Tetrahedron Letters, Vol. 33, No. 52, pp. 8145-8148, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

ONE-STEP STEREOSPECIFIC SYNTHESIS OF α,β-DEHYDROAMINO ACIDS AND DEHYDROPEPTIDES.

Federico Berti[a], Cynthia Ebert[b]*, Lucia Gardossi[b]

[a]Dipartimento di Scienze Chimiche, Università di Trieste, piazzale Europa 1, 34127 Trieste, Italy.

[b]Dipartimento di Scienze Farmaceutiche, Università di Trieste, piazzale Europa 1, 34127 Trieste, Italy.

Abstract: Dehydroamino acids and dehydropeptides were prepared by a one-pot reaction employing diethyl chloroposphate in the presence of sodium hydride. The reaction is stereospecific and proceeds without racemization.

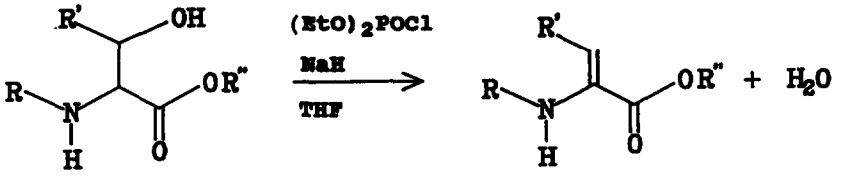
α,β-dehydroamino acids are important intermediates in the preparation of non-natural or optically pure amino acids[1] and for obtaining peptide amides in solid phase peptide synthesis[2]. Unsaturated amino acids are also fundamental constituents in various antibiotic and phytotoxic peptides [3,4] and the introduction of α,β-dehydroamino acids residues into naturally occurring peptide hormones, generally results in a marked variation of their conformation and biological activity[5]. Therefore the possibility of synthesizing directly dehydropeptides through stereoselective routes is particularly attractive for the development of the investigation of their peculiar conformational features and for structure-activity studies in unsaturated peptides[6].

Several syntheses of dehydroamino acids have been reported[3]. In general they are obtained by condensation[1,7] or by β-elimination from serine and threonine derivatives with suitable leaving groups[3]. Various reagents have also been employed to perform direct elimination, such as DiPCD (diisopropylcarbodiimide/copper(I) chloride)[8], N,N'-carbonyldiimidazole[9], and DAST (diethylaminosulfur trifluoride/pyridine)[10], the last procedure being also stereospecific. Likewise, the synthesis of dehydropeptides is performed by incorporating the corresponding β-substituted amino acids in the peptide chain and promoting the β-elimination in the peptide[3], thus overcoming the difficulties in activation of dehydroamino acids. Recently, an analogous method has been reported, employing phosphonoserine derivatives in the preparation of phosphonoserine peptides which finally, after deprotection of the carboxyl group, undergo β-elimination by treatment with an organic base[11].

Now we describe a facile, one step dehydration reaction which is effective for the synthesis of dehydroamino acids and dehydropeptides as well. The reaction consists in employing commercial diethyl chlorophosphate as activating agent for the hydroxy group, in the presence of NaH. According to the reaction conditions the phosphorilate intermediate gives directly the unsaturated products in high yields (Scheme 1). Therefore, neither preventive activation of hydroxy group nor deprotection steps are required; also amino acid coupling is avoided.

It is noteworthy that, when threonine derivatives are used the reaction is stereospecific giving exclusively the Z isomer.

It has been also verified that the procedure here reported does not involve racemization of the CBZ-protected amino acids[12].



Substrates	Products	R	R'	R"
1	5	CBZ	H	CH_2Ph
2	6	CBZ	CH_3	CH_3
3	7	CBZ-Ala	H	CH_3
4[14]	8	CBZ-Phe	CH_3	CH_3

Scheme 1

Synthesis of unsaturated compounds (5)-(8). 10mmol of amino acid or peptide were dissolved in dry THF[13] (50 ml). 80% Sodium hydride (450mg, 15mmol), was then added. The mixture was stirred under argon at room temperature for 30', then diethyl chlorophosphate was added (1.72g, 1.45mL, 10mmol). The reaction mixture was stirred for 3h and then poured in 50mL of aqueous 10% ammonium chloride. The aqueous phase was extracted with chloroform (3X). The combined extracts were washed with sat. brine, dried and evaporated to give an oily residue. Flash-chromatography of these materials gave the unsaturated compounds (5)-(8). Data for products 5 and 6 show a good agreement with values previously reported in ref. 9 and 11. Yields, physical and spectral data are given in Table 1.

ACKNOWLEDGEMENTS

Financial support from the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (Roma) is acknowledged. We are grateful to prof. Paolo Linda and prof. Fabio Benedetti for their helpful suggestions and contributions.

Table 1. Yields, Physical and Spectral Data for Compounds (5)-(8).

	Yield (%)	m.p. (°C)	IR (cm^{-1})	α_D (°)	^1H-NMR, (ppm) ($CDCl_3$)	^{13}C-NMR, (ppm) ($CDCl_3$)
5	75	47	3400, 1720-1690, 1615	-	5.16 (s, 2H, CH_2O) 5.26 (s, 2H, CH_2O), 5.90 (m, 1H, =CHH), 6.30 (m, 1H, =CHH), 7.40 (m, 11H, Ph + NH)	67.06 (CH_2O), 67.74 (CH_2O), 106.38 (CH_2=), 128.25, 128.38, 128.60, 128.66, 128.74, 128.74, 128.85, 131.05, 135.06 (C Ar), 135.83 (C=), 153.14 (CO), 163.59 (CO).
6	80	65 (dec)	3400, 1720-1680, 1610	-	1.75 (d, J=7Hz, 3H, CH_3), 3.68 (s, 3H, CH_3), 5.08 (s, 2H, CH_2), 6.10 (s, 1H, NH), 6.72 (q, J=7Hz, 1H, =CH), 7.30 (s, 5H, Ph)	29.72 (CH_3), 52.37 (OCH_3), 67.39 (CH_2O), 126.31 (=CH), 128.20, 128.29, 128.58, 133.37 (Ar), 136.03 (C=), 153.93 (CO), 165.05 (CO).
7	75	200 (dec)	3400,3080, 1720-1680, 1610	-61.2 (c=0.6) ($CHCl_3$)	1.39 (d, J=7.2Hz, 3H, CH_3), 3.82 (s, 3H, OCH_3), 4.35 (m, 1H, CH), 5.11 (dd, 2H, CH_2O), 5.56 (m, 1H, NH), 5.90 (d, J=1.3Hz, 1H, =CHH), 6.58 (d, J=1.3Hz, 1H, =CHH), 7.33 (s, 5H, Ph), 8.38 (m, 1H, NH)	18.20 (CH_3), 51.40 (CH), 52.98 (OCH_3), 67.19 (CH_2O), 109.53 (CH_2=), 128.1, 128.2, 128.53, 130.77 (C Ar), 136.12 (C=), 156.07 (CO), 164.3 (CO), 171.25 (CO)
8	75	129	3400, 1730-1680, 1610	-13.4 (c=0.6) (CH_3OH)	1.66 (d, J=7.3Hz, 3H, CH_3), 3.21 (m, 2H, CH_2Ph), 3.72 (s, 3H, OCH_3), 4.57 (m, 1H, CH), 5.09 (s, 2H, OCH_2Ph), 5.38 (s, 1H, NH), 6.79 (q, J=7.3Hz, 1H, =CH), 7.21-7.36 (m, 10H, Ph), 8.37 (s, 1H, NH)	24.95 (CH_3), 38.11 (CH_2Ph), 52.31 (OCH_3), 56.37 (CH), 67.21 (CH_2O), 125.65 (=CH), 127.12, 128.05, 128.25, 128.54, 128.74, 129.37, 134.7, 136.06 (Ar), 136.16 (C=), 156.11 (CO), 164.6 (CO), 169.33 (CO).

Satisfactory microanalysis was obtained for all the products.

REFERENCES AND NOTES

1. Schmidt U., Lieberknecht, A., Wild, J. *Synthesis* 1984, 53.
2. Noda, K., Gazis, D., E. Gross, E., Int. *J. Peptide Protein Res.* 1982, *19*, 413.
3. Schmidt, U., Lieberknecht, A., Wild, J., *Synthesis* 1988, 159 and references cited therein.
4. Wakamara, T., Shimbo, K., Sano, A., Fukase, K., Shiba, T., *Bull. Chem. Soc. Jpn.* 1983, 56, 2044.
5. Gupta, A., and V. S. Chauhan, V.S., *Biopolymers*, 1990, *30*, 395.
6. Ciajolo, M.R., Tuzi, A., Pratesi, C.R., Fissi, A., Pieroni, O., *Biopolymers*, 1990, 30, 911.
7. Shin, C., N. Takahashi, N., Yonezawa, Y., *Chem. Pharm. Bull.*, 1990, 38, 2020.

8. Balsamini, C., Duranti, E., Mariani, L., Salvatori, A., Spadoni, G., *Synthesis*, 1990, 779.
9. Andruszkiewicz, R., Czerwinski, A., *Synthesis*, 1982, 968.
10. Somekh, L., Shanzer, A., *J. Org. Chem.*, 1983, 48, 907.
11. Paquet, A., *Tetrahedron Lett.*, 1990, *31*, 5269.
12. We verified that incubating CBZ-Phe and CBZ-Ala according to the experimental conditions, their optical activities do not change.
13. Tetrahydrofuran (THF) was fractionated over calcium hydride and redistilled from potassium benzophenone ketyl under an argon atmosphere.
14. CBZ-Phe-Thr-OMe (4). Dicyclohexylcarbodiimide (970mg, 4.7mmol) was added to a solution of CBZ-Phe-OH (797mg, 4.7mmol) in dioxane (10mL) at 0°C. After 15' a solution of 1-hydroxybenzotriazole (635mg, 4.7mmol), triethylamine (476mg, 4.7mmol) and Thr-OMe hydrochloride (800mg, 4.7mmol) in dioxane (10mL) was added and the reaction mixture was stirred for 6h. The insoluble dicyclohexylurea was removed by filtration, the solvent evaporated, the residue dissolved in ethyl acetate (30mL), washed with aqueous citric acid (10%), sat. $NaHCO_3$ and water, dried over anhydrous Na_2SO_4. After evaporating the solvent the crude dipeptide was crystallized from ether. 1.7g, 86% . M.p. 114°C. IR: ,cm^{-1}: 3400, 1700-1660. 1H-NMR: (ppm) 1.41 (d, 3H, CH_3). 3.21 (m, 2H, CH_2Ph). 3.82 (s, 3H, OCH_3). 4.24 (m, 1H, CH-OH). 4.34 (m, 1H, CH (Phe)), 4.68 (m, 1H, CH (Thr)), 5.13 (dd, 2H, OCH_2Ph). 5.53 (s, 1H, NH), 5.91 (d, 1H, OH), 7.25-7.35 (m, 10H, Ph), 8.37 (s, 1H, NH).

(Received in UK 14 September 1992)