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A FACILE DEHYDRODIPEPTIDE SYNTHESIS BY THE COUPLING BETWEEN TWO α-DEHYDROAMINO ACIDS

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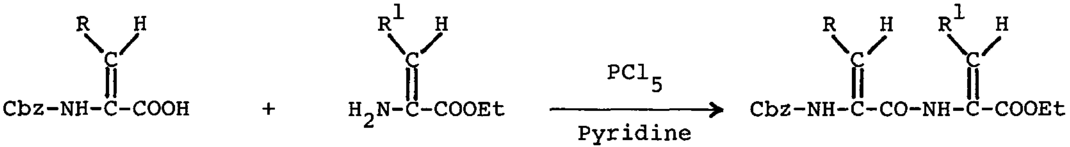
Summary: The direct coupling of N-Cbz-α-dehydroamino acid with N-free-α-dehydroamino acid ethyl ester was carried out by the acid chloride method to give a number of dehydrodipeptides.

Recently, increasing interests are being shown in the structure, biological activity, and synthesis of dehydropeptide (DHP), containing one or more α-dehydroamino acid (DHA) residues, which are very important constituents in a number of antibiotic and phytotoxic peptides.1-3)

In the preceding paper,4) we reported that the direct coupling of L-α-amino acid ester with N-benzyloxycarbonyl (Cbz)-DHA (1) as a carboxyl component by the mixed anhydride and DCC procedures gave various α-Cbz-amino-(Z)-α-alkenoylamino acid esters (2). Here, we describe a facile synthesis of DHP by one pot coupling between two different DHA.

To a solution of (Z)-1 (10 mmol) in dry THF (20 ml) was successively added portionwise with stirring PCl_5 (11 mmol) below 5°C, and then after 20 minutes a chilled solution of ethyl (Z)-α-amino-α-alkenoate (3; 10 mmol)5) in dry pyridine (15 ml) also dropwise below 5°C. After the reaction mixture was stirred for 3 h at room temperature, and then poured into ice-water (100 ml). The resulting aqueous solution was extracted three times with ethyl acetate (200 ml). The extracts were successively washed once with 3M-HCl and three times with water, and then dried over anhydrous Na_2SO_4. After evaporation of ethyl acetate under reduced pressure, the residual syrup was purified on a silica gel column using benzene-ethyl acetate (8 : 1 v/v) as eluent to give a pure syrup or crystals in *ca*. 50% yield. The compounds obtained were assigned to be ethyl α-Cbz-amino-(Z)-α-alkenoylamino-(Z)-α-alkenoate (4).



(Z)-1 (Z)-3 (Z,Z)-4

R = alkyl group. Cbz = $COOCH_2C_6H_5$

Table 1. Yields, physical constants, and spectral data of (Z,Z)-4.

Compound		Yield	Mp °C	IR, cm^{-1} [c]	NMR, δ in $CDCl_3$				
R	R^1	(%)		C=C	R-CH=	(J_{Hz})	R^1-CH=	(J_{Hz})	NH
CH_3	C_2H_5	41	syrup[a]	1680	6.77q	(7.5),	6.68t	(7.5),	7.30, 8.60
i-C_3H_7	C_2H_5	43	syrup[a]	1685	6.78d	(10.5),	6.42t	(7.5),	6.80, 7.82
C_2H_5	n-C_3H_7	51	syrup[a]	1685	6.70t	(7.5),	6.50t	(7.5),	6.88, 7.70
CH_3	i-C_3H_7	65	67-68[b]	1680	6.70q	(7.5),	6.60d	(10.5),	6.80, 7.70

a) Colorless syrup. b) Colorless needles from cyclohexane. c) Recorded in KBr.

Moreover, another preparative method of 4 has been investigated utillizing the base catalyzed β-elimination of (Z)-2 with a hydroxyl or mercapto group as a leaving group. The results will be reported and discussed elsewhere.

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