Dehydration of β-Hydroxyamino Acids with *N,N'*-Carbonyldiimidazole

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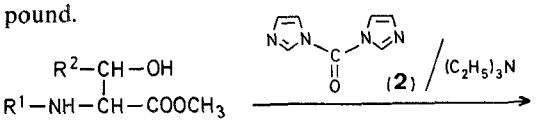
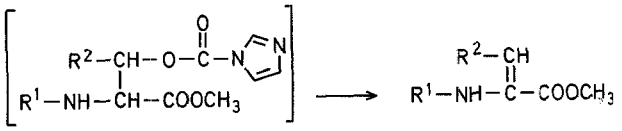
Recently, much attention has been paid to the synthesis and bioactivity of dehydropeptides containing dehydroamino acid moieties which are constituents of a number of antibiotics and plant toxins[1]. Dehydroalanine and dehydro-2-aminobutanoic acid derivatives have usually been prepared from serine and threonine derivatives by two different procedures: either β-elimination reactions of serine and threonine derivatives with a suitable leaving group[2,3] or direct eliminations of β-hydroxy groups from these amino acids[4,5,6].

Continuing our research program dealing with the synthesis of dehydroamino acids and peptides, we report here a new dehydration reaction of β-hydroxyamino acids **1** using *N,N'*-carbonyldiimidazole **(2)** as a dehydrating reagent. In spite of its utility in peptide chemistry, no report has been published on the dehydration of β-hydroxyamino acids with this compound.



1a-g



3a-g **4a-g**

1,3,4	R^1	R^2
a	$C_6H_5-CH_2-O-C(=O)-$ (Z)	H
b	$t\text{-}C_4H_9-O-C(=O)-$ (Boc)	H
c	$C_6H_5-CH_2-O-C(=O)-$	CH_3
d	$t\text{-}C_4H_9-O-C(=O)-$	CH_3
e	Z-Gly	H
f	Z-Ser	H
g	Z-Val	H

The reaction of *N,N'*-carbonyldiimidazole in the presence of triethylamine with protected serine **(1a, b)** and threonine **(1c, d)** in an inert solvent afforded the dehydroalanine **(4a, b)** and dehydro-2-aminobutanoic acid **(4c, d)** derivatives in good yields (Table). When dipeptides **1e-g** containing serine in the *C*-terminal position were allowed to react with reagent **2**, the dehydroalanine peptides **4e-g** were also obtained. Interestingly, **1f** underwent reaction with **2** to give seryl-dehydroalanine **4f**. However, it has been pointed out that **2** was completely inert towards the reaction with a series of dipeptides containing a serine residue in the *N*-terminal position (e.g. Z-Ser-Gly-OCH_3, Z-Ser-Ala-OCH_3, Z-Ser-Phe-OCH_3) and no reaction product was formed. Similarly, in the case of the reaction of **2** with serine amides [Z-Ser-NH_2, Z-Ser-$NH(CH_2)_2$—CH_3], no reaction product was obtained either.

The dehydroamino acid structure was confirmed by the characteristic signals of olefinic ($\delta = 5.65$–6.65 ppm) and vinyl ($\delta = 6.66$ ppm) protons in the N.M.R. spectra. The configuration of **4c, d** was determined to be (*Z*) by comparison of their N.M.R. spectra with those obtained by us[6] for the (*Z*)-isomers of **4c, d** prepared by an independent method.

In summary, the presented reaction proceeds under mild conditions giving the good yields of pure products and should be a useful synthetic method for dehydroalanine peptides. We are continuing investigations on extensions of the procedure reported here.

All melting points were measured in open capillary tubes and are not corrected. The ^{1}H-N.M.R. spectra were recorded at 80 MHz with a

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Table. Compounds **4a–g** prepared

Product	Yield [%]	m.p. [°C] found	m.p. [°C] reported	Molecular formula[a]	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]
4a	85	36–38°	37–38°[6]	$C_{12}H_{13}NO_4$ (235.2)	3.65 (s, 3H); 5.00 (s, 2H); 5.65 (s, 1H); 6.20 (s, 1H); 6.55 (s, 1H); 7.20 (s, 5H)
4b	83	oil		$C_9H_{15}NO_4$ (201.2)	1.70 (s, 9H); 3.82 (s, 3H); 5.85 (s, 1H); 6.40 (s, 1H); 6.65 (s, 1H)
4c	76	66–68°	65.5–67°[7]	$C_{13}H_{15}NO_4$ (249.3)	1.70 (d, J = 7 Hz, 3H); 3.60 (s, 3H); 5.10 (s, 2H); 6.32 (s, 1H); 6.66 (q, J = 7 Hz, 1H); 7.25 (s, 5H)
4d	71	71–73°	70–72°[8]	$C_{10}H_{17}NO_4$ (215.2)	1.55 (s, 9H); 1.75 (d, J = 7 Hz, 3H); 3.65 (s, 3H); 6.25 (s, 1H); 6.70 (q, J = 7 Hz, 1H)
4e	68	73–74°		$C_{14}H_{16}N_2O_5$ (292.3)	3.65 (s, 3H); 3.80 (d, J = 5.6 Hz, 2H); 5.05 (s, 2H); 5.77 (s, 1H); 5.85 (d, J = 5.6 Hz, 1H); 6.47 (s, 1H); 7.25 (s, 5H); 8.30 (s, 1H)
4f	65	oil		$C_{15}H_{18}N_2O_6$ (322.3)	3.30 (s, 1H, exchangeable with D_2O); 3.65 (s, 3H); 4.30 (d, J = 5.6 Hz, 2H); 4.9 (m, 1H); 5.10 (s, 2H); 5.75 (s, 1H); 5.92 (d, J = 8 Hz, 1H); 6.40 (s, 1H); 7.20 (s, 5H); 8.30 (s, 1H)
4g	71	116–118°	117–118°[2]	$C_{17}H_{22}N_2O_5$ (334.4)	0.90 (d, J = 3.6 Hz, 6H); 1.85 (m, 1H); 3.8 (m, 1H); 5.60 (d, J = 8 Hz, 1H); 5.80 (s, 1H); 6.46 (s, 1H); 7.20 (s, 5H); 8.10 (s, 1H)

[a] Satisfactory microanalyses obtained: C ±0.30, H ±0.20, N ±0.15.

Tesla BS-487 spectrometer with hexamethyldisiloxane as an internal standard. The dipeptides used were prepared by the carbodiimide method.

Dehydration of β-Hydroxyamino Acids; General Procedure:
A solution of the substrate **1a–g** (5 mmol), *N,N'*-carbonyldiimidazole (**2**; 0.81 g, 5 mmol) and triethylamine (0.7 ml, 5 mmol) in dry tetrahydrofuran (20 ml) is stirred at room temperature for 4–6 h. The solvent is evaporated in vacuo and the residue chromatographed on silica gel 60 (Merck). Elution with benzene/acetone (8 : 1) gives dehydroamino acid derivatives **4a–g** which crystallize from ethyl acetate/petroleum ether or diethyl ether/petroleum ether mixtures.

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