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Evidence for Alternative Mechanisms in the Amino-Cope Rearrangement

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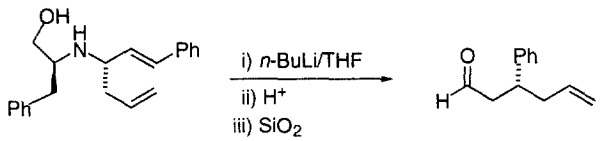
Abstract: The formal amino-Cope rearrangement of a 3-amino-1,5-diene substrate does not proceed solely by a concerted [3,3]-sigmatropic rearrangement mechanism.

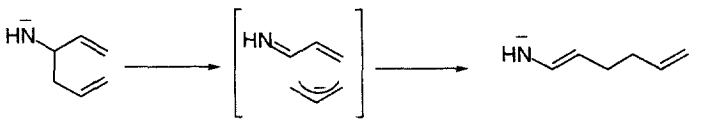
Keywords: amino-Cope rearrangement, amino-diene, dissociation/recombination

The amino-Cope rearrangement is receiving increased attention as a new synthetic protocol. Our group has developed a tandem amino-Cope rearrangement/enamine derivatization procedure,[1] and more recently we have established that an anionic variant of the amino-Cope rearrangement is possible.[2] We also reported the highly stereoselective rearrangement of a series of chiral 3-amino-1,5-diene substrates derived from β-aminoalcohols, in which the rearrangement was found to yield a β-substituted aldehyde product with an *e.e.* of up to 94% (Scheme 1).[3]



Scheme 1. Asymmetric anionic amino-Cope rearrangement

Other groups have also been active in this area.[4,5] Houk and Meyers studied[5] the rearrangement of 3-amino-1,5-dienes using *ab initio* calculations, and concluded that the concerted [3,3] rearrangement of acyclic 3-amino-1,5-diene substrates was disfavoured. The preferred reaction pathway was proposed to involve deallylation of the substrate *via* an allyl anion-imine intermediate (Scheme 2).



Scheme 2. Stepwise pathway for the anionic amino-Cope rearrangement

Prompted by this study we decided to prepare a suitable substrate that might allow more insight into whether the anionic amino-Cope rearrangement was a concerted [3,3]-sigmatropic process.

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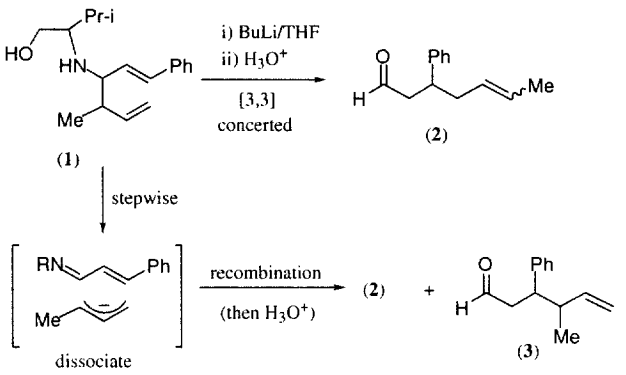
Substrate (**1**) was prepared by addition of crotonyl magnesium bromide to the imine derived from valinol and cinnamaldehyde.[3] We reasoned that the presence of a methyl group "marker" at position-4 of the 3-amino-1,5-diene substrate might allow us to detect the involvement of alternative reaction pathways during the rearrangement. As outlined in Scheme 3, a concerted [3,3] rearrangement of the substrate would only lead to product (**2**), with the methyl "marker" ultimately located at the terminal alkene position. However, should the rearrangement proceed (at least partly) by a competing mechanism, such as a dissociative pathway or a [1,3]-alkyl shift, the possibility of recombination to give the alternative products (**2**) and (**3**) would be feasible.



Scheme 3. Possible Reaction Products by Concerted and Dissociative Mechanisms

Compound (**1**) was treated as previously described[3] to give a 57% yield of the reaction products. Analysis of the product mixture by 250 MHz ^{1}H-NMR revealed a 1:1 mixture of the two possible products. Aldehyde (**2**) was formed as a 4:1 mixture of geometrical isomers, with the *trans* isomer predominating.[6] Compound (**3**) was formed as a equal mixture of diastereoisomers. We have indicated in Scheme 3 that dissociation leads to the imine/allyl anion intermediate as implied by Houk and Meyers.[5] It is, of course, feasible that a diradical intermediate may be involved. We have also not discounted a competing [1,3]-alkyl shift under the reaction conditions used which could lead to product (**3**).

In summary, the anionic amino-Cope rearrangement of a 4-alkyl-3-amino-1,5-diene substrate in THF does not proceed solely by a concerted [3,3] sigmatropic rearrangement mechanism. We are currently investigating whether this tendency extends to other classes of substituted 3-amino-1,5-dienes, our results will be presented in due course.

References:

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6. Greeves N, Lee WM. *Tetrahedron Lett.* **1997**, *38*, 6445-6448; We are grateful to Dr. Nick Greeves for providing us with copies of ^{1}H-NMR spectra of an authentic sample of product (**2**).