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A facile synthesis of *N*-benzylallylglycine

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Abstract

N-Benzylallylglycine can be prepared in good yield through a one-pot reaction of *N*-benzylhomoallylamine with glyoxylic acid monohydrate in methanol. The reaction method described requires only mild conditions and avoids the need for purification of the amino acid product.

Keywords: amines; amino acids and derivatives; aza-Cope rearrangement; iminium ion solvolysis; tandem reactions.

Allylglycine is a non-DNA encoded α-amino acid which possesses interesting biological activity.[1] In addition, allylglycine and its derivatives represent interesting synthons for the preparation of other amino acids and natural products.[2] A number of synthetic strategies have been utilised to synthesise allylglycine derivatives, including allylation of glycine equivalents,[3] [2,3]-aza-Wittig[4] and cationic aza-Cope rearrangements.[5,6]

For the synthesis of acyclic amino acids via cationic aza-Cope methodology the rearrangement requires a subsequent reaction to drive the equilibrium toward the desired product. To date this has been effected either via an iminium ion reduction as reported by Esch et al.[5] or an iminium ion hydrolysis step as reported by Agami et al. (Scheme 1).[6]

In this letter we wish to report a facile synthesis of the previously unreported *N*-benzylallylglycine based on an aza-Cope/tandem iminium ion solvolysis. In addition to the simplicity of the procedure, the method can afford the amino acid derivative in good yield and excellent purity without recourse to laborious purification techniques, e.g. liquid/liquid extraction or chromatography.

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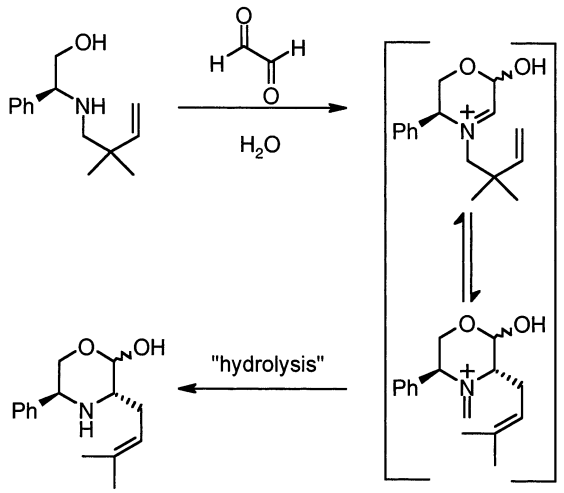
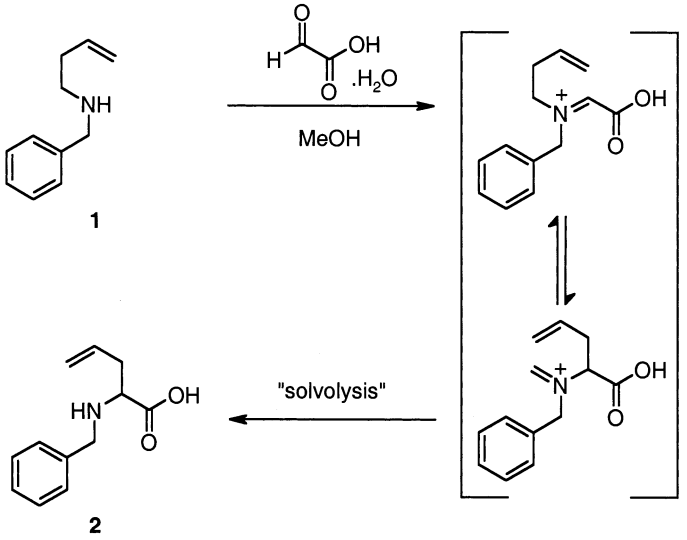


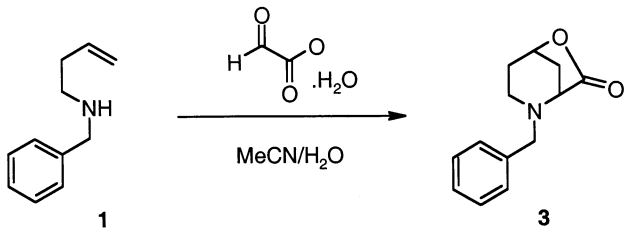
Scheme 1. Agami aza-Cope/iminium ion hydrolysis tandem reaction

N-Benzylallylglycine **2** was prepared by condensation of *N*-benzylbut-3-enylamine[7] **1** and glyoxylic acid monohydrate at room temperature in methanol (Scheme 2).[8] During the course of the reaction the product precipitated from solution as a white solid. The bulk of the methanol was then removed in vacuo and diethyl ether added. The insoluble *N*-benzylallylglycine **2** was then isolated via filtration and dried in vacuo. This facile procedure afforded the product **2** in an overall yield of 60% and 98% purity (measured by spectroscopic, HPLC and elemental analytical techniques).



Scheme 2. Synthesis of *N*-benzylallylglycine **2**

Analysis of the liquors from the reaction showed that the major by-product was the lactone **3**, which is derived from a competing ring closure mechanism. This is consistent with a reported synthesis of the lactone in which homoallylamine **1** is condensed with glyoxylic acid monohydrate in acetonitrile/water as solvent (Scheme 3).[9]



Scheme 3. Synthesis of lactone **3** in aqueous medium[9]

To begin evaluating the general scope and utility of the procedure, homoallylamines **4**, **5** and **6** (Fig. 1) were synthesised[10] and these amines reacted as outlined in Scheme 2. In each case the product should be *N*-benzylallylglycine **2** since the carbon atom to which the alkyl substituent is attached will be cleaved during the aza-Cope/tandem iminium ion hydrolysis.

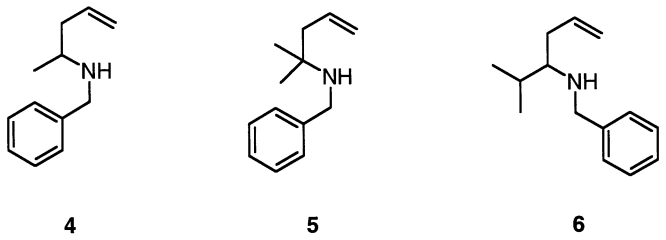


Figure 1.

In all cases the expected product **2** precipitated from the reaction solutions. Precipitation of *N*-benzylallylglycine **2** was considerably faster for reactions involving amines **4** and **6** than it was for amine **1** (approximately 5 min compared with 1 h). For amine **5** no precipitate was evident after stirring overnight at room temperature but precipitation did occur after heating the reaction mixture at reflux for 30 min. In addition to the apparent rate enhancing effect, the reaction of **6** afforded *N*-benzylallylglycine **2** in 88% yield as compared with 60% for the reaction of simple homoallylamine **1**. This result demonstrates that under these conditions the aza-Cope/tandem iminium ion solvolysis is more rapid than the competing cyclisation/lactonisation reaction.

In summary, an efficient one-pot synthesis of *N*-benzylallylglycine **2** has been developed through the condensation of *N*-benzylhomoallylamines with glyoxylic acid monohydrate in methanol. The scope of this method is currently being extended to other functionalised and chiral homoallylamines, and we intend to report the results of these studies in the near future.

Acknowledgements

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8. **Typical procedure**: *N*-(1-isopropyl-3-butenyl)benzylamine **6** (1 equiv.; 0.5 g, 2.5 mmol) was dissolved in HPLC grade methanol (7 mL) and stirred at room temperature. Glyoxylic acid monohydrate (1.1 equiv.; 0.25 g, 2.7 mmol) was then added in one portion and the resultant solution stirred at room temperature overnight (NB: ppt evident after 5 min). The bulk of the methanol was removed under reduced pressure and diethyl ether (20 mL) was added. The insoluble material was isolated by filtration, washed with diethyl ether (×3) and dried in vacuo to afford *N*-benzylallylglycine **2** (0.44 g, 88%) as a white solid. ^{1}H NMR (400 MHz, CD_3OD): δ 7.52–7.57 (m, 2H), 7.43–7.49 (m, 3H), 5.76–5.87 (m, 1H), 5.22–5.36 (m, 2H), 4.28 (s, 2H), 4.08 (t, 1H), 2.72–2.87 (m, 2H). ESI-MS $(M+H)^+$: 206.2, $(M-H)^-$: 203.8. Anal. calcd for $C_{12}H_{15}NO_2$: C, 68.86; H, 7.44; N, 6.69. Found C, 68.97; H, 7.23; N, 6.62. (Percentage calculated and found values adjusted for 1.94% water in sample as measured by Karl Fischer analysis).
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