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The diastereoselective synthesis of functionalised isoxazolidines using a Cope elimination/intramolecular nitrone cycloaddition strategy

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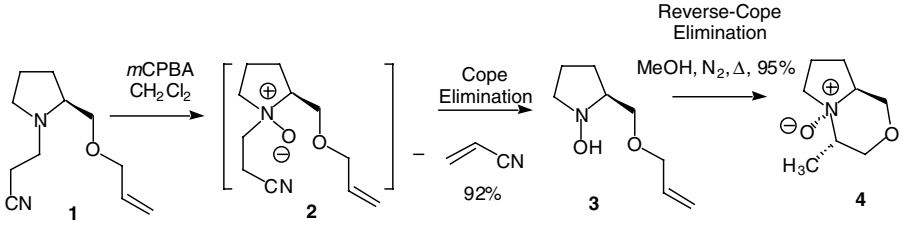
Abstract—Functionalised hydroxylamine derivatives of (*S*)-prolinol prepared by a Cope elimination have been found to undergo oxidation to the nitrone either in the presence of air or a catalytic quantity of TPAP. These undergo intramolecular cycloaddition to give tricyclic isoxazolidines with high diastereoselectivity.

In the accompanying paper we describe the synthesis of a functionalised morpholine *N*-oxide derivative **4** utilising a tandem Cope elimination/reverse-Cope elimination protocol[1] (Scheme 1).

We observed that if the reverse-Cope elimination was carried out in the presence of air then a minor product **5** was formed in addition to the *N*-oxide **4** (Scheme 2). Spectroscopic analysis indicated that it had the structure shown in Scheme 2 and it was formed as a single diastereoisomer.

This result could rationally be accounted for by the in situ oxidation of the secondary hydroxylamine **3** by air to give an intermediate nitrone **6**, which underwent an intramolecular cyclisation to give the racemic spirocyclic ether. Hydroxylamine **3** was found to undergo both the reverse Cope elimination and the oxidation/nitrone cycloaddition slowly at room temperature, particularly if they were in solution (MeOH or $CHCl_3$). However, **3** could be stored indefinitely at −20 °C under nitrogen. This type of oxidation of secondary hydroxylamines has been observed previously by Holmes and co-workers.[2] The intramolecular cycloaddition was rapid as we could not isolate any of the intermediate nitrone **6**. We then examined the use of an oxidant to accelerate the oxidation reaction. Thus, treatment of the hydroxylamine **3** with 5 mol% of TPAP and 1.5 equiv of *N*-methyl



Scheme 1.

Keywords: Cope elimination; Nitrones; Cycloaddition.
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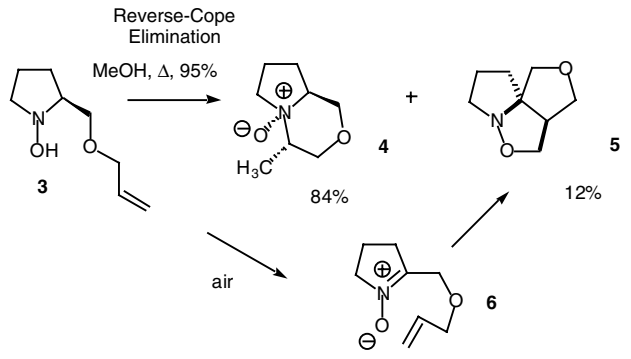


Scheme 2.

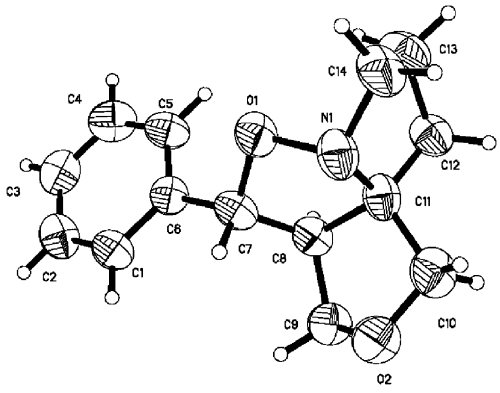


Figure 1.

morpholine *N*-oxide (NMNO) in MeCN[3] at room temperature resulted in quantitative formation of the spiro compound **5** in 1 h; again the product **5** was formed as a single diastereoisomer, containing a quaternary centre[4] (Scheme 3). The structure of **5** was established through NOE measurements.

In order to explore the scope and generality of the reaction we decided to prepare a number of derivatives in which there were additional substituents on the terminus of the alkene. Such substituents generally retard reverse-Cope eliminations.[5] The methods used are outlined in Scheme 4. Thus, the alcohol **7** was allylated by treatment with NaH and the functionalised allyl bromides **8**–**10** to give the ethers **11**–**13**. *N*-Oxidation followed by an in situ Cope elimination gave the hydroxylamines **14**–**16** in excellent yields. These could be isolated and purified by chromatography.

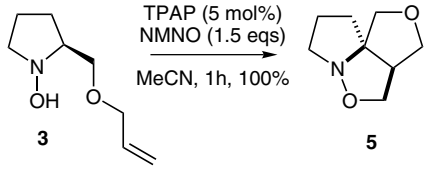
Treatment of the hydroxylamines **14**–**16** with catalytic TPAP (5 mol%) in the presence of NMNO (1.5 equiv) gave excellent yields of the cycloaddition products as single diastereoisomers. In the case of R = Ph the product of the reaction was characterised by X-ray crystallography (Fig. 1).

Substitution at the other end of the alkene was achieved by a similar protocol. Thus, allylation of the alcohol **7** with methallyl bromide gave the ether **21**. Oxidation and subsequent in situ Cope elimination gave the hydroxylamine **22** in excellent yield. Treatment of the hydroxylamine **22** with catalytic TPAP and NMNO gave the cycloaddition product **23** bearing two adjacent quaternary centres, along with the nitrone **24** in a 4:1.5 ratio (Scheme 5).

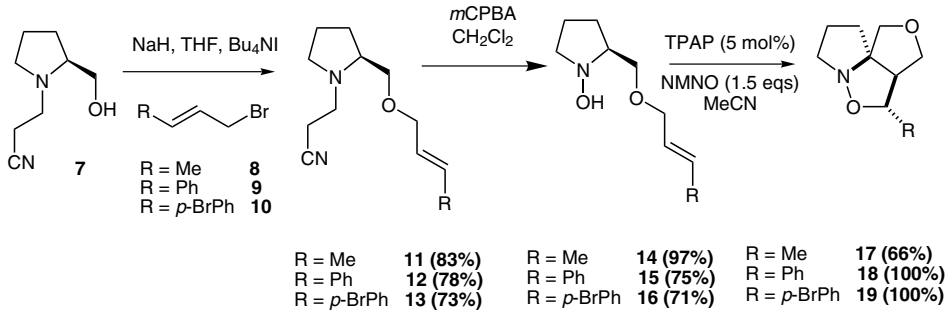
We also briefly examined the corresponding chemistry on the piperidinol system. Thus, the allyl ether **25** was prepared using methods described previously. Oxidation with *m*CPBA followed by an in situ Cope elimination gave the hydroxylamine **26**. Treatment of **26** with catalytic TPAP and NMNO gave the tricyclic product **27** in 92% yield as a single diastereoisomer. The stereochemistry was again determined by NOE measurements Scheme 6.

The N–O bond in the product spiro hydroxylamines could be cleaved using zinc in AcOH[6] yielding the novel hydroxy amines as shown in Scheme 7.

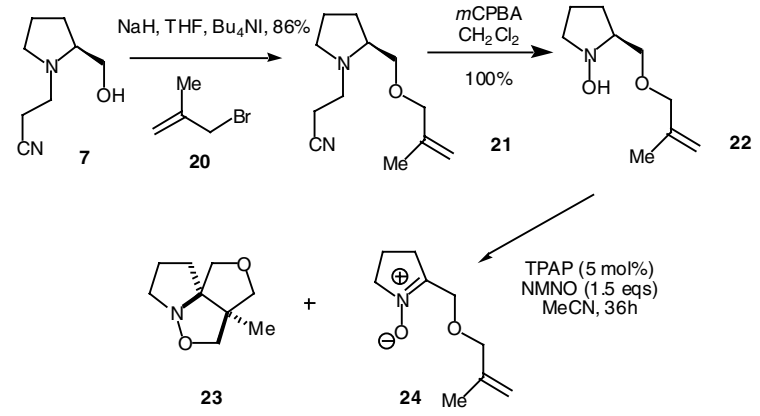
In summary, we have demonstrated that hydroxylamines generated from prolinol derivatives via a Cope elimination, undergo oxidation in the presence of catalytic TPAP/NMNO to generate the more substituted nitrones, which undergo intramolecular cycloaddition to



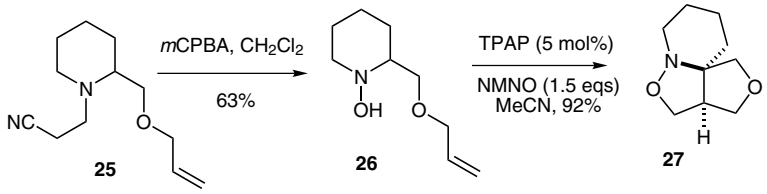
Scheme 3.



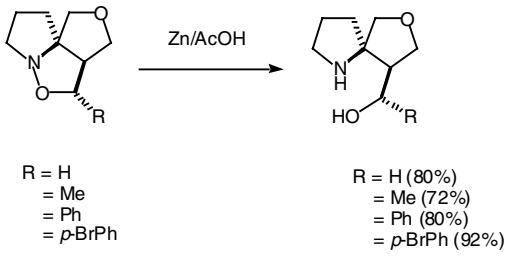
Scheme 4.



Scheme 5.



Scheme 6.



Scheme 7.

give tricyclic products bearing a quaternary centre with high diastereoselectivity.

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