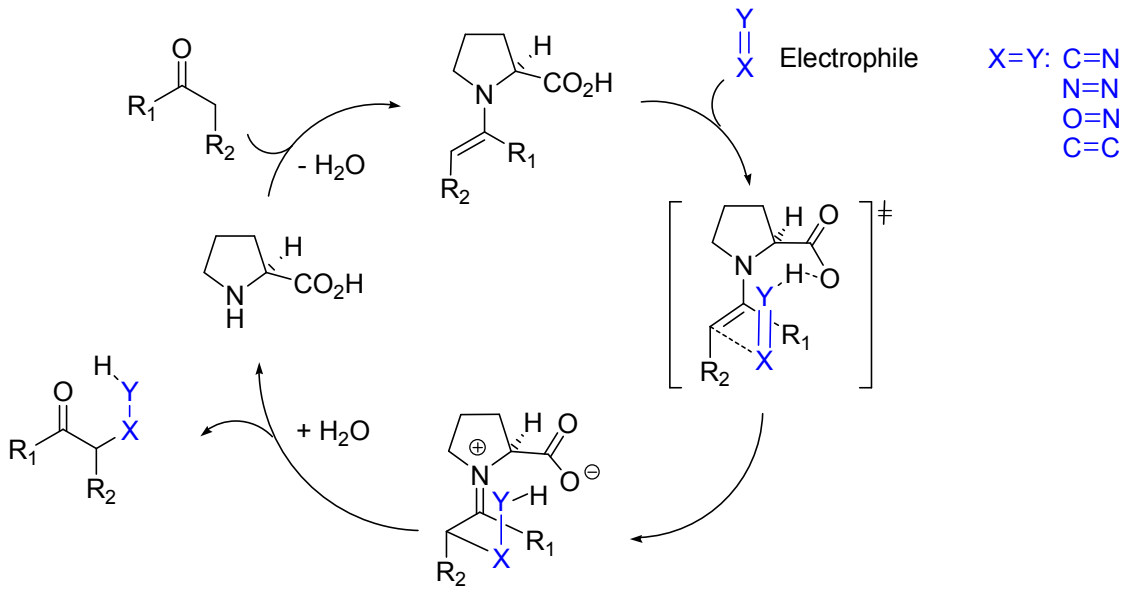
Despite to very recent introduction of this type of catalysis to synthetic chemistry, organocatalytic reactions look back on a venerable history. The first example of an asymmetric organocatalytic reaction was reported y in 1912, by Bredig and Fiske [220]. They reported a modestly enantioselective (≤ 10 % ee) alkaloid-catalyzed cyanohydrin synthesis. In the 1960s, Pracejus *et al.* showed that organocatalysts can give significant enantioselectivities. Using alkaloids as catalysts, afforded quite remarkable 74 % ee in the addition of methanol to phenylmethylketene [221]. The 1970s brought a milestone in the area of asymmetric organocatalysis, when two industrial groups led by Hajos at Roche and Wiechert at Schering published the first highly enantioselective catalytic aldol reactions using the simple amino acid proline as catalyst [222], where the resulting ketone is an important intermediate in steroid synthesis (Scheme 100). The cinchona alkaloids and proline stood as the only familiar organocatalysts for some time.



Scheme 100. The Hajos-Parrish-Eder-Sauer-Wiechert-reaction

3.1.1.4.2. Reactivity of proline

Proline is capable of promoting a variety of catalytic asymmetric transformations [153,207,210]. It can react as a nucleophile with carbonyl groups or Michael acceptors to form iminium ions or enamines (Scheme 103). The use of proline as a catalyst requires normally amounts in the range of 10-20 mol % and furthermore, the substrate itself (ketone or aldehyde) or DMSO serve as solvents.



Scheme 101. The S-proline-mediated enamine catalytic cycle [153d]

3.1.1.5 Pyrrolidine-tetrazole

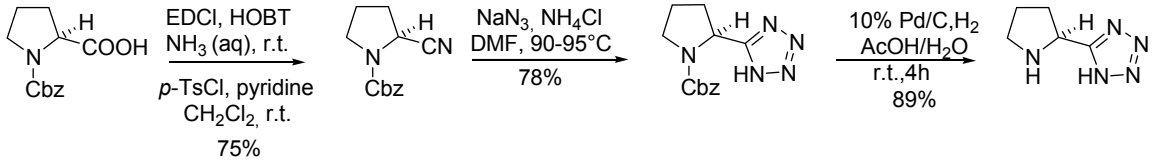
Proline-derived compounds have proven themselves to be real workhorse organocatalysts. They have been used in a variety of carbonyl compound transformations, where the catalysis is believed to involve the iminium form. These catalysts are cheap and readily accessible.

The organocatalysis system that has been studied extensively is the enantioselective proline-based one which accelerates a range of transformations including aldol reactions, Robinson annulation, Mannich reaction and Michael additions. Although proline is an ideal catalyst in terms of price and availability, often encountered drawbacks relates to low reactivity and low solubility of the catalyst. In addition, when these reactions are highly enantioselective, they require solvent such as DMSO due to the insoluble nature of the proline itself. An old “trick” in medicinal chemistry to improve the solubility of a carboxylic acid is the replacement of the acid functionality with a tetrazole moiety. A

second generation catalysts, in which the carboxylic acid of proline is replaced by a tetrazolic acid have therefore recently emerged and have been proven to show improved reactivity and/or selectivity for many organocatalyzed reactions [223].

3.1.1.5.1. History and synthesis

Although (*S*)-5-(pyrrolidine-2-yl)-tetrazole **114** has already been synthetized in 1971 by Grzonka *et al.* [224] and the phisico-chemical and biological properties have been investigated in the mild 1980s, its potential in asymmetric catalysis has been reported only in 2004 by Ley,[225] Yamamoto,[155] and Arvidsson *et al.* [226]. Starting from the commercial available *N*-benzyloxycarbonyl protected S-proline **202**, (*S*)-5-(pyrrolidine-2-yl)-tetrazole is obtained in five steps (Scheme 102).

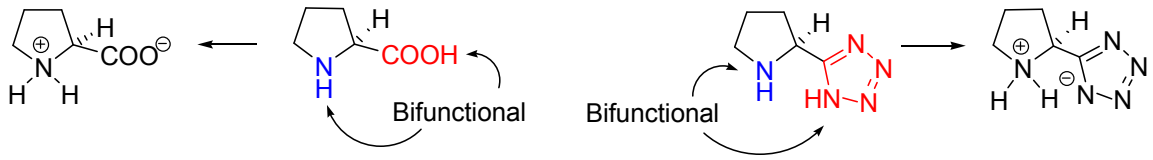


Scheme 102. Synthesis of (*S*)-5-(pyrrolidine-2-yl)-tetrazole **114** proposed by Ley [225]

3.1.1.5.2. Reactions

The use of pyrrolidine-tetrazole as a valuable alternative to proline as organocatalyst is increasing since 2004. In this section we present only a brief overview of some reported application of pyrrolidine-tetrazole in asymmetric catalysis.

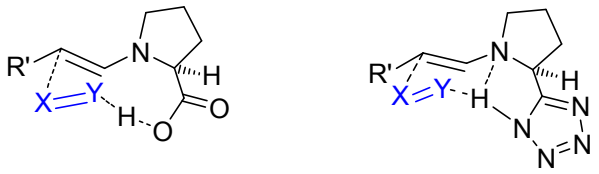
Proline itself can be regarded as a bifunctional catalyst, with a carboxlic acid and an amine moiety, as well as the pyrrolidine-tetrazole (Scheme 103). These two functionalities can both act as acid or base and can also facilitate chemical transformations.



Scheme 103. Bifunctional sites for S-proline and pyrrolidine-tetrazole

The higher reactivity and enantioselectivity often obtained with (*S*)-5-(pyrrolidine-2-yl)-tetrazole catalyst is ascribed to the lower pK_a and increased steric bulk of the

tetrazole moiety relative to S-proline. Tetrazole and S-proline have a pK_a value of ~ 8 and ~ 12, respectively in DMSO. The hydrogen bonding interactions in the transition state of the same reaction with the two catalysts are likely different and provide different levels of enantioselection [223] (Figure 42).

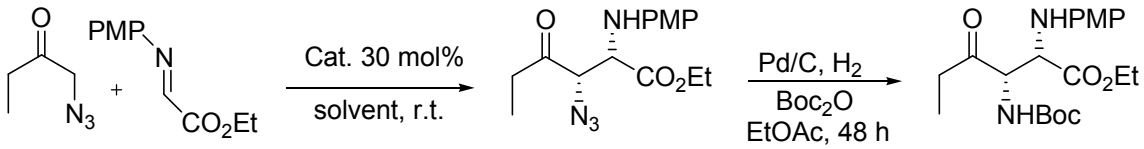


203 **204**

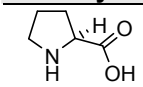
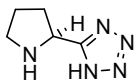
Figure 42. Proposed transition states **203** of S-proline and pyrrolidine-tetrazole **204** mediated enamine catalytic cycle

3.1.1.5.2.1. Asymmetric Mannich reaction

Barbas *et al.* recently reported the organocatalytic Mannich reaction of azido ketones with imines in the presence of the (*S*)-5-(pyrrolidine-2-yl)-tetrazole as catalyst to afford diamines with excellent yields and enantioselectivities [157]. The azido group controls the regioselectivity of the reaction providing access to chiral 1,2-diamines from azido ketones (Scheme 104).

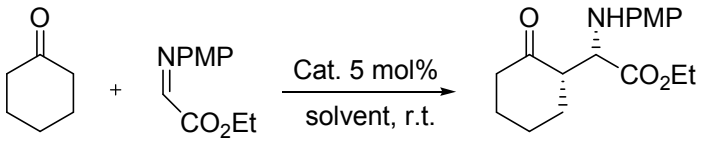


205 **206** **207** **208**

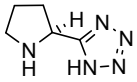
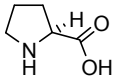
Catalyst	Solvent	Time	Yield	dr [*syn*/anti]	ee (*syn*)[%]
	DMSO	48	84	51:49	92
	DMSO	4	93	94:16	98
	CH_2Cl_2	120	93	83:17	90

Scheme 104. Organocatalytic asymmetric synthesis of 1,2-azidoamine

Ley et *al.* reported the application of (*S*)-5-(pyrrolidine-2-yl)-tetrazole to catalyze Mannich-type addition of ketones to *N*-PMP-protected α-imino ethyl glyxalate [225] (Scheme 105).



209 **206** **210**

Catalyst	Solvent	Time	Yield	Dr [*syn*/anti]	ee [%]
	CH_2Cl_2	2	65	>19:1	>99
	CH_2Cl_2	2	0	-	-

Scheme 105. Addition of cyclohexanone into *N*-PMP-protected α-imino ethyl glyxalate

It is interesting to note that the same reaction conditions with S-proline [227] gave no observable product after the same amount of time, indicating that organocatalyst solubility is a key in this reaction.

The proposed hydrogen-bonded transition state is similar to that suggested by Houk and Bahmanyar [228] (Figure 43). The PMP group on the imine sits axially to avoid clash with the tetrazole, thereby forcing the *E*-enamine to produce the *syn*-product.

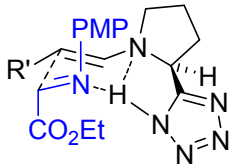
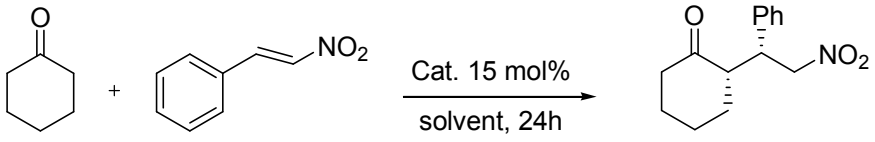


Figure 43. Proposed transition state for the pyrrolidine-tetrazole catalyzed Mannich reaction.

3.1.1.5.2.2. Asymmetric Nitro-Michael addition

(*S*)-5-(Pyrrolidine-2-yl)-tetrazole **114** is a suitable organocatalyst for nitro-Michael addition and overcomes the solvent-limits of the S-proline [229]. In alcoholic solvent, pyrrolidine-tetrazole outperforms the proline, both in terms of yield and enantioselectivity (Tables 14, 15).



206 **211** **212**

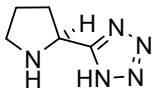
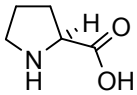
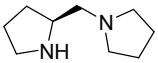
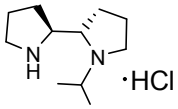
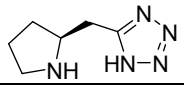
Author	Catalyst	Solvent	T [°C]	Yield[a] [%]	dr [b] [syn/anti]	ee [c] [%]
Ley [229]		CH_2Cl_2	20	20	>15:1	40
		CH_2Cl_2	40	98	>15:1	37
		DMSO	20	97	>15:1	35
		MeOH	20	61	>15:1	53
		EtOH	20	65	>15:1	65
		CH_2Cl_2	40	0	-	-
		MeOH	20	37	>15:1	57
		DMSO	20	93	>15:1	35
List [230]		DMSO	20	94	>20:1	23
Barbas [218c]		THF	20	7	48:1	56
Barbas [218b]		THF	20	86	48 :1	86
Alexakis [209]		$CHCl_3$	20	74	94:6	81
Ley [160a]		IPA-EtOH 1:1	20		>19:1	91

Table 14. Michael addition of cyclohexanone to nitrostyrene; [a] isolated yield; [b] based on ^1H NMR; [c] based on chiral HPLC

Using the pyrrolidine-tetrazole **114** as catalyst, the reaction can be performed with 1.5 equivalents of ketone [231]. The relative configuration of the product has been confirmed by X-ray analysis [229]. The improvement in enantioselectivity of the pyrrolidine-tetrazole catalyst over the proline suggests that there is an inherent difference between the two organocatalysts that alters the transition state. The proposed transition states involves the participation of the tetrazole in a hydrogen bonded framework as is suggested by Enders for proline (Figure 44).

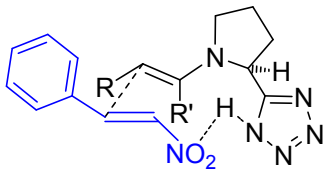
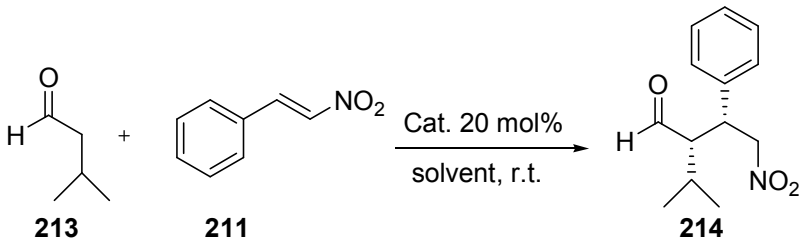


Figure 44. Proposed transition state in organocatalyzed asymmetric nitro-Michael addition

The nitro Michael addition of isovaleraldeyde to nitrostyrene is tested with several organocatalysts, but never with **114** or **115** (Table 15).



213 **211** **214**

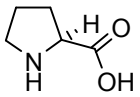
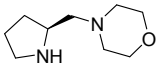
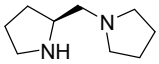
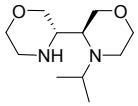
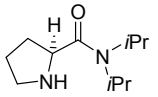
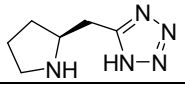
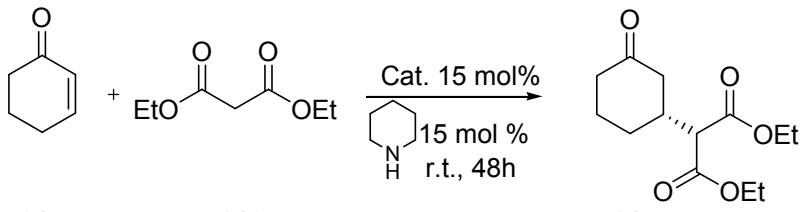
Author	Cat.	Solvent	Time [h]	Yield[a] [%]	dr[b] [anti/syn]	ee[c] (syn) [%]
Barbas [218a,218c]		THF	72	<5	93 :7	25
		THF	72	78	92 :8	72
		THF	72	80	80:20	75
Alexakis [232]		$CHCl_3$	72	85	94:6	88
Palomo [233]		CH_2Cl_2	20-24	>99 [d]	98:2	40
Ley [160a]		IPA:EtOH (1:1)	24	39-40	>19:1	37

Table 15. Michael addition of isovaleraldehyde to nitrosyrene. [a] isolated yield; [b] based on ^{1}H NMR; [c] based on chiral HPLC; [d] Determined by ^{1}H NMR

3.1.1.5.2.3. Asymmetric addition of malonates to enones



215 **216** **217**

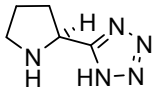
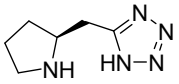
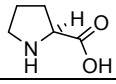
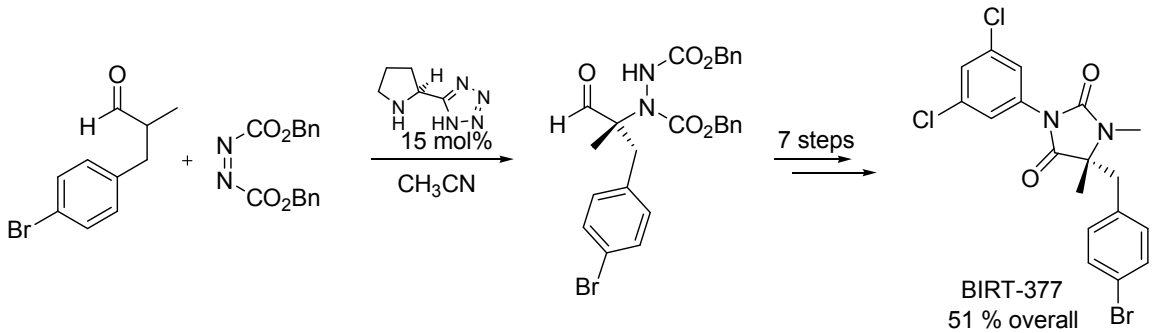
Cat.	Solvent	Conversion[a] [%]	ee [b] [%]
	CH_2Cl_2	89	79
	$CHCl_3$	69	89
	$CHCl_3$	40	0
	$CHCl_3$	62	38

Table 16. Organocatalyzed addition of malonate to cyclohexanone. [a] Estimated by ^{1}H-NMR; [b] Based on chiral HPLC

(*S*)-5-(Pyrrolidine-2-yl)-tetrazole **114** is an effective catalyst for the asymmetric addition of malonates to enones (Table 16). The reaction gives good results for a range of substrates providing the product with good enantioselectivities using 1.5 equivalents of enone as coupling partner [234].

3.1.1.5.2.4. Asymmetric α-amination of aldehydes

Barbas *et al.* recently reported the application of the pyrrolidin-tetrazole catalyzed α-amination of an aldehyde in a total synthesis sequence of the cell adhesion inhibitor BIRT-377 [223] (Scheme 106).

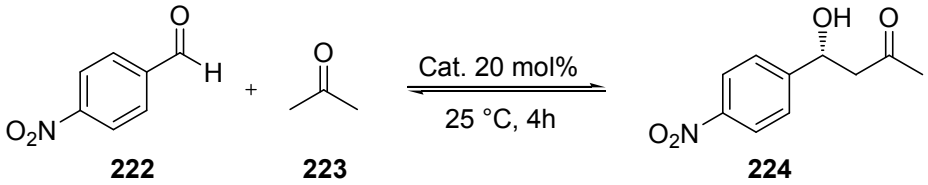


218 **219** **220** **221**

Scheme 106. Synthesis of BIRT-377

3.1.1.5.2.5. Aldol reactions

(*S*)-5-(Pyrrolidine-2-yl)-tetrazole **114** is a suitable organocatalyst for aldol reaction [226,235] (Table 17). The direct asymmetric aldol reaction between ketones and aldehydes relies on activation of the ketone partner through formation of the corresponding enamine as an intermediate through condensation with the secondary amine function of the catalyst (Scheme 109).



222 **223** **224**

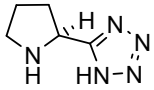
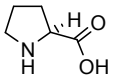
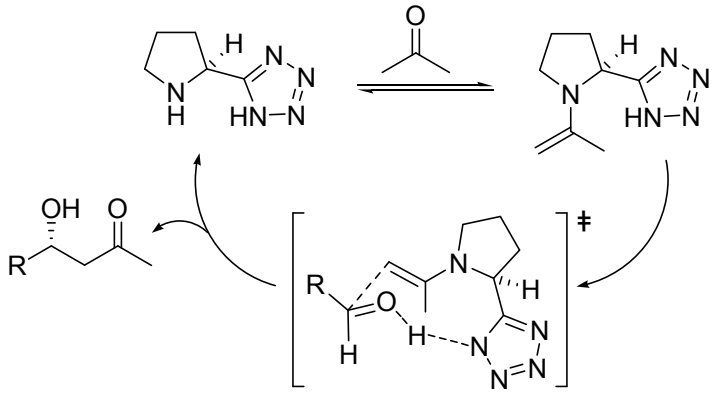
Cat.	Solvent	Yield [%]	ee [%]
	DMSO	93	76
	Dioxane	88	66
	DMF	93	70
	DMSO	75	73
	Dioxane	55	44
	DMF	50	70

Table 17. Organocatalyzed aldol reaction [226]

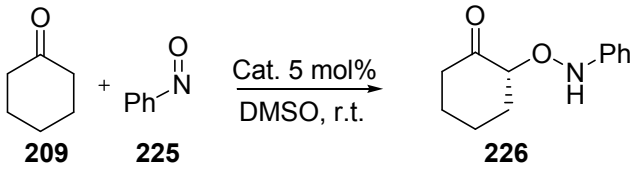


Scheme 107. Proposed mechanism for pyrrolidine-tetrazole catalyzed aldol reactions [226]

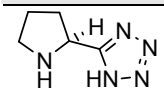
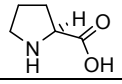
The pyrrolidine-tetrazole is more reactive and sometimes yields higher stereoselectivity compared to proline, when employed as organocatalyst. Arviddson *et al.* suggested that a possible explanation is that proline easily engages in bicyclic oxazolidinone formation, while pyrrolidine-tetrazole does not [226]. Consequently, more catalyst is available for forming the enamine intermediate in the aldol reaction in the case of pyrrolidine-tetrazole than when proline is used. In addition, factors related to the low solubility of proline contribute in reactivity.

3.1.1.5.2.6. *O*-Nitroso aldol reaction

Yamamoto *et al.* recently reported the use of the (*S*)-5-(pyrrolidine-2-yl)-tetrazole **114** as an efficient catalyst for *O*-nitroso aldol ractions [236] (Scheme 108).

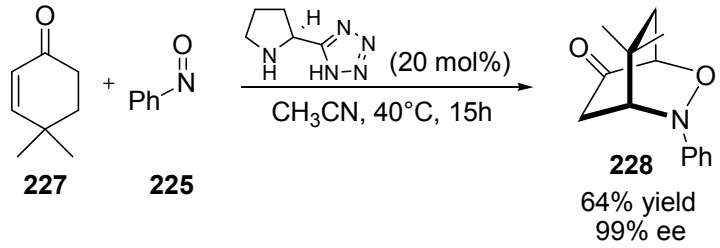


209 **225** **226**

Cat.	Time [h]	Yield [%]	ee [%]
	1	94	>99
	1	35	>99

Scheme 108. *O*-Nitroso aldol reaction of cyclohexanone with nitrosobenzene

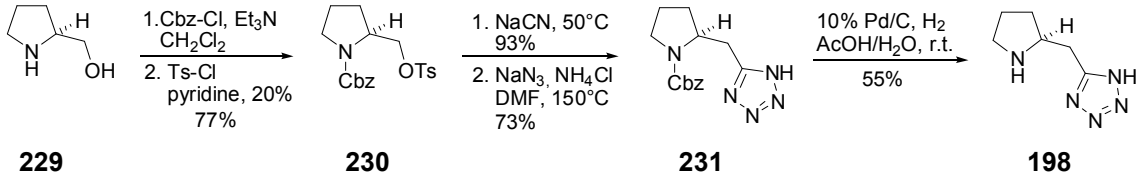
Using α,β-unsaturated ketones Yamamoto *et al.* reported the synthesis of a nitroso Diels-Alder adduct-type *via* an *O*-nitroso aldol reaction, followed by a Michael reaction (Scheme 109) [159].



Scheme 109. Stepwise *O*-nitroso aldol / Michael reaction

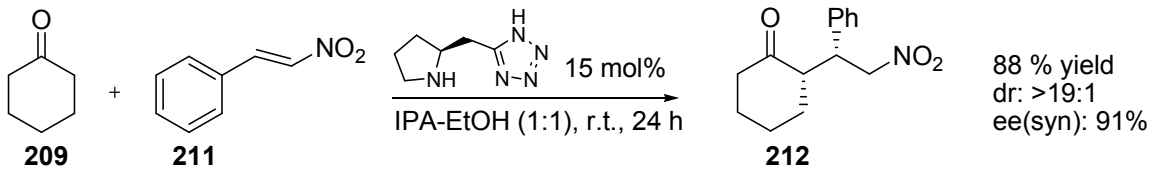
3.1.1.6. Homo-proline tetrazole

The synthesis and application of the homologue of the pyrrolidine-tetrazole has been reported by Ley and co-workers (Scheme 110) [160a,219].



Scheme 110. Synthesis of the homo-proline tetrazole

Homo-proline tetrazole catalyzes the asymmetric Michael addition of a ketone to a nitro-olefin. Its use gives improved entioselectivities in the Michael addition of carbonyl compounds to nitro olefins (Scheme 111) (Section 3.1.1.6.).



Scheme 111. Michael addition of cyclohexanone to nitrostyrene

Two possible transition states are proposed. Both involve an electrostatic interaction between the nitro group and the nitrogen of the pyrrolidine ring (Figure 45).

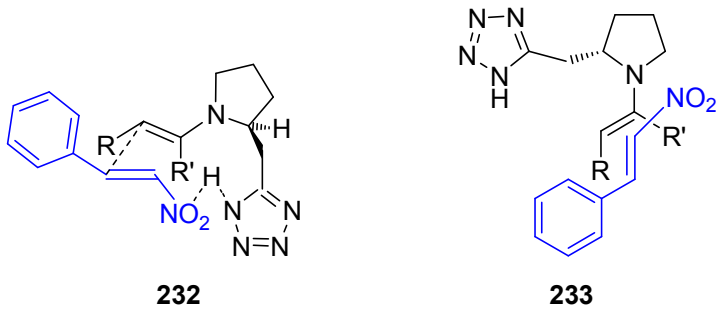
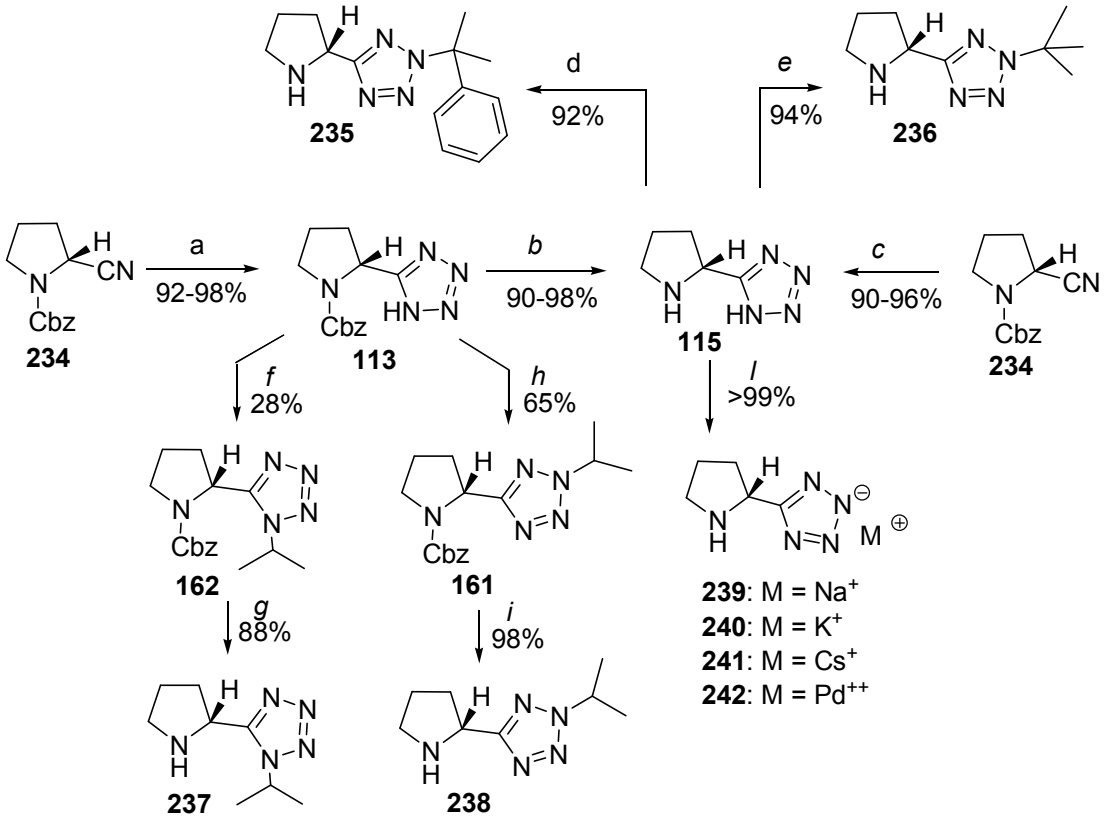


Figure 45. Hydrogen-bonded transition state **232**, and steric hindrance of tetrazole **233**

Screening of different ketones and nitro olefins suggests that the nature of the nitro-Michael acceptor has less effect on the stereoselectivity of the reaction than the ketone. This observation supports the second model of transition state since any electronic change of the nitro olefin could lead to a significant change in the interactions in the model **332** (Figure 45) [160a].

3.2. Organocatalysis: Results and Discussion

The initial aim in our investigation was to design a novel class of organocatalysts which could be used in solvents more commonly used in organic synthesis with highly lipophilic substrates. Using our new methodology for the synthesis of tetrazole rings starting from the corresponding nitrile with dialkylaluminum azide (Section 1.2.), we decided to prepare a variety of compounds based on pyrrolidine-tetrazole skeleton [142] which could find in the future application as a novel class of organocatalysts (Scheme 112).

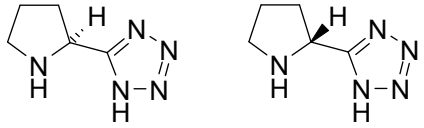


Scheme 112. Preparation of oganocatalysts based on pyrrolidine-tetrazole skeleton. *a*) Et_2AlN_3, xylene, 50 °C, 9 h; *b,i*) Pd/C (10 % wt), H_2, EtOH, r.t., 4 h; *c*) 2 equiv Et_2AlN_3, xylene, 55 °C, 9 h, then 85 °C, 9 h; *d*) α-methylstyrene, TFA, CH_2Cl_2, r.t., 3d; e) *t*-BuOH, H_2SO_4, TFA, CH_2Cl_2, r.t., 8 h; *f,h*) *i*-PrI, K_2CO_3, MeCN, r.t., 3d; *g*) Pd/C (10 % wt), H_2, EtOH, r.t., 7 h

3.2.1. Synthesis of a Novel Class of Organocatalysts

3.2.1.1. Synthesis of 5-pyrrolidine-2yl-tetrazole

5-Pyrrolidine-2yl-tetrazole represents a new proline-derived organocatalyst that was developed recently by ourself [142] and others [155,225,226]. Both the *S*- and the *R*-enantiomers may be prepared (Figure 46).

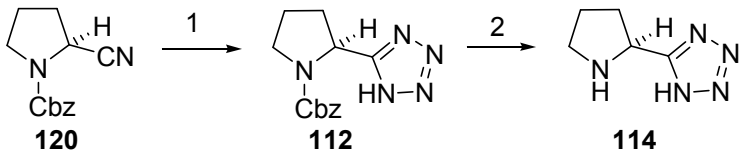


114 **115**

Figure 46. Structure of (*S*)-**114** and (*R*)-5-pyrrolidine-2yl-tetrazole **115**

The utility of this catalyst has been demonstrated in several types of reactions including Mannich and aldol reactions, and Michael additions (Section 3.1.3.1).

However, all the methods for the preparation of **114** and **115** suffer from some disadvantages in the tetrazole-forming step. The general methods to convert the nitrile into the corresponding pyrrolidine-tetrazole use ammonium azide [155,225,226] or triethylammonium azide [237] as azide sources which can form dangerous sublimates onto the side of the reaction vessel (Section 1.1.3.1.2.1.). Furthermore, the reported hydrogenation for the final cleavage of the Cbz-group requires the use of 9:1 acetic acid-water mixture under a hydrogen atmosphere (Scheme 113, Table 18).



120 **112** **114**

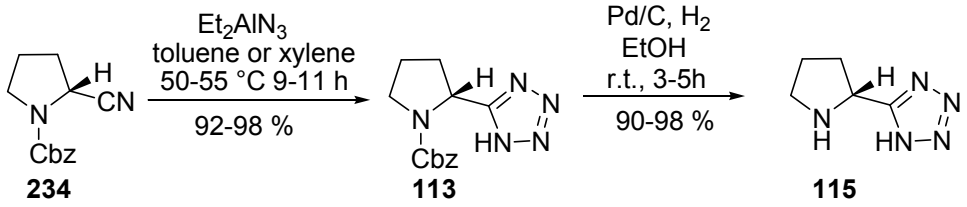
Scheme 113. General sequence for the preparation of (*S*)-5-(pyrrolidine-2-yl)-tetrazole **114** from the corresponding Cbz-protected nitrile **120**

STEP 1 Author	Reagent	Solvent	Time [h]	T [°C]	Yield
Sharpless [238]	NaN_3, $ZnBr_2$	H_2O/*i*-PrOH	16	reflux	91
Almquist [239]	NaN_3, NH_4Cl	DMF	6	90-95	100
Yamamoto [155]	NaN_3, NH_4Cl	DMF	6	95	95
Ley [225,229]	NaN_3, NH_4Cl	DMF	8	90-95	78
Ley [237]	NaN_3, $Et_3N{\cdot}HCl$	Toluene	24	95	95
Arvidsson [226]	NaN_3, $ZnBr_2$	H_2O/*i*-PrOH	16	reflux	98
Sedelmeier, Aureggi [142]	R_2AlN_3 (R=Me, Et)	Toluene or xylene	6-9	50	90-96

STEP 2 Author	Reagent	Solvent	Time [h]	T [°C]	Yield
Almquist [239]	H_2, Pd/C 10 %	AcOH/H_2O 9:1	4	r.t.	68
Yamamoto [155]	H_2, Pd/C 10 %	AcOH/H_2O 9:1	4	r.t.	95
Ley [229]	H_2, Pd/C 10 %	AcOH/H_2O 9:1	4	r.t.	89
Ley [237]	H_2, Pd/C 10 %	AcOH/H_2O/EtOH 1:1:1	-	-	98
Arvidsson [226]	H_2, Pd/C 10 %	No conditions			No yield given
Sedelmeier, Aureggi [142]	H_2, Pd/C 10 %	EtOH	4	r.t.	90-96

Table 18. Reported reaction conditions for the preparation of (*S*)-5-(pyrrolidine-2-yl)-tetrazole **114** from the corresponding Cbz-protected nitrile

For the first time we report a mild reaction conditions sequence which provides the desired tetrazoles **114** and **115** in high yield and high reproducibility proved from the fact that this sequence was also scaled-up in 1.5 kg for the preparation of the *R*-enantiomer (Scheme 114).



Scheme 114. Sequence for the synthesis of (*R*)-5-(pyrrolidine-2-yl)-tetrazole **115** from the corresponding Cbz-protected nitrile **234**

The formation of the tetrazole ring proceeds well under mild conditions. Using 2.4 equivalents of Et_2AlN_3 in toluene at room temperature, the reaction requires longer time to reach completion. However, under these condition, after 2 hours the reaction conversion observed by HPLC was 46 % and after 4 hours already 94 %. However, to

achieve total conversion (> 98% based on HPLC) the reaction requires 48 hours. Decreasing the amount of azide to 1.5 or 1.3 equivalents does not decrease the rate.

At 50 °C after only 2 hours, 95 % of reaction conversion was observed by HPLC, however the reaction reached total conversion after 9-12 hours. Dimethylaluminum azide (1M in hexane) was tested as an alternative to diethylaluminum azide, but the reaction requires 24 hours to reach completion probably because of the lower concentration of the reagent. The (*R*)- and the (*S*)-enantiomers of the starting nitrile, provide the corresponding tetrazole with the same yield.

The Cbz group is removed by hydrogenation using 10 % wt Pd/C in ethanol for 3 to 5 hours at room temperature. We have found that ethanol could be a more appropriate solvent [205] compared to the acetic acid-water system previously described by other groups [282a,293,301]. Once that the hydrogenation is completed, the catalyst is removed by filtration through celite and acetic acid and water should be used to remove trace of product on the celite layer. The filtrate is concentrated and the (*R*)-5-(pyrrolidine-2-yl)-tetrazole is crystallized from a solution of aqueous acetic acid/ ethanol. X-ray analysis of the product shows that (*R*)-5-(pyrrolidine-2-yl)-tetrazole exists as a zwitterionic form in the solid state (Figure 47) (See X-ray discussion; Chapter 4)

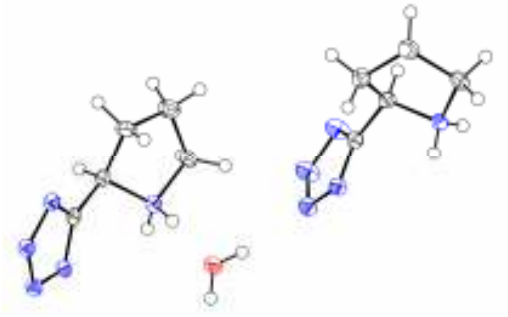
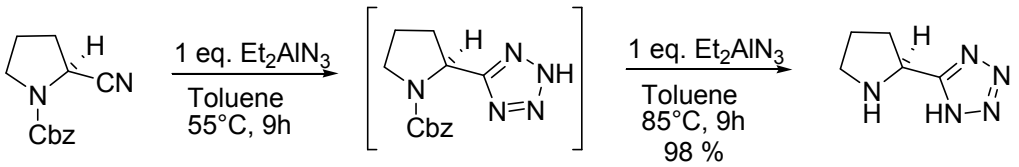


Figure 47. Structure of *(R)*-5-pyrrolidine-2-yl-tetrazole **115** in the crystal with thermal ellipsoids drawn at 50 % probability level

3.2.1.1.1. One-pot procedure for the synthesis of 5-pyrrolidine-2yl-tetrazole

We observed that the Cbz protecting group can be removed with the diethylaluminum azide at temperature higher that 65 °C. The pyrrolidine tetrazole **114** and **115** can be directly obtained in one-pot [142] by warming the reaction mixture at more than 65 °C with an excess of dialkylaluminum azide to provide first the cycloaddition and then the cleavage reaction (Scheme 115). Although purity of the 5-pyrrolidine-2-yl-tetrazole obtained with the one-pot procedure is high according to NMR, broad peaks by IR and low optical rotation value may suggests the presence of some water soluble inorganic materials that are difficult to remove.

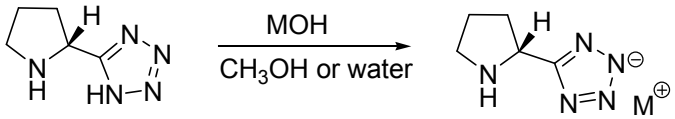


120 **112** **114**

Scheme 115. One-pot reaction for the preparation of 5-pyrrolidine-2-yl-tetrazole **114**

3.2.1.1.2. Preparation of pyrrolidine tetrazole metal salts

Neutralization of tetrazolic acid with metal hydroxide or analogues gives stable metal tetrazolate salts (Section 1.1.1.2.) [142]. Sodium, potassium and cesium salts of the (*R*)-5-pyrrolidine-2-yl-tetrazole are prepared mixing **115** with equimolar amounts of metal hydroxide in methanol or water at room temperature. Evaporation of the solvent leads the desired salt in quantitative yield (Scheme 116).

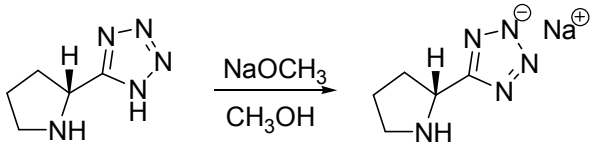


115

239: M = Na^+
240: M = K^+
241: M = Cs^+

Scheme 116. Preparation of pyrrolidine tetrazole metal salts **239**-**241**

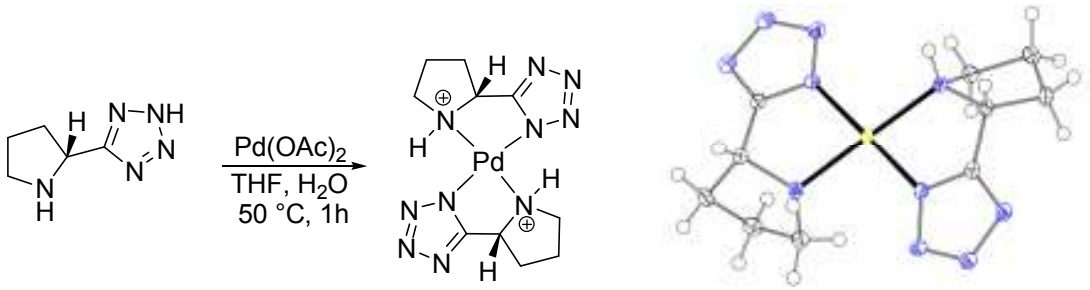
The (*R*)-5-pyrrolidine-2-yl-tetrazole sodium salt **239** can be also quantitatively prepared using sodium methanolate in methanol at room temperature (Scheme 117).



115 **239**

Scheme 117. Preparation of (*R*)-5-pyrrolidine-2-yl-tetrazole sodium salt **239**

The (*R*)-5-pyrrolidine-2-yl-tetrazole palladium (II) complex **242** is prepared in aqueous THF with palladium acetate (0.5 equivalents) at 50 °C (Scheme 118). The product crystallizes in quantitative yield after standing at room temperature for two hours to give a white crystalline material suitable for X-ray analysis (See X-ray discussion; Chapter 4).



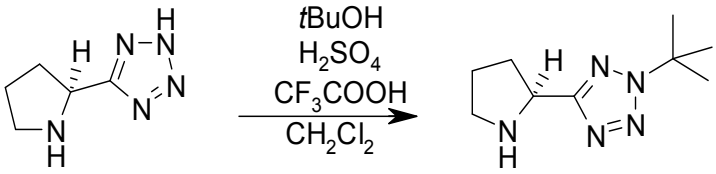
115 **242**

Scheme 118. Preparation and structure of (*R*)-5-pyrrolidine-2-yl-tetrazole palladium(II) complex **242** in the crystal (thermal ellipsoids drawn at 50 % probability level)

3.2.1.2. Synthesis of *N*-alkylated pyrrolidine tetrazoles

3.2.1.2.1. Synthesis of 2-*tert*-butyl-5-pyrrolidine-2-yl-2*H*-tetrazole (237, 243)

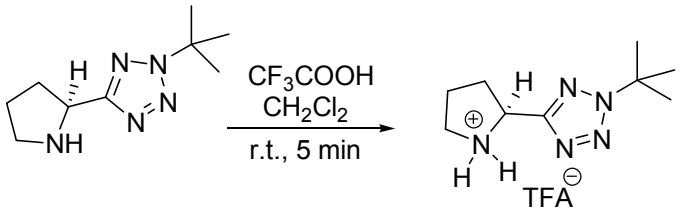
Both the pure enantiomeric forms of the 2-*tert*-butyl-5-pyrrolidine-2-yl-2*H*-tetrazole, **237** and **243**, are efficiently prepared in sulfuric acidic media with *tert*-butanol[142]. According to published data [98,174,175], the 2*N*-alkyl isomer is the only regioisomer obtained [98,142,176] (Section 2.1.). We believe that regioselectivity is due to the steric bulk of the alkylating agent. The reaction proceeds at room temperature in the presence of trifluoroacetic acid (ten folds excess), sulfuric acid and two equivalents of *tert*-butanol (Scheme 121). Basic extraction with dichloromethane and aqueous potassium carbonate or sodium hydroxide provides the free-base product as a brown oil.



114 **243**

Scheme 119. Preparation of 2-*tert*-butyl-5-pyrrolidine-2-yl-2*H*-tetrazole **243**

Brown crystals of (*R*)-2-(2-*tert*-butyl-2*H*-tetrazol-5-yl) pyrrolidinium trifluoro acetate **244** suitable for X-ray analysis are obtained by treating the free base with trifloro acetic acid in dichloromethane (Scheme 120, Figure 48) (See X-ray discussion; Chapter 4).



243 **244**

Scheme 120. Preparation of (*S*)-2-(2-*tert*-butyl-2*H*-tetrazol-5-yl) pyrrolidinium trifluoro acetate **244**

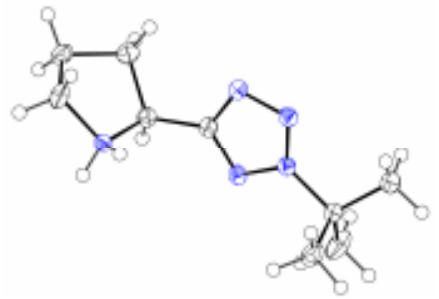
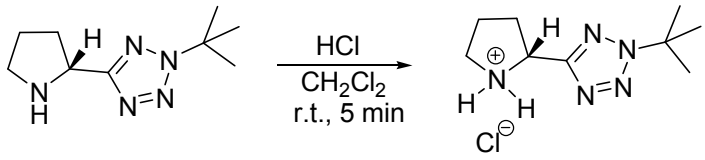


Figure 48. Structure of *(S)*-2-(2-*tert*-butyl-2*H*-tetrazol-5-yl) pyrrolidinium trifluoro acetate in the crystal with thermal ellipsoids drawn at 50 % probability level

2-*tert*-Butyl-5-pyrrolidine-2-yl-2*H*-tetrazole treated with equimolar amount of HCl in dichloromethane leads, after evaporation of the solvent, to the (*R*)-2-(2-*tert*-butyl-2*H*-tetrazol-5-yl) pyrrolidinium chloride **245** as a pink crystalline material (Scheme 121).

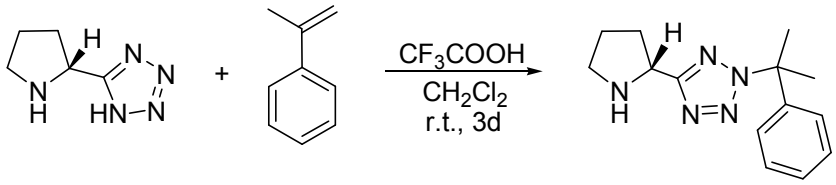


236 **245**

Scheme 121. Preparation of (*R*)-2-(2-*tert*-butyl-2*H*-tetrazol-5-yl) pyrrolidinium chloride **245**

3.2.1.2.2. Synthesis of 2-(1-methyl-1-phenyl-ethyl)5-*(R)*-pyrrolidine-2-yl-2*H*-tetrazole (235)

2-(1-Methyl-1-phenyl-ethyl)5-(*R*)-pyrrolidine-2-yl-2*H*-tetrazole **235** is efficiently prepared under acidic conditions (Scheme 122)[142]. Pyrrolidine-tetrazole **115** is first dissolved at room temperature in trifluoroacetic acid and dichloromethane, then treated with α-methylstyrene and stirred for three days. A basic extraction with aqueous sodium hydroxide neutralizes the excess of trifluoroacetic acid. The organic solvent is removed to afford a colorless oil which crystallizes upon standing at room temperature. Colorless single crystals suitable for X-ray analyses are obtained (Figure 45) by slow evaporation of a mixture of methanol / ethyl acetate (See X-ray discussion; Chapter 4).



115 **246** **235**

Scheme 122. Synthesis of 2-(1-methyl-1-phenyl-ethyl)-5-*(R)*-pyrrolidine-2-yl-2*H*-tetrazole **235**

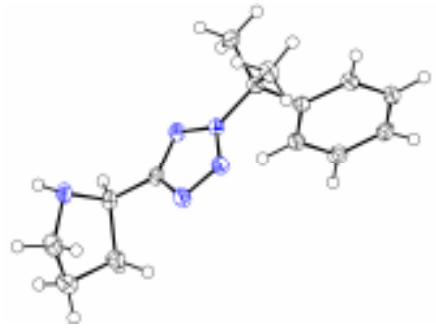
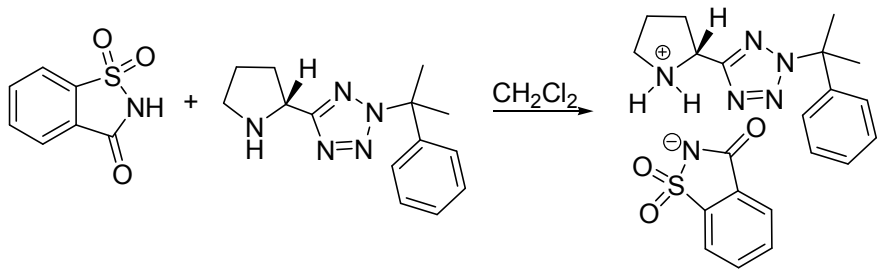


Figure 49. Structure of 2-(1-methyl-1-phenyl-ethyl)-5-*(R)*-pyrrolidine-2-yl-2*H*-tetrazole **235** in the crystal with thermal ellipsoids drawn at 50 % probability level

Colorless crystals of 2-[(1-methyl-1-phenyl-ethyl)-2*H*-tetrazol-5-yl] pyrrolidinium saccharinate **248** are obtained by mixing equimolar amount of **235** with *o*-benzoic acid sulfimide in dichloromethane (Scheme 123)[142]. Single crystals suitable for X-ray analysis are obtained by slow evaporation of the solvent (Figure 50) (See X-ray discussion; Chapter 4).



247 **235** **248**

Scheme 123. Preparation of 2-[(1-methyl-1-phenyl-ethyl)-2*H*-tetrazol-5-yl] pyrrolidinium saccharinate **248**

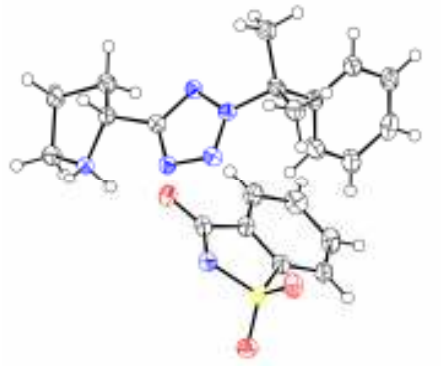
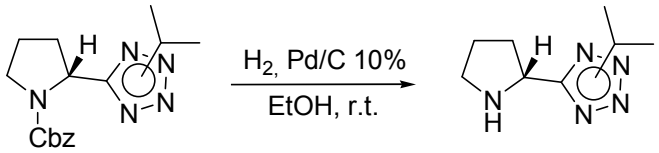


Figure 50. Structure of 2-[(1-methyl-1-phenyl-ethyl)-2*H*-tetrazol-5-yl] pyrrolidinium saccharinate **248** in the crystal with thermal ellipsoids drawn at 50 % probability level

3.2.1.2.3. Isopropyl-5-(*R*)-pyrrolidine-2-yl-tetrazole (237, 238)

The two regioisomers of the (*R*)-(isopropyl-tetrazol-5-yl)-pyrrolidine-1-carboxylic acid benzyl ester **237** and **238** are efficiently hydrogenated to provide the cleavage of the Cbz protecting group in ethanol at room temperature for 4 to 7 hours (Scheme 124) [142].



N1-isomer: **162**
N2-isomer: **161**

N2-isomer: **237**
N1-isomer: **238**

Product	Time [h]	Yield [%]
237	7	88
238	4	98

Scheme 124. Preparation of isopropyl-5-(*R*)-pyrrolidine-2-yl-tetrazole **237** and **238**

Yellow single crystals of the 1N-isomer **237** suitable for X-ray analysis are obtained by slow evaporation of a mixture of ethanol / dichloromethane (Figure 51; See X-ray discussion; Chapter 4).

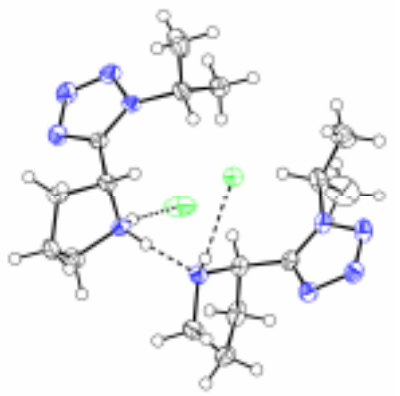
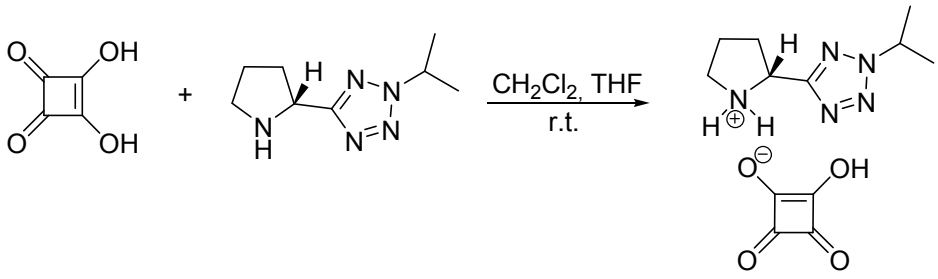


Figure 51. Structure of 1-isopropyl-5-(*R*)-pyrrolidine-2-yl-1*H*-tetrazole **237** in the crystal with thermal ellipsoids drawn at 50 % probability level

Brown single crystals of 2-isopropyl-5-(*R*)-pyrrolidine-2-yl-2*H*-tetrazole squaric acid salt **250** suitable for X-ray analysis are obtained by slow evaporation of a solution of dichloromethane / THF containing equimolar amounts of 3,4-dihydroxy-3-cyclobutene-1,2-dione and **238** (Scheme 125, Figure 52; See X-ray discussion; Chapter 4).



249 **238** **250**

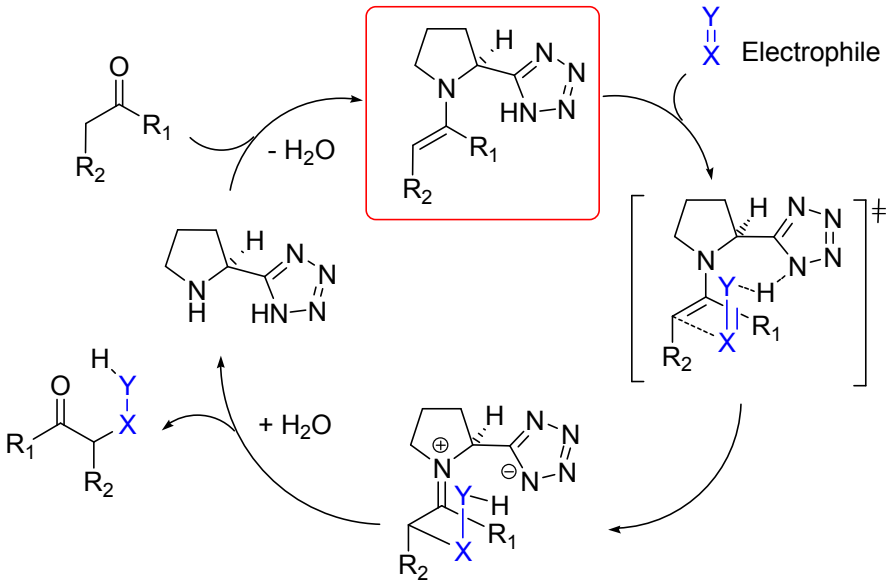
Scheme 125. Preparation of 2-isopropyl-5-*(R)*-pyrrolidine-2-yl-2*H*-tetrazole-squaric acid salt **250**

Figure 52. Structure of 2-isopropyl-5-*(R)*-pyrrolidine-2-yl-2*H*-tetrazole-squaric acid salt **250** in the crystal with thermal ellipsoids drawn at 50 % probability level.

3.2.2. Enamine

There is agreement in the scientific community that the proline- and analogues-mediated reactions of aldehydes and ketones with electrophiles involves an intermediate enamine. The proline-based organocatalyzed Michael addition of aldehyde to nitro olefins very likely proceeds *via* an enamine mechanism with amine-based organocatalysts[240]. Despite the increasing interest on organocatalysis confirmed by the increasing number of publications during the last years, there are not really evidences of the enamine intermediate in the catalytic cycle (Scheme 126).

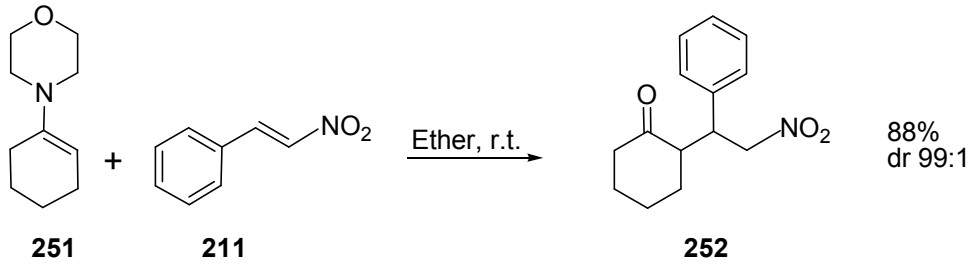
During the course of our studies, we have detected, characterized with spectroscopic analysis and, in some cases, isolated a variety of enamine derived from the condensation of aldehydes with the 5-pyrrolidine-2yl-tetrazole and its corresponding *N*-alkylated derivatives.



Scheme 126. Enamine catalytic cycle of the pyrrolidine-tetrazole mediated reactions

3.2.2.1. Introduction

Seebach *et al.* reported the diastereoselective Michael-addition of (*E*)-enamines to (*E*)-nitro olefins [241]. The reaction of nitrostyrene **211** with enamines pre-formed from ketones and morpholine leads to γ-nitroketones possessing diastereomeric purities of 90-99 % (Scheme 127). The Michael addition occurs with the (*Re*Re**)-approach of the two components in the Newman projection with a *gauche*-relationship of the donor and the acceptor π-system in the Michael addition (Figure 53).



Scheme 127. Diastereoselective Michael addition of enamine to nitrostyrene

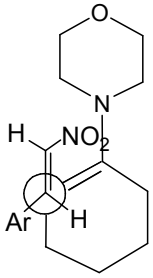
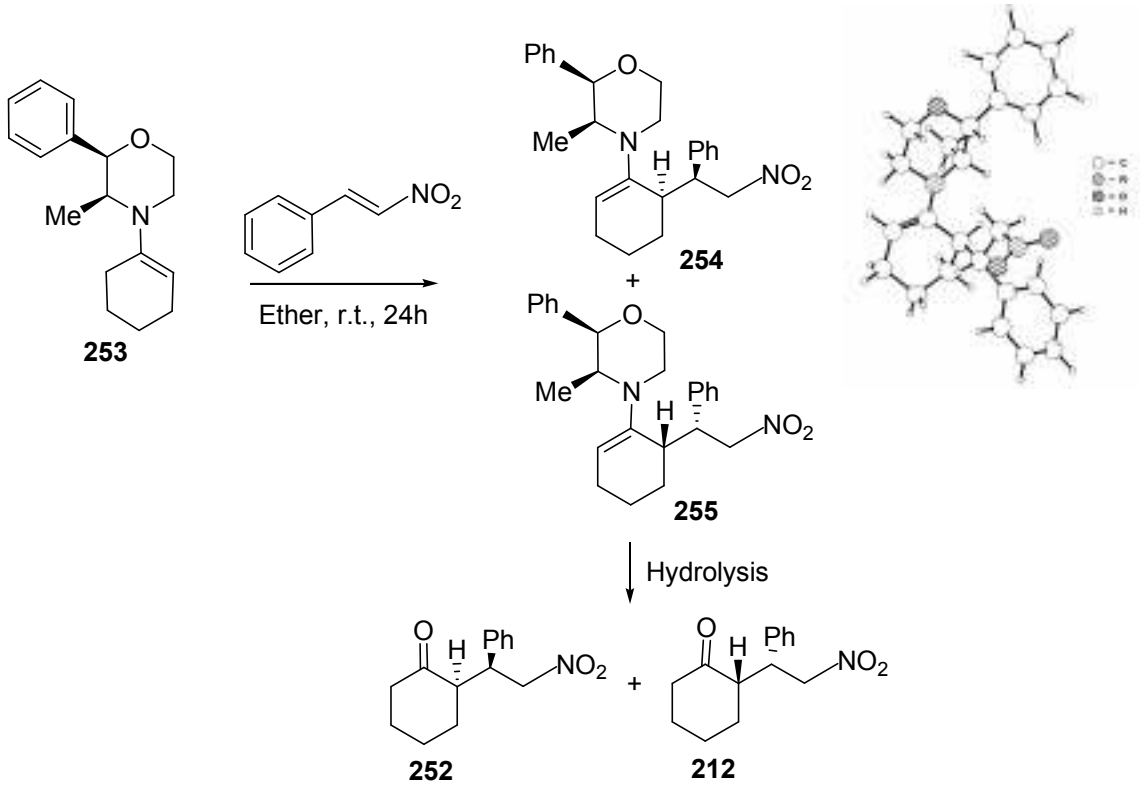


Figure 53. (*Re*Re**)-Approach

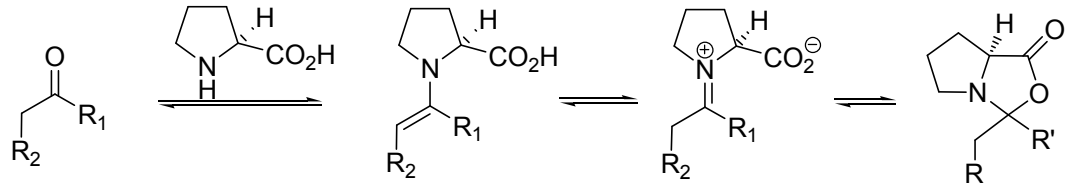
They also reported the chiral version of this Michael reaction pre-forming the enamine with a chiral morfoline and cyclohexanone, and treating it with nitrostyrene [242]. The X-ray structure of the resulting enamine intermediate was solved (Scheme 128).



Scheme 128. Asymmetric Michael addition and X-ray structure of the enamine-Michael-intermediate [305]

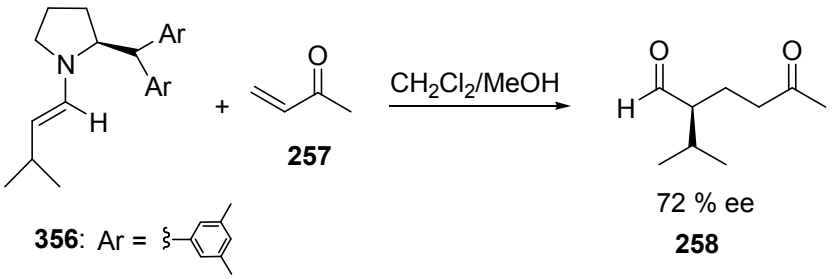
Seebach *et al.* recently reported the role of the equilibrium between the enamine intermediate and the oxazolidinone form in the catalytic cycle of the proline-catalyzed

Michael additions (Scheme 129), in which each species involved in the catalytic cycle are characterized by spectroscopic studies [243].



Scheme 129. Equilibrium between the enamine and oxazolidinone

Barbas *et al.* reported the detection of enamine formation through UV spectroscopy [214,218a,c], and Alexakis *et al.* reported the detection of an enamine intermediate by GC-MS [244]. Jørgensen *et al.* reported the reaction between a chiral pre-formed enamine with methyl vinyl ketone [211] to give the desired product with 72 % ee (Scheme 130).



Scheme 130. Michael addition of pre-formed enamine with methyl vinyl ketone

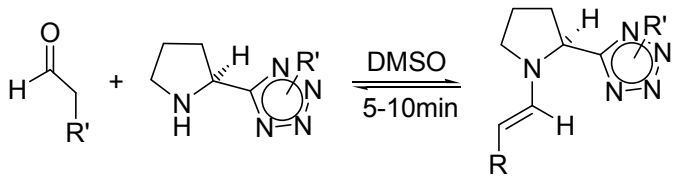
3.2.2.2. Enamine formation

We have tested our new catalysts in Michael addition of carbonyl compounds with nitrostyrene (Section 3.2.3.). The high *syn* selectivity we observed is in accordance with results obtained in conjugate additions of preformed enamines to nitro olefins mentioned above. Key feature of these catalysts are the presence of the secondary amine required for enamine formation. Further studies are needed to elucidate the mechanism of these Michael additions, which very likely proceed *via* an enamine mechanism.

Herein we report an enamine formation study between an aldehyde and our new class of organocatalysts based on pyrrolidine-tetrazole skeleton.

The enamine formation between a selection of aldehydes and ours pyrrolidine-tetrazole organocatysts is proven by spectroscopic studies (Scheme 131, Table 19). In a general procedure, equimolar amounts of aldehyde and catalyst are dissolved in d_6-DMSO. Signals corresponding to the enamine structure were detected in all the cases. ^{1}H NMR

spectra in d_6-DMSO revealed in all the cases a characteristic signal at δ 6.0-6.4 ppm with a coupling constant of *ca* 13.8 Hz (*doublet* or *singlet* depending on the starting aldehyde) attributed to the vinylic proton α to the nitrogen (hydrogen of the former aldehyde). The second characteristic signal of the enamine is the hydrogen at δ 4.0-4.9 ppm (^3J = 13.8 Hz) which corresponds to the β-vinylic proton.



Scheme 131. Equilibrium of the enamine formation [245]

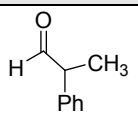
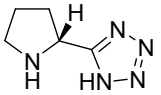
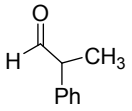
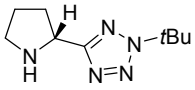
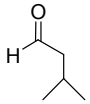
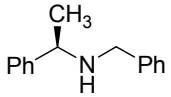
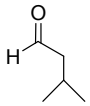
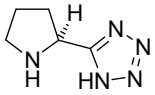
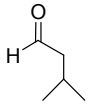
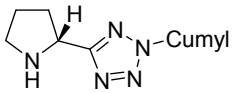
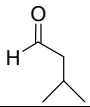
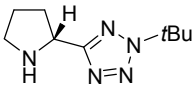
Entry	Aldehyde	Chiral Amine	Product	Enamine formation [%]	E/Z
1			**259**	90	75:25
2			**260**	98	84:16
3			**261**	23	
4			**262**	70	>99:1
5			**263**	>99	>99:1
6			**264**	>99	>99:1

Table 19. Enamine conversion based on ^{1}H NMR analysis

Based on NMR analysis, 5-{1-[-2-phenylprop-1-en-1-yl]-pyrrolidine-2-yl}-tetrazole **259** is formed after 5 minutes at room temperature with a conversion of 90 % (Table 19; entry 1). The *E*-enamine is the major product with a ratio *E* and *Z*-enamine of 75 to 25 (Figure 54). Using the 2-*tert*-butyl-5-pyrrolidine-2-yl-2*H*-tetrazole the equilibrium is almost shifted to the enamine (98 % conversion) with a ratio *E* and *Z*-enamine of 84 to 16 (Table 19; entry 2).

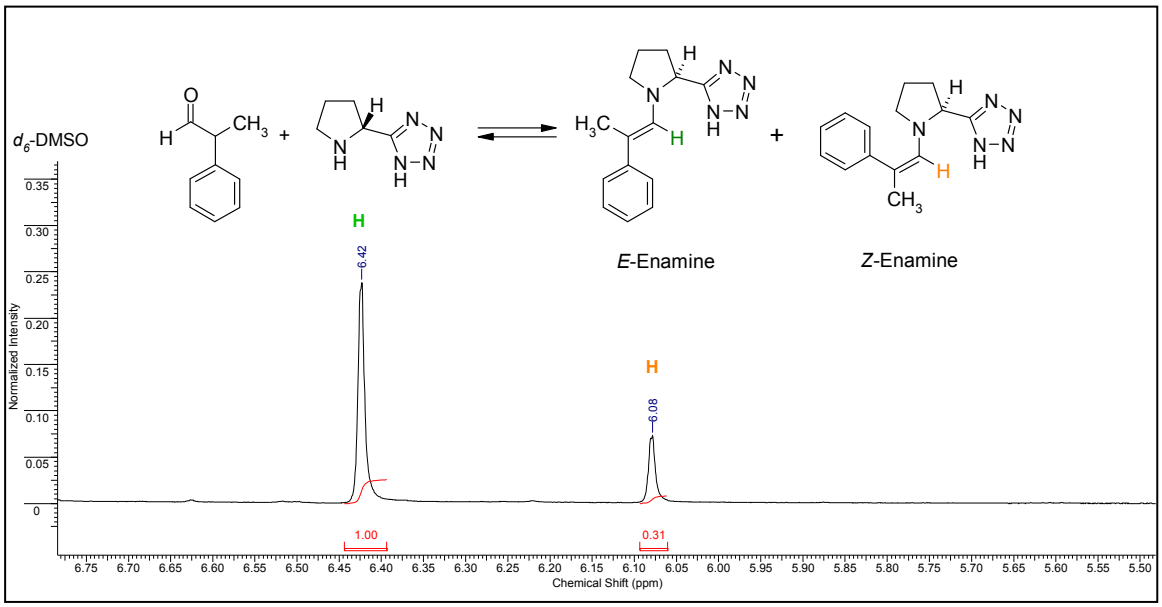


Figure 54. ^{1}H NMR signal of the enamine **259**

Using the (*R*)-(+)-*N*-benzyl-α-methylbenzylamine as chiral amine, only 23 % of enamine was detected by ^{1}H NMR analysis (Table 19; entry 3). Equimolecular amounts of isovaleraldehyde and (*S*)-5-pyrrolidine-2-yl-tetrazole **114** forms 67-70 % of *E*-enamine formation (Figure 55; Table 19; entry 4). The same experiment using S-proline revealed signals which can be attributed to those characteristic of enamines with a δ 3.99 (*dd*, ^{3}J = 13.8 Hz, 1H) and a δ 6.04 (*d*, ^{3}J = 13.8 Hz, 1H) (Figure 56; Table 19; entry 5).

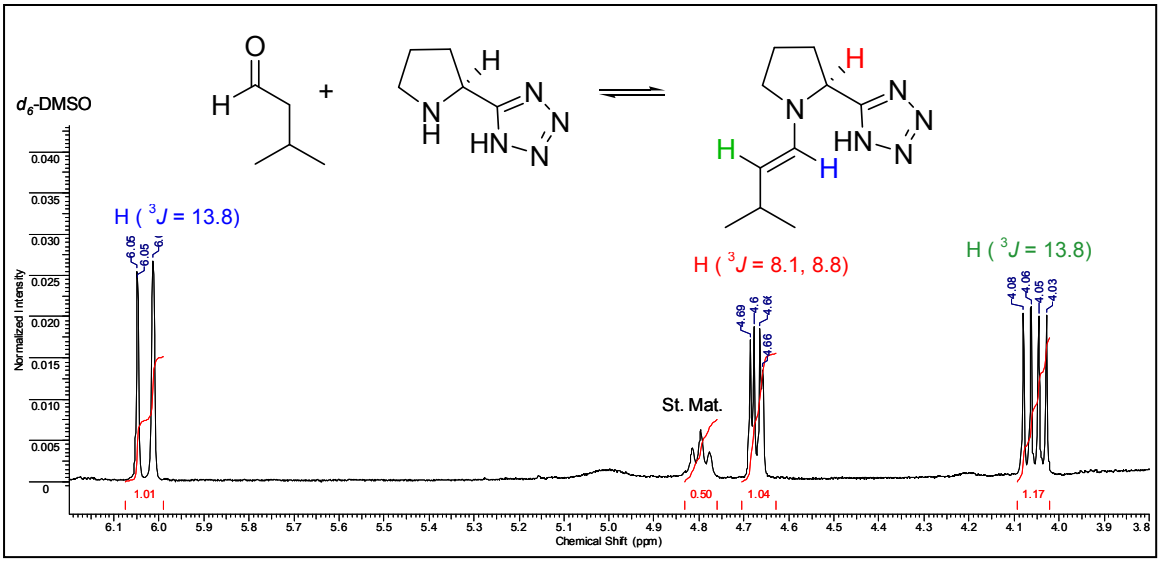


Figure 55. Enamine formation between isovaleraldehyde and (*S*)-5-pyrrolidine-2-yl-tetrazole **114**

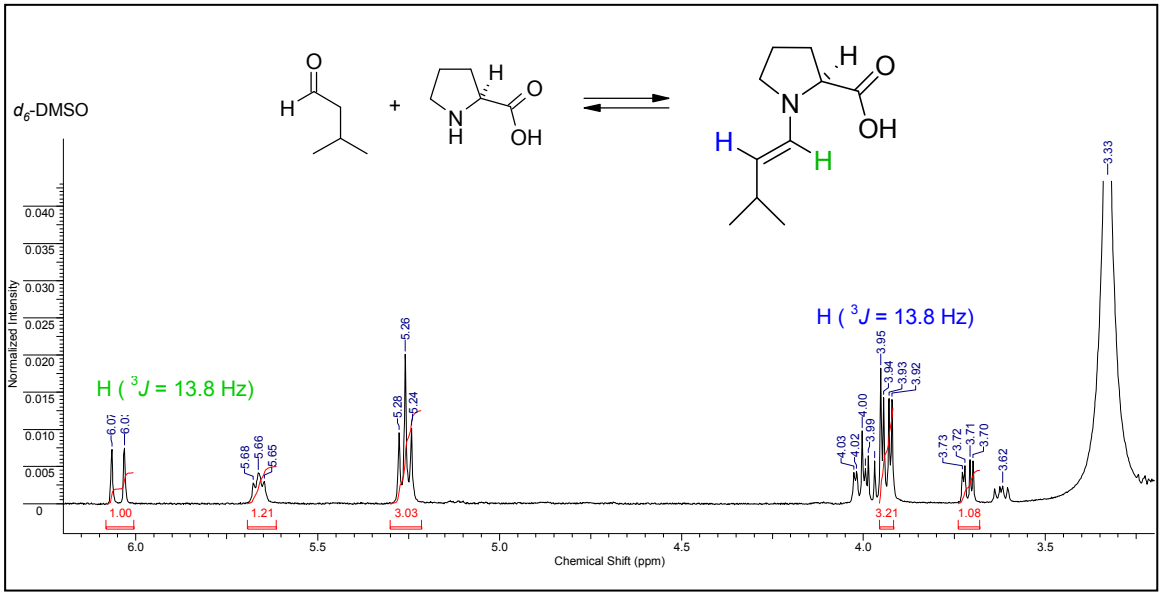
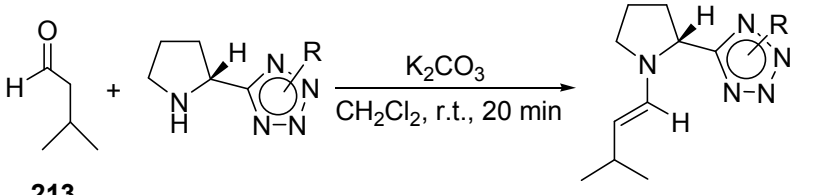


Figure 56. Reaction between isovaleraldehyde and S-proline. Characteristic signals of enamine formation

Using *N*-alkylated pyrrolidine tetrazoles (Table 19; entries 5, 6) as chiral amines with isovaleraldehyde, the equilibrium is shifted to the enamine formation and the signals of the stating amine and aldehyde are disappear. The same NMR experiment performed in $CDCl_3$ reveals a conversion of 90-94 %. This difference can be explained by the presence of hydrochloric acid in the solvent which could hydrolyze partially the enamine formed.

Enamine derived from the condensation of isovaleraldehyde (1.6 equivalents) and *N*-alkylated-tetrazoles can be isolated and characterized (For examples see Figures 57, 58). The reaction is carried out in dichloromethane with an excess of solid potassium carbonate to catch the water formed during the condensation to the enamine. The mixture is stirred at room temperature for twenty minutes, the potassium carbonate is filtered, the solvent and excess of isovaleraldehyde removed to give the product as a colorless oil in quantitative yield (Scheme 132). The enamines formed are characterized by spectroscopy (NMR, IR, MS; for more details see experimental part; Section 5.3.).



213

235: R = 2*N*-Cumyl
236: R = 2*N*-*t*-Bu
237: R = 1*N*-*i*-Pr
238: R = 2*N*-*i*-Pr

263: R = 2*N*-Cumyl
264: R = 2*N*-*t*-Bu
265: R = 1*N*-*i*-Pr
266: R = 2*N*-*i*-Pr

Scheme 132. Preparation of enamines

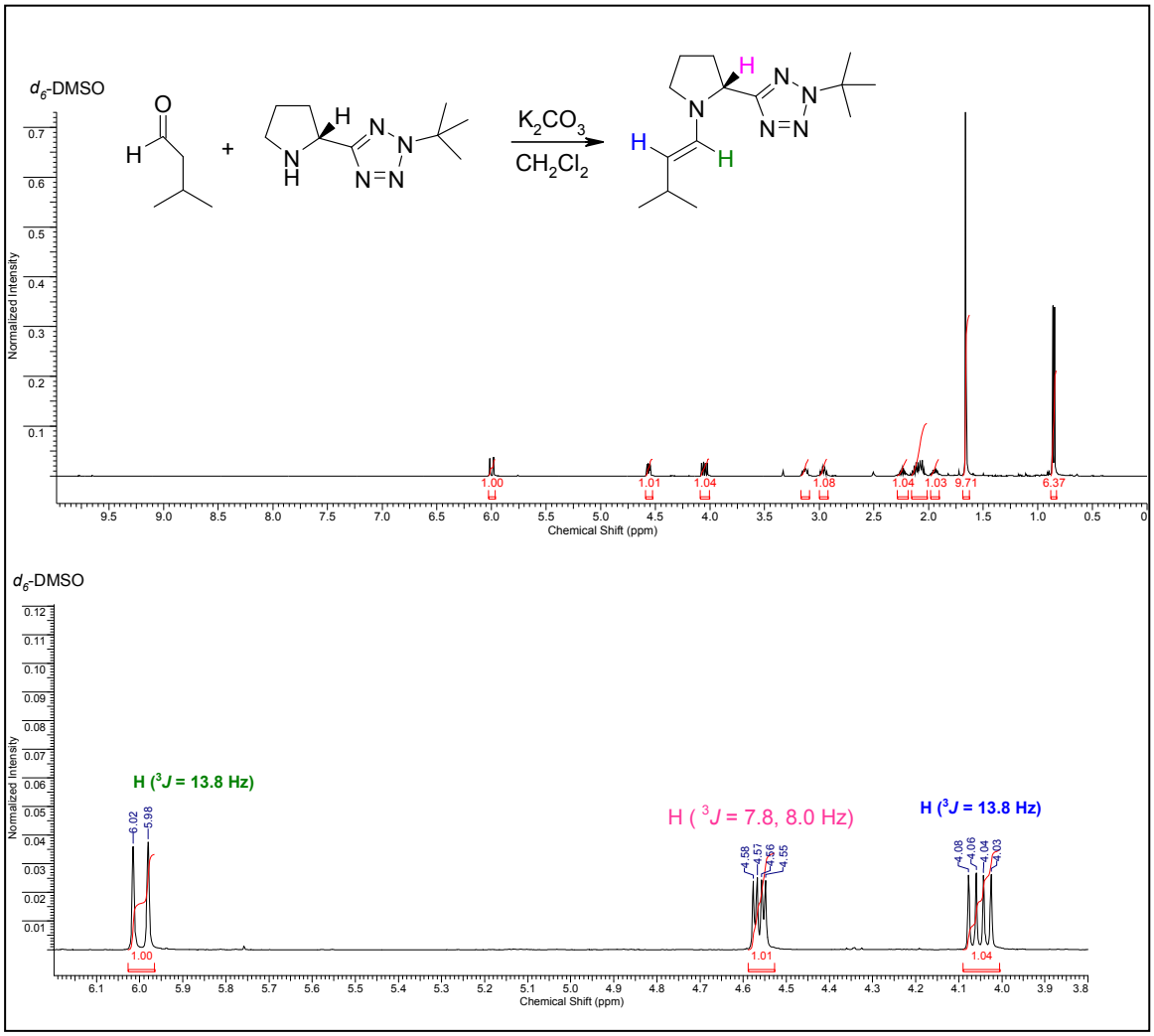


Figure 57. ^{1}H NMR spectrum of the enamine **264** formed from the condensation between isovaleraldehyde and 2-*tert*-butyl-5-(*R*)-pyrrolidine-2-yl-2*H*-tetrazole **236** (For more details see the experimental part; Section 5.3.)

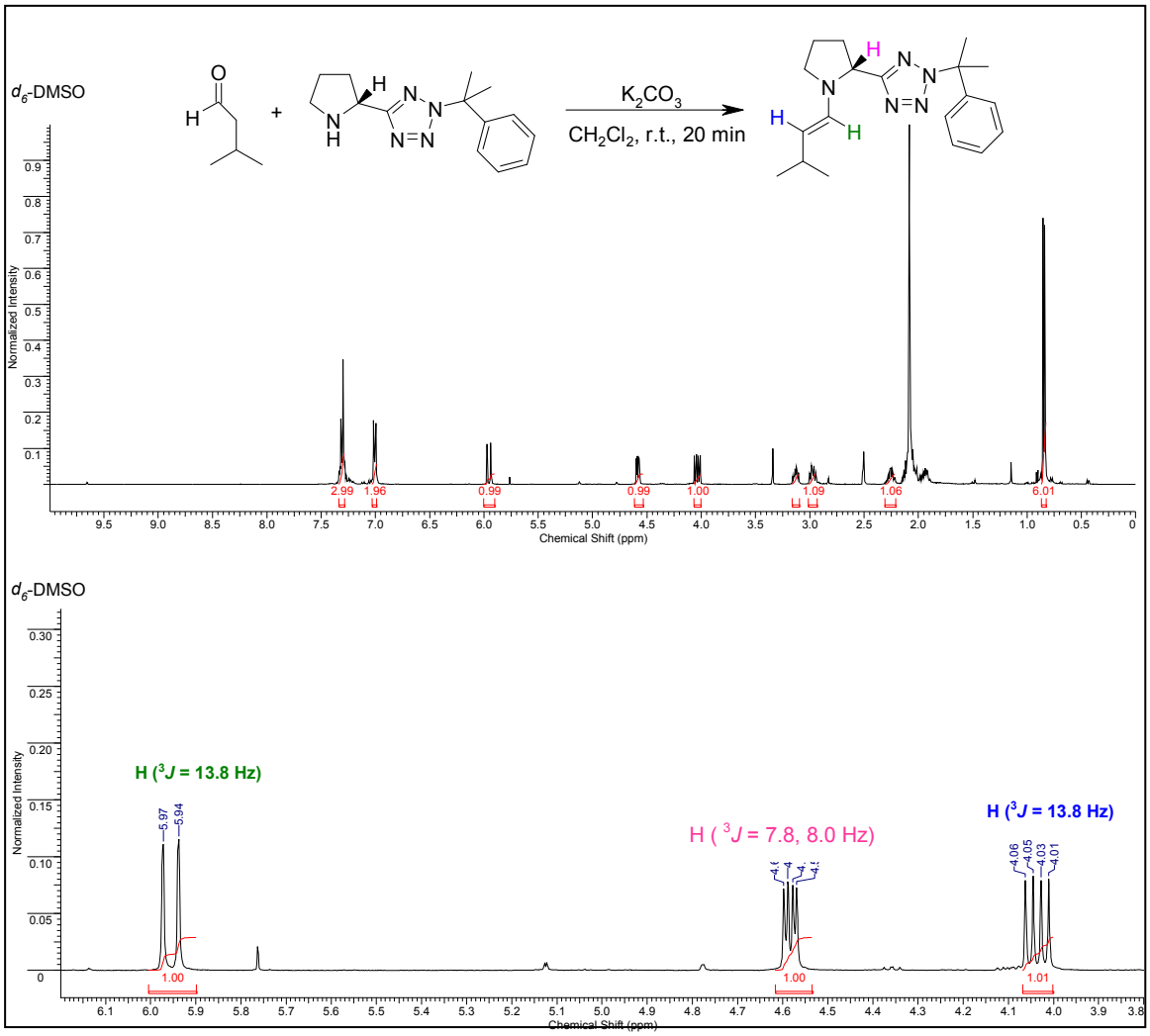


Figure 58. ^{1}H NMR spectrum of the enamine **263** formed from the condensation between isovaleraldehyde and 2-(1-methyl-1-phenyl-ethyl)5-(*R*)-pyrrolidine-2-yl-2*H*-tetrazole **235** (For more details see the experimental part; Section 5.3.)

3.2.2.3. Oxazolines formation

The treatment of α,α-diphenylprolinol with isolvaleraldehyde in dichloromethane in the presence of potassium carbonate provides to a bicyclic oxazoline compound **345** (Figure 59). Netherless, the use of cyclohexanone under the same reaction conditions does not yield the corresponding oxazoline derivative.

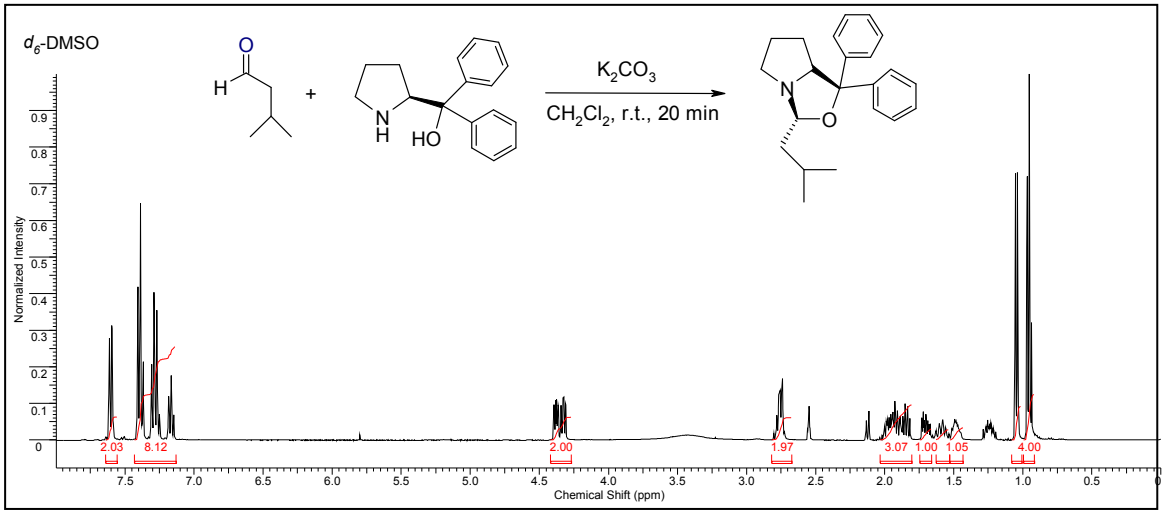


Figure 59. (3*R*,4*S*)-3-Isobutyl-1,1-diphenyl-tetrahydro-pyrrolo [1,2-c]oxazole **267** (For more details see the experimental part; Section 5.3.)

3.2.3. Michael Addition

Asymmetric C-C bond forming reactions are among the most challenging endeavors in organic synthesis. The Michael reaction is generally regarded as one of the efficient and effective transformations and studies concerning this reaction have played an important role in the development of modern organic chemistry [246].

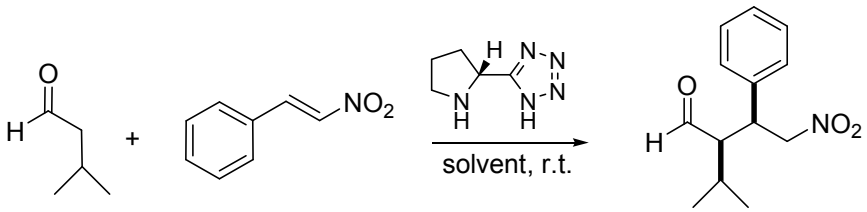
In organocatalysis, the most common feature of this reaction is the use of unmodified nucleophilic donors that, upon activation by intermediate enamine formation, add stereoselectively to the corresponding acceptor electrophiles under very mild conditions.

Proline was one of the first to be studied and it successfully catalyzed the reaction both in DMSO and alcoholic solvents. However, in most cases reported the enatioselectvities obtaine are relativly low (See Section 3.1.).

In order to test the efficacy of our new pyrrolidine-tetrazole based catalysts, the Michael addition of a carbonyl with nitrostyrene was selected.

3.2.3.1. Michael addition of isovaleraldehyde and nitrostyrene

The organocatylized Michael additions of isovaleraldehyde with nitrostyrene were screened at room temperature in different solvents and catalytic amounts of (*R*)-(tetrazol-5-yl)-pyrrolidine **115** (Table 20). The amounts of catalyst plays a role in the rate of the reaction and the best results are performed in general with 20 mol % of catalyst. The reaction proceeds smoothly in dichloromethane (Table 20; entries 4-7). Different amounts of catalyst do not influence the enantioselectivity, while slightly influence the diastereoselectivity which is higher with 20-40 mol % of catalyst. Good diastereoselectivity are obtained also in ethanol or acetonitrile (Table 20; entries 1-3, 9-10), although the enatioselectivity is lower. In ionic liquids the reaction is faster, but less selective (Table 20; entries 11-16).

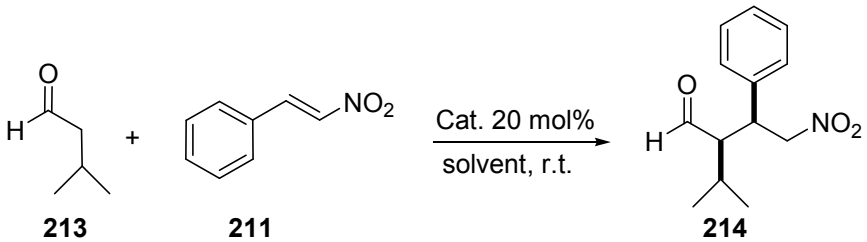


213 **211** **214**

Entry	Solvent	Cat [mol%]	Time [h]	Conversion[a] [%]	dr[b] [syn/anti]	ee [c] [%]syn
1	CH_3CN	5	43	36	13:1	30
2		10	23	>95	17:1	30
3		20	19	>95	19:1	31
4	CH_2Cl_2	5	47	57	14:1	49
5		10	30	>95	15:1	52
6		20	20	>98	19:1	56
7		40	20	>98	19:1	55
8	EtOH	10	28	93	17:1	24
9		20	20	>99	17:1	28
10		40	5	>95	25:2	19
11	$BumiPF_6$	5	24	>95	12:1	31
12		10	18	>95	12:1	31
13		20	5	>95	12:1	32
14	$EtmiBF_6$	5	15	>99	18:1	20
15		10	4	>99	18:1	29
16		20	3	>99	18:1	24

Table 20. Michael addition of isovaleraldehyde and nitrostyrene. [a] based on HPLC analysis of the reaction mixture; [b] based on HPLC analysis of the crude product; [c] based on chiral HPLC of the crude product

A selection of catalysts was tested at room temperature (Scheme 133; Table 23). The S-proline catalyzes the reaction in a shorter time compare to (*R*)-(tetrazol-5-yl)-pyrrolidine **115** (Table 21; entries 1-3; 6-8), while the enantioselectivity is in general lower. The diastereoselectivity in ethanol is higher for proline (Table 21; entry 7), while in dichloromethane or acetonitrile is lower (Table 21; entries 6,8). *N*-Alkyl-pyrrolidine-tetrazoles are not suitable catalysts for the Michael addition under these conditions (Table 21; entries 4, 5) as well as the L-prolinol (Table 21; entry 9).



213 **211** **214**

Scheme 133. Michael addition of isovaleraldehyde with nitrostyrene

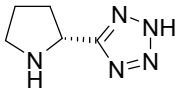
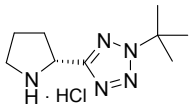
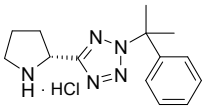
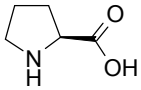
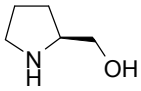
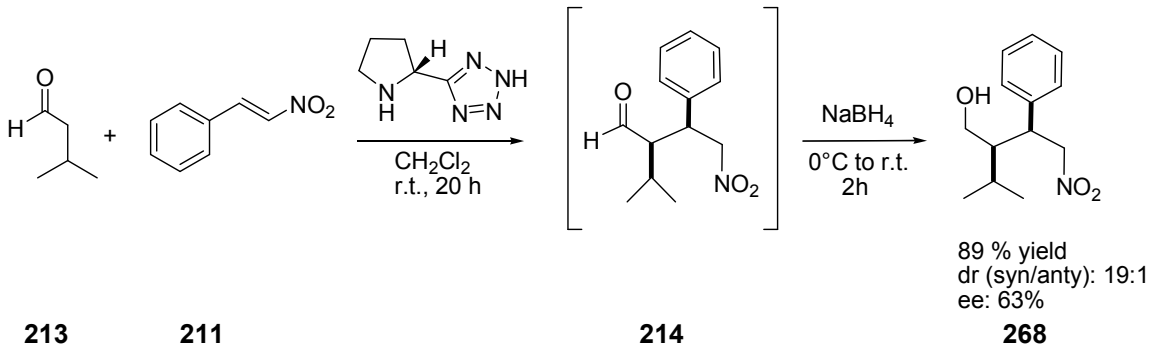
Entry	Solvent	Cat	Time [h]	Conversion[a] [%]	dr[b] [syn/anti]	ee [c] [%]syn
1	CH_2Cl_2		20	>98	19:1	56
2	EtOH		20	>98	17:1	28
3	CH_3CN		19	>95	19:1	31
4	CH_2Cl_2		120	35	7:1	26
5	EtOH		76	90	7:1	23
6	CH_2Cl_2		120	55	6:1	-
7	EtOH		5	>96	25:1	19
8	CH_3CN		21	>96	6:1	10
9	CH_2Cl_2		48	20	2:1	-

Table 21. Michael addition of isovaleraldehyde and nitrostyrene. [a] based on HPLC analysis of the reaction mixture; [b] based on HPLC analysis of the crude product; [c] based on chiral HPLC of the crude product

Interesting to note is that the (*R*)-(tetrazol-5-yl)-pyrrolidine **115** and its *N*-alkylated derivatives give the same enatiomer (enantiomer B: 13.01 min on chiral HPLC), while S-proline and the (*S*)-(tetrazol-5-yl)-pyrrolidine **114** the opposite one (enantiomer A: 8.26 min on chiral HPLC).

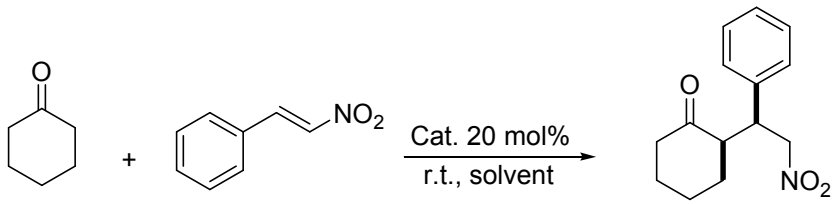
The product obtained from the Michael addition of isovaleraldehyde and nitrostyrene is sensitive to racemization on α-position. For this reason, we have found more appropriate the direct reduction to the corresponding more stable primary alcohol. However, no relevant increase of enantioselectivity was observed. When the Michael reaction reach completion, the mixture is cooled to 0 °C and treated with an excess of sodium borohydride (Scheme 134).



213 **211** **214** **268**

Scheme 134. Michael addition followed by reduction to primary alcohol **268**

3.2.3.2. Michael addition of cyclohexanone and nitrostyrene



209 **211** **212**

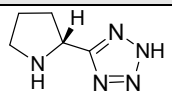
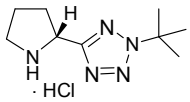
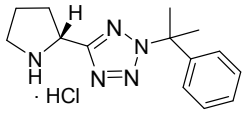
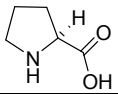
Entry	Solvent	Cat	Time [h]	Conversion[a] [%]	dr[b] [syn/anti]	ee [c] [%]syn
1	DMSO		5-7	>99	17:1	49
2	EtOH		30	>99	19:1	60
3	DMSO		30	>95	2:1	13
4	EtOH		30	>95	4:1	7
5	DMSO		40	>95	2:1	11
6	DMSO		5-8	>99	13:1	23
7	EtOH		30	>95	20:1	49

Table 22. Michael addition of cyclohexanone and nitrostyrene. [a] based on HPLC analysis of the mixture; [b] based on HPLC analysis of the crude product; [c] based on chiral HPLC of the crude product

The organocatalyzed Michael addition of cyclohexanone with nitrostyrene was screened at room temperature in DMSO and ethanol with different catalysts (Table 22). The reaction is performed with stoichiometric amounts of cyclohexanone with 20 mol% of catalyst at room temperature. According to published data [229,230] the 2-(*R*)-(tetrazol-5-yl)-pyrrolidine gives better diastereo- and enantioselectivity than proline in both DMSO and ethanol (Table 22; entries 1-4). The corresponding *N*-alkyl-tetrazoles catalyze the reaction only after the addition of small amount of hydrochloric acid. However the diastereoselectivities and the enantioselectivities are not satisfactory.

3.3. Organocatalysis: Conclusions

The enantioselective organocatalysis in which the reaction is mediated by a catalytic amount of chiral organic molecule is an emerging powerful tool in organic synthesis. The interest in this field has increased in the last few years, and more reactions and more class of organocatalysts are expected in the future. The hope is that organocatalysis will find a consistent application outside the academic environment for the synthesis of complex molecular structures.

Proline is one example of a versatile organocatalyst. However there are a number of drawbacks in the use of proline including its limited solvent solubility (reactions are often performed in DMSO). In addition a relatively high catalyst loading is usually required, commonly proline is used at levels of around 20 mol %. To overcome the above mentioned disadvantages of proline, the tetrazole analogue, namely the pyrrolidine tetrazole, is receiving considerable attention and represents a valuable alternative to proline, particularly as it avoids the use of solvent such as DMSO and can also be used in smaller quantities without compromising on enantioselectivity [225].

Taking in account the recently emerging interest in tetrazole analogues of proline, we have efficiently prepared a variety of new compounds based on the pyrrolidine-tetrazole skeleton which could represent a novel class of organocatalysts in the future [142].

Despite the considerable progress that has been made in the elucidation of mechanism involved in organocatalyzed reactions, we are only beginning to understand the basic factors that control the reactivity and selectivity in these reactions. Therefore the rational design of novel organocatalysts remains in most cases difficult.

One mechanism commonly accepted is the enamine-catalytic cycle in which the catalytic formation of an intermediate enamine generated from a carbonyl species and the chiral organocatalyst reacts with electrophiles. During our investigation we have detected, and in some cases isolated, the enamine-intermediates which are supposed to be involved in the enamine catatic-cycle. Unfortunately, we were not able to isolate single crystals of these compounds suitable for X-ray analysis which could give some additional important knowledge for the understanding of the mechanism involved.

In addition we have selected Michael addition of carbonyl compounds to nitrostyrene to test the efficiency of some new pyrrolidine-tetrazole based catalyst. In general the

pyrrolidine-tetrazole is superior to proline, and could be used in solvent such as dichloromethane where proline fails, and *N*-alkyl-pyrrolidine tetrazoles are not suitable catalysts for these reactions. Further investigations on the new organocatalysts herein described should be done in the future.

Chapter 4.
X-Ray Structures of Tetrazole Derivatives

As already discussed in Chapter 1.1, the tetrazole ring exists in two tautomeric forms, 1*H*- and 2*H*-form (Figure 60) [1]. In the gas phase calculations show that the 2*H* -tautomer is the favorite and in solution the 1*H*-form, which has an higher dipole moment, is the dominant tautomer. The 1*H*-tautomer is also the major isomer in the solid state and this is supported by X-ray crystallography data where intermolecular hydrogen bonds chains have been detected in the crystal structures [247,248,249] between the N-1 and N-4 atoms of adjacent rings with the proton preferentially located at the N-1 site.

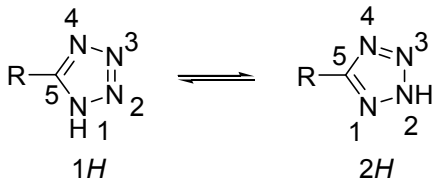


Figure 60. Tautomeric forms of tetrazole derivatives and numbering of the tetrazole ring

A variety of X-ray structures of our 5-substituted tetrazoles have been solved. All unsubstituted-tetrazoles herein reported (**109**, **119**, **17**), with exception of the pyrrolidine tetrazole derivative **115** which is present in the zwitterionic form, crystallized as its 1*H*-tautomer. Tetrazoles and tetrazolate complexes show the tetrazole ring to be a planar resonance hybrid [250]. The bond lengths and angles in the tetrazole and aryl rings of the structures herein reported are in accordance with literature data and are not discussed further [162,247,248,251]. Selected bond lengths and angles are listed in tables in this section.

4.1. 5-Thiophen-1*H*-tetrazole (109)

Yellow single crystals suitable for X-ray analysis are obtained by slow evaporation of an ethyl acetate solution (Figure 61; see Chapter 5.1). This compound crystallizes in the monoclinic space group Pc, with a = 9.962(2) Å, b = 9.213(2) Å, c = 7.219(2) Å, β = 110.516(9), Z = 4, V = 620.5(3) Å^3, D_c = 1.629 g/cm^3, R_1 = 0.0275, wR_2 = 0.0748. The asymmetric unit has two molecules with the sulfur atoms disordered over two

orientations A and B (Figure 62). Molecule **109.II,** position A is the major one with a ratio 65 : 35 of A to B. Molecule **109.I** the position A is also the major one but with a 85 : 15 A to B.

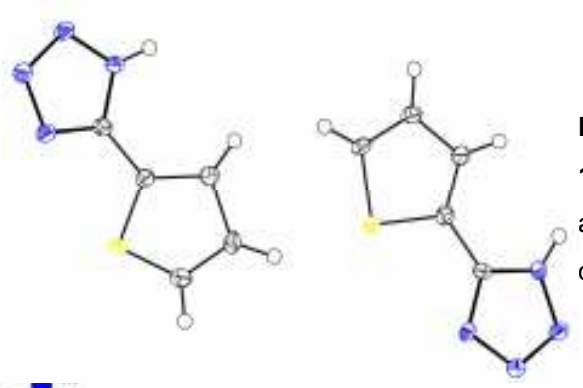
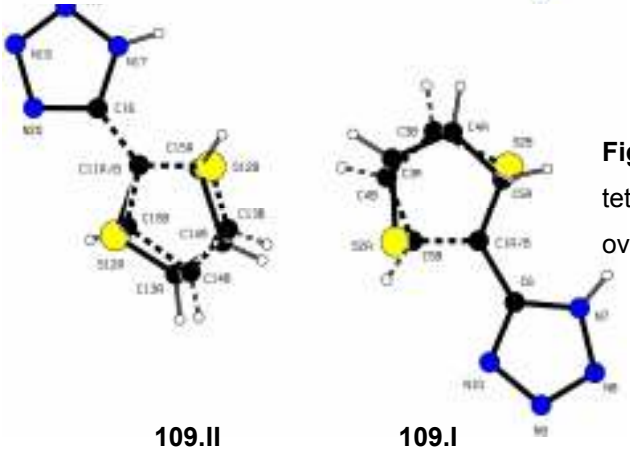


Figure 61. Structure of 5-thiophen-1*H*-tetrazole **109** in the crystals with thermal ellipsoids drawn at 50 % probability level. Minor orientation omitted for clarity



109.II **109.I**

Figure 62. Asymmetric unit of 5-thiophen-1*H*-tetrazole **109** with the thiophene ring disordered over two orientations A and B

The molecule **109.II** has the tetrazole and the thiophene rings twisted with respect to one another, with dihedral angles of 29.5(3)° and 31.1(5)° for the minor orientation B. In molecule **109.I** the two rings are almost planar with respect to one another with dihedral angles between the tetrazole and the thiphene rings of 4.5(2)° and 3.8(11)° for the minor orientation B. Within the limits of accuracy all bond lengths in the ordered part of the structure agree with expected values [251]. Further details are given in tables 25-27.

The tetrazole ring exists in two tautomeric forms N1- and N2 where the N1 and N2 are respectively the nitrogen atoms in α and β position to the carbon of the tetrazole ring (Introduction, Chapter 1), however the 5-thiophen-1*H*-tetrazole **109** crystallized exclusively in the 1*H*-tautomeric form. This could be also supported by the presence of a heteroatom such as sulphur which could be involved in an intra-molecular hydrogen bonds. However the intra-molecular N–H···S hydrogen bonds are not observed by X-ray analysis. Instead, the 1*H*-isomer is stabilized by inter-molecular hydrogen bonds with adjacent N-atoms (Table 26). The crystal packing is aided by N–H···N hydrogen bonds which form linear chains along the b-axis (Table 26).

Table 23. Bond lengths [Å] for 5-thiophen-1*H*-tetrazole **109**

Atoms	Bond length
C1A - S2A	1.711(2)
S2A - C3A	1.721(3)
S2B - C3B	1.715(16)
S2B - C1B	1.641(12)
C11A - S12A	1.676(3)
S12B - C11B	1.666(6)
S12A - C13A	1.519(6)
S12B - C13B	1.362(11)
C6 – N10	1.327(3)
C6 – N7	1.343(3)
C1 – N20	1.321(3)
C16 – N17	1.345(3)

Table 24. Bond angles [°] for **109**

Atoms	Angle
C1A - S2A - C3A	91.77(14)
C1B - S2B - C3B	93.4(10)
C13A - S12A - C11A	96.0(3)
C13B - S12B - C11B	100.9(7)

Table 25. Torsion angles [°] for **109**

Atoms	Angle
N7 –C6 – N10 – N9	-0.3(3)
N8 – N9 – N10 – C6	0.1(3)
N20 – C16 – N17 – N18	-0.7(3)
C16 – N17 – N18 – N19	0.0(3)

Table 26. Hydrogen bonds for 5-thiophen-1*H*-tetrazole **109** [Å and °]

D-H···A		d(D-H)	d(H···A)	d(D···A)	<(DHA)
N7 - H7...N20	#1	0.88	1.99	2.858(3)	168.5
N17 - H17...N10	#2	0.88	2.00	2.865(3)	165.9

Symmetry transformations used to generate equivalent atoms:
#1 x+1,y-1,z #2 x,y+1,z

4.2. 5-(Benzylthio)-*1H*-tetrazole (17)

Yellow single crystals suitable for X-ray analysis are obtained by slow evaporation of an ethyl acetate solution (Figure 63; see Chapter 5.1). This compound crystallizes in the monoclinic space group $P2_1$, with a = 15.323(4) Å, b = 5.761(2) Å, c = 41.875(2) Å, β = 100.517(10), Z = 16, V = 3634.4(16) $Å^3$, D_c = 1.405 g/cm^3, R_1 = 0.0318, wR_2 = 0.0832.

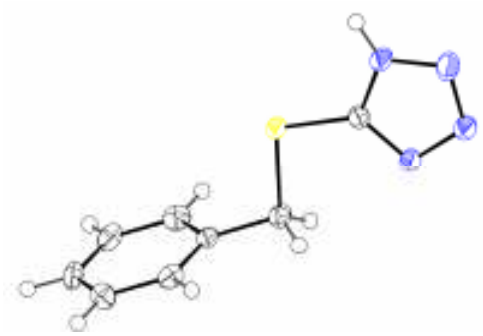


Figure 63. Structure of 5-(benzylthio)-*1H*-tetrazole **17** in the crystal with thermal ellipsoids drawn at 50 % probability level

The asymmetric unit consists of eight molecules (Figure 64). The 5-(benzylthio)-*1H*-tetrazole **17** has the tetrazole ring and the phenyl ring twisted with respect to one another (Table 27). The torsion angles described from the representative atoms C5-S6-C7-C8 are slightly different in each molecule of the asymmetric unit (Table 30). Within the limits of accuracy all bond lengths and angles agree with expected values. The representative distances and angles involving the sulfur atom are mentioned in table 8 and further representative details are given in tables 27-30.

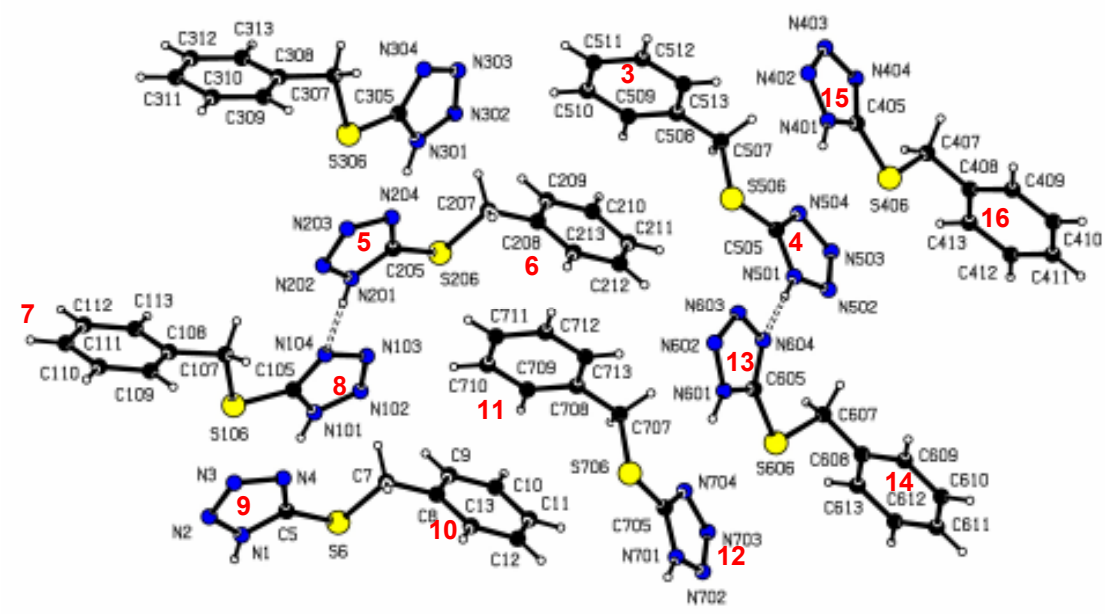


Figure 64. Crystal packing of 5-(benzylthio)-*1H*-tetrazole **17** and numbering of tetrazole and phenyl rings

Table 27. Dihedral angles between tetrazole and phenyl rings [°] for **17**. The numbering of the rings is shown in Figure 81

Rings	Angle
1, 2	86,93(17)
3, 4	80.29(16)
5, 6	84.63(17)
7, 8	74.91(17)
9, 10	81.0617)
11, 12	86.55(16)
13, 14	86.29(17)
15, 16	75.75(16)

Table 28. Bond lengths [Å] **17**

Atoms	Bond length
N1 - C5	1.336(4)
N4 - C5	1.323(4)
C5 - S6	1.731(3)
S6 - C7	1.832(3)
C7 - C8	1.512(4)

Table 29. Bond angles [°] for **17**

Atoms	Angle
N1 - C5 - S6	123.9(2)
C5 - S6 - C7	100.12(14)
C8 - C7 - S6	106.6(2)

Table 30. Torsion angles [°] for 5-(benzylthio)-*1H*-tetrazole **17**

Atoms	Angle
C5 – S6 – C7 – C8	170.6(2)
C105 – S106 – C107 – C108	162.8(2)
C205 – S206 – C207 – C208	164.2(2)
C305 – S306 – C307 – C308	153.4(2)
C405 – S406 – C407 – C408	162.0(2)
C505 – S506 – C507 – C508	171.3(2)
C605 – S606 – C607 – C608	154.6(2)
C705 – S706 – C707 – C708	162.7(2)

The crystal packing is aided by intermolecular N–H···N hydrogen bonds which form linear chains along the b-axis (Table 31). The 5-(benzylthio)-*1H*-tetrazole **17** crystallized exclusively in the 1*H*-tautomeric form. This fact could be explained looking the inter-molecular hydrogen-bonds in the crystal packing. The N–H···N hydrogen bonds form a linear chain between the N-H of the N1-tautomer of one molecule and the N1 position of the molecule neighbor.

Table 31. Hydrogen bonds for 5-(benzylthio)-*1H*-tetrazole **17** [Å and °]

D-H···A		d(D-H)	d(H···A)	d(D···A)	<(DHA)
N1 - H1...N304	#1	0.88	1.88	2.756(4)	173.7
N101 - H101...N4	#2	0.88	1.83	2.711(4)	175.1
N201 - H201...N104		0.88	1.86	2.735(4)	176.2
N301 - H301...N204	#2	0.88	1.83	2.709(4)	174.9
N401 - H401...N504	#3	0.88	1.83	2.709(4)	174.9
N501 - H501...N604		0.88	1.87	2.743(4)	174.5
N601 - H601...N704	#3	0.88	1.83	2.705(3)	175.0
N701 - H701...N404	#1	0.88	1.86	2.738(4)	174.5

Symmetry transformations used to generate equivalent atoms:

#1 x+1,y,z #2 x,y+1,z #3 x,y-1,z

4.3. (*R*)-5-(Tetrahydro-furan)-1*H*-tetrazole (119)

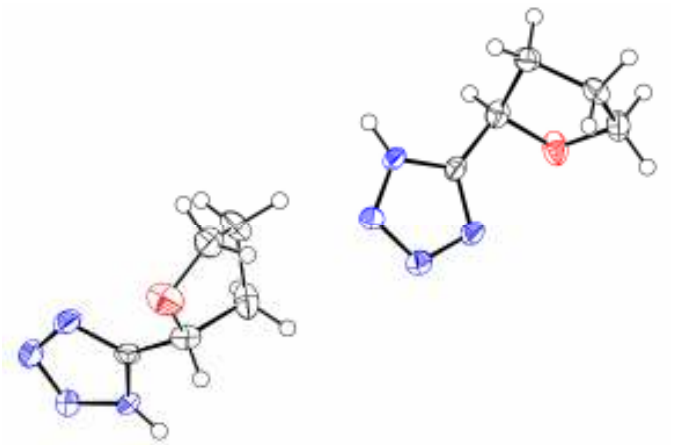
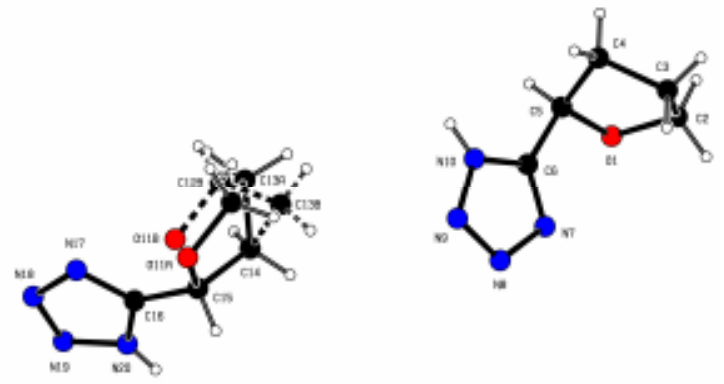


Figure 65. Structure of (*R*)-5-(tetrahydro-furan)-1*H*-tetrazole **119** in the crystal with thermal ellipsoids drawn at 50 % probability level

Colorless crystals suitable for X-ray analysis are obtained by slow evaporation of an ethyl acetate solution (Figure 65, see Chapter 5). This compound crystallizes in the orthorhombic space group $P2_12_12_1$, with a = 8.295(2) Å, b = 9.439(2) Å, c = 16.650(3) Å, Z = 8, V = 1303.6(5) Å^3, D_c = 1.428 g/cm^3, R_1 = 0.0301, wR_2 = 0.0664. The asymmetric unit consists of two molecules in which the tetrazole and the hydrofuran rings are twisted with respect to one another and the hydrofuran rings have an envelop conformation (Figure 66). In the molecule **119.II**, the furan ring is disordered over two orientations A and B with a ratio of 0.58 : 0.42. The two positions A and B are described with the angle O11A-C15-O11B of 17.0(3)° (Table 33). The torsion angle of molecule **119.II** in the A orientation, described by the atoms N17-C16-C15-O11A, is 18.6(3)° and the

corresponding torsion angle for the B orientation is similar to those of molecule **119.I** (4.9(3)° and 5.48(18)° respectively, Table 34).

Within the limits of accuracy all bond lengths and angles in the ordered part of the structure agree with expected values [251]. Further details are given in tables 32-34.



119.II **119.I**

Figure 66. Asymmetric unit of (*R*)-5-(tetrahydro-furan-2-yl)-2*H*-tetrazole with the tetrahydrofurane ring of the molecule **119.II** disordered over two orientations A and B

Table 32. Bond lengths [Å] for **119**

Atoms	Bond length
O1 - C5	1.4308(17)
O1 - C2	1.4427(18)
C5 - C6	1.502(2)
C15 - C16	1.490(2)

Table 33. Bond angles [°] for **119**

Atoms	Angle
C5 - O1 – C2	109.24(11)
O1 - C5 – C6	107.68(11)
O1 - C5 - C4	106.37(11)
O11A - C15 - C16	113.2(3)
O11A - C15 - O11B	17.0(3)
C16 - C15 - O11B	102.2(3)
O11A - C15 - C14	108.9(3)
O11B - C15 - C14	104.0(3)

Table 34. Torsion angles [°] for **119**

Atoms	Angle
O1 – C5 – C6 – N7	5.48(18)
O11A – C15 – C16 – N17	18.6(3)
O11B – C15 – C16 – N17	4.9(3)
N10 – C6 – N7 – N8	-0.30(14)
N7 – N8 – N9 – N10	-0.24(15)
N17 – N18 – N19 – N20	-0.26(15)
N17 – C16 – N20 – N19	0.05(15)

The crystal packing is aided by N–H···N hydrogen bonds (Table 35). The tetrazole ring exists in two tautomeric forms N1- and N2 where the N1 and N2 are respectively the nitrogen atoms in α and β position to the carbon of the tetrazole ring (Introduction, Chapter 1). However the (*R*)-5-(tetrahydro-furan-2-yl)-2*H*-tetrazole **119** crystallized exclusively in the 1*H*-tautomeric form. This fact is explained by the presence of an

intermolecular hydrogen-bond between the oxygen of one molecule and the N-H of the neighboring molecule.

Table 35. Hydrogen bonds for (*R*)-5-(tetrahydro-furan-2-yl)-2*H*-tetrazole **119** [Å and °]

D-H···A		d(D-H)	d(H···A)	d(D···A)	<(DHA)
N10 – H10...N7	#1	0.854(18)	2.102(18)	2.8981(18)	155.0(13)
N10 - H10...O1	#1	0.854(18)	2.447(16)	3.0820(17)	131.8(12)
N20 - H20...N17	#2	0.81(2)	2.07(2)	2.8475(18)	160.0(16)
N20 - H20...O11B	#2	0.81(2)	2.434(19)	2.997(6)	127.5(14)

Symmetry transformations used to generate equivalent atoms:

#1 -x,y+1/2,-z+3/2 #2 -x+2,y-1/2,-z+1/2

4.4. 4-[2-Benzene-sulphonyl-2-(2-methyl-2*H*-tetrazol-5-yl)-vinyl]-benzoic acid methyl ester (177)

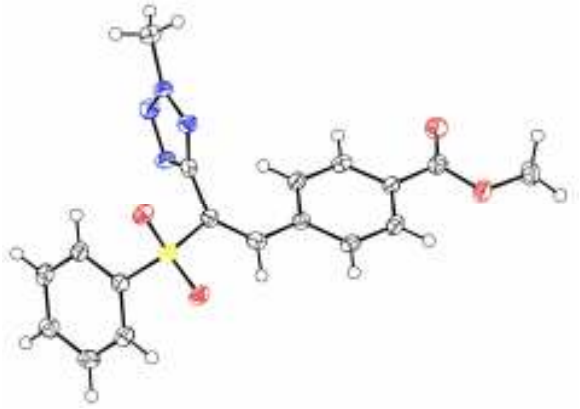


Figure 67. Structure of 4-[2-benzene-sulphonyl-2-(2-methyl-2*H*-tetrazol-5-yl)-vinyl]-benzoic acid methyl ester **177** in the crystal with thermal ellipsoids drawn at 50 % probability level

Colorless single crystals suitable for X-ray analysis are obtained by slow evaporation of a mixture of ethyl acetate / hexane (Figure 67; Chapter 5.2). This compound crystallizes in the monoclinic space group P-1, with a = 7.582(2) Å, b = 8.425(2) Å, c = 14.912(4) Å, α= 75.784(9)°, β = 87.969(9)° and γ = 72.584(9)°, Z = 2, V = 880.3(4) $Å^3$, D_c = 1.450 g/cm^3, R_1 = 0.0356, wR_2 = 0.0882.

Within the limit of accuracy all bond lengths and angles agree with expected values [251]. The main distance and angles are mentioned (Tables 36-38). The two phenyl rings are almost perpendicular to each other with an angle of 72.83(5)°. The tetrazole and the phenyl (C11) rings have a dihedral angle of 27.38(8)° and the tetrazole with the phenyl (C18) rings have a dihedral angle of 87.00(5)°. The phenyl ring (C18) and the carbonyl

group are in the same plane, while the phenyl ring and the double bond have a torsion angle of 4.1(3)° (Table 38).

The conformation of the molecule in the crystal is stabilized by an intra-molecular H-bond between O9 of sulphonyl group and N2 of the tetrazole. Analysis of supramolecular array reveals the presence of π-stacking between the phenyl rings based on C18, the distance between most proximate pairs of such rings in the supramolecular array being 3.8 Å .

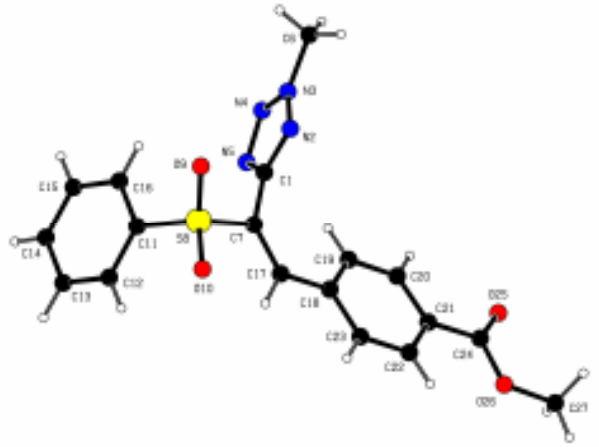


Figure 68. 4-[2-Benzene-sulphonyl-2-(2-methyl-2*H*-tetrazol-5-yl)-vinyl]-benzoic acid methyl ester **177** in the crystal

Table 36. Bond lengths [Å] for **177**

Atoms	Bonds Length
C1 – N2	1.331(2)
C1 – N5	1.351(2)
C1 – C7	1.476(2)
C7 – C17	1.339(2)
C7 – S8	1.7901(16)
S8 – O9	1.4379(12)
S8 – C11	1.766(16)

Table 37. Angles [°] for **177**

Atoms	Angle
N2 – C1 – N5	112.66(13)
N3 – C6 – H	109.5
C17 – C7 – C1	128.91(14)
C1 – C7 – S8	114.30(11)
O10 – S8 – O9	119.41(7)
C11 – S8 – C7	103.64(7)
C7 – C17 – C18	130.07(15)

Table 38. Torsion angles [°] for **177**

Atoms	Angle
C1 – N2 – N3 – N4	0.15(16)
C1 – N2 – N3 – C6	177.78(13)
C6 – N3 – N4 – N5	-177.55(13)
N5 – C1 – C7 – S8	-101.96(15)
C7 – S8 – C11 – C12	101.66(13)
C7 – S8 – C11 – C16	-75.61(13)
C1 – C7 – C17 – C18	4.1(3)
S8 – C7 – C17 – C18	-174.78(12)
C22 – C21 – C24 – O26	1.2(2)

4.5. (*R*)-5-Pyrrolidine-2-yl-tetrazole (115)

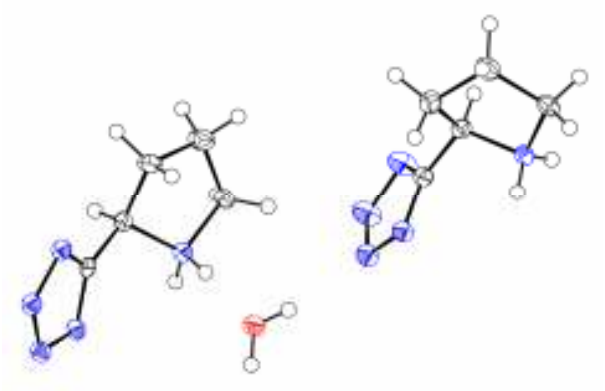


Figure 69. Structure of *(R)*-5-pyrrolidine-2-yl-tetrazole **115** in the crystal with thermal ellipsoids drawn at 50 % probability level

Colorless single crystals suitable for X-ray analysis are obtained by slow evaporation of a mixture of ethanol / water (Figure 69; Chapter 5.3). This compound crystallizes in the orthorhombic space group $P2_12_12_1$, with a = 10.213(8) Å, b = 11.634(9) Å, c = 12.222(9) Å, Z = 8, V = 1452.2(19) $Å^3$, D_c = 1.356 g/cm^3, R_1 = 0.0275, wR_2 = 0.0684. X-Ray diffraction shows that the (*R*)-5-pyrrolidine-2-yl-tetrazole **115** crystallizes in the hydrate form (Figures 69, 70). The asymmetric unit has two molecules which are present in the zwitterionic form. The solvent is coordinated to the nitrogen N11 of the pyrrolidine ring of **115.II** and the nitrogen N8 of the tetrazole ring in **115.I** (Figure 70).

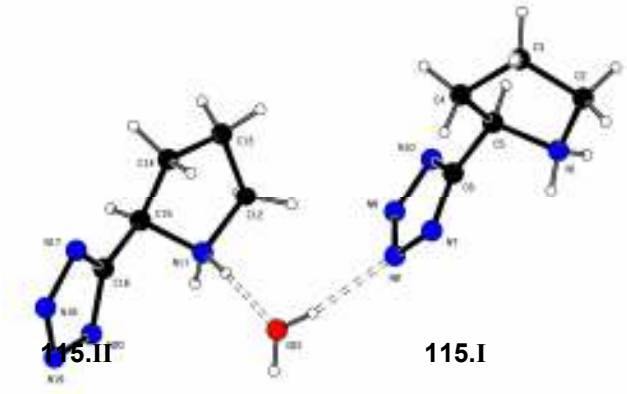


Figure 70. (*R*)-5-Pyrrolidine-2-yl-tetrazole in the crystal. Hydrogen bonds shown as dotted lines

The (*R*)-5-pyrrolidine-2-yl-tetrazole has the tetrazole ring and the pyrrolidine ring twisted with respect to one another. The torsion angle between the pyrrolidine and the tetrazole rings is 57.54(16)° for molecule **115.I** and 138.15(11)° for molecule **115.II** (Table 43). Within the limits of accuracy all bond lengths agree with expected values [251]. The main distances and angles of the tetrazole ring are mentioned (Tables 39-41). The pyrrolidine ring has an envelope conformation on C-5 in molecule **115.1** and on C15 in molecule **115.II**.

The crystal packing is aided by inter-molecular O–H···N hydrogen bonds and by inter-molecular N-H···N hydrogen bonds (Table 42).

Table 39. Bond lengths [Å] for (*R*)-5-pyrrolidin-2-yl-tetrazole **115**

Atoms	Bond length	Atoms	Bond length
N1 - C2	1.5109(17)	N11 - C12	1.5072(17)
N1 - C5	1.50008(17)	C15 – C16	1.4911(18)
C6 - N10	1.3338(19)	C16 - N20	1.3388(18)
C6 – N7	1.3304(17)	C16 – N17	1.3289(17)
C6 – C5	1.4895(18)	N19 - N20	1.344(3)
N9 - N10	1.3491(18)	C15 – C16	1.4911(18)
N11 - C15	1.4991(17)		

Table 40. Bond angles [°] for **115**

Atoms	Angle
C2 - N1 - C5	105.38(10)
C6 – C5 – N1	113.44(11)
N1 – C5 – C4	101.44(11)
N10 – C6 – N7	112.16(11)
C6 - N10 - N9	104.42(11)
C12 - N11 - C15	106.16(11)
C16 – C15 – N11	111.39(11)
C14 – C15 – N11	102.43(11)
N20 - C16 - C15	124.32(11)
C16 - N20 - N19	104.79(10)

Table 41. Torsion angles [°] for **115**

Atoms	Angle
N1 – C5 – C6 – N7	57.54(16)
N1 – C5 – C6 – N10	-44.69(13)
C6 – N7 – N8 – N9	0.05(13)
N8 – N9 – N10 – C6	-0.10(15)
N11 – C15 – C16 – N17	138.15(11)
N11 – C15 – C16 – N20	-126.62(13)
C16 – N17 – N18 – N19	0.44(12)
N17 – C16 – N20 – N19	0.24(13)

Table 42. Hydrogen bonds [Å and °] for the *R*-5-pyrrolidine-2-yl-tetrazole **115**

D-H···A		d(D-H)	d(H···A)	d(D···A)	<(DHA)
N1 - H1A...N20	#1	0.913(17)	1.999(17)	2.862(2)	157.0(14)
N1 - H1B...N18	#2	0.869(18)	1.964(19)	2.827(2)	171.8(15)
N11 - H11A...O21		0.889(19)	1.855(19)	2.734(2)	169.9(17)
N11 - H11B...N7	#3	0.908(19)	1.937(19)	2.835(2)	169.7(16)
N11 - H11B...N8	#3	0.908(19)	2.673(18)	3.476(3)	147.9(14)
O21 - H21A...N17	#4	0.85(2)	1.98(2)	2.825(2)	170.6(19)
O21 - H21B...N8		0.83(2)	2.01(2)	2.827(2)	165.9(19)
O21 - H21B...N9		0.83(2)	2.64(2)	3.301(2)	137.0(17)

Symmetry transformations used to generate equivalent atoms:

#1 -x+2,y-1/2,-z+1/2 #2 x,y,z+1 #3 -x+2,y+1/2,-z+1/2 #4 x+1/2,-y+3/2,-z

4.6. (*R*)-5-Pyrrolidine-2-yl-tetrazole palladium(II) complex (242)

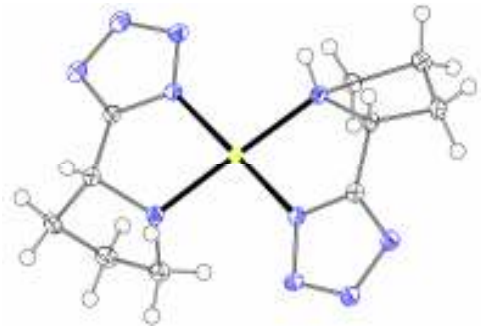


Figure 71. Structure of (*R*)-5-pyrrolidine-2-yl-tetrazole palladium(II) complex **242** in the crystal with thermal ellipsoids drawn at 50 % probability level

Colorless crystals suitable for X-ray analysis are obtained by slow evaporation of a mixture of THF / water (Figure 71; Chapter 5.3). This compound crystallizes in the orthorhombic space group $P2_12_12_1$, with a = 8.092(2) Å, b = 8.597(2) Å, c = 20.951(3) Å, Z = 4, V = 1457.5(5) $Å^3$, R_1 = 0.0152, wR_2 = 0.0369. The (*R*)-5-pyrrolidine-2-yl-tetrazole palladium(II) complex crystallizes in a mono-hydrated form and the X-Ray diffraction shows that the palladium(II) has a distorted square-planar geometry and its coordination sphere is defined by two (*R*)-5-pyrrolidine-2-yl-tetrazole ligands (Figure 72).

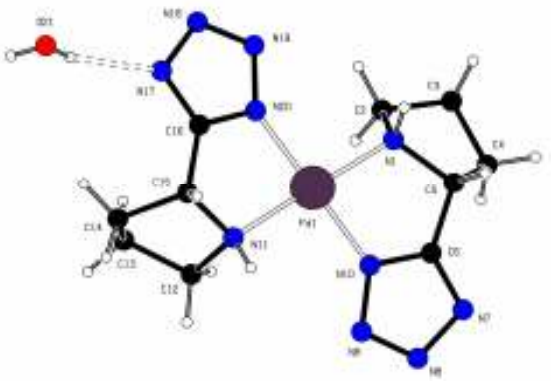


Figure 72. Structure of (*R*)-5-pyrrolidine-2-yl-1*H*-tetrazole palladium(II) complex **242** in the crystal

In the normal square-planar geometry the angle between the ligands (L) and the metal (M) L_1-M-L_3 and L_2-M-L_4 should be 180° and the angles defined by L_1-M-L_2 = L_2-M-L_3 = L_3-M-L_4 = L_4-M-L_1 = 90° (Figure 73). However, the N20-Pd-N11 and the N10-

Pd-N1 angles, respectively 81.36(7)° and 80.97(8)°, show the distorted square-planar environment at palladium (Figure 72, Table 43). All the five atoms lie within 0.2Å [Pd], within a least square plane defined by the four nitrogen atoms N1 N10 N11 N20.

Figure 73. Square-planar geometry

The torsion angles N11-C15-C16-N20 and N1-C5-C6-N10 of **242** (Table 37) are different to those found in the X-ray structure of (*R*)-5-pyrrolidine-2-yl-tetrazole hydrate **115** (Section 4.3). The (*R*)-5-pyrrolidine-2-yl-tetrazole palladium(II) complex **242** has the two ligands with the tetrazole and the pyrrolidine rings twisted with respect to one another and the torsion angels are given in table 43. Based on the method of Cramer and Pople, the conformation of the pyrrolidine rings can be described as twisted on C2-C3 and C12-C13. Within the limits of accuracy all bond lengths agree with expected values. The main distances and angles of the tetrazole ring are mentioned (Tables 43-45). The planarity and the bond lengths of the tetrazole ring are not influenced by the metal-coordination and are comparable with the data found for **115** (Section 4.3).

The crystal packing is aided by inter-molecular O–H···N hydrogen bonds which form chains along the b-axis and by inter-molecular N-H···N hydrogen bonds (Table 46).

Table 43. Torsion angles [°] for **237**

Atoms	Angle
N11 – C15 – C16 – N20	-20.4(3)
N1 – C5 – C6 – N10	-12.0(3)
C16 – N17 – N18 – N19	0.0(2)
N16 – N20 – N19 – N18	0.2(2)
C6 – N7 – N8 – N9	-0.4(2)
C6 – N10 – N9 – N8	-0.2(2)

Table 44. Bond lengths [Å] for **237**

Atoms	Bond length
Pd1 - N10	1.985(2)
Pd1 - N20	1.995(2)
Pd1 - N11	2.0560(18)
Pd1 - N1	2.0579(18)
N1 - C2	1.501(3)
N1 - C5	1.507(3)
C6 - N10	1.327(3)
N9 - N10	1.341(3)
N11 - C12	1.514(3)
N11 - C15	1.514(3)
C16 - N20	1.329(3)
N19 - N20	1.344(3)

Table 45. Angles [°] for **237**

Atoms	Angle
N10 - Pd1 - N20	177.87(8)
N10- Pd1 - N11	97.72(8)
N20 - Pd1 - N11	81.36(7)
N10 - Pd1 - N1	80.97(8)
N20 - Pd1 - N1	99.94(7)
N11 - Pd1 - N1	178.64(8)
C2 - N1 - C5	106.12(16)
C2 - N1 - Pd1	114.48(13)
C5 - N1 - Pd1	113.20(13)
C6 - N10 - N9	108.00(18)
C6 - N10 - Pd1	117.03(15)
N9 - N10 - Pd1	134.96(14)
C12 - N11 - C15	107.37(17)
C12 - N11 - Pd1	114.57(14)
C15 - N11 - Pd1	112.42(13)
N20 - C16 - C15	119.6(2)
C16 - N20 - N19	107.73(18)
C16 - N20 - Pd1	115.63(14)
N19 - N20 - Pd1	135.89(15)

Table 46. Hydrogen bonds [Å and °] for **237** complex.

D-H···A		d(D-H)	d(H···A)	d(D···A)	<(DHA)
N1 – H1...N7	#1	0.88(3)	2.14(3)	2.952(3)	154(2)
N11 – H11...N8	#2	0.91(3)	2.03(3)	2.899(3)	159(2)
O21 – H21A...N18	#3	0.79(3)	2.13(3)	2.903(3)	166(3)
O21 – H21B...N17		0.78(3)	2.18(3)	2.933(3)	161(4)

Symmetry transformations used to generate equivalent atoms:

#1 -x+2,y+1/2,-z+1/2 #2 -x+1,y+1/2,-z+1/2 #3 x-1/2,-y+5/2,-z

4.7. 1-Isopropyl-5-(*R*)-pyrrolidine-2-yl-1*H*-tetrazole (237)

Yellow single crystals suitable for X-ray analyses are obtained by slow evaporation of a mixture of ethanol / methylene chloride (Figure 74; Chapter 5.3). This compound crystallizes in the monoclinic space group C2, with a = 11.598(5) Å, b = 16.066(7) Å, c = 11.446(5) Å, β = 103.38(2)°, Z = 8, V = 2074.9(16) $Å^3$, D_c = 1.277 g/cm^3, R_1 = 0.0270, wR_2 = 0.0651.

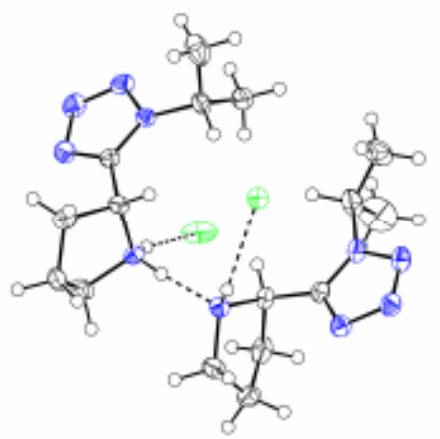


Figure 74. Structure of 1-isopropyl-5-(*R*)-pyrrolidine-2-yl-1*H*-tetrazole **237** in the crystal with thermal ellipsoids drawn at 50% probability level

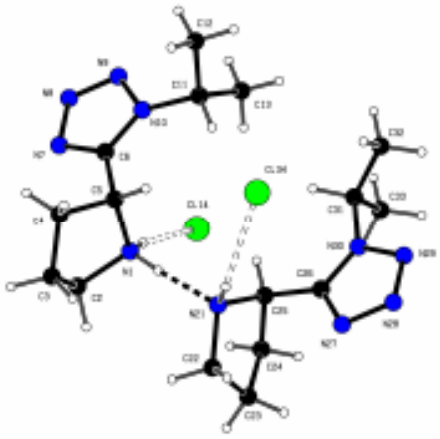


Figure 75. 1-Isopropyl-5-(*R*)-pyrrolidine-2-yl 1*H*-tetrazole **237**

X-ray diffraction shows that the 1-isopropyl-(*R*)-5-pyrrolidine-2-yl-1*H*-tetrazole **237** exists as hydrochloride (Figures 74, 75) and the hydrochloric acid is an impurity from the purification. The asymmetric unit has two 1-isopropyl-(*R*)-5-pyrrolidine-2-yl-1*H*-tetrazole molecules and two chloride ions on special positions. Therefore, the ratio of 1-isopropyl-(*R*)-5-pyrrolidine-2-yl-1*H*-tetrazole and chloride ion is 2:1 and only one of the two 1-isopropyl-(*R*)-5-pyrrolidine-2-yl-1*H*-tetrazole molecules in the asymmetric unit is protonated.

The 1-isopropyl-(*R*)-5-pyrrolidine-2-yl-1*H*-tetrazole has the tetrazole ring and the pyrrolidine ring twisted with respect to one another but the torsion angles of 237 are different to those found in the X-Ray structures of other pyrrolidine-tetrazole derivatives (Sections 4.4 - 4.10). Based on the method of Cramer and Pople, the conformation can be described as twisted on C2-C3 and C24-C25. Within the limits of accuracy all bond lengths agree with expected values. The main distances and angles of the tetrazole ring are mentioned (Tables 48-50).

Table 47. Bond lengths [Å] for 1-isopropyl-(*R*)-5-pyrrolidine-2-yl-1*H*-tetrazole **237**

Atoms	Bond length	Atoms	Bond length
N1 - C2	1.485(2)	N21 – C22	1.499(2)
N1 - C5	1.5008(19)	N21 – C25	1.484(2)
C6 - N10	1.342(2)	C25 – C26	1.498(2)
C6 – N7	1.325(2)	C26 - N27	1.323(2)
C6 – C5	1.498(2)	C26 – N30	1.339(2)
N10 – C11	1.481(2)	N30 – C31	1.480(2)

Table 48. Bond angles [°] for **237**

Atoms	Angle	Atoms	Angle
C2 – N1 – C5	106.56(11)	C12 – C11 – C13	112.35(14)
C6 – C5 – N1	109.93(12)	C22 – N21 – C25	108.40(12)
N10 – C6 – N7	108.52(13)	N21 – C25 – C26	111.47(13)
C6 – N10 – N9	108.16(12)	C26 – N30 – N29	108.36(13)
N10 – C11 – C12	109.24(14)		

Table 49. Torsion angles [°] for 1-isopropyl-(*R*)-5-pyrrolidine-2-yl-1*H*-tetrazole **237**

Atoms	Angle
N1 – C5 – C6 – N10	-101.74(16)
C6 – N7 – N8 – N9	-0.15(17)
N8 – N9 – N10 – C6	-0.52(16)
N21 – C25 – C26 – N30	-128.55(15)
C26 – N27 – N28 – N29	0.09(17)
N30 – C26 – N27 – N28	-0.40(16)

Table 50. Hydrogen bonds [Å and °] for 1-isopropyl-(*R*)-5-pyrrolidine-2-yl-1*H*-tetrazole **237**

D-H···A	d(D-H)	d(H···A)	d(D···A)	<(DHA)
N1 - H1A...Cl14	0.92	2.24	3.1413(16)	164.7
N1 - H1B...N21	0.92	1.78	2.6931(19)	174.0
N21 - H21A...Cl34	0.86(2)	2.53(2)	3.2540(17)	142.6(16)

The crystal packing is aided by inter-molecular N–H···N and N–H···Cl hydrogen bonds (Table 50). Four molecules **237** form a layer generating a channel along the c-axis where the chloride atoms are in the channels (Figure 76).

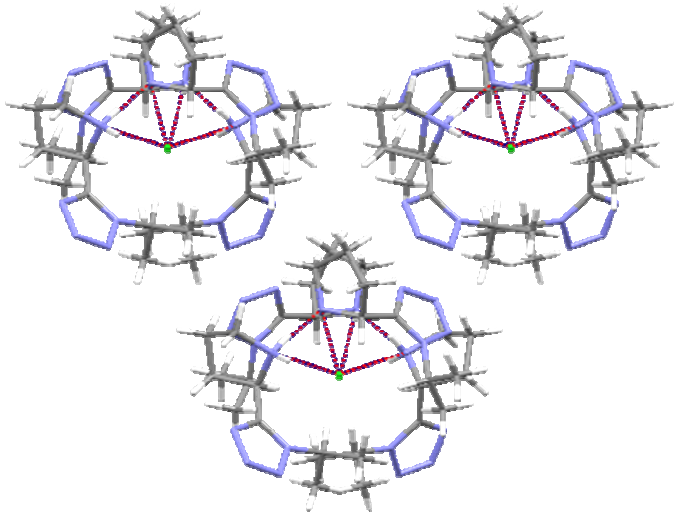


Figure 76. Crystal packing of **237** with H-bond interactions shown as dotted lines

4.8. 2-(1-Methyl-1-phenyl-ethyl)-5-*(R)*-pyrrolidine-2-yl-2*H*-tetrazole (235)

Colorless single crystals of **235** suitable for X-ray analyses are obtained by slow evaporation of a mixture of methanol / ethyl acetate (Figure 77; Chapter 5.3). This compound crystallizes in the orthorombic space group $P2_12_12_1$, with a = 6.140(2) Å, b = 7.526(2) Å, c = 29.490(4) Å, Z = 4, V = 1362.7(6) $Å^3$, D_c = 1.254 g/cm^3, R_1 = 0.0362, wR_2 = 0.0850.

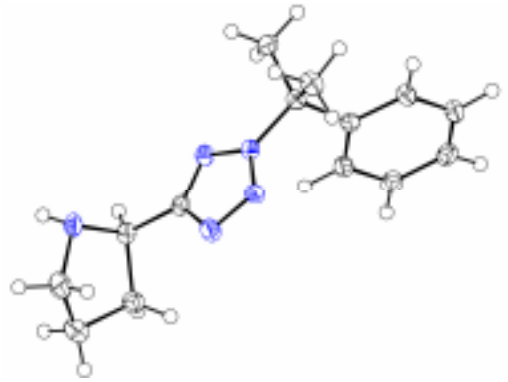


Figure 77. Structure of 2-(1-methyl-1-phenyl-ethyl)-5-(*R*)-pyrrolidine-2-yl-2*H*-tetrazole **235** in the crystal with thermal ellipsoids drawn at 50 % probability level

X-ray diffraction shows that 2-(1-methyl-1-phenyl-ethyl)-5-*(R)*-pyrrolidine-2-yl-2*H*-tetrazole **235** has the tetrazole ring and the pyrrolidine ring twisted with respect to one another (Table 53), but the torsion angle is different to those found in the X-ray structures of other pyrrolidine-tetrazole derivatives (Sections 4.4 - 4.10). Based on the method of Cramer and Pople, the conformation of the pyrrolidine ring can be described as twisted on C2-C3. Within the limits of accuracy all bond lengths and angles agree with expected values. The main distances and angles are mentioned (Tables 51-53).

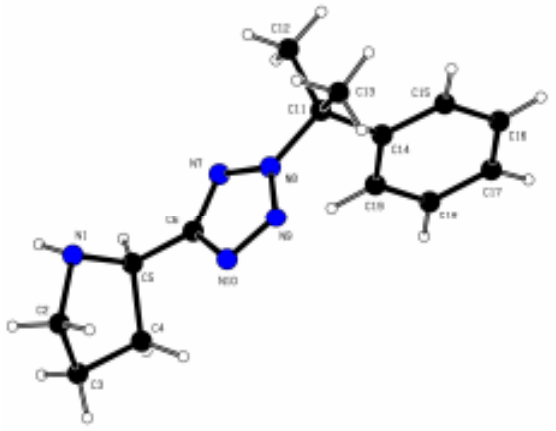


Figure 76. 2-(1-Methyl-1-phenyl-ethyl)-5-(*R*)-pyrrolidine-2-yl-2*H*-tetrazole **235**

Table 51. Bond lengths [Å] for 2-(1-methyl-1-phenyl-ethyl)-5-(*R*)-pyrrolidine-2-yl-1*H*-tetrazole **235**

Atoms	Bond length	Atoms	Bond length
N1 - C2	1.466(2)	C6 – C5	1.5011(18)
N1 - C5	1.4909(16)	N8 – C11	1.424(16)
C4 – C5	1.5521(19)	N7 – N8	1.3336(15)
C6 - N10	1.3534(18)	N8 – N9	1.3214(16)
C6 – N7	1.3312(18)	C11 - C14	1.5346(16)

Table 52. Bond angles [°] for 2-(1-methyl-1-phenyl-ethyl)-5-(*R*)-pyrrolidine-2-yl-1*H*-tetrazole **235**

Atoms	Angle
C2 - N1 - C5	105.84(11)
C6 – C5 – N1	108.53(10)
N1 – C5 – C4	106.93(10)
C6 – C5 – C4	112.53(11)
N10 – C6 – N7	111.86(11)
N7 – C6 – C5	124.28(11)
N7 – N8 – N9	113.49(10)
N8 – C11 – C12	108.14(10)
N8 – C11 – C13	106.67(10)
N8 – C11 – C14	108.74(10)
C15 – C14 – C11	120.08(12)

Table 53. Torsion angles [°] for the 2-(1-methyl-1-phenyl-ethyl)-5-(*R*)-pyrrolidine-2-yl-1*H*-tetrazole **235**

Atoms	Angles [°]
N1 – C5 – C6 – N10	73.96(15)
C6 – N7 – N8 – N9	0.32(12)
N8 – N9 – N10 – C6	- 0.05(13)
N9 – N8 – C11 – C14	79.89(14)

The planarity and the bond lengths of the tetrazole ring are not influenced by the presence of the cumyl group. The neighboring atoms of C11 form a slightly distorted tetrahedron (Table 52). The pyrrolidine ring is farther from the tetrazole ring in comparison to the un-alkylated (*R*)-5-pyrrolidine-2-yl-1*H*-tetrazole **115** (Section 4.4.). The phenyl and the tetrazole rings are twisted with respect to one another with a dihedral angle of 42.48(8)°. The crystal packing is aided by inter-molecular N–H···N hydrogen bonds between the pyrrolidine-rings (Table 54).

Table 54. Hydrogen bonds [Å and °] for the 2-(1-methyl-1-phenyl-ethyl)-5-(*R*)-pyrrolidine-2-yl-1*H*-tetrazole **312**

D-H···A		d(D-H)	d(H···A)	d(D···A)	<(DHA)
N1 – H1...N1	#1	0.89(2)	2.448(19)	3.2658(13)	152.9(16)

Symmetry transformation used to generate equivalent atoms:
#1 x-1/2,-y+3/2,-z+2

4.9. (*S*)-2-(2-*tert*-Butyl-2*H*-tetrazol-5-yl) pyrrolidinium trifluoro acetate (244)

Brown single crystals suitable for X-ray analyses are obtained by slow evaporation of a methylene chloride solution (Figure 78; Chapter 5.3). Compound **244** crystallizes in the monoclinic space group $P2_1$, with a = 5.955(2) Å, b = 7.704(2) Å, c = 16.113(4) Å, β = 98.457(9)°, Z = 2, V = 731.2(4) Å^3, D_c = 1.405 g/cm^3, R_1 = 0.0310, wR_2 = 0.0776. X-ray diffraction shows that the molecule of trifluoroacetic acid is coordinated to the nitrogen N1 of the pyrrolidine ring (Figures 78, 79). The (*S*)-2-(2-*t*butyl-2*H*-tetrazol-5-yl) pyrrolidinium has the tetrazole and the pyrrolidine rings twisted with respect to one another but with a torsion angles different to those found in the X-Ray structures of other pyrrolidine-tetrazole derivatives (Sections 4.4-4.10). Within the limits of accuracy all bond lengths agree with expected values. The main distances and angles are mentioned (Tables 55-57).

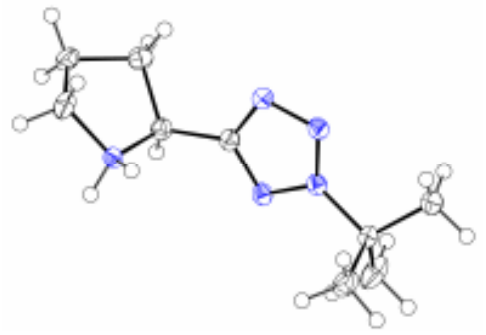


Figure 78. Structure of *(S)*-2-(2-*tert*-butyl-2*H*-tetrazol-5-yl) pyrrolidinium trifluoro acetate **244** in the crystal with thermal ellipsoids drawn at 50 % probability level

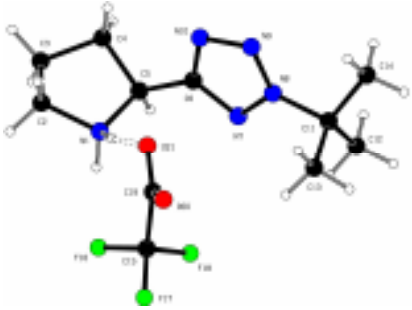


Figure 79. *(S)*-2-(2-*tert*-Butyl-2*H*-tetrazol-5-yl) pyrrolidinium trifluoro acetate **244**

The pyrrolidine ring has an envelope conformation on C3 and the distance between the tetrazole and the pyrrolidine rings is comparable to that found for **115** and **237** (Sections 4.4, 4.6) but shorter compared to 2-(1-methyl-1-phenyl-ethyl)-5-(*R*)-pyrrolidine-2-yl-tetrazole (Section 4.7). In the alkyl residue the environment of C11 is a slightly distorted tetrahedron (Table 55). The crystal packing is aided by intra-molecular N–H···O and N–H···F hydrogen bonds and by inter-molecular N-H···O hydrogen bonds between the pyrrolidine ring and the trifluoroacetic acetate along the a-axis (Table 50).

Table 55. Bond lengths [Å] for *(R)*-2-(2-*tert*-butyl-2*H*-tetrazol-5-yl) pyrrolidinium trifluoro acetate **244**

Atoms	Bond length
N1 - C2	1.505(2)
N1 - C5	1.5190(19)
C4 – C5	1.532(2)
C6 - N10	1.348(2)
C6 – N7	1.328(2)
C6 – C5	1.495(2)
N8 – N9	1.322(2)
N8 – N7	1.3292(18)
C11 – C14	1.515(2)

Table 56. Bond angles [°] for *(R)*-2-(2-*tert*-butyl-2*H*-tetrazol-5-yl) pyrrolidinium trifluoro acetate **244**

Atoms	Angle
C2 – N1 – C5	107.45(13)
C6 – C5 – N1	109.20(12)
N1 – C5 – C4	105.08(13)
N10 – C6 – N7	112.63(13)
N7 – N8 – C11	122.59(13)
C12 – C11 – C12	107.58(13)

Table 57. Torsion angles [°] for *(R)*-2-(2-*tert*-butyl-2*H*-tetrazol-5-yl) pyrrolidinium trifluoro acetate **244**

Atoms	Angle
N1 – C5 – C6 – N19	-89.33(17)
N10 – C6 – N7 – N8	0.31(15)
N8 – N9 – N10 – C6	0.75(15)
C6 – N7 – N8 – N9	0.19(15)
N7 – N8 – N9 – N10	-0.61(16)

Table 58. Hydrogen bonds [Å and °] for *(R)*-2-(2-*tert*-butyl-2*H*-tetrazol-5-yl) pyrrolidinium trifluoro acetate **244**

D-H···A		d(D-H)	d(H···A)	d(D···A)	<(DHA)
N1 - H1B...O21		0.87(2)	1.88(2)	2.7463(18)	171(2)
N1 - H1B...F16		0.87(2)	2.62(2)	3.0808(18)	113.9(17)
N1 - H1A...O20	#1	0.98(2)	1.76(2)	2.7331(19)	174.0(18)

Symmetry transformation used to generate equivalent atoms:

#1 x+1,y,z

4.10. 2-Isopropyl-5-*(R)*-pyrrolidine-2-yl-2*H*-tetrazole-squaric acid salt (250)

Brown single crystals suitable for X-ray analyses are obtained by slow evaporation of a methylene chloride solution (Figure 80; Chapter 5.3). This compound crystallizes in the orthorhombic space group $P2_12_12_1$, with a = 9.143(2) Å, b = 10.706(2) Å, c = 13.979(3) Å, Z = 4, V = 1368.3(5) $Å^3$, D_c = 1.433 g/cm^3, R_1 = 0.0235, wR_2 = 0.0576.

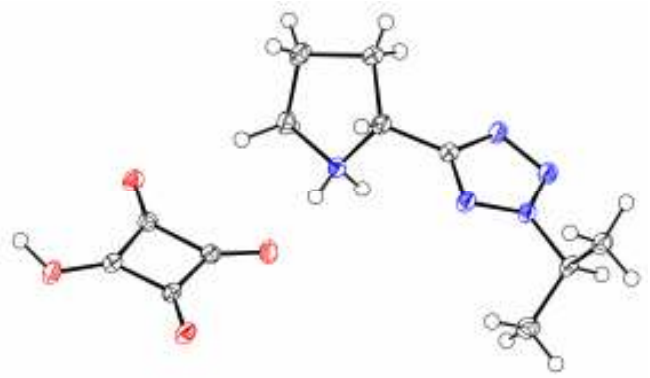


Figure 80. Structure of 2-isopropyl-5-*(R)*-pyrrolidine-2-yl-2*H*-tetrazole squaric acid salt **250** in the crystal with thermal ellipsoids drawn at 50 % probability level

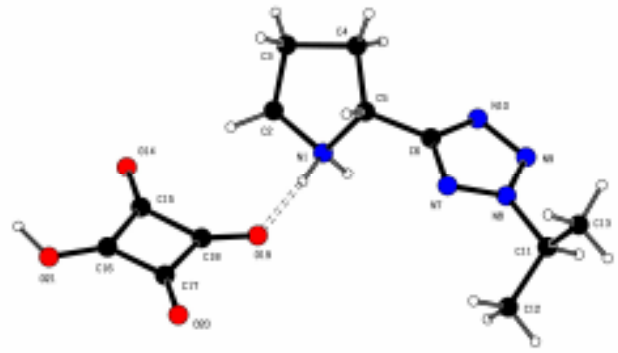


Figure 81. 2-Isopropyl-5-*(R)*-pyrrolidine-2-yl-2*H*-tetrazole squaric acid salt **250**

X-Ray diffraction shows that O19 in the cyclobutene moiety is H-bonded to N1 of the pyrrolidine ring (Figure 81). The 2-isopropyl-5-(*R*)-pyrrolidine-2-yl-2*H*-tetrazole squaric acid salt has the tetrazole and the pyrrolidine rings twisted with respect to one another, but the torsion angle is different to those found in the X-ray structures of the other pyrrolidine-tetrazole derivatives (Sections 4.4.-4.10)(Table 53). The dihedral angle between the squaric acid and the tetrazole ring is 14.42(8)°. Based on the method of Cramer and Pople,[314] the pyrrolidine ring has an envelope conformation on C4.

The distance between the pyrrolidine and the tetrazole rings is comparable to that of the (*R*)-5-pyrrolidine-2-yl-tetrazole **115** (Section 4.4.) and the 1-isopropyl-(*R*)-5-pyrrolidine-2-yl-1*H*-tetrazole **237** (Section 4.7.). Within the limits of accuracy all bond lengths and angels agree with expected values. The main distance and angles are mentioned (Tables 59-61).

Table 59. Bond lengths [Å] for 2-isopropyl-5-*(R)*-pyrrolidine-2-yl-2*H*-tetrazole squaric acid salt **250**

Atoms	Bond length
N1 – C2	1.5180(16)
N1 – C5	1.5235(16)
C5 – C6	1.4961(16)
C6 – N7	1.3275(16)
C6 – N10	1.3470(16)
N8 – C11	1.4794(15)
C11 – C12	1.5193(18)
C16 – C17	1.4330(17)
C18 – O19	1.2276(15)
C16 – O21	1.2944(15)
C15 – C18	1.5073(17)
C17 – C18	1.4793(17)

Table 60. Bond angles [°] for 2-isopropyl-5-*(R)*-pyrrolidine-2-yl-2*H*-tetrazole squaric acid salt **250**

Atoms	Angle
C2 - N1 - C5	107.97(9)
C6 – C5 – N1	109.17(10)
N1 – C5 – C4	116.80(10)
C5 – C6 – N7	122.58(10)
N7 - C6 – N10	112.82(10)
N7 – N8 – N9	114.04(10)
N8 – C11 – C12	109.21(10)
C16 – C15 – C18	88.10(9)
C16 – C18 – C17	88.95(9)

Table 61. Torsion angles [°] for **250**

Atoms	Angles [°]
N1 – C5 – C6 – N10	95.02(13)
N10 – C6 – N7 – N8	-0.98(12)
C6 – N7 – N8 – N9	0.88(12)
N7 – N8 – N9 – N10	-0.47(13)
C15 – C16 – C17 – C18	-2.14(9)
C16 – C17 – C18 – C15	2.07(9)

The crystal packing is aided by intra-molecular N–H···O hydrogen bonds between the pyrrolidine and the cyclobutene rings and by inter-molecular O–H···O hydrogen bonds between the cyclobutene rings along the b-axis (Table 62).

Table 62. Hydrogen bonds [Å and °] for 2-isopropyl-5-*(R)*-pyrrolidine-2-yl-2*H*-tetrazole squaric acid salt **250**

D-H···A		d(D-H)	d(H···A)	d(D···A)	<(DHA)
N1 - H1A...O19		0.919(18)	1.839(18)	2.7554(15)	175.1(17)
N1 - H1B...O14	#1	0.909(17)	2.005(17)	2.8487(14)	153.7(13)
O21 – H21...O20	#2	1.04(2)	1.46(2)	2.4970(12)	173.0(2)

Symmetry transformations used to generate equivalent atoms:

#1 -x+1,y+1/2,-z+3/2 #2 -x+2,y-1/2,-z+3/2

4.11. 2-[(1-Methyl-1-phenyl-ethyl)-2*H*-tetrazol-5-yl] pyrrolidinium saccharinate (248)

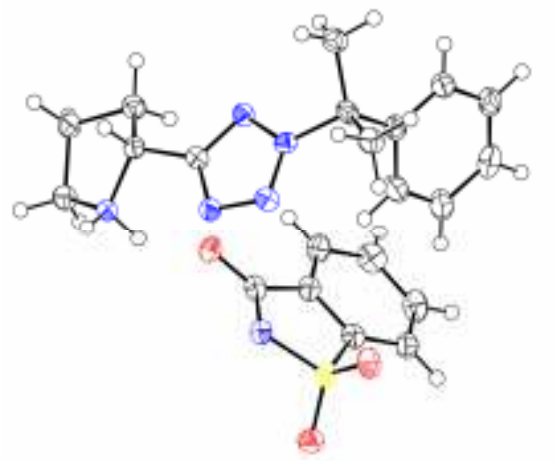
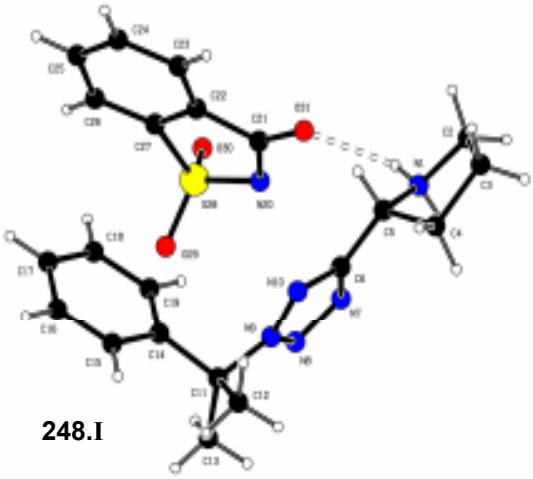
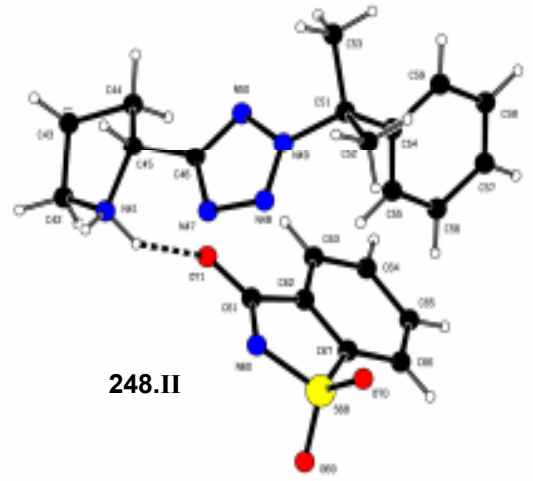


Figure 82. Structure of 2-[(1-methyl-1-phenyl-ethyl)-2*H*-tetrazol-5-yl] pyrrolidinium saccharinate **248** in the crystal with thermal ellipsoids drawn at 50 % probability level

Figure 83.



248.I



248.II

Colorless single crystals suitable for X-ray analyses are obtained by slow evaporation of a dichloromethane solution (Figure 82; Chapter 5.3). This compound crystallizes in the triclinic space group P1, with a = 9.721(2) Å, b = 9.821(3) Å, c = 12.530(3) Å, α = 99.4521(14)°, β = 91.691(13)°, γ = 112.443(14)°, Z = 2, V = 1085.0(5) $Å^3$, D_c = 1.348 g/cm^3, R_1 = 0.0553, wR_2 = 0.1161. The asymmetric unit has two molecules, each molecule has an hydrogen bond between the oxygen of the saccarinate and the NH of the pyrrolidine ring (Figure 83). The X-ray structure analysis of the 2-[(1-methyl-phenylethyl)-2*H*-tetrazol-5-yl] pyrrolidinium saccharinate **248** shows that the tetrazole and the pyrrolidine rings are twisted with respect to one another, but the torsion angles are different to those found in the other pyrrolidine-tetrazole derivatives (Sections 4.4.–4.10)(Table 65). The phenyl and tetrazole rings have a dihedral angles of 89.52(14)° in molecule **248.I** and 79.82(15)° in molecule **248.II**. The saccarinate moiety and the phenyl ring have a dihedral angle of 67.14(13)° in molecule **248.I** and 61.56(13)°

in molecule **248.II**. The distance between the tetrazole and the pyrrolidine rings are comparable to that found for molecule **235** (Table 65).

Within the limits of accuracy all bond lengths and angles agree with expected values. The main distances and angles are mentioned (Tables 63-65). The crystal packing is aided by intra-molecular N–H···O hydrogen bonds between the pyrrolidine ring and the saccarinate and by inter-molecular N–H···N hydrogen bonds (Table 66).

Table 63. Bond lengths [Å] **248**

Atoms	Bonds Length
N1 – C2	1.497(5)
N1 – C5	1.482(5)
C5 – C6	1.486(5)
N8 – N9	1.329(5)
N9 – N10	1.333(4)
N9 – C11	1.484(5)
C11 – C12	1.531(6)
C11 – C14	1.534(5)
C42 – N41	1.504(5)
N41 – C45	1.494(5)
C45 – C46	1.497(5)
N48 – N49	1.320(5)
N49 – N50	1.334(4)
N49 – C51	1.488(5)
C51 – C54	1.528(6)
C51 – C52	1.522(6)

Table 64. Angles [°] for **248**

Atoms	Angle
C2 - N1 - C5	105.9(3)
C6 – C5 – N1	110.8(3)
N1 – C5 – C4	101.9(3)
C6 – C5 – C4	117.7(3)
N10 – C6 – N7	112.5(3)
N7 – C6 – C5	124.6(3)
N7 – N8 – N9	106.1(3)
N9 – C11 – C12	105.3(3)
N9 – C11 – C13	108.2(3)
N9 – C11 – C14	107.8(3)
C45 – N41 – C42	107.8(3)
N41 – C45 – C46	110.2(3)
N41 – C45 – C44	103.8(3)
N47 – N48 – N49	106.2(3)
N49 – C51 – C53	106.4(3)
N49 – C51 – C52	107.8(3)
N49 – C51 – C54	108.9(3)

Table 65. Torsion angles [°] for 2-[(1-methyl-1-phenyl-ethyl)-2*H*-tetrazol-5-yl] pyrrolidinium saccharinate **248**

Atoms	Angle [°]
N1 – C5 – C6 – N10	-169.8(3)
N10 – C6 – N7 – N8	0.3(4)
C6 – N7 – N8 – N9	-1.0(4)
N7 – N8 – N9 – N10	1.4(4)
N41 – C45 – C46 – N50	151.3(3)
N50 – C46 – N47 – N48	0.1(4)
C46 – N47 – N48 – N49	0.2(4)

Table 66. Hydrogen bonds [Å and °] for 2-[(1-methyl-1-phenyl-ethyl)-2*H*-tetrazol-5-yl] pyrrolidinium saccharinate **248**

D-H···A		d(D-H)	d(H···A)	d(D···A)	<(DHA)
N1 - H1A...O31		0.82(5)	2.07(5)	2.739(4)	139(4)
N41 – H41A...O71		0.96(5)	1.80(5)	2.650(4)	146(4)
N1-H1A...N47	#1	0.82(5)	2.59(4)	3.012(5)	113(4)
N1-H1B...N60	#1	0.89(6)	1.99(6)	2.866(5)	166(5)
N41-H41B...N20	#2	0.86(5)	1.97(5)	2.773(5)	154(4)

Symmetry transformations used to generate equivalent atoms:

#1 x-1,y,z+1 #2 x+1,y,z-1

Chapter 5.
Expermental Part

All chemicals were obtained either from commercial suppliers or internal sources and used without further purification unless otherwise stated. The reagents and solvents are listed in each chapter of the experimental part. All reactions were carried out under an atmosphere of nitrogen or argon. All the products were satisfactorily characterized by melting point, TLC, UV, IR, ^{1}H and ^{13}C NMR, MS, HR-MS and when possible, comparison of their analytical data has been made with available literature data.

Melting points

All melting points were measured in open end glass capillary tubes on a Büchi 535 melting point apparatus and are uncorrected.

Thin-layer Chromatography

Thin-layer chromatographys were performed on Merck pre-coated glass silica gel plates of type 60 F_{254}. Compounds were identified with either ultraviolet light and / or iodine on silica gel and / or by treatment of the TLC plate with ninhydrin (5 % solution in ethanol) followed by heating.

Flash Chromatography

Compounds were purified on Merck silica gel 60, particle size 0.040-0.063 mm, at room temperature with a pressure of *ca*. 0.3 bar and eluted with the solvent system indicated.

High Performance Liquid Chromatography

HPLC analysis were performed with an Agilent Series 1100. The mobile phase was 0.5 % H_3PO_4 in water and acetonitrile, flow: 2 mL/min at 40 °C, injection volume: 5.0 µL, wavelength 220 nm. Column: Merck, Chromolith Performance RP-18e 100-4.6 mm.

UV / Vis Spectrometry

UV / Vis spectra were obtained using a Perkin Elmer Lambda19 UV / VIS / NIR spectrometer with the Perkin Elmer UV WinLab-Version 2.80.03 software or using a Varian Cary 300 Scan UV / VIS spectrophotometer with the Varian Cary WinUV 3.00 software. The performance of spectrophotometer in terms of wavelength and absorbance accuracy is monitored on a regular basis using reference materials (holmium glass). The spectra cover the UV as well as the visible light ranges (210 nm to 400 nm and 400 nm to 700 nm, respectively). The substance was dissolved in a solvent (methanol, ethanol or acetonitrile), measured using UV-transparent quartz cells with a 1 cm pathlengh and applying individual solvent-specific baseline correction. For each peak, the molar absorption is given in L/mol/cm.

Optical rotation

Optical rotation were measured on a Perkin Elmer polarimeter, Polarimeter 341, at the sodium D line (589 nm) at 20 °C. The solvent and concentrations (% m/m) are indicated. Optical rotations were obtained by subtracting zero- α-value of the solvent from the α-value of the sample solution. Before obtaining the α-value, all solutions (sample solutions and zero-value) were equilibrated at 20 °C for 15 minutes. The optical rotation value was calculated with the following formula: $[\alpha]_{\lambda}^{T}$

$$[\alpha]_{\lambda}^{T} = \frac{\alpha * V * 100}{m_s * 1 * (100 - LOD))}$$

$[\alpha]_{\lambda}^{T}$ = Specific optical rotation at the wavelength λ and temperature T;
α = Measured angle of rotation minus the zero value, with the corresponding sign in degrees; V = Volume of sample solution (mL); m_s = Mass (g) of sample; 1 = Path length of the cell (dm); *LOD* = Loss on drying of the sample in percent (if not determined: to be set to zero)

Infra-red spectrometry (IR)

Infrared spectra were measured as a solid film on a Bruker Hyperion microscope coupled with a Bruker TENSOR 27 FTIR spectrometer over a wave number range of 4000 - 600 cm^{-1}. Each sample was scanned 32 times with a 2 cm^{-1} resolution.

FT-IR spectrometry

FT-IR spectra were measured in solution on a Mettler Toledo ReactIR 4000 with a K6 conduit Dicomp probe over a wave number range of 4000 - 650 cm^{-1}. Each sample was scanned 128 times every 2 minutes.

Raman spectrometry

The FT-Raman spectrum were measured as solid on a Bruker RFS 100 FT Raman spectrometer equipped with a liquid nitrogen cooled germanium detector. The resolution was 4 cm^{-1} and 250 scans were accumulated by using a laser output of 250, 275 or 300 mW. The spectrum was corrected for instrumental response.

Nuclear magnetic resonance spectrometry (NMR)

NMR spectra were recorded on a Bruker dpX400 (operating at 400.13 MHz for ^{1}H and 100 Mz for ^{13}C) or a Bruker dpX500 (operating at 500.00 MHz for ^{1}H and 125 Mz for ^{13}C) or a Brukner dpX600 (operating at 600.00 MHz for ^{1}H and 150 Mz for ^{13}C) in the solvents indicated at 300 K and chemical shifts (in ppm) were referenced to residual solvent peaks ($CDCl_3$: 7.27 ppm for ^{1}H, 77.2 ppm for ^{13}C ; d_6-DMSO: 2.50 ppm for ^{1}H, 39.5 ppm for ^{13}C). Multiplicities are given as *s* = singlet, *d* = doublet, *t* = triplet, *q* = quartet, *m* = multiplet, *sep* = septet and *br* = broad signal.

Mass spectral data (MS)

Mass spectral data were recorded on a Water ZQ2000 Quadruple, electrospray mass spectrometer operating in positive or negative ion mode as indicated, or with a Varian 1200L Triple Quadrupole mass spectrometer.

High resolution (HR-MS) and high accuracy mass spectra

High resolution and high accuracy mass spectra were acquired on a 9.4 Tesla Bruker APEXIII Fourier Transform Ion Cyclotron Resonance Mass Spectrometer (FT / ICR -MS) equipped with an electrospray ion source operated in both positive and negative ion mode; 32 spectra were accumulated and internally calibrated using the signals from the Agilent ES tune mix solution.

X-Ray analyses

Diffraction data for all compounds were collected at 100 K with a Bruker AXS SMART 6000 CCD detector on a three-circle platform goniometer with Cu(K_α) radiation from a fine-focus sealed tube generator equipped with a graphite monochromator or a microfocus rotating anode equipped with multilayer optics. A semi-empirical absorption correction was applied, based on the intensities of symmetry-related reflections measured at different angular settings.[(1)] The structure was solved and refined on F^2 with the SHELXTL suite of programs.[(2)] Non-hydrogen atoms were refined with anisotropic displacement parameters, hydrogen atoms were located in DF maps and refined isotropically or in idealized positions using a riding model. Figures were generated with PLATON [(3)] or Mercury.[(4)]

Numeration of the structures

In most cases, the numbering of the structure is in agreement with the IUPAC name generated by the *Autonom*® program. In some cases, we have used arbitrary numbering, which is independent from the IUPAC name of the molecule.

(1) G. M. Sheldrick, SADABS, version 2004/1, University of Göttingen, Göttingen, Germany.
(2) G. M. Sheldrick, SHELXTL, version 6.12, Bruker AXS inc. Madison, Wisconsin, USA.
(3) A. L. Spek, PLATON, a Multi-Purpose Crystallographic Tool; Utrecht University: Utrecht, The Netherlands (http://www.cryst.chem.uu.nl/platon).
(4) C.F. Macrae, P.R. Edgington, P. McCabe, E. Pidcock, G.P. Shields, R. Taylor, M. Towler, J. van de Streek, *J. Appl. Cryst.* **2006**, *39*, 453.

5.1. Novel Click Chemistry for the Synthesis of 5-Substituted Tetrazoles from Organoaluminumazides and Nitriles Experimental part

5.1.1. Reagents and Solvents

All chemicals were obtained either from commercial suppliers or internal sources and used without further purification unless otherwise stated. The diethyl aluminum chloride was purchased from Sigma-Aldrich or Chemtura Organometallics (formerly Crompton GmbH). All reactions were carried out under an atmosphere of nitrogen or argon. All the products were satisfactorily characterized by melting point, TLC, UV, IR, ^{1}H and ^{13}C-NMR, MS, HR-MS and when possible, comparison of their analytical data has been made with available literature data.

5.1.1.1. Reagents

Reagent	Molecular Formula	MW (g/mol)	Quality
Acetic Acid	$C_4H_4O_2$	60.05	Fluka ; ≥96 %
1-Adamantane carbonitrile	$C_{11}H_{15}N$	161.25	Aldrich ; 97 %
Aluminum chloride anhydrous	$AlCl_3$	133.34	Fluka ; ≥ 99 % (AT)
Aluminum isopropoxide	$C_9H_{21}AlO_3$	204.25	Fluka ; > 98 % (Al)
Benzonitrile	C_7H_5N	103.13	Aldrich ; ≥ 99%
Benzylbromide	C_7H_7Br	171.04	Fluka ; ≥ 98 % (GC)
Benzylidenemalonitrile	$C_{10}H_6N_2$	154.17	Across ; 98 %
Bicyclo[4.2.0]-octa-1,3-triene-7-carbonitrile	C_9H_7N	129.16	Novartis ; 87 % (HPLC)
2-Bromo-1,3,2-benzodioxaborole	$C_6H_4BBrO_2$	198.82	Fluka ; ≥ 98 % (AT)
2-Bromobenzonitrile	C_7H_4BrN	182.03	Fluka ; ≥ 99 % (GC)
4'-Bromomethyl-biphenyl-2-carbonitrile	$C_{14}H_{10}BrN$	272.15	Novartis Production
But-2-ynedioic acid methyl ester	$C_6H_6O_4$	142.11	SEAC Lot2
ß-Chlorocatecholborane	$C_6H_4BClO_2$	154.36	Aldrich ; 97 &
2-Chlorobenzonitrile	C_7H_4ClN	137.57	Fluka ; ≥ 97 % (GC)

4-Chlorobenzonitrile	C_7H_4ClN	137.57	Fluka ; ≥ 97 % (Cl)
Cesium hydroxide Monohydrate	$CsHO.H_2O$	167.93	Fluka ; ≥ 95.0 % (T)
Cinnamonitrile	C_9H_5N	129.16	Fluka ; ≥ 97 % (GC)
4-Cyanobenzaldehyde	C_8H_5NO	131.14	Fluka ; ≥ 97 % (T)
4-Cyanobenzophenone	$C_{14}H_9NO$	207.23	Lancaster ; 98 %
4-Cyanophenyl-acetonitrile	$C_9H_6N_2$	142.16	Aldrich ; 97 %
2-Cyanopyridine	$C_6H_4N_2$	104.11	Aldrich ; 99 %
3-Cyanopyridine	$C_6H_4N_2$	104.11	Fluka ; ≥ 97 % (GC)
4-Cyanopyridine	$C_6H_4N_2$	104.11	Fluka ; ~ 98 % (GC)
(*S*)-2-Cyano-pyrrolidine-1-carboxylic acid benzyl ester	$C_{13}H_{14}N_2O_2$	230.27	Novartis
(*R*)-2-Cyano-pyrrolidine-1-carboxylic acid benzyl ester	$C_{13}H_{14}N_2O_2$	230.27	Novartis
(*S*)-2-Cyano-pyrrolidine-1-carboxylic acid *tert*-butyl ester	$C_{10}H_{16}N_2O_2$	196.25	Novartis
(*R*)-2-Tetrahydrofuran-2-carbonitrile	C_5H_7NO	97.15	Jülich Chemical Fine Lot H40183.01
Cyclohexene-1-carbonitrile	C_7H_9N	107.16	Lancaster ; 98 %
1,8-Diazabicyclo[5.4.0]undec-7-ene	$C_9H_{16}N_2$	152.24	Fluka ; ≥ 99.0 % (GC)
1,2-Dicyanobenzene	$C_8H_4N_2$	128.13	Aldrich ; 98 % (GC)
2,6-Pyridinedicarbonitrile	$C_7H_3N_3$	129.12	Aldrich ; 97 %
Diethylaluminum chloride	$C_4H_{10}AlCl$	120.56	Aldrich ; 1.8 M in toluene Chemtura Organometallics
Diisobutylaluminum chloride	$C_8H_{18}AlCl$	176.67	Aldich ; 97 %
Dimethylaluminum chloride	C_2H_6AlCl	92.51	Aldrich ; 1.0 M in Hexane
Dimethylcyanamide	$C_3H_6N_2$	70.09	Across ; 97 %
2,2-Diphenylpropionitrile	$C_{15}H_{13}N$	207.28	Alfa Aesar ; 97 %
Ethyl cyanoformate	$C_4H_5NO_2$	99.09	Fluka ; ≥ 98 % (GC)
2-Fluorobenzonitrile	C_7H_4FN	121.12	Fluka ; ≥ 98 % (GC)
4-Fluorobenzonitrile	C_7H_4FN	121.12	Merck ; > 99 % (GC)
Fumaronitrile	$C_4H_2N_2$	78.07	Lancaster ; 98+ %
2-Furonitrile	C_5H_3NO	93.09	Lancaster ; 98+ %
Hydrochloric acid	HCl	36.46	Fluka ; 2N standard solution Fluka ; ≥ 36.5 % (T)
2-Hydroxybenzonitrile	C_7H_5NO	119	Fluka ; ≥ 99 % (NT)
2-Iodobenzonitrile	C_7H_4NI	229.02	Trans World Chemicals 98%
6-Isopropyl-4-oxo-4H-chromene-3-carbonitrile	$C_{13}H_{11}NO_2$	213.24	Novartis
DL-Lactonitrile	C_3H_5NO	71.08	Fluka ; > 97.0 % (T)
Mandelonitrile	C_8H_7NO	133.15	Aldrich ; Tech.
(R)-(+)-Mandelonitrile	C_8H_7NO	133.15	Aldrich ; 97 %
Malononitrile	$C_3H_2N_2$	66.06	Fluka ; ≥ 98.0 % (GC)
5-(4'-Methyl-biphenyl-2yl)-1*H*-tetrazole	$C_{14}H_{12}N_4$	236.27	Novartis

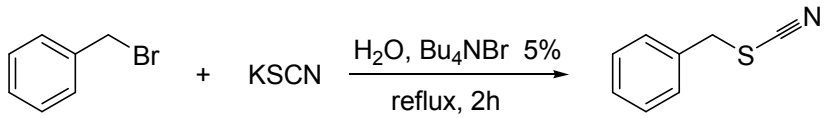
Methyl-4-formylbenzoate	$C_9H_8O_3$	164.16	Fluka ; ~95 % (HPLC)
α-Methylphenylacetonitrile	C_9H_9N	131.18	Alfa Aesar ; 97 %
Methyl phenylpropionate	$C_{10}H_8O_2$	160.17	Aldrich ; 97 %
Ninhydrin	$C_9H_6O_4$	178.14	Fluka ; ≥ 95.0 % (UV)
R-2-(4-Nitrobenezene- sulfonyloxy)-4-phenyl-butyrric acid ethyl ester	$C_{18}H_{19}NO_7S$	393.42	Novartis
4-Nitrobenzonitrile	$C_7H_5N_2$	148.12	Lancaster ; 97 %
Palladium on carbon	Pd	106.4	Engelhard 4505 ; Pd/C 10%
α-Methylbenzyl cyanide	C_9H_9N	131.17	Aldrich ; 96 %
Phenylsulphonyl acetonitile	$C_8H_7NO_2S$	181.22	Lancaster ; 98 %
Phenylthio-acetonitrile	C_8H_7NS	149.22	Fluka ; ≥ 95 % (GC)
Potassium carbonate	K_2CO_3	138.27	Fluka ; ≥ 99 % (AT)
Potassium hydrogen sulfate	$KHSO_4$	136.17	Riedel-deHaen ; Puriss.p.a.
Potassium hydroxide	KOH	56.11	Fluka ; ≥ 86 % (T)
Potassium thiocyanate	CKSNS	97.18	Fluka ; ≥ 99 % (AT)
Pyrazinecarbonitrile	$C_5H_3N_3$	105.1	Aldrich ; 99 %
2,6-Pyridine-dicarbonitrile	$C_7H_3N_3$	129.12	Aldrich ; 97 %
Pyrrole-2-carbonitrile	$C_5H_4N_2$	92.10	Lancaster ; 99 %
Sodium azide	NaN_3	65.01	Aldich ; 99 %
Sodium hydroxyde	NaOH	40.00	Fluka ; ≥ 97.0 % (T) Fluka ; p.a. ≥ 98 % (T)
Sodium nitrite	$NaNO_2$	69.00	Aldrich ; 99.5 %
Tetrabutylammonium bromide	$C_{16}H_{13}BrN$	322.38	Fluka ; ≥ 99 % (Br)
Thiophene-2-carbonitrile	C_5H_3NO	109.15	Lancaster ; 99 %
o-Tolunitrile	C_8H_7N	117.15	Merck ; For synthesis
trans-Cyclobutane-1,2-dicarbonitrile	$C_6H_6N_2$	106.13	Fluka ; ≥ 97 % (GC)
Triethyl aluminum	$C_6H_{15}Al$	114.17	Fluka ; ~1.8 M in toluene
2-Trifluoromethyl-phenyl-acetonitrile	$C_9H_6F_3N$	185.15	Lancaster ; 97 %
Trimethylsilylazide	$C_3H_9N_3Si$	115.21	Fluka ; ~ 97 % (GC)
Zinc chloride	$ZnCl_2$	136.29	Fluka ; ≥ 98.0 % (AT)

5.1.1.2. Solvents

Solvents	Quality
Acetonitrile	Merck ; for LC ARMAR Chemicals ; d_3-Acetonitrile 99.5 Atom % D
1-Butanol	Aldrich ; ≥ 99.5 %
Dichloromethane	Merck ; for analysis Fluka ; 99.5 % (GC)
Diethyl ether	Fluka; puriss. over molecular sieves
Dimethylformamide	Fluka; puriss. p.a., ≥ 99.8 %
Ethanol	Fluka ; absolute, ≥ 99.8 % (V/V) (GC)
Ethyl acetate	Fluka ; 99.5 %
Methanol	Fluka ; for analysis
Dichloromethane	Fluka; puriss. over molecular sieves
Toluene	Fluka ; puriss. over molecular sieve (H_2O ≤ 0.005 %) Fluka ; absolute, over sieve, ≥ 99.5 % (GC)

5.1.2. Synthesis of the Starting Material

Benzylthiocyanate (16)

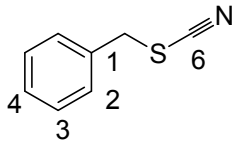


68 **16**

CAS Registry Number	3012-37-1
Molecular Formula	C_8H_7NS
Molecular Weight	149.22 g/mol
Methodology Ref.	W. P. Reeves, M. R. White, R. G. Hilbrich, L. L. Biegert, *Synth. Commun*. **1977**, *6*, 509
Analysis Ref.	a) C. R. Harrison, P. Hodge, *Synthesis* **1980**, *4*, 299; b) P. Molina, M. Alajarin, A. Ferao, M. J. Lidon, P. H. Fresneda, M. J. Vilarlana, *Synthesis* **1982**, *6*, 472; c) H. R. Snyder, J. C. Speck, *J. Am. Chem. Soc*. **1939**, *61*, 668; d) S. D. Ross, M. Finkelstein, R. C. Petersen, *J. Am. Chem. Soc*. **1961**, *83*, 4853; e) P.-Y. Renard, H. Schweber, P. Vayron, L. Josien, A. Valleix, C. Mioskowki,*Chem. Eur. J*. **2002**, *8*, 2910; f) H. L. Wheeler, H. F. Merraam, *J. Am. Chem. Soc*. **1901**, *23*, 283; g) J. F. King, T. Y. Tsang, M. M. Sbdel-Malik, N.C. Payne, *J. Am. Chem. Soc*. **1985,** *107*, 3224; h) Y. Yamamoto, Y. Morita, *Chem. Pharm. Bull.* **1984,** *32*, 2957; i) H. Maeda, T. Kawaguchi, M. Masaui, H. Ohmori, *Chem. Pharm. Bull.* **1990**, *38*, 1389; l) N. Iranpoor, H. Firouzabad, H. Shaterian, *Syn. Lett.* **2000**, *1*, 65

A 100 mL, three necked round bottomed flask, equipped with an overhead mechanical stirrer, is charged, at r.t., with benzylbromide (11.88 mL, 100 mmol), potassium thiocynate (38.88 g, 200 mmol, solution 50 % in water), and tetrabutyl ammonium bromide (1.611 g, 5 mmol). The resulting mixture is refluxed at 110 °C for two hours. The mixture is cooled down at r.t., and the product is extracted three times with ethyl acetate (20 mL portion). The combined organic phase is washed twice with water (30 mL portion). The solvent is removed, and the crude is subjected to bulb-to-bulb distillation (110-115 °C at $5.0 \cdot 10^{-1}$ mbar) to give the product as a yellow crystalline material (14.44 g, 97 % of yield).

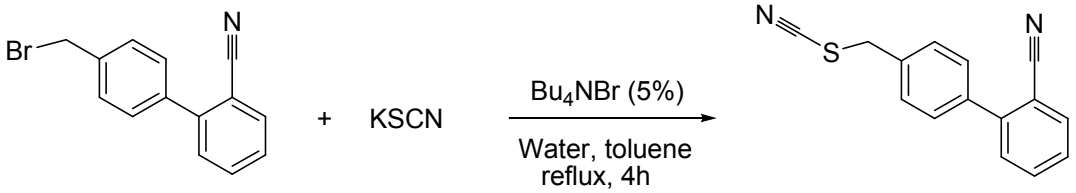
Compound characterization data:



mp: 37-40 °C; **TLC:** R_f(hexane / AcOEt 8:1) = 0.3; **HPLC:** 7.98 min; **UV** (EtOH): λ_{max}, nm (ε): 222 (8000), 201 (1690); **IR:** *v* 3063 (*w*, ν(C-H)), 2962 (*w,* ν(C-H)), 2147 (*s*, ν(C≡N)), 1493 (*w*, ν(C=C)), 1455 (*s*, ν(C=C)), 1427 (*s*, ν(C=C)), 769 (*s*, γ(C-H, Ph)), 698

(*s*, γ(Ph)) cm^{-1}; **^{1}H NMR** (400 MHz, d_6-DMSO): δ = 4.35 (*s*, 2H, H-C_5), 7.35 (*m*, 1H, H-C_4), 7.38 (*m*, 2H, H-C_3), 7.40 (*m*, 2H, H-C_2); **^{13}C NMR** (125 MHz, d_6-DMSO): δ = 37.4 (CH_2, C_5), 113,4 (CN, C_6), 128.7 (CH, C_4), 129.2 (CH, C_2), 129.5 (CH, C_3), 136.6 (Cq, C_1); **MS:** *m/z* 149 $[M]^+$, 129 $[M\text{-}HCN]^+$, 91 $[M\text{-}SCN]^+$.

4'-Thiocyanato methyl-biphenyl-2-carbonitrile (70)

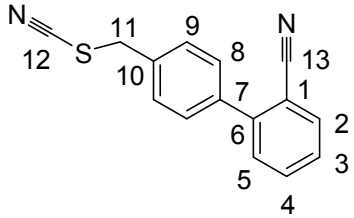


69 **70**

Molecular Formula	$C_{15}H_{10}N_2S$
Molecular Weight	250.32 g/mol
Methodology Ref.	W. P. Reeves, M. R. White, R. G. Hilbrich, L. L. Biegert, *Synth. Commun*. **1977**, *6*, 509

A 100 mL, three necked round-bottomed flask, is chaged, at r.t., with 4'-bromomethyl-biphenyl-2-carbonitrile (6.804 g, 25 mmol), dissolved in toluene (20 mL), potassium thiocynate (9.8 mL, 50 mmol, solution 50 %), and tetrabutyl ammonium bromide (403 mg, 1.25 mmol). The mixture is refluxed at 110 °C for four hours. The mixture is cooled to room temperature and the organic phase is separated, and washed twice with water (15 mL portion). The combined aqueous phase is extracted twice with toluene (10 mL portion). The solvent is removed, and the product is crystallized from ethyl acetate and diethyl ether to give the product as a yellow crystalline material (6.27 g, 99 % yield).

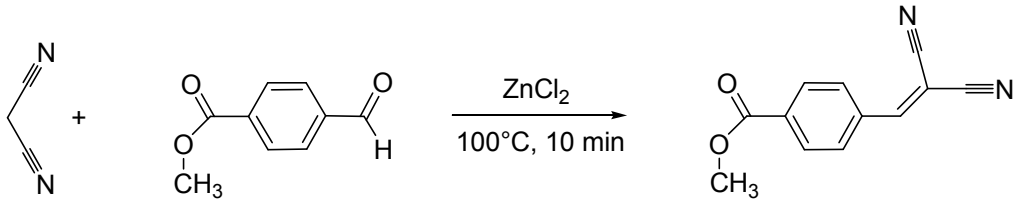
Compound characterization data:



mp: 88-90 °C; **TLC:** R_f (EtOAc / hexane 1:3) = 0.4; **HPLC:** 10.10 min; **UV** (EtOH): λ_{max}, nm (ε): 287 (5700), 255 (14340), 205 (4120); **IR:** ν 3037 (*w*, ν(C-H)), 2218 (*vs,* ν(Ar-C≡N), 2150 (*m*, ν(C≡N, -SCN)), 1595 (*w*, ν(C=C)), 1478 (*s* ν(C=C)), 851 (*m*, γ(C-H, Ph)), 773 (*s*, γ(C-H, Ph)) cm^{-1}; **^{1}H NMR** (400 MHz, d_6-DMSO): δ = 4.40 (*s*, 2H, H-C_{11}), 7.55 (*m*, 2H, H-C_9), 7.57 (*m*, 1H, H-C_3), 7.61 (*m*, 2H, H-C_8), 7.64 (*m*, 1H, H-C_5), 7.78 (*dt*, ^3J = 7.8 Hz, ^4J = 1.3 Hz, 1H, H-C_4), 7.94 (*m*, ^3J = 7.7 Hz, 1H, H-C_2); **^{13}C NMR**

(125 MHz, d_6-DMSO): δ = 36.6 (CH_2, C_{11}), 110.1 (Cq, C_1), 113.1 (Cq, C_{12}), 118.6 (Cq, C_{13}), 128.3 (CH, C_3), 129.2 (CH, C_9), 129.4 (CH, C_8), 130.1 (CH, C_5), 133.4 (CH, C_4), 133.8 (CH, C_2), 136.8 (Cq, C_{10}), 137.8 (Cq, C_7), 144.0 (Cq, C_6); **HR-MS:** calc'd for $[MNH_4]^+$ = 268.0903, found 268.0902 (ΔM (ppm) = 0.2), calc'd for $[MNa]^+$ = 273.0457, found 273.0456 (ΔM (ppm) = 0.4), calc'd for $[MK]^+$ = 289.0196, found 289.0197 (ΔM (ppm) = 0.2).

4-(2,2-Dicyanoethenyl)- benzoic acid methyl ester (73)

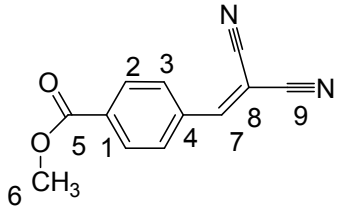


71 **72** **73**

CAS Registry Number	3129-16-6
Molecular Formula	$C_{12}H_8N_2O_2$
Molecular Weight	212.21 g/mol
Methodology Ref.	P. S. Rao, R. V. Venkataratnam, *Tetrahedron Lett.* **1991**, *32*, 5821
Analysis Ref.	T. B. Posner, C. D. Dennis, *J. Chem. Soc.*Perkin Trans. 2, **1976**, *6*, 729

A 25 mL, three necked round bottomed flask is charged at room temperature, with malonitrile (1.980 g, 30 mmol), methyl-4-formylbenzoate (4.923 g, 30 mmol) and zinc chloride (403 mg, 3 mmol). The mixture is warmed and kept at 100 °C for fifteen minutes. The resulting heterogenic mixture is cooled to room temperature, washed once with aqueous methanol (40 mL, 5 % solution) and filtered to give the product as a yellow crystalline material (5.99 g, 94 % yield).

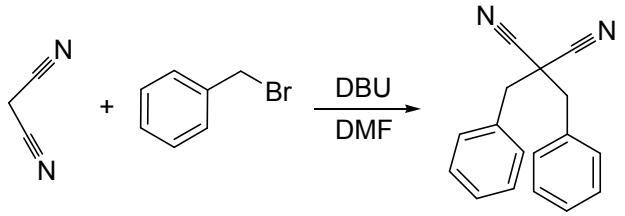
Compound characterization data:



mp: 152-160 °C; **TLC:** R_f(toluene / EtOAc 3:1) = 0.68; **HPLC:** 7.66 min; **UV** (MeOH): λ_{max}, nm (ε): 306 (25700); **IR:** ν 3080 (*w*, ν(C-H)), 3038 (*w*, ν(C-H)), 2960 (*w*, ν(C-H)), 2231 (*s*, ν(C≡N)), 1714 (*vs*, ν(C=O)), 1591 (*m*, ν(C=C)), 1561 (*s*, ν(C=C)), 1432 (*m*, ν(C=C)), 1291 (*s*, ν(C-O)), 1118 (*m*, ν(C-O)), 823 (*w*, γ(C-H, Ph) cm^{-1}; **^{1}H NMR** (400 MHz, d_6-DMSO): δ = 3.69 (*s*, 3H, H-C_6), 8.04 (*d*, $^3J_{2,3}$ = 6.9 Hz, 2H, H-C_3), 8.14 (*d*, $^3J_{2,3}$

= 6.9 Hz, 2H, H-C_2), 8.65 (*s*, 1H, H-C_7); **^{13}C NMR** (125 MHz, d_6-DMSO): δ = 52.6 (CH_3, C_6), 84.3 (Cq, C_8), 112.8 (Cq, CN), 113.9 (Cq, CN), 129.8 (CH, C_3), 130.5 (CH, C_2), 133.6 (Cq, C_1), 135.1 (Cq, C_4), 160.3 (CH, C_7), 165.2 (Cq, C_5); **MS:** *m/z* 212 $[M]^+$, 181 $[M\text{-}OCH_3]^+$, 153 $[M\text{-}COOCH_3]^+$.

2,2-Dibenzyl-malonitrile (74)

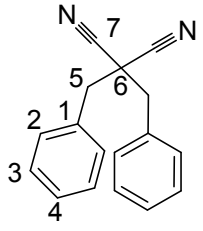


71 **68** **74**

CAS Registry Number	3779-31-5
Molecular Formula	$C_{17}H_{14}N_2$
Molecular Weight	246.31 g/mol
Methodology Ref.	T.-Y. Tsai, K.-S. Shia, H.-J. Liu, *Synlett* **2003**, *1*, 97
Analysis Ref.	a) J. J. Bloomfield, *J. Org. Chem.* **1961**, *26*, 4112; b) H. Normant, T. Cuvigny, *Bull. Soc. Chim. Fr.* **1965**, 1881; c) R. Sommer, W. P. Neumann, *Angew. Chem.* **1966**, *78*, 546; d) K. Friedrich, J. Rieser, *Synthesis* **1970**, *2*, 479; e) E. Diez-Barra, A. De la Hoz, A. Moreno, P. Sanchez-Verdu, *J. Chem. Soc.*, Perkin Trans. 1, **1991**, *10*, 2589; f) E. Diez-Barra, A. De la Hoz, A. Moreno, P. Sanchez-Verdu, *J. Chem. Soc.*, Perkin Trans. 1, **1991**, *10*, 2589

A 25 mL, three necked round-bottomed flask, is charged at room temperature, with malononitrile (330 mg, 5 mmol) dissolved in DMF (5 mL), 1.643 ml of DBU (1.643 mL, 12 mmol)(exothermic from 20 to 40 °C) and benzylbromide (1.3 mL, 11 mmol). The mixture is stirred height hours at 80 °C. The mixture is added, at 0 °C, drop wise to a solution of HCl (1 M) to give an heterogeneous brown mixture. The product is extracted three times with ethyl acetate (15 mL portion). The combined organic phase is washed wice with HCl (1 M, 15 mL portion). The solvent is removed to give the product as a brown oil which solidificates at room temperature (1.32 g, 80 % yield).

Compound characterization data:

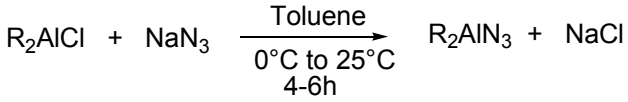


mp: 118-121 °C; **TLC:** R_f (toluene / EtOAc / AcOH 20:20:1) = 0.84; **HPLC:** 11.08 min; **UV** (EtOH): λ_{max}, nm (ε): 350 (570), 264 (790), 258 (850), 205 (15440); **IR:** ν 3080 (*w*, ν(C-H)), 309 (*w*, ν(C-H)), 2935 (*w*, ν(CH_2)), 2192 (*w,* ν(C≡N)), 1587 (*w*, ν(C=C)), 1497 (*s*, ν(C=C)), 1457 (*m*, ν(C=C)), 762 (*s*, γ(C-H, Ph)), 702 (*s*, γ(Ph)) cm^{-1}; **^{1}H NMR** (500 MHz, d_6-DMSO): δ = 3.49 (*s*, CH_2, H-C_5), 7.43 (*m*, 10H, H-C_{2-4}); **^{13}C NMR** (125 MHz, d_6-DMSO): δ = 41.4 (CH_2, C_5), 41.9 (Cq, C_6), 115.4 (Cq, C_7), 128.0 (CH, C_4), 128.3, 130.3 (CH, $C_{2,3}$), 133.5 (Cq, C_1); **MS:** *m/z* 246 $[MH]^+$, 91 $[PhCH_2]^+$.

5.1.3. Synthesis of Tetrazoles and Triazoles with Dialkylaluminum Azides

5.1.3.1. Typical procedures for the syntesis of 5-substituted tetrazoles

5.1.3.1.1. Typical procedure for the preparation of dialkylaluminum azide



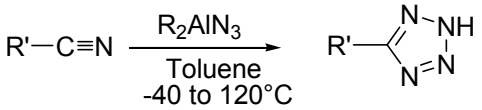
Scheme 137. Preparation of the dialkylaluminum azide

Notes: diethylaluminum chloride can be used in different solvents and molarities by following the same general procedure. For example solutions of diethylaluminum chloride were used in 1.8 M in toluene, in 2.5 M in toluene, in 2.7 M in xylene.

A 100 ml, four-necked, oven dried round-bottomed flask equipped with an overhead mechanical stirrer, is charged, at 0 °C, under an atmosphere of argon, with of sodium azide (5.46 g, 84 mmol). Diethylaluminum chloride (46.7 mL, 84 mmol, 2.7 M in toluene) are added with a syringe. After 15 minutes, the white heterogeneous mixture is gradually warmed to room temperature, and stirred for four to six hours. During the formation of the reagent, a suspension of sodium chloride is formed.

5.1.3.1.2. TP1: Typical procedure for 1-3 dipolar cycloadditions between dialkylaluminum azide and nitriles for the tetrazole ring formation

Cycloaddition:



Scheme 138. Synthesis of 5-substituted tetrazole

A 100 ml, four-necked, oven dried round-bottomed flask equipped with an overhead mechanical stirrer, containing a white suspension of diethylaluminum azide (84

mol, 2.7 M in toluene) is charged, at room temperature, under atmosphere of argon, with phenylsulphonyl acetonitrile (10.87 g, 60 mmol) in two equal portions in intervals of five minutes. The mixture is gradually heated to 55 °C (external temperature) and stirred for two hours.

Work up:

$$HNO_2 + HN_{3\,(g)} \rightarrow N_{2\,(g)} + N_2O_{\,(g)} + H_2O$$

Equation 1. Safe removal of hydrazoic acid

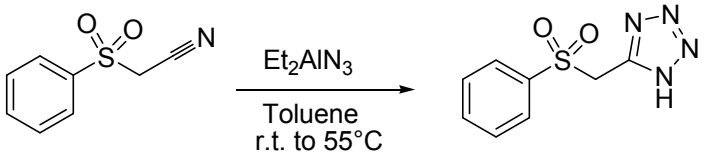
When the HPLC and the TLC analysis show >98 % conversion the reaction mixture is cooled to 0 °C and, to destroy the excess of azide, added to a solution of NaOH (15 %, 67 mL, 252 mmol), containing sodium nitrite (17.38 g, 252 mmol) (pH 13.5) (Equation 1). The pH is adjusted to 1.5 with 6M HCl . The biphasic mixture is transferred to a separatory funnel, and the product is extracted three times with ethyl acetate (20 mL portion); the combined organic phase is washed once with water (20 mL), and then concentrated by rotary evaporation (45 °C, 210 to 50 mbar) to afford 13.0 g of crude product which is re-dissolved in ethyl acetate (30 mL), transferred to a separatory funnel, and extracted three times with potassium carbonate (10 % solution, 25 mL portion) to the aqueous phase as the potassium salt (pH 11). The combined basic aqueous phase is cooled to 0 °C under stirring and carefully treated with 6M HCl to adjust the pH to 2.5, monitored with pH-paper or electrode. The product is extracted three times with ethyl acetate (20 ml portion). The combined organic phase is washed once with water (30 ml). The solvent is removed to give the tetrazole **75** as a yellow crystalline material which is crystallized from ethyl acetate / toluene (10.23 g, 76 %).

5.1.3.1.3. TP2: Typical procedure for the protection of the hydroxyl group for synthesis of the compounds 95, 100, 101 and 102

A 25 mL, two necked, oven dried round bottomed flask equipped with a stirring bar, is charged, under atmosphere of argon, with triethylaluminum (5 mL, 9 mmol, 1.8 M in toluene). The solution is cooled to 0 °C and the mandelonitrile (0.88 mL, 7 mmol) is carefully added over 15 minutes (exothermic from 0 to 40 °C). The mixture is stirred two hours from 0 °C to room temperature.

5.1.3.2. Synthesis of tetrazoles in the presence of sulfony, thio, thiocyano functional groups

5-Phenylsulfonylmethyl-1*H*-tetrazole (75)

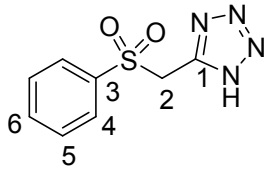


269 **75**

CAS Registry Number	54971-66-3
Molecular Formula	$C_8H_8N_4O_2S$
Molecular Weight	224.24 g/mol
Analysis Ref.	J. Polanski, K. Jarzembeck, *Pure Appl. Chem.* **2002**, *74*, 1227

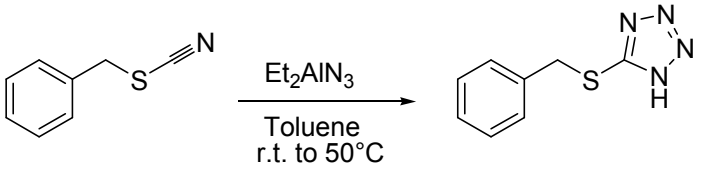
TP1: 1.4 equivalent of diethylaluminum azide (2.5 M in toluene) are used in a 60 mmol scale experiment. The reaction is heated for three hours at 55 °C to give 10.23 g of product as a yellow crystalline material after crystallization from toluene (76 % yield). The same reaction was done with 1.4 equivalent of diisobutylaluminum azide to obtain the same yield.

Compound characterization data:



mp: 172-174 °C; **TLC:** R_f (toluene / EtOAc / AcOH 20:20:1) = 0.44; **HPLC:** 3.60 min; **UV** (acetonitrile): λ_{max}, nm (ε): 271 (ε = 1610), 264 (1870), 217 (17520), 194 (39300); **IR:** ν 3000 (*m*, ν(C-H)), 2700-2500 (*brm*, ν(N-H)), 1555 (*w*, tetrazole), 1447 (*m*, ν(C=C)), 1401 (*m*, δ_{sim} (CH_2)), 1297 (*s*, $\nu_{asim}(SO_2)$), 1151 (*s*, $\nu_{sim}(SO_2)$) cm^{-1}; **^{1}H NMR** (500 MHz, d_6-DMSO): δ = 5.22 (*s*, 2H, H-C_2), 7.64 (*dd*, *J* = 8.8, 7.0 Hz, 2H, H-C_5), 7.77 (*m*, 3H, H-$C_{4,6}$), 17.05 (*br*, NH); **^{13}C NMR** (125 MHz, d_6-DMSO): δ = 50.3 (CH_2, C_2), 128.0 (CH, C_4), 129.5 (CH, C_5), 134.5 (CH, C_6), 137.9 (Cq, C_3), 148.5 (Cq, C_1); **MS:** *m/z* 223 [M-H^-], 141 [M-$CH_2CN_4H]^-$.

5-(Benzylthio)-*1H*-tetrazole (17)

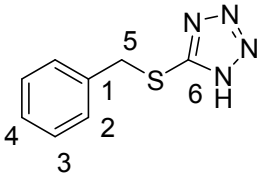


16 **17**

CAS Registry Number	21871-47-6
Molecular Formula	$C_8H_8N_4S$
Molecular Weight	192.24 g/mol
Analysis Ref.	a) W. G. Finnegan, R. A. Henry, R. Lofquist, *J. Am. Chem. Soc.* **1958**, *80*, 3908; b) E. B. W. LeBlanc, B. S. Banko, *Synth. Commun.* **1998**, *28*, 3591; c) Lieber Z. P. Demko, K. B. Sharpless, *J. Org. Chem.* **2001**, *66*, 7945, T. Enkoji, *J. Org. Chem.* **1961**, *26*, 4472

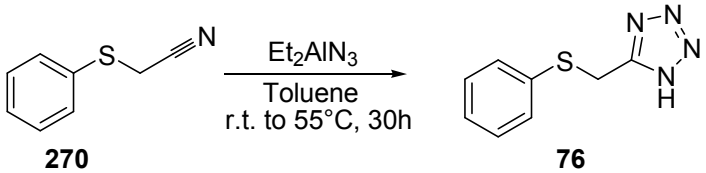
TP1: 1.5 equivalent of dithylaluminum azide (2.5 M in toluene) are used in a 20 mmol scale experiment. The reaction is heated for four hours and 30 min at 45 °C to give the product as a yellow crystalline material (1.77 g, 46 % yield).

Compound characterization data:



mp: 134-136 °C; **TLC:** R_f (toluene / EtOAc / AcOH 20:20:1) = 0.28; **HPLC:** 6.28 min; **UV** (acetonitrile): λ_{max}, nm (ε): 201 (30190); **IR:** ν 3050 (*w*, ν(C-H)), 2800-2200 (*brm*, ν(N-H)), 1532 (*m*, tetrazole), 1493 (*m,* ν(C=C)), 1454 (*m*, ν(C=C)), 1433 (*m*, ν(C=C)) cm^{-1}; **^{1}H NMR** (500 MHz, d_6-DMSO) δ = 4.50 (*s*, 2H, H-C_5), 7.26 (*t*, $^3J_{3,4}$ = 7.3 Hz, 1H, H-C_4), 7.31 (*t*, $^3J_{3,4}$ = $^3J_{2,3}$ = 7.3 Hz, 2H, ArH), 7.39 (*d*, $^3J_{2,3}$ = 7.3 Hz, 2H, ArH), 16.59 (*br,* NH); **^{13}C NMR** (125 MHz, d_6-DMSO) δ = 36.4 (CH_2, C_5), 128.1 (CH, C_4), 129.0 (CH, C_2), 129.3 (CH, C_3), 137.1 (Cq, C_1), 153.7 (Cq, C_6); **MS:** *m/z* 193 $[M+H]^+$, 191 $[M-H]^-$, 91 $[M-SCN_4H]^+$; **X-Ray:** the structure was confirmed by X-ray analysis (See X-ray discussion; Section 4).

Phenylsulfanylmethyl-1*H*-tetrazole (76)

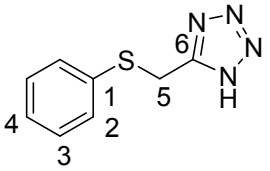


270 **76**

CAS Registry Number	18527-28-1
Molecular Formula	$C_8H_8N_4S$
Molecular Weight	192.24 g/mol
Analysis Ref.	a) R. L. Buchman, R. A. Portyka, Bristol-Myers Co. U.S. **1967**, US 3337576; b) R. L. Buchman, V. Spancmanis, R. A. Portyka, *J. Med. Chem.* **1969**, *12*, 1001; c) G. Sedelmeier, Novartis Pharma AG, **2005**, WO2005/14602 A1

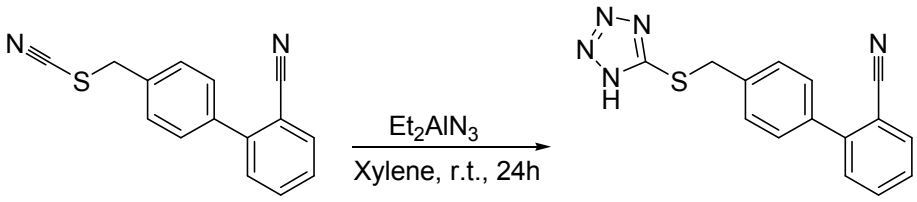
TP1: 1.4 equivalent of diethylaluminum azide (2.5 M in toluene) are used in a 6 mmol scale experiment. The reaction is heated for thirty hours at 55 °C to give the product as a yellow solide after crystallization from toluene (990 mg, 86 % yield).

Compound characterization data:



mp: 106-108 °C; **TLC:** R_f (toluene / AcOEt / AcOH 20:20:1) = 0.26; **HPLC:** 5.14 min; **UV** (EtOH): λ_{max}, nm (ε): 251 (3570); **IR:** ν 3100-2400 (*brs*, ν(N-H)), 3100 (*s*, ν(C-H)), 2974 (*s* ν(C-H), 1950-1750 (*w*, overtones γ(C-H, Ph)), 1571 (*s*, ν(C=C)), 1471 (*w*, ν(C=C)), 1439 (*s*, ν(C=C)) cm^{-1}; **^{1}H NMR** (500 MHz, d_6-DMSO): δ = 4.54 (*s*, 2H, H-C_5), 7.21 *m*, 1H, H-C_4), 7.30 (*m*, 2H, H-C_3), 7.34 (*m*, 2H, H-C_2), 16.40 (*br*, NH); **^{13}C NMR** (125 MHz, d_6-DMSO): δ = 24.8 (CH_2, C_5), 126.7 (CH, C_4), 128.9 (CH, Ar), 129.2 (CH, Ar), 134.0 (Cq, C_1), 155.0 (Cq, C_6); **MS:** *m/z* 191 $[M-H]^-$.

4'-(1*H*-Tetrazol-5-yl-sulfanylmethyl)-biphenyl-2-carbonitrile (77)

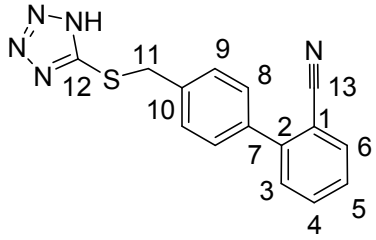


70 **77**

Molecular Formula	$C_{15}H_{11}N_5S$
Molecular Weight	293.35 g/mol

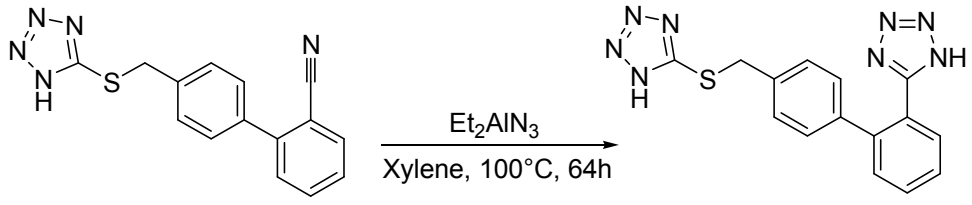
TP1: 1.5 equivalent of diethylaluminum azide (2.7 M in xylene) are used in a 3 mmol scale experiment. The reaction is stirred for twenty four hours at room temperature to give the product as an off white crystalline material (768 mg, 87 % yield).

Compound characterization data:



mp: 157-160 °C; **TLC:** R_f (toluene / EtOAc / AcOH 20:20:1) = 0.22; **HPLC:** 7.88 min; **UV** (MeOH): λ_{max}, nm (ε): 287 (5600), 254 (13570); **IR:** ν 3100-2400 (*s*, ν(N-H)), 3062 (*s*, ν(C-H)), 2923 (*s*, ν(C-H)), 2226 (*s*, ν(C≡N)), 1521 (*s*, ν(C=C)), 1482 (*s*, ν(C=C)), 838 (*m*, γ(C-H, Ph)), *7*63 (*s*, γ(C-H, Ph)) cm^{-1}; **^{1}H NMR** (400 MHz, d_6-DMSO): δ = 4.59 (*s*, 2H, H-C_{11}), 7.54 (*m*, 2H, H-C_9), 7.55 (*m*, 2H, H-C_8), 7.57 (*m*, 1H, H-C_4), 7.61 (*m*, 1H, H-C_6), 7.76 (*dt*, ^3J = 7.8, $^4J_{3,5}$ = 1.3 Hz, 1H, H-C_5), 7.93 (*dd*, $^3J_{3,4}$ = 8.6, $^4J_{3,5}$ = 1.3 Hz, 1H, H-C_3), 17.10 (*br*, NH); **^{13}C NMR** (125 MHz, d_6-DMSO): δ = 35.4 (CH_2, C_{11}), 110.1 (Cq, C_1), 118.5 (Cq, C_{13}), 128.3 (CH, Ar), 128.9 (CH, Ar), 129.3 (CH, Ar), 130.1 (CH, Ar), 133.5 (CH, C_6), 133.9 (CH, C_4), 137.1 (Cq, C_7), 137.5 (Cq, C_{10}), 144.0 (Cq, C_2), 153.8 (Cq, C_{12}); **MS:** *m/z* 294 $[M+H]^+$, 292 $[M-H]^-$; **HR-MS:** calc'd for $[M+H]^+$ = 294.0808 found 294.0807 (ΔM (ppm) = 0.3), calc'd for $[M+Na]^{-+}$ = 316.0627 found 316.0627 (ΔM (ppm) = 0.1).

5-{4'-[(1*H*-Tetrazol-5-ylthio)methyl]biphenyl-2-yl}-1*H*-tetrazole (78)

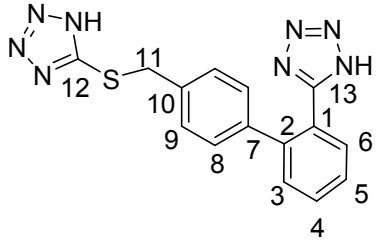


77 **78**

Molecular Formula	$C_{15}H_{12}N_8S$
Molecular Weight	336.38 g/mol

TP1: 2.8 equivalents of diethylaluminum azide (2.7 M in xylene) are used in a 1.73 mmol scale experiment. The reaction is stirred for three days from 90 to 110 °C to give the product as a yellow crystalline material (540 mg, 93 % yield).

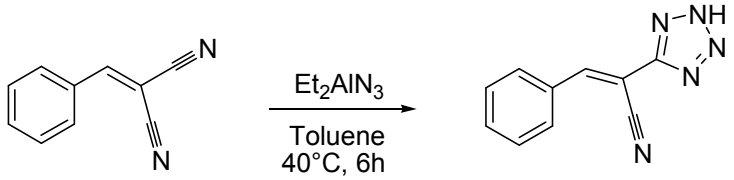
Compound characterization data:



mp: 180-182 °C; **TLC:** R_f (toluene / EtOAc / AcOH 10:20:2) = 0.30; **HPLC:** 6.24 min; **UV** (MeOH): λ_{max}, nm (ε): 203 (3480); **IR:** ν 3200-2350 (*brs*, ν(N-H)), 3060 (*s*, ν(C-H)), 3031 (*s*, ν(C-H)), 2906 (*s*, ν(C-H)), 1607 (*m*, ν(C=C)), 1572 (*w*, tetrazole), 1534 (*w*, tetrazole), 1487 (*s*, ν(C=C)), 1427 (*m*, ν(C=C)), 1487*s* ν(C=C), 840 (*m*, γ(C-H, Ph)), 747 (*s*, γ(C-H, Ph)) cm^{-1}; **^{1}H NMR** (400 MHz, d_6-DMSO): δ = 4.5 (*s*, 2H, H-C_{11}), 7.03 (*d*, $^3J_{8,9}$ = 8.2 Hz, 2H, H-C_8), 7.34 (*d*, $^3J_{8,9}$ = 8.2 Hz 2H, H-C_9), 7.63 (*m*, 4H, H-$C_{3\text{-}6}$), 16.50 (*br*, NH); **^{13}C NMR** (125 MHz, d_6-DMSO): δ = 35.5 (CH_2, C_{11}), 123.1 (Cq, C_1), 127.9 (CH, Ar), 128.9 (CH, Ar), 129.0 (CH, Ar), 130.6 (CH, Ar), 131.1 (CH, C_4), 136.0 (Cq, C_{10}), 138.5 (Cq, C_7), 141.0 (Cq, C_2), 153.7 (Cq, C_{13}), 154.4 (Cq, C_{12}); **MS:** *m/z* 337 $[MH]^+$, 335 $[M\text{-}H]^-$; **HR-MS:** calc'd for $[MH]^+$ = 337.0978, found 337.0978 (ΔM (ppm) < 0.1), calc'd for $[M+Na]^+$ = 359.0798, found 359.0798 (ΔM (ppm) < 0.1).

5.1.3.3. Synthesis of tetrazoles in the presence of double bonds

(*E*)-3-Phenyl-2-(2*H*-tetrazol-5-yl)acetonitrile (79)

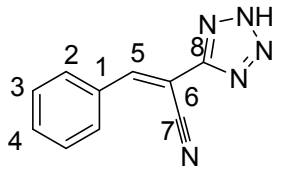


33 **79**

Molecular Formula	$C_{10}H_7N_5$
Molecular Weight	197.20 g/mol

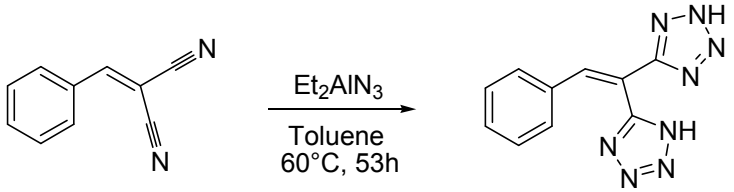
TP1: 2 equivalents of diethylaluminum azide (2.5 M in toluene) are used in a 2 mmol scale experiment. The reaction is stirred six hours at 45 °C to give the product as a white crystalline material (381 mg, 97 % yield).

Compound characterization data:



mp: 189-192 °C; **TLC**: R_f (toluene / AcOEt / AcOH 20:20:1) = 0.20; **HPLC**: 5.87 min; **UV** (MeOH): λ_{max}, nm (ε): 305 (15550), 225 (7590); **IR:** ν 3100-2500 (*brs*, ν(N-H)), 3109 (*m*, ν(C-H)), 3055 (*s*, ν(C-H)), 2991 (*s*, ν(C-H)), 2229 (*m*, ν(C≡N)), 1614 (*s*, ν(C=C)), 1589 (*s*, ν(C=C)), 1555 (*m*, tetrazole), 1454 (*m*, ν(C=C)), 771 (*m*, γ(C-H, Ph)), 688 (*m*, γ(Ph)) cm^{-1}; **^{1}H NMR** (500 MHz, d_6-DMSO): δ = 7.60 (*m*, 3H, H-$C_{3,4}$), 8.01 (*m*, 2H, H-C_2), 8.39 (*s*, 1H, H-C_5), 16.80 (*br*, NH); **^{13}C NMR** (150 MHz, d_6-DMSO) 97.2 (Cq, C_6), 115.6 (Cq, C_7), 128.8, 129.3 (CH, $C_{3,4}$), 129.8 (CH, C_2), 132.2 (Cq, C_1), 148.1 (CH, C_5), 155.2 (Cq, C_8); **MS:** *m/z* 236 $[M+K]^+$, 198 $[M+H]^+$, 196 $[M-H]^-$; **HR-MS**: calc'd for $[M-H]^-$ = 196.0629 found 196.0629 (ΔM (ppm) = 0.2).

5-[(*Z*)-2-Phenyl-1-(2*H*-tetrazol-5-yl)vinyl]-1*H*-tetrazole (80)

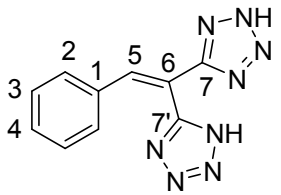


33 **80**

Molecular Formula	$C_{10}H_8N_8$
Molecular Weight	240.23 g/mol

TP1: 3 equivalents of diethylaluminum azide (2.7 M in xylene) are used in a 10 mmol scale experiment. The reaction is stirred for twenty four hours at 65 °C to give the product as a off white crystalline material (1.8 g, 75 % yield).

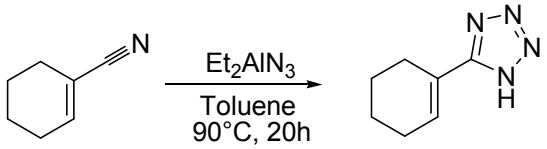
Compound characterization data:



mp: 203 °C, onset of exothermic decomposition: 204-368 °C with maximum at 211.5 °C; **TLC:** R_f (toluene / EtOAc / AcOH 20:20:1) = 0.04; **HPLC:** 4.04 min; **UV** (MeOH): λ_{max}, nm (ε): 289 (1410), 220 (860); **IR:** ν 3100-2500 (*brs*, ν(N-H)), 3088 (*s*, ν(C-H)), 3007 (*s*,

ν(C-H)), 1638 (*s*, ν(C=C)), 1568 (*s*, ν(C=C)), 1568 (*s*, tetrazole), 1453 (*w*, ν(C=C)), 761 (*s*, γ(C-H, Ph)), 690 (*m*, γ(Ph)) cm^{-1}; **^{1}H NMR** (400 MHz, d_6-DMSO): δ = 7.07 (*m*, 2H, H-C_2), 7.35 (*m*, 3H, H-$C_{3,4}$), 8.15 (*s*, 1H, H-C_5), 17.00 (*br*, NH); **^{13}C NMR** (125 MHz, d_6-DMSO): δ = 110.9 (Cq, C_6), 128.1 (CH, C_2), 129.3 (CH, C_3), 130.0 (CH, C_5), 133.3 (Cq, C_1), 140.8 (Cq, $C_{7,7'}$); **MS:** *m/z* 241 $[MH]^+$, 239 $[M-H]^-$.

5-(1-Cyclohexen-1-yl)-1*H*-tetrazole (81)

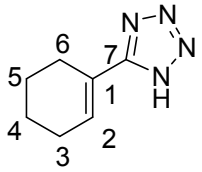


271 **81**

CAS Registry Number	188890-71-3
Molecular Formula	$C_7H_{10}N_4$
Molecular Weight	150.18 g/mol
Ref.	O. Kazuyuki, T. Makoto, M. Tohru, O. Hiroyuki, Ono Pharmaceutical Co., Ltd., Japan, **1997**, EP 761680 A2

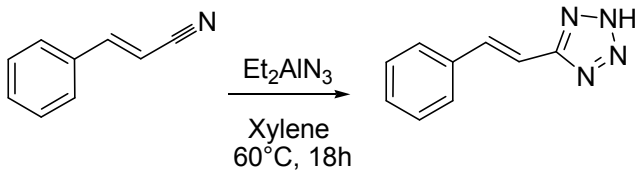
TP1: 1.4 equivalents of diethylaluminum azide (2.5 M in toluene) are used in a 7 mmol scale experiment. The reaction is heated for twenty hours at 90 °C to give the product as a white crystalline material after direct crystallization of the crude from a mixture of ethyl acetate / toluene 1:1 (680 mg, 65 % yield).

Compound characterization data:



mp: 151-153 °C; **TLC:** R_f(toluene / AcOEt / AcOH 20:20:1) = 0.32; **HPLC:** 4.43 min; **UV** (MeOH): λ_{max}, nm (ε): 230 (1100); **IR:** ν 3100-2600 (*brs*, ν(N-H)), 3108 (*m*, ν(C-H)), 2972-2931 (*s*, ν(C-H)), 1651 (*s*, ν(C=C)), 1556 (*s*, tetrazole), 1410 (*s*, tetrazole) cm^{-1}; **^{1}H NMR** (500 MHz, d_6-DMSO): δ = 1.61 (*m*, 2H, H-C_4), 1.70 (*m*, 2H, H-C_5), 2.21 (*m*, 2H, H-C_3), 2.45 (*m*, 2H, H-C_6), 6.77 (*m*, 1H, H-C_2), 16.20 (*br*, NH); **^{13}C NMR** (125 MHz, d_6-DMSO): δ = 21.1 (CH_2, C_4), 21.5 (CH_2, C_5), 24.8 (CH_2, C_3), 24.9 (CH_2, C_6), 122.7 (Cq, C_1), 132.7 (CH, C_2), 155.5 (C_q, C_7); **MS:** *m/z* 151 $[MH]^+$, 108 $[MH-HN_3]^+$, 149 $[M-H-N_2]^-$; **HR-MS:** calc'd for $[M-H]^-$ = 149.0833, found 149.0833 (ΔM (ppm) = 0.1).

5-Styryl-1*H*-tetrazole (82)

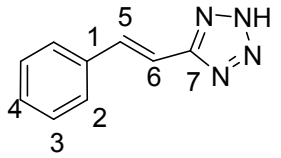


272 **82**

CAS Registry Number	220429-71-0
Molecular Formula	$C_9H_8N_4$
Molecular Weight	172.19 g/mol
Analysis Ref.	a) H. Detert, D. Schollmeier, *Synthesis* **1999**, *6*, 999; b) Z. P. Demko, K. B. Sharpless, *J. Org. Chem.* **2001**, *66*, 7945; c) G. Sedelmeier, Novartis Pharma AG, **2005**, WO2005/14602 A1

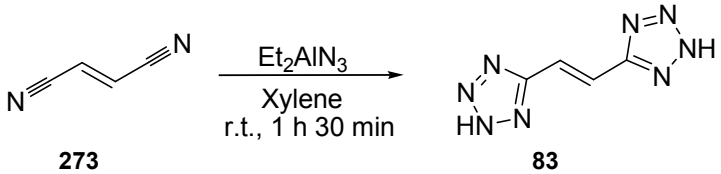
TP1: 1.3 equivalents of diethylaluminum azide (2.7 M in xylene) are used in a 10 mmol scale experiment. The reaction is stirred for 18 hours from 50 to 70 °C to give the product as an off white crystalline material obtained after crystallization from ethyl acetate (1.667 g, 97 % yield).

Compound characterization data:



mp: 158-160 °C; **TLC:** R_f (toluene / EtOAc / AcOH 20:20:1) = 0.46; **HPLC:** 6.26 min; **UV** (EtOH): λ_{max}, nm (ε): 284 (24660), 221 (12940), 208 (10160); **IR:** ν 3100-2400 (*brs*, ν(N-H)), 3062 (*m*, ν(C-H)), 3032 (*m*, ν(C-H)), 1960-1800 (*w*, overtones γ(C-H, Ph)), 1650 (*vs*, ν(C=C)), 1559 (*s*, tetrazole), 1420 (*s*, ν(C=C)), 974 (*s*, δ(C-H, C=C trans), 776 (*s*, γ(C-H, Ph)), 688 (*m*, γ(Ph)) cm^{-1}; **^{1}H NMR** (400 MHz, d_6-DMSO): δ = 7.35 (*d*, $^3J_{5,6}$ = 16.6 Hz, 1H, H-C_6), 7.44 (*m*, 3H, H-$C_{3,4}$), 7.66 (*d*, $^3J_{5,6}$ = 16.6 Hz, 1H, H-C_5), 7.74 (*m*, 2H, H-C_2), 16.50 (*br*, NH); **^{13}C NMR** (125 MHz, d_6-DMSO): δ = 110.5 (CH, C_6), 127.5 (CH, C_2), 129.0 (CH, C_3), 129.6 (CH, C_4), 134.9 (Cq, C_1), 137.8 (CH, C_5), 154.1 (Cq, C_7); **MS:** *m/z* 173 $[MH]^+$, 130 $[MH\text{-}HN_3]^+$, 186 $[MH\text{-}HN_3]^+$; **HR-MS**: calc'd for $[M\text{-}H]^-$ = 171.0676, found 171.0676 (ΔM (ppm) = 0.1).

Fumaryl-2*H*-tetrazole (83)

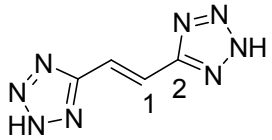


273 **83**

CAS Registry Number	18733-24-9
Molecular Formula	$C_4H_4N_8$
Molecular Weight	164.13g/mol
Analysis Ref.	Z. P. Demko, K. B. Sharpless, *J. Org. Chem.* **2001**, *66*, 7945

TP1: 1.6 equivalents of diethylaluminum azide (2.7 M in xylene) are used in a 6 mmol scale experiment. The reaction is stirred for two hours at room temperature to give the product as a light brown crystalline material (700 mg, 71 % yield).

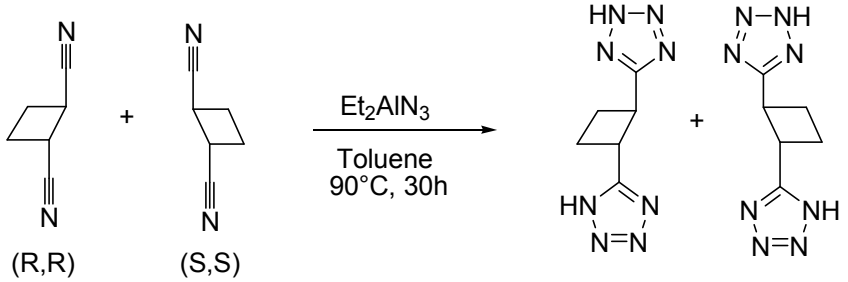
Compound characterization data:



mp: 275 °C; **TLC:** R_f (toluene / EtOAc / AcOH 20:20:1) = 0.04; **HPLC:** 2.10 min; **UV** (EtOH): λ_{max}, nm (ε): 261 (1520); **IR:** ν 3200-2800 (*brs*, ν(C-H), ν(N-H)), 3098 (*s*, ν(C-H)), 3043 (*s*, ν(C-H)), 1548 (*s*, tetrazole), 1427 (*m*, ν(C=C)) cm^{-1}; **^{1}H NMR**(500 MHz, d_6-DMSO): δ = 7.69 (*s*, 2H, H-C_1), 17.00 (*br*, NH); **^{13}C NMR**(125 MHz, d_6-DMSO): δ = 119.1 (CH, C_1), 152.9 (Cq, C_2); **MS:** *m/z* 165 $[MH]^+$, 163 $[M-H]^-$, 136 $[MH-N_2]^+$, 108 $[MH-N_2-N_2]^+$; **HR-MS:** calc'd for $[M-H]^-$ = 163.0486, found 163.0486 (ΔM (ppm) < 0.1).

5.1.3.4. Synthesis of tetrazoles from alkylnitriles

***trans*-Cyclobutane-1,2-di-1*H*-tetrazole (84)**

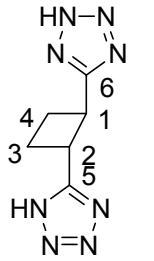


274 **84**

Molecular Formula	$C_6H_8N_8$
Molecular Weight	192.16 g/mol

TP1: 1.33 equivalents of diethylaluminum azide (1.8 M in toluene) are used in a 30 mmol scale experiment. The reaction is stirred for thirty hours at 90 °C to give the product as a white crystalline material after crystallization from ethyl acetate (3.47 g, 60% yield).

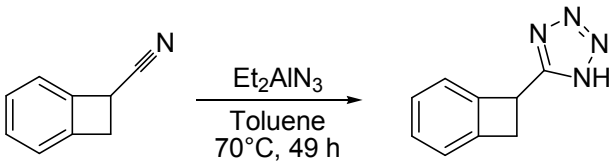
Compound characterization data:



Racemic

mp: 233-236 °C, onset of exothermic decomposition: 235-315 °C with maximum at 265 °C; **TLC:** R_f (toluene / EtOAc / AcOH 20:20:1, I_2) = 0.19; **IR:** ν 3250-2400 (*brs*, ν(N-H)), 2958 (*s*, ν(C-H)), 2921 (*s*, ν(N-H)), 1564 (*s*, tetrazole), 1446 (*m*, tetrazole), 1425 (*s*, tetrazole) cm^{-1}; **^{1}H NMR** (500 MHz, d_6-DMSO): δ = 2.42 (*m*, 4H, H-$C_{4,3}$), 4.12 (*m*, 2H, H-$C_{1,2}$), 16.45 (*br*, NH); **^{13}C NMR** (125 MHz, d_6-DMSO): δ = 24.4 (CH_2, $C_{4,3}$), 34.2 (CH, $C_{1,2}$), 157.1 (Cq, $C_{5,6}$); **MS:** *m/z* 193 $[M+H]^+$, 191 $[M-H]^-$, 148 $[M-H-HN_3]$; **HR-MS:** calc'd for $[M-H]^-$ = 190.0799 found 191.0800 (ΔM (ppm) = 0.4).

5-Bicyclo [4.2.0] octa-1,3,5-trien-7-yl-1*H*-tetrazole (85)

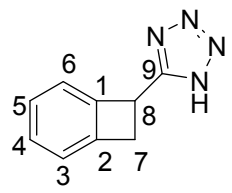


275 **85**

CAS Registry Number	188890-75-7
Molecular Formula	$C_9H_8N_4$
Molecular Weight	172.19 g/mol
Ref.	O. Kazuyuki, T. Makoto, M. Tohru, O. Hiroyuki, Ono Pharmaceutical Co., Ltd., Japan, **1997**, EP 761680 A2

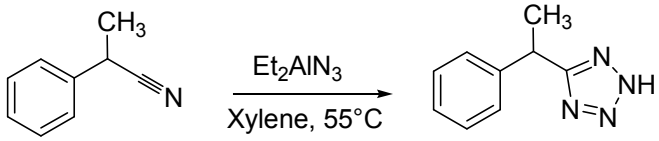
TP1: 1.5 equivalenst of diethylaluminum azide (1.8 M in toluene) are used in a 10 mmol scale experiment. The reaction is heated for forty nine hours at 70 °C to give the product as a white crystalline material after direct crystallization of the crude from ethyl acetate / toluene (2.53 g, 64 % yield).

Compound characterization data:



mp: 154-156 °C; **TLC:** R_f (toluene / EtOAc / AcOH 20:20:1) = 0.24; **HPLC:** 4.72 min; **UV** (EtOH): λ_{max}, nm (ε): 271 (1550), 265 (1720), 259 (1230); **IR:** ν 3053 (*m*, ν(C-H)), 3000-2400 (*brs*, ν(N-H)), 2998 (*s*, ν(C-H)), 1575 (*m*, tetrazole), 1457 (*s*, ν(C=C)), 1435 (*w*, ν(C=C)), 751 (*s*, γ(C-H, Ph) cm^{-1}; **^{1}H NMR** (500 MHz, d_6-DMSO): δ = 3.65 (*m*, 2H, H-C_7), 5.05 (*m*, 1H, H-C_8), 7.21 (*m*, 2H, C-$H_{3,6}$), 7.28 (*m*, 2H, H-$C_{3,4}$), 16.30 (*br*, NH); **^{13}C NMR** (125 MHz, d_6-DMSO): δ = 35.7 (CH, C_8), 36.2 (CH_2, C_7), 122.7, 123.2 (CH, $C_{3,6}$), 127.5, 128.4 (CH, $C_{4,5}$), 143.4 (Cq, C_2), 143.6 (Cq, C_1), 156.4 (Cq, C_9); **MS:** *m/z* 171 $[M-H]^-$.

5-(1-Phenyl-ethyl)-2*H*-tetrazole (86)

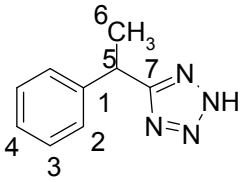


276 **86**

Molecular Formula	$C_9H_{10}N_4$
Molecular Weight	174.21 g/mol

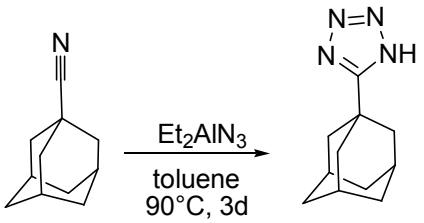
TP1: 1.33 equivalenst of diethylaluminum azide (2.7 M in xylene) are used in a 30 mmol scale experiment. The reaction is heated for twenty four hours at 60 °C to give the product as a white crystalline material (4.22 g, 81 % yield).

Compound characterization data:



mp: 98-99 °C; **TLC:** R_f (toluene / AcOEt / AcOH 20:20:1) = 0.44; **HPLC:** 4.39 min; **UV** (EtOH): λ_{max}, nm (ε): 258 (23); **IR:** ν 3200-2500 (*brs*, ν(N-H)), 3104 (*s*, ν(C-H)), 2977 (*s*, ν(CH_3)), 2937 (*s*, ν(C-H)), 1967-1670 (*w*, overtones γ(C-H, Ph)), 1555 (*s*, tetrazole), 1491 (*s*, ν(C=C)), 1453 (*s*, ν(C=C)), 755 (*s*, γ(C-H, Ph), 706 (*s*, γ(Ph)) cm^{-1}; **^{1}H NMR** (500 MHz, d_6-DMSO): δ = 1.65 (*d*, $^3J_{5,6}$ = 7.2 Hz, 3H, H-C_6), 4.53 (*q*, $^3J_{5,6}$ = 7.2 Hz, 1H, H-C_5), 7.25 (*m*, 3H, ArH), 7.32 (*m*, 2H, ArH), 16.18 (*br*, NH); **^{13}C NMR** (125 MHz, d_6-DMSO): δ = 20.3 (CH_3, C_6), 34.6 (CH, C_5), 127.1 (CH, $C_{2,4}$), 128.8 (CH, C_3), 142.0 (Cq, C_1), 158.6 (Cq, C_7); **MS:** *m/z* 175 $[M-H]^+$, 173 $[M-H]^-$, 145 $[M-H-N_2]^-$, 132 $[MH-NH_3]^+$; **HR-MS:** calc'd for $[M-H]^-$ = 173.0833, found 173.0833 (ΔM (ppm) = 0.1).

5-(1-Adamantyl)-1*H*-tetrazole (87)

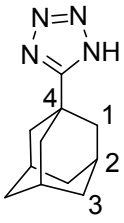


277 **87**

CAS Registry Number	60798-89-2
Molecular Formula	$C_{11}H_{16}N_4$
Molecular Weight	204.27g/mol
Ref.	a) T. J. Bleisch, S. A. Filla, P. L. Ornstein, Eli Lilly and Company, USA, **2002**, WO 2002053556 A2; b) C. P. Hegarty, H. C. Pietryk, American Home Products Corp., USA, **1977**, US 4032659.

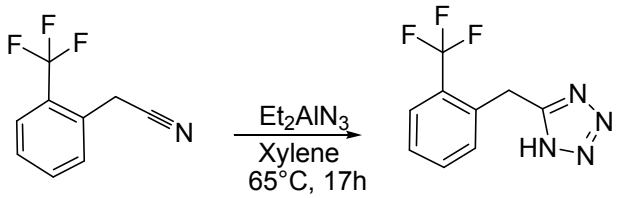
TP1: 2.23 equivalents of diethylaluminum azide (2.5 M in toluene) are used in a 3 mmol scale experiment. The reaction is stirred for three days at 90-110 °C to give the product as a white crystalline material (500 mg, 82 % yield).

Compound characterization data:



mp: 250-253 °C; **TLC:** R_f (toluene / EtOAc / AcOH 20:20:1, I_2) = 0.38; **IR:** ν 3100-2500 (*brm*, ν(N-H)), 2989 (*s*, ν(C-H)), 2934 (*s*, ν(C-H)), 2909 (*s*, ν(C-H)), 1560 (*w*, tetrazole), 1409 (*w*, tetrazole) cm^{-1}; **^{1}H NMR** (500 MHz, d_6-DMSO): δ = 1.75 (br*m*, 6H, H-C_3), 1.98 (br*m*, 6H, H-C_1), 2.05 (br*m*, 3H, H-C_2), 16.10 (*br*, NH); **^{13}C NMR** (125 MHz, d_6-DMSO): δ = 27.3 (CH_2, C_3), 32.0 (Cq, C_4), 35.7 (CH_2, C_1), 40.4 (CH, C_2), 162.0 (C_q, C_5); **MS:** *m/z* 205 $[MH]^+$, 203 $[M-H]^-$; **HR-MS:** calc'd for $[M+H]^+$ = 205.1448, found 205.1447 (ΔM (ppm) = 0.5), calc'd for $[M+Na]^+$ = 227.1267, found 227.1266 (ΔM (ppm) = 0.4).

5-(2-Trifluoromethyl) benzyl-1*H*-tetrazole (88)

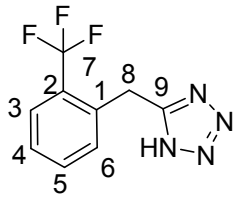


278 **88**

CAS Registry Number	220429-74-3
Molecular Formula	$C_9H_7N_4F_3$
Molecular Weight	228.17g/mol
Ref.	T. Utsunomiya *et. all*, Nissan Chem. Industries, **1999**, Patent written in Japanese, WO9906380 A1

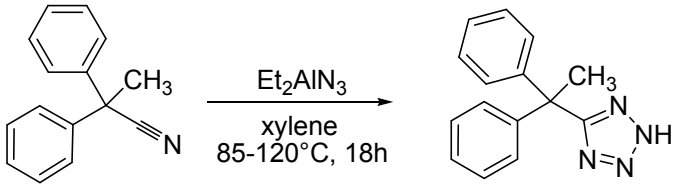
TP1: 1.5 equivalents of diethylaluminum azide (2.5 M in toluene) or dimethylaluminum azide (1 M in hexane) are used in a 4 mmol scale experiment. The reaction was heated for seventeen hours at 65 °C to give the product as a yellow crystalline material (730 mg, 80 % yield).

Compound characterization data:



mp: 135-137 °C; **TLC:** R_f(toluene / EtOAc / AcOH 20:20:1) = 0.38; **HPLC:** 6.51 min; **UV** (EtOH): λ_{max}, nm (ε): 271 (120), 264 (135), 257 nm (130); **IR:** ν 3134 (*w*, ν(C-H)), 3000-2450 (*brs*, ν(N-H)), 1586 (*w*, ν(C=C)), 1569-1547 (*w*, ν(C=C), tetrazole), 1428 (*w*, ν(C=C)), 1109 (*s*, ν(CF_3)), 771 (*s*, δ(Ph)) cm^{-1}; **^{1}H NMR** (500 MHz, d_6-DMSO): δ = 4.45 (*s*, 2H, H-C_8), 7.49 (*d*, $^3J_{5,6}$ = 7.6 Hz, 1H, H-C_6), 7.54 (*t*, $^3J_{4,5}$ = 7.6, $^3J_{3,4}$ = 7.8 Hz, 1H, H-C_4), 7.69 (*t*, ^3J = 7.6 Hz, 1H, H-C_5), 7.77 (*d*, $^3J_{3,4}$ = 7.8 Hz, 1H, H-C_3), 16.20 (*br*, NH); **^{13}C NMR** (125 MHz, d_6-DMSO): δ = 26.3 (CH_2, C_8), 124.4 (Cq, C_7), 126.1 (CH, C_3), 127.2 (Cq, C_2), 128.0 (CH, C_4), 132.3 (CH, C_6), 132.9 (CH, C_5), 133.6 (Cq, C_1), 154.5 (Cq, C_9); **MS:** 229 $[MH]^+$, 209 $[M\text{-}HF]^+$, 186 $[MH\text{-}HN_3]^+$; **HR-MS:** calc'd for $[M\text{-}H]^-$ = 227.0550, found 227.0550 (ΔM (ppm) = 0.2), calc'd for $[M+CF_3COO]^-$ = 341.0479, found 341.0480 (ΔM (ppm) = 0.3).

5-(1,1-Diphenylethyl)-2*H*-tetrazole (89)

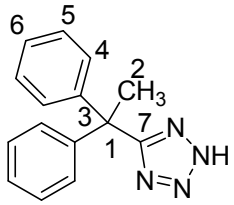


279 **89**

CAS Registry Number	132979-90-9
Molecular Formula	$C_{15}H_{14}N_4$
Molecular Weight	250.30 g/mol
Analysis Ref.	J. V. Duncia, M. E. Pierce, J. B. Santella, III, *J. Org. Chem*. **1991**, *56*, 2395

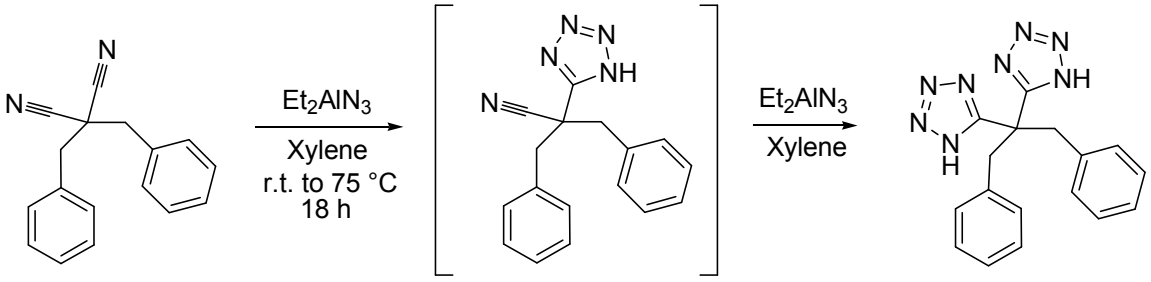
TP1: 1.3 equivalents of diethylaluminum azide (2.7 M in xylene) are used in a 5 mmol scale experiment. The reaction is stirred for heighteen hours from 85 to 120 °C to give the product as a white crystalline material (550 mg, 45 % yield).

Compound characterization data:



mp: 138-140 °C; **TLC:** R_f (toluene / EtOAc / AcOH 20:20:1) = 0.54; **HPLC:** 8.70 min; **UV** (EtOH): λ_{max}, nm (ε): 259 (520), 196 (52820); **IR:** ν 3091 (*m*, ν(C-H)), 3062 (*w*, ν(C-H)), 3025 (*m*, ν(C-H)), 2800-2350 (*brm*, ν(N-H)), 2918 (*m*, ν(CH_3)), 1900-1700 (*w*, overtones γ(C-H, Ph)), 1549 (*m*, tetrazole)), 1494 (*s*, ν(C=C)), 1447 (*m*, ν(C=C)), 1410 (*m*, ν(C=C)), 761 (*s*, γ(C-H, Ph)), 698 (*s*, γ(Ph)) cm^{-1}; **^{1}H NMR** (500 MHz, d_6-DMSO): δ = 2.18 (*s*, 3H, H-C_2), 7.07 (*m*, 4H, ArH), 7.30 (*m*, 6H, ArH), 16.20 (*br*, NH); **^{13}C NMR** (125 MHz, d_6-DMSO): δ = 28.2 (CH_3, C_2), 45.9 (Cq, C_1), 126.6 (CH, C_6), 127.1 (CH, Ar), 127.9 (CH, Ar), 144.7 (Cq, C_3); **MS:** *m/z* 251 $[MH]^+$; **HR-MS:** calc'd for $[M-H]^-$ = 173.0833, found 173.0833 (ΔM (ppm) = 0.1).

1,3-Diphenyl-2,2-bis-(5-tetrazoyl) propane (90)

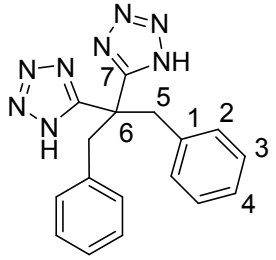


74 **280** **90**

CAS Registry Number	66012-54-2
Molecular Formula	$C_{17}H_{16}N_8$
Molecular Weight	332.36 g/mol
Analysis Ref.	H. Illy, Ciba-Geigy AG., Switz., Ger. Offen. **1978**, DE 2731323 (A1)

TP1: 1.6 equivalents of diethylaluminum azide (2.7 M in xylene) are used in a 1.88 mmol scale experiment. The reaction is stired for eighteen hours from room temperature to 75 °C to give the product as a brown crystalline material (488 mg, 87 % yield).

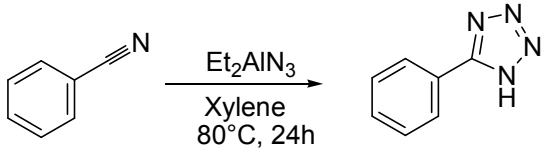
Compound characterization data:



mp: 217-220 °C; **TLC:** R_f (toluene / EtOAc / AcOH 20:20:1) = 0.6 ; **HPLC:** 7.69 min; **UV** (EtOH): λ_{max}, nm (ε): 259 (71); **IR:** ν 3200-2400 (*brs*, ν(N-H)), 3089 (*s*, ν(C-H)), 3028 (*s*, ν(C-H)), 3007 (*s*, ν(C-H)), 2962 (*s*, ν(C-H)), 1951-1740 (*w*, overtones γ(C-H, Ph), 1563 (*m*, tetrazole), 1497 (*m*, ν(C=C)), 1456 (*s*, ν(C=C)), 747 (*m*, γ(C-H, Ph), 700 (*s*, γ(Ph)) cm^{-1}; **^{1}H NMR** (500 MHz, d_6-DMSO): δ = 3.69 (*s*, 4H, H-C_5), 6.56 (*m*, 4H, H-C_2), 7.05 (*m*, 6H, H-$C_{3,4}$), 16.29 (*br*, NH); **^{13}C NMR** (125 MHz, d_6-DMSO): δ = 44.8 (Cq, C_6), 45.2 (CH_2, C_5), 126.5 (CH, C_4), 127.6 (CH, C_2), 129.2 (CH, C_3), 134.6 (Cq, C_1), 153.0 (Cq, C_7); **MS:** 331 $[M-H]^-$, 333 $[M-H]^-$.

5.1.3.5. Synthesis of tetrazoles from aromatic nitriles

5-Phenyl-1*H*-tetrazole (11)

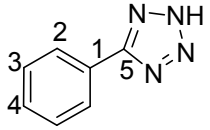


10 **11**

CAS Registry Number	18039-42-4
Molecular Formula	$C_7H_6N_4$
Molecular Weight	146.15 g/mol
Analysis Ref.	a) J. S. Mihina, R. M. Herbst, *J. Org. Chem.* **1950**, *15*, 1082; b) K. Sisido, K. Nabika, I. Tyuzo, S. Kozima, *J. Organomet. Chem.* **1971**, *33*, 337; c) J. Kaczmarek, Z. Grzonka, *Pol. J. Chem.* **1980**, *54*, 1297; d) B. S. Jursic, B. W. Leblanc, *J. Heterocycl. Chem.* **1998**, *35*, 405; e) Z. P. Demko, K. B. Sharpless, *J. Org. Chem.* **2001**, *66*, 7945; f) J.-J. Shie, J.-M. Fang, *J. Org. Chem.* **2003**, *68*, 1158; g) D. Amantini, R. Beleggia, F. Fringuelli, F. Pizzo, L. Vaccaro, *J. Org. Chem.* **2004**, *69*, 2896

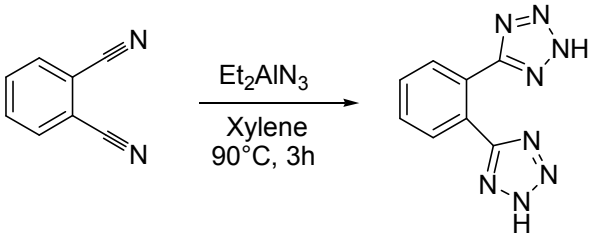
TP1: 1.3 equivalents of diethylaluminum azide (2.7 M in xylene) are used in a 5 mmol scale experiment. The reaction is stirred for twenty four hours at 80 °C to give the product as a white crystalline material obtained after crystallization from ethyl acetate (730 mg, 99 % yield).

Compound characterization data:



mp: 214-216 °C; **TLC:** R_f (toluene / AcOEt / AcOH 20:20:1) = 0.6; **HPLC:** 4.40 min; **UV** (EtOH): λ_{max}, nm (ε): 239 (14710), 199 (29680); **IR:** ν 3078 (*m*, ν(C-H)), 3056 (*m*, ν(C-H)), 3000-2400 (*brs*, ν(N-H)), 1609 (*s*, ν(C=C)), 1565 (*s* ,tetrazole or ν(C=C)), 1487 (*s*, ν(C=C)), 1466 (*s*, ν(C=C)), 688 (*s*, γ(Ph)) cm^{-1}; **^{1}H NMR** (500 MHz, d_6-DMSO): δ = 7.58 (*m*, 3H, H-$C_{3,4}$), 8.03 (*m*, 2H, H-C_2), 16.80 (*br*, NH); **^{13}C NMR**(125 MHz, d_6-DMSO): δ = 123.8 (Cq, C_1), 126.6 (CH, Ar), 129.0 (CH, Ar), 130.8 (CH, C_4), 154.7 (Cq, C_7); **MS:** *m/z* 147 $[MH]^+$, 104 $[MH\text{-}HN_3]^+$, **HR-MS:** calc'd for $[M\text{-}H]^-$ = 145.0520, found 145.0520 (ΔM (ppm) = 0.1).

5,5'-(1,2-Phenylene) bis -2*H*-tetrazole (91)

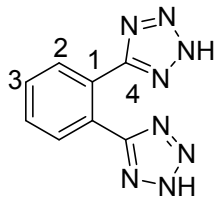


281 **91**

CAS Registry Number	73096-43-2
Molecular Formula	$C_8H_6N_8$
Molecular Weight	214.19 g/mol
Analysis Ref.	a) J. Kaczmarek, Z. Grzonka, *Pol. J. Chem*. **1980**, *54*, 1297; b) W. Ried, S. Aboul-Fetouh, *Tetrahedron* **1988**, *44*, 3399; c) Z. P. Demko, K. B. Sharpless, *J. Org. Chem*. **2001**, *66*, 7945; d) A. Fleming, F. Kelleher, M. F. Mahon, J. McGinley, V. Prajapati, *Tetrahedron* **2005**, *61*, 7002

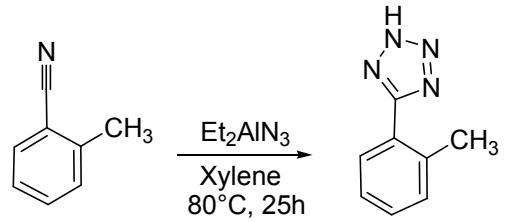
TP1: 1.4 equivalents of diethylaluminum azide (2.7 M in xylene) are used in a 5 mmol scale experiment. The reaction is stirred for three hours at 90 °C to give the product as an off white crystalline material (800 mg, 75 % yield).

Compound characterization data:



mp: 225-227 °C; **TLC:** R_f (toluene / EtOAc / AcOH 20:20:1) = 0.07; **HPLC:** 3.09 min; **UV** (EtOH): λ_{max}, nm (ε): 206 (21950); **IR:** *ν* 3200-2400 (*brs*, ν(N-H)), 3114 (*s*, ν(C-H)), 3054 (*s*, ν(C-H)), 1957-1780 (*w*, overtones γ(C-H, Ph)), 1606 (*m*, ν(C=C)), 1592 (*m*, ν(C=C)), 1556 (*s*, tetrazole), 1481 (*s*, ν(C=C)), 1453 (*s*, ν(C=C)) cm^{-1}; **^{1}H NMR** (500 MHz, d_6-DMSO): δ = 7.80 (*m*, 2H, H-C_2), 7.89 (*m*, 2H, H-C_3), 16.60 (*br*, NH); **^{13}C NMR** (125 MHz, d_6-DMSO): δ = 124.1 (Cq, C_1), 130.3 (CH, C_3), 130.9 (CH, C_2), 154.3 (Cq, C_4); **MS:** *m/z* 215 $[MH]^+$; **HR-MS:** calc'd for $[M-H]^-$ = 213.0643, found 213.0643 (ΔM (ppm) < 0.1).

5-(*o*-Methylphenyl)-2*H*-tetrazole (92)

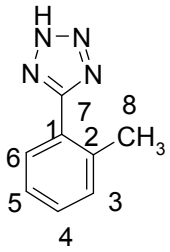


58 **92**

CAS Registry Number	51449-86-6
Molecular Formula	$C_8H_8N_4$
Molecular Weight	160.07 g/mol
Analysis Ref.	a) J. S. Mihina, R. M. Herbst, *J. Org. Chem*. **1950**, *15*, 1082; b) R. N. Butler, V. C. Garvin, *J. Chem. Soc.*, Perkin Trans. 1: Organic and Bio-Organic Chemistry (1972-1999), **1981**, *2*, 390; c) L. A. Flippin, *Tetrahedron Lett.* **1991**, *32*, 6857; d) K. Koguro, T. Oga, S. Mitsui, R. Orita, *Synthesis* **1998**, *6*, 910; e) B. S. Jursic, B. W. LeBlanc, *J. Heterocycl. Chem*. **1998**, *35*, 405

TP1: One equivalent of diethylaluminum azide (2.7 M in xylene) are used in a 7 mmol scale experiment. The reaction is stirred for twenty five hours at 80 °C to give the product as a white crystalline material (670 mg, 83 % yield).

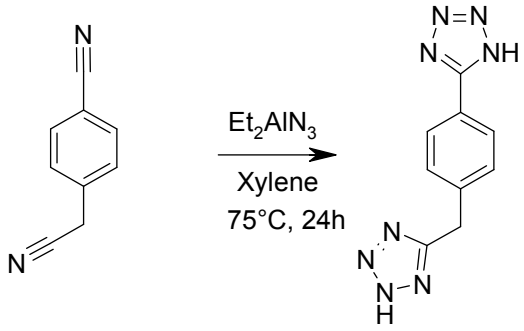
Compound characterization data:



mp: 150-151 °C; **TLC:** R_f (toluene / EtOAc / AcOH 20:20:1) = 0.46; **HPLC:** 4.43 min; **UV** (EtOH): λ_{max}, nm (ε): 273 (776), 234 (9330), 205 (23790); **IR:** 3105 (*w*, ע(C-H)), 3062 (*m*, ע(C-H)), 3000-2300 (*brs*, ע(N-H)), 2970 (*s*, ע$_{asim}$(CH_3)), 2843 (*s*, ע(C-H)), 1608

(*m*, ע(C=C)), 1563 (*s*, tetrazole), 1490 (*s*, ע(C=C)), 746 (*s*, γ(C-H, Ph) cm^{-1}; **^{1}H NMR**(500 MHz, d_6-DMSO): δ = 2.50 (*s*, 3H, H-C_8), 7.38 (*m*, 1H, H-C_5), 7.43 (*m*, 1H, H-C_3), 7.48 (*m*, 1H, H-C_4), 7.68 (*m*, 1H, H-C_6), 16.65 (*br*, NH); **^{13}C NMR** (125 MHz, d_6-DMSO): δ = 20.5 (CH_3, C_8), 123.8 (Cq, C_2), 126.3 (CH, C_5), 129.4 (CH, C_3), 130.7 (CH, C_4), 131.3 (CH, C_6), 137.0 (Cq, C_1), 155.0 (Cq, C_7); **MS:** *m/z* 159 $[MH]^+$, 131 $[M\text{-}H\text{-}N_2]^-$; **HR-MS:** calc'd for $[M\text{-}H]^-$ = 159.0676, found 159.0676 (ΔM (ppm) = 0.2).

5-[4-(1*H*-tetrazol-5-yl-methyl)-phenyl]-1*H*-tetrazole (93)

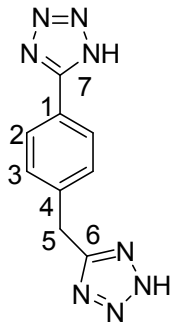


282 **93**

CAS Registry Number	66012-62-2
Molecular Formula	$C_9H_8N_8$
Molecular Weight	228.22 g/mol
Analysis Ref.	H. Illy, Ciba-Geigy A.-G., Switz., Ger. Offen. **1978**, DE 2731323 A1

TP1: 2.1 equivalents of diethylaluminum azide (2.7 M in xylene) are used in a 1.4 mmol scale experiment. The reaction is stirred for twenty four hours at 75 °C to the product as a white crystalline material (305 mg, 95 % yield).

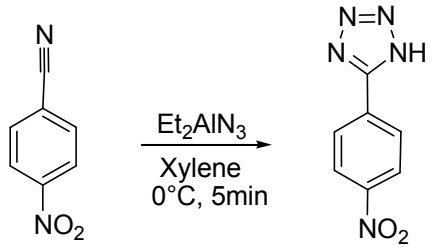
Compound characterization data:



mp: up to 250 °C; **TLC:** R_f (toluene / AcOEt / AcOH 20:20:1) = 0.24; **HPLC:** 3.44 min; **UV** (MeOH): λ_{max}, nm (ε): 243 (14580); **IR:** 3200-2300 (*brs*, ע(N-H)), 3091 (*w*, ע(C-H)), 3018 (*m*, ע(C-H)), 2988 (*m*, ע(C-H)), 2931 (*m*, ע(C-H)), 1577 (*m*, tetrazole), 1509 (*m*, ν(C=C)), 1451 (*m*, ע(C=C)) cm^{-1}; **^{1}H NMR** (500 MHz, d_6-DMSO): δ = 4.41 (*s*, 2H, H-C_5),

7.51 (*d*, $^3J_{2,3}$ = 8.3 Hz, 2H, H-C_3), 8.02 (*d*, $^3J_{2,3}$ = 8.3 Hz, 2H, H-C_2), 16.60 (*br*, NH); **^{13}C NMR**(125 MHz, d_6-DMSO): δ = 28.4 (CH_2, C_5), 127.3 (CH, Ar), 127.5 (Cq, Ar), 129.8 (CH, Ar), 139.1 (Cq, Ar), 155.0 (Cq, $C_{6,7}$); **MS:** *m/z* 227 $[M-H]^-$.

5-(4-Nitrophenyl)-1*H*-tetrazole (94)

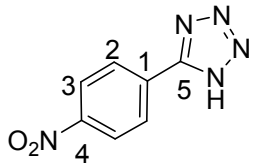


283 **94**

CAS Registry Number	16687-60-8
Molecular Formula	$C_7H_5N_5O_2$
Molecular Weight	191.15 g/mol
Analysis Ref.	a) Z. P. Demko, K. B. Sharpless, *J. Org. Chem*. **2001**, *66*, 7945; b) E. H. Master, S. I. Khan, K. A. Poojary, *Bioorg. Med. Chem.* **2005**, *13*, 4891

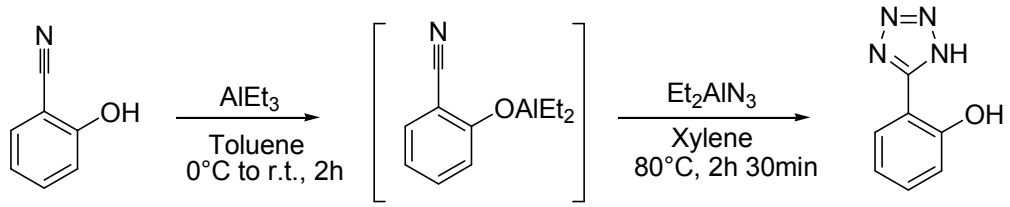
TP1: 1.5 equivalents of diethylaluminum azide (2.7 M in xylene) are used in a 5 mmol scale experiment. The reaction is stirred five minutes at 0 °C (addition of the starting nitrile very exhothermic with gas evolution) to give the product as a brown crystalline material (140 mg, 15 % yield).

Compound characterization data:



mp: 194-196 °C; **TLC:** R_f (toluene / AcOEt / AcOH 20:20:1) = 0.16; **HPLC:** 4.34 min; **UV** (EtOH): λ_{max}, nm (ε): 280 (11830); **IR:** ν 3250-2400 (*brm*, ν(N-H)), 3105 (*m*, ν(C-H)), 3079 (*m*, ν(C-H)), 1606 (*m*, ν(C=C)), 1553 (*m*, tetrazole), 1526 (*s*, ν(NO_2)), 1339 (*s*, ν(NO_2)) cm^{-1}; **^{1}H NMR** (500 MHz, d_6-DMSO): δ = 8.30 (*d*, $^3J_{2,3}$ = 12.0 Hz, 2H, H-C_2), 8.43 (*d*, $^3J_{2,3}$ = 12.0 Hz, 2H, H-C_3), 16.30 (*br*, NH); **^{13}C NMR** (125 MHz, d_6-DMSO): δ = 124.2 (CH, C_2), 127.8 (CH, C_3), 130.5 (Cq, C_4), 148.2 (Cq, C_1), 152.9 (Cq, C_5); **MS:** *m/z* 190 $[M-H]^-$, 162 $[M-H-N_2]^-$, 134 $[M-H-N_2-N_2]^-$.

5-(2-Hydroxy-phenyl)-1*H*-tetrazole (95)



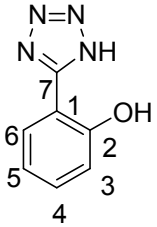
284 **285** **95**

CAS Registry Number	51449-77-5
Molecular Formula	$C_7H_6N_4O$
Molecular Weight	162.15 g/mol
Analysis Ref.	a) J. Kaczmarek, Z. Grzonka, *Polish J. Chem*. **1980**, *54*, 1297; b) A. Kumar, R. Narayanan, H. Shechter, *J. Org. Chem*. **1996**, *61*, 4462; c) K. Koguro, T. Oga, S. Mitsui, R. Orita, *Synthesis* **1998**, *6*, 910; d) G. Sedelmeier, Novartis Pharma AG, **2005**, WO2005/014602 A1

Protection of the hydroxyl group: TP2, Cycloaddition: TP1:

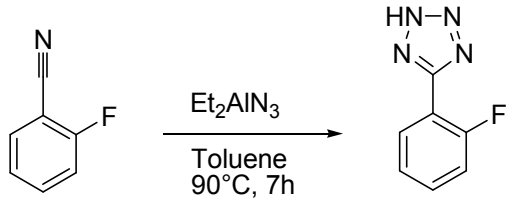
1.1 equivalents of diethylaluminum azide (2.7 M in xylene) are used in a 4 mmol scale experiment. The reaction is stirred for two hours and thirty minutes at 80 °C to give the product as a white crystalline material (628 mg, 97 % yield). The same experiment is done at room temperature for four hours to obtain the same yield .

Compound characterization data:



mp: 220-222 °C; **TLC:** R_f (toluene / AcOEt / AcOH) = 0.46; **HPLC:** 3.67 min; **UV** (EtOH): λ_{max}, nm (ε): 298 (516), 253 (843), 244 (1190), 208 (2710); **IR:** *ν* 3254 (*s*, ν(OH)), 3300-2500 (*brs*, ν(N-H)), 3065 (*s*, ν(C-H)), 1964-1600 (*w*, overtones γ(C-H, Ph)), 1615 (*vs*, ν(C=C)), 1548 (*s*, tetrazole), 1487 (*s*, ν(C=C)), 1466 (*vs*, ν(C=C)), 748 (*s*, γ(CH, Ph)) cm^{-1}; **^{1}H NMR** (500 MHz, d_6-DMSO): δ = 7.01 (*m*, ^3J = 8.0 Hz, 1H, H-C_5), 7.14 (*d*, ^3J = 8.2 Hz, 1H, H-C_3), 7.41 (*dt*, $^4J_{4,6}$ = 1.5 Hz, ^3J = 8.0 Hz, 1H, H-C_4), 8.00 (*dd*, $^4J_{4,6}$ = 1.5 Hz, ^3J = 8.0 Hz, 1H, H-C_6), 11.00 (*br*, OH), 16.00 (*br*, NH); **^{13}C NMR** (125 MHz, d_6-DMSO): δ = 110.4 (Cq, C_1), 116.3 (CH, C_5), 119.7 (CH, C_3), 129.0 (CH, C_6), 132.6 (CH, C_4), 151.6 (Cq, C_7), 155.3 (C_q, C_2); **MS:** *m/z* 161 $[M-H]^+$, 163 $[M+H]^+$.

5-(2-Fluoro-phenyl)-2*H*-tetrazole (96)

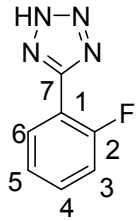


135 **96**

CAS Registry Number	50907-19-2
Molecular Formula	$C_7H_5N_4F$
Molecular Weight	164.14 g/mol
Analysis Ref.	a) E. F. George, W. R. Riddell, Imperial Chemical Industries Ltd., UK, **1975**, US 3865570; b) R. K. Russell, W. V. Murray, *J. Org. Chem*. **1993**, *58*, 5023; c) P. Malladi, S. Kantevari, C. K. S. Nair, (Council of Scientific and Industrial Research, India) **2001**, US 6326498 B1; d) K. Srinivas, C. K. S. Nair, S. Ramesh, M. Pardhasaradh, *Org. Prep. Proc. Int*. **2004**, *36*, 69; e) G. Sedelmeier, Novartis Pharma AG, **2005**, WO2005/14602 A1

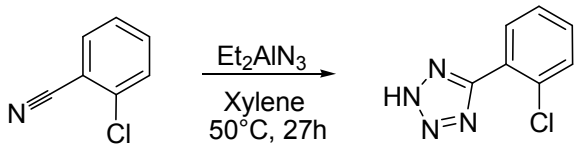
TP1: 1.3 equivalents of diethylaluminum azide (1.8 M in toluene) are used in a 15 mmol scale experiment. The reaction is stirred seven hours at 90 °C to give the product as a white crystalline material (2.348 g, 95 % yield). The same experiment was done at 55 °C stirring the reaction for 39 hours with the same yield.

Compound characterization data:



mp: 158-160 °C; **TLC:** R_f (toluene / EtOAc / AcOH 20:20:1) = 0.45; **HPLC:** 3.79 min.; **UV** (EtOH): λ_{max}, nm (ε): 275 (1610), 236 (12850), 197 (25630); **IR:** ν 3100-2400 (*brs*, ν(N-H)), 3063 (*m*, ν(C-H)), 3023 (*s*, ν(C-H)), 1900-1750 (*w*, overtones γ(C-H)), 1622 (*s*, ν(C=C)), 1587 (*m*, tetrazole), 1494 (*s*, ν(C=C)), 1234 (*s*, ν(C-F)), 752 (*s*, γ(C-H, Ph) cm^{-1}; **^{1}H NMR** (500 MHz, d_6-DMSO): δ = 7.45 (*m*, 1H, H-C_5), 7.50 (*m*, 1H, H-C_3), 7.68 (*m*, 1H, H-C_4), 8.06 (*m*, 1H, H-C_6), 16.5 (*br*, NH); **^{13}C NMR** (125 MHz, d_6-DMSO): δ = 112.5 (Cq, C_1), 116.6 (CH, C_3), 123.4 (CH, C_5), 130.2 (CH, C_6), 133.5 (CH, C_4), 158.1 (Cq, C_7), 159.8 (Cq, C_1); **MS:** *m/z* 165 $[MH]^+$, 163 $[M-H]^-$, 135 $[MH-N_2]^-$, 122 $[MH-HN_3]^+$.

5-(2-Chloro-phenyl)-2*H*-tetrazole (97)

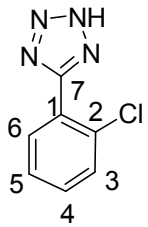


286 **97**

CAS Registry Number	50907-46-5
Molecular Formula	$C_7H_5ClN_4$
Molecular Weight	180.60 g/mol
Analysis Ref.	a) R. M. Herbst, K. R. Wilson, *J. Org. Chem.* **1957**, *22*, 1142; b) E. F. George, W. R. Riddell, Imperial Chemical Industries Ltd., UK, **1975** US 3865570; c) R. N. Butler, V. C. Garvin, *J. Chem. Soc.*, Perkin Trans. 1, **1981**, *2,* 390; d) K. Srinivas, C. K. S. Nair, S. Ramesh, M. Pardhasaradhi, *Org. Prec. Proc. Int.* **2004**, *36*, 69; e) G. Sedelmeier, Novartis A.-G., Switz. **2005**, WO 2005014602 A1

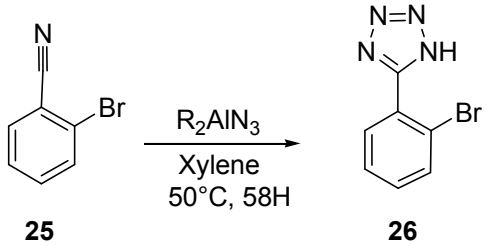
TP1: 1.3 equivalents of diethylaluminum azide (2.7 M in xylene) are used in a 4 mmol scale experiment. The reaction is stirred for twenty seven hours at 50 °C to give the product as a white crystalline material (680 mg, 95 % yield).

Compound characterization data:



mp: 173-175 °C; **TLC:** R_f (toluene / EtOAc / AcOH 20:20:1) = 0.48; **HPLC:** 4.28 min; **UV** (EtOH): λ_{max}, nm (ε): 235 (6770), 204 (2439); **IR:** ν 3200-2400 (*sbr*, ν(N-H)), 3108 (*w*, ν(C-H)), 3061 (*m*, ν(C-H)), 3034 (*m*, ν(C-H)), 3004 (*m*, ν(C-H)), 1603 (*s*, ν(C=C)), 1564 (*s*, tetrazole), 1472 (*m*, ν(C=C)), 748 (*s*, γ(C-H, Ph) cm^{-1}; **^{1}H NMR** (500 MHz, d_6-DMSO): δ = 7.55 (*m*, 1H, H-C_5), 7.63 (*m*, 1H, H-C_4), 7.71 (*m*, 1H, H-C_3), 7.80 (*m*, 1H, H-C_6), 16.90 (*br*, NH); **^{13}C NMR** (125 MHz, d_6-DMSO): δ = 124.1 (Cq, C_2), 127.8 (CH, C_5), 130.4 (CH, C_4), 131.7 (CH, C_3), 131.9 (Cq, C_1), 132.6 (CH, C_6); **MS:** *m/z* 181 $[MH]^+$, 179 $[M-H]^-$, 151 $[M-H-N_2]^-$.

5-(2-Bromo-phenyl)-1*H*-tetrazole (26)

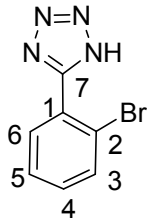


25 **26**

CAS Registry Number	73096-42-1
Molecular Formula	$C_7H_5N_4Br$
Molecular Weight	225.5 g/mol
Analysis Ref.	a) S. J. Wittember, B. G. Donner, *J. Org. Chem.* **1993**, *58*, 4139; b) J. W. Ellingboe, M. Antane, T. T. Nguyen, M. D. Collini, A. Schuyler, D. Hartupee, V. White, J. McCallum, *J. Med. Chem.* **1994**, *37*, 542; c) J. Boivin, S. Husinec, S. Z. Zard, *Tetrahedron* **1995**, *51*, 11737

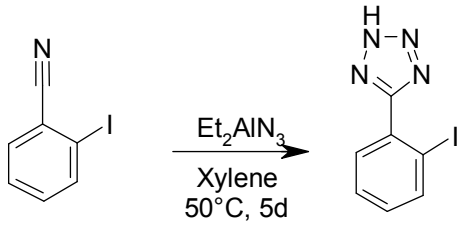
TP1: 1.5 equivalents of diethylaluminum azide (2.7 M in xylene), or 1.5 equivalents of dimethylaluminum azide (1 M in hexane) are used in a 3 mmol scale experiment. The reaction is stirred for thirty hours at 50 °C to give the product as a white crystalline material (480 mg, 71 % yield).

Compound characterization data:



mp: 174-176 °C; **TLC:** R_f (toluene / EtOAc / AcOH 20:20:1) = 0.4; **HPLC:** 4.14 min; **UV** (EtOH): λ_{max}, nm (ε): 203 (27320); **IR:** ν 3100-2400 (*brs*, ν(N-H)), 3068 (*m*, ν(C-H)), 3035 (*m*, ν(C-H)), 1988-1700 (*w*, overtones γ(C-H, Ph), 1605 (*s*, ν(C=C)), 1476 (*s*, ν(C=C)), 1447 (*s*, tetrazole), 749 (*s*, γ(C-H, Ph) cm^{-1}; **^{1}H NMR** (500 MHz, d_6-DMSO): δ = 7.55 (*m*, ^3J = 8.0 Hz, 2H, H-$C_{4,5}$), 7.7 (*dd*, $^3J_{3,4}$ = 8.0, J = 4.0 Hz, 1H, H-C_3), 7.85 (*dd*, J = 8.0, 4.0 Hz, 1H, H-C_6), 16.70 (*br*, NH); **^{13}C NMR** (125 MHz, d_6-DMSO): δ = 121.4 (Cq, C_1), 126.1 (Cq, C_2), 127.7 (CH, C_5), 131.6 (CH, C_4), 132.2 (CH, C_3), 133.1 (CH, C_6), 154.2 (Cq, C_7); **MS:** *m/z* 225 $[MH]^+$, 197 $[M\text{-}H\text{-}N_2]^-$, 182 $[MH\text{-}HN_3]^+$.

5-(2-Iodo-phenyl) -2*H*-tetrazole (98)

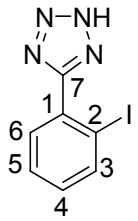


286 **98**

CAS Registry Number	73096-40-9
Molecular Formula	$C_7H_5N_4I$
Molecular Weight	272.05 g/mol
Analysis Ref.	a) J. Kaczmarek, H. Smagowski, Z. Grzonka, *J. Chem. Soc., Perkin Trans.* 2: Physical Organic Chemistry (1972-1999) **1979**, *12*, 1670; b) J. Kaczmarek, Z. Grzonka, *Pol. J. Chem.* **1980**, *54*, 1297; c) J. Boivin, S. Husinec, S. Z. Zard, *Tetrahedron* **1995**, *51*, 11737

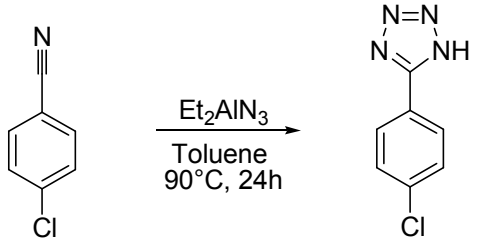
TP1: 1.3 equivalents of diethylaluminum azide (2.7 M in xylene) are used in a 3 mmol scale experiment. The reaction is stirred for three days at 50 °C to give the product as a white crystalline material (690 mg, 85 % yield).

Compound characterization data:



mp: 214-216 °C; **TLC:** R_f (toluene / AcOEt / AcOH 20:20:1) = 0.42; **HPLC:** 4.75 min; **UV** (EtOH): λ_{max}, nm (ε): 204 (20180); **IR:** ν 3027 (*w*, ν(C-H)), 3000-2300 (*brs*, ν(N-H)), 2996 (*w*, ν(C-H)), 1601 (*s*, ν(C=C)), 1569 (*w*, tetrazole), 1473 (*s*, ν(C=C)), 747 (*s*, γ(C-H, Ph) cm^{-1}; **^{1}H NMR** (500 MHz, d_6-DMSO): δ = 7.34 (*m*, $^3J_{3,4}$ = 8.03 Hz, 1H, H-C_4), 7.59 (*m*, 2H, H-$C_{5,6}$), 8.09 (*d*, $^3J_{3,4}$ = 8.03 Hz, 1H, H-C_3), 17.00 (*br*, NH); **^{13}C NMR** (125 MHz, d_6-DMSO): δ = 97.6 (Cq, C_2), 128.4 (CH, C_4), 130.5 (Cq, C_1), 131.2 (CH, C_5), 132.4 (CH, C_6), 139.7 (CH, C_3), 155.8 (Cq, C_7); **MS:** *m/z* 273 $[M+H]^+$, 271 $[M-H]^-$, 243 $[M-H-N_2]^-$; **HR-MS:** calc'd for $[M+H]^+$ = 272.9632, found 272.9630 (ΔM (ppm) = 0.5), calc'd for $[M+Na]^+$ = 294.9451, found 294.9450 (ΔM (ppm) = 0.3).

5-(4-Chloro-phenyl)-1*H*-tetrazole (1)

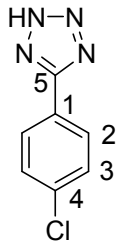


287 **1**

CAS Registry Number	16687-61-9
Molecular Formula	$C_7H_5N_4Cl$
Molecular Weight	180.59 g/mol
Analysis Ref.	a) E. F. George, W. R. Riddell, Imperial Chemical Industries Ltd., UK, **1975**, US 3865570; b) A. Antonowa, S. Hauptmann, *Zeitschrift fuer Chemie* **1976**, *16*, 17; c) J. Kaczmarek, Z. Grzonka, *Pol. J. Chem*. **1980**, *54*, 1297; d) N. Sadlej-Sosnowska, W. P. Oziminski, A. Krowczynski, *Chem. Phys*. **2003**, *294*, 65; e) F. Lenda, F. Guenoun, B. Tazi, N. Benlarbi, H. Allouchi, J. Martinez, F. Lamaty, *Eur. J. Org. Chem*. **2005**, *2*, 326; f) G. Sedelmeier, Novartis Pharma AG, **2005**, WO2005/14602 A1

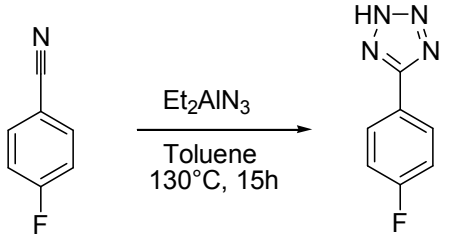
TP1: 1.57 equivalents of diethylaluminum azide (2.5 M in toluene) are used in a 40 mmol scale experiment. The reaction is stirred twenty four hours at 90 °C to give the product as a off white crystalline material (7.09 g, 97 % yield).

Compound characterization data:



mp: 255-257 °C; **TLC:** R_f (toluene / EtOAc / AcOEt / AcOH 20:20:1) = 0.40; **HPLC:** 5.86 min.; **UV** (EtOH): λ_{max}, nm (ε): 248 (34480); **IR:** ν 3200-2400 (*brs*, ν(N-H)), 3096 (*m*, ν(C-H)), 3071 (*m*, ν(C-H)), 3000 (*m*, ν(C-H)), 1900-1750 (*w*, overtones γ(C-H, Ph)), 1611 (*s*, ν(C=C)), 1566 (*w*, tetrazole), 1488 (*s*, ν(C=C)), 1436 (*s*, ν(C=C)), 1096 (*s*, ν(Ph-Cl)) cm^{-1}; **^{1}H NMR** (500 MHz, d_6-DMSO): δ = 7.69 (*m*, $^3J_{2,3}$ = 8.8 Hz, 2H, H-C_2), 8.04 (*d*, $^3J_{2,3}$ = 8.8 Hz, 2H, H-C_3), 17.00 (*br*, NH); **^{13}C NMR** (125 MHz, d_6-DMSO): δ = 123.1 (Cq, C_1), 128.7 (CH, C_3), 129.6 (CH, C_2), 135.9 (Cq, C_4), 154.8 (Cq, C_5); **MS:** *m/z* 179 $[M-H]^-$.

5-(4-Fluoro-phenyl)-1*H*-tetrazole (99)

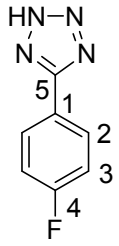


288 **99**

CAS Registry Number	50907-21-6
Molecular Formula	$C_7H_5FN_4$
Molecular Weight	164.14 g/mol
Analysis Ref.	a) E. F. George, W. R. Riddell, Imperial Chemical Industries Ltd., UK, **1975**, US 3865570; b) N. E. Takach, E. M. Holt, N. W. Alcock, R. A. Henry, J. H. Nelson, *J. Am. Chem. Soc*. **1980**, *102*, 2968; c) B. Verheyde, W. Dehaen, *J. Org. Chem*. **2001**, *66*, 4062

TP1: 1.5 equivalents of diethylaluminum azide (1.8 M in toluene) are used in a 5 mmol scale experiment. The reaction is stirred fifteen four hours at 130 °C to give the product as an off white crystalline material after crystallization from toluene (720 mg, 88 % yield).

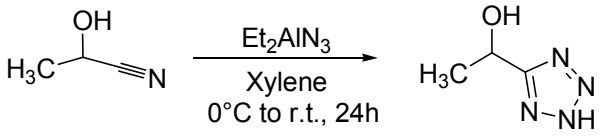
Compound characterization data:



mp: 209-211 °C; **TLC:** R_f (toluene / AcOEt / AcOH 20:20:1) = 0.41; **HPLC:** 4.73 min; **UV** (EtOH): λ_{max}, nm (ε): 240 (5440); **IR:** ν 3091 (*w*, ν(C-H)), 3073 (*w*, ν(C-H)), 3000-2300 (*brs*, ν(N-H)), 1900-1750 (*w*, overtones γ(C-H, Ph)), 1611 (*s*, ν(C=C)), 1572 (*w*, tetrazole), 1501 (*s*, ν(C=C)), 1446 (*s*, ν(C=C)), 843 (*s*, γ(C-H, Ph)) cm^{-1}; **^{1}H NMR** (500 MHz, d_6-DMSO): δ = 7.55 (*m*, $^3J_{2,3}$ = 8.8 Hz, 2H, H-C_2), 8.10 (*m*, $^3J_{2,3}$ = 8.8 Hz, 2H, H-C_3), 17.00 (*br*, NH); **^{13}C NMR** (125 MHz, d_6-DMSO): δ = 116.6 (CH, C_2), 121.0 (Cq, C_1), 129.4 (CH, C_3), 154.7 (Cq, C_5), 162.7 (Cq, C_4); **HR-MS:** calc'd for $[M-H]^-$ = 163.0426, found 163.0425 (ΔM (ppm) = 0.1).

5.1.3.6. Synthesis of tetrazoles in the presence od hydroxy group

1*H*-Tetrazole-5-methanol-α-methyl (100)

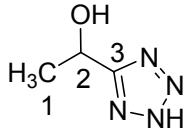


289 **100**

CAS Registry Number	155471-60-6
Molecular Formula	$C_3H_6N_4O$
Molecular Weight	114.05 g/mol
Analysis Ref.	B. E. Fisher, A. J. Tomson, J. P. Horwitz, *J. Org. Chem.* **1959**, *24*, 1650

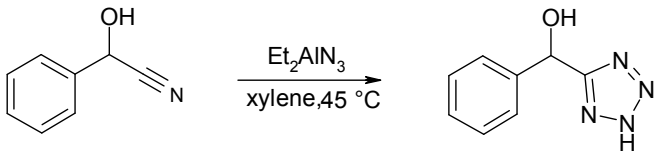
TP1: 1.3 equivalents of diethylaluminum azide (2.7 M in xylene) are used in a 10 mmol scale experiment. The reaction is stirred for twenty four hours from 0 °C to room temperature to give the product as a white crystalline material (780 mg, 65 % yield).

Compound characterization data:



mp: 120-122 °C; **TLC:** R_f (toluene / EtOAc / AcOH 20:20:1, CPS) = 0.2; **UV** (EtOH): λ_{max}, nm (ε): 273 (ε = 3); **IR:** ν 3382 (*s*, ν(O-H)), 3000-2400 (*brs*, ν(N-H)), 2987 (*s*, ν(C-H)), 2978 (*s*, ν(C-H)), 2950 (*m*, ν(C-H)), 1580 (*m*, (tetrazole)), 1463 (*w*, (tetrazole)), 1445 (*m*, (tetrazole)), 1256 (*s*, ν(C-O)), 1246 (*s*, ν(C-O)) cm^{-1}; **^{1}H NMR** (500 MHz, d_6-DMSO): δ = 1.48 (*d*, $^3J_{1,2}$ = 6.5 Hz, 3H, H-C_1), 5.08 (*q*, $^3J_{1,2}$ = 6.5 Hz, 1H, H-C_2), 6.01 (*br*, OH), 16.15 (*br*, NH); **^{13}C NMR** (125 MHz, d_6-DMSO): δ = 22.6 (CH_3, C_1), 60.6 (CH, C_2), 144.0 (Cq, C_3); **MS:** *m/z* 115 $[MH]^+$, 113 $[M-H]^-$; **HR-MS:** calc'd for $[M-H]^-$ = 113.0469, found 113.0469 (ΔM (ppm) = 0.1), calc'd for $[M+Cl]^-$ = 149.0236, found 149.0236 (ΔM (ppm) = 0.1).

Phenyl (2*H*-tetrazol-5-yl)-methanol (101) and (*R*)-enantiomer (102)



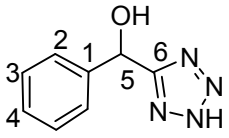
290 **101**

CAS Registry Number	40060-76-2 (racemic)
Molecular Formula	$C_8H_8N_4O$
Molecular Weight	176.18 g/mol
Analysis Ref.	Z. P. Demko, K. B. Sharpless, *J. Org. Chem.* **2001**, *66*, 7945

Protection of the hydroxyl group: TP2, Cycloaddition: TP1

1.5 equivalents of diethylaluminum azide (2.7 M in xylene) are used in a 7 mmol scale experiment. The reaction is stirred for one hour twenty minutes at 45 °C to give the product as a white crystalline material obtained after crystallization from ethyl acetate (1.04 g, 82.4 % yield). The same experiment is done with the pure (*R*)-enantiomer in a 3.5 scale experiment at 40 °C for one hour to give 610 mg of product with 99 % of yield after extractions.

Compound characterization data:

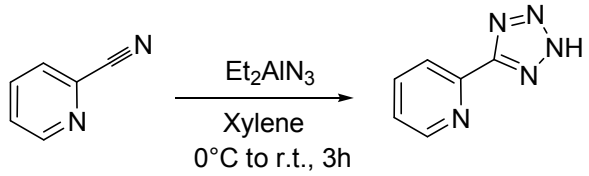


mp: 157-159 °C; **HPLC:** 2.428 min; **TLC:** R_f (toluene / EtOAc / AcOH 20:20:1) = 0.23; **Optical rotation:** (*R*)-enantiomer: $[\alpha]_D^{25}$ = -1.0 (in MeOH, c = 0.70); **UV** (EtOH): λ_{max}, nm (ε): 258 (ε = 25); **IR:** ν 3426 (*brs*, ν(O-H)), 3092 (*s*, ν(C-H)), 3066 (*s*, ν(C-H)), 3000-

23000 (*brs*, ν(N-H)), 2950 (*s*, ν(C-H)), 1495 (*w*, ν(C=C)), 1456 (*w*, ν(C=C)), 1434 (*w*, ν(C=C)), 1059 (*s*, ν(C-O)), 1041 (*m*, ν(C-O)), 754 (*m*, γ(C-H, Ph)), 696 (*s*, γ(Ph)) cm^{-1}; **^{1}H NMR** (500 MHz, d_6-DMSO): δ = 6.11 (*d*, *J* = 4 Hz, 1H, H-C_5), 6.75 (*br*, 1H, OH), 7.30 (*m*, 1H, H-C_4), 7.35 (*m*, 2H, H-C_3), 7.41 (*m*, 2H, H-C_2), 16.40 (*br*, NH); **^{13}C NMR** (125 MHz, d_6-DMSO): δ = 66.3 (CH, C_5), 126.3 (CH, C_2), 128.0 (CH, C_4), 128.4 (CH, C_3), 140.9 (Cq, C_1), 158.8 (Cq, C_6); **MS:** *m/z* 177 $[MH]^+$, 175 $[M-H]^-$, 159 $[MH-H_2O]^+$, 131 $[MH-H_2O-N_2]^+$; **HR-MS:** calc'd for $[M-H]^-$ = 175.0625, found 175.0625 (ΔM (ppm) = 0.1).

5.1.3.7. Synthesis of 5-substituted heteroaromatic tetrazoles

2-(2*H*-Tetrazol-5yl)-pyridine (103)

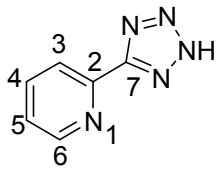


291 **103**

CAS Registry Number	33893-89-9
Molecular Formula	$C_6H_5N_5$
Molecular Weight	147.14 g/mol
Analysis Ref.	a) J. M. McManus, R. M. Herbst, *J. Org. Chem*. **1959**, *24*, 1462; b) Z. P. Demko, K. B. Sharpless, *J. Org. Chem*. **2001**, *66*, 7945; c) J.-J. Shie, J.-M. Fang, *J. Org. Chem*. **2003**, *68*, 1158

TP1: 1.3 equivalents of diethylaluminum azide (2.7 M in xylene) are used in a 5 mmol scale experiment. The reaction is stirred for three hours from 0°C to room temperature. The mixture is quenched with HCl (2 M) and the pH adjusted with potassium carbonate to pH 6, the aqueous phase is saturated with solid NaCl and extracted with ethyl acetate to give the product as a white crystalline material (490, mg 67 % yield).

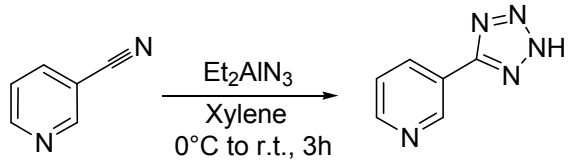
Compound characterization data:



mp: 210-212 °C; **TLC:** R_f (toluene / EtOAc / AcOH 10:20:1) = 0.07; **HPLC:** 2.23 min; **UV** (EtOH): λ_{max}, nm (ε): 273 (6450), 233 (11490); **IR:** ν 3092 (*s*, ν(C-H)), 3065 (*s*, ν(C-H)), 3032 (*s*, ν(C-H)), 3000-2400 (*brs*, ν(N-H)), 1640 (*w*, ν(C=C)), 1603 (*s*, ν(C=C)),

1558 (*s*, tetrazole), 796 (*s*, δ(pyrindine), 744 (*s*, δ(pyrindine) cm^{-1}; **^{1}H NMR** (500 MHz, d_6-DMSO): δ = 7.62 (*ddd*, $^3J_{5,6}$ = 4.8, $^3J_{4,5}$ = 7.7, $^4J_{3,5}$ = 1.3 Hz, 1H, H-C_5), 8.07 (*dt*, ^3J = 7.7, $^4J_{4,6}$ = 1.7 Hz, 1H, H-C_4), 8.21 (*ddd*, $^3J_{3,4}$ = 7.8, $^4J_{3,5}$ = 1.3, $^5J_{3,6}$ = 1.0 Hz, 1H, H-C_3), 8.77 (*ddd*, $^3J_{5,6}$ = 4.8, $^4J_{4,6}$ = 1.7, $^5J_{3,6}$ = 1.0 Hz, 1H, H-C_6), 17.15 (*br*, NH); **^{13}C NMR** (125 MHz, d_6-DMSO): δ = 122.2 (CH, C_5), 125.7 (CH, C_4), 137.8 (CH, C), 143.2 (Cq, C_2), 149.6 (CH, C_6), 154.3 (Cq, C_7); **MS:** *m/z* 148 $[MH]^+$, 146 $[M-H]^-$, 120 $[MH-N_2]^+$, 118 $[M-H-N_2]^-$; **HR-MS:** calc'd for $[M-H]^-$ = 146.0472, found 146.0472 (ΔM (ppm) = 0.1).

3-(2*H*-Tetrazol-5yl)-pyridine (104)

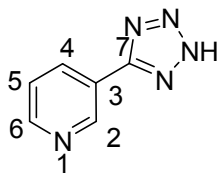


292 **104**

CAS Registry Number	3250-74-6
Molecular Formula	$C_6H_5N_5$
Molecular Weight	147.14 g/mol
Analysis Ref.	a) J. M. McManus, R. M. Herbst, *J. Org. Chem.* **1959**, *24*, 1462; b) M. Alterman, A. Hallberg, *J. Org. Chem.* **2000**, *65*, 7984; c) D. Amantini, R. Beleggia, F. Fringuelli, F. Pizzo, L. Vaccaro, *J. Org. Chem.* **2004**, *69*, 2896; d) T. T. Denton, X. Zhang, J. R. Cashman, *J. Med. Chem.* **2005**, *48*, 224

TP1: 1.3 equivalents of diethylaluminum azide (2.7 M in xylene) are used in a 5 mmol scale experiment. The reaction is stirred for three hours from 0 °C to room temperature. The mixture is quenched with HCl (2 M) and the pH adjusted with potassium carbonate to pH 6, the aqueous phase is saturated with solid NaCl and extracted to give the product as a white crystalline material after crystallization from a mixture of ethyl acetate / ethanol (570 mg, 78 % yield).

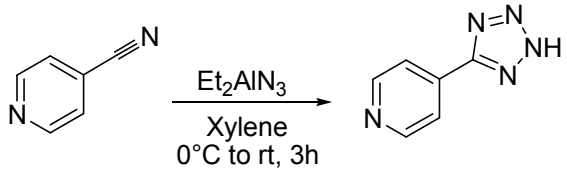
Compound characterization data:



mp: 226-228 °C; **TLC:** R_f (toluene / AcOEt / AcOH 10:20:2) = 0.04; **HPLC:** 1.72 min; **UV** (EtOH): λ_{max}, nm (ε): 272 (2190), 266 (2190), 233 (7650); **IR:** ν 3200-2400 (*brs*, ν(N-H)), 3086 (*s*, ν(C-H)), 3063 (*s*, ν(C-H)), 3036 (*s*, ν(C-H)), 1610 (*s*, ν(C=C)), 1583

(*m*, ν(C=C)), 1528 (*m*, tetrazole), 1485 (*m*, ν(C=C)) cm^{-1}; **^{1}H NMR** (500 MHz, d_6-DMSO): δ = 7.69 (*ddd*, $^3J_{5,6}$ = 4.9, $^3J_{4,5}$ = 7.9 Hz, 1H, H-C_5), 8.51 (*m*, $^3J_{4,5}$ = 7.9, $^4J_{4,6}$ = 1.7 Hz, 1H, H-C_4), 8.77 (*dd*, $^3J_{5,6}$ = 4.9, $^4J_{4,6}$ = 1.7 Hz, 1H, H-C_6), 9.28 (*m*, 1H, H-C_2), 16.70 (*br*, NH); **^{13}C NMR** (125 MHz, d_6-DMSO): δ = 121.2 (Cq, C_3), 124.6 (CH, C_5), 135.3 (CH, C_4), 147.1 (CH, C_2), 151.1 (CH, C_6), 153.6 (Cq, C_7); **MS:** *m/z* 148 $[MH]^+$, 146 $[M\text{-}H]^-$, 105 $[MH\text{-}HN_3]^+$; **HR-MS:** calc'd for $[M\text{-}H]^-$ = 146.0472, found 146.0472 (ΔM (ppm) = 0.1).

4-(2*H*-Tetrazol-5yl)-pyridine (105)

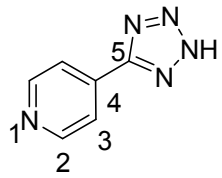


293 **105**

CAS Registry Number	14389-12-9
Molecular Formula	$C_6H_5N_5$
Molecular Weight	147.14 g/mol
Analysis Ref.	a) J. M. McManus, R. M. Herbst, *J. Org. Chem.* **1959**, *24*, 1462; b) H. Detert, D. Schollmeier, *Synthesis* **1999**, *6*, 999

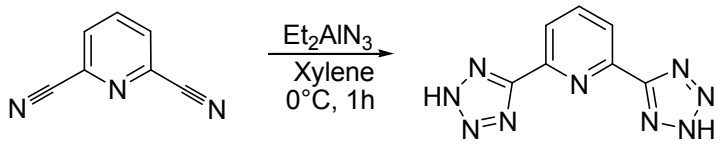
TP1: 1.3 equivalents of diethylaluminum azide (2.7 M in xylene) are used in a 5 mmol scale experiment. The reaction is stirred for three hours from 0 °C to room temperature. The mixture is quenched with HCl (2 M), and the pH adjusted with potassium carbonate to pH 6, the aqueous phase is saturated with solid NaCl and extracted to give the product as a white crystalline material obtained after crystallization from ethanol (700 mg, 95 % yield).

Compound characterization data:



mp: 255-258 °C; **TLC:** R_f (toluene / EtOAc / AcOH 10:20:1) = 0.04; **HPLC:** 1.38 min; **UV** (EtOH): λ_{max}, nm (ε): 253 (234); **IR:** ν 3200-3000 (*br*s, ν(N-H)), 3040 (*m*, ν(C-H)), 1619 (*s*, ν(C=C)), 1580 (*s*, tetrazole), 1448 (*s,* ν(C=C)) cm^{-1}; **^{1}H NMR** (500 MHz, d_6-DMSO): δ = 7.78 (*d*, $^3J_{2,3}$ = 6.0 Hz, 2H, H-C_3), 8.51 (*d*, $^3J_{2,3}$ = 6.0 Hz, 2H, H-C_2), 16.30 (*br*, NH); **^{13}C NMR** (125 MHz, d_6-DMSO): δ = 120.9 (CH, C_3), 139.4 (Cq, C_4), 149.8 (CH, C_2), 158.9 (Cq, C_5); **MS:** *m/z* 146 $[M\text{-}H]^-$, 118 $[M\text{-}H\text{-}N_2]^+$.

2,6-Bis-(2*H*-tetrazol-5-yl)-pyridine (106)

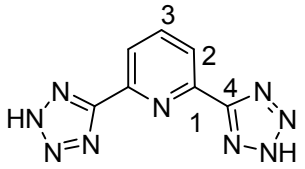


294 **106**

CAS Registry Number	68790-48-7
Molecular Formula	$C_7H_5N_9$
Molecular Weight	215.18 g/mol
Analysis Ref.	a) J. M. McManus, R. M. Herbst, *J. Org. Chem.* **1959**, *24*, 1462; b) M. Duati, S. Tasca, F. C. Lynch, H. Bohlen, J. G. Vos, S. Stagni, M. D. Ward, *Inorg. Chem*. **2003**, *42*, 8377

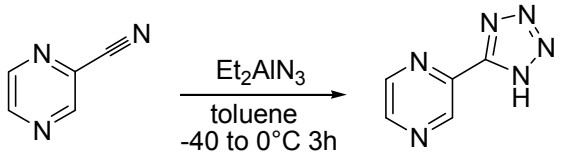
TP1: 3 equivalents of diethylaluminum azide (2.7 M in xylene) are used in a 2 mmol scale experiment. The reaction is stirred for one hour at 0 °C. The mixture reaction is quenched with HCl (2 M) and the pH adjusted with potassium carbonate to pH 6, the aqueous phase is saturated with solid NaCl and extracted to give the product as an off white crystalline material (360 mg, 84 % yield).

Compound characterization data:



mp: up to 260 °C; **TLC:** R_f (toluene / EtOAc / AcOH 10:20:1) = 0.03**; UV** (MeOH): λ_{max}, nm (ε): 281 (3360), 273 (3500), 266 (3170), 221 (9380); **HPLC:** 3.61 min; **IR:** *v* 3200-2600 (*brs*, ν(N-H)), 3119 (*s*, ν(C-H)), 3092 (*s*, ν(C-H)), 3080 (*s*, ν(C-H)), 3043 (*s*, ν(C-H)), 3015 (*s*, ν(C-H)), 1557 (*s*, tetrazole), 1455 (*s*, (C=C)) cm^{-1}; **^{1}H NMR** (500 MHz, d_6-DMSO): δ = 8.33 (*m*, 3H, H-C_{1-3}), 16.80 (*br*, NH); **^{13}C NMR** (125 MHz, d_6-DMSO): δ = 132.6 (CH, C_2), 133.8 (Cq, C_1), 140.3 (CH, C_3), 162.0 (Cq, C_4); **MS:** *m/z* 214 $[M-H]^-$.

2-(1*H*-Tetrazol-5-yl)-pyrazine (107)



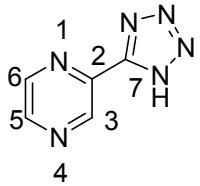
295 **107**

CAS Registry Number	16289-54-6
Molecular Formula	$C_5H_4N_6$
Molecular Weight	148.13 g/mol
Analysis Ref.	a) G. F. Holland, J. N. Pereira, *J. Med. Chem*. **1967**, *10*, 149; b) G.

	A. Wächter, M. C. Davis, A. R. Martin, S. G. Franzblau, *J. Med. Chem.* **1998**, *41*, 2436; c) Z. P. Demko, K. B. Sharpless, *J. Org. Chem.* **2001**, *66*, 7945

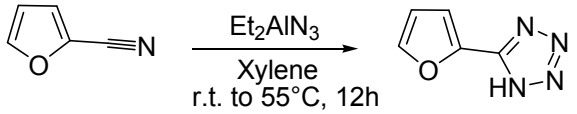
TP1: One equivalent of diisobutylaluminum azide (1.8 M in toluene) are used in a 4 mmol scale experiment. The reaction is stirred for three hours from - 40 to 0 °C. The mixture reaction is quenched with HCl (2 M) and the pH adjusted with potassium carbonate to pH 6, the aqueous phase is saturated with solid NaCl and the product extracted to give to give the product as an off white crystalline material obtained after crystallization from ethyl acetate (380 mg, 64 % yield).

Compound characterization data:



mp: 178-180 °C; **TLC:** R_f (toluene / EtOAc / AcOH 20:20:1) = 0.06; **HPLC:** 2.00 min; **UV** (EtOH): λ_{max}, nm (ε): 276 (9940), 227 (9800); **IR:** ν 3139 (*w*, ν(C-H)), 3097 (*w*, ν(C-H)), 3075 (*m*, ν(C-H)), 3000-2300 (*brm*, ν(N-H)), 1603 (*w*, ν(C=C)), 1572 (*w*, tetrazole), 1572 (*w*, pyridine) cm^{-1}; **^{1}H NMR** (500 MHz, d_6-DMSO): δ = 8.87 (*m*, *J* = 4.0 Hz, 1H, H-C_3), 9.39 (*d*, *J* = 4.0 Hz, 2H, H-$C_{5,6}$), 17.50 (*br*, NH); **^{13}C NMR** (125 MHz, d_6-DMSO): δ = 139.7 (Cq, C_2), 142.9 (CH, Ar), 144.4 (CH, Ar), 146.3 (CH, Ar), 153.2 (C_q, C_7); **MS:** *m/z* 147 $[M-H]^-$; **HR-MS:** calc'd for $[M-H]^-$ = 147.04247, found 147.04247 (ΔM (ppm) = 0.3).

5-Furan-2-yl-1*H*-tetrazole (108)

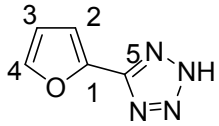


296 **108**

CAS Registry Number	23650-33-1
Molecular Formula	$C_5H_4N_4O$
Molecular Weight	136.11 g/mol
Analysis Ref.	a) E. F. George, W. R. Riddell, Imperial Chemical Industries Ltd., UK **1975**, US 3865570; b) A. Antonowa, S. Hauptmann, *Zeitschrift fuer Chemie* **1976**, *16*, 17; c) J.-J. Shie, J.-M. Fang, *J. Org. Chem.* **2003**, *68*, 1158; d) D. Amantini, R. Beleggia, F. Fringuelli, F. Pizzo, L. Vaccaro, *J. Org. Chem.* **2004**, *69*, 2896; e) F. Lenda, F. Guenoun, B. Tazi, N. Ben Iarbi, H. Allouchi, J. Martinez, F. Lamaty, *Eur. J. Org. Chem.* **2005**, *2*, 326

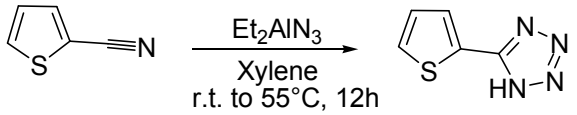
TP1: 1.2 equivalents of diethylaluminum azide (2.7 M in xylene) are used in a 5 mmol scale experiment. The reaction is stirred for twelve hours at 55 °C to give the product as a yellow crystalline material (591 mg, 87 % yield).

Compound characterization data:



mp: 198-200 °C; **TLC:** R_f (toluene / EtOAc / AcOH 20:20:1) = 0.31; **HPLC:** 2.86 min; **UV** (EtOH): λ_{max}, nm (ε): 255 (14490); **IR:** ν 3108 (*s*, ν(C-H)), 3073 (*w*, ν(C-H)), 3022 (*m*, ν(C-H)), 3000-2300 (*brs*, ν(N-H)), 1642 (*s*, ν(C=C)), 1541 (*s*, tetrazole)), 1488 (*w*, ν(C=C)) cm^{-1}; **^{1}H NMR** (500 MHz, d_6-DMSO): δ = 6.70 (*dd*, $^3J_{2,3}$ = 3.5 Hz, 1H, H-C_3), 7.26 (*dd*, $^3J_{2,3}$ = 3.5, $^4J_{2,4}$ = 1.7 Hz, 1H, H-C_2), 8.02 (*dd*, *J* = 1.7 Hz, 1H, H-C_4), 17.10 (*br*, NH); **^{13}C NMR** (125 MHz, d_6-DMSO): δ = 112.1 (CH, C_3), 112.6 (CH, C_2), 139.5 (Cq, C_1), 145.6 (CH, C_4), 154.2 (Cq, C_5); **MS:** *m/z* 137 $[MH]^+$, 135 $[M-H]^-$, 94 $[MH-HN_3]^+$; **HR-MS:** calc'd for $[M-H]^-$ = 135.0312, found 135.0312 (ΔM (ppm) < 0.1).

5-Thiophen-2-yl-1*H*-tetrazole (109)

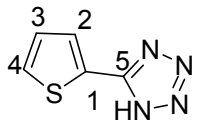


297 **109**

CAS Registry Number	59541-58-1
Molecular Formula	$C_5H_4N_4S$
Molecular Weight	152.18 g/mol
Analysis Ref.	a) B. Decroix, P. Dubus, J. Morel, P. Pastour, *Bull. Soc. Chim. Fr.* **1976**, 621; b) A. Antonowa, S. Hauptmann, *Zeitschrift fuer Chemie* **1976**, *16*, 17; c) J.-J. Shie, J.-M. Fang, *J. Org. Chem.* **2003**, *68*, 1158; d) F. Lenda, F. Guenoun, B. Tazi, N. Ben Iarbi, H. Allouchi, J. Martinez, F. Lamaty, *Eur. J. Org. Chem.* **2005**, 2, 326

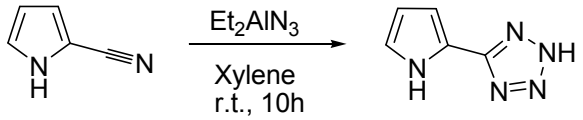
TP1: 1.2 equivalents of diethylaluminum azide (2.7 M in xylene) are used in a 5 mmol scale experiment. The reaction is stirred for twelve hours at 55 °C to give the product as a yellow crystalline material obtained after crystallization from a mixture of ethyl acetate / toluene (616 mg, 81 % yield).

Compound characterization data:



mp: 206-207 °C; **TLC:** R_f (toluene / EtOAc /AcOH 20:20:1) = 0.40; **HPLC:** 3.73 min; **UV** (EtOH): λ_{max}, nm (ε): 266 (237); **IR:** ν 3110 (*m*, ν(C-H)), 3076 (*s*, ν(C-H)), 3030 (*m*, ν(C-H)), 3000-2300 (*brs*, ν(N-H)), 1594 (*s*, ν(C=C)), 1507 (*m*, tetrazole), 1410 (*s*, ν(C=C)) cm^{-1}; **^{1}H NMR** (500 MHz, d_6-DMSO): δ = 7.28 (*dd*, $^3J_{2,3}$ = 3.7, $^3J_{3,4}$ = 5.0 Hz, 1H, H-C_3), 7.79 (*dd*, $^3J_{2,3}$ = 3.7, $^4J_{2,4}$ = 1.2 Hz, 1H, H-C_2), 7.86 (*dd*, $^3J_{3,4}$ = 5.0, $^4J_{2,4}$ = 1.2 Hz, 1H, H-C_4), 16.90 (*br*, NH); **^{13}C NMR** (125 MHz, d_6-DMSO): δ = 125.4 (Cq, C_1), 128.6 (CH, C_3), 129.1 (CH, C_2), 130.4 (CH, C_4), 151.3 (Cq, C_5); **MS:** *m/z* 153 $[MH]^+$, 151 $[M-H]^-$, 110 $[MH-HN_3]^+$, **X-Ray:** the structure was confirmed by X-ray analysis (See X-ray Discussion; Chapter 4).

5-(1*H*-Pyrrol-2-yl)-2*H*-tetrazole (110)

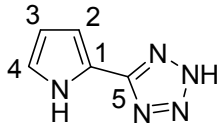


298 **110**

CAS Registry Number	31602-66-1
Molecular Formula	$C_5H_5N_5$
Molecular Weight	135.13 g/mol
Analysis Ref.	a) A. Antonowa, S. Hauptmann, *Zeitschrift für Chemie*, **1976**, *16*, 17; b) F. Lenda, F. Guenoun, B. Tazi, N. Benlarbi, H. Allouchi, J. Martinez, F. Lamaty, *Eur. J. Org. Chem.* **2005**, *2*, 326

TP1: 2.3 equivalents of diethylaluminum azide (2.7 M in xylene) are used in a 3 mmol scale experiment. The reaction is stirred for twenty four hours from 0 °C to room temperature to give the product as an off white crystalline material (670 mg, 82 % yield).

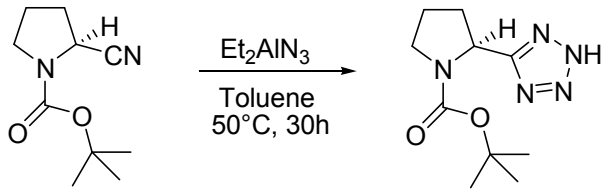
Compound characterization data:



mp: 230-232 °C; **TLC:** R_f (toluene / EtOAc / AcOH 20:20:1) = 0.41; **HPLC:** 2.26 min; **UV** (MeOH): λ_{max}, nm (ε): 262 (4850); **IR:** ν 3300 (*s*, ν(N-H, pyrrole)), 3072 (*w*, ν(C-H)), 3015 (*m*, ν(C-H)), 3000-2300 (*brm*, ν(N-H, tetrazole), 1636 (*s*, ν(C=C)), 1540 (*m*, tetrazole), 1469 (*s*, tetrazole) cm^{-1}; **^{1}H NMR** (500 MHz, d_6-DMSO): δ = 6.23 (*m*, 1H, H-C_3), 6.81 (*m*, 1H, H-C_2), 7.01 (*m*, 1H, H-C_4), 12.00 (*br*, NH), 16.50 (*br*, NH); **^{13}C NMR**(125 MHz, d_6-DMSO): δ = 109.6 (CH, C_3), 111.0 (CH, C_2), 115.5 (Cq, C_1), 122.5 (CH, C_4), 149.0 (Cq, C_5); **MS:** *m/z* 136 $[MH]^+$, 134 $[M-H]^-$, 106 $[M-H-N_2]^-$.

5.1.3.8. Synthesis of tetrazoles in the presence of amides, amines, esters and ethers

2-(2*H*-Tetrazol-5-yl)-pyrrolidine-1- carboxylic acid *tert*-butyl ester (111)



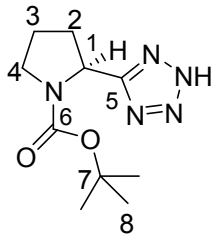
299 **111**

CAS Registry Number	867326-86-1
Molecular Formula	$C_{10}H_{17}N_5O_2$
Molecular Weight	239 g/mol
Analysis Ref.	a) T. Nowak, A. P. Thomas, Astrazeneca, **2005**, WO 2005040159 A1; b) M. G. Palermo, S. K. Sharma, C. Straub, R.-M. Wang, L. Zawel, Y. Zhang, Z. Chen, Y. Wang, F. Yang, W. Wrona, G. Liu, M. G. Charest, F. He, Novartis AG, **2005**, WO 2005097791 A1; c) V. Aureggi, G. Sedelmeier, Novartis Pharma AG, **2007**, WO 2007/009716

TP1: 1.2 equivalents of diethylaluminum azide (2.5 M in toluene) are used in a 5 mmol scale experiment. The reaction is stirred for thirty hours at 40 °C. The workup is done by using directly a solution of $KHSO_4$ (10 % solution) to pH 5 instead HCl, to avoid the cleavage of the Boc group to give the product as a white crystalline material (680 mg, 57 % yield).

The aqueous phase after work-up is evaporated and stirred 4h with ethanol. The suspension is filtered and the solvent removed to give the deprotected 2(*S)*-(1*H*-tetrazol-5-yl)-pyrrolidine as a white crystalline material (139 mg, 25 % yield).

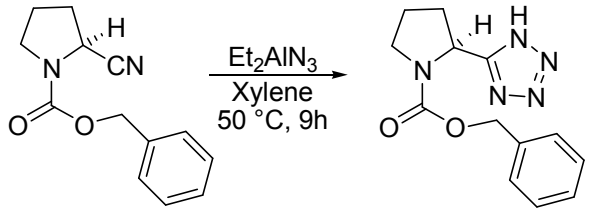
Compound characterization data:



mp: 122 °C; **TLC:** R_f (toluene / etylacetate / AcOH 20:20:1) = 0.22; **Optical rotation:** $[\alpha]^D$ = -75.68 ° (in MeOH, c = 0.63); **IR:** ν 3416 (*w*, ν(N-H)), 2977 (*s*, ν(C-H)), 1669 (*vs*, ν(C=O)), 1553 (*m*, tetrazole), 1423 (v*s*, ν(C-N)), 1372 (*m*, δ(-CH_3)), 1160 (*s*, ν(C-O)) cm^{-1}; **^{1}H NMR** (500 MHz, d_6-DMSO, 300 K) Rotamers (1:1): δ = 1.12, 1.37 (*s*, 9H, H-C_8), 1.90 (*m*, 2H, H-C_3), 2.1 (*m*, 1H, H-C_2), 3.40 (*m*, 2H, H-C_4), 5.08 (*m*, 1H, H-C_1), 16.37 (*br*, NH); (500 MHz, d_6-DMSO, 393 K): δ = 1.29 (*s*, 9H, H-C_8), 1.91 (*m*, 3H, H-$C_{2,3}$),

2.34 (*m*, 1H, H-C_2), 3.49 (*m*, 2H, H-C_4), 5.10 (*m*, 1H, H-C_1); **^{13}C NMR** (150 MHz, d_6-DMSO, 300 K) Rotamers (1:1): δ = 23.0, 23.1 (CH_2, C_3), 27.7, 28.1 (CH_3, C_8) 31.7, 32.9 (CH_2, C_2), 46.2, 46.4 (Cq, C_7), 51.3, 51.6 (CH_2, C_4), 79.1, 78.8 (CH, C_1), 152.8, 153.5 (Cq, C_5), 158.6, 159.3 (Cq, C_6); **MS:** *m/z* 240 $[MH]^+$, 238 $[M-H]^-$, 140 $[MH-Boc]^+$.

(*R*)-2-(2*H*-tetrazol-5-yl)-pyrrolidine-1-carboxylic acid benzyl ester (113) and (*S*-enantiomer-112)

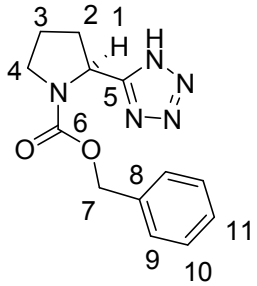


120 **112**

CAS Registry Number	(*R*) enantiomer: 839711-73-8 (*S*)-enantiomer: 33876-20-9
Molecular Formula	$C_{13}H_{15}N_5O_2$
Molecular Weight	273.30 g/mol
Analysis Ref.	a) R. G. Almquist, W. R. Chao, C. Jennings-White, *J. Med. Chem.* **1985**, *28*, 1067; b) Z. P. Demko, K. B. Sharpless, *Org. Lett*. *4*, **2002**, 2525; c) N. Momiyama, H. Torii, S. Saito, H. Yamamoto, *Proc. Natl. Acad. Sci. U.S.A*. **2004**, *101*, 5374; d) A. J. A. Cobb, D. M. Shaw, D. A. Longbottom, J. B. Gold, S. V. Ley, Org. Bio. Chem. **2005**, *3*, 84; e) V. Franckevicius, K. R. Knudsen, M. Ladlow, D. A. Longbottom, S. V. Ley, *Synlett* **2006**, *6*, 889; f) V. Aureggi, G. Sedelmeier, Novartis Pharma AG, **2007**, WO 2007/009716

TP1: 1.3 equivalents of diethylaluminum azide (2.7 M in xylene) are used in a 50 mmol scale experiment. The reaction is stirred for nine hours at 50 °C to give the product as a white crystalline material (13.9 g, 96 % yield). The (*R*)- and the (*S*)-enantiomers gave the same yield.

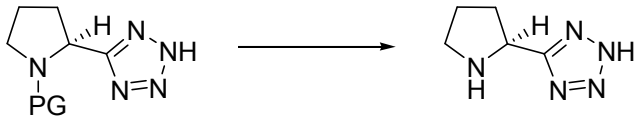
Compound characterization data:



mp: 84-86 °C, onset of exothermic decomposition: 204-291.38 °C with maximum at 253 °C; **TLC:** R_f (toluene / EtOAc / AcOH 20:20:1) = 0.22; **HPLC:** 5.46 min; **Optical**

rotation: <u>*R*-enantiomer</u>: $[\alpha]_D^{25}$ = +50.1 ° (in MeOH, c = 1.00), +49.7 ° (in EtOH, c = 1), +85.3 ° (in $CHCl_3$, c = 1.00), +41.8 ° (in DMSO, c = 1.00), +65.4 ° (in DMF, c = 0.99); <u>*S*-enantiomer</u>: $[\alpha]_D^{25}$ = -89.0 ° (in $CHCl_3$, c = 1.00); **UV** (acetonitrile): λ_{max}, nm (ε): 258 (23); **IR:** ν 3074 (*w*, ν(C-H)), 3035 (*w*, ν(C-H)), 3000-2300 (*brm*, ν(N-H)), 2973 (*w*, ν(C-H)), 2944 (*w*, ν(C-H)), 1694 (*vs*, ν(C=O)), 1552 (*m*, tetrazole), 1499 (*w*, ν(C=C)), 1443 (*s*, ν(C=C)), 1404 (*s*, ν(C-N)), 1132 (*s*, ν(C-O)), 693 (*w*, γ (Ph)) cm^{-1}; **^{1}H NMR** (500 MHz, d_6-DMSO, 300 K) Major rotamer: δ = 1.95 (*m*, 3H, H-$C_{2,3}$), 2.33 (*m*, 1H, H-C_3), 3.51 (*m*, 2H, H-C_4), 4.98 (*m*, 2H, H-C_7), 5.18 (*m*, 1H, H-C_1), 7.32 (*m*, 5H, H-$C_{9\text{-}11}$), 16.20 (*br*, NH); (500 MHz, d_6-DMSO, 394 K): δ = 1.95 (*m*, 3H, H-$C_{2,3}$), 2.33 (*m*, 1H, H-C_3), 3.51 (*m*, 2H, H-C_4), 4.98 (*m*, 2H, H-C_7), 5.18 (*m*, 1H, H-C_1), 7.32 (*m*, 5H, H-$C_{9\text{-}11}$), 16.20 (*br*, NH); **^{13}C NMR** (125 MHz, d_6-DMSO, 300 K) Rotamers (1:1): δ = 24.2 (CH_2, C_3), 32.0, 33.1 (CH_2, C_2), 46.7, 47.21 (CH_2, C_4), 52.2 (CH, C_1), 66.3, 66.6 (CH_2, C_7), 127.3 (CH, Ar), 127.9 (CH, Ar), 128.8 (CH, Ar), 137.0 (Cq, C_8), 153.9 (Cq, C_6), 154.5 (Cq, C_5); **MS:** *m/z* 274 $[MH]^+$, 272 $[M\text{-}H]^-$.

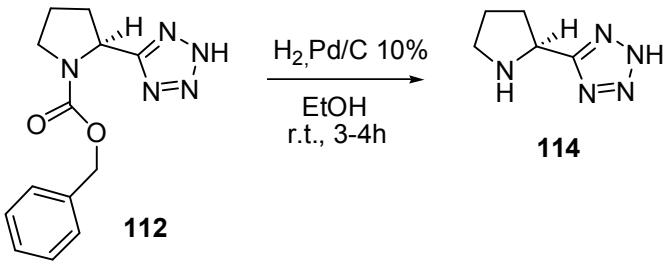
2(*S*)-(Tetrazol-5-yl)-pyrrolidine (114) and ((*R*)-enatiomer-115)



114

CAS Registry Number	(*S*)-enantiomer: 33878-70-5 (*R*)-enantiomer: 702700-79-6
Molecular Formula	$C_5H_9N_5$
Molecular Weight	139.16 g/mol
Analysis Ref.	a) R. G. Almquist, W.-R. Chao, C. Jennigs-White, *J. Med. Chem.* **1985**, *28*, 1067; b) N. Momiyama, H. Torii, S. Saito, H. Yamamoto, *PNAS* **2004**, *101*, 5374; c) A. Cobb, D. M. Shaw, D. A. Longbottom, J. B. Gold, S. V. Ley, *Org. Biom. Chem*. **2005**, *3*, 84; d) A. Hartikka, P. I. Ardvisson, *Eur. J. Org. Chem.* **2005**, *20*, 4287; e) V. Franckevicius, K. R. Knudsen, M. Ladlow, D. A. Longbottom, S. V. Ley *Synlett*. **2006**, *6*, 889; f) V. Aureggi, G. Sedelmeier, Novartis Pharma AG, **2007**, WO 2007/009716

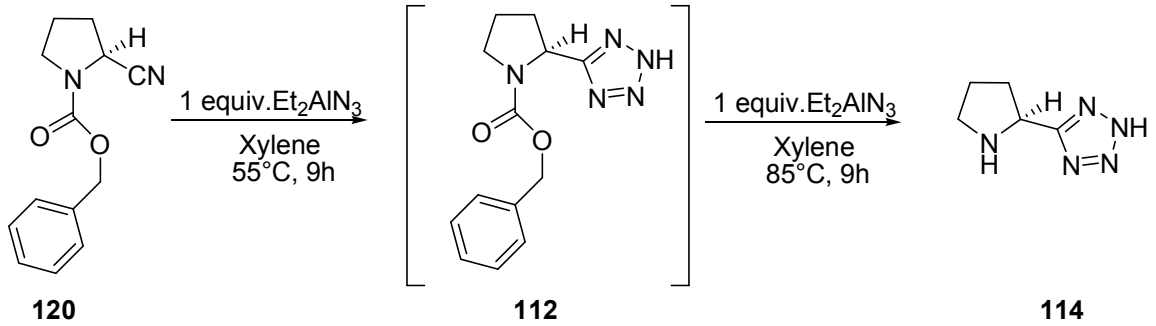
<u>Method 1 :</u>



112 **114**

(S)-2-(Tetrazol-5-yl)-pyrrolidine-1-carboxylic acid benzyl ester (15.33 g, 56.1 mmol) and palladium on carbon (150 g, 10 wt %) in ethanol (250 mL) are stirred under hydrogen at room temperature for four to six hours at room temperature. The catalyst is removed by filtration through celite, and the celite is washed sequentially twice with ethanol (15 mL portion), twice with acetic acid (8 mL portion), and twice with water (10 mL portion). The filtrate is concentrated under reduced pressure with a rotary evaporator to give the product (7.56 g, 97 % yield). The product is crystallized from acetic acid / ethanol (15 mL, 1:2) to give the pure product as a white crystalline material (7.3 g, 94 % of yield). The (*R*)- and (*S*)-enatiomers gave the same yield.

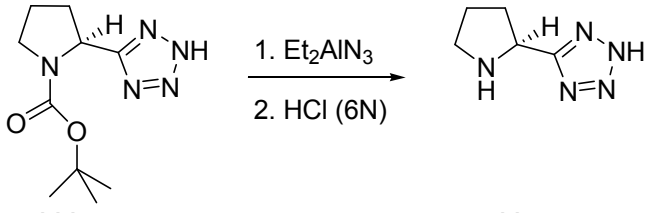
Method 2:



120 **112** **114**

TP1: 2 equivalents of diethylaluminum azide (2.5 M in toluene, or 2.7 M in xylene) are used in a 10 mmol scale experiment. The reaction is stirred for nine hours at 55 °C, then is warmed at 85 - 90 °C and stirred for additional nine hours. The mixture is quenched with HCl (2 M), the pH adjusted with potassium carbonate to pH 6.5 and the solvent is removed. Ethanol is added and the mixture is stirred for two to six hours. The mixture is filtered and the solvent removed. The crude is crystallized from ethanol to give 1.4 g of product as a white crystalline material in ≥ 98 % yield. The product contains some inorganic material.

Method 3:

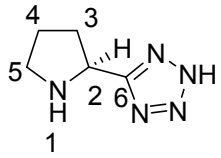


111 **114**

TP1:1.4 equivalents of diethylaluminum azide (2.7 M in xylene) are used in a 20 mmol scale experiment. The reaction is stirred for eight hours at 50 °C. The mixture is

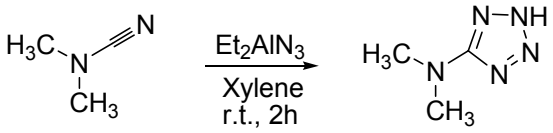
quenched at 0° C with HCl (6 M) to pH 1 and stirred over the night. The pH is adjusted with solid potassium carbonate to pH 6.5 and the solvent is removed. Ethanol is added and the mixture is stirred for two to six hours. The mixture is filtered and the solvent removed to give 2.8 g of product. The crude is crystallized from ethanol to give the product as a white crystalline material (2.26 g, 81 % yield). The product contains some inorganic material.

Compound characterization data:



Exothermic range: 269-365 °C (maximum: 275 °C); **TLC:** R_f (*n*BuOH / water / AcOH 3:3:1, ninhydrin) = 0.25; **Optical rotation:** (*S*)-enantiomer: $[\alpha]_D^{25}$ = -10.5 ° (in MeOH, c = 0.63), (*R*)-enantiomer: $[\alpha]_D^{25}$ = -2.6 ° (in water, c = 1.00), $[\alpha]_D^{25}$ = +11.0 ° (in MeOH, c = 1.00), $[\alpha]_D^{25}$ = +18.5 ° (in DMSO, c = 1.00), $[\alpha]_D^{25}$ = -13.2 ° (in AcOH, c = 1.00); **IR:** ν 3000-2600 (*brs*, ν(NH)), 2768 (*s*, ν(CH)), 1557 (*w*, tetrazole) 1462 (*w*, tetrazole) cm^{-1}; **^{1}H NMR** (500 MHz, d_6-DMSO): δ = 2.05 (*m*, 3H, H-$C_{3,4}$), 2.33 (*m*, 1H, H-C_4), 3.26 (*m*, 2H, H-C_5), 4.77 (*dd*, $^3J_{2,3}$ = 8.2, 7.3 Hz, 1H, H-C_2), 9.19 (NH_2: zwitterionic form confirmed by X-ray); **^{13}C NMR** (125 MHz, d_6-DMSO): δ = 23.2 (CH_2, C_4), 29.9 (CH_2, C_3), 44.3 (CH_2, C_5), 54.2 (CH, C_2), 171.1 (Cq, C_6); **MS:** *m/z* 139 $[M]^+$, 111 $[M\text{-}N_2]^+$, 83 $[CH_2CN_4\ H]^+$, 70 $[CHN_4\ H]^+$, 43 $[NHCNH_2]^+$; **X-Ray:** zwitterionic form confirmed by X-ray analysis (See X-ray Discussion; Chapter 4).

***N,N*-Dimethyl- 2*H*-tetrazol-5-amine (116)**



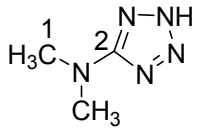
300 **116**

CAS Registry Number	5422-45-7
Molecular Formula	$C_3H_7N_5$
Molecular Weight	113.12 g/mol
Analysis Ref.	a) W. G. Finnegan, R. A. Henry, E. Lieber, *J. Org. Chem.* **1953**, *18*, 779; b) N. Sadlej-Sosnowska, *J. Phys. Org. Chem*. **2004**, *17*, 303

TP1: 1.5 equivalents of diethylaluminum azide (2.7 M in xylene) are used in a 5 mmol scale experiment. The reaction is stirred for two hours at room temperature. The mixture

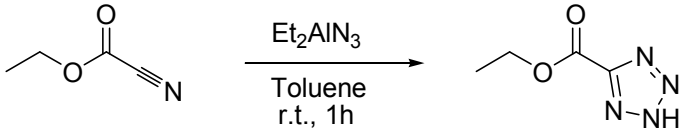
is quenched with HCl (2 M), the pH adjusted to 6 with potassium carbonate (10 % solution) and the aqueous phase saturated with solid sodium chloride. The product is extracted with ethyl acetate to give the product as a white crystalline material (400 mg, 71 % yield).

Compound characterization data:



mp: 206-208 °C; **TLC:** R_f (toluene / AcOEt / AcOH 20:20:1, ninhydrin) = 0.06; **UV** (MeOH): λ_{max}, nm (ε): 228 (1430); **IR:** ν 3000-2400 (*brs*, ν(N-H)), 2933 (*s*, ν(C-H)), 1555 (*w*, tetrazole), 1492 (*w*, tetrazole), 1427 (*s*, tetrazole), 1343 (*w*, δ(CH_3)) cm^{-1}; **^{1}H NMR** (500 MHz, d_6-DMSO): δ = 2.96 (*s*, 6H, H-C_1), 16.0 (*br*, NH); **^{13}C NMR**(125 MHz, d_6-DMSO): δ = 39.6 (CH_3, C_1), 163.6 (Cq, C_2); **MS:** *m/z* 114 $[MH]^+$, 112 $[M-H]^-$.

Ethyl-2*H*-tetrazole-5-carboxylate (117)

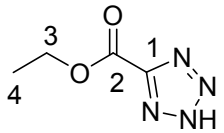


136 **117**

CAS Registry Number	55408-10-1
Molecular Formula	$C_4H_6N_4O_2$
Molecular Weight	142.09 g/mol
Analysis Ref.	a) E. Olivieri-Mandala, *Gazz. Chim. Ital*. **1911**, *41*, 59; b) M. S. Poonian, E. F. Nowoswiat, J. F. Blount, T. H. Williams, R. G. Pitcher, M. J. Kramer, *J. Med. Chem*. **1976**, *19*, 286; c) J. Diago-Meseguer, A. L. Palomo-Coll, J. R. Fernandez-Lizarbe, A. Zugaza-Bilbao, *Synthesis* **1980**, *7*, 547; d) P. M. O'Brien, D. R. Slislovich, J. A. Picard, H. T. Lee, C. F. Purchase, B. D. Roth, A. D. White, M. Anderson, S. B. Muller, *J. Med. Chem*. **1996**, *39*, 2354; e) N. Nazaré, V. Laux, A. Bauer, M. Wagner, Aventis Pharma, 2**004** EP1479679 A1

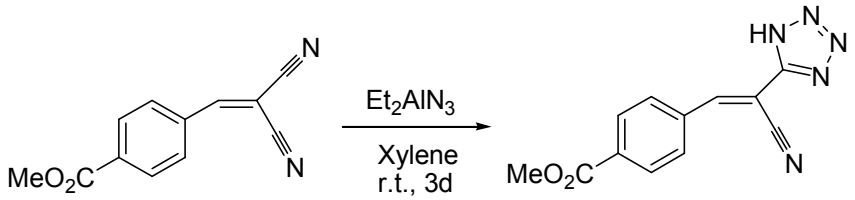
TP1: 1.3 equivalents of diethylaluminum azide (2.5 M in toluene) are used in a 10 mmol scale experiment. The reaction is stirred one hours at room temperature to give the product as an off white crystalline material (1.33 g, 94 % yield).

Compound characterization data:



mp: 92-94 °C; **TLC:** R_f (toluene / AcOEt / AcOH 20:20:1) = 0.19; **HPLC:** 1.98 min; **IR:** ν 3000-2400 (*brm*, ν(N-H)), 2948 (*w*, ν(C-H)), 2916 (*w*, ν(C-H)), 2882 (*w*, ν(C-H)), 2844 (*m*, ν(C-H)), 1750 (*vs*, ν(C=O)), 1543 (*m*, tetrazole), 1470 (*w*, tetrazole), 1455 (*w*, tetrazole), 1445 (*w*, tetrazole), 1223 (*s*, ν(C-O)) cm^{-1}; **^{1}H-NMR** (500 MHz, d_6-DMSO): δ = 1.35 (*t*, $^3J_{3,4}$ = 7.1 Hz, 3H, H-C_4), 4.41 (*q*, $^3J_{3,4}$ = 7.1 Hz, 2H, H-C_3), 16.5 (*br*, NH); **^{13}C NMR**(125 MHz, d_6-DMSO): δ = 13.9 (CH_3, C_4), 62.3 (CH_2, C_3), 150.7 (Cq, C_1), 156.6 (Cq, C_2); **MS:** *m/z* 142 $[M]^+$, 127 $[M\text{-}CH_3]^+$, 115 $[MH\text{-}N_2]^+$, 97 $[M\text{-}OC_2H_5]^+$, 69 $[CN_4H]^+$; **HR-MS:** calc'd for $[M\text{-}H]^-$ = 141.0418 found 141.0418 (ΔM (ppm) < 0.1).

4-[(E)-2Cyano-2-(1*H*-tetrazol-5-yl)-vinyl]-benzoic acid methyl ester (118)

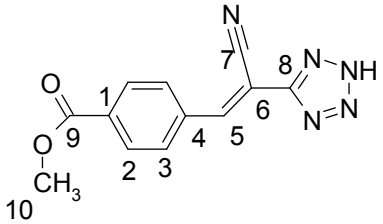


73 **118**

Molecular Formula	$C_{12}H_9N_5O_2$
Molecular Weight	255.24 g/mol

TP1: 1.6 equivalents of diethylaluminum azide (2.7 M in xylene) are used in a 10 mmol scale experiment. The reaction is stirred for three days at room temperature to give the product after crystallization from toluene as an off white crystalline material (1.38 g, 54 % yield).

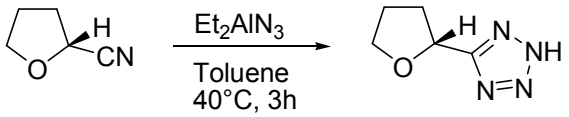
Compound characterization data:



mp: 204-206 °C; **TLC:** R_f (toluene / EtOAc / AcH 20:40:1) = 0.23 ; **HPLC:** 6.30 min; **UV** (MeOH): λ_{max}, nm (ε): 312 (21010); **IR:** ν 3270 (*s*, ν(NH)), 3089 (*w*, ν(C-H)), 2224 (*w*, ν(C≡N)), 1715 (*vs*, ν(C=O)), 1615 (*m*, ν(C=C)), 1565 (*w*, tetrazole), 1434 (*s*, ν(C=C)), 1291 (*s*, ν(C-O)), 1114(*s*, ν(C-O)) cm^{-1}; **^{1}H-NMR** (400 MHz, d_6-DMSO): δ = 3.89 (*s*, 3H, H-C_{10}), 8.11 (*m*, 4H, H-$C_{2,3}$), 8.41 (*s*, 1H, H-C_5), 16.50 (*br*, NH); **^{13}C-NMR** (150 MHz, d_6-DMSO): δ = 52.5 (CH_3, C_{10}), 101.0 (Cq, C_6), 115.7 (Cq, CN), 129.7 (CH, ArH), 129.8 (CH, ArH), 131.6 (Cq, C_1), 136.9 (Cq, C_4), 144.8 (CH, C_5), 156.0 (Cq, C_8), 165.5 (Cq,

C_9); **MS:** *m/z* 256 $[MH]^+$, 254 $[M-H]^-$; **HR-MS:** calc'd for $[M-H]^-$ = 254.06835 found 254.06832 (ΔM (ppm) = 0.1).

(*R*)-5-(Tetrahydro-furan-2-yl)-2*H*-tetrazole (119)

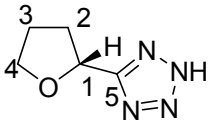


301 **119**

Molecular Formula	$C_5H_8N_4O$
Molecular Weight	140.15 g/mol

TP1:1.3 equivalents of diethylaluminum azide (1.8 M in toluene) are used in a 10 mmol scale experiment. The reaction is stirred for three hours at 40 °C. The crude was directly crystallizated from ethyl acetate to give the product as a white crystalline material (1.28 g, 92 % yield).

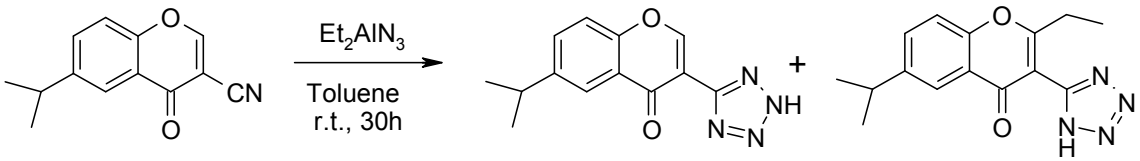
Compound characterization data:



mp: 108-109 °C; **TLC:** R_f (toluene / EtOAc / AcOH 20:20:1, CPS) = 0.16; **Optical rotation:** $[\alpha]_D^{25}$ = -9.0 ° (in MeOH, c = 0.96); **UV** (acetonitrile): λ_{max}, nm (ε): 279 (3); **IR:** ν 3200-2400 (*sbr*, ν(N-H)), 2979 (*s*, ν(C-H)), 1559 (*w*, tetrazole), 1538 (*m*, tetrazole), 1086 (*s*, ν(C-O)) cm^{-1}; **^{1}H NMR** (400 MHz, d_6-DMSO): δ = 1.95 (*m*, 2H, H-C_3), 2.20 (*m*, 2H, H-C_2), 3.86 (*m*, 2H, H-C_4), 5.24 (*dd*, 1H, H-C_1), 16.22 (*br*, NH); **^{13}C NMR** (125 MHz, d_6-DMSO): δ = 25.4 (CH_2, C_3), 31.4 (CH_2, C_2), 68.4 (CH_2, C_4), 70.8 (CH, C_1), 157.5 (Cq, C_6); **MS:** *m/z* 141 $[MH]^+$, 139 $[M-H]^-$; **X-Ray:** the structure was confirmed by X-ray analysis (See X-ray Discussion; Chapter 4).

5.1.3.9. Synthesis of tetrazoles in the presence of carbonyl groups

6-Isopropyl-3-(1*H*-tetrazol-5-yl)-chromen-4-one (122) and 2-ethyl-6-isopropyl-3-(1*H*-tetrazol-5-yl)-chroman-4-one (123)



121 **122** **123**

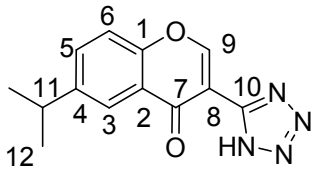
CAS Registry Number	**122**: 50743-59-4
Molecular Formula	**122**: $C_{13}H_{12}N_4O_2$ **123**: $C_{15}H_{16}N_4O_2$
Molecular Weight	**122**: 256.26 g/mol **123**: 284.32 g/mol
Analysis Ref.	**122**: A. Nohara, H. Kuriki, T. Saijo, H. Sugihara, M. Kanno, Y. Sanno, *J. Med. Chem.* **1977**, *20*, 141

TP1: 2.8 equivalents of diethylaluminum azide (2.5 M in toluene) or diethylaluminum azide (2.7 M in xylene) are used in a 4 mmol scale experiment. The reaction is stirred for twenty four hours at room temperature. The product after extraction is chromatographed (elution system: toluene / EtOAc / AcOH 50:10:1) to give 1.026 g of product (95 % yield) as a yellow crystalline materials (589 mg of P1, and 425 mg of P2) with P1 / P2 in ratio 3:2.

The same experiment was done with 1.3 equivalents of diethylaluminum azide (in xylene 2.7 M) in a 6 mmol scale experiment to obtain 1.54 g of product (96 % yield) as a yellow crystalline material with P1 / P2 in ratio 2:1.

Compound characterization data

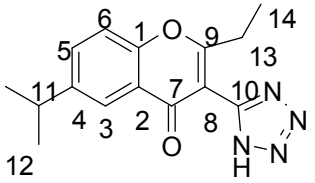
6-Isopropyl-3-(1*H*-tetrazol-5-yl)-chromen-4-one **122**:



mp: 210-214 °C; **TLC:** R_f (toluene / AcOEt / AcOH 50:10:1) = 0.3; **HPLC:** 7.57 min; **UV** (MeOH): λ_{max}, nm (ε): 307 (5570), 244 (21620); **IR:** ν 3221 (*s*, ν(N-H)), 3103 (*w*, ν(C-H)), 3027 (*w*, ν(C-H)), 2963 (*m*, $\nu_{asim}(CH_3)$), 2927 (*w*, ν(C-H)), 2869 (*w*, ν(C-H)), 1644 (*vs*, ν(C=O)), 1538 (*s*, ν(C=C)), 1480 (*s*, ν(C=C)), 1458 (*s*, ν(C=C)), 1298 (*m*, δ(CH_3)) cm^{-1}; **^{1}H NMR** (500 MHz, d_6-DMSO): δ = 1.30 (*d*, $^3J_{11,12}$ = 6.9 Hz, 6H, H-C_{12}), 3.10 (*sep*, $^3J_{11,12}$ = 6.9 Hz, 1H, H-C_{11}), 7.75 (*d*, $^3J_{5,6}$ = 8.6 Hz, 1H, H-C_6), 7.85 (*m*, 1H, H-C_5), 8.02 (*d*, $^4J_{3,5}$ = 2.2 Hz, 1H, H-C_3), 9.22 (*s*, 1H, H-C_9), 16.60 (*br*, NH); **^{13}C NMR**

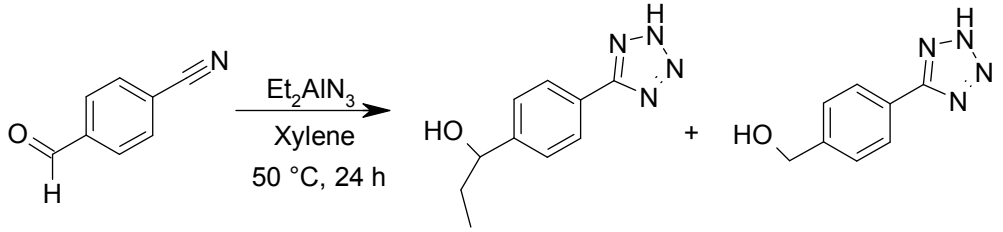
(150 MHz, d_6-DMSO): δ = 23.7 (CH_3, C_{12}), 33.0 (CH, C_{11}), 110.1 (Cq, C_8), 118.9 (CH, C_6), 121.7 (CH, C_3), 122.9 (Cq, C_2), 133.9 (CH, C_5), 147.0 (Cq, C_4), 154.2 (Cq, C_1), 158.4 (CH, C_9), 173.4 (Cq, C_7); **MS:** *m/z* 257 $[M+H]^+$, 255 $[M-H]^-$.

2-Ethyl-6-isopropyl-3-(1*H*-tetrazol-5-yl)-chroman-4-one **123**:



mp: 190-194 °C; **TLC:** R_f (toluene / AcOEt / AcOH 50:20:1) = 0.5; **HPLC:** 9.42 min; **IR:** ν 3262 (*s*, ν(N-H)), 3063 (*w*, ν(C-H)), 2775 (*w*, ν(C-H)), 2958 (*m*, ν(C-H)), 2933 (*m*, ν(C-H)), 2873 (*w*, ν(C-H)), 1632 (*vs*, ν(C=O)), 1573 (*m*, ν(C=C)), 1523 (*s*, ν(C=C)), 1483 (*s*, ν(C=C)), 1306 (*m*, δ(CH_3)) cm^{-1}; **^{1}H NMR** (500 MHz, d_6-DMSO): δ = 1.25 (*d*, $^3J_{11,12}$ = 6.9 Hz, 6H, H-C_{12}), 1.32 (*t*, $^3J_{13,14}$ = 7.0 Hz, 3H, H-C_{14}), 2.95 (*q*, $^3J_{13,14}$ = 7.0 Hz, 2H, H-C_{13}), 3.10 (*sep*, $^3J_{11,12}$ = 6.9 Hz, 1H, H-C_{11}), 7.69 (*d*, $^3J_{5,6}$ = 8.8 Hz, 1H, H-C_6), 7.8 (*dd*, $^3J_{5,6}$ = 8.8, $^4J_{3,5}$ = 2.3 Hz, 1H, H-C_5), 7.92 (*d*, $^4J_{3,5}$ = 2.3 Hz, 1H, H-C_3), 16.50 (*br*, NH); **^{13}C NMR** (150 MHz, d_6-DMSO): δ = 11.5 (CH_3, C_{14}), 23.2 (CH_3, C_{12}), 23.7 (CH_3, C_{12}), 26.5 (CH_3, C_{13}), 32.9 (CH, C_{11}), 118.0 (CH_q, C_8), 118.4 (CH, C_6), 121.5 (Cq, C_2), 121.6 (CH, C_3), 133.8 (CH, C_5), 146.7 (Cq, C_4), 153.8 (Cq, C_1), 159.2 (Cq, C_{10}), 172.6 (Cq, C_9), 174.3 (Cq, C_7); **MS:** *m/z* 285 $[M+H]^+$, 283 $[M-H]^-$.

1-[4-(2*H*-Tetrazol-5-yl)-phenyl]-propan-1-ol (125) and 4-(1*H*-tetrazol-5-yl)-benzenemethanol (126)



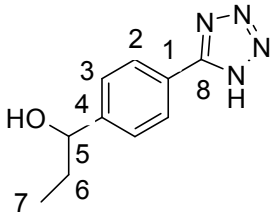
124 **125** **126**

CAS Registry Number	**126**: 501126-02-9
Molecular Formula	**125**: $C_{10}H_{12}N_4O$ **126**: $C_8H_8N_4O$
Molecular Weight	**125**: 204.23g/mol **126**: 176.07g/mol
Ref.	**126**: C. Betschart, K. Hayakawa, O. Irie, J. Sakaki, G. Iwasaki, R. Lattmann, M. Missbach, N. Teno, Novartis A.-G., Switz., Novartis Pharma G.m.b.H, **2003**, WO 2003020721 A1

TP1: 3 equivalents of diethylaluminum azide (2.7 M in xylene) are used in a 10 mmol scale experiment. The reaction is stirred for twenty four hours at 50 °C to give a mixture of products **125** and **126** (1.68 g, 85 % yield), in ratio **125** : **126** of ca 7:3. The product P1 is isolated via crystallization of the crude from ethyl acetate / toluene 1:1 (710 mg, 35 % yield; pure 92 % based on HPLC). The mother liquor is chromatographed to isolate 880 mg of product **126** (elution system: toluene / ethyl acetate / AcOH 40:20:1)(50 % yield).

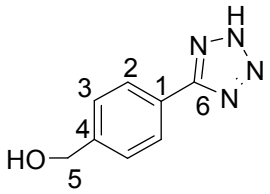
Compound characterization data:

1-[4-(2*H*-Tetrazol-5-yl)-phenyl]-propan-1-ol (**125**)



mp: 153-154 °C; **TLC:** R_f (toluene / EtOAc / AcOH 20:20:1) = 0.18; **HPLC:** 4.40 min; **UV** (MeOH): λ_{max}, nm (ε): 246 (18420); **IR:** ν 3334 (*brs*, ν(O-H)), 3100-2300 (*brs*, ν(N-H)), 3063 (*m*, ν(C-H)), 2974 (*s*, ν(C-H)), 2934 (*s*, ν(C-H)), 2873 (*s*, ν(C-H)), 1618 (*m*, ν(C=C)), 1569 (*m*, tetrazole), 1505 (*m*, ν(C=C)), 1052 (*s*, ν(C-O)), 750 (*m*, γ(C-H, Ph) cm^{-1}; **^{1}H NMR** (600 MHz, d_6-DMSO): δ = 0.84 (*t*, $^3J_{6,7}$ = 7.3 Hz, 3H, H-C_7), 1.64 (*q*, $^3J_{6,7}$ = 7.3 Hz, 2H, H-C_6) 4.54 (*m*, 1H, H-C_5), 5.31 (*m*, 1H, OH), 7.54 (*d*, $^3J_{2,3}$ = 8.2 Hz, 2H, H-C_3), 7.99 (*d*, $^3J_{2,3}$ = 8.2 Hz, 2H, H-C_2), 16.40 (*br*, NH); **^{13}C NMR** (150 MHz, d_6-DMSO): δ = 9.6 (CH_3, C_7), 31.9 (CH_2, C_6), 73.0 (CH, C_5), 126.6 (CH, C_2), 126.8 (CH, C_3), 149.6 (Cq, C_8); **MS:** *m/z* 205 $[MH]^+$, 203 $[M-H]^-$, 203 $[M-H-CH_3OH]^-$; **HR-MS:** calc'd for $[M-H]^-$ = 203.0938, found 203.0938 (ΔM (ppm) < 0.1).

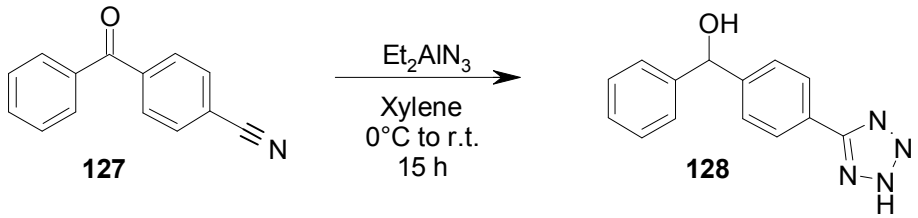
4-(2*H*-Tetrazol-5-yl)-benzenemethanol (**126**)



mp: 197-200 °C; **TLC:** R_f (toluene / EtOAc / AcOH 20:20:1) = 0.11; **HPLC:** 3.01 min; **UV** (MeOH): λ_{max}, nm (ε): 245 (13620); **IR:** ν 3228 (*brs* ν(O-H)), 3099 (*s*, ν(C-H)), 3064 (*s*, ν(C-H)), 3027 (*s*, ν(C-H)), 3000-2450 (*brs*, ν(N-H)), 2925 (*s*, ν(C-H)), 1619 (*s*, ν(C=C)), 1583 (*m*, ν(C=C)), 1436 (*m*, ν(C=C)), 1017 (*s*, ν(C-O)), 740 (*m*, γ(C-H, Ph) cm^{-1}; **^{1}H NMR** (500 MHz, d_6-DMSO): δ = 4.59 (*s*, 2H, H-C_5), 5.37 (*br*, 1H, OH), 7.54 (*d*, $^3J_{2,3}$ = 8.2 Hz, 2H, H-C_3), 8.02 (*d*, $^3J_{2,3}$ = 8.2 Hz, 2H, H-C_2), 16.83 (*br*, NH); **^{13}C NMR**

(125 MHz, d_6-DMSO): δ = 62.4 (CH_2, C_5), 122.4 (Cq, C_1), 126.8 (CH, C_2), 127.1 (CH, C_3), 146.1 (Cq, C_4), 155.1 (Cq, C_7); **MS:** *m/z* 175 $[M-H]^-$, 147 $[M-H-N_2]^-$.

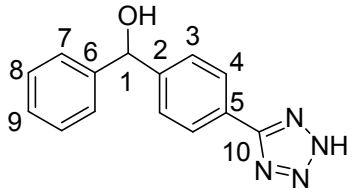
Pheny-l-[4-(1*H*-tetrazol-5-yl)phenyl] methanol (128)



Molecular Formula	$C_{14}H_{12}N_4O$
Molecular Weight	204.56 g/mol

TP1: 1.1 equivalents of diethyl aluminum azide (2.7 M in xylene) are used in a 2 mmol scale experiment. The reaction is stirred over the night from 0 °C to room temperature to give the product as a light brown crystalline material (190 mg, 38 % yield).

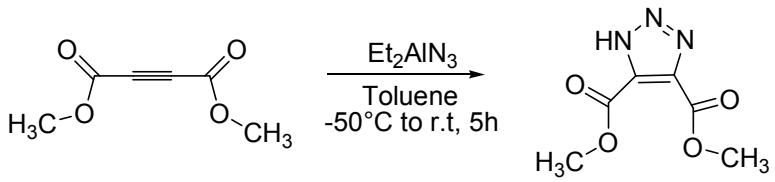
Compound characterization data:



mp: up to 250 °C; **TLC:** R_f (toluene / EtOAc / AcH 20:20:1) = 0.45; **HPLC:** 6.22 min; **UV** (EtOH): λ_{max}, nm (ε): 250 (400); **IR:** ν 3473 (*brm*, ν(O-H)), 3100-2500 (*brs*, ν(N-H)), 3087 (*m*, ν(C-H)), 3027 (*s*, ν(C-H)), 1655 (*m*, ν(C=C)), 1577 (*w*, tetrazole), 1496 (*m*, ν(C=C)), 1438 (*s*, ν(C=C)), 1024 (*m*, ν(C-O)), 762 (*m*, γ(C-H, Ph)), 701 (*s*, γ(Ph) cm^{-1}; **^{1}H NMR** (400 MHz, d_6-DMSO): δ = 5.79 (*s*, 1H, H-C_1), 6.08 (*br*, 1H, OH), 7.24 (*m*, 1H, H-C_9), 7.32 (*m*, 2H, ArH), 7.41 (*m*, 2H, ArH), 7.60 (*d*, $^3J_{3,4}$ = 8.2 Hz, 2H, H-C_3), 8.00 (*d*, $^3J_{3,4}$ = 8.2 Hz, 2H, H-C_2), 16.90 (*br*, NH); **^{13}C NMR** (125 MHz, d_6-DMSO): δ = 73.6 (CH, C_1), 122.2 (Cq, C_5), 125.9 (CH, Ar), 126.5 (CH, Ar), 126.6 (CH, C_9), 126.7 (CH, Ar), 127.8 (CH, Ar), 144.7 (Cq, C_6), 148.4 (Cq, C_2), 154.3 (Cq, C_{10}); **MS:** *m/z* 251 $[M-H]^-$.

5.1.3.10. Synthesis of triazoles

1*H*-[1,2,3]-triazole-4,5-dicarboxylic acid methyl ester (130)

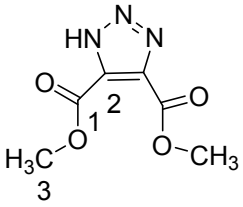


129 **130**

CAS Registry Number	707-94-8
Molecular Formula	$C_6H_7N_3O_4$
Molecular Weight	185.14 g/mol
Analysis Ref.	a) J. J. Looker, *J. Org. Chem.* **1965**, *30*, 638; b) L. Fisera, F. Povazanec, P. Zalupsky, J. Kovac, D. Pavlovic, *Collect. Czech. Chem. Commun.* **1983**, *48*, 3144; c) K. Harju, M. Vahermo, I. Mutikainen, J. Yli-Kauhaluoma, *J. Comb. Chem.* **2003**, *5*, 826

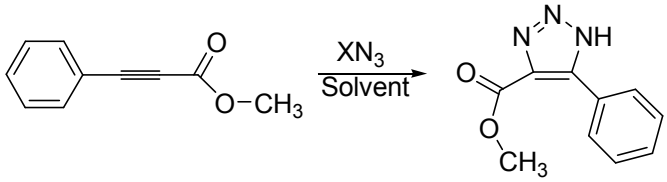
TP1: One equivalent of diethylaluminum azide (1.8 M in toluene) are used in a 3 mmol scale experiment. The reaction is stirred for five hours from – 50 to 0 °C to give the product as a yellow crystalline material (400 mg, 72 % yield).

Compound characterization data:



mp: 121-123 °C; **TLC:** R_f (toluene / EtOAc / AcOH 20:20:1) = 0.28; **HPLC:** 2.90 min; **UV** (MeOH): λ_{max}, nm (ε): 215 (674); **IR:** ν 3240 (*sbr*, ν(N-H)), 2968 (*w*, ν(CH_3)), 1741 (*vs*, ν(C=O)) cm^{-1}; **^{1}H NMR**(500 MHz, d_6-DMSO) 3.86 (*s*, 6H, H-C_3), 16.27 (*br*, NH); **^{13}C NMR** (125 MHz, d_6-DMSO): δ = 52.7 (CH_3, C_3), 138.6 (Cq, C_2), 160.3 (Cq, C_1); **MS:** *m/z* 184 $[M-H]^-$; **HR-MS**: calc'd for $[M-H]^-$ = 184.0364, found 184.0364 (ΔM (ppm) = 0.1).

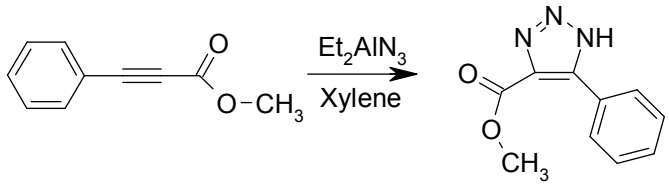
5-Phenyl-1*H*-[1,2,3]triazole-4-carboxylic acid methyl ester (132)



131 **132**

CAS Registry Number	40235-35-6
Molecular Formula	$C_{10}H_9N_3O_2$
Molecular Weight	203.20 g/mol
Analysis Ref.	a) G. Beck, Gerhard, D. Guenther, Farbwerke Hoechst A.-G. Ger. Offen. **1973**, DE 2138522; b) G. Beck, D. Guenther, *Chem. Ber.* **1973**, *106*, 2758

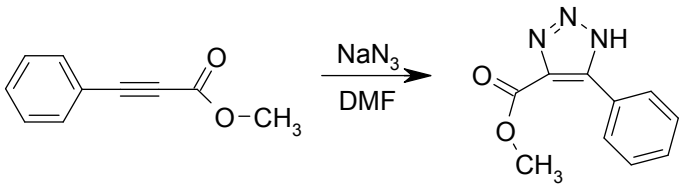
Method 1:



131 **132**

TP1: 1.1 equivalents of diethylaluminum azide (2.7 M in xylene) is used in a 2 mmol scale experiment. The reaction is stirred for three days at room temperature to give the product as a yellow crystalline material (230 mg, 57 % yield).

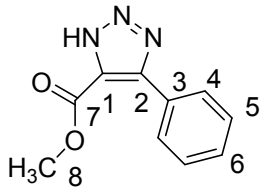
Method 2:



131 **132**

TP1: 1.1 equivalents of sodium azide in DMF is used in a 4 mmol scale experiment. The reaction is stirred for one and half hour at 70 °C to give the product as a yellow crystalline material (570 mg, 70 % yield).

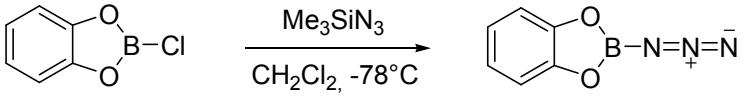
Compound characterization data:



mp: 106-108 °C; **TLC:** R_f (toluene / AcOEt / AcOH 20:20:1) = 0.52; **HPLC:** 3.62 min; **UV** (MeOH): λ_{max}, nm (ε): 243 (990); **IR:** ν 3460 (*w*, overtones ester), 3300-2900 (*brs*, ν(N-H)), 3037 (*m*, ν(C-H)), 2967 (*m*, ν(C-H)), 1743 (*s*, ν(C=O)), 1533 (*w*, ν(C=C)), 1480 (*s*, ν(C=C)), 1275 (*m*, ν(C-O)), 755 (*s*, γ(CH, Ph)), 684 (*m*, γ(Ph)) cm^{-1}; **^{1}H NMR** (400 MHz, d_6-DMSO): δ = 3.81 (*s*, 3H, H-C_8), 7.43 (*m*, 3H, H-$C_{5,6}$), 7.73 (*m*, 2H, H-C_4), 15.85 (*br*, NH); **^{13}C NMR** (125 MHz, d_6-DMSO): δ = 51.7 (CH_3, C_8), 118.8 (Cq, C_3), 127.9 (CH, Ar), 128.6 (CH, Ar), 128.9 (CH, C_6), 161.0 (Cq, C_7); **MS:** *m/z* 202 $[M-H]^-$.

5.1.3.11. Synthesis of alternative azides

[1,3,2] Benzodioxaborole-2-azido (134)



133 **134**

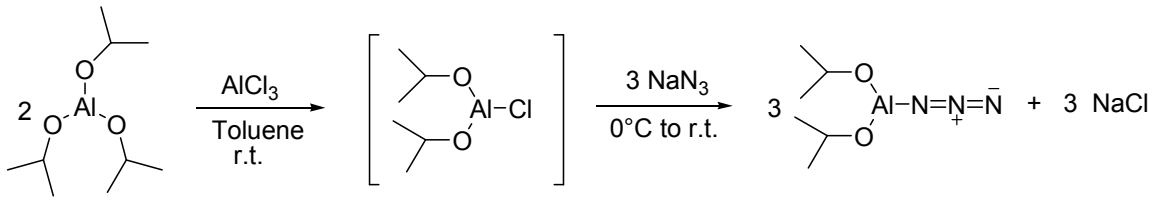
CAS Registry Number	258331-21-4
Molecular Formula	$C_6H_4BN_3O_2$
Molecular Weight	160.93 g/mol
Analysis Ref.	W. Fraenk, T. Habereder, H. Nöth, K. Polborn, T. M. Klapötke, *J. Chem. Soc. Dalton Trans.* **1999**, *23*, 4283

A 5 mL, one necked round-bottomed flask, is charged with ß-chloro-catecholborane (462 mg, 3 mmol) dissolved in dichloromethane (1 mL) and treated, at -78°C, with trimethylsilylazide (0.6 mL, 4.5 mmol). The solution is gradually warmed to room temperature, and stirred for two hours. The solvent and the excess of trimethylsilylazide are removed to give 950 mg of white crystalline material. The product is hydrolyzed after few minutes. The same experiment was done with the 2-bromo-1,3,2-benzodioxaborole to obtain the same result.

Compound characterization data:

mp: 68-69 °C; **FT-IR:** ν 2169*s* ν(B-N_3) cm^{-1}.

Diisopropoxyde aluminum azide (139)



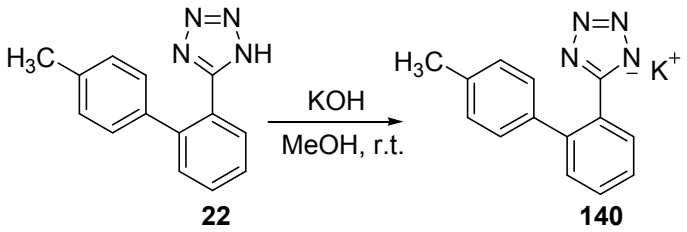
137 **138** **139**

A solution of aluminum isopropoxyde (4.085 g, 20 mmol) in toluene (11 ml) is treated, at 0 °C, with aluminum chloride (1.33 g, 10 mmol). The mixture is warmed at room temperature and stirred over the night. The mixture is treated with granular sodium azide (1.95 g, 30 mmol) at 0 °C , and than gradually warmed at room temperature and stirred over the night. The with suspension is centrifuged to obtain an upper solution and two solid layers.

NO PRODUCT ISOLATED!!

5.1.3.12. Tetrazolate salts

5-(4'-Methyl-biphenyl-2-yl)-tetrazole potassium salt (140)

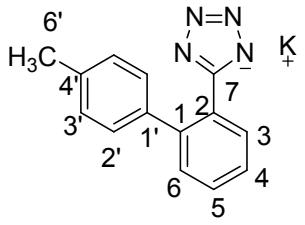


22 **140**

CAS Registry Number	860644-27-5
Molecular Formula	$C_{14}H_{11}N_4K$
Molecular Weight	274.36 g/mol
Ref.	M. Lusina, T. Cindric, J. Tomaic, M. Peko, L. Pozaic, N. Musulin, *J. Pharm.* **2005**, *291*, 127

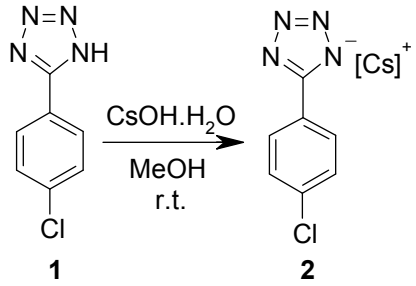
5-(4'-Methyl-biphenyl-2-yl)-1*H*-tetrazole (4.725 g, 20 mmol), KOH (1.122 g, 20 mmol) are dissolved in methanol (26 mL) and stirred two hours at room temperature. The solvent is removed to give 5.44 g of product in ≥ 99 % yield.

Compound characterization data:



mp: up to 260 °C; **TLC:** R_f (toluene / AcOEt / AcOH 20:20:1) = 0.7; **HPLC:** 7.19 min.; **UV** (MeOH): λ_{max}, nm (ε): 249 (1290), 202 (3810); **IR:** ν 3052 (*w*, ν(C-H)), 3025 (*m*, ν(C-H)), 2919 (*w*, ν(C-H)), 2863 (*m*, ν(C-H)), 1505 (*m*, ν(C=C)), 1458 (*s*, ν(C=C)), 1422 (*m*, ν(C=C)), 826 (*s*, γ(C-H, Ph)), 765 (*s*, γ(C-H, Ph)) cm^{-1}; **^{1}H NMR** (500 MHz, d_6-DMSO): δ = 2.25 (*s*, 3H, H-$C_{6'}$), 6.95 (*m*, 4H, H-$C_{2',3'}$), 7.32 (*m*, 3H, H-$C_{4,5,6}$), 7.49 (*m*, 1H, H-C_3); **^{13}C NMR** (125 MHz, d_6-DMSO): δ = 20.6 (CH_3, $C_{6'}$), 126.4 (CH, $C_{2'}$), 127.58 (CH, $C_{3'}$), 128.0 (CH, C_4), 128.9 (CH, C_6), 129.9 (CH, C_3), 130.5 (CH, C_5), 132.0 (Cq, C_2), 135.1 (Cq, $C_{1'}$), 138.8 (Cq, C_1), 140.5 (Cq, C_4), 160.4 (Cq, C_7); **MS:** *m/z* 235 $[M-K]^-$, 207 $[M-K-N_2]^-$

5-(4-Chloro-phenyl)-tetrazole cesium salt (2)

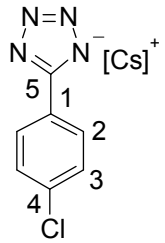


1 **2**

Molecular Formula	$C_7H_4ClN_4Cs$
Molecular Weight	312.49 g/mol

A 25 ml, one necked round-bottomed flask is charged, at room temperature, with 4-chloro-phenyltetrazole **1** (542 mg, 3 mmol) and cesium hydroxide monohydrate (504 mg, 3 mmol) in methanol (5 mL). The mixture is stirred at room temperature for one hour. The solvent is removed and the product is dried in vacuum for four hours at 30 °C to give a white crystalline material in ≥ 99 % yield (940 mg).

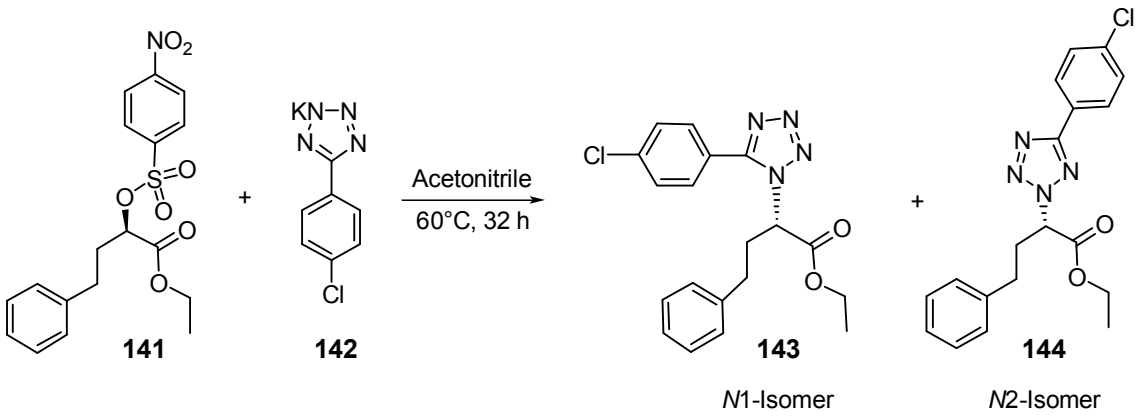
Compound characterization data:



mp: up to 250 °C; **TLC:** R_f (toluene / AcOEt / AcOH 20:20:1) = 0.39; **HPLC:** 5.12 min; **UV** (MeOH): λ_{max}, nm (ε): 248 (9650); **IR:** *v* 3262 (*brs*, ν(C-H)), 1439 (*s*, ν(C=C)), 1422 (*s*, ν(C=C)), 1093 (*s*, ν(C-Cl)), 841 (*s*, γ(C-H, Ph) cm^{-1}; **^{1}H NMR** (500 MHz, d_6-DMSO): δ = 7.41 (*d*, $^3J_{2,3}$ = 8.6 Hz, 2H, H-C_2), 7.96 (*d*, $^3J_{2,3}$ = 8.6 Hz, 2H, H-C_3); **^{13}C NMR** (125 MHz, d_6-DMSO): δ = 127.3 (CH, C_2), 128.4 (CH, C_3), 131.2 (Cq, C_4), 131.5 (CH, C_1), 159.7 (Cq, C_5); **MS:** *m/z* 181 $[MH\text{-}Cs]^+$.

5.1.3.13. Nucleophilic substitution with tetrazoles

(*S*)-2-[5-(4-Chloro-phenyl)-tetrazol-2-yl]-4-phenyl-buthyric acid ethyl ester (143) and (*S*)-2-[5-(4-Chloro-phenyl)-tetrazol-1-yl]-4-phenyl-buthyric acid ethyl ester (144)

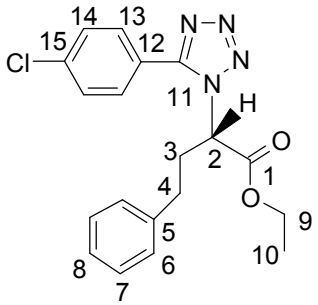


Molecular Formula	**143**:	$C_{19}H_{19}ClN_4O_2$	**144**:	$C_{19}H_{19}ClN_4O_2$
Molecular Weight	**143**:	370.84 g/mol	**144**:	370.84 g/mol

A 25 mL, three necked round bottomed flask, is charged, at room temperature, with 5-(4-chloro-phenyl)-1*H*-tetrazole **1** (722 mg, 4 mmol), methanol (10 mL) and potassium hydroxide (225 mg, 4 mmol). The mixture is stirred one hour at room temperature. The solvent is removed, the resulting crystalline material is dried one hour in vacuum and added at room temperature to a solution containing (*R*)-2-(nitro-benzenesulfonyloxy)-4-phenyl-butyric acid ethyl ester **141** (1.179 g, 3 mmol) in acetonitrile (7 mL). The reaction is stirred thirty two hours at 60 °C. The solvent is removed to give the crude (2.05 g) which is re-dissolved in ethyl acetate (30 mL) and extracted twice with potassium carbonate (10 % solution, 20 mL portion). The solvent is removed to give 1.01 g of a colorless oil which is chromatographed (elution system: hexane / ethyl acetate 9:1) to give the pure N1-isomer **143** (150 mg, 13 % yield) and the N2-isomer **144** (900 mg, 79 % yield) as oils.

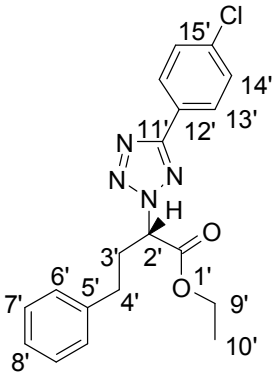
Compound characterization data:

N1-Isomer (**143**)



TLC: R_f (hexane / EtOAc 9:1) = 0.06; **HPLC:** 11.53 min; **^{1}H NMR** (500 MHz, d_6-DMSO) Major rotamer (ratio 1:6) δ = 1.11 (*t*, $^3J_{9,10}$ = 7.06 Hz, 3H, H-C_{10}), 2.61 (*m*, 4H, H-$C_{3,4}$), 4.21 (*q*, $^3J_{9,10}$ = 7.1 Hz, 2H, H-C_9), 5.49 (*dd*, $^3J_{2,3}$ = 7.1, 7.3 Hz, 1H, H-C_2), 7.01 (*m*, 2H, H-C_6), 7.18 (*m*, 3H, H-$C_{7,8}$), 7.63 (*m*, $^3J_{13,14}$ = 8.8 Hz, 4H, H-$C_{13,14}$); **^{13}C NMR** (125 MHz, d_6-DMSO): δ = 13.7 (CH_3, C_{10}), 30.8 (CH_2, C_3), 31.9 (CH_2, C_4), 59.5 (CH_2, C_9), 62.4 (CH, C_2), 122.0 (Cq, C_5), 126.3 (CH, C_8), 128.2 (CH, C_6), 128.5 (CH, C_7), 129.5 (CH, C_{13}), 130.8 (CH, C_{14}), 136.5 (Cq, Ar), 139.6 (Cq, Ar), 154.4 (Cq, C_{11}), 167.6 (Cq, C_1); **MS:** *m/z* 371 $[MH]^+$**.**

N2-Isomer (**144**)



TLC: R_f (hexane / EtOAc 9:1) = 0.18; **HPLC:** 13.38 min; **UV** (MeOH): λ_{max}, nm (ε): 248 (2210); **IR:** ν 3063 (*w*, ν(C-H)), 3028 (*w*, ν(C-H)), 2982 (*m*, ν(C-H)), 2937 (*m*, ν(C-H)), 1749 (*vs*, ν(C=O)), 1607 (*s*, ν(C=C)), 1497 (*w*, ν(C=C)), 1456 (*s*, ν(C=C)), 1204 (*s*, ν(C-O)), 1092 (*s*, ν(Ph-Cl)), 758 (*s*, γ(C-H, Ph)), 701 (*s*, γ(Ph)) cm^{-1}; **^{1}H NMR** (500 MHz, d_6-DMSO): δ = 1.15 (*t*, $^3J_{9',10'}$ = 7.3 Hz, 3H, H-$C_{10'}$), 2.60 (*m*, 4H, H-$C_{3',4'}$), 4.18 (*q*, $^3J_{9',10'}$ = 7.3 Hz, 2H, H-$C_{9'}$), 5.99 (*m*, 1H, H-$C_{2'}$), 7.14 (*m*, 3H, H-$C_{6',8'}$), 7.25 (*m*, 2H, H-$C_{7'}$), 7.62 (*d*, $^3J_{13',14'}$ = 9.0 Hz, 2H, H-$C_{14'}$), 8.08 (*d*, $^3J_{13',14'}$ = 9.0 Hz, 2H, H-$C_{13'}$); **^{13}C NMR** (125 MHz, d_6-DMSO): δ = 13.9 (CH_3, $C_{10'}$), 31.3 (CH_2, $C_{3'}$), 31.8 (CH_2, $C_{4'}$), 62.5 (CH_2, $C_{9'}$), 64.9 (CH, $C_{2'}$), 125.2 (Cq, $C_{5'}$), 126.2 (CH, $C_{8'}$), 128.3 (CH, C_6), 128.4 (CH, $C_{7'}$), 128.6 (CH, $C_{13'}$), 129.4 (CH, $C_{14'}$), 135.4 (Cq, Ar), 139.8 (Cq, Ar), 163.4 (Cq, C_{11}), 167.3 (Cq, C_1); **MS:** *m/z* 371 $[MH]^+$**.**

5.2. Alkylation of Tetrazole Rings

5.2.1. Reagents and solvents

All chemicals were obtained either from commercial suppliers or internal sources and used without further purification unless otherwise stated. All reactions were carried out under an atmosphere of nitrogen or argon. All the products were satisfactorily characterized by melting point, TLC, UV, IR, ^{1}H and ^{13}C-NMR, MS, HR-MS and when possible, comparison of their analytical data has been made with available literature data.

5.2.1.1. Reagents

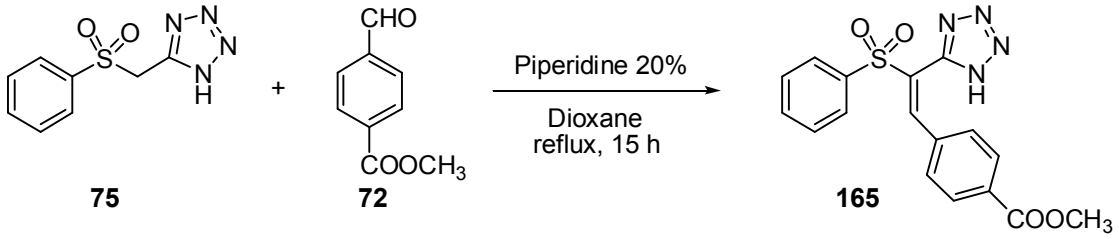
Reagent	Molecular Formula	MW (g/mol)	Quality
Benzhydryl bromide	$C_{13}H_{11}Br$	247.1	Lancaster ; 95 %
Benzylbromide	C_7H_7Br	171.04	Fluka ; ≥ 98 % (GC)
Chlorotriphenylmethane	$C_{19}H_{15}Cl$	278.78	Lancaster ; 98+ %
Hydrochloric acid	HCl	36.5	Fluka ; 2N standard solution Fluka ; ≥ 32 % (T)
2-Iodopropane	C_3H_7I	169.99	Fluka ; ≥ 97 % (GC)
Methyl-4-formylbenzoate	$C_9H_8O_3$	164.16	Fluka ; ~95 % (HPLC)
3-Methyl-1-*p*-tolyltriazene	$C_8H_{11}N_3$	149.19	Aldrich ; 98 %
Piperidine	$C_5H_{11}N$	85.16	Fluka ; ~98 % (GC)
Potassium hydrogen carbonate	KOH	56.11	Fluka ; ≥ 86 % (T)
Potassium carbonate	K_2CO_3	138.27	Fluka ; ≥ 99 % (AT)
Triethylamine	$C_6H_{15}N$	101.19	Fluka ; ≥ 99.5 %

5.2.1.2. Solvents

Solvents	Quality
Acetone	Fluka ; ≥ 99.5 % (GC)
Acetonitrile	Merck ; for LC ARMAR Chemicals ; d_3-Acetonitrile 99.5 Atom % D
Chloroform	Fluka ; ≥ 99.5 % (GC) ARMAR Chemicals; $CDCl_3$ 100 Atom % D, stab. with Ag
Dichloromethane	Merck ; for analysis Fluka ; 99.5 % (GC)
Dimethylsulfoxide	ARMAR Chemicals ; d_6-DMSO 99.9 Atom % D
1,4-Dioxane	Fluka; puriss. p.a., ≥ 99.5 %
Ethyl acetate	Fluka ; 99.5 %
Heptane	Fluka ; ≥ 99.0 % (GC)
Hexane	Fluka ; ≥ 99.0 % (GC)
Isopropyl acetate	Fluka ; ≥ 99.0 % (GC)
Methylen chloride	Fluka; puriss. over molecular sieves
Tetrahydrofuran	Fluka; puriss. p.a., ≥ 99.5 % (GC)
Toluene	Fluka ; absolute over molecular sieves, ≥ 99.5 % (GC)

5.2.2. Synthesis of the Starting Materials

4-[2-Benzensulfonyl-2-(1*H*-tetrazol-5-yl)-vinyl]-benzoic acid methyl ester (165)

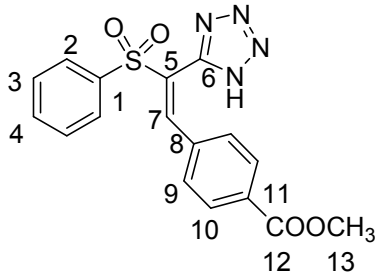


75 **72** **165**

Molecular Formula	$C_{17}H_{14}N_4O_4S$
Molecular Weight	370.39 g/mol

A 200 mL four necked bottomed-flask, equipped with an overhead mechanical stirrer and a water removed system, is charged at room temperature, with 5-phenylsulfonylmethyl-1*H*-tetrazole **75** (6.727 g, 30 mmol), methyl-4-formyl benzoate (7.387 g, 45 mmol) and piperidine (511 mg, 6 mmol) dissolved in dioxane (90 mL). The mixture is gradually warmed to refluxing 130 °C (external temperature) and stirred 15 hours. The solution is cooled to room temperature and the solvent is removed to give 21.8 g of crude as a brown oil. The crude is dissolved with a solution of ethyl acetate and toluene (1:1) and washed three times with HCl (2 M) to remove the piperidine in the aqueous phase. The collective aqueous phase is washed twice with ethyl acetate (30 mL portion). The solvent is removed, the brown oil is re-dissolved in ethyl acetate (40 mL) and the product is extracted three times with a solution of $KHCO_3$ (15 % solution, 30 mL portion). The combined aqueous phase is washed twice with ethylacetate (30 mL portion). The basic aqueous phase is cooled to 0 °C and treated with HCl (6 M) to pH 2.5 monitored with an electrode or a pH paper. The product is extracted four times with ethyl acetate (30 mL portion). The solvent is removed and the product is crystallized from ethyl acetate to give 3.4 g, with 30 % of yield.

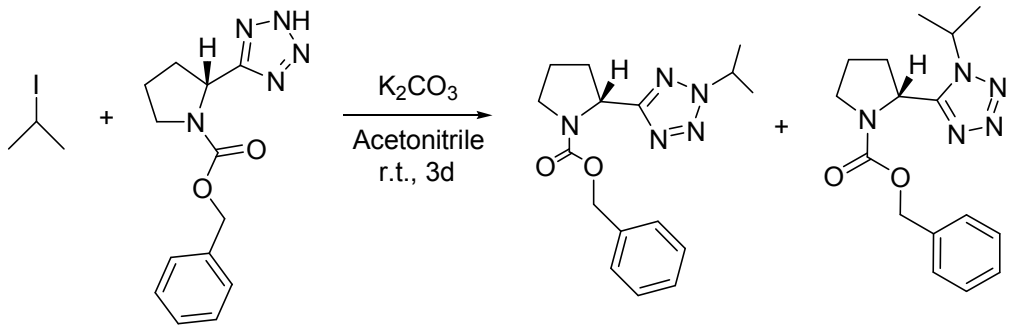
Compound characterization data:



mp: 180-182 °C; **TLC:** R_f (toluene / EtOAc / AcOH 20:20:1) = 0.16; **HPLC:** 11.26 min **UV** (acetonitrile): λ_{max}, nm (ε): 286 (2180); **IR:** ν 3100-2400 (*brw*, ν(N-H)), 3069 (*w*, ν(C-H)), 1724 (*vs*, ν(C=O)), 1631(*s,* ν(C=C)), 1434 (*s,* ν(C=C)), 1308 (*s* $\nu_{asim}(SO_2)$), 1291 (*s,* ν(C-O)), 1152 (*s,* $\nu_{sim}(SO_2)$), 1085 (*s,* ν(C-O)) cm^{-1}; **^{1}H NMR** (500 MHz, d_6-DMSO): δ = 3.81 (*s*, 3H, H-C_{13}), 7.21 (*m*, 2H, H-C_9), 7.63 (*m*, 2H, H-C_3), 7.76 (*m*, 1H, H-C_4), 7.77 (*m*, 2H, H-C_2), 7.86 (*m*, 2H, H-C_{10}), 8.44 (*s*, 1H, H-C_7), 16.80 (*br*, NH); **^{13}C NMR** (125 MHz, d_6-DMSO): δ = 52.6 (CH_3, C_{13}), 128.7 (CH, C_2), 129.9 (CH, C_{10}), 130.1 (CH, C_3), 130.6 (Cq, C_5), 130.7 (CH, C_9), 132.0 (Cq, C_{11}), 134.9 (CH, C_4), 136.1 (Cq, C_8), 138.4 (Cq, C_1), 144.9 (CH, C_7), 165.8 (C=O, C_{12}); **MS:** *m/z* 369 $[M-H]^-$, 141 $[PhSO_2]^-$; **HR-MS:** calc'd for $[MH]^+$ = 371.0809, found 371.0809 (ΔM (ppm) < 0.1), calc'd for $[M+Na]^+$ = 393.0628, found 393.0628 (ΔM (ppm) < 0.1).

5.2.3. Alkylation of the Tetrazole Ring

(*R*)-2-(Isopropyl-tetrazole-5-yl)-pyrrolidine-1-carboxylic acid benzyl ester (161, 162)



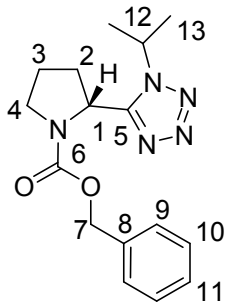
302 **113** **161** **162**

CAS Registry Number	N1-isomer: 920748-49-8 N2-isomer: 920748-47-6
Molecular Formula	$C_{16}H_{21}N_5O_2$
Molecular Weight	315.17 g/mol
Analysis Ref.	V. Aureggi, G. Sedelmeier, Novartis Pharma AG, **2007**, WO 2007/009716

A 200 mL, three necked bottomed flask, is charged at room temperature with *(R)*-2-(1*H*-tetrazol-5-yl)-pyrrolidine-1-carboxylic acid benzyl ester (12.3 g, 45 mmol), in acetonitrile (130 mL) and potassium carbonate (24.84 g, 180 mmol). After five minutes 2-iodopropane is added (9.28 mL, 90 mmol) and the mixture is stirred for three days. The mixture is transferred into a 500 mL flask and the acetonitrile is removed with the rotary evaporator. Water (40 mL) is added (pH 8.5) and the product is extracted four times with ethyl acetate (50 mL portion). The combined organic phase is washed once with water (40 mL). The solvent is removed to give an orange oil which contains both the N1- and the N2-isomers (N2/N1-isomer 72:28 based on HPLC analysis). The crude is chromatographed (eluent: ethyl acetate / hexane 1:3) to give 9.163 g of pure N2-regioisomer **161** (65 % yield) and N1-isomer **162** (28 % yield) as colorless oils.

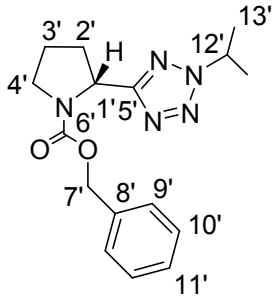
Compound characterization data:

N1-Isomer (**162**)



TLC: R_f (hexane / EtOAc 3:1) = 0.12; **HPLC:** 8.53 min; **UV** (EtOH): λ_{max}, nm (ε): 258 (22), 205 (1010); **IR:** ν 3064 (*w*, ν (C-H)), 3034 (*w*, ν (C-H)), 2984 (*w*, ν (C-H)), 1704 (*s*, ν (C=O)), 1447 (*m*, ν (C=C)), 1415 (*s*, ν (C-N)), 1357 (*s*, δ(CH_3)), 1123 (*s*, ν(C-O)), 699 (*w*, γ(Ph)) cm^{-1}; **^{1}H NMR** (400 MHz, d_6-DMSO, 300 K) Rotamers (1:1): δ = 1.30, 1.53 (*dd*, $^3J_{12,13}$ = 6.5 Hz, 6H, H-C_{13}), 1.90 (*m*, 2H, H-C_3), 2.2 (*m*, 2H, H-C_2), 3.58 (*m*, 2H, H-C_4), 4.90 (*m*, 3H, H-$C_{7,12}$), 5.31 (*dd*, $^3J_{1,2}$ = 8.0, 8.1 Hz, 1H, H-C_1), 6.97 (*m*, 1H, H-C_{11}), 7.35 (*m*, 4H, H-$C_{9,10}$); (400 MHz, d_6-DMSO, 394 K): δ = 1.45 (*d*, 6H, H-C_{13}), 1.95 (*m*, 2H, H-C_3), 2.25 (*m*, 2H, H-C_2), 3.58 (*m*, 2H, H-C_4), 4.80 (*m*, 1H, H-C_{12}), 4.93 (*s*, 1H, H-C_7), 5.25 (*m*, 1H, H-C_1), 7.12 (*m*, 2H, ArH), 7.28 (*m*, 3H, ArH); **^{13}C NMR** (125 MHz, d_6-DMSO, 300 K) Rotamers (1:1): δ = 21.7, 22.2 (CH_3, C_{13}), 22.5, 23.9 (CH_2, C_3), 31.4, 32.3 (CH_2, C_2), 46.3, 46.8 (CH_2, C_4), 49.9, 50.1 (CH_2, C_7), 50.1, 50.3 (CH, C_{12}), 66.2, 66.3 (CH, C_1), 127.4, 127.5 (CH, Ar), 127.8, 127.9 (CH, C_{11}), 128.3, 128,4 (CH, Ar), 136.2, 136.7 (Cq, C_8), 153.2, 153.9 (Cq, C_5), 155.5, 155.9 (Cq, C_6); **MS:** *m/z* 316 $[MH]^+$; **HR-MS:** calc'd for $[MH]^+$ = 316.1768, found 316.1767 (ΔM (ppm) = 0.2); calc'd for $[M+Na]^+$ = 338.1588, found 338.1586 (ΔM (ppm) = 0.4).

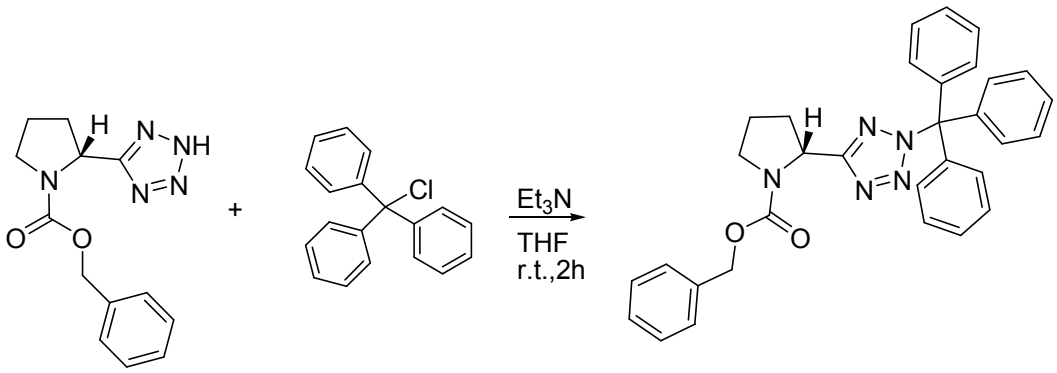
N2-Isomer (**161**)



TLC: R_f (hexane / EtOAc 3:1) = 0.25; **HPLC:** 7.65 min; **UV** (EtOH): λ_{max}, nm (ε): 205 (1321); **IR:** 3064 (*w*, ν (C-H)), 3033 (*w*, ν (C-H)), 2984 (*w*, ν (C-H)), 2955 (*w*, ν (C-H)), 1707 (*s*, ν (C=O)), 1448 (*m*, ν (C=C)), 1412 (*s*, ν (C-N)), 1356 (*s*, δ(CH_3)), 1116 (*s*, ν(C-O)), 698 (*w*, γ(Ph)) cm^{-1}; **^{1}H NMR** (400 MHz, d_6-DMSO, 300 K) Rotamers (1:1): δ =

1.45, 1.51 (*dd*, $^{3}J_{12',13'}$ = 6.5 Hz, 6H, H-$C_{13'}$), 1.95 (*m*, 3H, H-$C_{2',3'}$), 2.33 (*m*, 1H, H-$C_{2'}$), 3.53 (*m*, 2H, H-$C_{4'}$), 4.95 (*m*, 3H, H-$C_{7',12'}$), 5.18 (*dd*, $^{3}J_{1',2'}$ = 8.0 Hz, 1H, H-$C_{1'}$), 7.02 (*m*, 1H, H-$C_{11'}$), 7.29 (*m*, 4H, H-$C_{9',10'}$); (400 MHz, d_6-DMSO, 394 K): δ = 1.51 (*dd*, 6H, H-$C_{13'}$), 1.98 (*m*, 3H, H-$C_{2',3'}$), 2.35 (*m*, 1H, H-$C_{2'}$), 3.53 (*m*, 2H, H-$C_{4'}$), 4.97 (*m*, 3H, H-$C_{7',12'}$), 5.18 (*m*, 1H, H-$C_{1'}$), 7.18 (*m*, 2H, ArH), 7.25 (*m*, 3H, ArH); **^{13}C NMR** (125 MHz, d_6-DMSO, 300 K) Rotamers (1:1): δ = 21.7, 21.8 (CH_3, $C_{13'}$), 23.5, 23.7 (CH_2, $C_{3'}$), 31.9, 32.8 (CH_2, $C_{2'}$), 46.2, 46.7 (CH_2, $C_{4'}$), 52.5, 53.1 (CH_2, $C_{7'}$), 55.9 (CH, $C_{12'}$), 65.7, 65.9 (CH, $C_{1'}$), 126.8, 127.4 (CH, Ar), 127.6, 127.8 (CH, $C_{11'}$), 128.1, 128,4 (CH, Ar), 136.7, 136.9 (Cq, $C_{8'}$), 153.6, 153.8 (Cq, $C_{5'}$), 167.2, 167.6 (Cq, $C_{6'}$); **MS:** *m/z* 316 $[MH]^+$, 272 $[MH\text{-}CO_2]^+$; **HR-MS:** calc'd for $[MH]^+$ = 316.1768, found 316.1768 (ΔM (ppm) = 0.1); calc'd for $[M+Na]^+$ = 338.1588, found 338.1587 (ΔM (ppm) = 0.3).

(*R*)-2-(2-Trityl-2*H*-tetrazol-5-yl)-pyrrolidine-1-carboxylic acid benzyl ester (164)

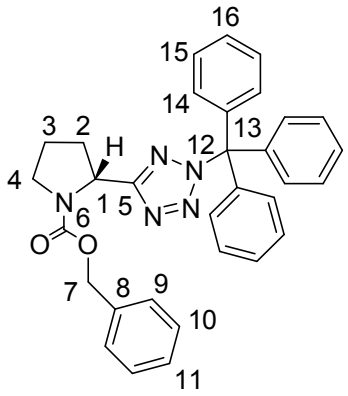


113 **163** **164**

Molecular Formula	$C_{32}H_{29}N_5O_2$
Molecular Weight	515.62 g/mol

A 25 mL, three necked round-bottomed flask, is charged at room temperature, with (*R*)-2-(1*H*-tetrazol-5-yl)-pyrrolidine-1-carboxylic acid benzyl ester **113** (546 mg, 2 mmol) and chlorotriphenylmethane (613 mg, 2.2. mmol) in THF (8 mL). The solution is then treated with triethyl amine (0.362 mL, 2.6 mmol) and stirred at room temperature for two hours. The mixture is filtered, the solvent is removed and the crude (1.15 g, colorless gel) is chromatographed (elution system: heptane / ethyl acetate 5:1) to give the product **164** as a colorless oil (1.03 g, 77 % of yield).

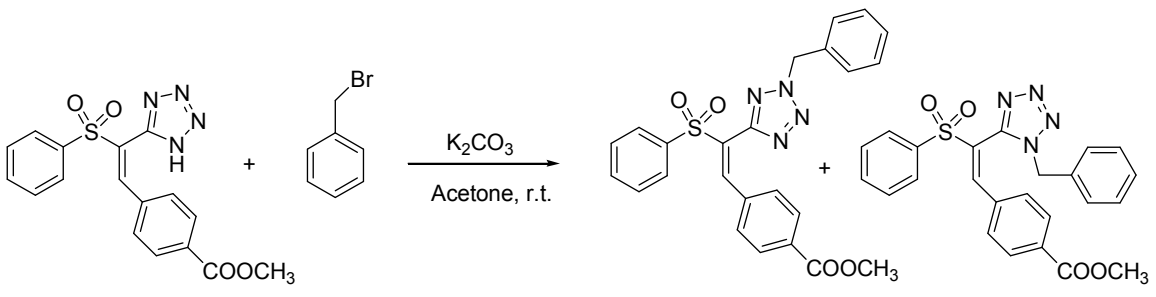
Compound characterization data:



TLC: R_f (heptane / EtOAc 5:1) = 0.1; **HPLC:** 12.72 min; **UV** (MeOH): λ_{max}, nm (ε): 259 (76); **IR:** ν 3090 (*w*, ν(C-H)), 3062 (*w*, ν(C-H)), 3033 (*w*, ν(C-H)), 2978 (*w*, ν(C-H)), 2953 (*w*, ν(C-H)), 1960-1800 (*w*, overtones γ(C-H, Ph)), 1703 (*s*, ν(C=O)), 1494 (*m*, ν(C=C)), 1448 (*s*, ν(C=C)), 1414 (*s*, ν(C-N)), 748 (*s*, γ(C-H, Ph)), 699 (*s*, γ(Ph)) cm^{-1}; **^{1}H NMR** (400 MHz, d_6-DMSO) Major rotamers (ratio 2:3): δ = 1.93 (*m*, 3H, H-$C_{2,3}$), 2.34 (*m*, 1H, H-C_2), 3.48 (*m*, 2H, H-C_4), 4.98 (*m*, 2H, H-C_7), 5.22 (*dd*, $^3J_{1,2}$ = 6.8, 7.0 Hz, 1H, H-C_1), 6.95 (*m*, 6H, ArH), 7.30 (*m*, 14H, ArH); **^{13}C NMR** (125 MHz, d_6-DMSO) Rotamers (ratio 2:3): δ = 22.7, 23.5 (CH_2, C_3), 31.9, 32.8 (CH_2, C_2), 46.2, 46.8 (CH_2, C_4), 52.5, 53.1 (CH, C_1), 65.8, 65.9 (CH_2, C_7), 82.2 (Cq, C_{12}), 126.8 (CH, ArH), 124.4, 127.5 (CH, Ar), 127.9 (CH, ArH), 128.1, 128.3 (CH, ArH), 129.5, 129.6 (CH, C_{14}), 136.6, 136.9 (Cq, C_8), 140.9, 140.9 (Cq, C_{13}), 153.5, 153.8 (Cq, C_6), 166.8, 167.1 (Cq, C_5); **MS:** *m/z* 538 $[M+Na]^+$; **HR-MS:** calc'd for $[M+Na]^+$ = 538.2214, found 538.2212 (ΔM (ppm) = 0.3); calc'd for $[M+K]^+$ = 554.1953, found 554.1953 (ΔM (ppm) = 0.1).

5.2.3.1. Benzylation of the tetrazole ring

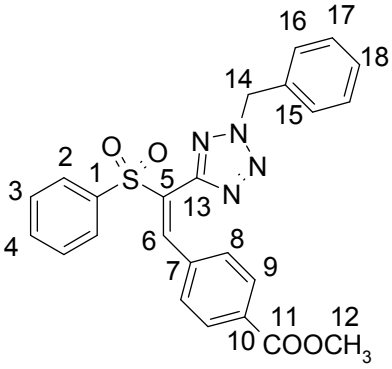
4-[2-Benzenesulfonyl-2-(benzyl-tetrazol- 5-yl) -vinyl]-benzoic acid methyl ester (166, 167)



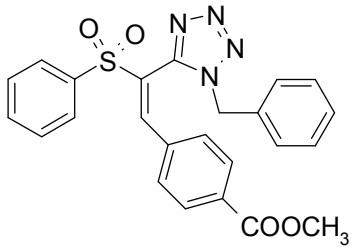
Molecular Formula	$C_{24}H_{20}N_4O_4S$
Molecular Weight	460.51 g/mol

A 25 mL, three necked round bottomed flask, is charged at room temperature, with 4-[2-benzensulfonyl-2-(1*H*-tetrazol-5-yl)-vinyl]-benzoic acid methyl ester **165** (741 mg, 2 mmol), dissolved in acetone (7.5 mL). The solution is treated with potassium carbonate (553 mg, 4 mmol) and benzyl bromide (410 mg, 2.4 mmol). The mixture is stirred over the night. The acetone is removed by rotary evaporator, water is added (10 mL) and the product is extracted three times with isopropyl acetate (15 mL portion). The collective organic phase is washed once with water (15 mL). The solvent is removed to give 1.06 g of crude. The product is flash chromatographed (toluene / ethyl acetate 14:1) to give 640 mg as a mixture of N1 and N2-isomers in ratio 1:1 with 69 % of yield.

Compound characterization data:



N2-Isomer

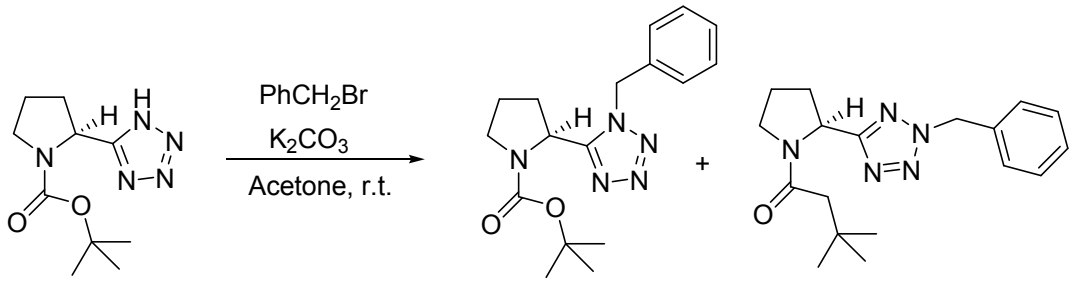


N1-Isomer

mmp: 53-55 °C; **TLC:** R_f (toluene / EtOAc 5:1) = 0.23; **HPLC:** 16.07; 16.34 min; **UV** (EtOH): λ_{max}, nm (ε): 289 (25650), 201 (41850); **IR:** ν 3419 (*w* overtones (C=O)), 3100 (*w,* ν(C-H)), 2855 (*w,* ν(C-H)), 1724 (*s,* ν(C=O)), 1631 (*s* ν(C=C)), 1434 (*s,* ν(C=C, Ph)), 1308 (*s,* $\nu_{asim}(SO_2)$), 1291 (*s,* ν(C-O)), 1152 (*s,* $\nu_{sim}(SO_2)$), 1085 (*s,* ν(C-O)) cm^{-1}; **^{1}H NMR** (500 MHz, d_6-DMSO): δ = 3.86 (*s*, 3H, H-C_{12}, N1-isomer), 3.87 (*s*, 3H, H-C_{12}, N2-isomer), 5.23 (*br*, 1H, H-C_{14}, N1-isomer), 5.53 (*br*, 1H, H-C_{14}, N1-isomer), 5.94 (*s*, 2H, H-C_{14}, N2-isomer), 7.1 (*m*, 6H, H-$C_{8,16}$, N1- and N2-isomers), 7.40 (*m*, 1H, ArH, N1-isomer), 7.58 (*m*, 1H, ArH, N2-isomer), 7.75 (*m*, 6H, ArH, N1- and N2-isomers), 8.46 (*s*, 1H, H-C_6, N2-isomer B), 8.57 (*s*, 1H, H-C_6, N1-isomer); (500 MHz, d_6-DMSO, 353 K) 3.86 (*s*, 3H, H-C_{12}, N1-isomer), 3.87 (*s*, 3H, H-C_{12}, N2-isomer), 5.21 (*br*, 2H, H-C_{14}, N1-isomer), 5.96 (*s*, 2H, H-C_{14}, N2-isomer), 7.1 (*m*, 6H, H-$C_{8,16}$, N2- and N2-isomers), 7.40 (*m*, 1H, ArH, N1-isomer), 7.58 (*m*, 1H, ArH, N2-isomer), 7.75 (*m*, 6H, ArH, N1- and N2-isomers), 8.45 (*s*, 1H, H-C_6, N2-isomer), 8.57 (*s*, 1H, H-C_6, N1-isomer); **^{13}C NMR** (125 MHz, d_6-DMSO) More relevant data: δ = 51.9 (CH_3, C_{12}, N1-and N2-isomers), 50.8

(CH_2, C_{14}, N1-isomer), 56.7 (CH_2, C_{14}, N2-isomer), 128.2 (CH, Ar), 128.5 (CH, Ar), 129.3 (CH, Ar), 130.0 (CH, Ar), 130.4 (CH, Ar), 130.8 (CH, Ar), 131.4 (CH, Ar), 134.4 (CH, Ar), 135.1 (Cq, Ar), 145.0 (CH, C_6, N2-isomer), 148.0 (CH, C_6, N1-isomer), 165.6 (Cq, C_{11}); **MS:** *m/z* 369 $[M-H]^-$, 141 $[PhSO_2]^-$; **HR-MS:** calc'd for $[MH]^+$ = 371.0809, found 371.0809 (ΔM (ppm) < 0.1), calc'd for $[M+Na]^+$ = 393.0628, found 393.0628 (ΔM (ppm) < 0.1).

(*S*)-*tert*-butyl-2-(benzyl-tetrazol-5-yl)-pyrrolidine-1-carboxylate (168, 169)



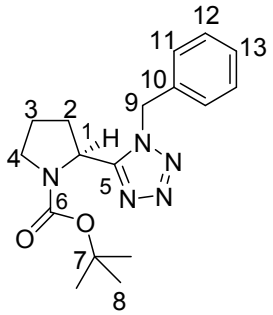
111 *N1*-Isomer **168** *N2*-Isomer **169**

Molecular Formula	$C_{17}H_{23}N_5O_2$
Molecular Weight	329.19 g/mol

A 25 mL, three necked round-bottomed flask, is charged, at room temperature, with the boc-pyrrolidine tetrazole **111** (956 mg, 4 mml) in acetone (9 mL), benzyl bromide (820 mg, 4.8 mmol) and potassium carbonate (1.106 g, 8 mmol). The mixture is stirred over the night at room temperature. The mixture is quenched with water (20 mL) and the product extracted four times with ethyl acetate (25 mL portion). The solvent is removed to give 1.320 g of crude which is chromatographed (elution system: hexane / ethyl acetate 3:1) to afford the the 650 mg of N2-isomer **169** (49 % yield) and 580 mg of N1-isomer **168** (44 % yield) as yellow oils.

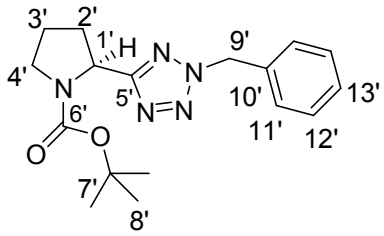
Compound characterization data:

N1-Isomer (**168**)



TLC: R_f (hexane / EtOAc 3:1) = 0.6; **HPLC:** 9.56 min; **UV** (MeOH): λ_{max}, nm (ε): 257 (342); **IR:** ν 3066 (*w*, ʋ(C-H)), 3034 (*w*, ʋ(C-H)), 2977 (*m*, $ʋ_{asim}(CH_3)$), 2930 (*w*, ʋ(C-H)), 1696 (*vs*, ʋ(C=O)), 1456 (*s*, ʋ(C=C)), 1396 (*vs*, ʋ(C-N)), 1367 (*s*, δ$(CH_3)_3$), 1163 (*s*, ʋ(C-O)) cm^{-1}; **^{1}H NMR**(500 MHz, d_6-DMSO, 394 K): δ = 1.27 (*s*, 9H, H-C_8), 1.85 (*m*, 1H, H-C_3), 1.90 (*m*, 1H, H-C_3), 2.05 (*m*, 1H, H-C_2), 2.18 (*m*, 1H, H-C_2), 3.48 (*m*, 2H, H-C_4), 5.17 (*m*, 1H, H-C_1), 5.66 (*m*, 2H, H-C_9), 7.28 (*m*, 2H, H-C_{11}), 7.34 (*m*, 3H, H-$C_{12,13}$); **^{13}C NMR** (150 MHz, d_6-DMSO, 300 K) Major rotamer: δ = 22.8 (CH_2, C_3), 27.7 (CH_3, C_8), 32.0 (CH_2, C_2), 46.2 (CH_2, C_4), 50.0 (CH, C_1), 50.9 (CH_2, C_9), 79.9 (Cq, C_7), 128.0 (CH, C_{11}), 128.5 (CH, C_{13}), 128.9 (CH, Ar), 134.5 (Cq, C_{10}), 157.2 (Cq, C_6), 168.7 (Cq, C_5); **MS:** *m/z* 330 $[MH]^+$, 230 $[MH\text{-}Boc]^+$; **HR-MS:** calc'd for $[MH]^+$ = 330.1925, found 330.1925 (ΔM (ppm) = 0.1), calc'd for $[M+Na]^+$ = 352.1744, found 352.1744 (ΔM (ppm) = 0.1).

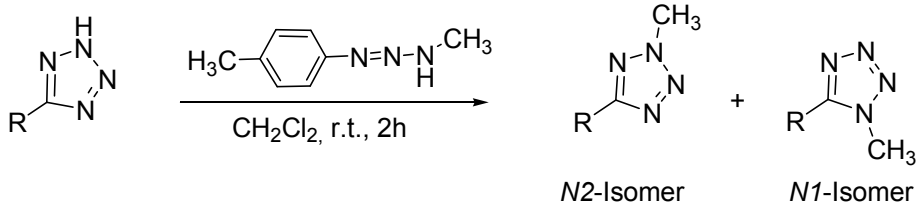
N2-Isomer (**169**)



TLC: R_f (hexane / EtOAc 3:1) = 0.75; **HPLC:** 10.38 min; **IR:** ν 3067 (*w*, ʋ(C-H)), 3035 (*w*, ʋ(C-H)), 2977 (*m*, ʋ(C-H)), 1698 (*vs*, ʋ(C=O)), 1456 (*m*, ʋ(C=C)), 1395 (*s*, ʋ(C-N)), 1367 (s, δ$(CH_3)_3$), 1163 (*s*, ʋ(C-O)) cm^{-1}; **^{1}H NMR** (400 MHz, d_6-DMSO) Major rotamer: δ = 0.98 (*s*, 9H, H-$C_{8'}$), 2.05 (*m*, 4H, H-$C_{2',3'}$), 3.45 (*m*, 2H, H-$C_{4'}$), 4.95 (*m*, 1H, H-$C_{1'}$), 5.90 (*s*, 2H, H-$C_{9'}$), 7.34 (*m*, 5H, H-$C_{11'\text{-}13'}$); **^{13}C NMR** (150 MHz, d_6-DMSO) Major rotamer: δ = 22.9 (CH_2, $C_{3'}$), 27.6 (CH_3, $C_{8'}$), 32.8 (CH_2, $C_{2'}$), 46.2 (CH_2, $C_{4'}$), 52.5 (CH, $C_{1'}$), 55.7 (CH_2, $C_{9'}$), 78.4 (Cq, $C_{7'}$), 128.4 (CH, Ar), 128.5 (CH, $C_{13'}$), 129.2 (CH, Ar), 134.2 (Cq, $C_{10'}$), 157.8 (Cq, $C_{6'}$), 168.7 (Cq, $C_{5'}$); **MS:** *m/z* 330 $[MH]^+$, 230 $[MH\text{-}Boc]^+$

5.2.4. Methylation of the Tetrazole Ring

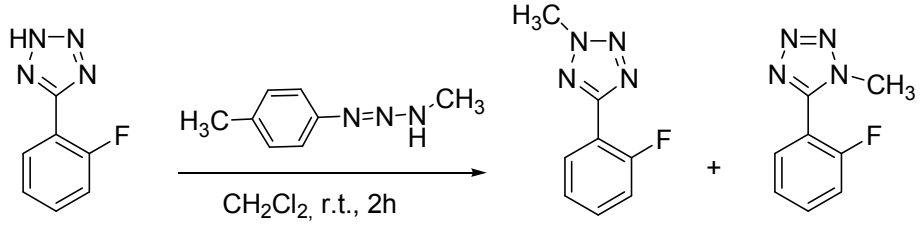
5.2.4.1. TP3: Typical procedure for the methylation of the tetrazole ring



Scheme 139. Methylation of the tetrazole ring

A 25 mL, three necked round bottomed flask, is charged at 0 °C, under atmosphere of argon, with 2-fluoro-phenyl-tetrazole (821 mg, 5 mmol) dissolved in dichloromethane (10 mL) and treated with 3-methyl-1-*p*-tolyltriazene (1.119 g, 7.5 mmol). The mixture is gradually warmed at room temperature and stirred for two hours. When the HPLC and the TLC analysis show > 98 % conversion the reaction mixture is cooled to 0 °C and quenched with HCl (2 M, 10 mL). The biphasic mixture is transferred to a separatory funnel and the product is extracted three times with dichloromethane (10 mL portion) ; the combined organic phase is washed three times HCl (2 M, 10 mL portion). The solvent is removed to give 740 mg of a pink crystalline material and the crude is chromatographed (elution system: hexane / ethyl acetate 3:1) to give the N2-isomer (520 mg, 82.5 % yield) and the N1-isomer (110 mg, 17.5 % yield).

5-(2-Fluoro-phenyl)-*N*-methyl-tetrazole (145, 146)



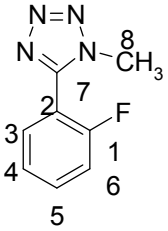
Molecular Formula	$C_8H_7FN_4$
Molecular Weight	178.17 g/mol

TP3: 1.5 equivalents of 3-methyl-1-*p*-tolyltriazene are used in a 5 mmol scale experiment. The reaction is stirred two hours at room temperature to give 740 mg of pink

crystalline material (N2/N1-isomer = 71:29 based on HPLC analysis). The crude is chromatographed to give 520 mg of N2-isomer **146** as an orange solid (58 % yield) and 110 mg of N1-isomer **145** as an orange oil (12 % yield).

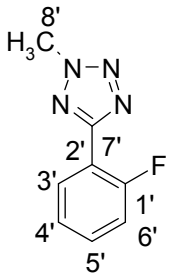
Compound characterization data:

N1-Isomer (**145**)



mp: 74-77 °C; **TLC:** R_f (hexane / AcOEt 3:1) = 0.16; **HPLC:** 6.37 min; **UV** (EtOH): λ_{max}, nm (ε): 269 (1250), 224 (8570); **IR:** ν 3073 (*w*, ν(C-H)), 2961 (*w*, ν(CH_3)), 1623 (*m*, ν(C=C)), 1585 (*w*, tetrazole), 1480 (*s*, ν(C=C)), 1436 (*s*, ν(C=C)), 1223 (*s*, ν(C-F)) cm^{-1}; **Raman:** 3080 (*w*, ν(C-H)), 2961 (*w*, ν_{sim}(-CH_3)), 1526 (*m*, tetrazole), 1223 (*w*, ν(C-F)) cm^{-1}; **^{1}H NMR** (500 MHz, d_6-DMSO): δ = 4.03 (*s*, 3H, H-C_8), 7.46 (*m*, 2H, H-$C_{4,6}$), 7.72 (*m*, 2H, H-$C_{3,5}$); **^{13}C NMR** (125 MHz, d_6-DMSO): δ = 34.0 (CH_3, C_8), 113.2 (Cq, C_2), 117.3 (CH, C_6), 126.2 (CH, C_4), 129.5 (CH, C_3), 132.8 (CH, C_5), 153.7 (Cq, C_7), 160.7 (Cq, C_1); **MS:** *m/z* 179 $[MH]^+$;

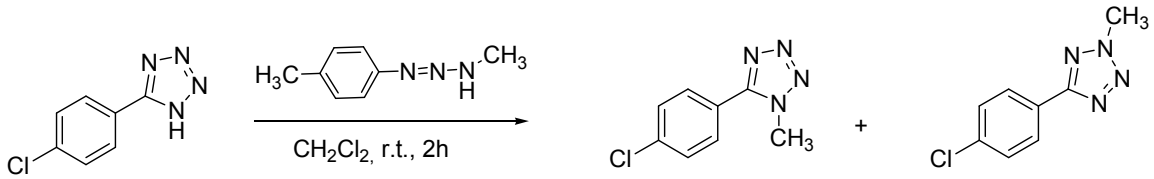
N2-Isomer (**146**)



mp: 70-74 °C; **TLC:** R_f (hexane / AcOEt 3:1) = 0.37; **HPLC:** 8.90 min; **UV** (EtOH): λ_{max}, nm (ε): 283 (1400), 275 (1880), 234 (14450); **IR:** ν 3068 (*w*, ν(C-H), 2961 (*w*, ν(CH_3), 2000-1700 (*w*, overtones γ(CH, Ph)), 1546 (*w*, tetrazole), 1482 (*s*, ν(C=C)), 1436 (*s*, ν(C=C)), 1219 (*s*, ν(C-F)) cm^{-1}; **Raman:** 3070 (*w*, ν(C-H), 2964 (*w*, ν_{sim} (-CH_3)), 1545 (*w*, tetrazole)) cm^{-1}; **^{1}H NMR** (500 MHz, d_6-DMSO): δ = 4.45 (*s*, 3H, H-$C_{8'}$), 7.38 (*m*, 2H, H-$C_{4',6'}$), 7.58 (*m*, 1H, H-$C_{5'}$), 8.03 (*dt*, *J* = 1.7, 7.5 Hz, 1H, H-$C_{3'}$); **^{13}C NMR** (125 MHz, d_6-DMSO): δ = 38.3 (CH_3, $C_{8'}$), 113.5 (Cq, $C_{2'}$), 117.2 (CH, $C_{6'}$), 126.0 (CH, $C_{4'}$), 132.1 (CH, $C_{3'}$), 134.0 (CH, $C_{5'}$), 162.1 (Cq, $C_{7'}$), 163.3 (Cq, C_1); **MS:** *m/z* 179 $[MH]^+$;

HR-MS: calc'd for $[MH]^+$ = 179.07275, found 179.0727 (ΔM (ppm) = 0.6), calc'd for $[M+Na]^+$ = 201.0547, found 201.0546 (ΔM (ppm) = 0.7).

5-(4-Chloro-phenyl)-*N*-methyl-tetrazole (147, 148)



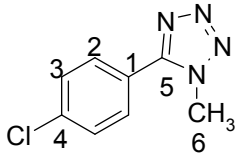
1 *N1*-Isomer **147** *N2*-Isomer **148**

CAS Registry Number	**147**: 77455-52-8; **148**: 69746-35-6
Molecular Formula	$C_8H_7ClN_4$
Molecular Weight	194.62 g/mol
Analysis Ref.	a) C. W. Roberts, G. F. Fanta, J. D. Martin, *J. Org. Chem.* **1959**, *24*, 654; b) R. N. Butler, V. C. Garvin, *J. Chem. Soc.*, Perkin Trans.1: Organic and Bio-Organic Chemistry **1981**, *2*, 390

TP3: 1.5 equivalents of 3-methyl-1-p-tolyltriazene are used in a 4 mmol scale experiment. The reaction is stirred two hours at room temperature to give 600 mg of brown crystalline material (N2/N1-isomer = 75:25 based on HPLC analysis). The crude is chromatographed (elution system hexane / ethyl acetate 5 : 1) to give 340 mg of N2-isomer **148** (44 % yield) and 100 mg of N1-isomer **147** (13 % yield).

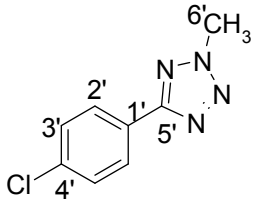
Compound characterization data:

N1-Isomer (**147**)



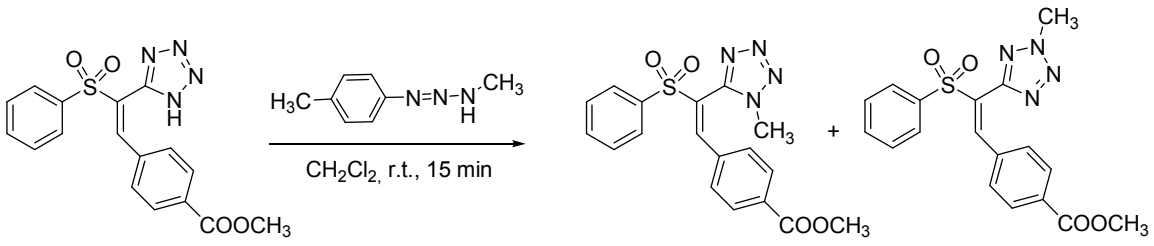
mp: 120 °C; **TLC:** R_f (hexane / AcOEt 4:1)= 0.08; **HPLC:** 5.61 min; **UV** (MeOH): λ_{max}, nm (ε): 234 (1570); **IR:** ν 3100 (*w*, ν(C-H)), 3076 (*w*, ν(C-H)), 3036 (*w*, ν(C-H)), 3016 (*w*, ν(C-H)), 3100 (*w*, ν(C-H)), 2962 (*w*, ν(CH_3)), 1604 (*s*, ν(C=C)), 1470 (*s*, ν(C=C)), 1454 (*s*, ν(C=C)), 1094 (*s*, ν(Ph-Cl)) cm^{-1}; **Raman:** 1535 (*w*, tetrazole) cm^{-1}; **^{1}H NMR** (500 MHz, d_6-DMSO): δ = 4.15 (*s*, 3H, H-C_6), 7.68 (*d*, $^3J_{2,3}$ = 8.4 Hz, 2H, H-C_3), 7.86 (*d*, $^3J_{2,3}$ = 8.4 Hz, 2H, H-C_2); **^{13}C NMR** (125 MHz, d_6-DMSO) 35.1 (CH_3, C_6), 122.7 (Cq, C_4), 129.3 (CH, C_3), 130.6 (CH, C_2), 136.1 (Cq, C_1), 153.2 (Cq, C_5); **MS:** *m/z* 195 $[MH]^+$, 138 $[MH-HN_3]^-$.

N2-Isomer (**148**)



mp: 108 °C; **TLC:** R_f (hexane / AcOEt 4:1) = 0.31; **HPLC:** 8.21 min; **UV** (MeOH): λ_{max}, nm (ε): 201 (3000), 246 (2030); **IR:** ν 3062 (*w*, ν(C-H)), 3035 (*w*, ν(C-H)), 2953 (*w*, ν(CH_3)), 2925 (*w*, ν(CH_3)), 2855 (*w*, ν(CH_3)), 1607 (*m*, ν(C=C)), 1466 (*s*, ν(C=C)), 1452 (*s*, ν(C=C)), 1089 (*s*, ν(Ph-Cl)) cm^{-1}; **Raman:** 1526 (*w*, tetrazole) cm^{-1}; **^{1}H NMR** (500 MHz, d_6-DMSO): δ = 4.41 (*s*, 3H, H-$C_{6'}$), 7.61 (*d*, $^3J_{2',3'}$ = 8.5 Hz, 2H, H-$C_{3'}$), 8.03 (*d*, $^3J_{2',3'}$ = 8.5 Hz, 2H, H-$C_{2'}$); **^{13}C NMR** (125 MHz, d_6-DMSO): δ = 40.1 (CH_3, $C_{6'}$), 125.8 (Cq, $C_{4'}$), 128.1 (CH, $C_{3'}$), 129.5 (CH, $C_{2'}$), 135.2 (Cq, $C_{1'}$), 163.2 (Cq, $C_{5'}$); **MS:** *m/z* 195$[MH]^+$.

4-[2-Benzene-sulphonyl-2-(-methyl-tetrazol-5-yl)-vinyl]-benzoic acid methyl ester (177, 178)



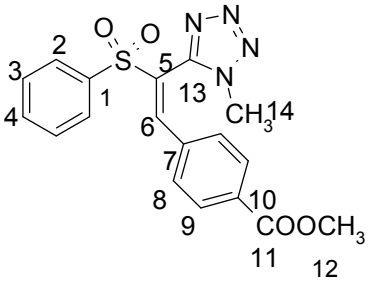
165 **178** **177**

Molecular Formula	$C_8H_7FN_4$
Molecular Weight	384.39 g/mol

TP3: 1.3 equivalents of 3-methyl-1-*p*-tolyltriazene are used in a 3 mmol scale experiment. The reaction is stirred fifteen minutes at room temperature to give 1.09 g of brown crystalline material (N2/N1-isomer = 57:43 based on HPLC analysis). The crude is chromatographed to give 757 mg of N2-isomer **177** (66 % yield) and 161 mg of N1-isomer **178** (14% yield).

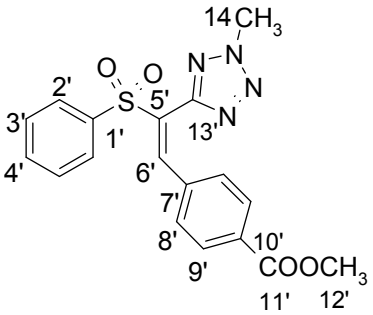
Compound characterization data:

N1-Isomer (**178**)



mp: 158-160 °C; **TLC:** R_f (hexane / AcOEt 3:2) = 0.26; **HPLC:** 9.35 min; **UV** (EtOH): λ_{max}, nm (ε): 288 (27890); **IR:** ν 3050 (*w*, ν(C-H)), 2950 (*w,* ν(-CH_3)), 2000-1750 (*w,* overtones γ(C-H, Ph)), 1727 (v*s,* ν(C=O)), 1641(*s,* ν(C=C)), 1446 (*s,* ν(C=C)), 1321 (*s*, $\nu_{asim}(SO_2)$), 1285 (*s*, ν(C-O)), 1148 (*s,* $\nu_{sim}(SO_2)$) cm^{-1}; **Raman:** ν 1720 (*w*, ν(C=O)), 1642 (*s*, ν(C=C)), 1610 (*s*, ν(C=C)), 1517 (*w*, tetrazole) cm^{-1}; **^{1}H NMR** (500 MHz, d_6-DMSO): δ = 3.75 (*s*, 3H, H-C_{12}), 3.83 (s, 3H, H-C_{14}), 7.19 (*d*, $^3J_{8,9}$ = 8.4 Hz, 2H, H-C_8), 7.67 (*dd*, ^3J = 7.7 Hz, 2H, H-C_3), 7.81 (*m*, 3H, H-$C_{2,4}$), 7.91 (*d*, $^3J_{8,9}$ = 8.4 Hz, 2H, H-C_9), 8.60 (*s*, 1H, H-C_6); **^{13}C NMR** (125 MHz, d_6-DMSO): δ = 40.5 (CH_3, C_{14}), 52.8 (CH_3, C_{12}), 127.2 (CH, C_2), 128.8 (CH, C_9), 130.3 (CH, Cq, $C_{3,5}$), 130.6 (CH, C_8), 132.5 (Cq, C_{10}), 135.3 (CH, C_4), 135.4 (Cq, C_7), 137.9 (Cq, C_1), 147.2 (CH, C_6), 147.8 (Cq, C_{13}), 165.7 (Cq, C_{11}); **HR-MS:** calc'd for $[MH]^+$ = 385.0965, found 385.0967 (ΔM (ppm) = 0.4), calc'd for $[M+Na]^+$ = 407.0785, found 407.0786 (ΔM (ppm) = 0.4).

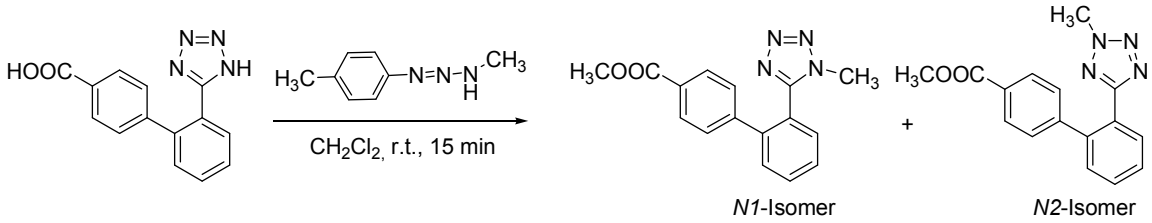
N2-Isomer (**177**)



mp: 156-158 °C; **TLC:** R_f (hexane / AcOEt 3:2) = 0.19; **HPLC:** 9.54 min.; **UV** (EtOH): λ_{max}, nm (ε): 286 (25620); **IR:** ν 2951 (*w*, ν(C-H)), 2000-1800 (*w*, overtones γ(C-H, Ph)), 1715 (*s*, ν(C=O)), 1639 (*m*, ν(C=C)), 1447 (*w*, ν(C=C)), 1326 (*s*, $\nu_{asim}(SO_2)$), 1287 (*s*, ν(C-O)), 1158 (*s,* $\nu_{sim}(SO_2)$) cm^{-1}; **Raman:** 1718 (*w*, ν(C=O)), 1641 (*s*, ν(C=C)), 1639 (*s*, (C=C)), 1509 (*w*, tetrazole) cm^{-1}; **^{1}H NMR** (500 MHz, d_6-DMSO): δ = 3.83 (*s*, 3H, H-$C_{12'}$), 4.40 (*s*, 3H, H-$C_{14'}$), 7.31 (*d*, $^3J_{8',9'}$ = 8.4 Hz, 2H, H-$C_{8'}$), 7.65 (*dd*, ^3J = 7.7, 8 Hz, 2H, H-$C_{3'}$), 7.75 (*t*, ^3J = 7.7 Hz, 1H, H-$C_{4'}$), 7.86 (*m*, 4H, H-$C_{2',9'}$), 8.43 (*s*, 1H, H-$C_{6'}$);

^{13}C NMR (125 MHz, d_6-DMSO): δ = 34.4 (CH_3, $C_{14'}$), 52.9 (CH_3, $C_{12'}$), 128.8 (CH, $C_{2'}$), 129.8 (CH, $C_{9'}$), 130.0 (CH, $C_{3'}$), 130.9 (CH, $C_{8'}$), 131.7 (Cq, $C_{10'}$), 131.8 (Cq, $C_{5'}$), 134.8 (CH, $C_{4'}$), 136.3 (Cq, $C_{7'}$), 138.8 (Cq, $C_{1'}$), 144.8 (CH, $C_{6'}$), 156.9 (Cq, $C_{13'}$), 165.9 (Cq, $C_{11'}$); **HR-MS:** calc'd for $[MH]^+$ = 385.0965, found 385.0965 (ΔM (ppm) < 0.1), calc'd for $[M+Na]^+$ = 407.0785, found 407.0785 (ΔM (ppm) < 0.1); **X-Ray:** the structure of the N2-isomer was confirmed by X-ray analysis (See X-ray discussion; Chapter 4).

4-[1-Ethylidene-2-(*N*-methyl-terazol-5-yl)-penta-2,4-dienyl]-benzoic acid methyl ester (149, 150)



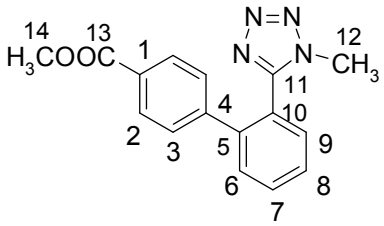
187 **149** **150**

Molecular Formula	$C_{16}H_{14}N_4O_2$
Molecular Weight	294.26 g/mol

TP3: 1.25 equivalents of 3-methyl-1-*p*-tolyltriazene are used in a 4 mmol scale experiment. The reaction is stirred four hours at room temperature to give 1.03 g of brown crystalline material (N2/N1-isomer = 73:27 based on HPLC analysis). The crude is chromatographed to give 620 mg of N2-isomer **150** as a brown oil (53 % yield), and 200 mg of N1-isomer **149** as a white crystalline material (17 % yield).

Compound characterization data:

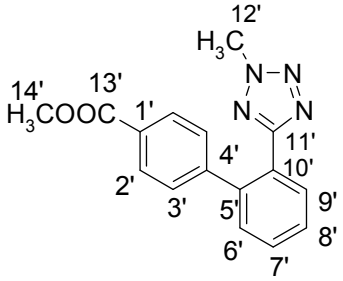
N1-Isomer (**149**)



mp: 117-120 °C; **TLC:** R_f (hexane / EtOAc 3:2) = 0.20; **HPLC:** 12.02; **UV** (MeOH): λ_{max}, nm (ε): 260 (1790), 200 (3640); **IR:** ν 3100 (*w*, ν(C-H)), 2950 (*w*, ν(C-H)), 2000-1800 (*w*, overtones γ(C-H, Ph)), 1725 (*vs*, ν(C=O)), 1610 (*m*, ν(C=C)), 1545 (*w*, tetrazole), 1282 (*vs*, ν(C-O)), 776 (*m*, δ(C-H, Ph)) cm^{-1}; **Raman:** ν 1719 (*w*, ν(C=O)), 1610 (*s*, ν(C=C)), 1543 (*w*, tetrazole) cm^{-1}; **^{1}H NMR** (500 MHz, d_6-DMSO): δ = 3.56 (*s*,

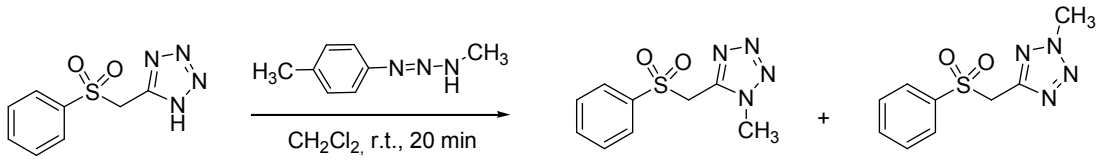
3H, H-C_{12}), 3.85 (*s*, 3H, H-C_{14}), 7.24 (*d*, $^3J_{2,3}$ = 8.5 Hz, 2H, H-C_3), 7.74 (*m*, 4H, H-$C_{6,7,8,9}$), 7.90 *(d*, $^3J_{2,3}$ = 8.5 Hz, 2H, H-C_2); **^{13}C NMR** (125 MHz, d_6-DMSO): δ = 33.8 (CH_3, C_{12}), 52.3 (CH_3, C_{14}), 122.3 (CH, C_3), 128.7 (CH, Ar), 128.8 (CH, Ar), 128.9 (CH, Ar), 129.4 (Cq, C_1), 130.4 (CH, Ar), 131.1 (CH, C_2), 131.8 (Cq, C_5), 140.6 (Cq, C_{10}), 143.6 (Cq, C_4), 154.1 (Cq, C_{11}), 165.8 (Cq, C_{13}); **MS:** *m/z* 295 $[MH]^+$; **HR-MS:** calc'd for $[MH]^+$ = 295.1190, found 95.1190 (ΔM (ppm) < 0.1), calc'd for $[M+Na]^+$ = 317.1009, found 317.1009 (ΔM (ppm) = 0.1).

N2-Isomer (**150**)



TLC: R_f (hexane / EtOAc 3:2) = 0.35; **HPLC:** 14.03 min.; **UV** (MeOH): λ_{max}, nm (ε): 259 (1270), 233 (2100), 200 (3870); **IR:** ν 3060 (*w*, ν(C-H)), 2953 (*w*, ν(-CH_3)), 2000-1900 (*w*, overtones γ(C-H, Ph)), 1721 (v*s*, ν(C=O)), 1610 (*m*, ν(C=C)), 1526 (*w*, tetrazole), 1281 (v*s*, ν(C-O)), 756 (*s*, δ(C-H, Ph)) cm^{-1}; **Raman:** ν 1721 (w, ν(C=O)), 1610 (*s,* ν(C=C)), 1526 (*w,* tetrazole) cm^{-1}; **^{1}H NMR** (500 MHz, d_6-DMSO): δ = 3.86 (*s*, 3H, H-$C_{12'}$), 4.29 (*s*, 3H, H-$C_{14'}$), 7.29 (*d*, $^3J_{2',3'}$ = 6.5 Hz, 2H, H-$C_{3'}$), 7.53 (*m*, 1H, H-$C_{6'}$), 7.64 (*m*, $^3J_{8',9'}$ = 7.5 Hz, 2H, H-$C_{7',8'}$), 7.81 (*m*, $^3J_{8',9'}$ = 7.5 Hz, 1H, H-$C_{9'}$), 7.90 (*d*, $^3J_{2',3'}$ = 6.5 Hz, 2H, H-$C_{2'}$); **^{13}C NMR** (125 MHz, d_6-DMSO): δ = 48.6 (CH_3, $C_{12'}$), 52.2 (CH_3, $C_{14'}$), 127.7 (CH, $C_{3'}$), 128.3 (CH, Ar), 128.5 (CH, Ar), 128.9 (CH, Ar), 129.4 (Cq, $C_{1'}$), 130.4 (CH, Ar), 130.5 (CH, $C_{2'}$), 130.7 (Cq, $C_{5'}$), 140.2 (Cq, $C_{10'}$), 145.2 (Cq, $C_{4'}$), 164.2 (Cq, $C_{11'}$), 166.1 (Cq, $C_{13'}$); **MS:** *m/z* 295 $[MH]^+$;

5-Benzenesulphonylmethyl)-*N*-methyl-tetrazole (179, 180)



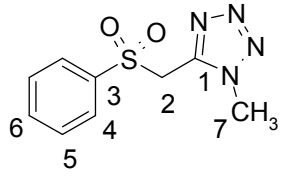
75 *N1*-Isomer **180** *N2*-Isomer **179**

Molecular Formula	$C_9H_{10}N_4O_2S$
Molecular Weight	238.24 g/mol

TP3: 1.4 equivalents of 3-methyl-1-*p*-tolyltriazene are used in a 10 mmol scale experiment. The reaction is stirred twenty minutes at room temperature to give 2.78 g of brown crystalline material (N2/N1-isomer = 52/48 based on HPLC analysis). The crude is chromatographed (elution system toluene / ethyl acetate 3:1) to give 907 mg of N2-isomer **179** (52 % yield) and 855 mg of N1-isomer **180** (48 % yield).

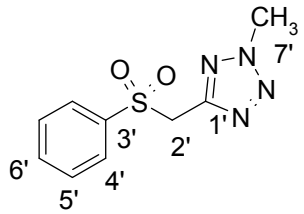
Compound characterization data:

N1-Isomer (**180**)



mp: 182-184 °C; **TLC:** R_f (toluene / EtOAc 3:1) = 0.21; **HPLC:** 4.55 min; **UV** (acetonitrile): λ_{max}, nm (ε): 273 (1080), 266 (1290), 259 (918), 219 (12810), 194 (39970); **IR:** ν 3095 (*w*, ν(C-H)), 3072 (*w*, ν(C-H)), 3006 (*m*, ν(C-H)), 2954 (*m*, ν(C-H)), 2000-1750 (*w*, overtones γ(C-H, Ph), 1584 (*w*, ν(C=C)), 1522 (*w*, tetrazole), 1466 (*m*, ν(C=C)), 1448 (*s*, ν(C=C)), 1315 (*s*, $\nu_{asim}(SO_2)$), 1159 (*s*, $\nu_{sim}(SO_2)$) cm^{-1}; **Raman:** 1522 (*w*, tetrazole), 1160 (*m*, $\nu_{sim}(SO_2)$) cm^{-1}; **^{1}H NMR** (500 MHz, d_6-DMSO): δ = 4.12 (*s*, 3H, H-C_7), 5.48 (*s*, 2H, C-H_2), 7.73 (*m*, 2H, H-C_4), 7.86 (*m*, 3H, H-$C_{5,6}$); **^{13}C NMR** (125 MHz, d_6-DMSO): δ = 34.2 (CH_3, C_7), 49.0 (CH_2, C_2), 128.2 (CH, C_4), 129.5 (CH, C_5), 134.7 (CH, C_6), 137.6 (Cq, C_3), 146.5 (Cq, C_1); **MS:** *m/z* 239 $[MH]^+$, 237 $[M-H]^-$; **HR-MS:** calc'd for $[MH]^+$ = 239.05972, found 239.0596 (ΔM (ppm) = 0.3), calc'd for $[MNH_4]^+$ = 256.0863, found 256.0862 (ΔM (ppm) = 0.2), calc'd for $[MNa]^+$ = 261.047, found 261.0416 (ΔM (ppm) = 0.2).

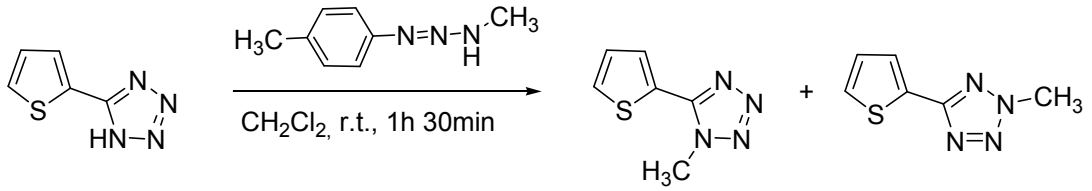
N2-Isomer (**179**)



mp: 137-139 °C; **TLC:** R_f (toluene / EtOAc 3:1) = 0.35; **HPLC:** 4.62 min.; **UV** (acetonitrile): λ_{max}, nm (ε): 272 (1190), 265 (1410), 259 (990), 216 (16890), 194 (41680); **IR:** ν 3098 (*w*, ν(C-H)), 3061 (*w*, ν(C-H)), 2995 (*s*, ν(C-H)), 2936 (*m*, ν(C-H)), 2000-1750 (*w*, overtones γ(C-H, Ph), 1584 (*w*, ν(C=C)), 1494 (*w*, tetrazole), 1445 (*s*, ν(C=C)),

1319 (*s*, $\nu_{asim}(SO_2)$), 1160 (*s*, $\nu_{sim}(SO_2)$) cm^{-1}; **^{1}H NMR** (500 MHz, d_6-DMSO): δ = 4.33 (s, 3H, H-$C_{7'}$), 5.13 (*s*, 2H, C-$H_{2'}$), 7.62 (*m*, 2H, H-$C_{4'}$), 7.73 (*m*, 3H, H-$C_{5',6'}$); **^{13}C NMR** (125 MHz, d_6-DMSO): δ = 39.5 (CH_3, $C_{7'}$), 51.6 (CH_2, $C_{2'}$), 128.1 (CH, $C_{4'}$), 129.3 (CH, $C_{5'}$), 134.2 (CH, $C_{6'}$), 138.2 (Cq, $C_{3'}$), 156.1 (Cq, $C_{1'}$); **MS:** *m/z* 239 $[MH]^+$, 237 $[M-H]^-$; **HR-MS:** calc'd for $[MH]^+$ = 239.05972, found 239.0596 (ΔM (ppm) = 0.5), calc'd for $[MNH_4]^+$ = 256.0863, found 256.0862 (ΔM (ppm) = 0.4), calc'd for $[MNa]^+$ = 261.047, found 261.0415 (ΔM (ppm) = 0.6).

N-Methyl-5-thiophen-2-yl-tetrazole (181, 182)



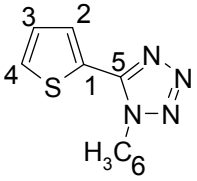
109 *N1*-Isomer **182** *N2*-Isomer **181**

Molecular Formula	$C_6H_6N_4S$
Molecular Weight	166.21 g/mol

TP3: 1.5 equivalents of 3-methyl-1-*p*-tolyltriazene are used in a 0.86 mmol scale experiment. The reaction is stirred two hours at room temperature to give 300 mg of a yellow solid (N2/N1-isomer = 66:34 based on HPLC analysis). The crude is chromatographed (elution system hexane / ethyl acetate 5:1) to give 78 mg of N2-isomer **181** (55 % yield) and 60 mg of N1-isomer **182** (42 % yield) as an off white cristalline materials.

Compound characterization data:

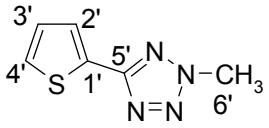
N1-Isomer (**182**)



mp: 110-111 °C; **TLC:** R_f (hexane / AcOEt 5:1) = 0.05; **HPLC:** 3.37 min; **UV UV** (MeOH): λ_{max}, nm (ε): 271 (8130), 254 (7900); **IR:** ν 3089 (*s*, ν(C-H)), 3079 (*w*, ν(C-H)), 2960 (*w*, ν(CH_3), 1575 (*s*, thiophene), 1489 (*s*, tetrazole), 1448 (*s*, thiophene) cm^{-1}; **^{1}H NMR** (400 MHz, d_6-DMSO): δ = 4.20 (*s*, 3H, H-C_6), 7.29 (*dd*, $^3J_{3,4}$ = 5.0 Hz, 1H, H-C_3),

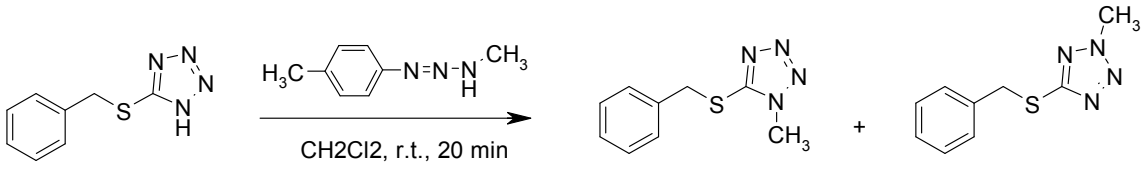
7.81 (*d*, $^3J_{2,3}$ = 3.8 Hz, 1H, H-C_2), 7.92 (*d*, $^3J_{3,4}$ = 5.0 Hz, 1H, H-C_4); **^{13}C NMR** (100 MHz, d_6-DMSO): δ = 35.2 (CH_3, C_6), 124.0 (Cq, C_1), 128.8 (CH, C_3), 130.4 (CH, C_2), 131.2 (CH, C_4), 149.4 (Cq, C_5); **HR-MS:** calc'd for $[M+H]^+$ = 167.0386, found 167.0386 (ΔM (ppm) = 0.2), calc'd for $[M+Na]^+$ = 189.0205, found 189.0205 (ΔM (ppm) = 0.3).

N2-Isomer (**181**)



mp: 84-85 °C; **TLC:** R_f (hexane / AcOEt 5:1) = 0.22; **HPLC:** 5.75 min; **UV** (MeOH): λ_{max}, nm (ε): 268 (11120), 255 (10620); **IR:** ν 3119 (*s*, ν(C-H)), 3096 (*w*, ν(C-H)), 3077 (*w*, ν(C-H)), 2957 (*w*, ν(CH_3), 1573 (*s*, thiophene), 1478 (*s*, tetrazole) cm^{-1};**^{1}H NMR** (400 MHz, d_6-DMSO): δ = 4.40 (*s*, 3H, H-$C_{6'}$), 7.25 (*dd*, ^3J = 5.02 Hz, 1H, H-$C_{3'}$), 7.78 (*d*, $^3J_{2',3'}$ = 3.3 Hz, 1H, H-$C_{2'}$), 7.80 (*d*, $^3J_{3',4'}$ = 5.02 Hz, 1H, H-$C_{4'}$); **^{13}C NMR** (100 MHz, d_6-DMSO): δ = 36.2 (CH_3, $C_{6'}$), 127.7 (CH, $C_{3'}$), 128.3 (Cq, $C_{1'}$), 128.4 (CH, $C_{2'}$), 129.0 (CH, $C_{4'}$), 160.2 (Cq, $C_{5'}$); **HR-MS:** calc'd for $[M+H]^+$ = 167.0386, found 167.0386 (ΔM (ppm) = 0.1), calc'd for $[M+Na]^+$ = 189.0205, found 189.0205 (ΔM (ppm) = 0.3).

5-Benzylsulfanyl-*N*-methyl-tetrazole (183, 184)



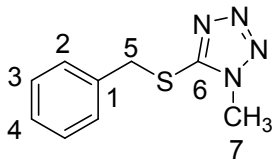
17 *N1*-Isomer **184** *N2*-Isomer **183**

Molecular Formula	$C_9H_{10}N_4S$
Molecular Weight	206.27 g/mol

TP3: 1.5 equivalents of 3-methyl-1-*p*-tolyltriazene are used in a 1.87 mmol scale experiment. The reaction is stirred one hour at room temperature to give 400 mg of an orange oil (N1/N2-isomer = 52:48 based on HPLC analysis). The crude is chromatographed (elution system hexane / ethyl acetate 5:1) to give 205 mg of N2-isomer **183** (53 % yield) and 125 mg of N1-isomer **184** (32 % yield).

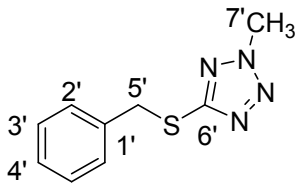
Compound characterization data:

N1-Isomer (**184**)



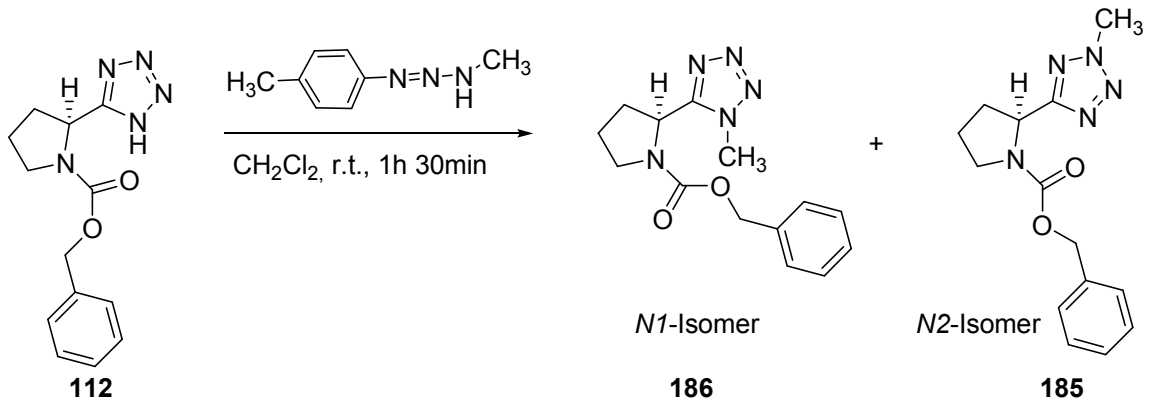
TLC: R_f (Hexane / EtOAc 5:1) = 0.06; **HPLC:** 6.54 min; **IR:** ν 3086 (*w*, ɣ(C-H)), 3062 (*w*, ɣ(C-H)), 3030 (*w*, ɣ(C-H)), 2949 (*w*, ɣ(C-H)), 1958-1813 (*w*, overtones γ(C-H, Ph)), 1585 (*w*, ɣ(C=C)), 1495 (*s*, ɣ(C=C)), 1455 (*w*, ɣ(C=C)), 700 (*w*, γ(Ph) cm^{-1}; **^{1}H NMR** (400 MHz, d_6-DMSO): δ = 3.84 (*s*, 3H, H-C_7), 4.52 (*s*, 2H, C-H_5), 7.31 (*m*, 3H, H-$C_{3,4}$), 7.40 (*m*, 2H, H-C_2); **^{13}C NMR** (100 MHz, d_6-DMSO): δ = 33.5 (CH_3, C_7), 36.7 (CH_2, C_5), 127.7 (CH, C_4), 128.5 (CH, C_3), 128.9 (CH, C_2), 136.5 (Cq, C_1), 153.1 (Cq, C_6); **HR-MS:** calc'd for $[M+H]^+$ = 207.0699, found 207.0698 (ΔM (ppm) = 0.5), calc'd for $[M+Na]^+$ = 229.0518, found 229.0517 (ΔM (ppm) = 0.4).

N2-Isomer (**183**)



TLC: R_f (Hexane / EtOAc 5:1) = 0.20; **HPLC:** 7.90 min; **UV** (MeOH): λ_{max}, nm (ε): 243 (2900); **IR:** ν 3063 (*w*, ɣ(C-H)), 3030 (*w*, ɣ(C-H)), 2956 (*w*, ɣ(C-H)), 2930 (*w*, ɣ(C-H)), 1954-1808 (*w*, overtones γ(C-H, Ph)), 1602 (*w*, ɣ(C=C)), 1496 (*m*, ɣ(C=C)), 1454 (*s*, ɣ(C=C)), 702 (*w*, γ(Ph) cm^{-1}; **^{1}H NMR** (400 MHz, d_6-DMSO): δ = 4.33 (*s*, 3H, H-$C_{7'}$), 4.45 (*s*, 2H, C-$H_{5'}$), 7.29 (*m*, 3H, H-$C_{3',4'}$), 7.40 (*m*, 2H, H-$C_{2'}$); **^{13}C NMR** (100 MHz, d_6-DMSO): δ = 35.4 (CH_3, $C_{7'}$), 39.8 (CH_2, $C_{5'}$), 127.4 (CH, $C_{4'}$), 128.4 (CH, $C_{3'}$), 128.9 (CH, $C_{2'}$), 137.0 (Cq, $C_{1'}$), 162.4 (Cq, $C_{6'}$); **HR-MS:** calc'd for $[M+H]^+$ = 207.0699, found 207.0697 (ΔM (ppm) = 0.9), calc'd for $[M+Na]^+$ = 229.0518, found 229.0518 (ΔM (ppm) = 0.3).

(*S*)-2-(*N*-Methyl-tetrazol-5-yl)-pyrrolidine-1-carboxylic acid benzyl ester (185, 186)



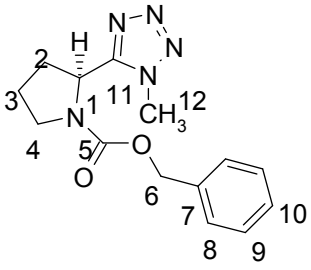
112 **186** **185**

CAS Registry Number	920748-45-4
Molecular Formula	$C_{14}H_{17}N_5O_2$
Molecular Weight	287.32 g/mol
Analysis Ref.	V. Aureggi, G. Sedelmeier, Novartis Pharma AG, **2007**, WO 2007/009716

TP3: 1.5 equivalents of 3-methyl-1-*p*-tolyltriazene are used in a 8 mmol scale experiment. The reaction is stirred one and half hour at room temperature to give 2.61 g of a brown oil (N2/N1-isomer = 75:25 based on HPLC analysis). The crude is chromatographed (elution system hexane / ethyl acetate 3 : 1) to give 1.4 g of N2-isomer **185** (61 % yield) and 710 mg of N1-isomer **186** (31 % yield) as colorless oils.

Compound characterization data:

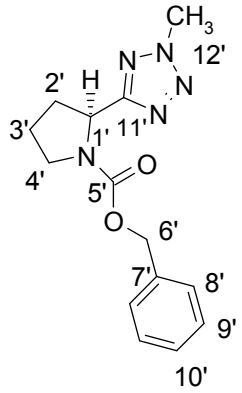
N1-Isomer (**186**)



TLC: R_f (hexane / AcOEt 4:1) = 0.08**; HPLC:** 7.08 min; **UV** (EtOH): λ_{max}, nm (ε): 258 (21); **IR:** ν 3056 (*w*, ν(C-H)), 3034 (*w*, ν(C-H)), 2996 (*w*, ν(C-H)), 2960 (*w*, ν(CH_3)), 1703 (*s*, ν(C=O)), 1468 (*w*, ν(C=C)), 1414 (*s*, ν(C-N)), 1110 (*m*, ν(C-O)), 751 (*m*, γ(C-H, Ph), 704 (*w*, γ(Ph)) cm^{-1}; **^{1}H NMR** (400 MHz, d_6-DMSO, 300 K) Rotamers (4:3): δ = 2.02 (*m*, 2H, H-C_3), 2.17 (*m*, 1H, H-C_2), 2.32 (*m*, 1H, H-C_2), 3.54 (*m*, 2H, H-C_4), 3.81 (*s*, 3H, H-C_{12}, rotamers 4:3, minor rotamer), 4.10 (*s*, 3H, H-C_{12}, major rotamer), 4.90 (*m*, 2H, H-C_6, minor rotamer), 5.01 (*m*, 2H, H-C_6, major rotamer), 5.21 (*m*, 1H, H-C_1), 6.99 (*m*, 2H, Ar), 7.33 (*m*, 3H, Ar); (400 MHz, d_6-DMSO, 394 K): δ = 2.02 (*m*, 2H, H-C_3), 2.18 (*m*, 1H, H-C_2), 2.37 (*m*, 1H, H-C_2), 3.60 (*m*, 2H, H-C_4), 3.96 (*br*, 3H, H-C_{12}), 4.96

(*m*, 2H, H-C_6), 5.19 (*m*, 1H, H-C_1), 7.18 (*br*, 2H, Ar), 7.29 (*m*, 3H, Ar); **^{13}C NMR** (125 MHz, d_6-DMSO, 300 K) Rotamers: δ = 23.1, 24.1 (CH_2, C_3), 31.1, 32.2 (CH_2, C_2), 33.3, 33.7 (CH_3, C_{12}), 46.3, 46.8 (CH_2, C_4), 49.7, 50.2 (CH, C_1), 66.2, 66.3 (CH_2, C_6), 127.5, 127.9 (CH, Ar), 127.9 (CH, C_{10}), 128.3, 128.4 (CH, Ar), 136.3, 136.7 (Cq, C_7), 153.2, 154.0 (Cq, C_5), 156.3, 156.7 (Cq, C_{11}); **MS:** *m/z* 288 $[MH]^+$.

N2-Isomer (**185**)



TLC: R_f (hexane / AcOEt 4:1)= 0.31**; HPLC:** 8.03 min; **UV** (MeOH): λ_{max}, nm (ε): 258 (6), 205 (418); **IR:** ν 3064 (*w*, ν(C-H)), 3033 (*w*, ν(C-H)), 2957 (*w*, ν(C-H)), 2881 (*w*, ν(C-H)), 1704 (*s*, ν(C=O)), 1586 (*w*, ν(C=C)), 1498 (*w*, ν(C=C)), 1447 (*m*, ν(C=C)), 1412 (*s*, ν(C-N)), 1116 (*s*, ν(C-O)), 741 (*w*, γ(C-H, Ph)), 699 (*w*, γ(Ph) cm^{-1}; **^{1}H NMR** (400 MHz, d_6-DMSO, 300 K) rotamers (1:1): δ = 1.85 (*m*, 1H, H-$C_{2'}$), 1.92 (*m*, 2H, H-$C_{3'}$), 2.30 (*m*, 1H, H-$C_{2'}$), 3.50 (*m*, 2H, H-$C_{4'}$), 4.27, 4.30 (*s*, 3H, H-$C_{12'}$), 4.95 (*m*, 2H, H-$C_{6'}$), 5.17 (*m*, $^3J_{1',2'}$ = 8.0 Hz, 1H, H-$C_{1'}$), 7.01 (*m*, 1H, H-$C_{10'}$), 7.30 (*m*, 4H, H-$C_{8',9'}$); (400 MHz, d_6-DMSO, 394 K): δ = 1.97 (*m*, 3H, H-$C_{2',3'}$), 2.33 (*m*, 1H, H-$C_{2'}$), 3.54 (*m*, 2H, H-$C_{4'}$), 4.23 (*s*, 3H, H-$C_{12'}$), 5.00 (*m*, 2H, H-$C_{6'}$), 5.18 (*br*, 1H, H-$C_{1'}$), 7.21 (*m*, 5H, H-$C_{8',9',10'}$); **^{13}C NMR** (125 MHz, d_6-DMSO, 300 K) rotamers (1:1): δ = 22.7, 23.5 (CH_2, $C_{3'}$), 31.8, 32.8 (CH_2, $C_{2'}$), 39.5 (CH_3, $C_{12'}$), 46.2, 46.7 (CH_2, $C_{4'}$), 52.5, 53.0 (CH, $C_{1'}$), 65.5, 65.9 (CH_2, $C_{6'}$), 127.0, 127.5 (CH, Ar), 127.6, 127.8 (CH, $C_{10'}$), 128.2, 128.4 (CH, Ar), 136.8, 136.9 (Cq, $C_{7'}$), 153.5, 153.8 (Cq, $C_{5'}$), 167.7, 167.9 (Cq, $C_{11'}$); **MS:** *m/z* 288 $[MH]^+$, 244 $[MH\text{-}CO_2]^+$.

5.3. Organocatalysis

5.3.1. Reagents and Solvents

All chemicals were obtained either from commercial suppliers or internal sources and used without further purification unless otherwise stated. All reactions were carried out under an atmosphere of nitrogen or argon. All the products were satisfactorily characterized by melting point, TLC, UV, IR, ^{1}H and ^{13}C NMR, MS, HR-MS and when possible, comparison of their analytical data has been made with available literature data.

5.3.1.1. Reagents

Reagent	Molecular Formula	MW (g/mol)	Quality
Acetic acid	$C_4H_4O_2$	60.05	Fluka ; ≥ 96 %
(*R*)-(+)-*N*-Benzyl-α-methylbenzylamine	$C_{15}H_{17}N$	211.30	Aldrich ; 98 %
Cesium hydroxide Monohydrate	$CsHO.H_2O$	167.93	Fluka ; ≥ 95.0 % (T)
Cyclohexanone	$C_6H_{10}O$	98.15	Fluka ; ≥ 99.5 % (GC)
3,4-Dihydroxy-3-cyclobutene-1,2-dione	$C_4H_2O_4$	114.6	Fluka ; ≥ 97.0 % (NT)
(s)-(-)-α,α-Diphenylprolinol	$C_{17}H_{19}NO$	253.35	Lancaster ; 98 %
Hydrochloric acid	HCl	36.45	Fluka ; 2N standard solution
Isovaleraldehyde	$C_5H_{10}O$	86.14	Fluka ; ≥ 98 %
α-Methylstyrene	C_9H_{10}	118.18	Fluka ; ≥ 98 % (GC)
Ninhydrin	$C_9H_6O_4$	178.14	Fluka ; ≥ 95.0 % (UV)
trans-β-Nitrostyrene	$C_8H_7NO_2$	149.15	Fluka ; ≥ 98.0 % (GC)
Palladium on carbon	Pd	106.4	Engelhard 4505 ; Pd/C 10%
Palladium acetate	$(CH_3CO_2)_2Pd$	224.51	Aldrich ; 99.98%
2-Phenylpropionaldehyde	$C_9H_{10}O$	134.18	Aldrich ; 98 %
Potassium carbonate	K_2CO_3	138.27	Fluka ; ≥ 99 % (AT)
Potassium hydroxide	KOH	56.11	Fluka ; ≥ 86 % (T)
D-Proline	$C_5H_9NO_2$	115.13	Fluka ; ≥ 99 % (NT)
L-Proline	$C_5H_9NO_2$	115.13	Fluka ; ≥ 99.5 % (NT)
Saccharin	$C_7H_5NO_3S$	183.18	Fluka ; ≥ 99.0 % (T)
Sodium hydroxyde	NaOH	40.00	Fluka ; ≥ 98 % (T) Fluka ; solution 2N

Sodium methylate	CH_3ONa	54.02	Fluka ; 95 %
Sulfuric acid	H_2SO_4	98.08	Fluka ; 95/97 % (T)
Trifluoroacetic acid	$C_2F_3O_2H$	114.09	Fluka ; ≥ 98.0 % (T)

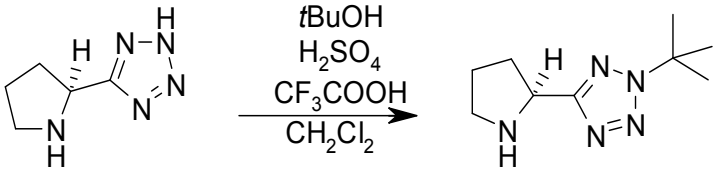
5.3.1.2. Solvents

Solvents	Quality
Acetonitrile	Merck ; for LC ARMAR Chemicals ; d_3-Acetonitrile 99.5 Atom % D
n-Butanol	Aldrich ; ≥ 99.5 %
tert-Butanol	Fluka ; ≥ 99 % (GC)
Chloroform	Fluka ; ≥ 99.5 % (GC) ARMAR Chemicals; $CDCl_3$ 100 Atom % D, stab. with Ag
Dichloromethane	Merck ; for analysis Fluka ; 99.5 % (GC)
Diethyl ether	Fluka; puriss. over molecular sieves
Dimethylsulfoxide	Fluka ; 99.5 % (GC) ARMAR Chemicals ; d_6-DMSO 99.9 Atom % D
Ethanol	Fluka ; absolute, ≥ 99.8 % (V/V) (GC)
Ethyl acetate	Fluka ; 99.5 %
Hexane	Fluka ; ≥ 99.0 % (GC)
Methanol	Fluka ; for analysis
Dichloromethane	Fluka; puriss. over molecular sieves
Tetrahydrofuran	Fluka; puriss. p.a., ≥ 99.5 % (GC)

5.3.2. Synthesis of Pyrrolidine-Tetrazole Derivatives

5.3.2.1. Synthesis of *N*-alkylated pyrrolidine tetrazoles and their salts

2-*t*-Butyl-5-(*S*)-pyrrolidine-2-yl-2*H*-tetrazole (243) and (*R*)-enantiomer (236)

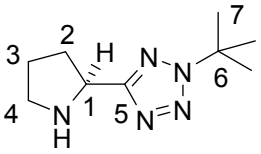


114 **243**

CAS Registry Number	920748-18-1
Molecular Formula	$C_9H_{17}N_5$
Molecular Weight	195.26 g/mol
Analysis Ref.	V. Aureggi, G. Sedelmeier, Novartis Pharma AG, **2007**, WO 2007/009716

A 100 mL, three necked-round bottomed flask, is charged at 0 °C with (*S*)-5-pyrrolidine-2-yl-1*H*-tetrazole **114** (5.56 g, 40 mmol) and trifluoroacetic acid (34.2 mL, 444 mmol). Then sulfuric acid (2.6 mL, 95 - 97 %) and *tert*-butanol (5.92 g, 80 mmol) in dichloromethane (8 mL) are added. The mixture is stirred at room temperature over the night. The mixture is quenched with ice-water (20 mL), and the product is extracted three times with dichloromethane (20 mL portion). The aqueous phase is treated with solid potassium carbonate until pH 8.5 and re-extracted twice with dichloromethane (20 mL portion). The combined organic phase is washed three times with NaOH (0.5 N, 25 mL portion). The solvent is removed to give 7.34 g of the pure product as a yellow oil (94 % yield). The reaction gave the same yield also with the (*R*)-enantiomer.

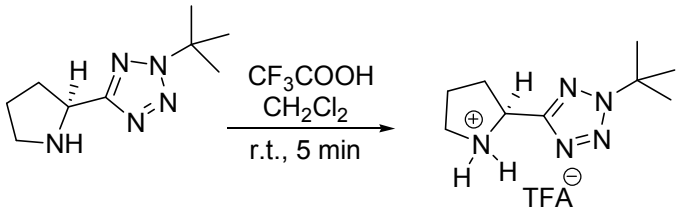
Compound characterization data:



p*Ka* = 8.1; **TLC:** R_f (*n*BuOH / H_2O / AcOH 3:3:1, ninhydrin) = 0.44; **Optical rotation:** (*R*)-enantiomer: $[\alpha]_D^{25}$ = +7.2 ° (in MeOH, c = 1.08); **IR:** ν 2982 (*s*, $\nu_{asim}(CH_3)$), 2960 (*s*, ν(C-H)), 1500 (*w*, tetrazole)), 1478 (*s*, tetrazole)), 1461 (*w*, tetrazole)), 1372 (*s*, $\delta(CH_3)$) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.69 (*s*, 9H, H-C_7), 1.9 (*m*, 3H, H-$C_{2,3}$), 2.22 (*m*,

1H, H-C_2), 2.39 (*br*, NH), 2.97 (*m*, 1H, H-C_4), 3.15 (*m*, 1H, H-C_4), 4.45 (*dd*, $^3J_{1,2}$ = 7 Hz, 1H, H-C_1,); **^{13}C NMR** (125 MHz, d_6-DMSO): δ = 25.2 (CH_2, C_3), 28.7 (CH_3, C_7), 31.8 (CH_2, C_2), 46.3 (CH_2, C_4), 53.1 (CH, C_1), 63.1 (Cq, C_6), 168.5 (Cq, C_5); **MS:** *m/z* 218 $[M+Na]^+$, 196 $[MH]^+$, 70 $[C_4H_8N]^+$; **HR-MS:** calc'd for $[MH]^+$ = 196.1557, found 196.1557 (ΔM (ppm) = 0.1), calc'd for $[M+Na]^+$ = 218.1376, found 218.1376 (ΔM (ppm) = 0.2).

(*R*)-2-(2-*t*-Butyl-2*H*-tetrazol-5-yl) pyrrolidinium trifluoro acetate (244)

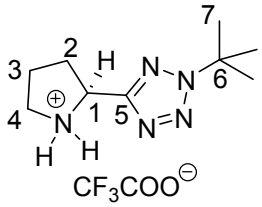


243 **244**

CAS Registry Number	920748-33-0
Molecular Formula	$C_{11}H_{18}F_3N_5O_2$
Molecular Weight	309.28 g/mol
Analysis Ref.	V. Aureggi, G. Sedelmeier, Novartis Pharma AG, **2007**, WO 2007/009716

A 10 mL round bottomed flask, is charged at room temperature, with 2-*tert*-butyl-5-(*R)*-2-pyrrolidine-2-yl-2*H*-tetrazole **243** (390 mg, 2 mmol) in dichloromethane (2 mL), then trifluoroacetic acid (228 mg, 2 mmol) is added. The mixture is stirred five minutes at room temperature and then the solvent is removed to obtain 615 mg of product as a brown crystalline material in ≥ 99 % yield.

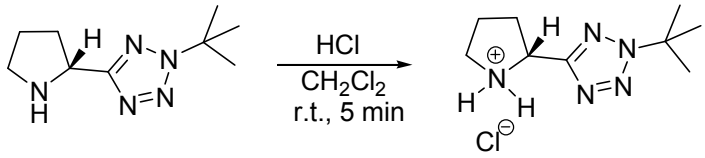
Compound characterization data:



mp: 87-90 °C; **TLC:** R_f (*n*BuOH / H_2O / AcOH 3:3:1, ninhydrin) = 0.43; **UV** (EtOH): λ_{max}, nm (ε): 204 (2860); **IR:** ν 2988 (*m*, ν(C-H)), 2559 (*brm*, ν(N-H)), 1658 (*s*, ν(C=O, TFA)), 1508 (*w*, tetrazole), 1375 (*m*, δ(CH_3)), 1202 (*s*, TFA), 1184 (*s*, TFA), 1136 (*m*, TFA), 836 (*w*, TFA), 724 (*s*, TFA), cm^{-1}; **^{1}H NMR** (400 MHz, d_6-DMSO): δ = 1.71 (*s*, 9H, H-C_7), 2.10 (*m*, 2H, H-C_3), 2.21 (*m*, 1H, H-C_2), 2.44 (*m*, 1H, H-C_2), 3.33 (*m*, 2H, H-C_4), 4.49 (*dd*, $^3J_{1,2}$ = 7.8 Hz, 1H, H-C_1), 9.46 (*br*, 2H, NH_2); **^{13}C NMR** (100 MHz, d_6-

DMSO): δ = 23.6 (CH_2, C_3), 29.1 (CH_3, C_7), 29.5 (CH_2, C_2), 45.6 (Cq, C_4), 53.4 (CH, C_1), 64.8 (Cq, C_5), 162.3 (Cq, C_5); **MS:** *m/z* 196 $[MH\text{-}TFA]^+$, 140 $[MH\text{-}tBu\text{-}TFA]^+$; **X-Ray:** the structure was confirmed by X-ray analysis (See X-ray discussion; Chapter 4).

(*R*)-2-(2-*t*-Butyl-2*H*-tetrazol-5-yl) pyrrolidinium chloride (245)

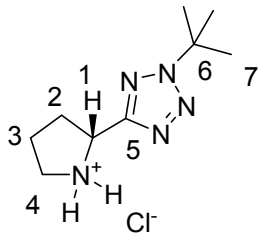


236 **245**

CAS Registry Number	920748-20-5
Molecular Formula	$C_9H_{18}ClN_5$
Molecular Weight	231.71 g/mol
Analysis Ref.	V. Aureggi, G. Sedelmeier, Novartis Pharma AG, **2007**, WO 2007/009716

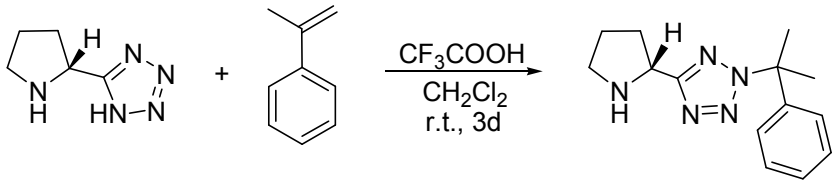
A 5 mL round bottomed flask, is charged at 0 °C, with 2-*tert*-butyl-5-(*R)*-2-pyrrolidine-2-yl-2*H*-tetrazole (195 mg, 1 mmol) in dichloromethane (2 mL) and HCl (2 N, 0.5 mL, 1 mmol). The mixture is stirred five minutes at room temperature and the solvent is removed to obtain 232 mg of the desired product as a pink crystalline material in ≥ 99 % yield.

Compound characterization data:



mp: 160-164 °C, degradation starting at 136 °C; **TLC:** R_f (*n*BuOH / H_2O / AcOH 3:3:1 ninhydrin) = 0.44; **IR:** ν 2984 (*s*, ν(C-H)), 2940 (*s*, ν(C-H), 2821 (*s*, ν(C-H)), 2553 (*brs*, ν(C-H)), 1515 (*w*, tetrazole), 1456 (*m*, tetrazole), 1515 (*w*, tetrazole), 1375 (*s*, δ(CH_3)) cm^{-1}; **^{1}H NMR** (600 MHz, d_6-DMSO): δ = 1.75 (*s*, 9H, H-C_7), 2.23 (*m*, 3H, H-$C_{2,3}$), 2.43 (*m*, 1H, H-C_2), 3.31 (*m*, 2H, H-C_4), 4.48 (*br*, 1H, H-C_1), 9.40 (*br*, 1H, NH), 10.30 (*br*, 1H, NH); **^{13}C NMR** (150 MHz, d_6-DMSO): δ = 23.3 (CH_2, C_3), 29.2 (CH_3, C_7), 30.0 (CH_2, C_2), 45.1 (CH_2, C_4), 52.9 (CH, C_1), 64.5 (Cq, C_6), 161.7 (Cq, C_5); **MS:** *m/z* 196 $[M\text{-}HCl]^+$.

2-(1-Methyl-1-phenyl-ethyl)5-*(R)*-pyrrolidine-2-yl-2*H*-tetrazole (235)

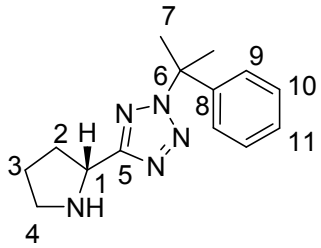


115 **246** **235**

CAS Registry Number	920748-24-9
Molecular Formula	$C_{14}H_{19}N_5$
Molecular Weight	257.33 g/mol
Analysis Ref.	V. Aureggi, G. Sedelmeier, Novartis Pharma AG, **2007**, WO 2007/009716

A 100 mL, three necked round-bottomed flask is charged, at room temperature under an argon atmosphere, with *R*-5-pyrrolidine-2-yl-tetrazole **115** (4.16 g, 30 mmol) and trifluoroacetic acid (4 mL) to obtain a yellow solution. The solution is diluted with dichloromethane (20 mL) and then α-methylstirene (4.55 mL, 35 mmol) are added at room temperature, in three portion over a period of ten minutes. The homogeneous yellow mixture is stirred for three days. The mixture is transferred into a separatory funnel and washed four times with NaOH (1 N, 20 mL portion) and once with water (20 mL) to remove the trifluoroacetic acid. The organic phase is evaporated to give an oil which crystallize by standing twenty minutes at room temperature. The white crystalline material is washed with a small amount of hexane to remove the excess of methylstyrole, and then re-crystallized from methanol / ethyl acetate 1:3 to give the pure product as a white crystalline material (7.10 g, 92 % yield).

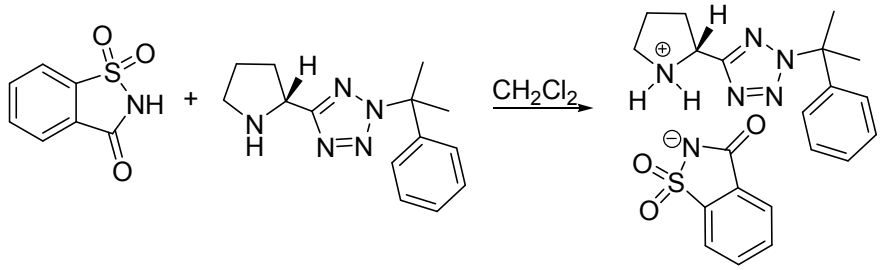
Compound characterization data:



mp: 38-40 °C; **TLC:** R_f (*n*BuOH / H_2O / AcOH 3:3:1, ninhydrin) = 0.5; **HPLC:** 4.80 min; **Optical rotation:** $[\alpha]_D^{25}$ = +4.4° (in MeOH, c = 1.00), $[\alpha]_D^{25}$ = +24.9° (in CH_2Cl_2, c = 1.00); **IR:** ν 3267 (*w*, ν(N-H)), 3091 (*w*, ν(C-H)), 3061 (*w*, ν(C-H)), 3010 (*m*, ν(C-H)), 2992 (*s*, ν(C-H)), 2984 (*s*, ν(C-H)), 2959 (*s*, ν(C-H)), 2863 (*s*, $\nu_{sim}(CH_3)$), 1962-1677 (*w*, overtones γ(C-H, Ph)), 1600 (*w*, ν(C=C)), 1497 (*s*, ν(C=C)), 1448 (*s*, ν(C=C)), 1367 (*s*, $\delta(CH_3)$), 766 (*s*, γ(C-H, Ph)), 697 (*s*, ν(Ph)) cm^{-1}; **^{1}H NMR** (500 MHz, d_6-DMSO): δ = 1.83 (*m*, 3H, H-$C_{2,3}$), 2.09 (s, 6H, H-C_7), 2.10 (*m*, 1H, H-C_2), 2.75 (*br*, 1H, NH), 2.27 (*m*,

1H), 2.87 (*m*, 2H, H-C_4), 4.36 (*dd*, $^3J_{1,2}$ = 7.6, 7.8 Hz, 1H, H-C_1), 7.07 (*m*, 2H, H-C_9), 7.34 (*m*, 3H, H-$C_{10,11}$); **^{13}C NMR** (150 MHz, d_6-DMSO): δ = 25.3 (CH_2, C_3), 28.7 (CH_3, C_7), 31.3 (CH_2, C_2), 46.3 (CH_2, C_4), 53.2 (CH, C_1), 67.8 (Cq, C_6), 124.6 (CH, C_9), 127.6 (CH, C_{11}), 128.7 (CH, C_{10}), 144.2 (Cq, C_8), 168.8 (Cq, C_5); **MS:** *m/z* 258 $[MH]^+$, 140 $[MH\text{-Cumyl}]^+$; **HR-MS:** calc'd for $[MH]^+$ = 258.1713, found 258.1712 (ΔM (ppm) = 0.4); **X-Ray:** the structure was confirmed by X-ray analysis (See X-ray discussion; Chapter 4).

2-[(1-Methyl-1-phenyl-ethyl)-2*H*-tetrazol-5-yl] pyrrolidinium saccharinate (248)

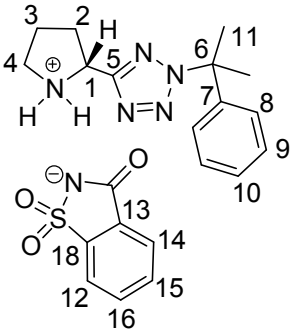


247 **235** **248**

CAS Registry Number	920748-28-3
Molecular Formula	$C_{21}H_{24}N_6O_3S$
Molecular Weight	440.52 g/mol
Analysis Ref.	V. Aureggi, G. Sedelmeier, Novartis Pharma AG, **2007**, WO 2007/009716

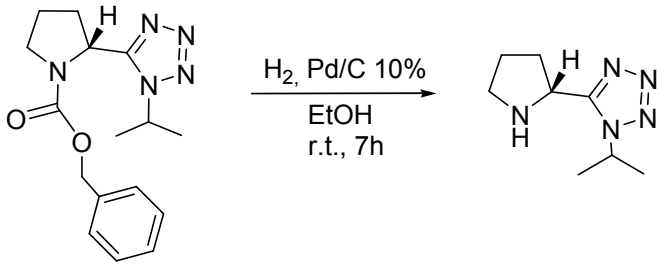
A 10 mL round bottomed flask is charged with 2-(methyl-1phenyl-ethyl)-5-(*R*)-pyrrolidine-2-yl-2*H*-tetrazole (128 mg, 0.5 mmol), and *o*-benzoic acid sulfimide (91 mg, 0.5 mmol) in dichloromethane (2 mL) to obtain a colorless solution. The solvent is removed to obtain a colorless oil which is dissolved in dichloromethane (0.5 mL) and diethyl ether (1 mL). The product crystallized after standing at room temperature for three hours into an open flask. The white crystalline material is filtered, and washed with diethyl ether / dichloromethane (3:1, 1 mL) to give 110 mg of product. The mother liquor is lead standing over the night into a closed flask. The product is filtered to give 110 mg as second crop.

Compound characterization data:



mp: 108-111 °C; **UV** (EtOH): λ_{max}, nm (ε): 264 (204), 201 (6130); **IR:** ν 2993 (*m*, ν(C-H)), 2958 (*m*, ν(C-H)), 2558 (*brm*, ν(N-H)), 1651 (*m*, ν(C=O)), 1587 (*m*, ν(C=C)), 1458 (*m*, ν(C=C)), 1448 (*m*, ν(C=C)), 1335 (*m*, δ(CH_3)), 1152 (*s*, $\nu_{asim}(SO_2)$), 770 (*s*, γ(C-H, Ph)), 700 (*s*, γ(Ph)) cm^{-1}; **^{1}H NMR** (500 Mz, d_6-DMSO): δ = 2.13 (*s*, 6H, H-C_{11}), 2.07 (*m*, 2H, H-C_3), 2.31 (*m*, 2H, H-C_2), 3.35 (*m*, 2H, H-C_4), 5.04 (*dd*, $^3J_{1,2}$ = 8.0 Hz, 1H, H-C_1), 7.13 (*m*, 2H, H-C_8), 7.30 (*m*, 1H, H-C_{10}), 7.34 (*m*, 2H, H-C_9), 7.59 (*m*, 3H, H-$C_{14\text{-}16}$), 7.66 (*m*, 1H, H-C_{12}), 9.48 (*br*, 2H, NH_2^+); **^{13}C NMR** (150 MHz, d_6-DMSO): δ = 23.1 (CH_2, C_3), 28.7 (CH_3, C_{11}), 28.9 (CH_2, C_2), 45.3 (CH_2, C_4), 53.2 (CH, C_1), 69.0 (Cq, C_6), 119.2 (CH, Ar), 122.6 (CH, Ar), 124.7 (CH, C_8), 127.9 (CH, C_{10}), 128.6 (CH, C_9), 131.2 (CH, Ar), 131.7 (CH, Ar), 134.5 (Cq, Ar), 143.5 (Cq, Ar), 145.0 (Cq, Ar), 161.8 (Cq, C_{17}), 167.5 (Cq, C_5); **MS:** *m/z* 258 $[M_B]^+$, 140 $[M_B\text{-Cumyl}]^+$, 182 $[M_A]^-$; **X-Ray:** the structure was confirmed by X-ray analysis (See X-ray discussion; Chapter 4).

1-Isopropyl-5-(*R*)-pyrrolidine-2-yl-1*H*-tetrazole (237)



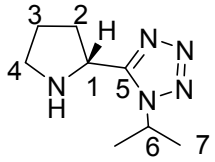
162 **237**

CAS Registry Number	920748-42-1
Molecular Formula	$C_8H_{15}N_5$
Molecular Weight	181.24 g/mol
Ref.	V. Aureggi, G. Sedelmeier, Novartis Pharma AG, **2007**, WO 2007/009716

(*R*)-1-(1-isopropyl-1*H*-tetrazol-5-yl)-pyrrolidine-1-carboxylic acid benzyl ester **162** (2.8 g, 8.89 mmol) and palladium on charcoal (0.3 g, 10 wt %) in ethanol (60 mL) are stirred under hydrogen at room temperature for seven hours. The catalyst is removed by

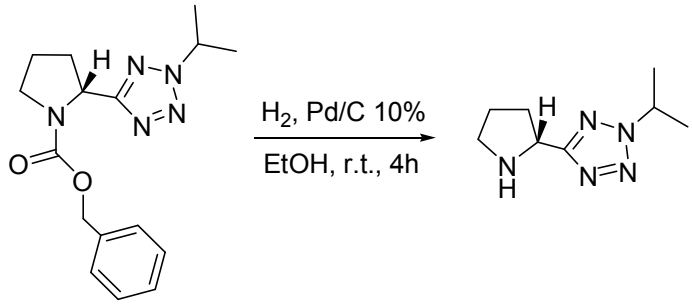
filtration through celite and the celite is washed sequentially twice with ethanol (30 mL portion) and twice with dichloromethane (20 mL). The filtrate is concentrated under reduced pressure (45 °C, 170 to 30 mbar) and dried under vacuum at room temperature for two to five hours ($3.7 \cdot 10^{-1}$ mbar) to affort the desired product as a yellow oil which crystallized as hydrochloride after standing at room temperature (1.69 g, 88 % yield).

Compound characterization data:



mp: 178-180 °C; **TLC:** R_f (*n*BuOH / H_2O / AcOH 3:3:1, ninhydrin) = 0.40; **Optical rotation:** $[\alpha]_D^{25}$ = +5.2 ° (in MeOH, c = 0.80); **IR:** ν 3200-2800 (*brs*, ν(N-H)), 2977 (*s*, ν(C-H)), 2954 (*s*, ν(C-H)), 2880 (*s*, $\nu_{sim}(CH_3)$), 1505 (*w*, tetrazole), 1453 (*s*, tetrazole), 1371 (*s*, δ(CH_3)) cm^{-1}; **^{1}H NMR** (500 MHz, d_6-DMSO) Tautomers (1:1): δ = 1.48 (*d*, $^3J_{6,7}$ = 6.5 Hz, 6H, H-C_7), 1.51 (*d*, H-C_7, $^3J_{6,7}$ = 6.5 Hz), 1.85 (*m*, 1H, H-C_3), 1.96 (*m*, 1H, H-C_3), 2.20 (*m*, 2H, H-C_2), 3.01 (*m*, 1H, H-C_4), 3.07 (*m*, 1H, H-C_4), 4.77 (*dd*, $^3J_{1,2}$ = 7.5 Hz, 1H, H-C_1), 5.04 (*sep*, $^3J_{6,7}$ = 6.5 Hz, 1H, H-C_6), 7.19 (*br*, 1H, NH); **^{13}C NMR** (150 MHz, d_6-DMSO): δ = 22.3 (CH_3, C_7), 22.4 (CH_3, C_7), 24.8 (CH_2, C_3), 30.0 (CH_2, C_2), 46.0 (CH_2, C_4), 50.3 (CH_2, C_6), 50.8 (CH, C_1), 154.0 (Cq, C_5); **HR-MS**: calc'd for $[M+H]^+$ = 182.1400, found 182.1400 (ΔM (ppm) = 0.1), calc'd for $[MNa]^+$ = 204.1220, found 204.1219 (ΔM (ppm) = 0.3); **X-Ray:** the hydrochloride structure was confirmed by X-ray analysis with NH_2^+ every two molecules (See X-ray discussion; Chapter 4).

2-Isopropyl-5-(*R*)-pyrrolidine-2-yl-2*H*-tetrazole (238)



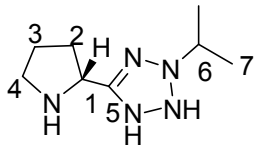
161 **238**

CAS Registry Number	920748-26-1
Molecular Formula	$C_8H_{15}N_5$
Molecular Weight	181.24 g/mol
Ref.	V. Aureggi, G. Sedelmeier, Novartis Pharma AG, **2007**, WO

	2007/009716

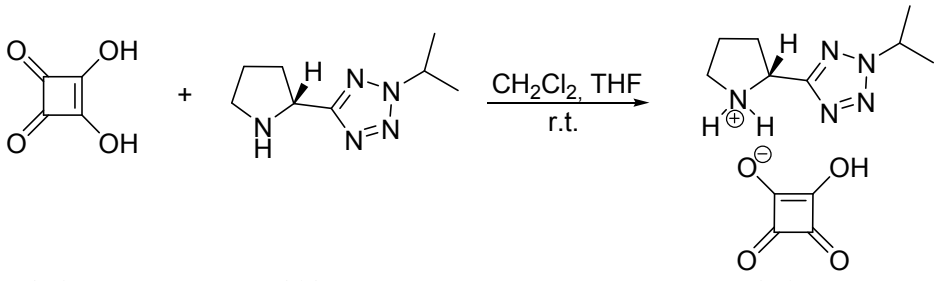
(*R*)-2-(2-Isopropyl-2*H*-tetrazol-5-yl)-pyrrolidine-1-carboxylic acid benzyl ester **161** (9.0 g, 28.53 mmol) and palladium on charcoal (0.9 g, 10 wt %) in ethanol (180 mL) are stirred under hydrogen at room temperature for four hours. The catalyst is removed by filtration through celite and the celite is washed sequentially twice with ethanol (50 mL portion) and twice with dichloromethane (30 mL portion). The filtrate is concentrated under reduced pressure (45 °C, 170 to 30 mbar) and dried under vacuum at room temperature for two to five hours ($3.7 \cdot 10^{-1}$ mbar) to affort the desired product as a yellow oil (5.1 g, 98 % yield).

Compound characterization data:



TLC: R_f (*n*BuOH / H_2O / AcOH 3:3:1, ninhydrin) = 0.42; **Optical rotation:** $[\alpha]_D^{25}$ = +6.6 ° (in MeOH, c = 1.00), $[\alpha]_D^{25}$ = -1.6 ° (in DMSO, c = 1.00), $[\alpha]_D^{25}$ = +15.8 ° (in CH_2Cl_2, c = 1.00); **UV** (EtOH): λ_{max}, nm (ε): 203 (224); **IR:** ν 3334 (*brm*, ν(N-H)), 2978 (*s*, ν(C-H)), 2960 (*w*, ν(C-H)), 2875 (*s*, $\nu_{sim}(CH_3)$), 1499 (*m*, tetrazole), 1458 (*s*, tetrazole), 1372 (*s*, δ(CH_3)) cm^{-1}; **^{1}H NMR** (500 MHz, d_6-DMSO): δ = 1.55 (*d*, $^3J_{6,7}$ = 6.8 Hz, 6H, H-C_7), 1.85 (*m*, 3H, H-$C_{2,3}$), 2.15 (*m*, 1H, H-C_2), 2.90 (*m*, 2H, H-C_4), 4.33 (*br*, NH), 4.43 (*dd*, $^3J_{1,2}$ = 7.3, 6.8 Hz, 1H, H-C_1), 5.07 (*sep*, $^3J_{6,7}$ = 6.7 Hz, 1H, H-C_6); **^{13}C NMR** (125 MHz, d_6-DMSO): δ = 21.8 (CH_3, C_7), 25.3 (CH_2, C_3), 31.2 (CH_2, C_2), 46.2 (CH_2, C_4), 53.1 (CH, C_1), 56.4 (CH, C_6), 168.3 (Cq, C_5); **MS:** *m/z* 182 $[MH]^+$, 113 $[MH\text{-}C_4H_7N]^+$, 70 $[C_4H_8N]^+$; **HR-MS:** calc'd for $[M+H]^+$ = 182.1400, found 182.1400 (ΔM (ppm) = 0.3), calc'd for $[M+Na]^+$ = 204.1220, found 204.1219 (ΔM (ppm) = 0.1).

2-Isopropyl-5-(*R*)-pyrrolidine-2-yl-2*H*-tetrazole squaric acid salt (250)

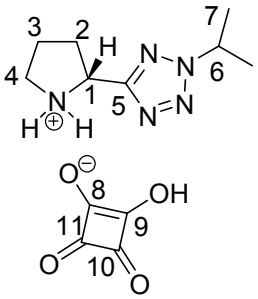


249 **238** **250**

Molecular Formula	$C_{12}H_{17}N_5O_4$
Molecular Weight	295.31 g/mol

A 5 mL round bottomed flask is charged with 2-isopropyl-5-(*R*)-pyrrolidine-2-yl-2*H*-tetrazole **238** (181 mg, 1 mmol) and 3,4-dihydroxy-3-cyclobutene-1,2-dione (114 mg, 1 mmol) in THF (1 mL) and dichloromethane (1 mL) to obtain a brown solution. After standing over the night at room temperature, a mixture 1 : 1 of methanol and chloroform (1 mL) are added to the brown oil. Diethyl ether (1.5 mL) is added at room temperaturen and the product crystallized after standing at room temperature for one day into an open flask as a brown solide.

Compound characterization data:

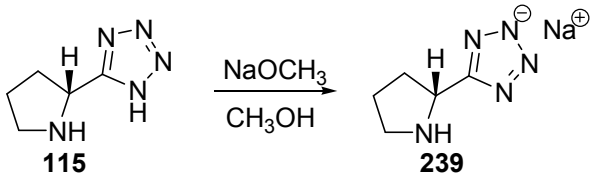


mp: 110-112 °C; **UV**: c = 0.0098 g/L in MeOH: a) λ_{max} 258 (ε = 20604), b) λ_{max} 244 nm (ε = 22089); **Optical rotation**: $[\alpha]_D^{25}$ = +12.8° (in MeOH, c = 1.00); **IR**: ν 3511 (*brs*, ν (O-H), 3393 (*brm*, ν(N-H), 2983 (*brs*, ν(C-H), 1648 (*s*, ν(C=O)), 1562 (*brs*, ν(C=C), tetrazole) cm^{-1}; **^{1}H NMR** (500 MHz, d_6-DMSO): δ = 1.58 (*d*, $^3J_{6,7}$ = 6.8 Hz, 6H, H-C_7), 2.08 (*m*, 2H, H-C_3), 2.26 (*m*, 1H, H-C_2), 2.45 (*m*, 1H, H-C_2), 3.35 (*m*, 2H, H-C_4), 5.02 (*dd*, $^3J_{1,2}$ = 7.8, 8.0 Hz, 1H, H-C_1), 5.16 (*sep*, $^3J_{6,7}$ = 6.8 Hz, 1H, H-C_6), 8.31 (*br*, OH), 9.45 (*br*, NH), 10.09 (*br*, 1H, NH); **^{13}C NMR** (150 MHz, d_6-DMSO): δ = 21.6, 21.8 (CH_3, C_7), 23.2 (CH_2, C_3), 29.0 (CH_2, C_2), 45.3 (CH_2, C_4), 53.1 (CH, C_1), 56.7 (CH, C_6), 161.8 (Cq, C_5), 193.8 (Cq, $C_{8\text{-}11}$); MS: *m/z* 182 $[M_B+H]^+$, 113 $[M_A-H]^+$, 182 $[M_A]^-$; **X-Ray**: the structure was confirmed by X-ray analysis (See X-ray discussion; Chapter 4).

5.3.2.2. Synthesis of pyrrolidine tetrazole metal salts

(*R*)-5-Pyrrolidine-2-yl-tetrazole sodium salt (239)

Method A:

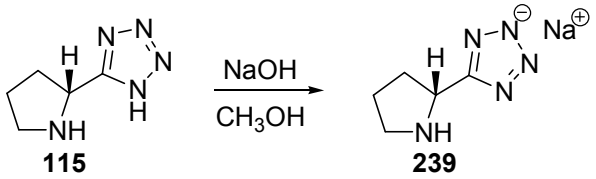


115 **239**

CAS Registry Number	920748-22-7
Molecular Formula	$C_5H_8N_5Na$
Molecular Weight	161.14 g/mol
Ref.	V. Aureggi, G. Sedelmeier, Novartis Pharma AG, **2007**, WO 2007/009716

A 25 mL round bottomed flask is charged, at room temperature, with (*R*)-5-pyrrolidine-2-yl-tetrazole **115** (417 mg, 3 mmol) in methanol (6 mL). Sodium methylate (170 mg, 3 mmol) are added at room temperature and the resulting solution is stirred one hour. The solvent is removed and the product is dried in vacuum at room temperature for three hours to give a white crystalline material in quantitative yield.

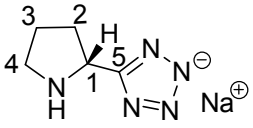
Method B:



115 **239**

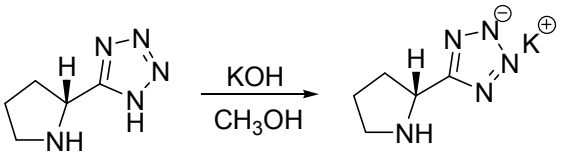
A 10 mL flask is charged at room temperature, with (*R*)-5-pyrrolidine-2-yl-tetrazole **115** (417 mg, 3 mmol) dissolved in NaOH (1 N, 3 mL) and methanol (1 mL). The colorless solution is stirred for twenty minutes at room temperature and then the solvent is removed to give 484 mg of white crystalline material. The product is re-dissolved in methanol (1.5 mL) at 60 °C. The colorless solution is cooled at 0 °C and treated with diethylether (2.5 mL). The product crystallized after standing three hours at room temperature in an open flask to give a white crystalline material in ≥ 99 % yield.

Compound characterization data:



mp: 62-64 °C; **TLC:** R_f (*n*BuOH / water/ AcOH 3:3:1, ninhydrin) = 0.26; **Optical rotation:** $[\alpha]_D^{25}$ = +17.9 ° (in MeOH, c = 0.66); **IR:** ν 2981 (*s*, ν(C-H)), 2963 (*s*, ν(C-H)), 2587 (*brs*, ν(N-H)), 1606 (*brs*, tetrazole), 1455 (*s*, tetrazole), 1440 (*s*, tetrazole), 1422 (*s*, tetrazole), cm^{-1}; **^{1}H NMR** (600 MHz, d_6-DMSO): δ = 1.9 (*m*, 3H, H-$C_{2,3}$), 2.17 (*m*, 1H, H-C_2), 3.10 (*m*, 2H, H-C_4), 4.55 (*dd*, $^3J_{1,2}$ = 7.3, 7.5 Hz, 1H, H-C_1); **^{13}C NMR** (150 MHz, d_6-DMSO): δ = 24.0 (CH_2, C_3), 31.0 (CH_2, C_2), 45.0 (CH_2, C_4), 54.7 (CH, C_1), 166.3 (Cq, C_5); **MS:** *m/z* 140 $[MH-Na]^+$; **HR-MS:** calc'd for $[M-Na]^-$ = 138.0785, found 138.0785 (ΔM (ppm) = 0.2).

(*R*)-5-Pyrrolidine-2-yl-tetrazole potassium salt (240)

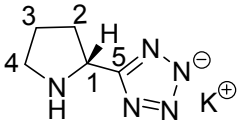


115 **240**

CAS Registry Number	920748-30-7
Molecular Formula	$C_5H_8N_5K$
Molecular Weight	177.26 g/mol
Ref.	V. Aureggi, G. Sedelmeier, Novartis Pharma AG, **2007**, WO 2007/009716

A 10 mL flask is charged at room temperature, with (*R*)-5-pyrrolidine-2-yl-tetrazole (347 mg, 2.5 mmol), and KOH (140 mg, 2.5 mmol) in methanol (4 mL). The colorless solution is stirred for twenty minutes at room temperature and then the solvent is removed to give a white crystalline material (440 mg). The product is re-dissolved in of methanol (1.5 mL) at 60 °C. The colorless solution is cooled at room temperaure and treated with diethylether (2.5 mL). The solution is cooled at 0 °C and the product crystallized after standing in an open flask three hours at room temperature to give a whie crystalline material in ≥ 99 % yield.

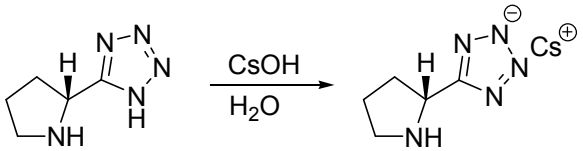
Compound characterization data:



mp: 58-62 °C; **TLC:** R_f (*n*BuOH / water/ AcOH 3:3:1, ninhydrin) = 0.24; **Optical rotation:** $[\alpha]_D^{25}$ = +22.7 ° (in MeOH, c = 0.99); **IR:** ν 2975 (*brs*, ν(C-H)), 2879 (*brm*, ν(C-H)), 2581 (*brw*, ν(N-H)), 1489 (*w*, tetrazole), 1429 (*brs*, tetrazole), 1410 (*brs*, tetrazole)

cm^{-1}; **^{1}H NMR** (600 MHz, d_6-DMSO): δ = 1.69 (*m*, 3H, H-$C_{2,3}$), 1.94 (*m*, 1H, H-C_2), 2.66 (*m*, 1H, H-C_4), 3.02 (*m*, 1H, H-C_4), 4.09 (*dd*, $^3J_{1,2}$= 6.8 Hz, 1H, H-C_1); **^{13}C NMR** (125 MHz, d_6-DMSO): δ = 25.4 (CH_2, C_3), 32.5 (CH_2, C_2), 44.2 (CH_2, C_4), 54.9 (CH, C_1), 173.5 (Cq, C_5); **HR-MS:** calc'd for $[M-K]^-$ = 138.0785, found 138.0785 (ΔM (ppm) < 0.1).

(*R*)-5-Pyrrolidine-2-yl-tetrazole cesium salt (241)

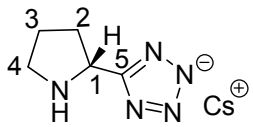


115 **241**

CAS Registry Number	920748-36-3
Molecular Formula	$C_5H_8N_5Cs$
Molecular Weight	217.06 g/mol
Analysis Ref.	V. Aureggi, G. Sedelmeier, Novartis Pharma AG, **2007**, WO 2007/009716

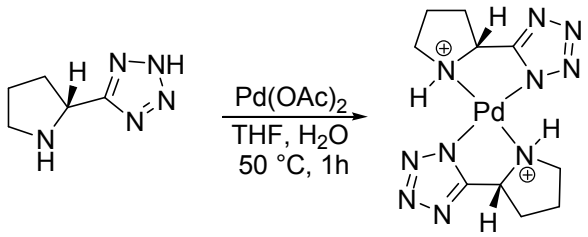
A 10 mL flask is charged, at room temperature, with (*R*)-5-pyrrolidine-2-yl-tetrazole **115** (417 mg, 3 mmol) dissolved in water (4 mL), and with cesium hydroxide monohydrate (504 mg, 3 mmol). The colorless solution is stirred for twenty minutes at room temperature and then the solvent is removed to give 810 mg of white crystalline material. The product is re dissolved in methanol (1.5 mL) at 50 °C, and the colorless solution is treated with diethylether (2.5 mL). The solution is first cooled at 0 °C, and the product crystallized after standing in an open flask three hours at room temperature. The product is filtered give 650 mg of a white crystalline material in ≥ 98 % yield.

Compound characterization data:



mp: 55-58 °C; **TLC:** R_f (*n*BuOH / water/ AcOH 3:3:1, ninhydrin) = 0.25; **IR:** ν 2975 (*brs*, ν(C-H)), 2876 (*brm*, ν(C-H)), 1537 (*brs*, tetrazole), 1428 (*brs*, tetrazole), 1408 (*brs*, tetrazole) cm^{-1}; **^{1}H NMR** (400 MHz, d_6-DMSO): δ = 1.71 (*m*, 3H, H-$C_{2,3}$), 1.94 (*m*, 1H, H-C_2), 2.70 (*m*, 1H, H-C_4), 3.04 (*m*, 1H, H-C_4), 4.12 (*dd*, $^3J_{1,2}$ = 6.8 Hz, 1H, H-C_1); **^{13}C NMR** (125 MHz, d_6-DMSO): δ = 25.6 (CH_2, C_3), 32.7 (CH_2, C_2), 46.3 (CH_2, C_4), 54.8 (CH, C_1), 164.0 (Cq, C_5); **HR-MS:** calc'd for $[M-Cs]^-$ = 138.0785, found 138.0785 (ΔM (ppm) = 0.1).

(*R*)-5-Pyrrolidine-2-yl-tetrazole palladium (II) complex (242)

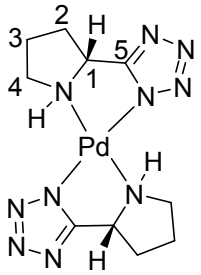


115 **242**

Molecular Formula	$C_{10}H_{18}N_{10}OPd$
Molecular Weight	400.74 g/mol
Analysis Ref.	V. Aureggi, G. Sedelmeier, Novartis Pharma AG, **2007**, WO 2007/009716

A 10 mL, one necked round bottomed flask is charged, at room temperature, with (*R*)-5-pyrrolidine-2-yl-tetrazole **115** (139 mg, 1 mmol) and palladium acetate (112 g, 0.5 mmol) dissolved in a solution of THF / water (1.5 mL, 2:1). The mixture is warmed one hour under stirring at 50 °C. The product crystallized in ≥ 98 % yield from the solvent after standing at room temperature for two hours.

Compound characterization data:

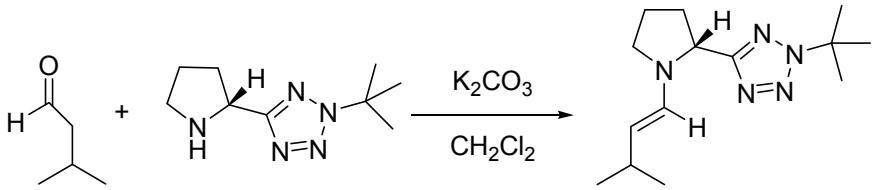


mp: 268-271 °C decomposition; **UV** (EtOH): λ_{max}, nm (ε): 288 (48), 204 (2650); **IR:** ν 3132 (*sbr*, ν(N-H)), 2989 (*m*, ν(C-H)), 2955 (*m*, ν(C-H)), 2876 (*w*, ν(C-H)), 1507 (*w*, tetrazole), 1452 (*s*, tetrazole), 1404 (*s*, tetrazole) cm^{-1}; **^{1}H NMR** (600 MHz, d_6-DMSO): δ = 1.87 (*m*, 3H, H-$C_{2,3}$), 2.44 (*m*, 1H, H-C_2), 3.44 (*m*, 2H, H-C_4), 4.51 (*dd*, 1H, $^3J_{1,2}$ = 7.3 Hz H-C_1), 7.57 (*m*, NH^+); **^{13}C NMR** (150 MHz, d_6-DMSO): δ = 26.4 (CH_2, C_3), 31.0 (CH_2, C_2), 52.2 (CH_2, C_4), 56.9 (CH, C_1), 167.2 (Cq, C_5); **X-Ray:** the structure was confirmed by X-ray analysis (See X-ray discussion; Chapter 4).

5.3.3. Enamines Formation

5.3.3.1. Typical procedures for the enamine formation

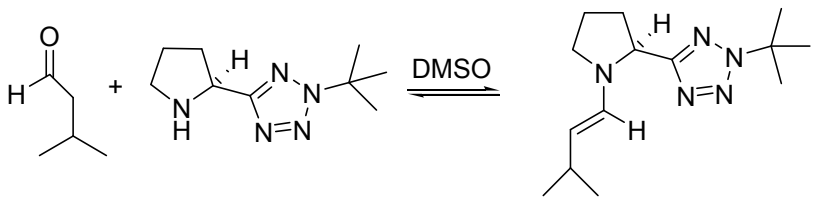
5.3.3.1.1. TP4: Typical procedure for the enamine formation



Scheme 140. Enamine formation

A 25 mL, round-bottomed flask is charged, at room temperature, with (*R*)-*tert*-butyl-pyrrolidine tetrazole (487 mL, 2.5 mmol) dissolved in dichloromethane (3 ml), potassium carbonate (691 mg, 5 mmol) and then isovaleraldehyde (0.37 mL, 4 mmol) in dichloromethane (2 mL). The mixture is stirred at room temperature for twenty minutes, the potassium carbonate is filtered, the solvent and excess of isovaleraldehyde are removed with the rotary evaporator to give the product as a colorless oil in (673 mg, ≥ 99 % yield).

5.3.3.1.2. TP5: Typical procedure for the enamine formation: NMR tube experiment

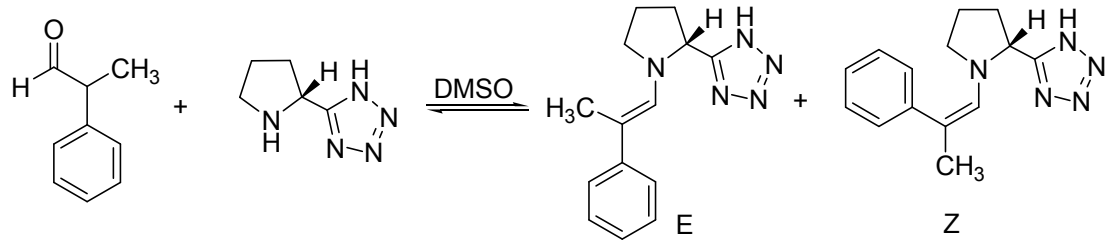


Scheme 141. Equilibrium of the enamine formation

A NMR tube is charged, at room temperature, with 2-*tert*-butyl-5-(*S*)-pyrrolidine-2-yl-2*H*-tetrazole (19.5 mg, 0.1 mmol) dissolved in *d*-DMSO (0.5 ml) and with isovaleraldehyde (8.6 ml, 0.1 mmol) in of *d*-DMSO (0.3 ml).

5.3.3.2. Enamine formation from aldeydes

5-{1-[-2-Phenylprop-1-en-1-yl]-pyrrolidine-2-yl}-tetrazole (259)



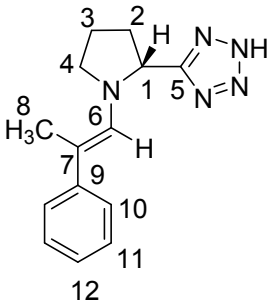
303 **115** **259a** **259b**

Molecular Formula	$C_{14}H_{17}N_5$
Molecular Weight	255.32 g/mol

TP5: One equivalent of 2-phenylpropionaldehyde and one equivalent of 2(*R)*-(tetrazol-5-yl)-pyrrolidine **115** are used in a 0.1 mmol scale experiment. The mixture is checked via H-NMR after five minutes and shows 90 % of enamine formation (75 % E-isomer , 25 % Z-isomer).

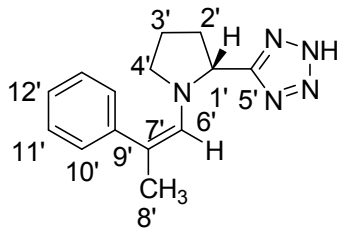
Compound characterization data:

E-Isomer (**259a**)



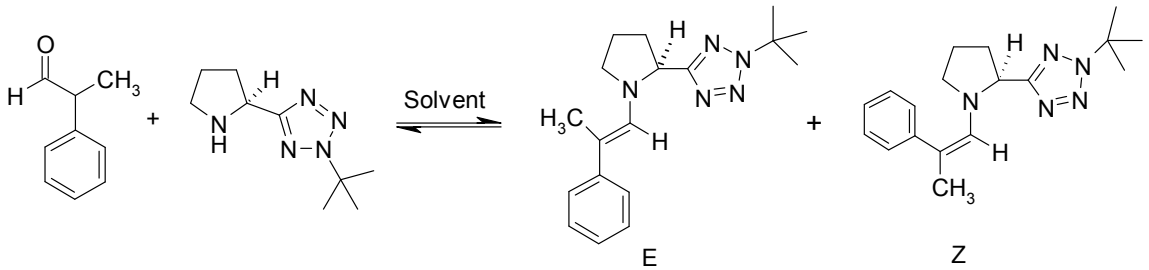
^{1}H NMR (400 MHz, d_6-DMSO): δ = 1.96 (*s*, 3H, H-C_8), 2.08 (*m*, 3H, H-$C_{2,3}$), 2.33 (*m*, 1H, H-C_2), 3.26 (*m*, 1H, H-C_4), 3.68 (*m*, 1H, H-C_4), 4.90 (*dd*, $^3J_{1,2}$ = 7.5 Hz, 1H, H-C_1), 6.42 (*s*, 1H, H-C_6), 7.23 (*m*, 5H, H-$C_{10\text{-}12}$).

Z-Isomer (**259b**)



^{1}H NMR (400 MHz, d_6-DMSO): δ = 1.87 (*s*, 3H, H-$C_{8'}$), 2.08 (*m*, 3H, H-$C_{2',3'}$), 2.25 (*m*, 1H, H-$C_{2'}$), 3.09 (*m*, 1H, H-$C_{4'}$), 3.26 (*m*, 1H, H-$C_{4'}$), 4.73 (*dd*, $^3J_{1',2'}$ = 7.0, 6.8 Hz, 1H, H-$C_{1'}$), 6.1 (*s*, 1H, H-$C_{6'}$), 7.1 *m*, 5H, H-$C_{10'-12'}$).

2-*tert*-Butyl-5-{1-[2-phenylprop-1-en-1-yl]-pyrrolidine-2-yl}-2*H*-tetrazole (260)



303 **243** **260a** **260b**

Molecular Formula	$C_{18}H_{28}N_5$
Molecular Weight	311.42 g/mol

Method 1:

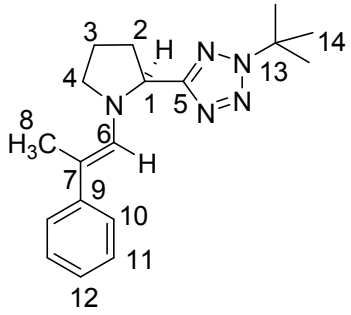
TP5: One equivalent of 2-phenylpropionaldehyde and one equivalent of 2(S)-*tert*-butyl-5-pyrrolidine-2-yl-2*H*-tetrazole **243** are used in a 0.09 mmol scale experiment in d^6-DMSO. The is mixture is checked via H-NMR after seventeen hours and shows 98 % of enamine formation (51 % E-isomer , 49 % Z-isomer).

Method 2:

TP5: One equivalent of 2-phenylpropionaldehyde and one equivalent of 2(*S*)-*tert*-butyl-5-pyrrolidine-2-yl-2*H*-tetrazole **243** are used in a 0.09 mmol scale experiment in CD_3CN. The is mixture is checked via H-NMR after seventeen hours and shows 90 % of enamine formation (84 % E-isomer , 16 % Z-isomer).

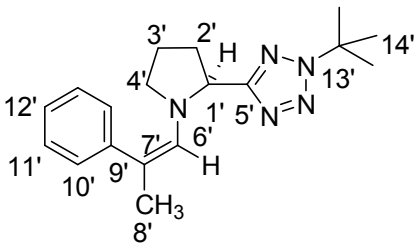
Compound characterization data:

E-Isomer (**260a**)



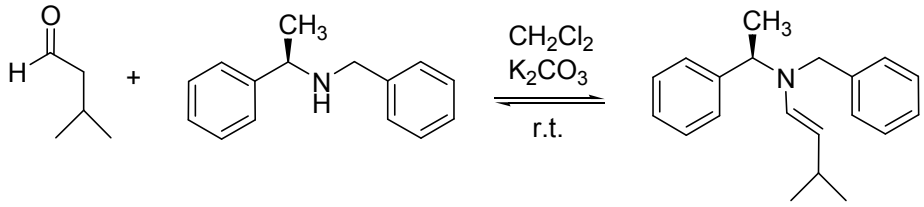
^{1}H NMR (400 MHz, d_6-DMSO): δ = 1.65 (*s*, 9H, H-C_{14}), 1.95 (*s*, 3H, H-C_8), 1.95 (*m*, 3H, H-C_3), 2.06-2.30 (*m*, 2H, H-C_2), 3.04-3.63 (*m*, 2H, H-C_4), 4.80 (*dd*, $^3J_{1,2}$ = 7.0, 7.3 Hz, 1H, H-C_1), 6.44 (*s*, 1H, H-C_6), 7.05-7.20 (*m*, 5H, H-$C_{10\text{-}12}$); (400 MHz, CD_3CN): δ = 1.70 (*s*, 9H, H-C_{14}), 2.02 (*d*, $^4J_{6,8}$ = 1.2 Hz, 3H, H-C_8), 2.10-2.36 (*m*, 4H, H-$C_{2,3}$), 3.34 (*m*, 1H, H-C_4), 3.69 (*m*, 1H, H-C_4), 4.78 (*dd*, $^3J_{1,2}$ = 7.0, 7.5 Hz, 1H, H-C_1), 6.41 (*d*, $^4J_{6,8}$ = 1.2 Hz, 1H, H-C_6), 7.10-7.29 (*m*, 5H, H-$C_{10\text{-}12}$).

<u>*Z*-Isomer (**260b**)</u>



^{1}H NMR (400 MHz, d_6-DMSO): δ = 1.68 (*s*, 3H, H-$C_{14'}$), 1.86 (*s*, 3H, H-$C_{8'}$), 1.73-1.95 (*m*, 2H, H-$C_{3'}$), 2.06-2.30 (*m*, 2H, H-$C_{2'}$), 3.04-3.63 (*m*, 2H, H-$C_{4'}$), 4.67 (*dd*, $^3J_{1',2'}$ = 7.0 Hz, 1H, H-$C_{1'}$), 6.11 (*s*, 1H, H-$C_{6'}$), 7.05-7.20 (*m*, 5H, H-$C_{10'\text{-}12'}$); (400 MHz, CD_3CN): δ = 1.73 (*s*, 9H, H-$C_{14'}$), 1.92 (*d*, $^4J_{6',8'}$ = 1.0 Hz, 3H, H-$C_{8'}$), 2.15-2.6 (*m*, 4H, H-$C_{2',3'}$), 3.11 (*m*, 2H, H-$C_{4'}$), 4.65 (*dd*, $^3J_{1',2'}$ = 7.0, 7.3 Hz, 1H, H-$C_{1'}$), 6.12 (*d*, $^4J_{6',8'}$ = 1.0 Hz, 1H, H-$C_{6'}$), 7.10-7.29 (*m*, 5H, H-$C_{10'\text{-}12'}$).

(*R*,*E*)-*N*-Benzyl-3-methyl-*N*-(1-phenylethyl)-but-1-en-1-amine (261)

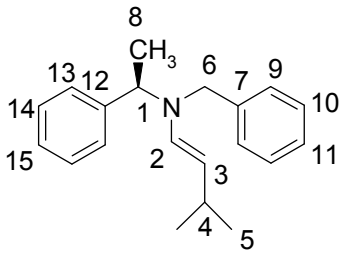


213 **304** **261**

Molecular Formula	$C_{20}H_{25}N$
Molecular Weight	279.43 g/mol

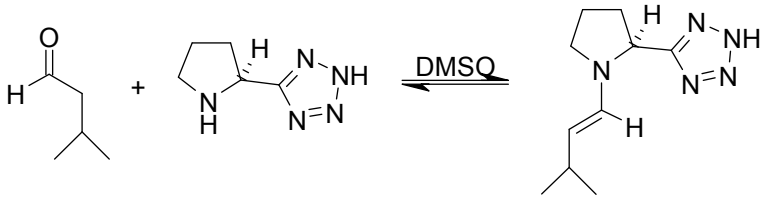
TP4: 1.67 equivalents of isovaleraldehyde are used in 3 mmol scale experiment. The reaction is stirred for five hours at room temperature to give a mixture of starting amine and desired enamine as a colorless oil (23 % of enamine by ^{1}H-NMR).

Compound characterization data:



^{1}H NMR (400 Mz, d_6-DMSO): δ = 0.82 (*d*, $^3J_{4,5}$ = 6.7 Hz, 6H, H-C_5), 1.40 (*d*, $^3J_{1,8}$ = 7.0 Hz, 3H, H-C_8), 2.11 (*m*, $^3J_{4,5}$ = 6.7 Hz, 1H, H-C_4), 3.81 (*d*, $^2J_{6,6'}$ = 15.6 Hz, 1H, H-C_6), 3.92 (*d*, $^2J_{6,6'}$ = 15.6 Hz, 1H, H-$C_{6'}$), 4.09 (*dd*, $^3J_{2,3}$ = 13.8 Hz, 1H, H-C_3), 4.24 (*q*, $^3J_{1,8}$ = 7.0 Hz, 1H, H-C_1), 6.06 (*d*, $^3J_{2,3}$ = 13.8 Hz, 1H, H-C_2), 7.21 (*m*, 10H, ArH).

5-{1-[(1*E*)-3-Methylbut-1-en-1-yl]-pyrrolidine-2-yl}-tetrazole (262)

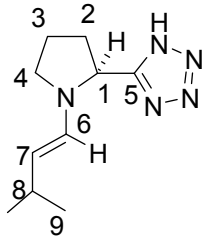


213 **114** **262**

Molecular Formula	$C_{10}H_{17}N_5$
Molecular Weight	207.28 g/mol

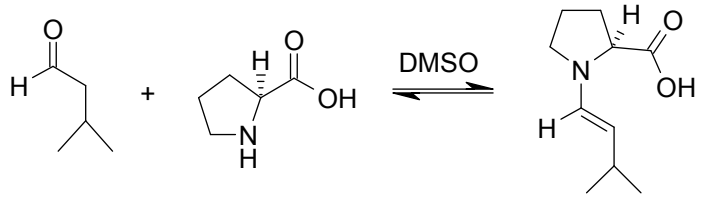
TP5: One equivalent of isovaleraldehyde and one equivalent of 2(*S)*-(tetrazol-5-yl)-pyrrolidine **114** are used in a 0.095 mmol scale experiment. The mixture is checked via H-NMR after five minutes and shows 70 % of enamine conversion.

Compound characterization data:



^{1}H NMR (400 MHz, d_6-DMS): δ = 4.05 (*dd*, $^3J_{6,7}$ = 13.8 Hz, 1H, H-C_7), 4.67 (*dd*, $^3J_{1,2}$ = 8.1, 8.8 Hz, 1H, H-C_1), 6.0 (*d*, $^3J_{6,7}$ = 13.8 Hz, 1H, H-C_6)

1-[(1*E*)-3-Methylbut-1-en-1-yl]-(*S*)-proline (305)

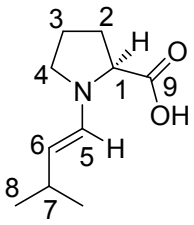


213 **193** **305**

Molecular Formula	$C_{10}H_{17}NO_2$
Molecular Weight	183.25 g/mol

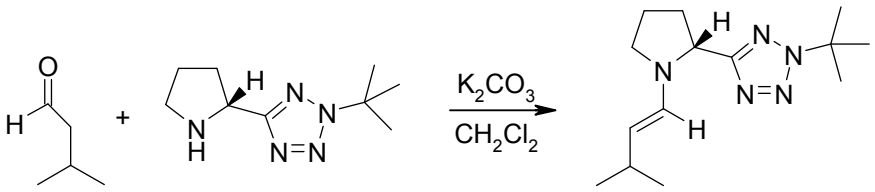
TP5: One equivalent of isovaleraldehyde are used in 0.1 mmol scale experiment. The mixture is checked via H-NMR after five minutes and shows 18 % of enamine formation.

Compound characterization data:



^{1}H NMR (400 Mz, d_6-DMSO): δ = 3.99 (*dd*, $^3J_{5,6}$ = 13.8 Hz, 1H, H-C_5), 6.04 (*d*, $^3J_{5,6}$ = 13.8 Hz, 1H, H-C_5)

2-*tert*-Butyl-5-[(*R*)-1-(*E*)-3-methyl-but-1-enyl)-pyrrolidine-2-yl]-2*H*-tetrazole (264)

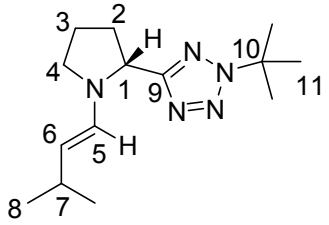


213 **236** **264**

Molecular Formula	$C_{14}H_{29}N_5$
Molecular Weight	263.39 g/mol

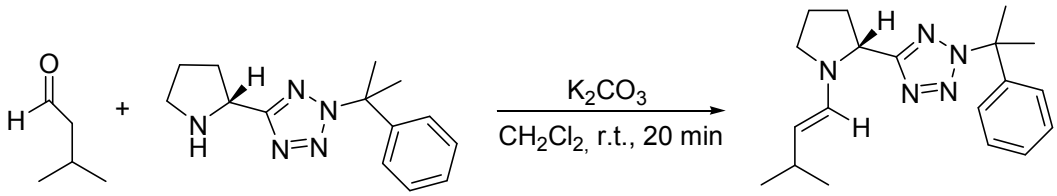
TP4: 1.6 equivalents of isovaleraldehyde are used in a 2.5 mmol scale experiment. The reaction is stirred for twenty minutes at room temperature to give 659 mg of product as a colorless oil in ≥ 99 % yield.

Compound characterization data:



IR: ν 3040 (*w*, ν(C-H)), 2955 (*vs*, $\nu_{asim}(CH_3)$), 2869 (*s*, $\nu_{sim}(CH_3)$, ν(C-H), 1655 (*s*, ν(C=C)), 1372 (*s*, δ(CH_3)), 936 (*m*, δ(C-H, C=C trans)) cm^{-1}; **^{1}H NMR** (400 Mz, d_6-DMSO): δ = 0.85 (*d*, $^3J_{7,8}$ = 6.5 Hz, 6H, H-C_8), 1.66 (*s*, 9H, H-C_{11}), 1.93 (*m*, 1H, H-C_3), 2.06 (*m*, 1H, H-C_7), 2.10 (*m*, 2H, H-$C_{2,3}$), 2.24 (*m*, 1H, H-C_2), 2.96 (*m*, 1H, H-C_4), 3.13 (*m*, 1H, H-C_4), 4.05 (*dd*, $^3J_{5,6}$ = 13.8, $^3J_{6,7}$ = 7.0 Hz, 1H, H-C_6), 4.57 (*dd*, $^3J_{1,2}$ = 7.8, 8.0 Hz, 1H, H-C_1), 6.00 (*d*, $^3J_{5,6}$ = 13.8 Hz, 1H, H-C_5,); **^{13}C NMR** (125 Mz, d_6-DMSO): δ = 23.5 (CH_2, C_3), 24.2 (CH_3, C_8), 28.7 (CH_3, C_{11}), 28.8 (CH, C_7), 31.0 (CH_2, C_2), 48.2 (CH_2, C_4), 55.5 (CH, C_1), 63.3 (Cq, C_{10}), 107.2 (CH, C_6), 131.9 (CH, C_5), 167.1 (Cq, C_9); **MS:** *m/z* 264 $[MH]^+$, 248 $[M\text{-}CH_3]^+$, 138 [M-*t*Butyl-tetrazole]$^+$.

5-[(*R*)-1-(*E*)-3-Methyl-but-1-enyl)-pyrrolidine-2-yl]-2-(1-methyl-1-phenyl-ethyl)-2*H*-tetrazole (263)

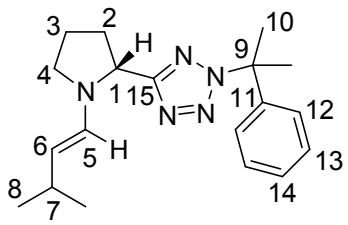


213 **235** **263**

Molecular Formula	$C_{19}H_{27}N_5$
Molecular Weight	325.46 g/mol

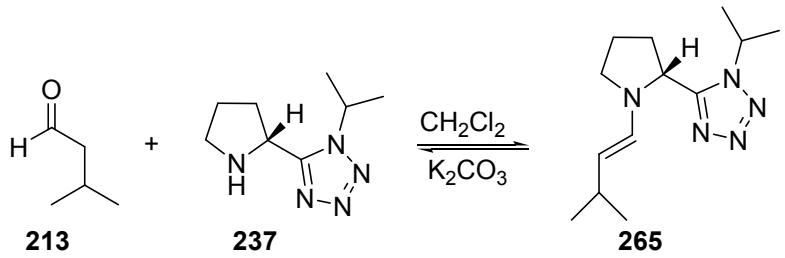
TP4: 1.67 equivalents of isovaleraldehyde are used in 1 mmol scale experiment. The reaction is stirred for twenty minutes at room temperature to give 326 mg of product as a colorless oil in ≥ 98 % yield.

Compound characterization data:



IR: ν 3091 (*w*, ɣ(C-H)), 3061 (*w*, ɣ(C-H)), 3030 (*w*, ɣ(C-H)), 2954 (*vs*, $ɣ_{asim}(CH_3)$), 2867 (*s*, $ɣ_{sim}(CH_3)$), 1655 (*s*, ɣ(C=C)), 1602 (*w*, ɣ(C=C)), 1498 (*s*, ɣ(C=C)), 1449 (*s*, ɣ(C=C)), 1371 (*s*, δ(CH_3)), 936 (*m*, δ(C-H, C=C trans)), 762 (*s*, γ (C-H, Ph)), 698 (*s*, γ (Ph) cm^{-1}; **^{1}H NMR** (400 Mz, d_6-DMSO): δ = 0.84 (*d*, $^3J_{7,8}$ = 6.5 Hz, 6H, H-C_8), 1.93 (*m*, 2H, H-C_3), 2.06 (*s*, 6H, H-C_{10}), 2.06 (*m*, 1H, H-C_7), 2.22 (*m*, 2H, H-C_2), 2.96 (*m*, 1H, H-C_4), 3.12 (*m*, 1H, H-C_4), 4.03 (*dd*, $^3J_{5,6}$ = 13.8, $^3J_{6,7}$ = 7.0 Hz, 1H, H-C_6), 4.57 (*dd*, $^3J_{1,2}$ = 7.8 , 8.0 Hz 1H, H-C_1), 5.95 (*d*, $^3J_{5,6}$ =13.8 Hz, 1H, H-C_5); **^{13}C NMR** (125 Mz, d_6-DMSO): δ = 23.3 (CH_2, C_3), 24.1, 24.2 (CH_3, C_8), 28.6, 28.7 (CH_3, C_{10}), 31.2 (CH_2, C_2), 48.2 (CH_2, C_4), 55.4 (CH, C_1), 68.0 (Cq, C_9), 107.3 (CH, C_6), 124.4 (CH, C_{12}), 127.6 (CH, C_{14}), 128.5 (CH, C_{13}), 131.7 (CH, C_5), 144.3 (Cq, C_{11}), 167.5 (Cq, C_{15}); **MS:** *m/z* 326 $[MH]^+$.

(*R*,*E*)-1-Isopropyl-5-[1-(3-methylbut-1-enyl)-pyrrolidine-2-yl]-1*H*-tetrazole (265)

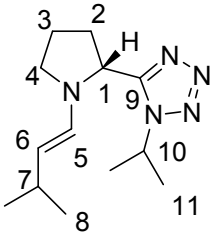


213 **237** **265**

Molecular Formula	$C_{13}H_{25}N_5$
Molecular Weight	249.36 g/mol

TP4: Two equivalents of isovaleraldehyde are used in 1 mmol scale experiment. The reaction is stirred for twenty minutes at room temperature to give 250 mg of product as an orange oil in ≥ 99 % yield.

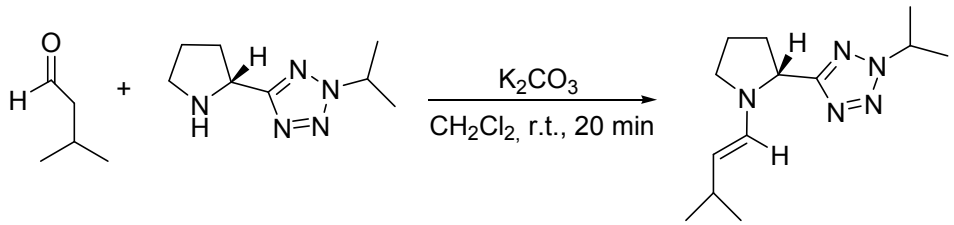
Compound characterization data:



^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.81 (*m*, 6H, H-C_8), 1.48 (*d*, $^3J_{10,11}$ = 6.5 Hz, 3H, H-C_{11}), 1.53 (*d*, $^3J_{10,11}$ = 6.8 Hz, 3H, H-C_{11}), 1.83-2.09 (*m*, 3H, H-$C_{2,3}$), 1.94-2.09 (*m*, 1H, H-C_7), 2.35 (*m*, 1H, H-C_2), 3.00 (*m*, 1H, H-C_4), 3.33 (*m*, 1H, H-C_4), 4.10 (*dd*, $J^3_{5,6}$ = 13.8, $J^3_{6,7}$ = 7.0 Hz, 1H, H-C_6), 4.66 (*dd*, $^3J_{1,2}$ = 7.0, 7.5 Hz, 1H, H-C_1), 4.81 (*m*, 1H, H-C_{10}, $^3J_{10,11}$ = 6.5, 6.8 Hz), 5.79 (*d*, $^3J_{5,6}$ = 13.8 Hz, 1H, H-C_5); **^{13}C NMR** (100 MHz, $CDCl_3$): δ

= 22.9 (CH_3, C_8), 23.8 (CH_2, C_3), 24.0 (CH_3, C_{11}), 29.4 (CH, C_7), 32.6 (CH_2, C_2), 50.5 (CH_2, C_4), 51.0 (CH, C_{10}), 55.7 (CH, C_1), 111.5 (CH, C_6), 131.4 (CH, C_6), 154.9 (Cq, C_9).

(*R*,*E*)-2-Isopropyl-5-[1-(3-methylbut-1-enyl)-pyrrolidine-2-yl]-2*H*-tetrazole (266)

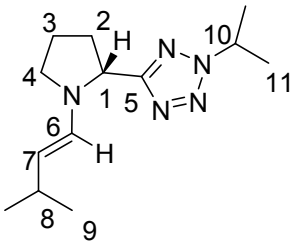


213 **238** **266**

Molecular Formula	$C_{13}H_{23}N_5$
Molecular Weight	249.36 g/mol

TP4: 2 equivalents of isovaleraldehyde are used in 1 mmol scale experiment. The reaction is stirred for twenty minutes at room temperature to give 250 mg of product as a colorless oil in ≥ 99 % yield.

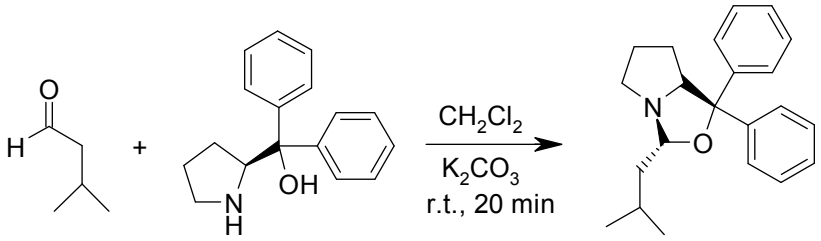
Compound characterization data:



IR: ν 3049 (*w*, ɣ(C-H)), 2955 (*vs*, $ɣ_{asim}(CH_3)$, ɣ(C-H)), 2869 (*s*, $ɣ_{sim}(CH_3)$), 1654 (*s*, ɣ(C=C)), 1459 (*vs*, tetrazole), 1371 (*s*, δ(CH_3)), 936 (*m*, δ(C-H, C=C trans)) cm^{-1}; **^{1}H NMR** (500 MHz, d_6-DMSO): δ = 0.86 (*d*, $^3J_{8,9}$ = 7.0 Hz, 6H, H-C_9), 1.54 (*d*, $^3J_{10,11}$ = 6.5 Hz, 6H, H-C_{11}), 1.94 (*m*, 1H, H-C_3), 2.09 (*m*, 4H, H-$C_{2,3,8}$), 2.24 (*m*, 1H, H-C_2), 2.96 (*m*, 1H, H-C_4), 3.13 (*m*, 1H, H-C_4), 4.04 (*dd*, $^3J_{6,7}$ = 13.8, $^3J_{7,8}$ = 7.0 Hz, 1H, H-C_7), 4.57 (*dd*, $^3J_{1,2}$ = 7.8, 8.0 Hz, 1H, H-C_1), 5.08 (*m*, $^3J_{10,11}$ = 6.5 Hz, 1H, H-C_{10}), 6.01 (*d*, $^3J_{6,7}$ = 13.8 Hz, 1H, H-C_6); **^{13}C NMR** (125 MHz, d_6-DMSO): δ = 21.8 (CH_3, C_9), 23.4 (CH_3, C_{11}), 24.3 (CH_2, C_3), 28.8 (CH, C_8), 31.1 (CH_2, C_2), 48.2 (CH_2, C_4), 55.5 (CH, C_{10}), 55.8 (CH, C_1), 107.1 (CH, C_7), 131.9 (CH, C_6), 167.4 (Cq, C_5); **MS:** *m/z* 250 $[MH]^+$, 249 $[M]^+$, 234 $[M\text{-}CH_3]^+$, 138 [M-*i*-Propyl-tetrazole]$^+$.

5.3.3.3. Oxazolines formation

(3*R*,4*S*)-3-Isobutyl-1,1-diphenyl-tetrahydro-pyrrolo [1,2-c]oxazole (267)

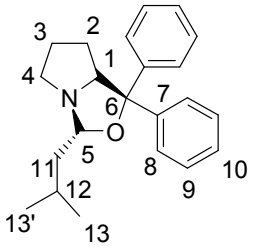


213 **306** **267**

Molecular Formula	$C_{23}H_{31}NO$
Molecular Weight	337.51 g/mol

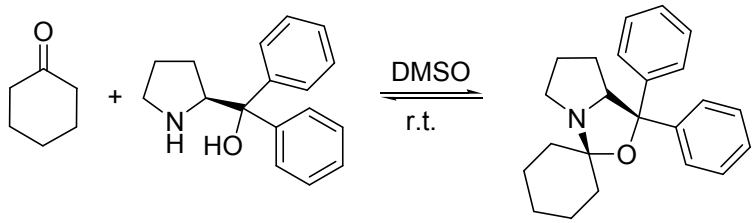
TP4: Two equivalents of isovaleraldehyde are used in 0.71 mmol scale experiment. The reaction is stirred for twenty minutes at room temperature to give 240 mg of product as a colorless oil in ≥ 99 % yield.

Compound characterization data:



IR: ν 3085 (*w*, ɣ(C-H)), 3059 (*w*, ɣ(C-H)), 3024 (*w*, ɣ(C-H)), 2956 (*brs*, $ɣ_{asim}(CH_3)$, ɣ(C-H)), 2870 (*s*, $ɣ_{sim}(CH_3)$), 1950-1766 (*w*, overtones γ(C-H, Ph)), 1599 (*w*, ɣ(C=C)), 1491 (*s*, ɣ(C=C)), 1448 (*s*, ɣ(C=C)), 1385 (*w*, δ(CH_3)), 1156 (*m*, ɣ(C-O)), 1017 (*s*, ɣ(C-O)), 751 (*s*, γ(C-H)), 702 (*s*, γ(Ph)) cm^{-1}; **^{1}H NMR** (500 Mz, d_6-DMSO): δ = 0.89 (*d*, $^3J_{12,13}$ = 6.5 Hz, 3H, H-C_{13}), 0.99 (*d*, $^3J_{12,13'}$ = 6.5 Hz, 3H, H-$C_{13'}$), 1.19 (*m*, 1H, H-C_2), 1.42 (*m*, 1H, H-C_3), 1.52 (*m*, 1H, H-C_3), 1.64 (*m*, 1H, H-C_{11}), 1.79 (*m*, 1H, H-C_{11}), 1.87 (*m*, 2H, H-$C_{2,12}$), 2.70 (*m*, 2H, H-C_4), 4.27 (*m*, $^3J_{1,2}$ = 7.0 Hz, 1H, H-C_1), 4.34 (*m*, 1H, H-C_5), 7.10 (*m*, 1H, ArH), 7.21 (*m*, 3H, ArH), 7.34 (*m*, 4H, ArH), 7.55 (*m*, 2H, ArH); **^{13}C NMR** (125 Mz, d_6-DMSO): δ = 22.3, 24.1 (CH_3, $C_{13,13'}$), 28.7 (CH_2, C_2), 39.1 (CH_2, C_{11}), 46.3 (CH_2, C_4), 25.9 (CH_2, C_3), 25.5 (CH, C_{12}), 73.1 (CH, C_1), 86.8 (Cq, C_6), 89.2 (CH, C_5), 125.9 (CH, Ar), 126.0 (CH, Ar), 126.5 (CH, Ar) 126.7 (CH, Ar), 127.8 (CH, Ar), 128.1 (CH, Ar), 144.2 (Cq, C_7), 147.2 (Cq, C7'); **MS:** *m/z* 322 $[MH]^+$.

(7a'*S*)-1',1'-diphenyltetrahydro-1'*H*-spiro[cyclohexane-1,3'-pyrrolo[1,2-*c*][1,3]oxazole] (307)



209 **306** **307**

Molecular Formula	$C_{23}H_{27}NO$
Molecular Weight	333.48 g/mol

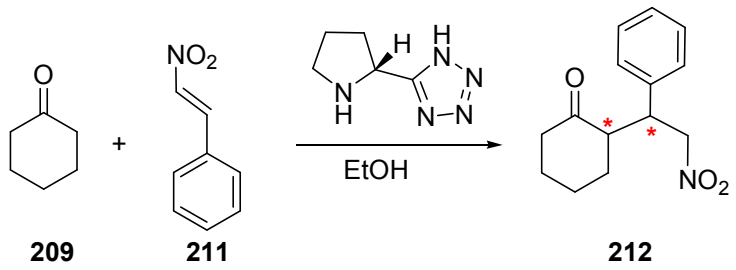
TP5: One equivalent of cyclohexanone is used in 0.1 mmol scale experiment

NO PRODUCT OBSERVED !

5.3.4. Organocatalysis

5.3.4.1. Typical procedures for Michael additions

5.3.4.1.1. TP6: Typical procedure for the Michael Addition

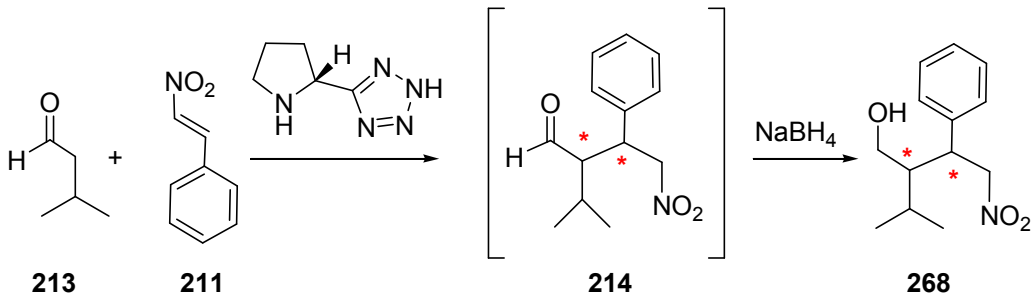


209 211 212

Scheme 142. Michael addition organocatalized

A 5 ml, one necked round bottomed flask, is charged, at room temperature, with cyclohexanone (0.155 ml, 1.5 mmol) dissolved in ethanol (1.5 ml), (*R*)-(tetrazol-5-yl)-pyrrolidine as catalyst (42 mg, 0.3 mmol) and nitrostyrole (223 mg, 1.5 mmol). The mixture is stirred for thirty hours at room temperature. The mixture is quenched with HCl (3 ml), the aquesus phase is saturated with solid NaCl and the product extracted three times with dichloromethane (4 ml portions). The solvent is removed to give 380 mg of a yellow crystalline material. The crude is chromatographed (elution system: hexane / ethyl acetate 6:1) to give the product as a colorless crystalline material (360 mg, 97 % of yield).

5.3.4.1.2. TP7: Typical procedure for the Michael Addition followed by reduction to primary alcohol



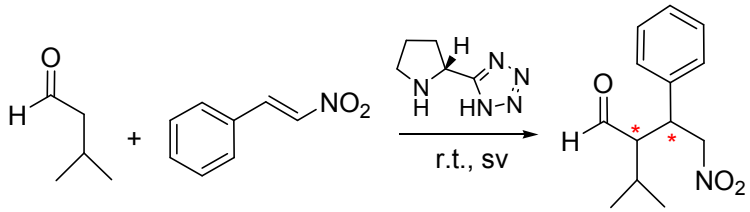
213 211 214 268

Scheme 143. Michael addition followed by reduction

A 5 ml, one necked round bottomed flask, is charged, at room temperature, with isovaleraldehyde (0.61 ml, 6 mmol) dissolved in dichloromethane (5 ml), 2(*R*)-(tetrazol-

5-yl)-pyrrolidine **115** as catalyst (55 mg, 0.4 mmol) and nitrostyrole (298 mg, 2 mmol). The mixture is stirred for twenty hours at room temperature. The mixture is cooled at 0 °C, ethanol (1.5 ml) is added and the mixture is carefully treated with sodium borohydrure (113.5 mg, 3 mmol). The mixture is gradually warmed at room temperature and stirred two hours. The mixture is cooled at 0 °C and quenched with HCl (2 ml, solution 2 M). The organic phase is washed twice with water (4 ml portion), the solvent is removed to give 474 mg of a brown oil. The crude is chromatographed (elution system: hexane / ethyl acetate 9:1) to give the product as a yellow oil (422 mg, 89 % yield).

(2*S*,3*R*)-2-(1-methylethyl)-4-nitro-3-phenylbutyraldehyde (214)

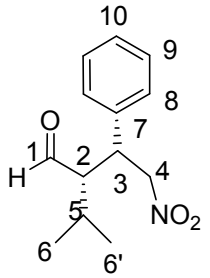


213 **211** **214**

CAS Registry Number	(*S*,*R*) isomer: 475294-91-8 (*R*,*S*) isomer: 384354-46-5 (*S*,*S*) isomer: 768370-38-3
Molecular Formula	$C_{13}H_{17}NO_3$
Molecular Weight	235.28 g/mol
Analysis Ref.	a) G. M. Betancort, C. F. Barbas, III, *Org. Lett.* **2001**, *3*, 3737; b) T. Ishii, S. Fujioka, Y. Sekiguchi, H. Kotsuki, *J. Am. Chem. Soc.* **2004**, *126*, 9558; c) P. Kotrusz, S. Toma, H.-G. Schmalz, A. Adler, *Eur. J. Org. Chem.* **2004**, *7*, 1577; d) O. Andrey, A. Alexakis, A. Tomassini, G.Bernardinelli, *Ad. Synth. Cat.* **2004**, *346*, 1147; e) S. Mosse, M. Laars, K. Kriis, T. Kanger, A. Alexakis, *Org. Lett.* **2006**, *8*, 2559; f) S. Mosse, A. Alexakis, *Org. Lett.* **2006**, *8*, 3577; g) Y. Li, X.-Y. Liu, G. Zhao, *Tetrahedron: Asymm.* **2006**, *17*, 2034

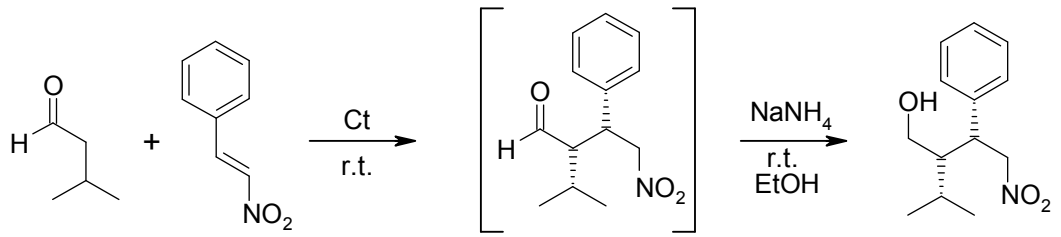
TP6: 2 equivalents of isovaleraldehyde are used in a 10 mmol scale experiment in dichloromethane with 2(*R)*-(tetrazol-5-yl)-pyrrolidine as catalyst as catalysts (20 %). The reaction is stirred for twenty hours at room temperature to give the product after chromatography as a colorless oil (1.82 g, 77 % yield, 57 % ee, syn / anti 8:1).

Compound characterization data:



TLC: syn: R_f(hexane / EtOAc 4:1) = 0.33, Anti: R_f(hexane / EtOAc 4:1) = 0.43; **HPLC:** syn: 10.04 min, anti: 9.62 min; **Chiral HPLC:** (syn isomer) A: 8.26 min, B: 13.01 min; **Optical rotation:** $[\alpha]_D^{25}$ = + 6.04° (in MeOH, c = 0.96); **IR:** ν 3065 (*w*, ν(C-H)), 3031 (*w*, ν(C-H)), 2965 (*m*, $\nu_{asim}(CH_3)$), 2936 (*w*, ν(C-H)), 2875 (*w*, $\nu_{sim}(CH_3)$), 1718 (*s*, ν(C=O)), 1554 (*s*, $\nu_{asim}(NO_2)$), 1496 (*w*, ν(C=C)), 1466 (*w*, ν(C=C)), 1456 (*w*, ν(C=C)), 1379 (*m*, $\nu_{sim}(NO_2)$), 761 (*w*, γ (C-H, Ph)), 703 (*w*, γ(Ph)) cm^{-1}; **^{1}H NMR** (600 MHz, d_6-DMSO): δ = 0.74 (*d*, $^3J_{5,6}$ = 7.0 Hz, 3H, H-C_6), 0.96 (*d*, $^3J_{5,6'}$ = 7.0 Hz, 3H, H-$C_{6'}$), 1.48 (*m*, $^3J_{5,6/6'}$ = 7.0 Hz, 1H, H-C_5), 2.83 (*m*, $^3J_{1,2}$ = 2.8 Hz, 1H, H-C_2), 3.83 (*dt*, $^3J_{3,4}$ = 5.3, $^3J_{2,3}$ = 10.6 Hz, 1H, H-C_3), 4.79 (*dd*, $^3J_{3,4}$ = 5.3 Hz, 2H, H-C_4), 7.33 (*m*, 5H, H-$C_{8\text{-}10}$), 9.83 (*d*, $^3J_{1,2}$ = 2.8 Hz, 1H, H-C_1); **^{13}C NMR** (150 Mz, d_6-DMSO): δ = 16.6 (CH_3, C_6), 21.2 (CH_3, $C_{6'}$), 27.3 (CH, C_5), 41.6 (CH, C_3), 57.6 (CH, C_2), 78.9 (CH_2, C_4), 127.5 (CH, C_{10}), 128.3 (CH, C_9), 128.6 (CH, C_8), 137.9 (Cq, C_7), 205.6 (CHO, C_1); **MS:** *m/z* 253 $[M+NH_4]^+$.

(2*S*,3*R*)-2-Isopropyl-4-nitro-3-phenylbutan-1-ol (268)

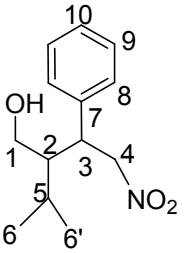


213 **211** **214** **268**

Molecular Formula	$C_{13}H_{19}NO_3$
Molecular Weight	237.30 g/mol

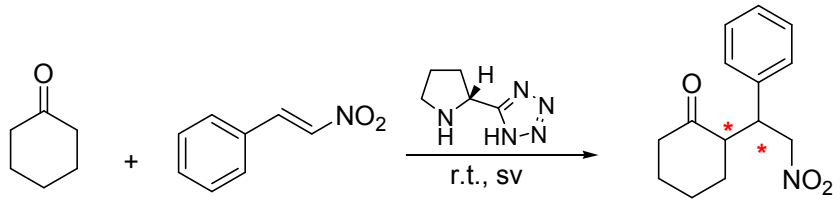
TP7: Three equivalents of isovaleraldehyde are used in two mmol scale experiment with the 2(*R*)-(tetrazol-5-yl)-pyrrolidine **115** as catalyst (20 %) to give the product after chromatography as a brown oil (422 mg, 89 % yield, 63 % ee of enantiomer B, syn / anti 19:1).

Compound characterization data:



TLC: syn: R_f(hexane / EtOAc 9:1) = 0.06; **HPLC:** syn: 9.29 min, anti: 8.94 min; **Chiral HPLC:** (syn-isomer) enantiomer A: 11.63 min; enantiomer B: 13.78 min; **Optical rotation:** $[\alpha]_D^{25}$ = + 21.4 ° (in MeOH, c = 1.00); **IR:** ν 3433 (*w*, ν(O-H)), 3087 (*w*, ν(C-H)), 3064 (*w*, ν(C-H)), 3030 (*w*, ν(C-H)), 2961 (*m*, $\nu_{asim}(CH_3)$), 2930 (*w*, ν(C-H)), 2875 (*w*, $\nu_{sim}(CH_3)$), 1551 (*vs*, $\nu_{asim}(NO_2)$), 1496 (*w*, ν(C=C)), 1466 (*w*, ν(C=C)), 1455 (*w*, ν(C=C)), 1382 (*m*, $\nu_{sim}(NO_2)$), 1035 (*w*, ν(C-O)), 758 (*w*, γ (C-H, Ph)), 702 (*m*, γ (Ph)) cm^{-1}; **^{1}H NMR** (600 MHz, d_6-DMSO): δ = 0.72 (*d*, $^3J_{5,6}$ = 7.0 Hz, 3H, H-C_6), 0.87 (*d*, $^3J_{5,6'}$ = 7.0 Hz, 3H, H-$C_{6'}$), 1.43 (*m*, 1H, H-C_5), 1.54 (*m*, 1H, H-C_2), 3.51 (*m*, 2H, H-C_1), 3.56 (*m*, 1H, H-C_3), 4.66 (*m*, 1H, OH), 5.08 (*m*, 2H, H-C_4), 7.21 (*m*, 1H, H-C_{10}), 7.27 (*m*, 2H, H-C_9), 7.30 (*m*, 2H, H-C_8); **^{13}C NMR** (150 Mz, d_6-DMSO): δ = 17.3 (CH_3, C_6), 21.6 (CH_3, $C_{6'}$), 26.5 (CH, C_5), 45.3 (CH, C_3), 49.0 (CH, C_2), 58.2 (CH_2, C_1), 79.2 (CH_2, C_4), 127.0 (CH, C_{10}), 128.0 (CH, C_8), 128.4 (CH, C_9), 140.2 (Cq, C_7); **MS:** *m/z* 236 $[M-H]^-$; **HR-MS:** calc'd for $[M-H]^-$ = 236.12922, found 236.12926 (ΔM (ppm) = 0.2).

2-[-2-Nitro-1-phenylethyl]-cyclohexanone (212)

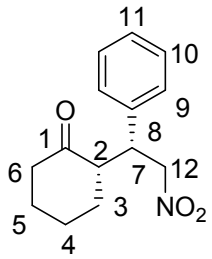


209 **211** **212**

CAS Registry Number	(*R*,*R*) isomer: 54568-74-8 (*S*,*S*) isomer: 84025-87-6 (*R*,*S*) isomer: 84025-84-3 (*S*,*R*) isomer: 84025-83-2
Molecular Formula	$C_{14}H_{17}NO_3$
Molecular Weight	247.29 g/mol
Analysis Ref.	a) S. J. Blarer, W. B. Schweizer, D. Seebach, *Helv. Chim. Acta* **1982**, *65*, 1637; b) M. A. Brook, D. Seebach, *Can. J. Chem.* **1987**, *65*, 836; c) A. J. A. Cobb, D. M. Shaw, D. Longbottom, J. B. Gold, V. S. Ley, *Org. Bioo. Chem.* **2005**, *3*, 84; d) Y. Xu, A. Cordova, *Chem. Commun.* **2006**, *4*, 460

TP6: Stoichiometric amount of cyclohexanone are used in a 1.5 mmol experiment in ethanol with 2-(*R*)-(tetrazol-5-yl)-pyrrolidine as catalyst as catalysts (20 %). The reaction is stirred for thirty hours at room temperature to give the product after chromatography as a white crystalline material (360 mg, 97 % yield, 60 % ee enantiomer A, syn / anti 19:1).

Compound characterization data:



mp: 103-106 °C; **TLC:** R_f(hexane / EtOAc 5:1) = 0.2; **HPLC:** syn: 8.44 min, anti: 7.97 min; **Chiral HPLC:** (syn-isomer) enatiomer A: 13.03 min, enantiomer B: 17.10 min; **Optical rotation:** $[\alpha]_D^{25}$ = -6.2° (in MeOH, c = 0.81); **IR:** ν 3085 (*w*, ν(C-H)), 3057 (*w*, ν(C-H)), 3029 (*w*, ν(C-H)), 2957 (*w*, ν(C-H)), 2936 (*w*, ν(C-H)), 1699 (*s*, ν(C=O)), 1552 (*s*, $\nu_{asim}(NO_2)$), 1495 (*w*, ν(C=C)), 1450 (*w*, ν(C=C)), 1385 (*m*, $\nu_{sim}(NO_2)$), 747 (*w*, γ (C-H, Ph)), 698 (*m*, γ (Ph)) cm^{-1}; **^{1}H NMR** (600 MHz, d_6-DMSO): δ = 1.08 (*m*, 1H, H-C_3), 1.46 (*m*, 3H, H-C_3), 1.50 (*m*, 1H, H-C_5), 1.51 (*m*, 1H, H-C_4), 1.64 (*m*, 1H, H-C_4), 1.96 (*m*, 1H, H-C_5), 2.27 (*m*, 1H, H-C_6), 2.41 (*m*, 1H, H-C_6), 2.83 (*m*, 1H, H-C_2), 3.67 (*m*, 1H, H-C_7), 4.86 (*m*, 2H, H-C_{12}), 7.23 (*m*, 1H, H-C_{11}), 7.30 (*m*, 4H, H-$C_{9,10}$); **^{13}C NMR** (150 Mz, d_6-DMSO): δ = 24.3 (CH_2, C_4), 27.9 (CH_2, C_5), 32.3 (CH_2, C_3), 42.1 (CH, C_6), 43.4 (CH, C_7), 51.4 (CH, C_2), 78.8 (CH_2, C_{12}), 127.2 (CH, C_{11}), 128.4 (CH, C_{10}), 128.5 (CH, C_9), 138.4 (Cq, C_8), 211.6 (Cq, C_1); **MS:** *m/z* 248 $[MH]^+$.

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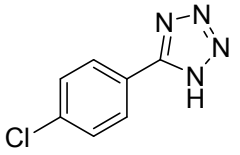
Molecules



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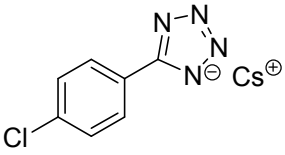

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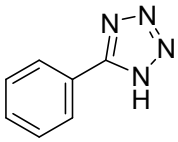

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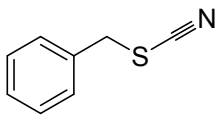

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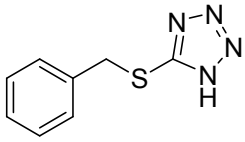

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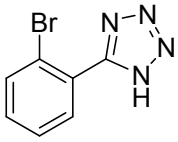

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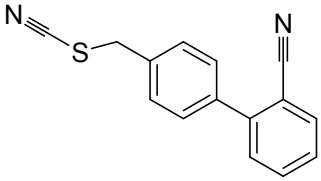

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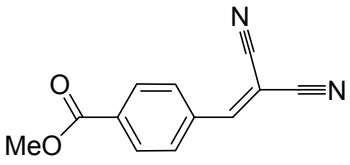

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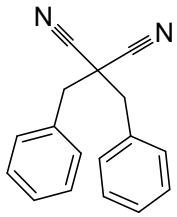

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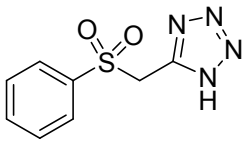

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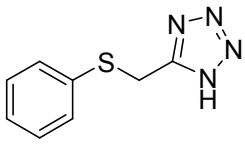

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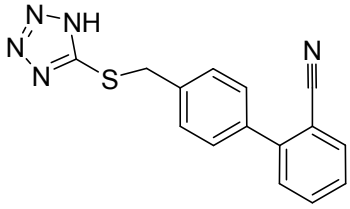

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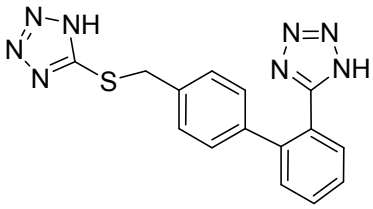

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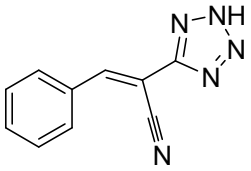

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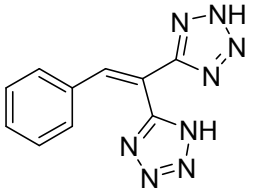

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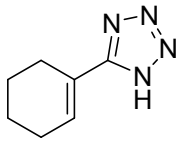

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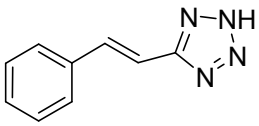

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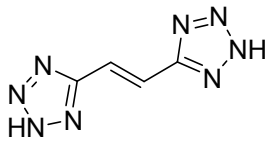

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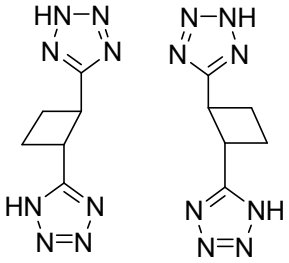

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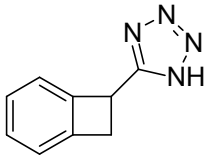

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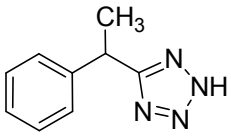

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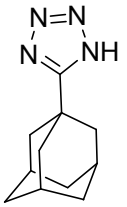

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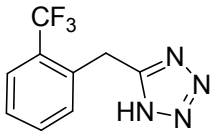

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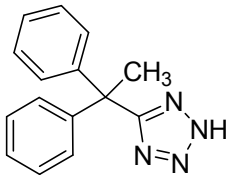

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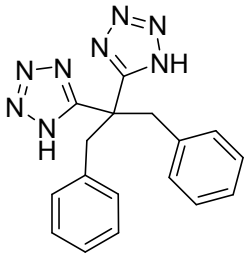

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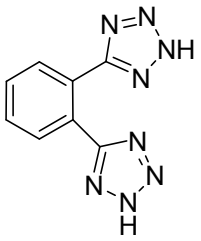

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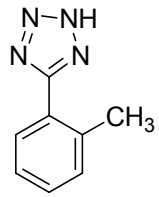

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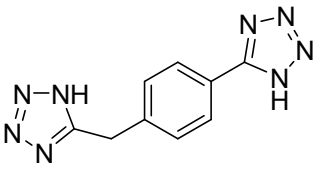

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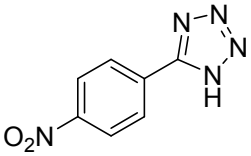

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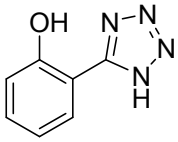

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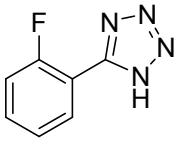

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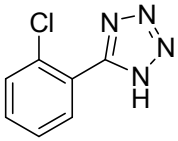

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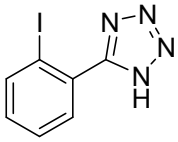

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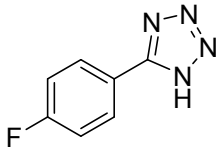

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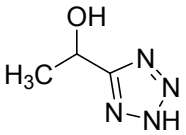

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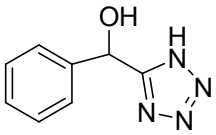

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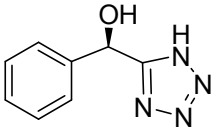

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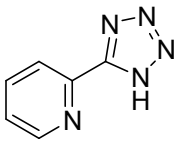

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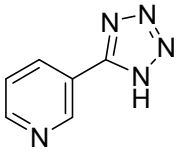

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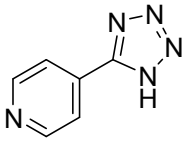

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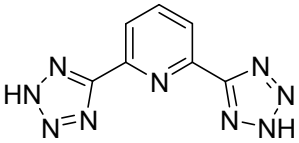

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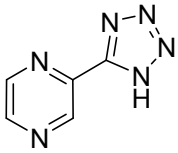

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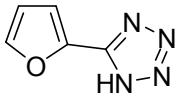

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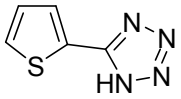

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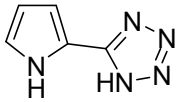

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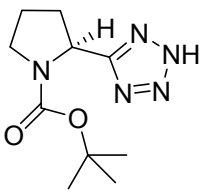

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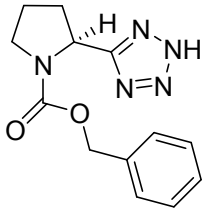

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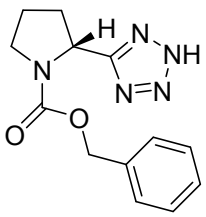

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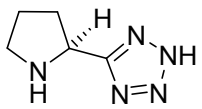

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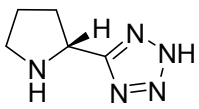

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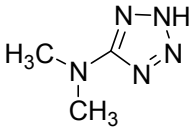

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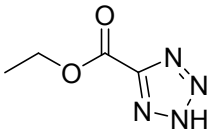

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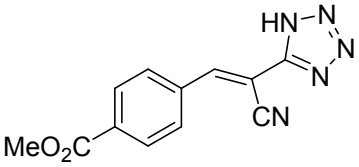

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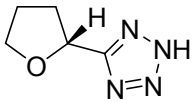

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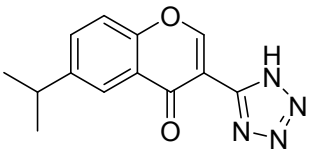

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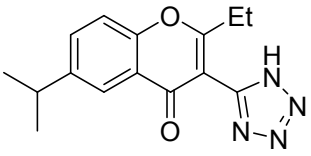

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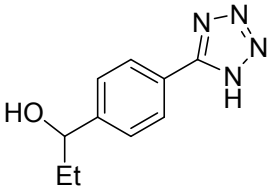

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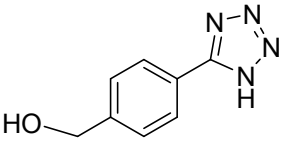

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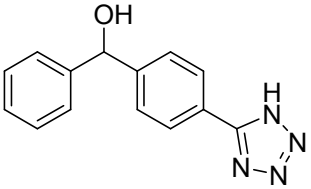

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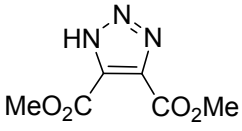

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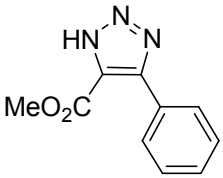

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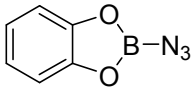

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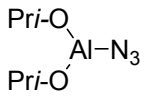

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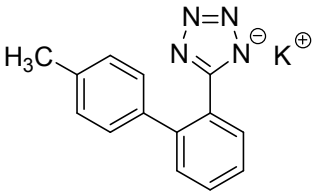

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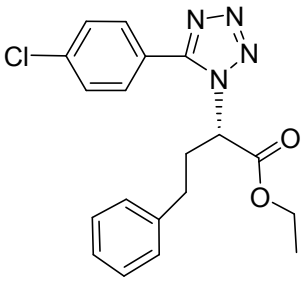

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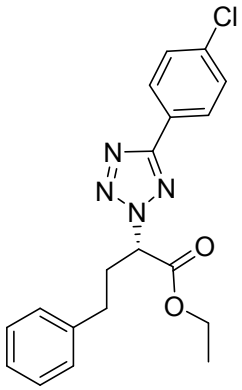

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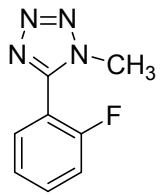

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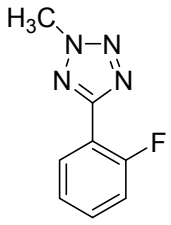

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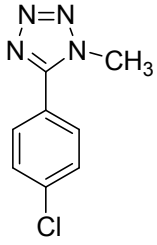

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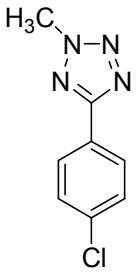

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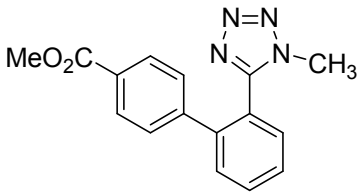

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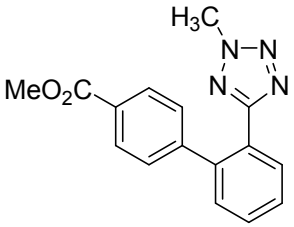

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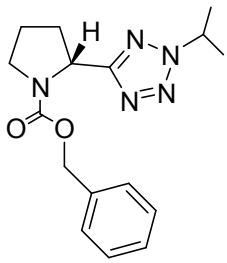

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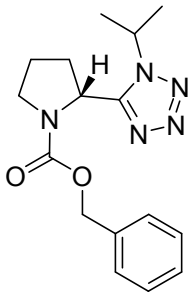

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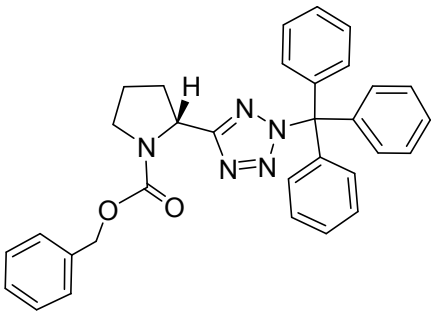

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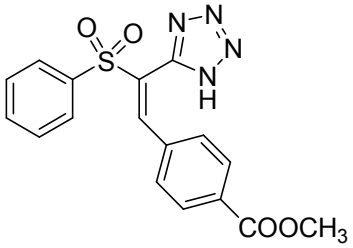

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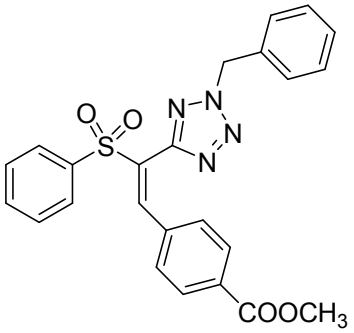

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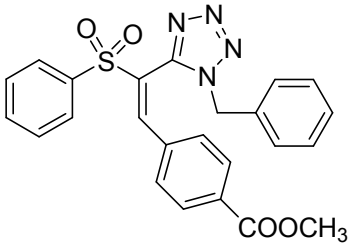

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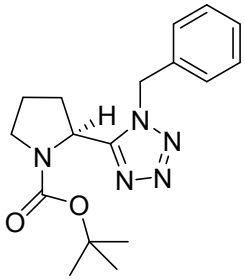

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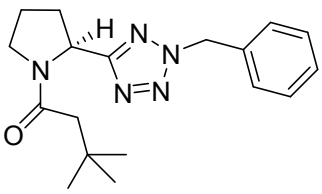

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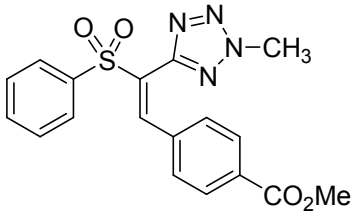

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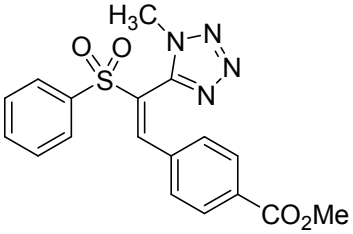

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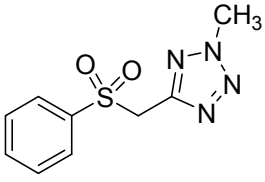

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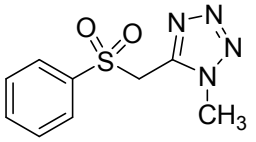

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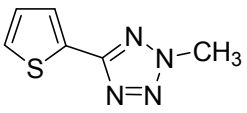

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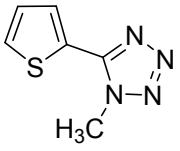

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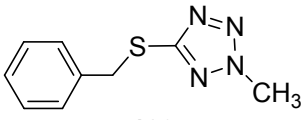

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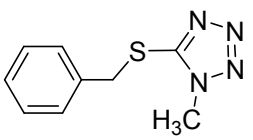

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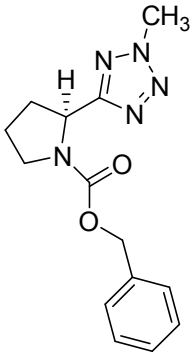

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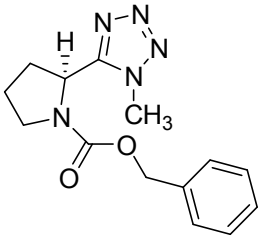

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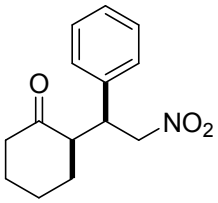

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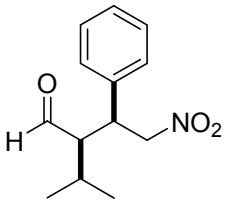

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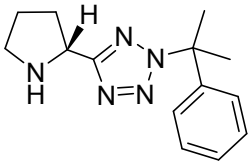

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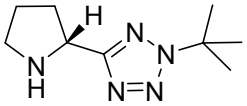

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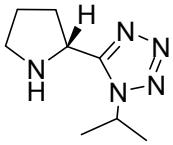

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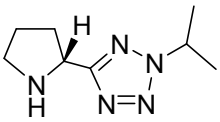

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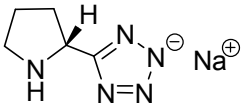

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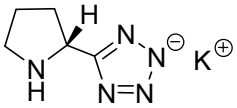

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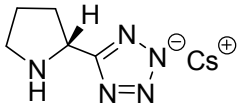

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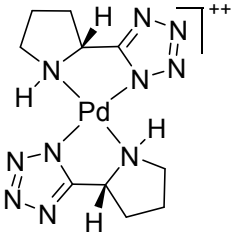

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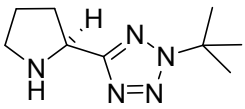

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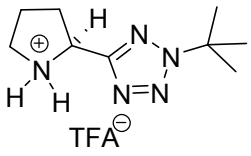

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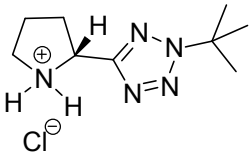

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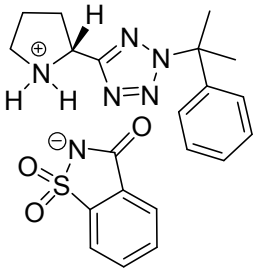

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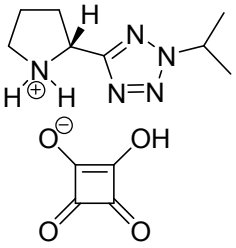

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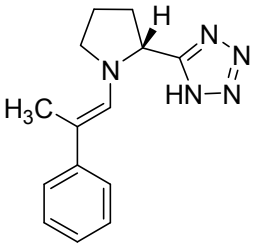

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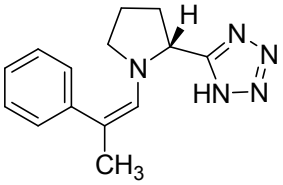

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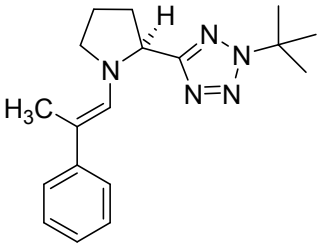

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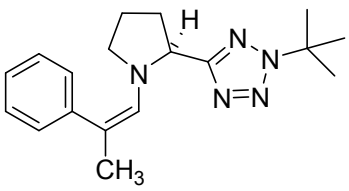

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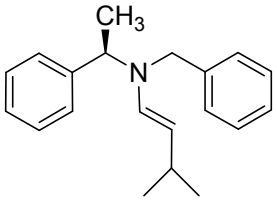

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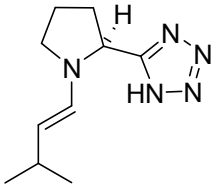

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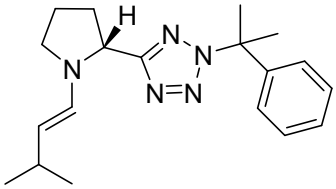

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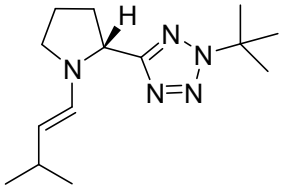

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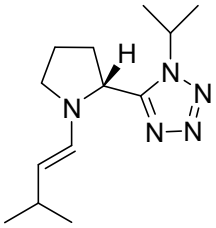

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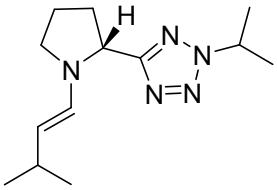

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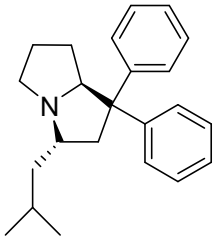

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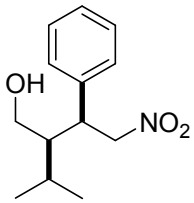

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