Intramolecular Generation and Rearrangement of Ammonium Ylides from Copper Carbenoids: a General Method for the Synthesis of Cyclic Amines

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Tandem intramolecular formation and [2,3]-sigmatropic rearrangement of ammonium ylides from copper carbenoids is a general method for the preparation of cyclic amines.

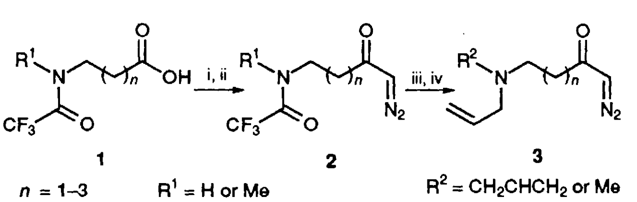
The formation of ylides by reaction of metal carbenoids, generated catalytically from diazo carbonyl compounds, with heteroatom-containing substrates is a mild and efficient alternative to traditional base-promoted methods of ylide generation.[1] When appropriately functionalised substrates are used, the ylide intermediates undergo subsequent rearrangement,[2] and both ylide formation and rearrangement can be accomplished in a single operation.[1]

Tandem ylide generation and rearrangement can be used to prepare heterocycles when performed in an intramolecular fashion.[1] The preparation of sulfur-containing heterocycles by this process has been studied extensively,[1,3] and recently, we and others have shown that the process can be extended to the synthesis of cyclic ethers.[4,5] In contrast, the synthesis of cyclic amines by [2,3]-sigmatropic rearrangement of ammonium ylides, generated in an *intramolecular* fashion from carbenoids, has received scant attention.[6] The only previous examples of catalytic generation and rearrangement of ammonium ylides are the study by Doyle *et al.* of the [2,3]-rearrangement of ammonium ylides generated *intermolecularly* from rhodium carbenoids,[7] and recent studies by West *et al.* on tandem *intramolecular* ammonium ylide generation and Stevens [1,2]-rearrangement.[8]

We now wish to report results from the first systematic study of the tandem *intramolecular* formation and [2,3]-sigmatropic rearrangement of ammonium ylides from copper carbenoids, which demonstrate the power and scope of this tandem process for the synthesis of cyclic amines.

In order to investigate the formation and rearrangement of ammonium ylides from carbenoids, we required a short and high yielding route to amino α-diazo ketones. Because of the incompatability of free amino functionality with conventional methods of diazo ketone formation, we adopted a strategy in which the amino group was masked during diazo ketone formation (Scheme 1). Thus, the appropriate amino acid was *N*-protected as the trifluoroacetamide **1**, and converted to the α-diazo ketone **2** by standard methods. Deprotection and alkylation at nitrogen with allyl bromide then completed the synthesis of the cyclisation precursors **3c–e**. α-Diazo ketone **3a** was prepared by reaction of diallylamine with 1-diazo-but-2-one by the method of Rosenquist and Chapman,[9] and **3b** was synthesised by reaction of *N*-methylallylamine with 1-bromo-4-diazobutan-3-one in the presence of triethylamine.[8a]

Intramolecular cyclisation of carbenoids derived α-diazo ketones **3** afforded the ammonium ylides **4**, which then underwent [2,3]-sigmatropic rearrangement to the corresponding cyclic amines (Scheme 2). Thus, treatment of substrates **3** with $Cu(acac)_2$ (2 mol%) in benzene at reflux afforded the anticipated products **5** in good yield (Table 1).



1 **2** **3**

n = 1–3 R^1 = H or Me R^2 = CH_2CHCH_2 or Me

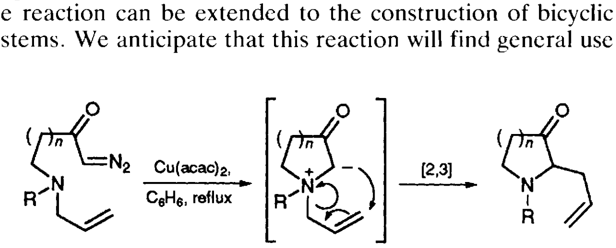
Scheme 1 *Reagents and conditions*: i, $(COCl)_2$, DMF (cat.), CH_2Cl_2, 0 °C → room temp.; ii, CH_2N_2, Et_2O, 0 °C (79–85%, 2 steps); iii, OH^- aq., room temp.; iv, CH_2CHCH_2Br (1 or 2 equiv.), K_2CO_3, THF, room temp. (37–54%, 2 steps)

The formation of five-, six- and seven-membered cyclic amines (**5a–d**) proceeded by ylide formation and rearrangement without significant competing carbon–hydrogen insertion. When $Rh_2(OAc)_4$ was employed as the catalyst for the reaction, lower yields of the corresponding cyclic amines **3** were obtained.†

We also explored the use of copper(II) hexafluoroacetylacetonate $[Cu(hfacac)_2]$ as a catalyst for metal carbenoid generation. Although $Cu(hfacac)_2$ is an excellent catalyst or the synthesis of cyclic ethers from α-diazo ketones,[4b] reactions were slow and did not proceed to completion when this complex was used to catalyse the cyclisation of the nitrogen-containing substrates **3**. We believe that the ineffectiveness of $Cu(hfacac)_2$ as a catalyst is attributable to catalyst deactivation by coordination of the substrate or product.[7]

After we had established that simple cyclic amines could be prepared by the tandem insertion and rearrangement reaction, we explored the cyclisation of the α-diazo ketone **6** to the indolizidines **8a**,**b** (Scheme 3). Treatment of **6** with a catalytic amount of $Cu(acac)_2$ (2 mol%) in benzene at reflux gave exclusively the indolizidine **8a**,‡ *via* the *cis*-fused bicyclic ammonium ylide **7**, rather than the epimeric compound **8b** which would have arisen from a *trans*-fused bicyclic ammonium ylide. Indolizidine **8a** is thermodynamically less stable than the diastereoisomer **8b**, and partial epimerisation of **8a** occurred during purification by chromatography on silica gel. Complete conversion of **8a** to **8b** was accomplished by exposure of **8a** to a suspension of silica gel in diethyl ether at room temperature. The relative configuration of the stereogenic centres of **8b** was established by stereoselective reduction of this ketone to the crystalline alcohol **9** using L-Selectride (Scheme 3), and analysis of this compound by X-ray crystallography. Thus, the configuration of the cyclisation product **8a** was shown to be 3(*S**), 8a(*S**).

In summary, we have demonstrated that intramolecular tandem generation and [2,3]-sigmatropic rearrangement of the ammonium ylides from copper carbenoids, can be used to prepare medium-sized cyclic amines in good yield, and that the reaction can be extended to the construction of bicyclic systems. We anticipate that this reaction will find general use

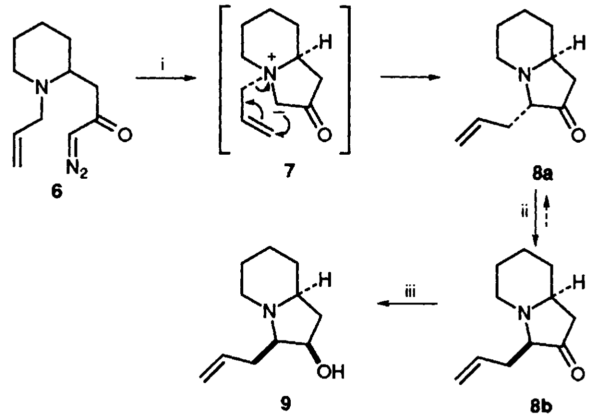


3 **4** **5**

Scheme 2

Table 1

Substrate	*n*	R	Isolated yield of **5** (%)
3a	1	CH_2CHCH_2	76
3b	1	Me	72
3c	2	CH_2CHCH_2	79
3d	3	Me	84
3e	4	CH_2CHCH_2	39



Scheme 3 *Reagents and conditions*: i, Cu(acac)$_2$ (2 mol%), C_6H_6, reflux (62%); ii, silica gel, Et_2O, room temp. (72%); iii, L-Selectride, THF, −78 °C (91%)

for the synthesis of cyclic amines, and we are currently investigating the application of the process to the synthesis of natural product targets.

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Footnotes

† The $Rh_2(OAc)_4$-catalysed cyclisation of the α-diazo ketones **3** in benzene at reflux gave the following yields of the cyclic amines **5a** 70%, **b** 58%, **c** 73%, **d** 56%, **e** 5%.

‡ None of the other diastereomeric indolizidine **8b** was detected by ^1H NMR (250 MHz) analysis of the crude product from the reaction.