# The synthesis of α, β–dehydroamino acid esters from hydroxyamino esters using haloacetyl halides

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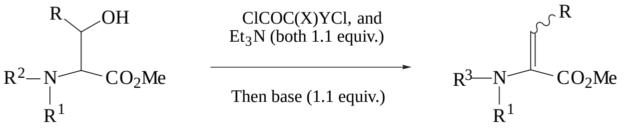
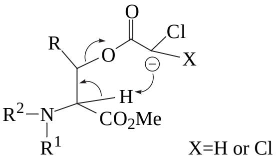
The preparation of dehydroamino acid esters from reaction of β–hydroxy–α–amino esters with dichloroacetyl chloride, chloroacetyl chloride or trichloroacetyl chloride in the presence of base has been investigated.

The synthesis of α,β–dehydroamino acids has attracted considerable interest in recent years.[1] These compounds, which are constituents of a variety of biologically important peptides,[1,2] are also valuable intermediates for the preparation of both natural and unnatural optically active amino acids.[3] A number of methods are now available for the preparation of dehydroamino acids and one important and well–used approach involves the β–elimination of serine and threonine derivatives which contain suitable leaving groups. Olsen and co–workers,[4] for example, have made use of a two–step chlorination/base induced elimination method, but reagents including diethyl chlorophosphate,[5] oxalyl chloride,[6] *N*,*N*′–carbonyldiimidazole,[7] DiPCD [diisopropylcarbodiimide/copper(I) chloride][8] and DAST (diethylaminosulfur trifluoride/pyridine)[9] are now available which allow the direct elimination of these hydroxyamino acids to be performed in one step. In this paper we describe a new and direct approach to a variety of dehydroamino derivatives from serine and threonine which benefits from the efficient, mild and cheap nature of the process. In addition, synthetically useful dehydroamino acid esters incorporating *N*–haloacetyl groups can be prepared via a one–pot dehydration–acylation procedure. The approach is based on the reaction of haloacetyl halides with the hydroxyamino ester **1a–e**, **7a–d** in the presence of a base as shown in Table 1.[10]

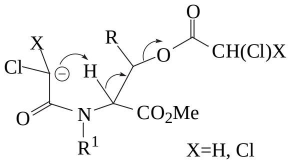
The reactions involve the formation of an intermediate diester, which can be isolated, or more conveniently treated with a further equivalent of base to effect elimination (in a one–pot reaction) to give the dehydroamino acid ester **3a–e**, **9a–d**, **11**, **13** in 39–89% yield. Whereas elimination using dichloroacetyl chloride or chloroacetyl chloride proceeds under similar conditions the use of trichloroacetyl chloride requires harsher conditions and/or longer reaction times. These results are consistent with an intramolecular mechanism of elimination in which initial deprotonation occurs at the amide or ester side–chain, as shown by **6a** and **16**, respectively, rather than at the α–centre. Mechanistic investigations suggest that for the formation of dehydroamino esters **9a–d** and **11**, amide deprotonation–elimination is of greater importance than ester deprotonation–elimination (although both mechanisms could be operating).



**1a-e, 7a-d** X=Y=H or X=H; Y=Cl or X=Y=Cl **3a-e, 9a-d, 11, 13**



**6a**



**16**

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Techniques used: TLC, m.p., microanalysis, FTIR, $^1$H and $^{13}$C NMR, LRMS, HRMS

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Schemes: 5

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**Table 1** Formation of dehydroamino acid esters

| Alcohol | R | R$^1$ | R$^2$ | R$^3$ | Haloacetyl halide | Base/ Conditions | Alkene | Alkene Yield (%) | Z-/E-ratio† |
|---|---|---|---|---|---|---|---|---|---|
| **1a** | H | Bz | H | H | ClCOCHCl$_2$ | Et$_3$N/r.t. | **3a** | 67 | – |
| **1b** | H | CBZ | H | H | ClCOCHCl$_2$ | DBU/heat | **3b** | 48 | – |
| **1c** | H | BOC | H | H | ClCOCHCl$_2$ | DBU/heat | **3c** | 68 | – |
| **1c** | H | BOC | H | H | ClCOCH$_2$Cl | DBU/heat | **3c** | 64 | – |
| **1d** | Me | BOC | H | H | ClCOCHCl$_2$ | DBU/heat | **3d** | 58 | ≥20:1 |
| **1e** | Me | BOC | Bn | Bn | ClCOCHCl$_2$ | DBU/heat | **3e** | 89 | 3:1 |
| **7a** | H | H | H | COCHCl$_2$ | ClCOCHCl$_2$ | Et$_3$N/r.t. | **9a** | 88 | – |
| **7b** | H | Bn | H | COCHCl$_2$ | ClCOCHCl$_2$ | Et$_3$N/r.t. | **9b** | 89 | – |
| **7b** | H | Bn | H | COCH$_2$Cl | ClCOCH$_2$Cl | Et$_3$N/heat | **11** | 78 | – |
| **7b** | H | Bn | H | COCCl$_3$ | ClCOCCl$_3$ | DBU/heat | **13** | 85 | – |
| **7c** | Me | H | H | COCHCl$_2$ | ClCOCHCl$_2$ | DBU/heat | **9c** | 39 | >20:1 |
| **7d** | Me | Bn | H | COCHCl$_2$ | ClCOCHCl$_2$ | DBU/heat | **9d** | 73 | 13:1 |

† As indicated by the $^1$H NMR spectrum[4]; Bz = benzoyl

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## References cited in this synopsis

1 *(a)* U. Schmidt and A. Lieberknecht, J. Wild, *Synthesis*, 1988, 159. *(b)* S.A. Burrage, T. Raynham and M. Bradley, *Tetrahedron Lett.*, 1998, **39**, 2831. *(c)* P.W. Groundwater, T. Sharif, A. Arany, D.E. Hibbs, M.B. Hursthouse and M. Nyerges, *Tetrahedron Lett.*, 1998, **39**, 1433.

2 *(a)* C-g. Shin, K. Okumura, A. Ito and Y. Nakamura, *Chem. Lett.*, 1994, 1301. *(b)* Y. Nakamura, A. Ito and C-g. Shin, *Bull. Chem. Soc. Jpn.*, 1994, **67**, 2151.

3 *(a)* J.R. Axon and A.L.J. Beckwith, *J. Chem. Soc., Chem. Commun.*, 1995, 549. *(b)* J.M. Jiménez, R. Casas and R.M. Ortuño, *Tetrahedron Lett.*, 1994, **35**, 5945. *(c)* M. Tamura and K. Harada, *Bull. Chem. Soc. Jpn.*, 1980, **53**, 561. *(d)* P.A. Lander and L.S. Hegedus, *J. Am. Chem. Soc.*, 1994, **116**, 8126. *(e)* C. Cativiela, J.I. García, J.A. Mayoral, E. Pires, A.J. Royo and F. Figueras, *Tetrahedron*, 1995, **51**, 1295. *(f)* U. Schmidt, S. Kumpf and K. Neumann, *J. Chem. Soc., Chem. Commun.*, 1994, 1915.

4 *(a)* A. Srinivasan, R.W. Stephenson and R.K. Olsen, *J. Org. Chem.*, 1977, **42**, 2253 and 2256. *(b)* A. Srinivasan, K.D. Richards and R.K. Olsen, *Tetrahedron Lett.*, 1976, 891.

5 F. Berti, C. Ebert and L. Gardossi, *Tetrahedron Lett.*, 1992, **33**, 8145.

6 D. Ranganathan, K. Shah and N. Vaish, *J. Chem. Soc., Chem. Commun.*, 1992, 1145.

7 R. Andrusziewicz and A. Czerwinski, *Synthesis*, 1982, 968.

8 C. Balsamini, E. Duranti, L. Mariani, A. Salvatori and G. Spadoni, *Synthesis*, 1990, 779.

9 L. Somekh and A. Shanzer, *J. Org. Chem.*, 1983, **48**, 907.

10 Part of this work has appeared as a preliminary communication: K. Goodall and A.F. Parsons, *Tetrahedron Lett.*, 1995, **36**, 3259.