



Cyclisation of Aminyl Radicals Derived from Amino Acids

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Abstract: α -Amino acid aminyl radicals have been generated from sulfenamide precursors using Bu_3SnH . The aminyl radicals undergo 5-*exo-trig* cyclisation reactions onto suitably placed *N*-alkenyl or α -alkenyl chains on the amino acids with reasonable diastereoselectivity. The α -ester of the amino acid imparts electrophilic behaviour to the aminyl radicals and facilitates cyclisation onto alkenes.

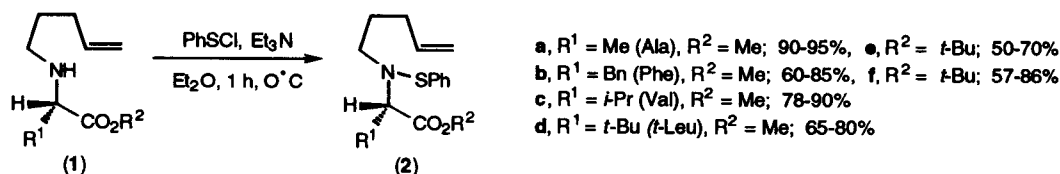
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Aminyl radicals have been intensively studied in recent years¹⁻⁹ and have been fully reviewed.¹ We have developed the use of sulfenamides²⁻⁴ and imines⁵ as precursors for aminyl radicals and applied the protocols to the synthesis of a range of bicyclic nitrogen heterocycles, *e.g.* pyrrolizidines and indolizidines. The development of radical reactions which can be carried out with stereochemical control, especially those involving radical cyclisation, has been at the forefront of synthetic organic chemistry.¹⁰ The application of radical cyclisation to heterocyclic synthesis is receiving increasing attention.¹¹ α -Chiral radicals have been used with success to impart stereoselectivity in both intramolecular and bimolecular reactions.¹⁰ To this end, we have further developed the sulfenamide methodology² using α -chiral aminyl radicals derived from α -amino acids as precursors. The synthesis of novel amino acids is of central interest¹² but with only limited applications from radical chemistry.¹³ The radical chemistry of amino acids has been recently reviewed.¹⁴ In this paper we describe the first examples of radical cyclisations of aminyl radicals derived from amino acids.

Cyclisation of α -amino acid aminyl radicals can be envisaged in three directions using suitably placed alkenyl substituents, *i.e.* on the α -amino group, on the side chain or on the α -carboxyl group. The first two options are reported herein and the study of the third is underway.

Neutral aminyl radicals are nucleophilic with the consequence that the rate of 5-*exo* cyclisation is the same as the reverse ring-opening reaction.^{1,2,6} In order to facilitate useful cyclisation in synthetic reactions aminyl radicals need to be made electrophilic, *e.g.* by protonation to yield aminium radicals^{1,7,8} (the rate of cyclisation of *N*-butyl-4-pentenamine increases from $1.5 \times 10^4 \text{ s}^{-1}$ to $4 \times 10^7 \text{ s}^{-1}$ at 25 °C)⁷ or complexation with Lewis acids (*e.g.* MgBr_2 increases the rate of cyclisation 6.2 fold).⁷ Similarly, amidyl radicals are also electrophilic and cyclise faster than neutral aminyl radicals.^{1,4,9} In our studies reported in this paper we have shown that the α -ester group imparts moderate electrophilicity to the aminyl radicals generated from α -amino-esters and facilitates cyclisation. The electron withdrawing effects can be predicted because α -amino esters are *ca.* 10^3 times less basic than the corresponding amines.

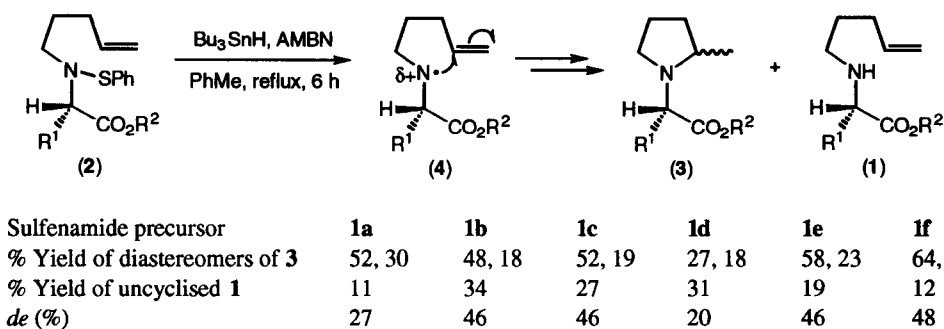
The sulfenamide precursors **2a-f** required for cyclisation of amino acid aminyl radicals onto *N*-alkenyl chains were synthesised by reaction between the amino esters **1a-f** and benzenesulfonyl chloride² (Scheme 1). The benzenesulfonyl chloride was preformed just prior to addition by reaction between PhSSPh and sulfuryl chloride. The reactions were rapid at 0 °C and the products were purified using flash silica chromatography. The sulfenamides were unstable on neutral alumina in contrast to sulfenamides of ordinary amines which were



Scheme 1. Synthesis of sulfenamide precursors for *N*-alkenyl α -amino acid aminyl radicals

stable on alumina but unstable on silica.² Synthesis of the precursors using *N*-(benzenesulfonyl)phthalimide² gave cleaner crude products but lower yields.

The sulfenamide precursors **2a–f** were cyclised using normal Bu_3SnH conditions¹⁵ to yield mixtures of two diastereomers **3a–f** and uncyclised α -amino esters **1a–f** (Scheme 2). A blank reaction without Bu_3SnH showed that the sulfenamides were stable in refluxing toluene. The yields and diastereomeric excesses (*de*) of the cyclised products were calculated using ^1H NMR spectroscopy with an internal standard and the values shown are an average of three experiments. The diastereomers could be separated with difficulty and the major diastereomer in each case was fully characterised and the minor isomer was determined in a mixture. Analysis of crude products using GC/MS indicated traces (<1%) of 6-*endo* cyclisation except for sulfenamide **1d** which gave *ca.* 5% of 6-*endo* cyclised material. This is possibly due to larger steric hindrance for 5-*exo* cyclisation than for the other intermediate aminyl radicals **4a–c**.



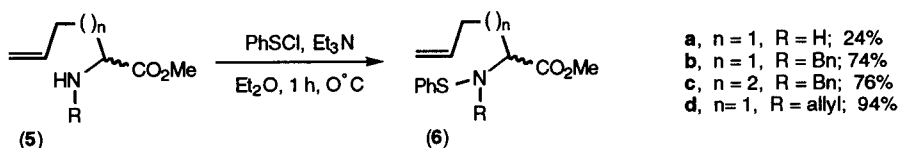
Scheme 2. Cyclisation of *N*-alkenyl sulfenamide precursors via α -amino acid aminyl radicals

The relative yields of 5-*exo* cyclised products **3** to uncyclised α -amino esters **1** via intermediate aminyl radicals **4** are much higher than for the cyclisation of ordinary *N*-alkyl-4-pentenamines.^{1,4,6–9} The obvious explanation is that the α -ester imparts electrophilicity to the intermediate aminyl radicals **4** thereby facilitating faster cyclisation. However, the result could also be explained by a decrease in the rate of the reverse ring-opening compared to that for *N*-alkyl-4-pentenamines.

The cyclisations show interesting diastereoselectivity of cyclisation for α -chiral aminyl radicals but could not be increased above *ca.* 50%. For the methyl esters **1a–d** the *de* increased for the α -substituent ($\text{R}^1 = \text{Me} < \text{Bn}$, *iso*-Pr) as expected but dropped when the bulky *tert*-butyl group of *tert*-leucine was present. The use of *tert*-butyl esters improved the *de* for alanine (**1e** versus **1a**) but made no difference for valine (**1f** versus **1b**). We considered that if the rate of hydrogen abstraction from the radical generating reagent by the intermediate aminyl radical could be lowered then a higher yield of cyclisation and/or *de* could be predicted. However, unexpectedly the opposite was observed when the reaction with **1a** was repeated using *tris*-(trimethylsilyl)-silane $[(\text{TMS})_3\text{SiH}]$ in place of Bu_3SnH .¹⁶ The yield of the cyclised diastereomers **3a** was 21% and 7% (*de* = 50%) and uncyclised **1a** (72%). $(\text{TMS})_3\text{SiH}$ was less useful than Bu_3SnH and was not further investigated.

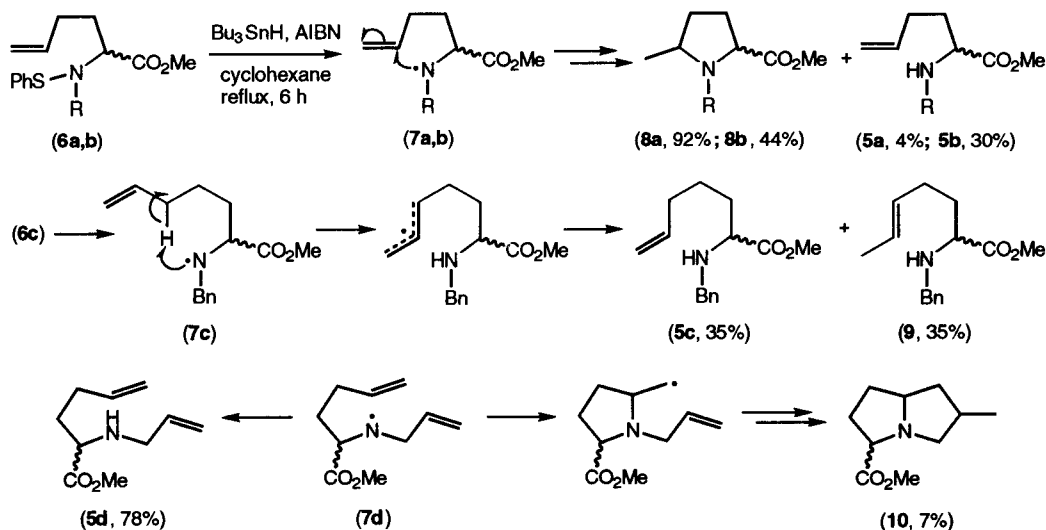
The second part of the study of the cyclisation of α -amino acid aminyl radicals onto a suitably placed alkenyl substituent on the side chain was examined. For initial convenience the racemic α -alkenyl amino acids

5a-d were used in our study and were synthesised by alkylation of the benzal imine of methyl glycine. Synthesis of the *D*- and *L*-enantiomers is underway using known methodology. The sulfenamide precursors **6a-d** were synthesised by the same procedure as for *N*-alkenyl amino acids **1** using reaction between the amino acids **5a-d** and benzenesulfonyl chloride (Scheme 3). The yields were not optimised. The lower yield of the primary sulfenamide **6a** was due to poor stability on the silica column which resulted in a number of by-products, of which the major one was the corresponding *N*-(benzenesulfonyl)imine.



Scheme 3. Synthesis of sulfenamide precursors for α -alkenyl α -amino acid aminyl radicals

The cyclisations were carried using the same conditions with Bu_3SnH except that cyclohexane was used in place of toluene.¹⁵ AMBN, trade name for 2-[(*E*)-2-(1-cyano-1-methylpropyl)-1-diazenyl]-2-methylbutanenitrile], was used in place of AIBN because of its greater solubility in cyclohexane compared with AIBN. The yields of products were measured using ^1H NMR spectroscopy with an internal standard prior to separation and characterisation. The cyclisation of sulfenamide **6a** was most successful and gave mainly cyclisation to the proline derivative **8a** with a *de* of 57%. The intermediate aminyl radical **7b** resulting from the *N*-benzyl sulfenamide **6b** gave poorer cyclisation than radical **7a** and is similar to the aminyl radicals **4a-f** resulting from the *N*-alkenyl sulfenamide. The poorer yields of cyclisation resulting from these dialkyl aminyls **7b** and **4a-f**, relative to the primary aminyl radical **7a** is partly explained by their lower electrophilicity.



Scheme 4. Cyclisation of α -alkenyl sulfenamide precursors via α -amino acid aminyl radicals

The attempted 6-*exo* cyclisation of the intermediate aminyl radical **7c** from sulfenamide **6c** gave a 1:1 mixture of the alkenes **5c** and **9** clearly indicating faster 1,5-hydrogen abstraction than 6-*exo* cyclisation. The analogous aminyl radicals lacking the α -ester undergo 6-*exo* cyclisation and not 1,5-hydrogen abstraction indicating that the electrophilicity imparted by the α -ester causes the H-abstraction for the intermediate aminyl radical **7c**.² Cyclisation of sulfenamide **6d** was also not very successful and gave a low yield of diastereomers

of the aminyl radical expected pyrrolizidine **10** (7%) with a diastereomeric ratio of 3:1. We propose that the low yield of 5-*exo*, 5-*exo* tandem cyclisation for sulfenamide **6d** is probably also due to the lower electrophilicity of the dialkyl aminyl intermediate **7d**. In the tandem cyclisation of 'ordinary' aminyl radicals the reversibility of aminyl radical cyclisation is overcome by trapping the monocyclised intermediate radical by the second cyclisation to give exclusive bicyclic products.² The comparison suggests that the reversibility of cyclisation of the α -ester aminyl radical **7d** is less favourable than for 'ordinary' aminyl radicals. Use of (TMS)₃SiH for the tandem cyclisation gave similar results.

Our initial studies have shown that the α -ester in alkenyl α -amino esters imparts sufficient electrophilicity to facilitate reasonable yields of cyclisation and provides further evidence that the polarity of intermediate aminyl radicals in cyclisation reactions is crucial. The induction of stereoselectivity in the cyclisations by the α -chiral centre of the α -amino acids is encouraging and further studies are required.

Acknowledgements

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