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DIETHYLPHOSPHORYL CYANIDE. A NEW REAGENT FOR THE SYNTHESIS OF AMIDES.

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We have recently reported[1,2] two new methods for the formation of peptides from carboxyl and amino components, which appear to be practically free of racemization. One method[1] involves the use of the adducts of phosphorus compounds and tetrahalomethanes as a coupling reagent. The other[2] involves the use of diphenylphosphoryl azide(DPPA).

Further investigation of organophosphorus compounds as a coupling reagent reveals that diethylphosphoryl cyanide(DEPC) is also an efficient and useful reagent for the amide bond formation and is applicable to the racemization-free peptide synthesis.

DEPC is easily prepared by the reaction of triethylphosphite with cyanogen bromide according to the literature,[3] and boils at 93-96° (14 mmHg).[4]

Amides of various types can be obtained by the simple mixing of carboxylic acids and amines with DEPC in the presence of triethylamine.

$$RCO_2H + R'NH_2 \xrightarrow[Et_3N]{NC\cdot P(O)(OEt)_2} RCONHR'$$

Some typical yields of amides prepared by this method are listed in Table. Both aromatic and aliphatic acids easily react with both aromatic and aliphatic amines. The reaction is rapid, clean and free of contamination with side products. It is noteworthy that N-carbobenzoxyampicillin phenacyl ester can be

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conveniently prepared from the reaction of N-carbobenzoxy-D-phenylglycine with phenacyl 6-aminopenicillanate.

The addition of a tertiary amine such as triethylamine to generate a carboxylate anion from a carboxylic acid may be essential to promote the reaction smoothly since the yield of the coupling of benzoic acid with cyclohexylamine decreased from 97% to 70% when the reaction was carried out without triethylamine. Furthermore, the widely used coupling reagent N,N'-dicyclohexylcarbodiimide did not give any trace of N-cyclohexylbenzamide from benzoic acid and cyclohexylamine, proving the superiority of DEPC to N,N'-dicyclohexylcarbodiimide.

The most intriguing feature is that the method can be efficiently applied to the peptide synthesis which is substantially free of racemization. The supersensitive Young test[5] gave analytically pure benzoyl-L-leucylglycine ethyl ester in 86% yield with 96% L-isomer. No chloride ion effect[6] was observed even in a highly polar solvent dimethylformamide in which large peptides can be often soluble. This result may promise the convenient synthesis of peptides with a high degree of steric homogeneity.

A representative procedure is as follows. To a stirred mixture of benzoyl-L-leucine(1 equiv.) and glycine ethyl ester hydrochloride(1.1 equiv.) in dimethylformamide is added DEPC(1.1 equiv.) in dimethylformamide at 0°, followed by the addition of triethylamine(2.1 equiv.). The mixture was stirred at 0° for 30 min and at room temperature for 1-4 hr. The mixture was diluted with benzene-ethyl acetate, and washed successively with 5% aqueous hydrochloric acid, water, saturated aqueous sodium bicarbonate, and saturated aqueous sodium chloride. Drying and evaporation gave crude crystals of benzoyl-L-leucylglycine ethyl ester, which was purified by silica gel column chromatography.

The mechanism of the above amide formation will be quite similar to that of the DPPA coupling,[2] and its detail and the synthetic utility of DEPC are being currently explored.

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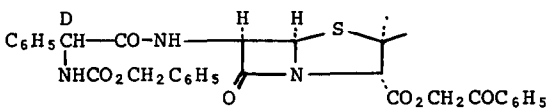
Table. Preparation of Amides.

$$RCO_2H + R'NH_2 \xrightarrow[Et_3N]{NC\cdot P(O)(OEt)_2} RCONHR'$$

in Dimethylformamide

Amide*[1]	Mp or Bp (mm), °c	Yield, %
$C_6H_5CONH(CH_2)_3CH_3$	112 (0.2)	94
$C_6H_5CON(CH_2CH_3)_2$	111 (2)	91
$C_6H_5CONHC_6H_{11}$	151-152	97
〃	〃	70*[2]
〃	—	0*[3]
$m\text{-}CH_3C_6H_4CON(CH_2CH_3)_2$	126-127 (2)	86
$C_6H_5CH_2CONHC_6H_5$	118-119	83
$CH_3(CH_2)_4CONHC_6H_5$	97.5-98	84
$CH_3(CH_2)_4CONHCH_2C_6H_5$	52-52.5	85
	172-173*[4]	61*[5]
$C_6H_5CONHCH(CH_2CH(CH_3)_2)CONHCH_2CO_2C_2H_5$	158-160*[6]	86

*1 All compounds have been characterized satisfactorily by elemental and spectral analysis.

*2 Without triethylamine.

*3 By N,N'-dicyclohexylcarbodiimide.

*4 $[\alpha]_D^{20}$+97°(c 1, $CHCl_3$).

*5 Crude yield 95%.

*6 $[\alpha]_D^{23}$-32.7°(c 2.3, EtOH).

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1) S. Yamada and Y. Takeuchi, Tetrahedron Letters, 1971, 3595.

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3) A. Takamizawa, Y. Sato, and S. Tanaka, Yakugaku Zasshi, 85, 298(1965).

4) A freshly prepared DEPC was proved to be a mixture of cyanide and isocyanide by its infra-red spectrum. Upon standing at room temperature for several weeks, the isocyanide was decomposed. Redistillation gave a pure cyanide.

5) M.W. Williams and G.T. Young, J. Chem. Soc., 1963, 881.

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