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FACILE SYNTHESIS OF N-Cbz-α-DEHYDROAMINO ACIDS AND THEIR DIPEPTIDE DERIVATIVES

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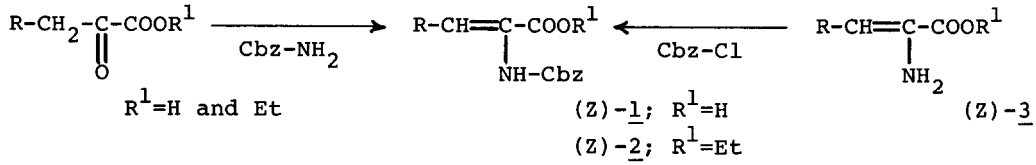
Summary: N-Cbz-α-dehydroamino acids (DHA) were prepared by the condensation of α-keto acid with benzyl carbamate by one step and the subsequent coupling of the DHA with L-α-amino acid esters was carried out to give many kinds of dehydrodipeptides.

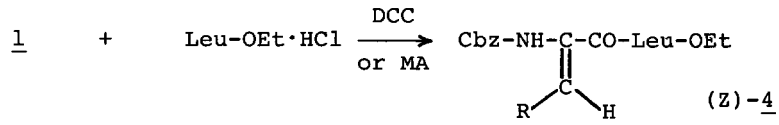
Recently, much interest has been directed to the dehydropeptide (DHP), which was pointed out to play some important roles in life biological process.[1,2] It has been well-known two indirect methods for the synthesis of DHP, i. e., methods by the reaction of unsaturated azlactone with α-amino acid[3,4] and by the base-catalyzed β-elimination of peptides with a leaving group,[5,6] but no report has been appeared on the direct coupling of α-dehydroamino acid (DHA) with α-amino acid, except for only two examples[7,8] involving the earlier work by one of the authors (C. S.).

In the present paper, we wish to communicate the synthesis of DHA N-protected with benzyloxycarbonyl (Cbz) group [(Z)-2-Cbz-amino-2-alkenoic acid (1)] and that of dehydrodipeptide derivatives from 1 and α-amino acid esters by usual ways.

According to the method reported previously,[9] the direct condensation of equimolar 2-oxoalkanoic acid (0.05 mol) with benzyl carbamate in the presence of *p*-toluenesulfonic acid (3 g) in dry benzene (60 ml) was carried out under reflux for 4 h to give 1 in *ca.* 90% yield. Compound 1 was identical with that prepared independently by the hydrolysis of ethyl (Z)-2-Cbz-amino-2-alkenoate (2), derived from the acylation of ethyl (Z)-2-amino-2-alkenoate (3)[10] with Cbz-Cl by usual method. Similarly, the condensation of 2-oxoalkanoic acid with toluene sulfonamide gave 2-tosylamino-2-alkenoic acid in *ca.* 80% yield. Subsequently, 1 was

coupled with L-α-amino acid (Gly, Ala, Val, Leu, and Phe) ethyl esters hydrochloride by ethyl chloroformate mixed anhydride (MA) (2 molar Et_3N and formate in THF-$CHCl_3$ below 0 °C for 1 h) or by dicyclohexylcarbodiimide (DCC) procedure (2 molar Et_3N in $CHCl_3$ at 0 °C for 3 h) to give the expected (Z)-Cbz-dehydroalkylglycyl- or dehydrophenylalanylamino acid ethyl esters (4) in *ca.* 50% yields. Moreover, the coupling of 1 with 3 is now in progress. In the Table, only 1 and Leu derivatives of DHP are listed.





a; R=CH_3, b; R=C_2H_5, c; R=*n*-C_3H_7, d; R=*i*-C_3H_7, e; R=C_6H_5

Table. Yields, physical constants, and spectral data of 1 and 4.

Compd No.	Yield,% A[a]	Yield,% B[b]	Mp °C[c]	NMR, δ[f] vinyl-H(J_{Hz})	Compd No.	Yield[d] %	Mp °C[e]	NMR, δ[f] vinyl-H(J_{Hz})	$[\alpha]_D^{25}$ in MeOH
1a	73	84	152-153	6.50(7.0)	4a	54	60-62	6.46(7.0)	-23.7(c=1.1)
1b	80	92	100-101	6.40(7.0)	4b	42	73-74	6.40(7.6)	-30.6(c=1.0)
1c	82	91	126-127	6.41(7.0)	4c	57	53-54	6.40(7.2)	-20.9(c=1.1)
1d	79	93	105-106	6.27(10.0)	4d	55	74-75	6.25(10.2)	-29.1(c=0.9)
1e	92	92	170-171	7.35-7.42[g]	4e	46	90-91	7.18	-18.8(c=1.0)

a) Yield from 2-oxoalkanoic acid and benzyl carbamate. b) Yield in the hydrolysis of 2. c) Colorless needles from cyclohexane-benzene. d) Yield by MA method. e) Colorless needles from diisopropyl ether. f) Measured in $CDCl_3$. g) Overlapped with phenyl protons.

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