Synthesis of Unsaturated α-Amino Acids using the Ramberg–Bäcklund Reaction

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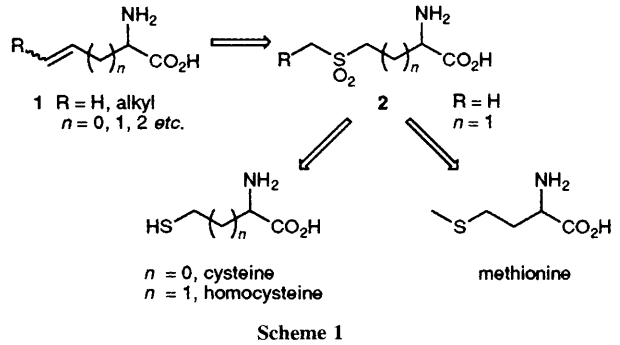
A novel, and potentially versatile, procedure for the preparation of unsaturated α-amino acids in homochiral form is illustrated by the conversion of methionine into allylglycine (as its Boc, *tert*-butyl ester derivative) using the Ramberg–Bäcklund reaction in the key step.

Unsaturated α-amino acids have attracted considerable attention[1,2] as enzyme inhibitors, antibiotics, biosynthetic probes and as precursors to cyclopropane-based amino acids.[3] In view of our interest in the Ramberg–Bäcklund reaction,[4–6] we envisaged its use in the key step (**2** → **1**) of the novel synthetic route to unsaturated α-amino acids **1** shown in Scheme 1.

In principle the α-halo sulfone precursors for α,β- and β,γ-unsaturated amino acids (**1**, $n = 0$ and 1) should be readily accessible in homochiral form from cysteine and homocysteine or methionine, respectively. Precursors to longer chain γ-mercaptoamino acids are also available.[7] One attraction of such an approach is that terminally substituted alkenes (**1**, R ≠ H) should be readily available, the substituents being introduced by alkylation of the precuror thiols or by α-sulfonyl anion alkylation. We also hoped that the mild conditions we have recently developed for the Ramberg–Bäcklund reaction[4] would preclude/minimise racemisation and enable the novel amino acids to be prepared in homochiral form. In this communication we reveal the viability of this idea by converting methionine into an allylglycine derivative, suitably protected for further elaboration, in optically enriched form (Scheme 2).

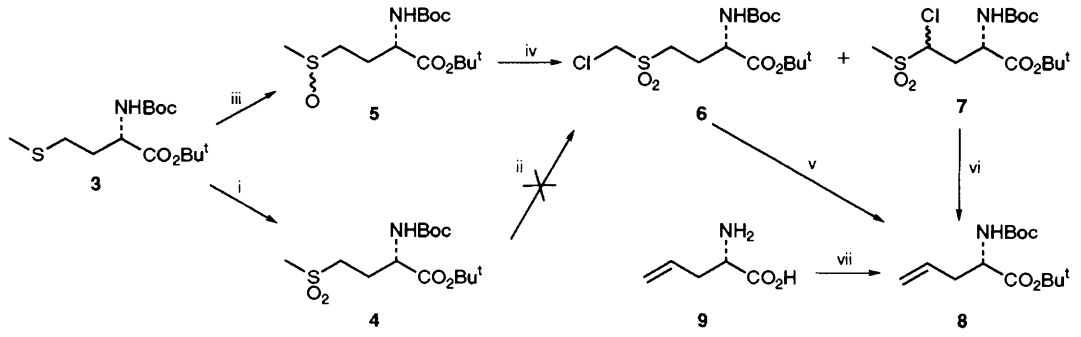


Scheme 1

The protected derivative **3**[8] of L-methionine was efficiently converted into sulfone **4**† but all attempts to generate and chlorinate the corresponding α-sulfonyl anion were unsuccessful. Partial success was achieved by reversing the order of events. Thus, NCS chlorination of sulfide **3** followed by oxidation (MCPBA, CH_2Cl_2) did on one occasion produce the required α-chloro sulfones **7** in *ca.* 40% yield but this sequence was extremely difficult to reproduce. A reliable method was eventually developed by preparing sulfoxides **5** and carrying out the chlorination with SO_2Cl_2 using Durst's procedure.[9] The resulting α-chloro sulfoxides were oxidised directly to the corresponding sulfones **6** and **7** (48–51; *ca.* 1:15), the non-chlorinated sulfone **4** also being obtained (15%). The chloromethyl sulfone **6** could be separated from the diastereoisomeric mixture **7** by chromatography but the crystalline chloromethylene diastereoisomers **7** were chromatographically identical. Treatment of mixture **7** with KOBu^t in THF gave the protected allylglycine **8** in 21–91% yield.‡ An authentic sample of **8**, prepared from L-allylglycine **9** (Aldrich) using standard reagents, was shown to be identical to the synthetic material by ^1H and ^{13}C NMR spectroscopic analysis and by chromatography. Efficient and reproducible rearrangement (64–78%) could be achieved by (*i*) carrying out the reaction under homogeneous conditions adding a solution of **7** in THF to a solution of KOBu^t in THF at −78 °C, and (*ii*) using 5 equiv. of base. A low temperature was essential to minimise racemisation; we obtained essentially optically pure **8** when the reaction temperature was kept below −30 °C. The authentic material had an $[\alpha]_D = +12.5$ (*c* 1, CH_2Cl_2), and the synthetic samples had values ranging from +12.4 to 12.7 when

† All new compounds gave consistent spectral and analytical/mass spectrometric data.

‡ Compound **6** was also converted into **8** in 54% yield using similar conditions.



Scheme 2 *Reagents and conditions*: i, Oxone, aq. MeOH (93%); ii, $KN(SiMe_3)_2$, then *N*-chlorosuccinimide (NCS); iii, *m*-chloroperbenzoic acid (MCPBA), CH_2Cl_2 (94%); iv, (a) SO_2Cl_2, CaO (b) MCPBA, CH_2Cl_2 **7**, *ca.* 45%; **6**, *ca.* 3%; **4**, 15%; v, $KOBu^t$, tetrahydrofuran (THF), −78 °C (54%); vi, $KOBu^t$, THF −78 to −30 °C (64–78%); vii, (a) $(Bu^tOCO)_2O$, MeOH, Et_3N (b) $CCl_3C(=NH)OBu^t$, $BF_3{\cdot}OEt_2$ (72% over two steps)

low temperatures were employed, but up to +2.6 when the reaction was allowed to warm to 0 °C. To emphasise the importance of temperature control, we have shown that the product **8** undergoes almost complete racemisation, with accompanying decomposition, after treatment with 5 equiv. of $KOBu^t$ in THF for 30 min at room temperature {46% recovery, $[\alpha]_D$ *ca.* +0.3 (*c* 0.4, CH_2Cl_2)}. By contrast, a similar experiment from −78 to −30 °C over 1 h resulted in an almost quantitative recovery of **8** with an essentially unchanged $[\alpha]_D$ [+12.1 (*c* 0.85, CH_2Cl_2)].

We are currently optimising the route to the Ramberg–Bäcklund precursors from methionine as well as investigating the other applications of this methodology as outlined in Scheme 1.

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