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The Synthesis of Functionalised β-Hydroxyhydroxylamines *via* the Ring Opening of Epoxides and Their Use in Reverse Cope Cyclisations

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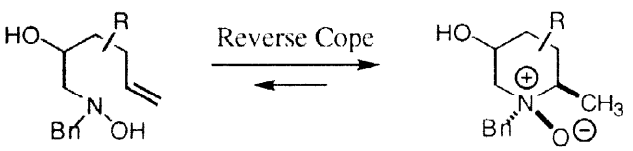
Abstract: Functionalised epoxides have been found to undergo high yielding and regioselective ring opening with hydroxylamines in methanol to give β-hydroxyhydroxylamines. Suitable substrates were found to undergo a reverse Cope cyclisation on heating in $CHCl_3$ to give functionalised piperidine *N*-oxides.

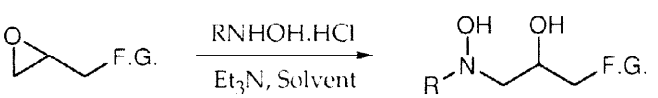
As part of our work on the chemistry of tertiary amine *N*-oxides[1] we have been investigating the use of the reverse-Cope cyclisation in the synthesis of a range of functionalised nitrogen heterocycles.[2] This rather underutilised reaction offers great scope for the synthesis of a range of nitrogen heterocycles. The lack of use of the reaction is due to the difficulty in preparing the appropriate unsaturated hydroxylamines and also because the reaction is often reversible. With this in mind, we chose to prepare substrates containing a β-hydroxyhydroxylamine, which upon reverse Cope cyclisation, would yield a β-hydroxyamine oxide. This would be particularly valuable since 3-hydroxypiperidines are commonly found in alkaloids.[3] There is also the potential for the amine oxide to be stabilised by an intramolecular or intermolecular hydrogen bond between the amine oxide oxygen and the hydroxyl group, driving the equilibrium over to the right hand side (Scheme 1).

Scheme 1.



There are a number of methods for the synthesis of functionalised hydroxylamines,[4] including the alkylation of hydroxylamine, the reduction of nitro and nitroso compounds, oximes and nitrones, addition reactions to nitrones and activated alkenes and the oxidation of secondary amines. In order to prepare the desired β-hydroxyhydroxylamines, we proposed to ring open functionalised epoxides with *N*-alkylhydroxylamines. We were surprised to find that there are very few examples of the ring opening of epoxides with hydroxylamines, and the few cases that have been reported are simple *O*-protected glycidol ethers.[5] Accordingly, we have examined the ring opening of a range of functionalised epoxides with three different hydroxylamines and found that the reaction is high yielding and regioselective (Scheme 2).

Scheme 2.



The results are summarised in Table 1. We initially examined the role of the solvent and found that methanol was the solvent of choice. The use of THF or CH_2Cl_2 led to reduced yields of the desired product.

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Table 1: Ring opening of epoxides with hydroxylamines

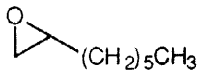
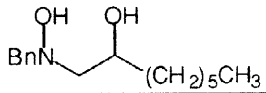
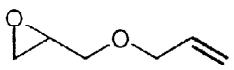
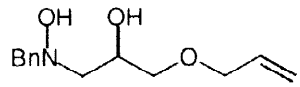
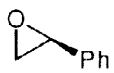
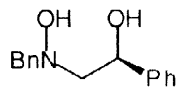
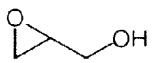
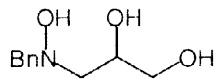
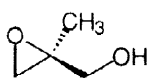
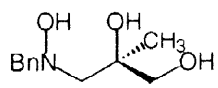
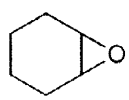
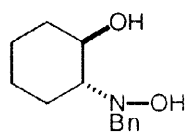
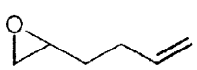
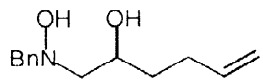
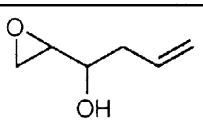
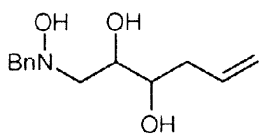
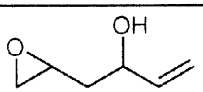
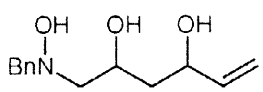
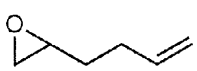
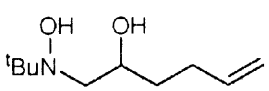
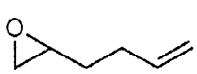
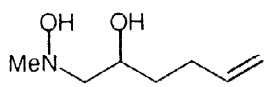
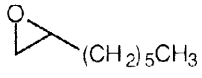
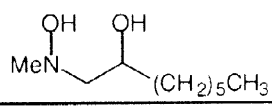
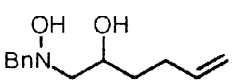
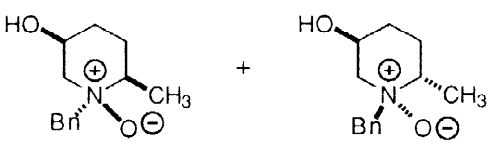
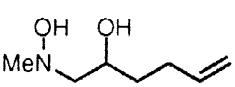
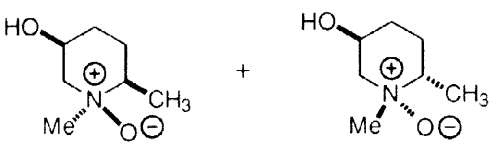
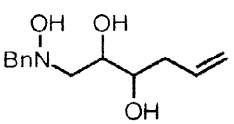
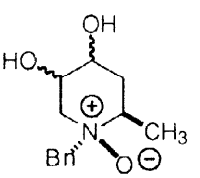
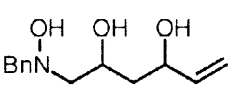
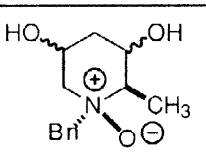
Entry	Epoxide	Conditions	Product	% Yield
1		BnNHOH. HCl, Et_3N, MeOH, r.t.		80
2		BnNHOH. HCl, Et_3N, MeOH, r.t.		85
3		BnNHOH. HCl, Et_3N, MeOH, r.t.		50
4		BnNHOH. HCl, Et_3N, MeOH, r.t.		93
5		BnNHOH. HCl, Et_3N, MeOH, r.t.		96
6		BnNHOH. HCl, Et_3N, MeOH, r.t.		66
7		BnNHOH. HCl, Et_3N, MeOH, r.t.		85
8		BnNHOH. HCl, Et_3N, MeOH, r.t.		75
9		BnNHOH. HCl, Et_3N, MeOH, r.t.		68
10		^{t}BuNHOH. HCl, Et_3N, MeOH, r.t.		60
11		MeNHOH. HCl, Et_3N, MeOH, r.t.		65
12		MeNHOH. HCl, Et_3N, MeOH, r.t.		86

Table 1 shows that a range of substituents on the epoxide are tolerated including free alcohols and alkenes. In the case of *N*-benzylhydroxylamine the reactions were complete after stirring at room temperature for 72 hours.[6] In the case of *N*-methylhydroxylamine the reaction was complete within 24 hours, conversely *tert*-butyl hydroxylamine required 1 week to reach completion. In general the yields are very good and the use of *N*-benzylhydroxylamine was particularly pleasing as the benzyl group can be readily removed at a later stage. In all but one case ring opening took place at the less hindered end of the epoxide. The exception was styrene oxide where two products were isolated. The major product corresponded to ring opening at the less hindered carbon. A small amount of the regioisomer corresponding to ring opening at the more substituted carbon was isolated. There are two examples of the opening of chiral epoxides (entries 3 and 5).

In order to establish if the reverse-Cope cyclisation would occur, unsaturated hydroxylamines 7 and 11 of Table 1 were heated at reflux in $CHCl_3$ for 48 hours (entries A and B in Table 2). Two more polar products were formed and isolated in 51% and 82% yield respectively as 1:1 and 3:2 mixtures of two racemic compounds. These were identified as the diastereoisomeric 3-hydroxypiperidine *N*-oxides. The ^{1}H-NMR cleared showed the loss of the alkene protons in the starting material and appearance of doublets corresponding to the C-6 methyl groups. These amine oxides were stable and did not undergo Cope elimination on standing at room temperature.

Table 2: Reverse Cope cyclisation of unsaturated hydroxylamines

Entry	Substrate	Products	% Isolated yield
A			51
B			82
C			73
D			69

The potential of this reaction is shown in the synthesis of the dihydroxylated piperidine *N*-oxides in entries C and D. The two parent epoxides were obtained from a single alkene precursor 1,5-hexadien-3-ol by epoxidation with *m*CPBA. The epoxides were separated and ring opened with *N*-benzylhydroxylamine. Reverse Cope cyclisation was effected by heating in $CHCl_3$ for 5 days to yield the dihydroxylated piperidine *N*-oxides as a mixture of stereoisomers. Thus this approach allows for the rapid preparation of functionalised piperidines for biological evaluation.

In summary, we have shown that functionalised epoxides undergo regioselective ring opening by hydroxylamines in high yield under mild conditions. The unsaturated β-hydroxyhydroxylamines undergo

reverse-Cope cyclisation on heating in $CHCl_3$ to give functionalised piperidine *N*-oxides. We are currently applying this methodology to the synthesis of a number of homochiral piperidine and pyrrolidine targets and investigating methods for control of diastereoselectivity in the reverse Cope cyclisation.

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M. S. Malinovskii and V. A. Martyushenko, *Chem. Abs.* **1966**, *64*, 625.
G. Zinner and A. W. Ritter, *Angew. Chem.* **1962**, *74*, 21.
6. Preparation of 3-(*N*-Benzyl-*N*-hydroxy) aminopropane-1,2-diol:
To a stirred solution of glycidol (0.150g, 2.0 mmol) in anhydrous methanol (1.5 ml) was added BnNHOH.HCl (0.260g, 1.6 mmol) and triethylamine (0.182g, 1.8 mmol). The solution was stirred at room temperature for 96 hours. Aqueous $NaHCO_3$ solution (5%, 1.5 ml) was added and the solution stirred for 15 minutes. The solution was extracted with ethyl acetate (2 x 5ml), the combined organic layers were dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude material was purified by column chromatography (silica, EtOAc) to give the product as an oil (0.300g, 93%), δ_H (300 MHz, $CDCl_3$) 7.15 (5H, s), 5.4-4.6 (1H, bs), 3.96-3.83 (1H, m), 3.70 (2H, s), 3.55-3.42 (1H, m), 3.38-3.28 (1H,m), 2.75-2.52 (2H, m); δ_C (75MHz, $CDCl_3$) 136.6, 130.2, 128.4, 127.7, 69.7, 65.3, 64.9, 62.1, υ_{max}(film) 3360, 2920, 2880, 2850, 1495 and 1455 cm^{-1}, m/z (FAB) 198 $[M+H]^+$, 180, 136, 120 and 91. $[M+H]^+$ $C_{10}H_{16}NO_3$ requires 198.11302, found 198.11332.