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The synthesis of highly functionalized morpholine N-oxides from ephedrine and pseudoephedrine utilizing a tandem Cope elimination/reverse Cope elimination protocol

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Abstract—Highly functionalized monocyclic morpholine N-oxides can be prepared in three steps starting from ephedrine and pseudoephedrine utlizing a tandem Cope elimination/reverse Cope elimination.

The reverse Cope elimination is emerging as a powerful method for the synthesis of a wide variety of heterocyclic systems.[1] The synthesis of simple pyrrolidine and piperidine based derivatives using this methodology was established by Black and Doyle in 1978.[2] Recently the work of Ciganek et al.,[3] our group,[4] and Palmer and Jäger[5] have demonstrated the scope and limitations of this reaction in the synthesis of chiral functionalized pyrrolidines. Elegant use of this methodology in the total syntheses of several alkaloids has been demonstrated by Oppolzer et al.,[6] Holmes and co-workers[7] and Knight and Salter.[8] The synthesis of piperidine based compounds is less well documented, but is equally as viable as demonstrated first by House and Lee[9] and later by O'Neil et al.[10] In this Letter we report the synthesis of monocyclic functionalized, homochiral, morpholine amine N-oxides using the tandem Cope elimination/reverse Cope reaction. The synthesis of chiral morpholine derivatives is of interest due to their extensive potential as therapeutic agents.[11] Morpholine amine N-oxides with up to four contiguous chiral centres can be prepared utilizing our methodology.

The synthesis of morpholine amine N-oxides **6** and **7** begins with the known β-amino alcohol (1*S*,2*S*)-(+)-pseudoephedrine **1**, and is shown in Scheme 1.

Treatment of pseudoephedrine **1** with acrylonitrile gave the corresponding *N*-cyanoethyl derivative **2**, which was O-alkylated with allyl bromide to give **3**. Treatment of **3** with purified (~95%) *meta*-chloroperbenzoic acid in CH_2Cl_2 yielded the intermediate N-oxide **4**, which underwent Cope elimination in situ to give hydroxylamine **5**. On heating in CH_2Cl_2, hydroxylamine **5** underwent reverse Cope elimination to give morpholine amine N-oxide **6** as a single diastereoisomer in 32% yield (Scheme 1). This tandem Cope/reverse Cope methodology has been established within our group and has been demonstrated in the synthesis of bicyclic chiral morpholine derivatives,[12] however, this is the first example of the synthesis of a monocyclic morpholine N-oxide using the reverse Cope elimination.

All attempts to isolate pure hydroxylamine **5** by chromatography met with failure. In order to investigate the effect of solvent on the reaction, after consumption of the *N*-cyanoethyl derivative **3**, the reaction mixture was filtered, the dichloromethane removed, and the residue taken up in methanol and heated to reflux for 3 days. This gave the two diastereoisomeric N-oxides **6** and **7** in a 3:2 ratio, in a combined yield of 82%. It is likely that hydrogen bonding solvents such as MeOH stabilize the N-oxide products. Conclusive determination of the stereochemistry of these compounds required a further transformation. Treatment of N-oxide **6** with BH_3·THF gave the parent tertiary amine **8** in 62% along with the borane complex of the parent tertiary amine **9** (Scheme 2).

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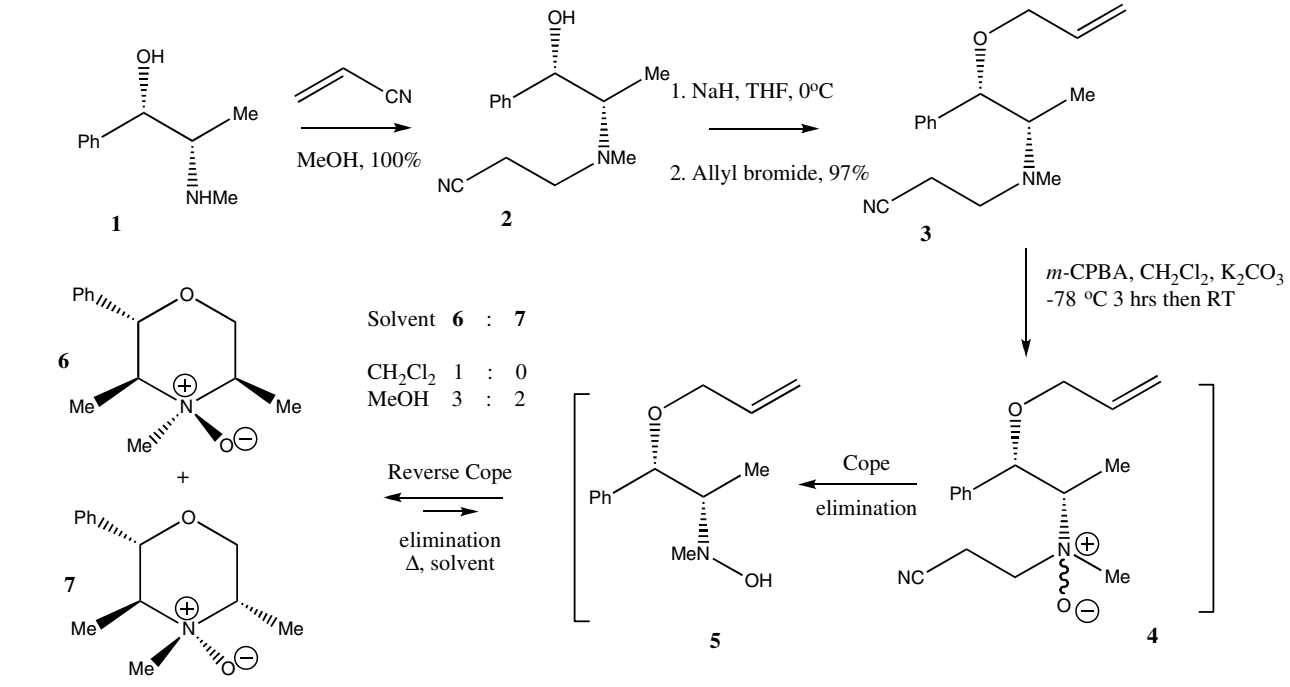
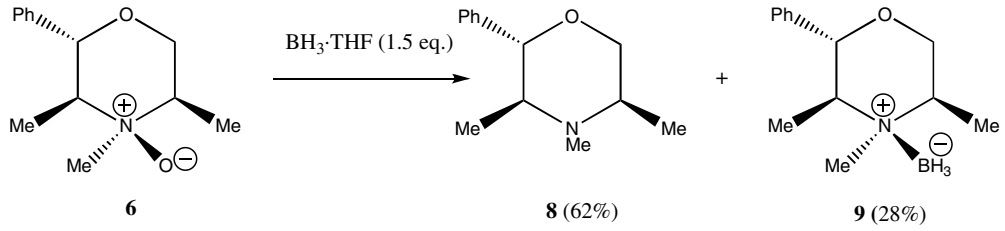


Scheme 1.



Scheme 2.

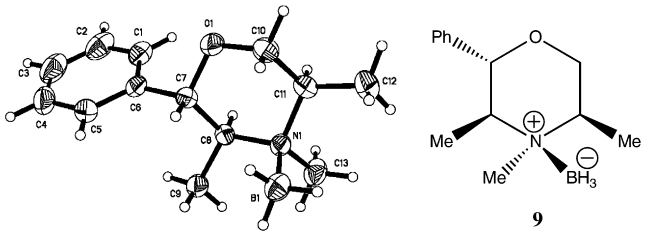
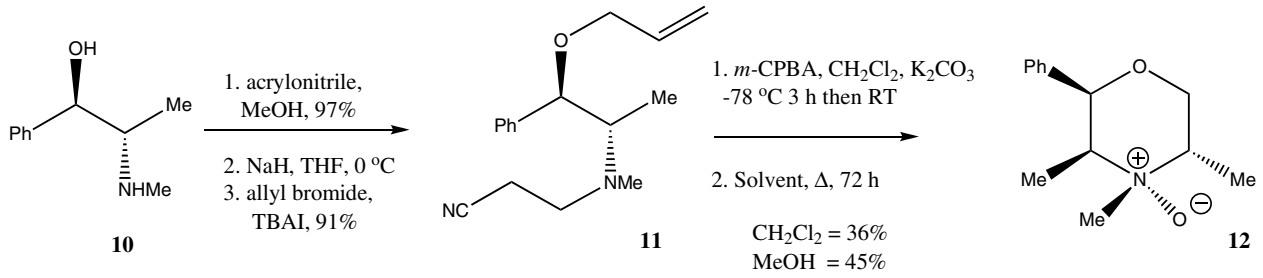


Figure 1.

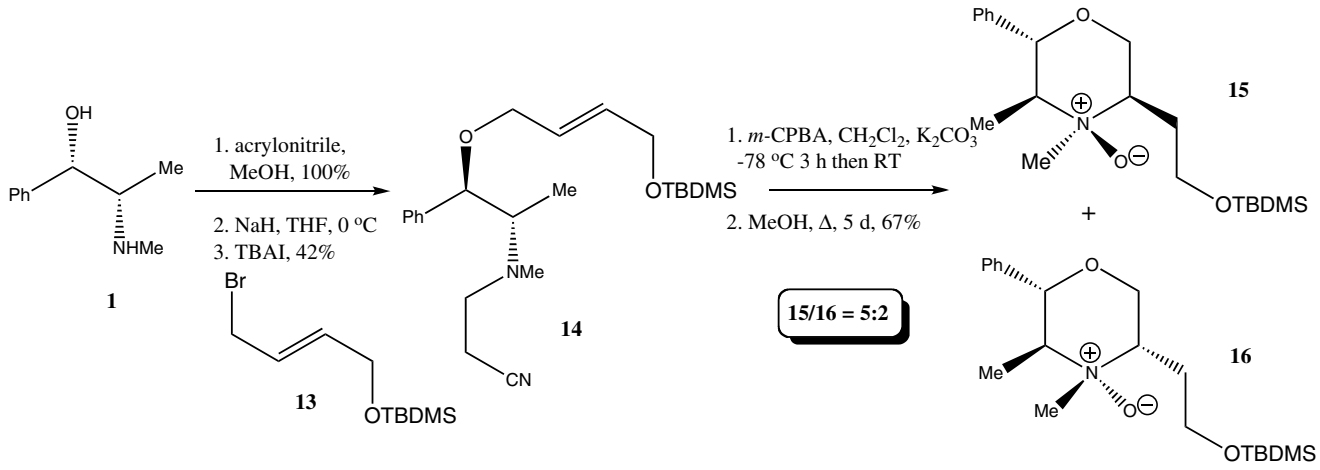
The stereochemistry of compound **6** was determined by the X-ray crystallographic analysis of the borane salt **9** (Fig. 1).[13] This was supported by NOESY experiments on the parent compound **6**.

The same methodology was also applied to (1*R*,2*S*)-(−)-ephedrine **10** (Scheme 3). The precursor for the tandem Cope elimination/reverse Cope elimination **11** was made in 88% yield over two steps. Oxidation of amine **11** with *m*-CPBA gave an intermediate N-oxide, which then underwent Cope elimination in situ. The resulting hydroxylamine was not isolated but after heating to reflux in CH_2Cl_2 yielded the morpholine amine N-oxide **12** in 36% yield as a single diastereoisomer. When the dichloromethane solvent was removed and the crude hydroxylamine taken up and heated to reflux in methanol for 3 days, the yield of N-oxide **12** was increased to 45%. Once again all attempts to isolate the intermediate hydroxylamine by chromatography met with failure. The stereochemistry of **12** was determined by NOE analysis.

In order to incorporate further functionality in the molecule, we prepared the substituted alkene **14**. The presence of an allylic oxygen has been reported to favour the reverse Cope elimination.[8] The allylic bromide derivative **13** (Scheme 4) was synthesized in two steps using a reported procedure.[14] When the previously described methodology was used to synthesize the reverse Cope elimination precursor **14**, the yield for the O-allylation, was significantly lower than expected. This could be possibly explained by the fact that the allylic bromide **13** appeared to be somewhat unstable. Selective N-oxidation of **14** followed by in situ Cope elimination gave a hydroxylamine. Again no attempt was made to isolate this species. On heating the intermediate hydroxylamine to reflux in methanol, reverse Cope elimination gave the morpholine N-oxides **15** and **16** in a 67% yield as a 5:2 mixture of diasteroisomers. These could be separated



Scheme 3.



Scheme 4.

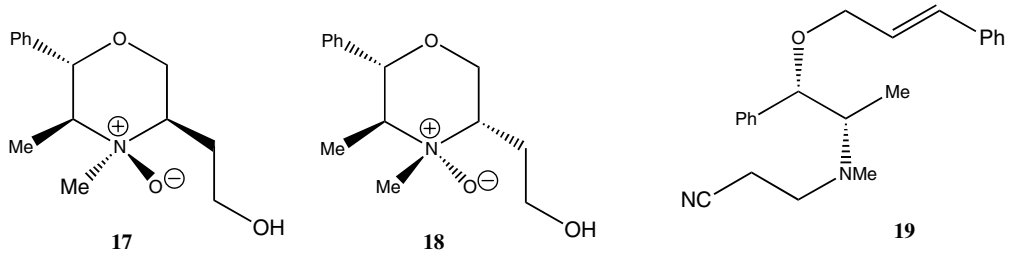


Figure 2.

by using rapid flash chromatography (Scheme 4). Prolonged exposure of this mixture to silica gel resulted in the loss of the TBDMS protecting group to give compounds **17** and **18** (Fig. 2).

We also prepared the phenyl substituted alkene **19** (Fig. 2) using the methodology described above, but after oxidation and Cope elimination, the resulting hydroxylamine failed to undergo reverse Cope elimination in either refluxing dichloromethane or methanol. This was attempted with both ephedrine and pseudoephedrine substrates. This result highlights the activating effect of the allylic oxygen.[8]

In summary, we have reported new syntheses of highly functionalized chiral, monocyclic morpholine amine *N*-oxides utilizing the reverse Cope elimination. Out future efforts will focus around adapting this methodology further, and investigating the wide variety of further transformations possible from amine N-oxides.

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Supplementary data

The following supplementary data is available: (1) detailed descriptions of experimental procedures, (2) ^{1}H

NMR spectra. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.01.047.

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