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# A New and Efficient Preparation of α,β-Dehydroamino Acids

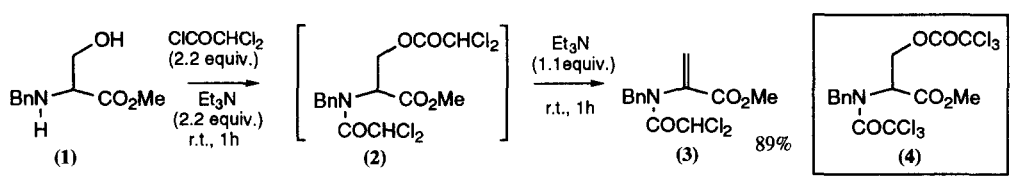
**Karen Goodall and Andrew F. Parsons***

Department of Chemistry, University of York, Heslington, York, YO1 5DD, U.K.

***Abstract:*** *A new one-pot synthesis of dehydroamino acids has been developed by reaction of β-hydroxy-α-amino acids with dichloroacetyl chloride and a tertiary amine base. The reaction proceeds in 58-89% yield.*

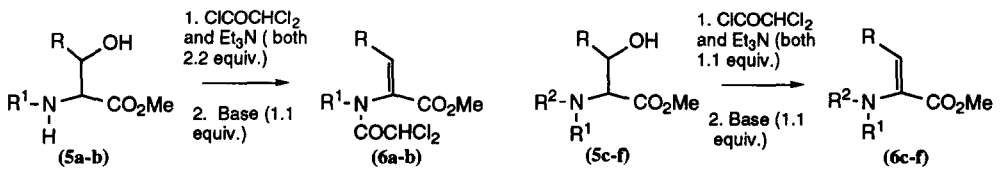
α,β-Dehydroamino acids represent an important class of compound as they are key intermediates in amino acid and peptide synthesis[1] and are constituents of a variety of naturally occurring antibiotic and phytotoxic peptides.[2] As a consequence several syntheses of dehydroamino acids have been reported.[2] One important and well-used approach involves the β-elimination reactions of serine and threonine derivatives containing suitable leaving groups.[3] A number of reagents including diethyl chlorophosphate,[4] oxalyl chloride,[5] N,N'-carbonyldiimidazole,[6] DiPCD [diisopropylcarbodiimide/copper(I) chloride][7] and DAST (diethylaminosulfur trifluoride/pyridine)[8] have also been employed to perform the direct elimination. We now wish to describe a new direct approach to a variety of dehydroamino acid derivatives which benefits from the efficient, mild and cheap nature of the process.

The approach involves reaction of dichloroacetyl chloride with the hydroxyamino acid, such as the DL-serine derivative (**1**), in dichloromethane in the presence of triethylamine as shown in the Scheme. The reaction involves the intermediacy of the dichloroester (**2**), which can be isolated, or more conveniently treated with a further equivalent of base *in situ* to effect elimination of dichloroacetic acid and hence afford the desired dehydroamino acid (**3**). It is of interest to note that the corresponding trichloroester intermediate (**4**) does not lead to dehydroamino acid formation under the same reaction conditions.[9]




**SCHEME**

A variety of dehydroamino acids derived from both DL-serine and DL-threonine are accessible in good to excellent yield (see Table). Triethylamine and $ClCOCHCl_2$ are used to prepare the dichloroester intermediate and $Et_3N$ or DBU to effect elimination. Thus amino acids (**5a**) and (**5b**) (which contain a nucleophilic nitrogen) undergo direct elimination in addition to *N*-dichloroacylation in a similar manner to (**1**) while the *N*-benzoyl or *N*-BOC derivatives (**5c-f**) lead to the efficient formation of dehydroamino acids (**6c-f**).[10]




| (5) | R | $R^1$ | $R^2$ | Base/ Conditions | Yield of (6) (%) |
|---|---|---|---|---|---|
| a | H | H | - | $Et_3N$/r.t. | 88 |
| b | Me | Bn | - | DBU/heat | 73 |
| c | H | Bz | H | $Et_3N$/r.t. | 67 |
| d | H | BOC | H | DBU/heat | 68 |
| e | Me | BOC | H | DBU/heat | 58 |
| f | Me | BOC | Bn | DBU/heat | 89 |

Bn = benzyl, Bz = benzoyl.

**TABLE**

Finally, it is noted that when the threonine derivatives **(5b)** and **(5e-f)** are used the reaction yields the Z-isomer (as indicated from the $^1H$ NMR spectra[3]) stereoselectively (*e.g.* Z:E, 3:1 to ≥20:1). We are currently exploring the scope and limits of this procedure in addition to examining the mechanistic implications.

## Typical Procedure

Preparation of **(3)**: Dichloroacetyl chloride (1ml, 10.5mmol) in dry $CH_2Cl_2$ (2ml) was added dropwise to a stirred solution of **(1)** (1g, 4.8mmol) in $CH_2Cl_2$ (60ml) containing $Et_3N$ (1.5ml, 10.6mmol) at r.t.. Further $Et_3N$ (0.75ml, 5.3mmol) was added after 1h and then the reaction was stirred for 1h. The solution was washed with 10% aqueous citric acid, water, brine, dried ($MgSO_4$) and evaporated *in vacuo* to afford crude product. Purification using column chromatography on silica afforded **(3)** (1.28g, 89%) as a colourless oil.

**Acknowledgements**

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9. The elimination of trichloroacetic acid from **(4)** could be achieved in low yield (30%) by using an excess of triethylamine and heating for 24h.
10. All new compounds exhibited satisfactory spectral and analytical (high resolution mass and/or combustion) data.

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