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The synthesis of functionalised chiral bicyclic lactam and lactone N-oxides using a tandem Cope elimination/reverse Cope elimination protocol

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Abstract—Functionalised hydroxylamine derivatives of (*S*)-proline and (*R*)-pipecolic acid have been prepared using a Cope elimination. These undergo reverse Cope elimination onto a pendant double bond to give bicyclic lactam and lactone N-oxides containing three contiguous chiral centres, this extends the scope and applicability of the reverse Cope elimination in the synthesis of heterocyclic systems by incorporation of the lactone and lactam structural motifs.

The reverse Cope elimination is rapidly becoming a valuable and powerful method for the synthesis of a wide variety of heterocyclic systems.[1–19] Recently we reported the synthesis of functionalised chiral morpholines derived from (*S*)-prolinol.[20] These compounds were prepared using a tandem Cope elimination/reverse Cope elimination protocol. We now report the development of this protocol to the first reported synthesis of chiral bicyclic lactam and lactone N-oxides using the reverse Cope elimination.

Our initial investigations started with (*S*)-proline. Treatment of this with acrylonitrile and potassium hydroxide in water, followed by Soxhlet extraction with acetone gave **1** in an 84% yield.[21] The coupling of allylamine to **1** proved more problematic with several methods being tried. These included the use of DCC with DMAP, EDCI with DIEA and the use of oxalyl chloride. The most successful method by far was the use of triethylamine and methyl chloroformate to form the mixed anhydride. Allylamine was then added in a one-pot procedure, to give **2** in a 62% yield. Treatment of tertiary amine **2** with *m*-CPBA gave selectively N-oxide **3**. This then spontaneously underwent Cope elimination under the reaction conditions to generate hydroxylamine **4** in an 81% yield. This could be purified by flash column chromatography, but ^{1}H NMR analysis indicated that it had started to undergo reverse Cope elimination to the bicyclic lactam N-oxide **5** at room temperature. This reaction was accelerated by heating **4** in methanol under a nitrogen atmosphere to give a 52% yield of N-oxide **5** containing three contiguous chiral centres and the lactam functionality. The reaction was also performed in chloroform and resulted in a 48% yield of **5** (Scheme 1). The configuration of the two newly formed contiguous chiral centres was confirmed by NOE experiments. Irradiation of H-9a gave a strong enhancement with the methyl group at C-4, which confirmed the (4*S*,5*S*) configuration.

In addition to the reverse Cope product **5** the unsaturated amide **6** was also isolated. Using methanol as the reaction solvent, **6** was formed in a 23% yield. In chloroform this increased to 41%. This compound is possibly formed from the minor diastereomer of the reverse Cope elimination **5a**, which is set up stereochemically to eliminate water with the proton and N-oxide being *anti* to one another. Amide **6** was a yellow crystalline solid and its structure was confirmed by X-ray crystallography (Fig. 1).[22]

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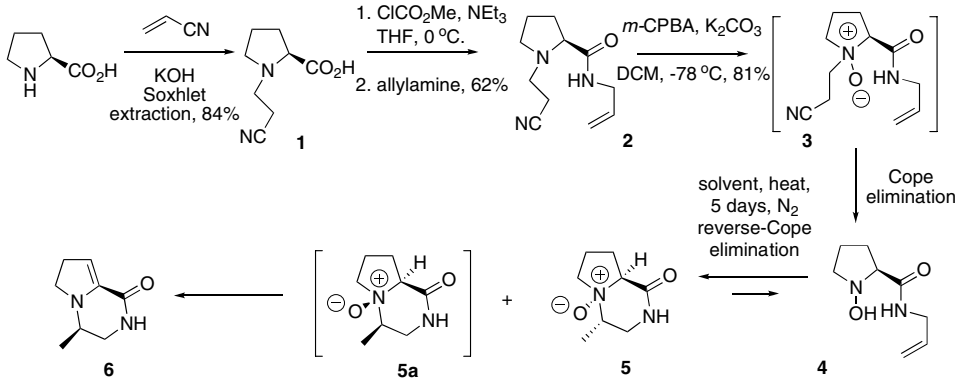


Scheme 1.

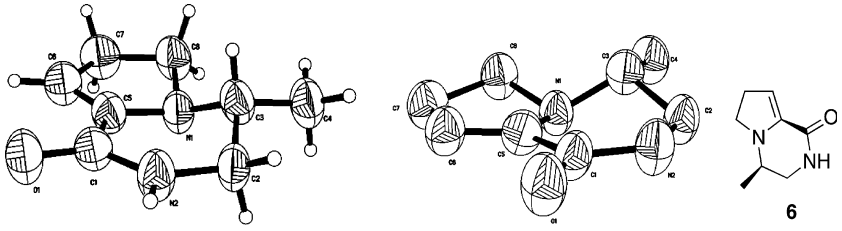
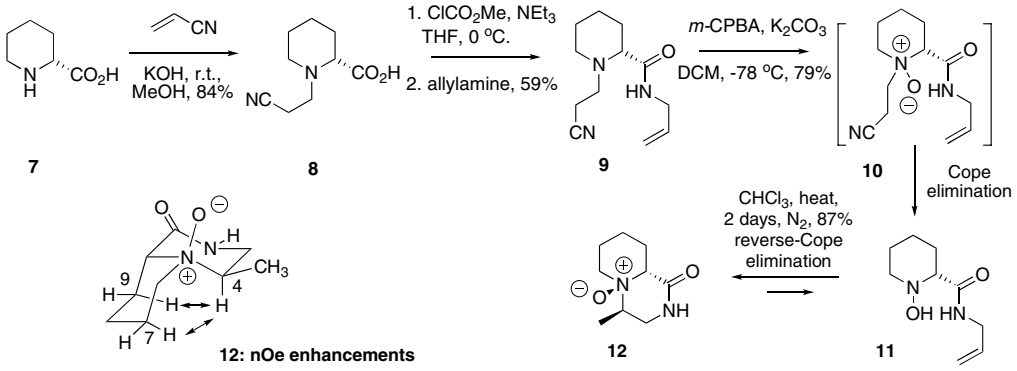


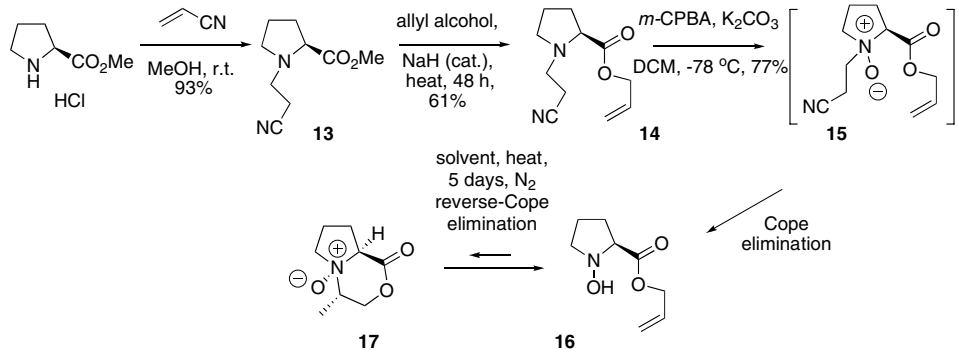
Figure 1. X-ray structure of bicyclic lactam **6**.

In order to investigate the effect of ring size on the reaction we studied the derivatives of pipecolic acid. Racemic pipecolic acid was resolved using L-tartaric acid to give amine **7**.[23] Addition of acrylonitrile to **7** using KOH gave **8** in a quantitative yield. The mixed anhydride methodology was applied to the coupling of allylamine to **8** as this had been successful in the previous system, giving amide **9** in a 59% yield. Treatment of **9** with *m*-CPBA gave selectively N-oxide **10**. This then spontaneously underwent Cope elimination under the reaction conditions to generate hydroxylamine **11** in a 79% yield. This could be purified by flash column chromatography, but again ^{1}H NMR measurements indicated that it had started to undergo reverse Cope elimination to give bicyclic lactam N-oxide **12** at room temperature. This reaction was accelerated by heating **11** in chloroform under nitrogen to give an 87% yield of N-oxide **12** as a single diastereoisomer (Scheme 2). The configuration of the two newly created chiral centres was again confirmed by NOE measurements. Thus, the irradiation of H-4ax gave enhancements with H-7ax and H-9ax. These NOEs not only settled the stereochemistry of this isomer as (4*R*,5*R*), but also suggest a distorted *trans*-decalin conformation for the system.

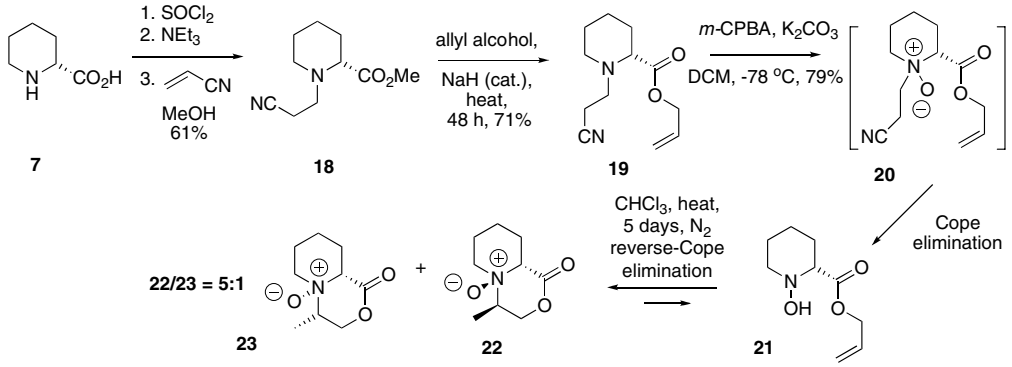
As incorporation of the lactam functionality had been successful, incorporation of the lactone functionality was investigated. In this case it was envisaged that allyl alcohol could be prepared by using an ester exchange reaction. Therefore, the methyl ester hydrochloride salt of (*S*)-proline was used as the starting material. This was treated with acrylonitrile in methanol to give **13** in a 93% yield. Addition of allyl alcohol was achieved by treating **13** with 6 equiv of allyl alcohol and a catalytic quantity of NaH, this gave **14** in a 61% yield. Treatment of **14** with *m*-CPBA selectively gave N-oxide **15**, which spontaneously underwent Cope elimination to generate hydroxylamine **16** in a 77% yield. Heating hydroxylamine **16** in chloroform, under nitrogen for 5 days unfortunately gave an inseparable mixture of hydroxyl-



Scheme 2.



Scheme 3.



Scheme 4.

amine **16** and the reverse Cope product **17** as a single diastereomer, with the equilibrium lying in favour of the hydroxylamine in a ratio of 9:1. The ratio was determined from the alkene protons of **16** and the distinctive methyl protons of **17** appearing as a doublet at 1.2 ppm. Attempts to carry out this reaction in alternative solvents failed to improve this ratio (Scheme 3).

As the pipecolic lactam had been higher yielding than the proline derivative it was hoped that the same trend would be seen with the lactone leading to the isolation of a pure bicyclic lactone N-oxide. In this case the previously resolved (*R*)-pipecolic acid **7** was treated with thionyl chloride, triethylamine and then acrylonitrile in methanol to give **18** in a 60% yield. Treatment of **18** with a catalytic quantity of NaH, using allyl alcohol as the solvent gave **19** in a 71% yield. Oxidation of **19** gave N-oxide **20**, which spontaneously underwent Cope elimination to give hydroxylamine **21** in an 89% yield. Heating hydroxylamine **21** in chloroform under nitrogen at reflux for 5 days gave again an inseparable mixture of hydroxylamine **21** and N-oxide **22** in a more favourable ratio of 6:1, but as two diastereomers in a ratio of 5:1 (Scheme 4).

In conclusion, we have demonstrated that the novel tandem Cope elimination/reverse Cope elimination protocol can be applied to more complex systems using derivatives of (*S*)-proline and (*R*)-pipecolic acid. This has led to the first reported synthesis of chiral bicyclic lactam and lactone N-oxides by the reverse Cope elimination. The lactone bicyclic compounds have been observed by ^{1}H NMR but are inseparable from the hydroxylamine starting material in both cases.

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Supplementary data

The following supplementary data is available: (1) detailed descriptions of experimental procedures, (2) X-ray data for compound **6**, (3) ^{1}H NMR spectra. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.01.045.

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