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Synthesis and Diels-Alder Reactivity of Functionalized Aminodienes and Bis-Dienes.

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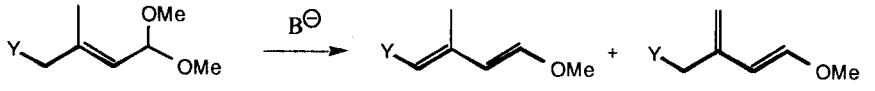
Abstract: γ-Amino α,β-unsaturated dimethyl acetals are direct precursors of (E)-1-methoxy-2-methylamino-1,3-butadiene and of the corresponding bis-dienes, which are useful partners in cycloadditions. Copyright © 1996 Published by Elsevier Science Ltd

Because cyclic structures are at the heart of many synthetically challenging compounds, the Diels-Alder reaction remains a source of constantly renewed attention. The diene-dienophile assembling can constitute a strongly convergent step in a synthesis, provided both partners bring an optimized functional pattern to the edifice. However, to remain efficient, the cycloaddition approach to complex structures requires highly functionalized and stereocontroled dienes and dienophiles, and these quite often constitute the limiting factor to otherwise attracting retrosynthetic pathways. Our interest in the field of terpenoid and polyethylenic chemistry[1] has led us to propose a general method relying on the conjugated-elimination[2] induced on α,β-unsaturated γ-functionalized acetals to prepare 1,4-disubstituted 1,3-dienes (Scheme 1).[3]



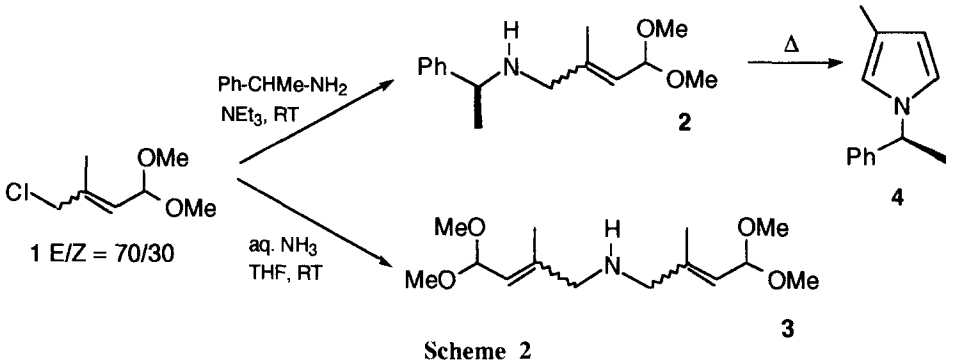
Y = OAr, SAr, NR^1R^2 Y = OAr, SAr, NR^1R^2 Y = NR^1R^2

Scheme 1.

We have reported that refluxing chloroacetal **1**[4] in THF with light secondary amines leads in excellent yields to the corresponding aminoacetals.[3c] Our previous report had however been restricted to the preparation of tertiary aminoacetals, while secondary ones are also of interest. We now report new developements of this methodology to the stereocontrolled synthesis of aminodienes **5,6** and dimeric (bis) aminodienes **8** as well as model cycloaddition-reactions using these compounds. Dienamines are indeed well-known for their high Diels-Alder reactivity.[5]

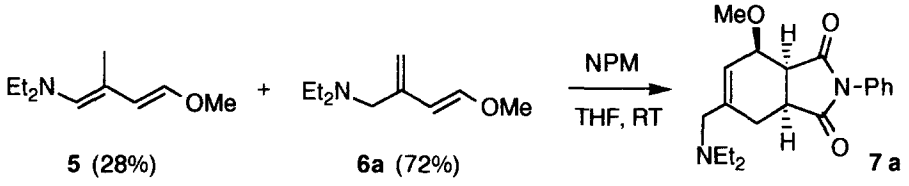
The chlorine substitution on **1** by chiral α-methylbenzylamine slowly yields **2** at room temperature (Scheme 2). Warming speeds up the process but must be handled with care since increasing amounts of corresponding N-substituted pyrrole **4** progressively accumulate in the medium. This latter product probably

comes from an intramolecular substitution in **2** giving an intermediate hemiaminal that quickly aromatizes in these conditions. Finally, **2** can be obtained in 58% yield after nine days at room temperature or in 46% (after flash-chromatography) at 75°C in four days. Its stereochemistry follows from that of precursor **1**. The possibility of preparing bis-aminoacetals in a comparable way being also relevant,[3d] we used aqueous ammonia in an heterogeneous mixture with **1** in THF. After 15 days at room temperature, the bis-acetal **3** is obtained in 90% yield as a mixture of mainly the 1E, 1'E (≈75%) and 1E,1'Z (≈25%) isomers, that is more or less the statistical combination of the ethylenic moieties.[4] Only traces of the corresponding monomeric (primary) and trimeric (tertiary) aminoacetals are detected by GC/MS analysis of the organic phase.



Scheme 2

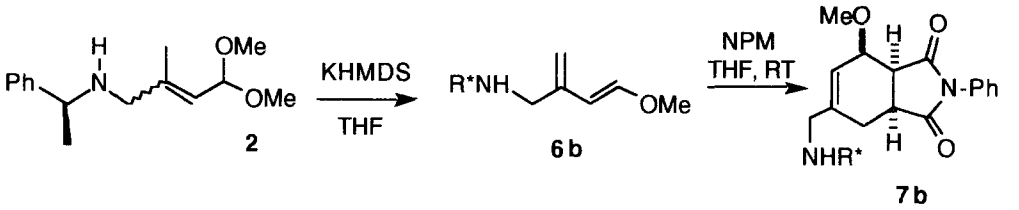
The influence of the bulkiness of both base and amine on the regioselectivity of this deprotonation step of tertiary aminoacetals has already been underlined.[3c] These aminoacetals indeed promote the competition between deprotonations of the methylene position and the vinylic methyl. In the latter case one gets access to 1,3-dienes containing an exo-methylene group which are also useful synthons.[6] Therefore we can obtain, after deprotonation, a mixture of two isomers, for instance **5+6a** when starting from the corresponding diethylaminoacetal. The crude mixture **5+6a** can be directly added to N-phenylmaleimide (NPM). After 12h at room temperature in THF and flash chromatography on silicagel, only **7a** is recovered in 60% yield. The configuration of **7a** indicates that this cycloaddition takes place following a purely endo approach.



Scheme 3

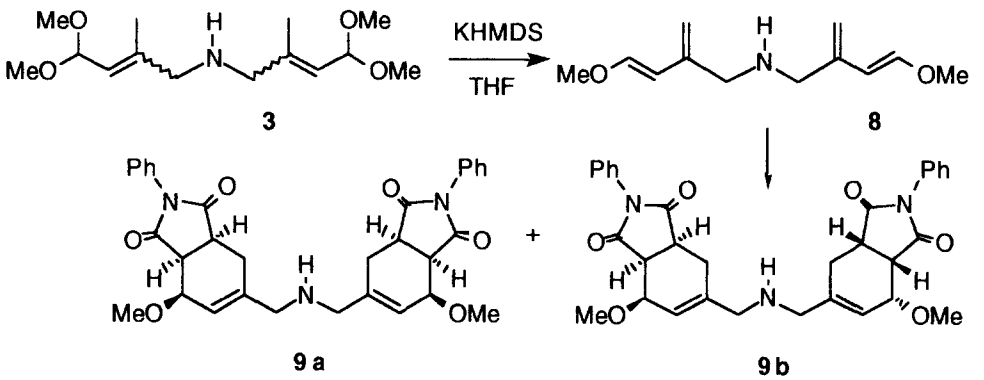
Interestingly, deprotonation of secondary aminoacetal **2** using the bulky potassium bis(trimethylsilyl) amide (KHMDS) yields exclusively the "exo" type diene **6b**,[7] probably because of the preliminary deprotonation of the nitrogen atom in **2** which deactivates its α-position. The fragile diene **6b** can be flash-chromatographed in the presence of triethylamine and is recovered in 46% yield. It may also be used as a crude starting material for the cycloaddition and its good reactivity toward NPM gives access to the expected adduct **7b** in 12h with 52% yield after flash chromatography. Albeit derived of a pure endo type approach, the diastereoselectivity remains

very modest, reaching only 14% in these conditions. This disappointing result may probably be ascribed to the relatively remote position occupied by the chiral center and the well-known flexibility of dienes which are, in general, poor chiral inductors in cycloadditions.[8] There are however only few investigations on dienes bearing a chiral center in the 2-position, and derived cycloadducts present highly variable d.e. values.[9]



Scheme 4

Similarly, the deprotonation of bis-acetal **3** turns out to be totally regio and stereoselective since it provides the bis "exo" diene **8** in the pure 3E,3'E configuration. There again, **8** may be either flash-chromatographid (in 60% yield) or used as a crude compound in the following cycloaddition step. NPM reacts in THF or ether at room temperature in 12h and gives the mixture of diastereomers **9** in 77% yield after purification. The diastereoselectivity stems from a syn or anti approach of the second dienophile with respect to the first one but, in both compounds, each bicyclic system reflects an endo type approach. The d.e., as measured by HPLC, is 41%. Type **9** structures may have interesting applications to rapid approaches of pseudodisaccharides, polycyclic cage compounds[10a] or host-guest chemistry partners.[10b]



Scheme 5

In conclusion, the application of the δ-elimination reaction to γ-amino-α,β-unsaturated acetals **2** and **3** is a simple and efficient way to prepare stereoselectively 1-methoxy-3-methylaminobutadienes **6** and **8**. These dienes are very reactive and can be efficiently added to NPM to provide pure endo cycloadducts in good yields. The bis-diene **8** similarly gives access to tetracyclic systems in 41% d.e. Attempts to prepare selectively "endo"-type dienes such as **5a** and applications to various dienophiles, including aldehydes and imines[10d] are currently under way.

Acknowledgment. We thank the Rhône-Poulenc Chimie Co. for generous samples of chloroacetal **1**.

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4. Acetal **1** is an industrial intermediate (Rhône-Poulenc Chimie) available as a ≈ 75:25 E/Z mixture.
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7. General procedure for deprotonation : A solution of 1g of KHMDS (5 eq.) in 4 ml THF is added, under an inert atmosphere and at room temperature, to a solution of 0.25g of acetal **2** in 3 ml THF. The medium is heated to reflux during 4h30 then quenched with water at RT. The aqueous layer is then extracted with CH_2Cl_2, dried on $MgSO_4$ and evaporated under reduced pressure.
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