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The diastereoselective synthesis of functionalised spirocyclic lactams and lactones using a Cope elimination/intramolecular nitrone cycloaddition strategy

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Abstract—Functionalised hydroxylamine derivatives of (*S*)-proline and pipecolic acid have been prepared using a Cope elimination. These hydroxylamines have been found to undergo oxidation to the nitrone either in the presence of air or a catalytic quantity of TPAP. An intramolecular 1,3-dipolar cycloaddition then occurs between the nitrone and pendant double bond to give tricyclic lactams and lactones with high diastereoselectivity.

Previously there have been few general methodologies for the construction of azaspirocyclic ring systems.[1–7] The azaspirocyclic substructure is seen in numerous biologically active alkaloids such as (+)-lactacystin,[8] histrionicotoxin,[9] sibirine,[10] nitramine,[11] amanthaspiramide F[12] and cylindricine C.[13] The spirolactam substructure is also present in several different conformationally constrained peptidomimetics, for example, those developed by Hinds et al. and Casamitijana and co-workers.[14,15]

Recently, we reported the preparation of functionalised isoxazolidines using a Cope elimination/intramolecular nitrone cycloaddition strategy.[16] Incorporation of the lactam and lactone functionalities into our spirocyclic compounds was imperative in expanding the scope and applicability of our synthetic strategy. We now wish to report the synthesis of tricyclic lactams and lactones derived from (*S*)-proline and pipecolic acid. In addition the use of 4(*R*)-hydroxy-2-(*S*)-proline allows us to report the synthesis of a homochiral spirocyclic lactone.

The synthesis of the tricyclic lactams began with the (*S*)-proline derived amide **1**. The synthesis of all precursor amides and esters are described in the accompanying paper.[17] Treatment of **1** with *m*-CPBA gave the *N*-oxide **2**. This then underwent Cope elimination in situ to generate the hydroxylamine **3** in 81% yield. Oxidation of hydroxylamine **3** with 5 mol % TPAP and 1.5 equiv of *N*-methyl morpholine *N*-oxide (NMNO) in MeCN[18,19] at room temperature gave the stable nitrone **4** in 98% yield. Previously related nitrones have not been stable and have rapidly undergone 1,3-dipolar cycloaddition.[17] The explanation for the stability of **4** lies in the hydrogen bonding between the *N*-oxide and NH. This was confirmed by ^{1}H NMR analysis which shows the NH shifting from 7.0 ppm in **3** to 10.1 ppm in **4**. The 1,3-dipolar cycloaddition was achieved by heating **4** in acetonitrile at reflux for 5 days to give **5** as a single diastereoisomer in 91% yield (Scheme 1).[20–22] Spirocyclic lactam **5** was also formed by refluxing **3** in methanol open to the air for 5 days in a 58% yield, the oxidant in this case was oxygen in the air. The stereochemistry of **5** was assigned unambiguously by NOE studies. Irradiation of the signal for the H-3a′ proton gave an enhancement with one of the hydrogens at C-8, so fixing the relative configuration. We have also recently reported that the hydroxylamines generated by Cope elimination will undergo reverse Cope elimination under different reaction conditions.[23] Examples of the incorporation of the lactam and lactone functionalities into the reverse Cope elimination protocol can be found in the accompanying paper.[17]

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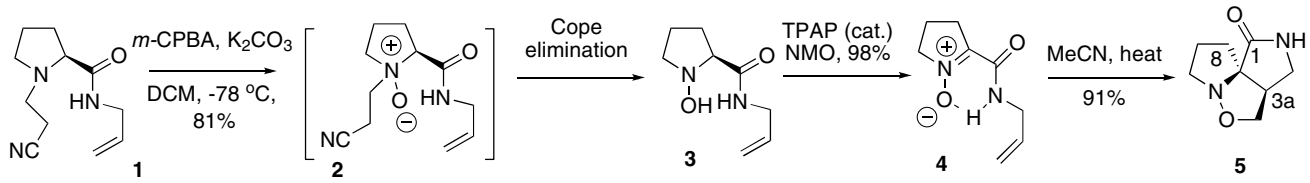


Scheme 1.

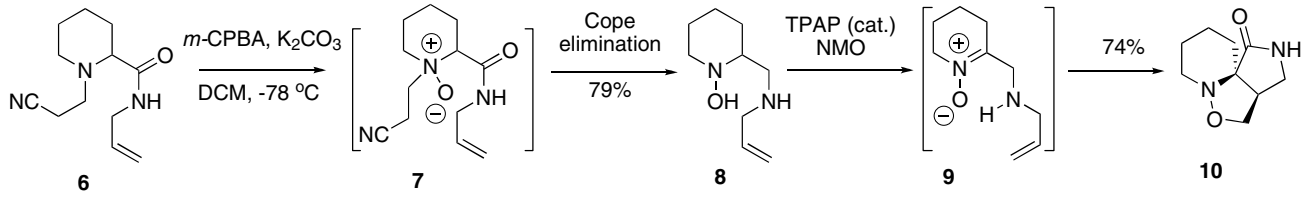
In order to investigate the effect of ring size on the cycloaddition, racemic pipecolic acid was used as a substrate. Amide **6** was selectively oxidised using *m*-CPBA to give the *N*-oxide **7**, which then underwent spontaneous Cope elimination to give **8** in 79% yield. Oxidation of the hydroxylamine **8** with catalytic TPAP and NMNO gave in this case the tricyclic lactam **10** in 74% yield (Scheme 2). In this case none of the nitrone **9** was isolated indicating that the pipecolic derivatives are more reactive.

As the lactam functionality had been successfully incorporated into the synthetic strategy, our attention turned to the incorporation of a lactone moiety. Formation of hydroxylamine **13** was achieved using *m*-CPBA to give selectively the *N*-oxide **12**, which then underwent spontaneous Cope elimination to give **13** in 77% yield. Oxidation of the hydroxylamine **13** using a catalytic quantity of TPAP and 1.5 equiv of NMNO gave the tricyclic spiro lactone **15** in 79% yield (Scheme 3). Spiro lactone **15** was also formed in a 28% yield by heating **13** at reflux, open to the air in chloroform for 5 days.

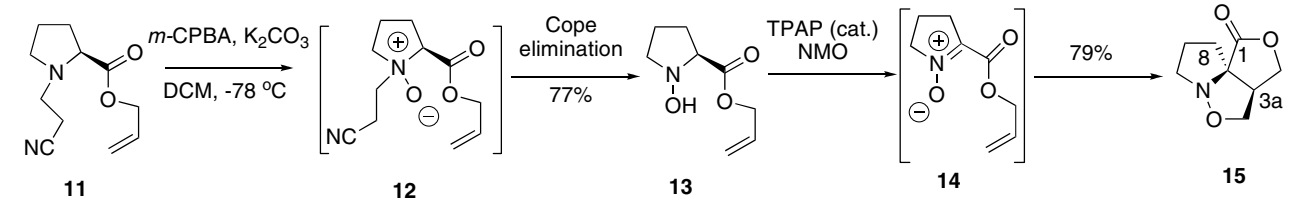
None of the nitrone **14** was isolated from the reaction as it spontaneously underwent 1,3-dipolar cycloaddition. In this case the stereochemistry could not be determined by NOE spectroscopy as the key protons to be irradiated overlapped on the ^{1}H NMR spectrum. However, by analogy with the tricyclic lactam **5** the stereochemistry for **15** which is shown below was assigned.

A similar synthetic route was used in the preparation of the analogous pipecolic acid derivative. Formation of hydroxylamine **18** was achieved using *m*-CPBA to give selectively the *N*-oxide **17**, which then underwent spontaneous Cope elimination to give **18** in 89% yield. Oxidation of the hydroxylamine **18** as before gave the tricyclic spiro lactone **20** in an 83% yield via the unisolable nitrone **19** (Scheme 4).

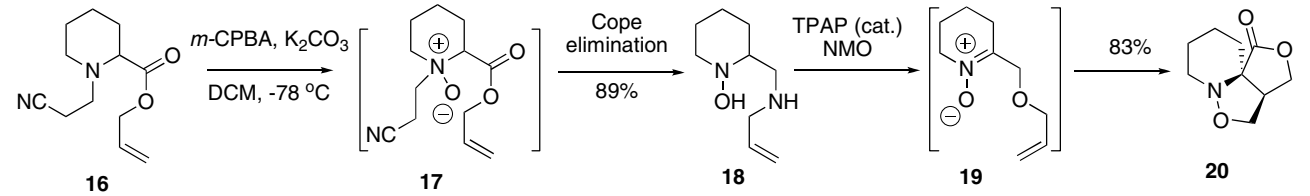
With the lactone functionality easily incorporated into our tricyclic systems it seemed logical to see if these tricyclic compounds could be made with a fixed chiral centre, as any previously incorporated chirality had been



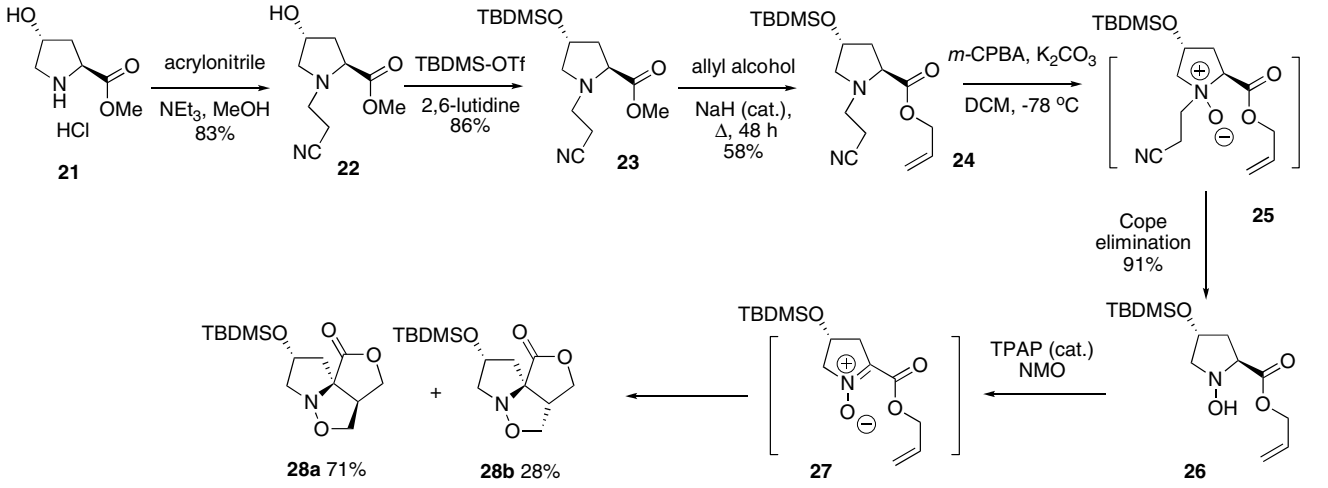
Scheme 2.



Scheme 3.



Scheme 4.

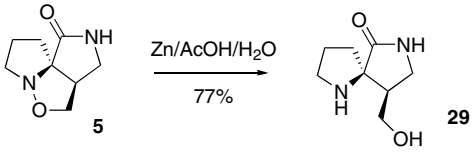


Scheme 5.

lost during formation of the nitrone, with subsequent 1,3-dipolar cycloaddition leading to racemic material. It was therefore reasonable to presume that inclusion of a fixed chiral centre in the pyrrolidine ring would lead to the desired chiral cycloadduct (Scheme 5). The 4-hydroxyproline derivative **21** is commercially available and was converted to the cyanoethylated product **22** in 83% yield by reaction with acrylonitrile. The 4-hydroxy group was then protected using 2,6-lutidine and TBDMSOTf to give **23** in 86% yield. Ester exchange with allyl alcohol was achieved using a catalytic quantity of NaH to give **24** in a 58% yield. Oxidation of **24** using *m*-CPBA gave the *N*-oxide **25**, this then underwent spontaneous Cope elimination of acrylonitrile, and gave hydroxylamine **26** in a 91% yield. Oxidation to the nitrone **27** followed by spontaneous 1,3-dipolar cycloaddition gave, interestingly, two diastereomers that were separable by flash column chromatography. The major diastereomer **28a** was isolated in 71% yield and the minor diastereomer **28b** was isolated in 28% yield. Diastereoisomer **28a** was also formed by heating **26** at reflux in methanol, open to the air for 4 days in a 36% yield.

The stereochemistry of the major diastereomer was confirmed by NOE measurements. The formation of the minor diastereomer had never been seen in any of our previous systems.

Conversion of these tricyclic compounds into their bicyclic derivatives by cleavage of the N–O bond was of considerable interest, with the bicyclic spiro structure being seen more commonly in several natural products and peptidomimetics. This cleavage proved to be more difficult than initially anticipated. Several methods were attempted, including reductive cleavage using H_2 Pd/C, Zn/AcOH and Zn/AcOH/Cu(OAc)$_2$. Oxidative cleavage using *m*-CPBA was also tried. However, all these methods failed. An adaptation of the Zn/AcOH method developed by Chiacchio et al. proved more successful, leading to bicyclic compound **29** in a 77% yield (Scheme 6).[24]



Scheme 6.

To conclude, we have demonstrated that the Cope elimination/intramolecular nitrone cycloaddition strategy can be applied to incorporate the lactam and lactone structural motifs into complex tricyclic spiro adducts. Incorporation of a fixed chiral centre has also been achieved.

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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.2007.01.046.

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