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Scope and limitations of the alkylidene carbene 1,5-CH insertion reactions of α-amino acid-derived substrates

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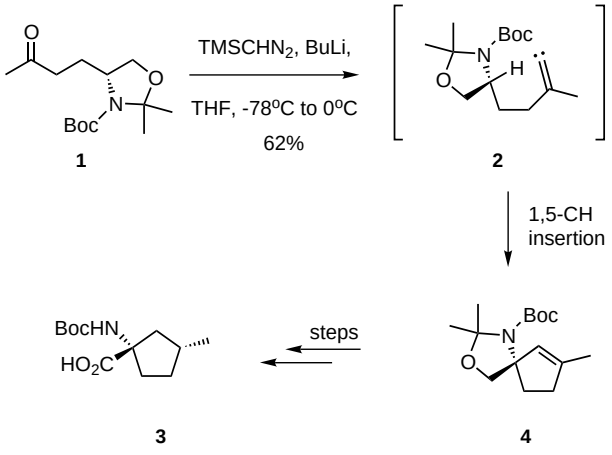
Abstract—A range of α-amino acid-derived cyclisation precursors were synthesised from suitably protected α-amino esters, via a Dibal-H/Wittig/catalytic hydrogenation strategy and each of these was subjected to alkylidene carbene-forming conditions (lithio(trimethylsilyl)diazomethane, THF). The cyclisations proceeded in poor to good yield, with the best cyclisations occurring to produce spirocyclic products. © 2002 Published by Elsevier Science Ltd.

The asymmetric construction of quaternary stereocentres continues to be an interesting and challenging area of organic chemistry.[1] Of the synthetic approaches available, selective CH-insertion into an existing tertiary stereocentre offers a particularly direct solution to the problem and under the correct conditions this can be achieved with a high degree of selectivity.[2]

We have recently reported a method for the asymmetric construction of nitrogen-bearing quaternary stereocentres using an alkylidene carbene 1,5-CH insertion reaction as a key step, and that this methodology can be used for α,α-dialkyl-α-amino acid synthesis (Scheme 1).[3] Due to this initial success, we extended our work to examine the alkylidene carbene CH-insertion reaction of a range of other α-amino acid derived substrates, and we now wish to report our preliminary findings.



Scheme 1.

In order to study the effects of a variety of amino acid side chains on the alkylidene carbene CH-insertion reaction, a range of cyclisation precursors was synthesised. The desired materials were elaborated readily from suitably protected versions of the parent amino acids, proline, threonine, glycine, alanine, leucine and phenyl alanine using the DIBAL-H/Wittig/reduction sequence outlined below (Scheme 2).[4]

With a range of ketone precursors in hand, we were now in a position to examine the key alkylidene carbene CH-insertion reaction. A cold (−78°C) solution of lithio(trimethylsilyl)diazomethane (LTDM)[5] in THF was treated with each of the ketones (Scheme 2) to generate the corresponding diazoalkenes. Upon warming from −78 to 0°C, nitrogen was expelled and the alkylidene carbenes were generated (c.f. **2**, Scheme 1). The results of the subsequent cyclisation reactions are summarised below (Scheme 3).

Both the proline- and threonine-derived precursors **6** and **8** cyclised to produce the desired spirocyclic products in acceptable yield (53 and 45%, respectively). Pleasingly, both chiral GC (β-cyclodextrin, 100°C) and ^{1}H NMR showed that **18** was produced with >95% retention of stereochemistry at the nitrogen bearing stereocentre.[6] We were expecting the rather simple glycine-derived ketone **10** to perform similarly well in the cyclisation reaction, but we were a little disappointed to find that the corresponding cyclopentene **19** was only produced in 29% yield. Following this finding,

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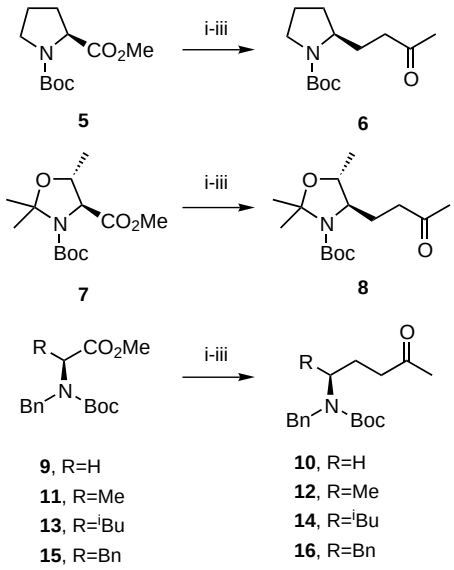
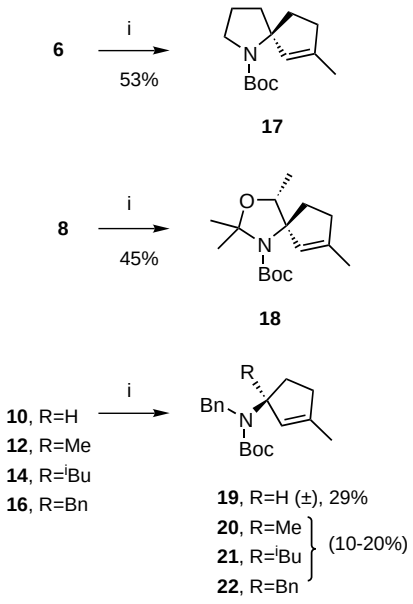


Scheme 2. *Reagents*: (i) DIBAL-H, PhMe (56–68%); (ii) $Ph_3PCHC(O)Me$, CH_2Cl_2 (83–90%); (iii) H_2/Pd (10% on C), EtOAc (92–94%).



Scheme 3. *Reagents and conditions*: (i) (a) $TMSCHN_2$, BuLi, THF, −78°C (1 h); (b) add ketone (THF solution) over 15 min, then −78°C (1 h); (c) warm −78→0°C (1 h).

we were not surprised when cyclisation of the more hindered ketones **12**, **14** and **16** proved rather difficult, and the corresponding cyclopentenes **20**, **21**, and **22** could only be isolated in very low yield (10–20%). We were unable to calculate precise yields for these three CH-insertion reactions, as the crude reaction mixtures contained a number of unidentifiable by-products, some of which were inseparable from the desired cyclopentenes.

From the successful cyclisations of **1** (62%), **6** (53%) and **8** (45%) it can be seen that both *N*-Boc and *N*-alkyl substituents are tolerated in the CH-insertion reaction. Functional group incompatibility with the reaction conditions, therefore, cannot account for the poor reactions of the acyclic precursors **12**, **14** and **16**. The results presented above seem to suggest that having some degree of conformational organisation in the ketone precursor (cf. **1**, **6** and **8**) is beneficial to the cyclisation process and that this is the major difference between the successful and unsuccessful CH-insertions. Careful consideration should therefore be paid to the choice of protecting groups used for the nitrogen atom, as this seems to have a significant impact on the course of the alkylidene carbene 1,5-CH insertion reaction.[7] We are currently examining alternative protecting group strategies in conjunction with other methods of carbene formation, in order to develop a useful, general synthetic method for the formation of asymmetric nitrogen-bearing quaternary stereocentres.

Acknowledgements

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6. Although compound **17** had an $[\alpha]_D$ −75.8 (*c* 1.33, $CHCl_3$), we were unable to determine its % ee using either chiral GC or HPLC, and we are currently trying to determine a suitable assay for this purpose.
7. We have performed a preliminary study on the *N*,*N*-dibenzyl version of **10**, but the results of this cyclisation were very similar to those obtained with **10** itself. We were able to isolate 23% of the desired cyclopentene product but this was accompanied by a variety of unidentified products.