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The synthesis and functionalisation of quinuclidine enamine *N*-oxide and borane complex

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Abstract

The synthesis of quinuclidine enamine *N*-oxide and quinuclidine enamine borane complex is described. Selective deprotonation of the double bond allows the direct functionalisation at the α-position with a range of electrophiles.

Keywords: carbanions; *N*-oxides; enamines; boron; boron compounds.

The quinuclidine nucleus is the core component of the cinchona alkaloids, a family of natural products, which not only exhibit antimalarial activity but have also found widespread use in numerous asymmetric transformations.[1]

We recently reported the use of quinuclidine *N*-oxide as a potential replacement for hexamethylphosphoric triamide (HMPA) in a number of synthetically important reactions.[2] In order to increase the scope of this reagent system we envisaged that the incorporation of additional metal binding sites α to the nitrogen would increase the metal binding capability of these reagents. In addition, we were intrigued by the possibility of linking two quinuclidine units together to yield a dimeric species such as compound **2**, which would almost certainly possess enhanced metal binding properties. One potential building block for **2** was the enamine *N*-oxide **1** shown in Fig. 1. Examination of the literature showed that this was an unknown compound, although the parent enamine has been prepared and studied by Grob.[3] We predicted that selective deprotonation of enamine *N*-oxide **1** at the unsaturated α carbon should be possible, allowing for the functionalisation of this position. Subsequent dimerisation should then be possible if appropriate functionality had been incorporated.

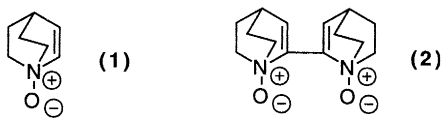

Fig. 1.

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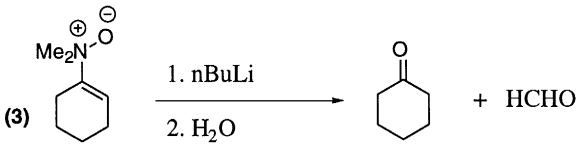
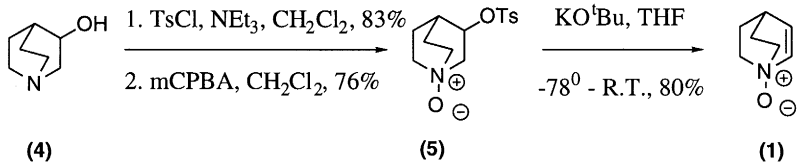
Enamine *N*-oxides have been prepared previously;[4] however, they have been reported to undergo fragmentation reactions on treatment with strong bases. In the example shown in Scheme 1, deprotonation of **3** presumably occurs on one of the methyl groups, subsequent fragmentation to yield an iminium salt, followed by hydrolysis to give cyclohexanone and formaldehyde.



Scheme 1.

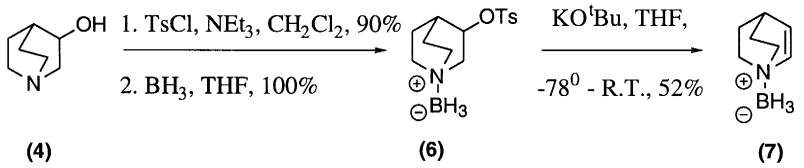
In our approach to dimers such as **2** we have synthesised the enamine *N*-oxide **1** from commercially available 3-hydroxyquinuclidine using the route outlined in Scheme 2.



Scheme 2.

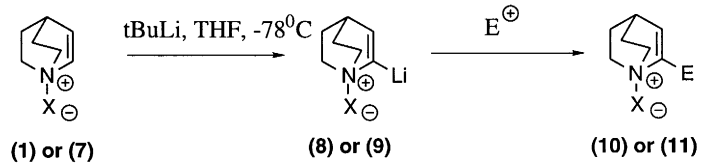
Thus, tosylation of 3-hydroxyquinuclidine **4** followed by *N*-oxidation proceeded smoothly to give the *N*-oxide **5**. Treatment of the *N*-oxide **5** with 1 equiv. of KO^{t}Bu at −78°C, followed by warming to room temperature, furnished the desired enamine *N*-oxide in good yield. *N*-Oxide **1** is a colourless, hygroscopic solid. It is conveniently dried and stored over P_2O_5. The ^{1}H NMR of **1** in $CDCl_3$ showed two characteristic vinyl protons at δ 6.71 and 6.48, the low chemical shift of these protons indicating the powerful inductive effect of the nitrogen.[5]

We also found that the corresponding borane complex of the enamine could be prepared by an analagous route (Scheme 3).



Scheme 3.

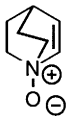
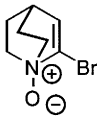
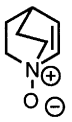
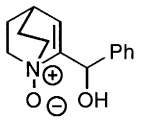
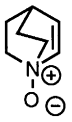
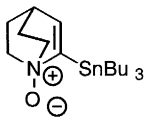
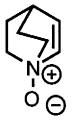
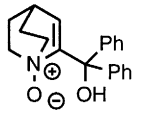
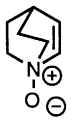
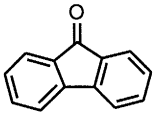
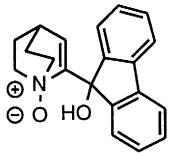
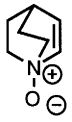
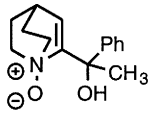
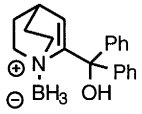
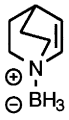
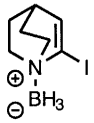
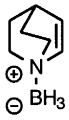
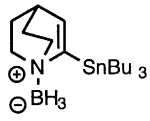
Having established a reliable protocol for the synthesis of **1** and **7** we next examined their deprotonation.[6,7] Treatment of **1** or **7** with 1 equiv. of ^{t}BuLi at −78°C in anhydrous THF gave the vinyl carbanions **8** or **9**. Quenching of these species with a suitable electrophile yielded the 2-functionalised quinuclidine enamine derivatives (Scheme 4).



Scheme 4.

A range of electrophiles were examined. In each case the ^{1}H NMR spectrum showed that the vinyl signal at δ 6.71 due to the proton adjacent to the quinuclidine nitrogen had disappeared. The results are summarised in Table 1. With non-enolisable ketones and aldehydes (entries 2, 4 and 5) the yields of the

Table 1
Reactions of 2-lithio quinuclidine enamine *N*-oxide and borane complex

Entry	Substrate	Electrophile	Product	% Yield
1		Br_2		74
2		PhCHO		78
3		Bu_3SnCl		75
4				60
5				85
6				20
7				81
8		I_2		86
9		Bu_3SnCl		56

addition products are good. These products are generally stable crystalline materials with the *N*-oxide oxygen hydrogen bonded to the OH group. The lower yield with acetophenone is most likely due to competing enolisation. The introduction of heteroatoms (entries 1, 3, 8 and 9) again went in good yield.

In summary, we have prepared the quinuclidine enamine *N*-oxide **1** and the quinuclidine enamine borane complex **7** in good yield. Both of these species have been shown to undergo clean lithiation at the vinylic position and the resulting carbanions can be trapped out with a range of electrophiles. We are currently examining the coupling reactions of these functionalised quinuclidines in the construction of dimeric species.

Acknowledgements

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5. Data for azabicyclo[2.2.2]oct-2-ene *N*-oxide (1): δ_H (300 MHz, $CDCl_3$) 1.83 (2H, m, N–CH_2C*H*H), 1.99 (2H, m, NCH_2CH*H*), 2.85 (1H, m, C*H*), 3.30 (2H, m, N–C*H*H), 3.56 (2H, m, N–CH*H*), 6.48 (1H, t, *J*=7 Hz), 6.71 (1H, d, *J*=7 Hz). δ_C (75 MHz, $CDCl_3$) 29 (*C*H), 31 (N–(CH_2)$_2$–(*C*H_2)$_2$), 70 (N–(*C*H_2)$_2$), 134 (N–CH=*C*H), 151 (N–*C*H=CH). MS(CI) $[M+H]^+$ *m/z*: 126.09167; $C_7H_{12}NO$ requires: 126.09189.
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