FORMATION OF HIGHLY SUBSTITUTED PYRROLE DERIVATIVES: AN UNEXPECTED DOMINO REACTION

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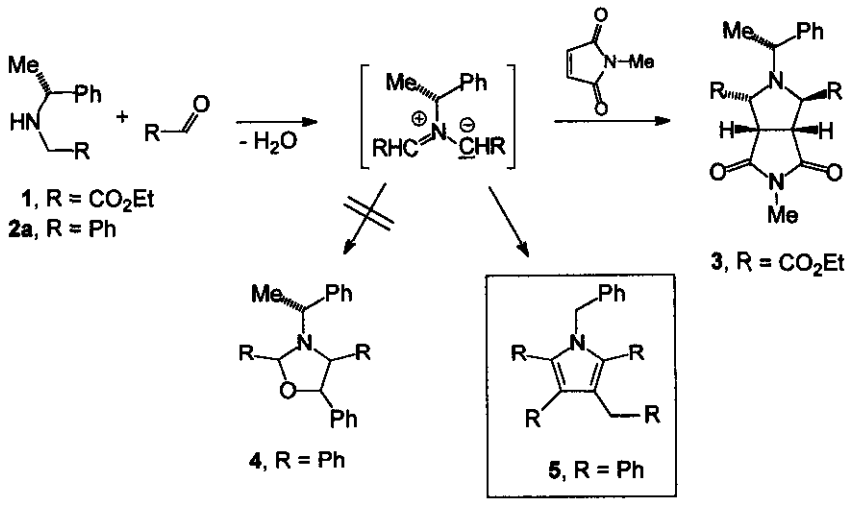
Abstract – An unexpected multistep domino reaction for the preparation of highly substituted pyrrole derivatives is described. During this reaction, which uses a secondary benzylic amine (e.g. *N*-benzyl-(1-phenylethyl)amine) and benzaldehyde as starting materials, a methyl group is transformed into a quaternary sp^2-carbon atom and three equivalents of benzaldehyde are reduced.

Domino reactions allow a simple and efficient preparation of a variety of complex compounds.[1-3] The utilization of sequential transformations is not only very elegant, it also has a positive effect on the environmental balance (decrease in the number of purification steps and the required amount of solvent, better time efficiency). Here we describe a multistep domino reaction in which a methyl group is transformed into a quaternary sp^2-carbon atom while three equivalents of benzaldehyde are reduced.

Recently, we reported on one-pot procedures which allow a simple stereoselective preparation of highly functionalized pyrrolidine derivatives, using readily available starting materials.[4,5] These reactions include the *in situ* generation of *N*-substituted azomethine ylides and a subsequent 1,3-dipolar cycloaddition reaction [6] with different dipolarophiles.

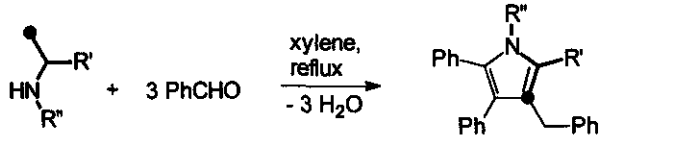
The one-pot reaction of the optically active *N*-substituted glycine ester (**1**) with ethyl glyoxalate and a dipolarophile is an efficient method for the preparation of enantiomerically pure proline derivatives (e.g. **3** using *N*-methylmaleimide as dipolarophile; Scheme 1). Similar reactions with dibenzylamine and benzaldehyde give rise to phenyl-substituted oxazolidine derivatives.[5] With the intention of preparing the oxazolidine (**4**) in enantiomerically pure form, we chose 1-phenylethylamine as a chiral auxiliary. Surprisingly, the reaction of *N*-benzyl-(1-phenylethyl)amine (**2a**) with benzaldehyde in toluene, with the azeotropic removal of water, did not provide the oxazolidine derivative (**4**), but a microcrystalline com-

pound (**5**) in good yield. **5** is formed by the reaction of one equivalent of amine (**2a**) and three equivalents of benzaldehyde.[7] Three equivalents of water are separated during the reaction. The absence of a methyl group (^{1}H and ^{13}C NMR) in the isolated compound (**5**) is striking since its molecular formula ($C_{36}H_{29}N$) indicates the introduction of this carbon atom by the amine (**2a**).



Scheme 1. One-pot reaction of amines (**1**) and (**2a**) with aldehydes

Due to the insufficient information resulting from the NMR data, we repeated the reaction using a methyl ^{13}C labelled amine (**2a**) to determine the substitution pattern of this carbon atom in compound (**5**). The ^{13}C NMR spectrum shows the characteristic increase in intensity of the signal at 119.5 ppm, belonging to a quaternary sp^2-carbon atom. Furthermore, two quaternary and one secondary carbon atoms show coupling constants (^1J = 24 up to 35 Hz) to the labelled carbon atom. On the basis of these results we put forward the structure proposal shown in Scheme 2, the highly substituted pyrrole derivative (**5**).



2a, R' = Ph, R" = Bn
2b, R' = Ph, R" = Me
2c, R' = 1-naphthyl, R" = Bn

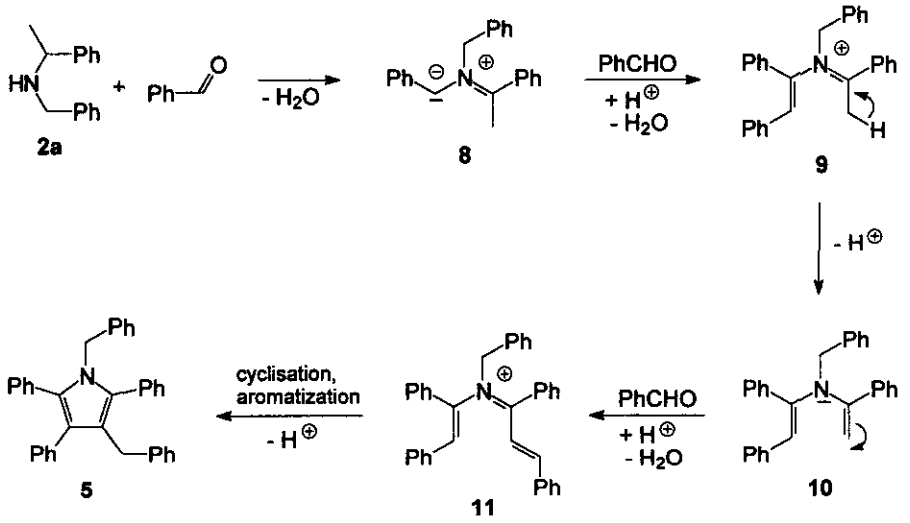
5, R' = Ph, R" = Bn
6, R' = Ph, R" = Me
7, R' = 1-naphthyl, R" = Bn

Scheme 2. Synthesis of pyrroles (**5 - 7**)

This structure is in good agreement with the MS spectrum, showing $[M - C_7H_7]^+$ (m/z = 384), $[M - C_7H_7 - C_6H_6]^+$ (m/z = 306), $[M - C_7H_7 - C_7H_5N]^+$ (m/z = 281) and $[M - C_7H_7 - C_6H_6 - C_7H_5N]^+$ (m/z = 203) as

fragment ions. Thus, the methyl group was oxidized during the reaction, while at the same time three equivalents of benzaldehyde were reduced.

The mechanism of this unexpected reaction is not known in detail, yet. We postulate a multistep domino reaction, which includes a triple condensation of different nucleophilic intermediates with benzaldehyde, followed by cyclisation and aromatization (Scheme 3). In a first step, the azomethine ylide **(8)** is formed by the condensation of the amine **(2a)** with the aldehyde and subsequent deprotonation. The reaction of the ylide with a second equivalent of benzaldehyde leads to the enamine **(9)**, which is deprotonated to the bisenamine **(10)**. A further nucleophilic attack provides the intermediate **(11)**, which builds up the five-membered heterocyclic ring by cyclisation. The following stabilization cascade (similar to a Nazarov-type cyclization) results in the formation of the aromatic pyrrole system **(5)**.[8,9]



Scheme 3. Postulated intermediates during the formation of pyrrole **(5)**

In addition, the postulated structure was verified by the use of the secondary amines **(2b)** and **(2c)**, which gave rise to the corresponding pyrrole derivatives **(6)** and **(7)**, respectively. The ^{1}H NMR spectrum of the biaryl derivative **(7)** is characterized by two AB-signals. The steric demand of the naphthyl substituent leads to an atropic isomerism, which is shown in the diastereotopy of the benzylic protons.

The simple preparation of **5**, **6** and **7** shows that the observed domino reaction represents a more general approach towards these pyrrole derivatives.

EXPERIMENTAL

Representative Procedure. Preparation of 1,3-Dibenzyl-2,4,5-triphenylpyrrole **(5)**: A solution of amine **(2a)** (4.22 g, 20 mmol) and benzaldehyde (6.36 g, 60 mmol) in xylene (30 mL) was refluxed for 3 d under

Dean/Stark conditions. Afterwards the solvent was removed *in vacuo*. The crude product was recrystallized from ethanol to give **5** (7.17 g, 76 %) as a microcrystalline white solid: mp 138 °C; IR (KBr, cm^{-1}) 3064 , 3005, 2919, 1598, 1450. ^1H NMR (200 MHz) δ 3.82 (s, 2H), 5.05 (s, 2H), 6.56-6.60 (m, 2H), 6.94-7.23 (m, 23H). ^{13}C NMR (75 MHz) δ 30.6, 48.6, 119.5, 124.1, 125.0, 125.2, 125.9, 126.5, 126.7, 127.1, 127.5, 127.8, 127.9, 127.9, 128.0, 128.1, 130.3, 130.5, 131.0, 132.7, 132.7, 132.8, 133.4, 135.9, 139.0, 143.1. MS m/z 475 (M^+, 100), 384 (47), 306 (8), 281 (14), 203 (28), 103 (4), 91 (17). HRMS Calcd for $C_{36}H_{29}N$: 475.2300, found: 475.2312. Anal. Calcd for $C_{36}H_{29}N$: C, 90.91; H, 6.15; N, 2.94. Found: C, 90.78; H, 6.29; N, 2.81.

6: Viscous yellow oil upon column chromatography (eluent petroleum ether:ethyl acetate 90:10); yield 38 %; IR (KBr, cm^{-1}) 3056, 2922, 1652, 1601, 1450. ^1H NMR (200 MHz) δ 3.28 (s, 3H), 3.70 (s, 2H), 6.75-6.78 (m, 2H), 6.87-7.34 (m, 18H). ^{13}C NMR (50 MHz) δ 31.35, 34.34, 119.24, 124.01, 125.67, 125.94, 127.15, 127.77, 128.31, 128.44, 128.61, 128.81, 128.86, 129.15, 131.01, 131.48, 132.70, 133.30, 133.47, 133.83, 136.81, 143.71. MS m/z 399 (M^+, 100), 384 (2), 322 (42), 202 (6), 118 (16), 105 (23), 91 (10), 77 (17). Anal. Calcd for $C_{30}H_{25}N$: C, 90.19; H, 6.31; N, 3.50. Found: C, 90.33; H, 6.19; N, 3.32.

7: White solid; yield 55 %; mp 152 °C; IR (KBr, cm^{-1}) 2360, 2345. ^1H NMR (200 MHz) δ AB-signal (δ_A = 3.64, δ_B = 3.80, J = 15.7 Hz), AB-signal (δ_A = 4.62, δ_B = 5.00, J = 16.1 Hz), 6.44-6.48 (m, 2H), 6.70-6.75 (m, 2H), 6.93-7.32 (m, 18H), 7.41-7.51 (m, 2H), 7.74-7.87 (m, 3H). ^{13}C NMR (50 MHz) δ 31.4, 49.1, 121.3, 124.4, 125.3, 125.6, 125.8, 126.1, 126.4, 126.6, 126.8, 127.0, 127.3, 128.1, 128.1, 128.3, 128.5, 128.6, 128.7, 128.8, 130.6, 130.8, 131.0, 131.2, 131.7, 132.8, 133.4, 133.9, 134.0, 136.7, 139.6, 143.1. MS m/z 525 (M^+, 100), 434 (18), 356 (26), 343 (29), 203 (12), 91 (36). Anal. Calcd for $C_{40}H_{31}N$: C, 91.39; H, 5.94; N, 2.66. Found: C, 91.22; H, 5.82; N, 2.74.

ACKNOWLEDGEMENTS

We thank the *Deutsche Forschungsgemmeinschaft* and the *Fonds der Chemischen Industrie* for financial support.

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7. Pyrrole **(5)** was prepared starting from the racemic and the enantiomerical pure amine **(2a)**.
8. We did not obtain a pyrrole derivative using *N*-benzyl-(1-phenylpropyl)amine and benzaldehyde as starting materials. This result is still in good accord with the postulated mechanism, because a final stabilization by aromatization affords the unfavorable elimination of a methyl group in this case.
9. The synthesis of pyrrole derivatives from azomethine ylides has already been described. However, both the substrates and the mechanism are different from the reaction described in this note: H. Quast and W. von der Saal, *Chem. Ber.*, **1984**, *117*, 1591.

Received, 24th July, 1998