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Synthesis of Substituted 1-Thiocyanatobutadienes and their Application in a *Diels-Alder*/[3,3] Sigmatropic Rearrangement Tandem Reaction

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Summary. The retrosynthetic analysis of *Ibogamine*, a natural psychotropic alkaloid with exceptional anti-addictive properties found in both enantiomeric forms, requires an efficient access to a racemic cyclohexene. This cyclohexene can be obtained *via* the sequence *Diels-Alder*/[3,3] sigmatropic rearrangement reaction starting from substituted 1-thiocyanatobutadienes. An efficient synthesis of the enone, a stable precursor of 1-thiocyanatobutadienes, is reported. Enolisation of this enone was studied to find the optimal conditions to get the desired 1-thiocyanatobutadienes with good *Z*-selectivity.

Keywords. Enols; *Ibogamine*; Rearrangements; Tandem reactions; Total synthesis.

Introduction

The number of synthetic steps in a total synthesis strongly influences the efficiency. An attractive way to reduce the length of a synthetic pathway is to combine several transformations into one-pot reactions so called tandem, domino, or cascade reaction [1–3]. The tandem process *Diels-Alder* reaction/[3,3] sigmatropic rearrangement combines two well-known pericyclic reactions in one single synthetic step, which allows to obtain interesting synthetic building blocks efficiently [4]. Starting from (*E*)-1-thiocyanatobuta-1,3-diene (**1**) and acryloyl chloride led to a *cis*/*trans* 85:15 mixture of diastereoisomers of 1,4-substituted cyclohexene **3** in 84% yield [5] (Scheme 1). The cyclohexene **3** is a precursor for the preparation of the skeleton of *Iboga*-type alkaloids. The isothiocyanate **3** can be easily transformed in three steps to the 2-azabicyclo[2.2.2]oct-5-ene **4** [5] (Scheme 1). This

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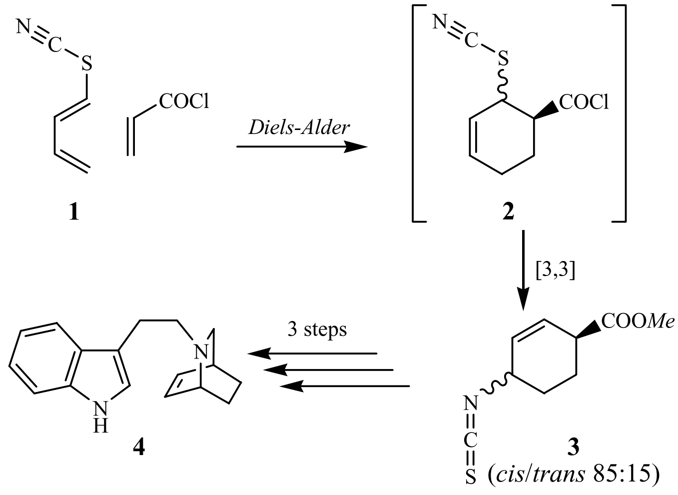
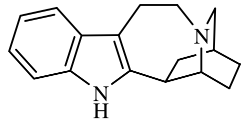


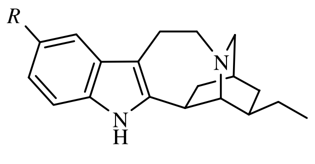
Scheme 1

bicyclic compound has been used by *Trost et al.* for the synthesis of *desethylibogamine* (**5**) [6, 7].

Ibogamine (**6a**), as other *Iboga*-type alkaloids, has been isolated from an African plant *Tabernanthe iboga* [8], which has well-known psychotropic activities. Studies on rodents have proven that **6a** shows exceptional multi-drug anti-addictive properties [8–10]. Unfortunately, despite the encouraging results described by *Lotsof* [11] about treatment of opioid withdrawal with *ibogaine* (**6b**) on human patients, systematic clinical studies have not been carried out. Since the first total synthesis of **6a** by *Büchi* [12] in 1965, eleven other total synthesis have been reported [7, 13–21] but none of them is cost- and material-efficient enough to allow the production of this compound or of derivatives of this compound in large scale industrial production.

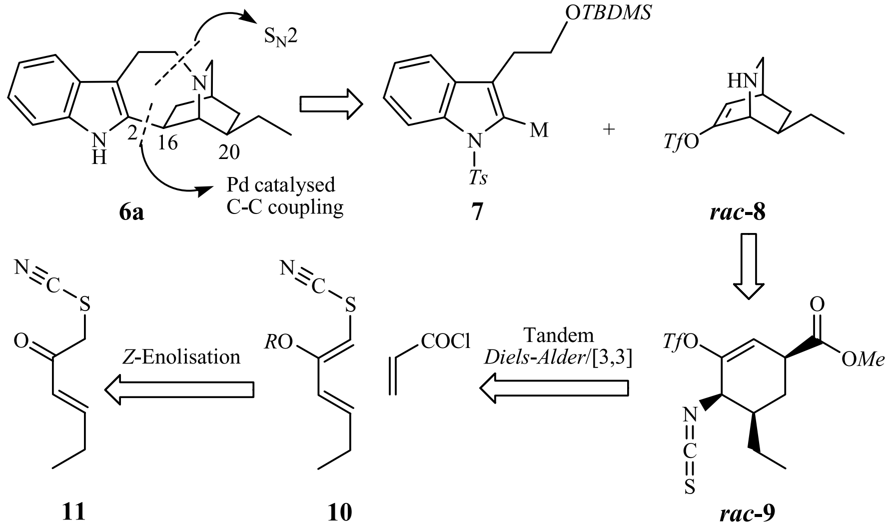


5 (+/-)-*Desethylibogamine*



6a *R* = H: (+/-)-*Ibogamine*
6b *R* = O*Me*: (+/-)-*Ibogaine*

In most of the reported total syntheses of *ibogamine* (**6a**), the crucial step is the formation of the C–C bond between the carbons C(2) corresponding to the α-position of the indole ring and C(16) one of the α-positions of the bridgehead carbon connected to the N-atom. In the total synthesis reported by *Trost et al.* this crucial C–C bond was formed using a palladium-catalysed *Heck*-type C–C coupling, in the presence of stoechiometric amounts of a silver salt [7]. The goal of our studies is to develop an alternative procedure for the synthesis of the strategic C–C bond avoiding use of stoechiometric quantities of a silver salt. Introducing a triflate protected enolate on carbon C(16) should allow to test different catalytic C–C

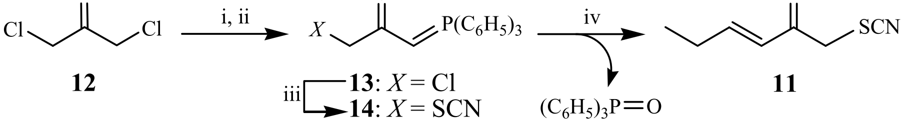


Scheme 2

coupling conditions. *Ibogamine* (**6a**), contrary to the model compound *desethylibogamine* (**5**), possesses an additional ethyl group in a pseudo-equatorial position on carbon C(20). The retrosynthetic analysis of **6a** based on the formation of the strategic C–C bond described above leads to two major building blocks of similar size: the indole derivative **7** (M=B(OH)$_2$, ZnCl) and the isoquinuclidine ring **rac-8**. We propose to obtain the isoquinuclidine ring **rac-8** *via* our tandem process *Diels-Alder* reaction/[3,3] sigmatropic rearrangement starting from the 2,4-substituted 1-thiocyanatobuta-1,3-diene **10**. In this paper the synthesis of diene **10** *via* a *Z*-enolisation of the enone **11** is reported and the stereoselectivity of this enolisation is studied.

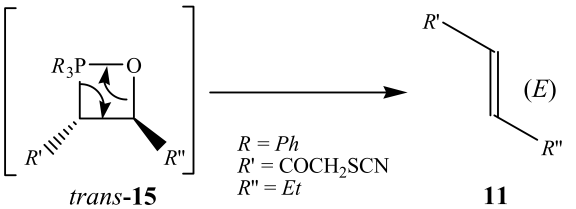
Results and Discussions

The initial step of the synthesis of enone **11** is the preparation of the phosphorane **13**. According to the procedure described by *Hudson et al.* [22], we started our synthesis from the highly toxic, commercially available 1,3-dichloroacetone **12**. According to the literature procedure the intermediate salt formed from the S_N2 reaction between the dichloroketone and triphenylphosphine was isolated in 85% yield. The salt was then deprotonated in a separate step to get the ylide **13**. To improve the yield and to reduce the time of exposure to toxic α-chloroketones, we developed a one-pot



Reagents and conditions: (i) P*Ph*$_3$, *THF*, reflux, 4h; (ii) Na$_2$CO$_3$, *Me*OH, rt, 30 min, 97%; (iii) KSCN, KI$_{cat}$, *Et*OH, 55°C, 5h, 96%; (iv) propionaldehyde, 40°C, 6h, 70%

Scheme 3



trans-**15** **11**

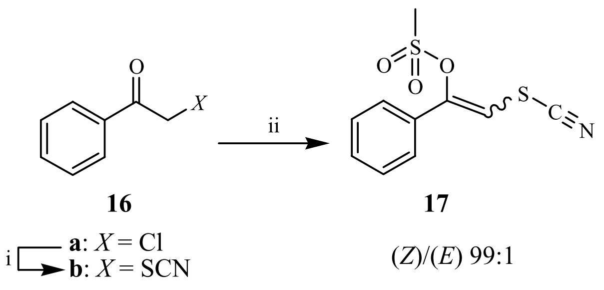
Scheme 4

process. Using this one-pot procedure the ylide **13** could be isolated in almost quantitative yield. Displacement of the first chlorine atom of 1,3-dichloroacetone **12** by triphenylphosphine was monitored by the disappearance of the ^{31}P signal of triphenylphosphine ($\delta_P = -4.4$ ppm) in its ^{31}P NMR (Scheme 3). The second S_N2 reaction replacing the chloride by nucleophilic attack of the sulphur atom of the thiocyanate anion was carried out in ethanol. In order to accelerate the reaction, the presence of a catalytic quantity of iodide was needed, as has been reported by *Sapi et al.* [23]. Thus, the thiocyanate **14** was obtained in very good yield and satisfactory purity so that the raw material could be used in the following step without further purification.

The *Wittig* reaction was assumed to be *E*-selective due to the stabilisation of ylide **14** by the adjacent carbonyl group. As assumed the *E*-enone **11** was obtained as a consequence of the thermodynamic equilibrium between the more stable *trans*-oxaphosphetane **15** and its *cis*-diastereoisomer during the *Wittig* reaction (Scheme 4).

Propionaldehyde was both the solvent and the reactant of our *Wittig* reaction. The progress of the reaction was monitored by the growth of the ^{31}P signal of triphenylphosphine oxide ($\delta_P = 30.1$ ppm) in ^{31}P NMR. The α,β-unsaturated ketone **11** is probably undergoing unwanted polymerisations, which make the purification difficult. Thus, after filtration on a short silica gel column, the enone **11** was purified by a bulb-to-bulb distillation (100°C, 10^{-1} mbar). By this straight forward three-steps process enone **11** could be obtained in 65% total yield starting from 1,3-dichloroacetone **12**.

In order to optimize the reaction conditions for the enolisation model **16b** was chosen. Synthesis of thiocyanate **16b** was carried out using a similar procedure as for the synthesis of **14** starting from commercially available phenacyl chloride **16a** (Scheme 5).



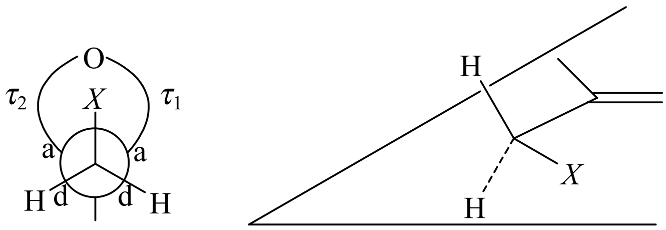
16 **17**

a: *X* = Cl
b: *X* = SCN

(*Z*)/(*E*) 99:1

Reagents and conditions: (i) KSCN, KI_{cat}, *Et*OH, rt, 4h, 86%; (ii) *Ms*Cl, Et_3N, CH_2Cl_2, rt, 45 min, 40%

Scheme 5

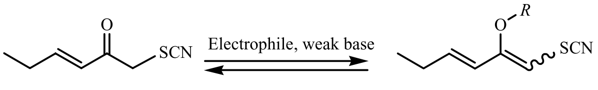


Scheme 6

The enolisation of α-halogenoketones usually leads to the kinetic (*Z*)-diastereoisomer [24]. The α-thiocyanatoketones can be viewed as pseudohalogen analogues of α-halogenoketones. The stereoselectivity of the enolisation can be explained using τ-bonds, also called "banana" bonds or bent bonds [25–28]. Using a *Newman* projection to describe the most stable ground state conformation of the α-halogenoketone, the strongest electron withdrawing substituent in the α-position of the carbonyl group (the halogen or the pseudohalogen) has to be in a *syn*-coplanar position relative to the C–O τ-bond (Scheme 6). In this conformation all bonds are staggered, the two hydrogen atoms, which are the best donor atoms, are in a *anti*-periplanar position compared to the two strongly electron attracting C–O τ-bonds (Scheme 6).

Having the precursors for our enolates in hand, we studied the stereoselectivity of the enolisation process of our enone **11** under thermodynamic conditions, using triethylamine or *Hünig*'s base. With our model compound **16b**, an excellent stereoselectivity of the enolisation was observed under our experimental conditions. Compound **17** was obtained as a (*Z*)/(*E*)-mixture with a diastereoselectivity of

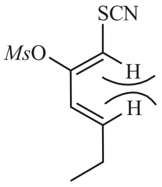
Table 1. Study of stereoselectivity of the enolisation of enone 11 under thermodynamic conditions



11 **10a-10e** (*ZE*)/(*EE*)

10	*R*	Procedure	(*ZE*)/(*EE*)[d]	*Yield*
a	*TMS*	*A*[a]	87:13	78%
b	*TBDMS*	*A*[a]	62:38	–[e]
c	*Ms*	*B*[b]	100:0	71%
d	*Ts*	*B*[b]	85:15	–[f]
e	*Tf*	*C*[c]	65:35[g]	72%[h]

[a] Procedure *A*: 2.2 eq triethylamine + 2 eq electrophile + 1 eq enone **11** in ether as solvent at rt for 1 h; [b] procedure *B*: 2–10 eq triethylamine + 1.2–5 eq electrophile + 1 eq enone **11** in CH_2Cl_2 as solvent at 0°C for 30 min; [c] procedure *C*: 1.4 eq diisopropylethylamine + 1.25 eq electrophile + 1 eq enone **11** in CH_2Cl_2 as solvent at 0°C for 30 min; [d] stereoselectivity estimated by ^1H NMR analysing the product of the *Diels-Alder* reaction; only the (*ZE*)-diastereoisomer can react in a *Diels-Alder* reaction; [e] under the conditions of procedure *A*, the diene **10b** could not be isolated, due to hydrolysis; the stereoselectivity was tentatively assigned based on the analysis of the raw material; [f] diene **10c** was isolated but not purified; [g] both diastereoisomers (*ZE*) and (*EE*) could be separated by chromatography on a silica gel column and the diasteriomeric ratio was estimated by ^{19}F NMR; [h] the synthesis of diene **10e** was also carried out under kinetic conditions resulting in a better stereoselectivity



10c

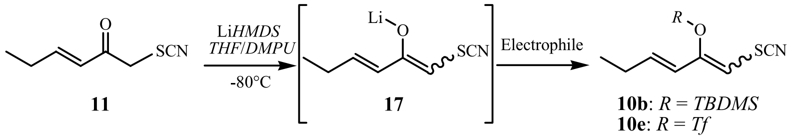
Scheme 7

99:1 (Scheme 5). As described in Table 1, four different electrophiles were used to trap the enol, applying three different experimental procedures (Table 1).

As predicted for the formation of the 1(*Z*),3(*E*)-diastereoisomers was favoured compared to the formation of the 1(*E*),3(*E*)-diastereoisomers. Using the procedure *B* and mesyl chloride as an electrophile the best diastereoselectivity was observed (*de* > 99%). A N*O*ESY experiment showed a crosspeak between H-C(1) and H-C(4) (Scheme 7) proving the structure of compound **10c**. The observed N*O*ESY crosspeak is only compatible with the *s-cis* conformation of the 1(*Z*), 3(*E*)-diastereoisomer.

Applying the conditions *D* for the enolisation of enone **11** under kinetic control the dienes **10b** and **10e** were obtained. The lithium enolate **17** is formed under low-temperature conditions. The enolate is then quenched by various electrophiles to get the desired substituted 1-thiocyanatobuta-1,3-diene **10b** and **10e**. As indicated in Table 2 very good yields were obtained under these conditions. A satisfactory diastereoselectivity was observed with *TBDMS*Cl as an electrophile (*de* = 60% in favour of 1(*Z*),3(*E*)-diastereoisomer of the silylated 1-thiocyanatohexa-1,3-diene **10b**). Using triflic anhydride as an electrophile, the influence of addition of *DMPU* as a co-solvent on diastereoselectivity was studied. A good diastereoselectivity (*de* = 78%) was observed without the use of the co-solvent. Addition of *DMPU* (20% in *THF*) improved the diastereoisomeric excess to *de* = 95%.

Table 2. Stereoselectivity of the enolisation of enone **11** under kinetically controlled condition



10	*R*	Procedure	*THF*/*DMPU*	(*ZE*)/(*EE*)[b]	Yield
b	*TBDMS*	*D*[a]	10:0	80:20	90%
e	*Tf*	*D*[a]	10:0	89:11[c]	50%[d]
e	*Tf*	*D*[a]	8:2	97.5:2.5[c]	85%

[a] Procedure *D*: 1.1 eq Li*HMDS* in *THF*/*DMPU* as solvent at −80°C for 45 min + 1.1 eq electrophile + 1 eq enone **11** in *THF* as solvent at 0°C for 1 h; [b] stereoselectivity estimated by ^{1}H NMR analysing the product of the *Diels-Alder* reaction; only the (*ZE*)-diastereoisomer can react in a *Diels-Alder* reaction; [c] the diastereomeric ratio was estimated by ^{19}F NMR; [d] non optimised

Conclusions

An efficient three-step synthesis of enone **11** has been developed giving **11** in 65% total yield. The stereoselectivity of the enolisation of **11** was studied under thermodynamically controlled conditions using different electrophiles to trap the enolate. Excellent diastereoisomeric excesses were observed and the best diastereoselectivity was found using mesyl chloride as an electrophile (*de* > 99%) yielding the 1(*Z*),3(*E*)-1-thiocyanatohexa-1,3-dien-2-yl methanesulfonate (**10c**). Under kinetically controlled conditions the 1-thiocyanatobuta-1,3-dienes **10b** and **10e** could be obtained. The addition of *DMPU* as a co-solvent was studied in the case of the 1-thiocyanatobuta-1,3-diene **10e**. The diastereoselectivity (*de* = 78%) could be improved using *DMPU* (*de* = 95%). Efficient synthesis of five different substituted 1-thiocyanatobuta-1,3-dienes **10a**–**10e** are reported in good total yields. Their efficiency in our *Diels-Alder*/[3,3] sigmatropic rearrangement tandem reaction will be studied in view of the development of a new total synthesis of (*rac*)-*Ibogamine* (**6a**).

Experimental Part

All moisture-sensitive reactions were carried out under Ar and N_2 using oven-dried glassware. All reagents were of commercial quality if not specifically mentioned. Solvents were freshly distilled prior to use. Flash chromatography (FC): Brunschwig silica gel 60, 0.032–0.063 mm; under positive pressure. TLC: Merck precoated silica gel thin-layer sheets 60 F 254, detection by UV and treatment with basic $KMnO_4$ sol. Mp: Gallenkamp MFB-595. IR spectra: Perkin Elmer Spectrum One FT-IR, in cm^{-1}. NMR spectra: Bruker Avance-400 (400 MHz (^1H), 162 MHz (^{31}P), and 100 MHz (^{13}C)) and Varian Gemini-2000 (188 MHz (^{19}F)), at rt, chemical shifts δ in ppm rel. to Si*Me*$_4$ (=0 ppm) as internal reference, coupling constants J in Hz. ESI-MS Finnigan LCQ. Elemental analyses of novel compounds agreed favourably with calculated values.

1-Chloro-3-(triphenyl-5λ-phosphanylidene)propan-2-one (**13**)

Triphenylphosphine (52.90 g, 200.9 mmol) in 75 cm^3 of dry *THF* was added to a solution of 25.12 g of 1,3-dichloroacetone (197.8 mmol) in 25 cm^3 of dry *THF*. The mixture was heated to reflux for 4 h and the solvent was then removed. The resulting white salt was dissolved in 100 cm^3 of methanol, and an aqueous solution (1.55 *M*) of 10.48 g of Na_2CO_3 (98.9 mmol) was added. The mixture was allowed to stand for 30 min and the white precipitate was dried in air to provide a white powder of pure **13** (67.58 g, 191.6 mmol, 97%). Ylide **13** has been described by *Hudson et al.* [22]. Mp 179–180°C (Ref. [22] 178–179°C); $R_f = 0.25$ (CH_2Cl_2/*Me*OH 97/3); ^{31}P NMR (162 MHz, $CDCl_3$): $\delta = 16.9$ ppm; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.68$–7.62 (m, 6H, H-5^2), 7.60–7.54 (m, 3H, H-5^4)), 7.50–7.45 (m, 6H, H-5^3), 4.28 (d, ^2J(3-P)=23.9 Hz, 1H, H-3), 4.02 (s, 2H, H-1) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 185.1$ (s, 1C, C-2), 133.1 (s, 6C, C-5^3), 133.0 (s, 3C, C-5^4), 128.9 (d, ^3J(5^2-P)=12.5 Hz, 6C, C-5^2), 126.2 (d, ^1J(5^1-P)=91.3 Hz, 3C, C-5^1), 51.4 (d, ^1J(3-P)=114.5 Hz, 1C, C-3), 47.3 (d, ^3J(1-P)=16.1 Hz, 1C, C-1) ppm.

1-Thiocyanato-3-(triphenyl-5λ-phosphanylidene)propan-2-one (**14**, $C_{22}H_{18}NOPS$)

Ylide **13** (64.42 g, 182.6 mmol) in 300 cm^3 of ethanol was added to a solution of 21.30 g of potassium thiocyanate (219.1 mmol) in 350 cm^3 of hot ethanol and 3.03 g of KJ (18.3 mmol) were added. The mixture was allowed to stir at 55°C for 5 h and cooled to rt. The potassium salts were filtered off, most of the solvent was evaporated in the rotavap, and 400 cm^3 of CH_2Cl_2 were added. The potassium salts were filtered off again and washed with cold CH_2Cl_2. The resulting solution was concentrated to dryness to provide pure **14** (65.75 g, 175.1 mmol, 96%), mp 146–148°C. $R_f = 0.39$ (CH_2Cl_2/*Me*OH 97/3); ^{31}P NMR (162 MHz, $CDCl_3$): $\delta = 16.1$ ppm; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.70$–7.52 (m, 9H, H-5^2, H-5^4), 7.51–7.42 (m, 6H, H-5^3), 3.96 (d, ^2J(3-P)=24.0 Hz, 1H, H-3), 3.92 (s, 2H, H-1) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 181.5$ (d, ^2J(2-P)=3.1 Hz, 1C, C=O), 133.1 (d, ^4J(5^3-P)=9.9 Hz, 6C, C-5^3), 132.6 (d, ^3J(5^4-P)=3.0 Hz, 3C, C-5^4), 129.2 (d, ^3J(5^2-P)=12.7 Hz, 6C, C-5^2), 125.7 (d, ^1J(5^1-P)=91.2 Hz, 3C, C-5^1), 114.1 (SCN), 52.9 (d, ^1J(3-P)=108.5 Hz, 1C, C-3), 43.1 (d, ^3J(1-P)=19.1 Hz, 1C, C-1) ppm; IR (KBr): $\bar{\nu} = 2994$, 2153, 1577, 1548, 1482, 1438, 1228, 1108, 764, 747, 719, 692, 518, 507 cm^{-1}.

(E)-1-Thiocyanatohex-3-en-2-one (**11**, C_7H_9NOS)

A solution of 44.35 g of ylide **14** (118.1 mmol) in 86 cm^3 of freshly distilled propanal is allowed to stir at 40°C for 6 h under Ar and cooled to rt. The mixture was concentrated and quickly filtered on a short silica gel column (200 g; *n*-hexane/CH_2Cl_2 1/1). The resulting brown oil was purified by bulb-to-bulb distillation (100°C at 10^{-1} mbar) to provide a malodorous pale yellow oil (12.80 g, 82.5 mmol, 70%). $R_f = 0.42$ (CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.03$ (dt, ^3J(4-3)=16.0 Hz, ^3J(4-5)=6.3 Hz, 1H, H-4), 6.19 (dt, ^3J(3-4)=16.0 Hz, ^4J(3-5)=1.7 Hz, 1H, H-3), 4.24 (s, 2H, H-1), 2.31 (qdd, ^3J(5-6)=7.4 Hz, ^3J(5-4)=6.3 Hz, ^4J(5-3)=1.7 Hz, 2H, H-5), 1.10 (t, ^3J(6-5)=7.4 Hz, 3H, H-6) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): $\delta = 190.5$ (C=O), 153.6 (C-4), 126.5 (C-3), 111.9 (SCN), 42.7 (C-1), 25.9 (C-5), 11.9 (C-6) ppm; IR (film): $\bar{\nu} = 2972$, 2935, 2878, 2158, 1687, 1626, 1460, 1392, 1341, 1297, 1245, 1180, 1109, 1081, 1015, 977, 909 cm^{-1}.

1-Phenyl-2-thiocyanatoethanone (**16b**)

According to the procedure described for **14**, 5.96 g of phenacyl chloride (38.5 mmol) were treated with 4.70 g of KSCN (48.4 mmol) and 0.66 g of KJ (4.0 mmol) giving 5.90 g of **16b** (33.3 mmol, 86%) as brown crystals. Thiocyanate **16b** has been already isolated by *Prakash et al.* [29] as an oil. Recrystallisation in *n*-hexane/*Ac*O*Et* 2/1 gave needle shaped yellow crystals. Mp 81–82°C; $R_f = 0.38$ (*n*-hexane/*Ac*O*Et* 3/1); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.96$ (ddm, ^3J(3^2-3^3)=8.4 Hz, ^4J(3^2-3^4)= 1.3 Hz, 2H, H-3^2), 7.69 (tt, ^3J(3^4-3^3)=7.4 Hz, ^4J(3^4-3^2)=1.3 Hz, 1H, H-3^4), 7.55 (dd, ^3J(3^3,3^2)=8.4 Hz, ^3J(3^3,3^4)=7.4 Hz, 2H, H-3^3), 4.76 (s, 2H, H-2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 190.9$ (C=O), 134.9 (C-3^4), 134.1 (C-3^1), 129.3 (C-3^3), 128.6 (C-3^2), 112.0 (SCN), 43.1 (C-2) ppm; IR (KBr): $\bar{\nu} = 2937$, 2156, 1678, 1593, 1448, 1379, 1326, 1296, 1202, 998, 757, 687, 630 cm^{-1}.

(Z)-1-Phenyl-2-thiocyanatovinyl methanesulfonate (**17**, $C_{10}H_9NO_3S_2$)

Triethylamine (141 mg, 1.4 mmol) was added to a solution of 177 mg of **16b** (1.0 mmol) in 5 cm^3 of dry CH_2Cl_2 under Ar. After cooling to 0°C, 143 mg of methanesulfonyl chloride (1.25 mmol) were slowly introduced at 0°C (10 min). After warming to rt, the resulting mixture was stirred for additional 45 min, diluted in 25 cm^3 of CH_2Cl_2, and washed with 25 cm^3 of H_2O whose *pH* was adjusted to 3–5 with aqueous HCl (1 *M*). The organic layer was then washed with brine, dried ($MgSO_4$), and the solvent was evaporated to dryness to provide a green powder of a mixture of the two stereoisomers (*Z*)/(*E*) (99/1) **17** (102 mg, 0.4 mmol, 40%). $R_f = 0.21$ (*n*-hexane/*Ac*O*Et* 3/1); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.56$–7.50 (m, 2H, H-3^3), 7.50–7.42 (m, 3H, H-3^2, H-3^4), 6.50 (s, 1H, H-2(*E*)), 6.44 (s, 1H, H-2(Z)), 3.15 (s, 3H, H-3(Z)), 3.01 (s, 3H, H-3(*E*)) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 151.0$ (C-1), 132.2 (C-3^1), 131.2 (C-3^4), 129.3 (C-3^2), 126.2 (C-3^3), 109.5 (SCN), 105.9 (C-2), 39.9 (C-3) ppm; IR (KBr): $\bar{\nu} = 3068$, 3036, 2934, 2164, 1681, 1622, 1354, 1264, 1172, 1008, 961, 864, 801, 779, 718, 524, 505 cm^{-1}.

*General Procedures for the Synthesis of the Substituted 1-Thiocyanatobutadienes **10a–10e***

Procedure A: To a stirred 0.6 *M* solution of 2.2 eq of triethylamine in diethylether at rt under Ar were added dropwise 2.0 eq of the corresponding electrophile. 1.0 eq of **11** was then added dropwise to the solution for 5 min. The resulting mixture was magnetically stirred at rt for 1 h and the solvent was evaporated. Freshly distilled *n*-pentane was added to the crude product, the salts were filtered off and washed with freshly distilled *n*-pentane again. After evaporating the *n*-pentane *in vacuo*, the product was isolated without further purification.

Procedure B: To a stirred 0.8 *M* solution of 1.0 eq of **11** in CH_2Cl_2 at 0°C under Ar were added 2.0–10.0 eq of triethylamine. A 3.0 *M* solution of 1.2–5.0 eq of the corresponding electrophile in CH_2Cl_2 was then added dropwise to the solution for 30 min. The resulting mixture was magnetically stirred at 0°C for 30 min and then diluted in CH_2Cl_2. The organic phase was then washed with H_2O, dried ($MgSO_4$), and concentrated *in vacuo* to obtain the raw product that was then purified by chromatography on a silica gel column.

Procedure C: To a stirred 0.2 *M* solution of 1.0 eq of **11** in CH_2Cl_2 at rt under Ar were added 1.4 eq of diisopropylethylamine. After cooling to 0°C, 1.25 eq of the corresponding electrophile were added dropwise to the solution during 5 min. The resulting mixture was magnetically stirred at 0°C for 30 min and then diluted in CH_2Cl_2. The organic phase was washed with saturated aqueous NH_4Cl, H_2O, dried ($MgSO_4$), and concentrated *in vacuo* to get the product that was purified by chromatography on a silica gel column.

Procedure D: A solution of 1.1 eq of Li *bis*(trimethyldisilyl)amide (1 *M* in *THF*) was diluted 3 times in a *THF*/*DMPU* mixture to get a 0.33 *M* solution, which was cooled to −90°C. A 1.0 *M* solution of 1.0 eq of **11** in freshly distilled *THF* was then added dropwise while maintaining the temperature of the solution below −80°C. The orange solution was then magnetically stirred at −85°C for 45 min and 1.1 eq of the corresponding electrophile were added dropwise maintaining the temperature of the solution below −80°C. The temperature was then allowed to warm slowly to 0°C and the mixture was stirred for additional 1 h at 0°C. After diluting three times the reactions mixture with *n*-hexane, the solution was poured onto saturated aqueous NH_4Cl. The organic phase was washed with H_2O and brine, dried ($MgSO_4$), and concentrated *in vacuo* to get the product that was purified by chromatography on a silica gel column.

Trimethyl((3E)-1-thiocyanatohexa-1,3-dien-2-yloxy)silane (**10a**, $C_{10}H_{17}NOSSi$)

Procedure *A*: Freshly distilled enone **11** (0.40 g, 2.58 mmol) was reacted with 0.56 g of trimethylchlorosilane (5.15 mmol) to obtain **10a** as a yellow oil (0.46 g, 2.02 mmol, 78%) and (*ZE*)/(*EE*) mixture (87/13). Compound **10a** was extremely sensitive towards hydrolysis. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 6.65$ (dt, ^3J(3-4)=15.4 Hz, ^4J(3-5)=1.1 Hz, 1H, H-3(*EE*)), 6.37 (dt, ^3J(4-3)=15.3 Hz, ^3J(4-5)=6.2 Hz, 1H, H-4(*EE*), 6.08 (dt, ^3J(4-3)=15.3 Hz, ^3J(4-5)=6.2 Hz, 1H, H-4(*ZE*), 5.89 (dt, ^3J(3-4)=15.4 Hz, ^4J(3-5)=1.1 Hz, 1H, H-3(*ZE*)), 5.25 (s, 1H, H-1(*ZE*)), 5.12 (s, 1H, H-1(*EE*)), 2.16 (qdd, ^3J(5-6)=7.4 Hz, ^3J(5-4)=6.3 Hz, ^4J(5-3)=1.1 Hz, 2H, H-5), 1.03 (t, ^3J(6-5)=7.4 Hz, 3H, H-6), 0.29 (s, 9H, H-2^1) ppm.

tert-Butyldimethyl((3E)-1-thiocyanatohexa-1,3-dien-2-yloxy)silane (**10b**, $C_{13}H_{23}NOSSi$)

Procedure *D*: Enone **11** (0.47 g, 3.00 mmol) was reacted with a 1.0 *M* solution of 0.50 g of *tert*-butyldimethylchlorosilane (3.31 mmol) in freshly distilled *THF*. After purification by quick filtration on silica gel with *n*-hexane/*AcOEt* 95/5, compound **10b** was obtained as yellow oil (0.73 g, 2.71 mmol, 90%) and (*ZE*)/(*EE*) mixture (80/20) that could not be separated. R_f (*ZE*) = 0.79, R_f (*EE*) = 0.89 (*n*-hexane/*AcOEt* 10/1); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.63$ (dt, ^3J(3-4)=15.2 Hz, ^4J(3-5)=1.6 Hz, 1H, H-3(*EE*)), 6.42 (dt, ^3J(4-3)=15.2 Hz, ^3J(4-5)=6.5 Hz, 1H, H-4(*EE*), 6.07 (dt,

^3J(4-3)=15.5 Hz, ^3J(4-5)=6.5 Hz, 1H, H-4(*ZE*)), 5.85 (dt, ^3J(3-4)=15.5 Hz, ^4J(3-5)=1.6 Hz, 1H, H-3(*ZE*)), 5.23 (s, 1H, H-1(*ZE*)), 5.10 (s, 1H, H-1(*EE*)), 2.23 (qdd, ^3J(5-6) = 7.4 Hz, ^3J(5-4) = 6.5 Hz, ^4J(5-3)=1.6 Hz, 2H, H-5(*EE*)), 2.13 (qdd, ^3J(5-6)=7.4 Hz, ^3J(5-4)=6.5 Hz, ^4J(5-3)=1.6 Hz, 2H, H-5(*ZE*)), 1.07 (t, ^3J(6-5)=7.4 Hz, 3H, H-6(*EE*)), 1.02 (t, ^3J(6-5)=7.4 Hz, 3H, H-6(*ZE*)), 1.00 (s, 9H, H-2^3(*ZE*)), 0.96 (s, 9H, H-2^3(*ZE*)), 0.20 (s, 6H, H-2^1(*EE*)), 0.19 (s, 6H, H-2^1(*ZE*)) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 161.7$ (C-2(*EE*)), 157.7 (C-2(*ZE*)), 141.4 (C-4(*EE*)), 137.8 (C-4(*ZE*)), 124.5 (C-3(*ZE*)), 120.7 (C-3(*EE*)), 112.0 (SCN(*EE*)), 111.5 (SCN(*ZE*)), 90.0 (C-1(*ZE*)), 85.8 (C-1(*EE*)), 25.8 (C-2^3(*ZE*)), 25.7 (C-5(*ZE*)), 25.6 (C-2^3(*EE*)), 25.4 (C-5(*EE*)), 18.5 (C-2^2(*EE*)), 18.3 (C-2^2(*ZE*)), 13.0 (C-6(*ZE*)), 13.0 (C-6(*EE*)), −3.4 (C-2^1(*EE*)), −4.4 (C-2^1(*ZE*)) ppm.

According to procedure *A* using a 1.0 *M* solution of *tert*-butyldimethylchlorosilane in diethylether, a (*ZE*)/(*EE*) mixture (63/37) of impure **10b** was obtained.

(1Z,3E)-1-Thiocyanatohexa-1,3-dien-2-yl methanesulfonate (**10c**, $C_8H_{11}NO_3S_2$)

Procedure *B*: Enone **11** (0.54 g, 3.48 mmol) in 35 cm^3 of CH_2Cl_2 was reacted with a 0.5 *M* solution of 0.50 g of methanesulfonylchloride (4.35 mmol) in CH_2Cl_2 and 1.34 g of triethylamine (13.23 mmol). Isolation according to *A* to get **10c** as yellow oil (0.58 g, 2.49 mmol, 71%). $R_f = 0.20$ (CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.36$ (dtd, ^3J(4-3)=15.8 Hz, ^3J(4-5)=6.6 Hz, ^5J(4-1)=0.5 Hz, 1H, H-4), 6.18 (dd, ^5J(1-4)=0.5 Hz, ^3J(1-3)=0.5 Hz, 1H, H-1), 5.97 (dtd, ^3J(3-4)=15.8 Hz, ^4J(3-5)=1.3 Hz, ^4J(3-1)=0.5 Hz, 1H, H-3), 3.05 (s, 3H, H-2^1), 2.19 (qdd, ^3J(5-6)=7.4 Hz, ^3J(5-4)=6.3 Hz, ^4J(5-3)=1.3 Hz, 2H, H-5), 1.03 (t, ^3J(6-5)=7.4 Hz, 3H, H-6) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): $\delta = 175.9$ (C-2), 148.2 (SCN), 139.0 (C-4), 114.4 (C-3), 41.7 (C-2^1), 25.7 (C-5), 12.8 (C-6) ppm; ^{1}H N*O*ESY: cross peak between $\delta = 6.36$ and 6.18 ppm.

(3E)-1-Thiocyanatohexa-1,3-dien-2-yl 4-methylbenzenesulfonate (**10d**, $C_{14}H_{15}NO_3S_2$)

Procedure *B*: Enone **11** (0.31 g, 2.00 mmol) was reacted with a 0.4 *M* solution of 0.76 g of *p*-toluenesulfonyl chloride (4.00 mmol) in CH_2Cl_2 and 2.02 g of triethylamine (20.00 mmol). A (*ZE*)/(*EE*) mixture (65/35) of impure **10d** (0.50 g) was obtained by this procedure. $R_f = 0.14$ (14% *Ac*O*Et* in *n*-hexane). ESI-MS: $m/z = 332.1$ $[M + Na]^+$.

(3E)-1-Thiocyanatohexa-1,3-dien-2-yl trifluoromethanesulfonate (**10e**, $C_8H_8F_3NO_3S_2$)

Procedure *D*: Enone **11** (130 mg, 0.84 mmol) was reacted with a 1.0 cm^3 of a 1 *M* Li*HMDS* solution diluted with 2 cm^3 of a 7/3 mixture of *THF*/*DMPU*. Triflic anhydride (0.16 cm^3, 0.94 mmol) was added. Compound **10e** was obtained as yellow oil (205 mg, 0.71 mmol, 85%) and (*ZE*)/(*EE*) mixture (97.5/2.5). Both diastereoisomers could be separated by chromatography on a silica gel column using *n*-hexane/*Ac*O*Et* 95/5 as an eluant. ESI-MS: $m/z = 310.0$ $[M + Na]^+$.

1(Z),3(E)-Diastereoisomer: $R_f = 0.34$ (*n*-hexane/*Ac*O*Et* 95/5); ^{19}F NMR (188 MHz, $CDCl_3$): $\delta = -73.16$ ppm; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.32$ (dt, ^3J(4-3)=15.6 Hz, ^3J(4-5)=6.5 Hz, 1H, H-4), 6.09 (s, 1H, H-1), 6.02 (dt, ^3J(3-4)=15.6 Hz, ^4J(3-5)=1.6 Hz, 1H, H-3), 2.24 (qdd, ^3J(5-6)=7.4 Hz, ^3J(5-4)=6.5 Hz, ^4J(5-3)=1.6 Hz, 2H, H-5), 1.07 (t, ^3J(6-5)=7.4 Hz, 3H, H-6) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 150.3$ (C-2), 141.7 (C-4), 120.1 (C-3), 116.9 (C(SCN)), 108.4 (C-2^1), 104.9 (C-1), 25.8 (C-5), 12.6 (C-6) ppm.

1(E),3(E)-Diastereoisomer: $R_f = 0.49$ (*n*-hexane/*Ac*O*Et* 95/5); ^{19}F NMR (188 MHz, $CDCl_3$): $\delta = -73.65$ ppm; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.49$ (dt, ^3J(4-3)=15.4 Hz, ^3J(4-5)=6.5 Hz, 1H, H-4), 6.35 (dt, ^3J(3-4)=15.4 Hz, ^4J(3-5)=1.5 Hz, 1H, H-3), 6.10 (s, 1H, H-1), 2.32 (m, ^3J(5-6)=7.4 Hz, ^3J(5-4)=6.5 Hz, ^4J(5-3)=1.5 Hz, 2H, H-5), 1.11 (t, ^3J(6-5)=7.4 Hz, 3H, H-6) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 151.3$ (C-2), 144.8 (C-4), 126.0 (SCN), 116.9 (C-3), 108.3 (C-2^1), 103.0 (C-1), 26.3 (C-5), 12.6 (C-6) ppm.

The same procedure without the use of *DMPU* led to a (*ZE*)/(*EE*) mixture (89/11) of **10e** in 50% yield which was not optimised.

Procedure *C*: Enone 11 (0.40 g, 2.57 mmol) was reacted with triflic anhydride. Compound **10e** was then purified by chromatography on a silica gel column by using CH_2Cl_2 as an eluant to get a (*ZE*)/(*EE*) mixture (65/35) (0.53 g, 1.85 mmol) in 72% yield which was not optimised.

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