Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 3655–3658
Tetrahedron Letters

The synthesis of chiral functionalised morpholine *N*-oxides using a tandem Cope elimination/reverse-Cope elimination protocol

Ian A. O'Neil,[a,*] Ed Cleator,[a] V. Elena Ramos,[a] Alan P. Chorlton[b] and David J. Tapolczay[b]

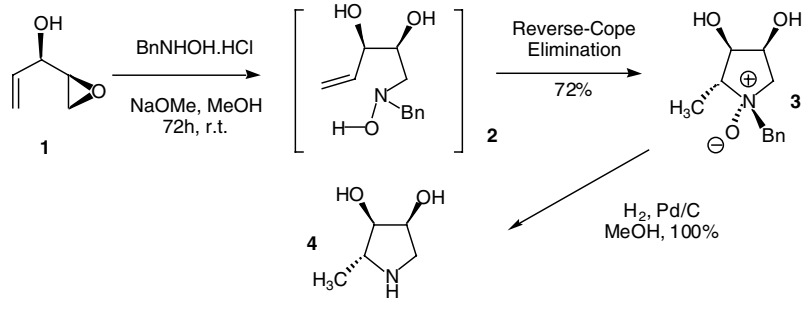
[a]*Robert Robinson Laboratories, Department of Chemistry, University of Liverpool, Crown Street, Liverpool L69 7ZD, UK*
[b]*Millennium Pharmaceuticals, 75, Sidney Street, Cambridge, MA, USA*

Received 26 January 2004; revised 27 February 2004; accepted 5 March 2004

Abstract—Hydroxylamine derivatives of (*S*)-prolinol have been generated using a Cope elimination. These undergo reverse-Cope elimination onto a pendant double bond to give morpholine *N*-oxides containing three contiguous chiral centres.

The reverse-Cope elimination is emerging as a powerful method for the synthesis of a range of heterocyclic systems.[1,2] We[3] and Jäger and Palmer[4] have recently reported the synthesis of a highly functionalised chiral pyrrolidine derivative via the regioselective ring opening of a chiral epoxide **1** with *N*-benzylhydroxylamine. The intermediate hydroxylamine **2** underwent reverse-Cope elimination at room temperature to give the pyrrolidine *N*-oxide **3** as a single stereoisomer (Scheme 1).

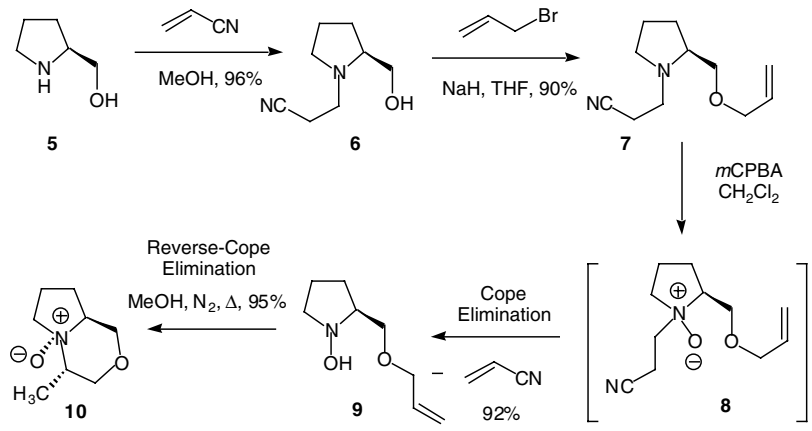
We now wish to report the synthesis of highly functionalised chiral morpholine *N*-oxides, which utilises a Cope elimination to generate an intermediate hydroxylamine; this then undergoes reverse-Cope elimination onto a suitably positioned alkene, generating two new chiral centres in the process. Thus, prolinol **5** was treated with acrylonitrile in methanol to give the cyanoethyl adduct **6** in 96% yield. Allylation of the alcohol gave tertiary amine **7** in 90% yield. Upon treatment with 1 equiv of *m*CPBA the amine **7** was selectively oxidised to give the *N*-oxide **8**. The *N*-oxide **8** underwent Cope elimination under the reaction conditions[2p] to generate the hydroxylamine **9** in 92% yield. This could be purified by flash chromatography, but ^{1}H NMR indicated that it had started to undergo reverse-Cope elimination to give the morpholine *N*-oxide **10** at room temperature. This process was facilitated simply by heating the hydroxylamine **9** in methanol under a nitrogen atmosphere to



Scheme 1.

Keywords: Cope elimination; Reverse-Cope elimination; Amine oxides.
* Corresponding author. Tel.: +44-151-794-3485; fax: +44-151-794-3588; e-mail: ion@liv.ac.uk

0040-4039/$ - see front matter © 2004 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2004.03.040



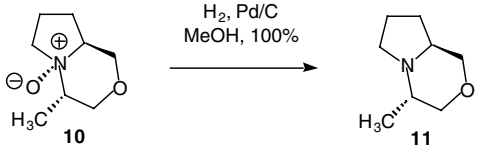
Scheme 2.

give a 95% yield of the morpholine *N*-oxide **10** containing three contiguous chiral centres, as a single diastereoisomer (Scheme 2).

Reduction of the morpholine *N*-oxide **10** by catalytic hydrogenation gave the morpholine **11** (Scheme 3).

The structure of the reverse-Cope elimination product was established by NOE experiments on the morpholine **11** (Fig. 1). There was a clear NOE between the methyl group at C-4 and the H-9 proton.

Interestingly, reoxidation of the amine **11** with *m*CPBA gave a 3.5:1 mixture of the parent amine oxide **10** and its diastereoisomer **12** (Scheme 4).



Scheme 3.

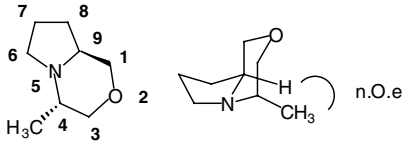
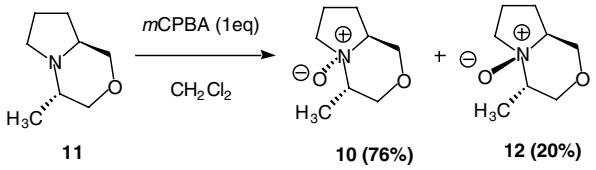
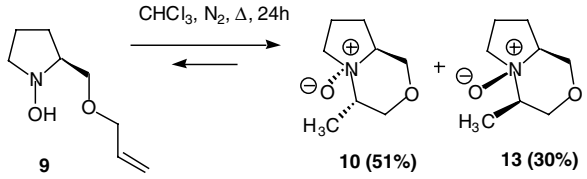


Figure 1. NOE between the C-9 proton and the C-4 methyl group in morpholine **11**.



Scheme 4.

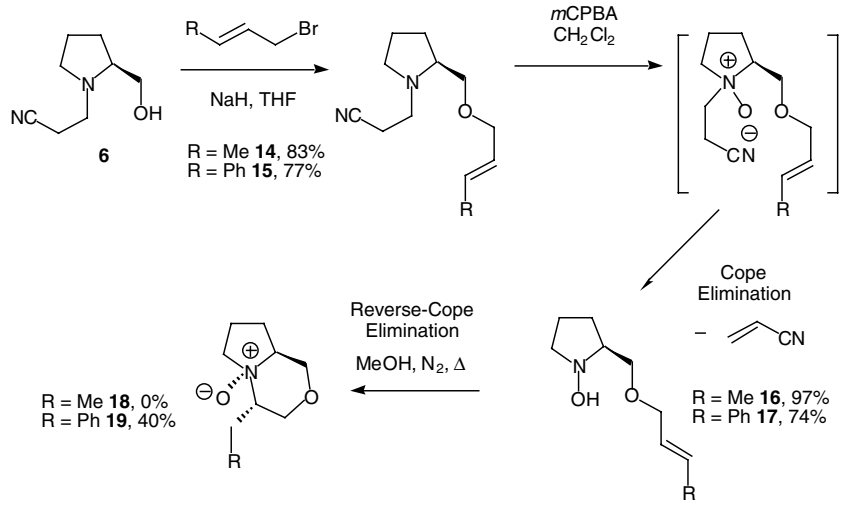


Scheme 5.

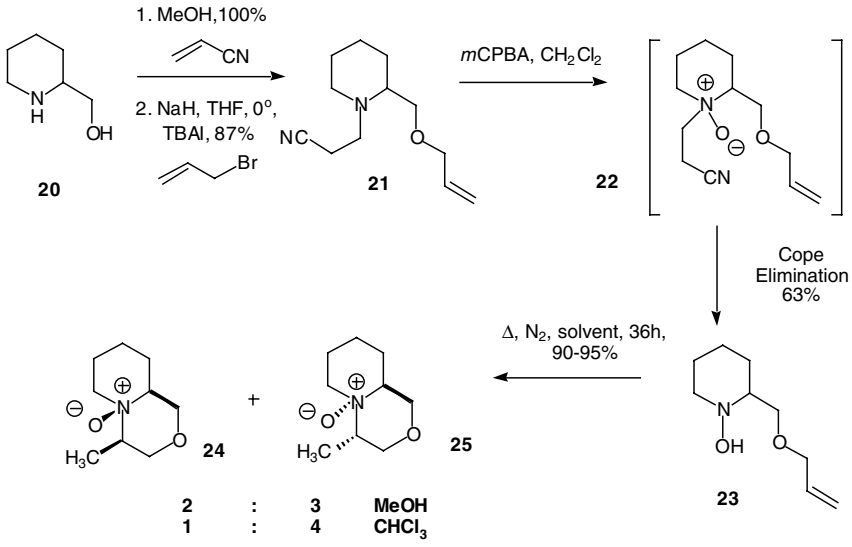
By changing the solvent to refluxing $CHCl_3$ it was found that a second diastereoisomeric *N*-oxide **13** was also formed as the minor component in the reaction (Scheme 5). The two diastereoisomers were separable by flash chromatography.

We next examined the effect of substituents on the terminus of the double bond. In most cases such substituents slow down the rate of the reverse-Cope elimination.[2g] We prepared the hydroxylamine substrates **16** and **17** bearing an additional methyl and a phenyl substituent, respectively, using a modification of the earlier procedure. It was found that on heating the hydroxylamine **16** bearing a methyl group on the double bond in methanol under nitrogen, no reverse-Cope elimination occurred. However, with a phenyl substituent present the reverse-Cope product **19** was isolated in a 40% yield along with recovered starting material. To the best of our knowledge this is the first example of a reverse-Cope elimination on a double bond with a terminal substituent that generates a six membered ring product (Scheme 6).

We also examined the effect of ring size on the reaction. Thus, racemic piperidinol was subjected to a similar reaction sequence to generate the tertiary amine **21** in 87% over two steps. Oxidation of **21** with *m*CPBA gave the hydroxylamine **23** in 63% yield. On heating in MeOH a 2:3 ratio of the diastereoisomeric *N*-oxides **24** and **25** was formed in a combined 93% yield. Again a solvent dependence was observed; when $CHCl_3$ was used as the solvent the ratio of **24**–**25** changed to a 1:4 (Scheme 7). Assignments of the structures **24** and **25** were made by NOE measurements.



Scheme 6.



Scheme 7.

In summary, we have demonstrated that the novel tandem Cope elimination/reverse-Cope elimination protocol is a powerful method for the high yielding synthesis of homochiral morpholine derivatives.

Acknowledgements

I.O.N. would like to thank Millennium Pharmaceuticals for their continued support of this work and Manuel Perez for the NOE measurements.

References and notes

1. Cooper, N. J.; Knight, D. W. *Tetrahedron* **2004**, *60*, 243.
2. (a) Knight, D. W.; Staples, E. R. *Tetrahedron Lett.* **2002**, *43*, 6771; (b) Knight, D. W.; Salter, R. *Tetrahedron Lett.* **1999**, *40*, 5915; (c) Holmes, A. B.; Adams, J. P.; Davies, I. E.; Roughley, S. D.; Williams, G. M. *J. Am. Chem. Soc.* **1999**, *121*, 4900; (d) Knight, D. W.; Bell, K. E.; Coogan, M. P.; Gravestock, M. B.; Thornton, S. R. *Tetrahedron Lett.* **1997**, *38*, 8545; (e) Knight, D. W.; Coogan, M. P.; Gravestock, M. B.; Thornton, S. R. *Tetrahedron Lett.* **1997**, *38*, 8549; (f) Knight, D. W.; Leese, M. P.; Wheildon, A. R. *Tetrahedron Lett.* **1997**, *38*, 8553; (g) Ciganek, E.; Read, J. M., Jr; Calabrese, J. C. *J. Org. Chem.* **1995**, *60*, 5795, and 5803; (h) Oppolzer, W.; Bochet, C. G.; Spivey, A. C. *J. Am. Chem. Soc.* **1994**, *116*, 3139; (i) Holmes, A. B.; Forbes, I. T.; Fox, M. E.; Thompson, M. *J. Chem. Soc. Perkin Trans. 1* **1994**, 3379; (j) Gravestock, M. B.; Knight, D. W.; Thornton, S. R. *J. Chem. Soc., Chem. Commun.* **1993**, 169; (k) Ciganek, E. *J. Org. Chem.* **1990**, *55*, 3007; (l) O'Neil, I. A.; Cleator, E.; Southern, J. M.; Hone, N.; Tapolczay, D. *J. Synlett* **2000**, 695; (m) O'Neil, I. A.; Southern, J. M. *Tetrahedron Lett.* **1998**, *39*, 9089; (n) O'Neil, I. A.; Woolley, J. C.; Southern, M. J.; Hobbs, H. *Tetrahedron Lett.* **2001**, *42*, 8243; (o) O'Neil, I. A.; Cleator, E.; Southern, J. M.; Bickley, J.; Tapolczay,

D. J. *Tetrahedron Lett.* **2001**, *42*, 8251; (p) O'Neil, I. A.; Cleator, E.; Tapolczay, D. J. *Tetrahedron Lett.* **2001**, *42*, 8247.

3. O'Neil, I. A.; Cleator, E.; Southern, J. M.; Hone, N.; Tapolczay, D. J. *Synlett* **2000**, 1408.
4. Palmer, A. M.; Jäger, V. *Synlett* **2000**, 1405.