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A Novel Pyrrole Synthesis**

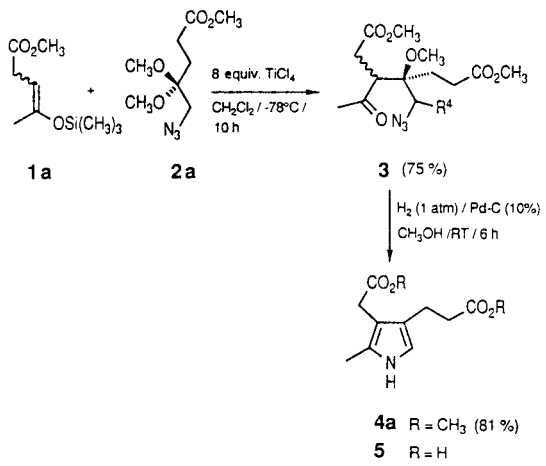
By *Hugo Bertschy, Anne Meunier*, and *Reinhard Neier**

The importance of pyrroles as natural products can be traced to the many functions which are fulfilled by tetrapyrrolic ligands.[1] The most important example of a natural alkyl-substituted pyrrole is porphobilinogen, the precursor for all tetrapyrrolic ligands. Biosynthetically, porphobilinogen is formed with the help of δ-aminolevulinic acid dehydratase (EC 4.2.1.24) in a condensation reaction starting from two molecules of δ-aminolevulinic acid.[2] Formally, this transformation corresponds to a Knorr pyrrole synthesis. Up to now, however, this synthetic path could not be imitated in vitro.

Two mechanisms have been postulated for the enzyme-catalyzed synthesis of porphobilinogen, but no unequivocal proof for either of them has been put forward.[3] The mechanism proposed by *Shemin* is especially attractive for chemists, because the reaction sequence starts with the key step, the formation of the C–C bond. The problem of regioselectivity is solved right at the beginning and all the successive steps follow from the natural reactivity of the intermediates. This is in contrast to the proposed mechanism for the Knorr pyrrole synthesis,[4] where the C–N bond is formed first. In the Knorr synthesis the C–C bond formation occurs regioselectively only if the intermediate enamine is stabilized by conjugation. It is therefore difficult to synthesize alkyl-substituted pyrroles using a Knorr reaction.

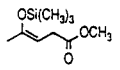
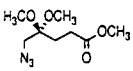
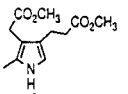
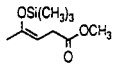
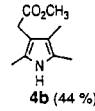
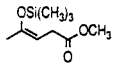
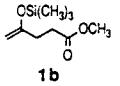
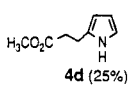
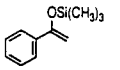
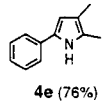
We report here the regioselective synthesis of alkyl-substituted pyrroles, which follows *Shemin*'s proposal for the biosynthesis of porphobilinogen. Regioselectively formed silyl enol ethers are used in a crossed aldol reaction[5] (Scheme 1). The aldol products are transformed into mono-, di-, tri-, and tetraalkyl-substituted pyrroles (Table 1). Annelated and aryl-substituted pyrroles can also be synthesized via this sequence. The substitution pattern is determined by the aldol reaction. This sequence allows the synthesis of pyrroles starting with aldol products under very mild conditions.

In order to use *Mukaiyama*'s crossed aldol reaction for the synthesis of pyrroles, adequate derivatives of α-amino ketones had to used. The azido group has been used successfully as a synthetic equivalent for amino groups. The acetal of α-azido ketones can be easily synthesized in two steps starting from α-halo ketones.[6] The synthesis of the second component, the silyl enol ethers, has been described already.[7]



Scheme 1. Synthesis of the pyrrole **4a** via crossed aldol reaction (RT = room temperature).

Table 1. Synthesis of alkylpyrroles using the regioselective aldol reaction followed by cyclization.

No.	Silyl enol ether [a]	Acetal [b]	Reaction conditions [c]	Product (yield [%]) [d]
1	 **1a**	 **2a**	1. A, 75 % 2. B, 81 %	 **4a** (61 %)
2	 **1a**	 **2b**	1. A, 84 % 2. B, 52 %	 **4b** (44 %)
3	 **1a**	 **2c**	1. A, 80 % 2. B, 63 %	 **4c** (50 %)
4	 **1b**	 **2c**	1. A, 98 % 2. B, 26 %	 **4d** (25%)
5	 **6**	 **2b**	1. A, 85 % 2. C, 89 %	 **4e** (76%)

[a] Acetal:silyl enol ether = 1:1.1. [b] Acetals **2a** and **2b** were synthesized starting from the azido ketones [6]. Compound **2c** was synthesized starting from commercially available 2-bromo-1,1-dimethoxyethane (1.5 equiv. NaN_3/DMSO·KI (cat.)/90 °C/5 d). [c] A: 6 equiv. $TiCl_4/CH_2Cl_2/-78$ °C/6–8 h (trial 1:8 equiv. $TiCl_4$), yield calculated starting from the acetal; B: H_2/Pd-C 10%/CH_3OH room temperature 6 h–2 d; C: PBu_3/C_6H_6/room temperature/5 d. yield relative to the unpurified aldol product; after crystallization (trial 1), after flash chromatography (hexane/EtOAc) (trials 4, 5), after kugelrohr distillation (80–120 °C/10^{-3} Torr) (trials 2, 3). [d] Total yield.

[*] Priv.-Doz. Dr. R. Neier, Dipl.-Chem. H. Bertschy, Dr. A. Meunier
Organisch-chemisches Institut der Universität
Pérolles, CH-1700 Fribourg (Switzerland)

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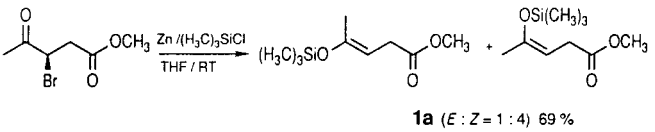
However, only the synthesis of the mixture of the two regioisomers **1a** and **1b** has been reported. We succeeded in synthesizing **1a** and **1b** regioselectively starting from the corresponding bromides (Scheme 2). The α-bromo ketones could be transformed reductively with zinc and trimethylchlorosilane into the pure silyl enol ethers **1a** and **1b** (69% and 76% yield, respectively). The addition of tetramethylethylenediamine after the reduction but before workup is crucial for the success of the reductive silylation.[8]

The key step of our synthetic plan, the aldol reaction between a silyl enol ether and an α-azido acetal generally gave product in good yield (75%–98%, compare Table 1). A great excess of $TiCl_4$ was used to accelerate the aldol reaction. The separation of the mixture of diastereoisomers formed in the aldol reaction was not necessary for the synthesis of pyrroles. The aldol product could be directly treated with phosphanes in a Staudinger reaction or reduced with hydrogen[9] to give pyrroles in good yields (26%–89%, compare Table 1). Only the corresponding pyrrole could be isolated. The purification of the sensitive alkyl-substituted pyrroles was the most difficult task in this reaction sequence. The products are very unstable in the presence of tiny amounts of acids. Therefore, the workup for each product had to be optimized. The catalytic reduction has been successful in most cases. Removal of the catalyst by filtration followed by evaporation of the solvent often furnished a product of good spectroscopic purity.

This novel pyrrole synthesis allows the formation of unstablized alkylpyrroles in a regioselective manner. The synthetic strategy follows the proposal of *Shemin* for the biosynthesis of porphobilinogen. The enzymatic synthesis of the pyrrole **5** starting from one molecule of levulinic acid and one molecule of δ-aminolevulinic acid has been described.[10] Therefore, the synthesis of the pyrrole **4a** mimics formally the biosynthetic process by which the pyrrole **5** is formed.



1a (*E* : *Z* = 1 : 4) 69%

Scheme 2. Regioselective synthesis of the silyl enol ether **1a** under reductive conditions (RT = room temperature).

Typical Experimental Procedure

Aldol product **3**: To a solution of azido acetal **2a** (2.17 g, 0.01 mol) in 50 mL of CH_2Cl_2, 8.8 mL (0.08 mol) of $TiCl_4$ was added in two portions at −78 °C under nitrogen atmosphere. Silyl enol ether **1a** (2.43 g, 0.012 mol) in 50 mL of CH_2Cl_2 was slowly added in such a manner that the temperature did not rise above −70 °C. The red-brown suspension was stirred for 10 h at −78 °C. The reaction was then quenched by adding 100 mL of ice water. After the separation of the two phases, the water phase was extracted with 3 × 50 mL of CH_2Cl_2. The organic phases were washed with 2 × 50 mL of saturated NaCl and dried with $MgSO_4$ and the solvent was removed. Removing methyl levulinate by distillation (40 °C, 10^{-3} Torr) gave 2.58 g of a raw material with the following composition: aldol product **3** as a mixture of diastereoisomers (71%); two products of elimination (4%); methyl 5-azidolevulinate (9%, yields are calculated relative to **2a**).

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