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A convenient synthesis of secondary hydroxylamines

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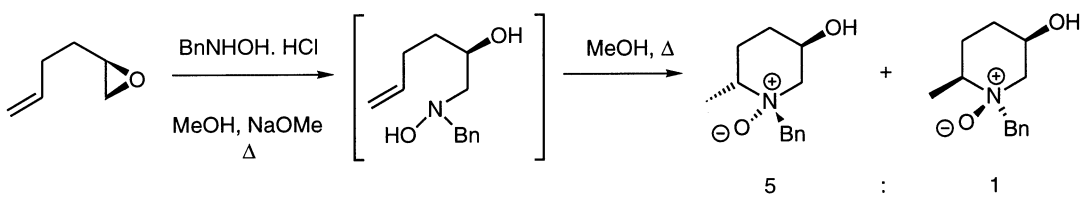
Abstract—The oxidation of a range of β-cyanoethyl tertiary amines with *m*CPBA gives the corresponding *N*-oxides, which can be isolated or undergo Cope-elimination to give secondary hydroxylamines in excellent yield. © 2001 Published by Elsevier Science Ltd.

As part of our studies on the use of the reverse-Cope cyclisation in the synthesis of nitrogen heterocycles we have shown that functionalised hydroxylamines can be readily prepared by the ring opening of epoxides with simple *N*-alkylhydroxylamines (Scheme 1). The reaction is regioselective and gives access to the desired substrates for the subsequent reverse-Cope cyclisations.[1]

Various other methods are available for the synthesis of secondary hydroxylamines, but most have serious limitations. These include the oxidation of secondary amines,[2] reduction or addition of an appropriate nucleophile to a nitrone,[3] addition of organometallic reagents to nitro or nitroso compounds,[4] the addition of hydroxylamines to α,β-unsaturated systems,[5] the reverse Cope cyclisation,[6] use of the Mitsunobu reaction[7] and the Cope elimination of suitable tertiary amine *N*-oxides.[8] This latter method has generally not been widely exploited due to the high temperatures required and the problems associated with regiochemistry of the elimination in many cases. There have been isolated reports of the use of electron withdrawing groups placed β to the *N*-oxide facilitating the elimination. Nagasawa et al.[9] have reported that the use of an appropriately positioned β-electron withdrawing nitrile allows the elimination to occur at significantly lower temperatures. In their system, proline (**1**) was treated with acrylonitrile to give the corresponding tertiary amine (**2**). This was then oxidised with *m*CPBA in methanol to give the *N*-oxide as a single diastereoisomer. The stereochemistry of the product was assigned on the basis of IR as the isomer (**3**) in which the *N*-oxide and the carboxylic acid were *trans*. This is in contrast to our earlier work on related systems and it is more probable that the product is the *cis* isomer (**4**).[10]

The *N*-oxide (**3**) was reported to undergo Cope elimination on warming in acetone to give the hydroxylamine (**5**) in a moderate 50% yield (Scheme 2).

We recently required a number of chiral hydroxylamines and have examined this reaction in more detail. We have found that it is an excellent method for the synthesis of a range of secondary hydroxylamines. The parent secondary amines (**6**) were treated with acrylonitrile in methanol to give the tertiary β-cyanoethyl amines (**7**) in excellent yield. Oxidation of these compounds with mCPBA gave the corresponding *N*-oxides (**8**). If the reaction was carried out in methanol as the



Scheme 1.

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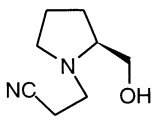
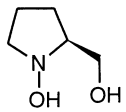
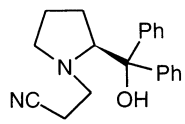
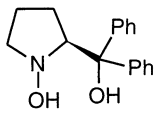
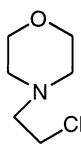
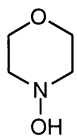
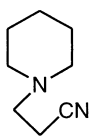
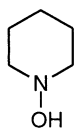
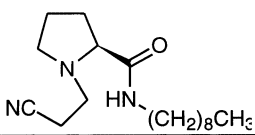
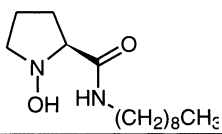
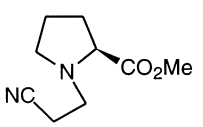
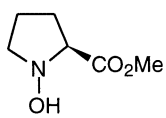
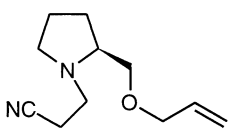
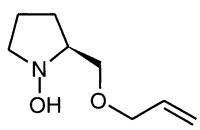
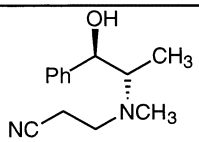
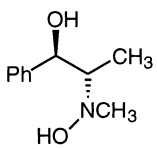
solvent the *N*-oxides could be isolated and characterised, although they slowly decomposed on standing.

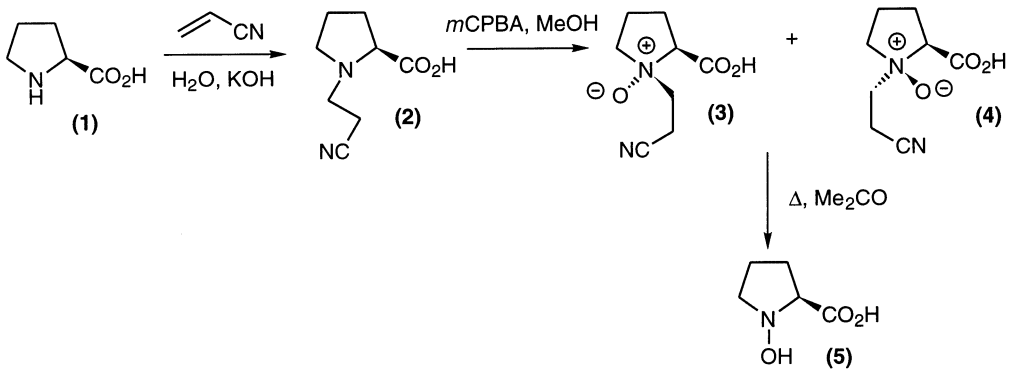
This is presumably a consequence of the methanol hydrogen bonding to the *N*-oxide. However, if the oxidation was performed in a non hydrogen bonding solvent such as CH_2Cl_2 then the intermediate *N*-oxide (**8**) underwent Cope elimination in situ to generate the hydroxylamine (**9**) in excellent yield (Scheme 3).

The reaction works for both cyclic and acyclic systems (Table 1). Apart from entries 3 and 4 in Table 1, all of the secondary hydroxylamines reported are new compounds.

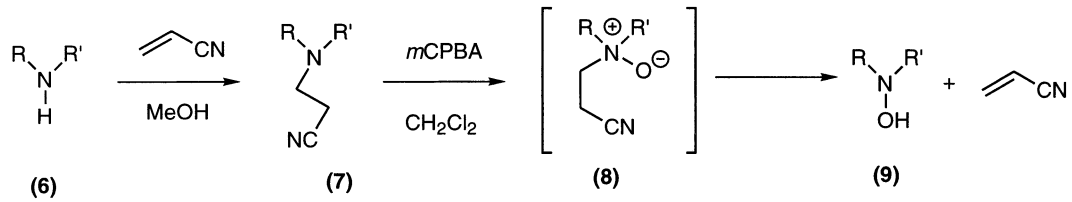
We are currently exploring the use of these chiral hydroxylamines in asymmetric transformations and their scope in the synthesis of a range of nitrogen based heterocycles.

Table 1. Synthesis of secondary hydroxylamines via Cope elimination of β-cyanoethylamines (see Scheme 3)

Entry	Substrate	% Yield β Cyano ethylamine	Product	% Yield Hydroxylamine
1		**90**		**68**
2		**100**		**96**
3		**100**		**93**
4		**94**		**72**
5		**97**		**93**
6		**93**		**96**
7		**90**		**90**
8		**89**		**95**



Scheme 2.



Scheme 3.

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