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A New Reagent for the *tert*-Butyloxycarbonylation of Amino Acids

The introduction of the *tert*-butyloxycarbonyl (BOC-) group for the protecting of amino group has been a major contribution to peptide syntheses.

Although *tert*-butyl *p*-nitrophenyl carbonate[1] and *tert*-butyl azidoformate[2] have been commonly used as *tert*-butyloxycarbonylating reagents, the *tert*-butyl *p*-nitrophenyl carbonate method usually gives poor yields of the resulting BOC-amino acids whereas the *tert*-butyl azidoformate method requires many steps for the preparation of the azidoformate.

In the present study, *tert*-butyl pentachlorophenyl carbonate (BOC-OPCP) was found to be a useful reagent for the same purpose.

BOC-OPCP could be readily prepared in good yield as a stable crystalline by the reaction of pentachlorophenyl chloroformate[3] with *tert*-butyl alcohol in a benzene solution in the presence of pyridine. Crystalline BOC-OPCP, m.p. 116~117° (80% yield), was obtained from ethanol-benzene. Its structure is supported by the analytical and infrared data. *Anal.* Calcd. for $C_{11}H_9O_3Cl_5$: C, 36.05; H, 2.48; Cl, 48.58. Found : C, 36.04; H, 2.39; Cl, 48.39. IR ν_{max}^{KBr} cm^{-1} : 1775 (C=O), 1250 ($C(CH_3)_3$).

Table I. Preparation of *tert*-Butyl- and *tert*-Amyl-oxycarbonyl Amino Acids by *tert*-Alkyl Pentachlorophenyl Carbonate Method

Compound	Yield (%)	m.p. (°C) Found	m.p. (°C) lit.	$[\alpha]_D$ (temp., °C) Found	$[\alpha]_D$ (temp., °C) lit.
BOC-deriv. of					
Alanine	61	73 ~ 74	83 ~ 84[1]	−24.5(23)	−22.4(25)[1]
β-Alanine	71	76 ~ 78	73 ~ 74[6]		
β-Benzylaspartate	60	101	101[7]	−17.4(23)	−19.5(22)[7]
Isoleucine[a]	64	50 ~ 58	49 ~ 57[1]	+ 2.8(23)	+ 3.0(25)[1]
Leucine[b]	71	70 ~ 73	67 ~ 72[1]	−24.2(23)	−24 (25)[1]
Methionine	87	Oil	Oil[1]		
Nitroarginine	63	102 ~104	98 ~102[8]	− 5.8(23)	− 5.9(28)[8]
Phenylalanine·DCHA[c]	85	210 ~212	210 ~212[9]	+29.2(23)	+28.9(25.5)[9]
Proline	73	135 ~137	136 ~137[1]	−59.1(23)	−60.2(25)[1]
Tryptophan	73	140.5~141	136.5~140.5[1]	−19.6(23)	−18.2(25)[1]
Valine	83	Oil	Oil[2]		
AOC-deriv. of					
Glycine	67	80 ~ 32	82.5~ 84[5]		
Methionine	89	Oil	Oil[5]		
Phenylalanine·DCHA[c]	90	204 ~206.5	198 ~199[5]	+35.2(23)	+27.4(21)[5]
Tryptophan	75	132 ~133	121 ~123[5]	+ 7.2(23)	+ 7.1(21)[5]

a) Hemihydrate. *b*) Hydrate. *c*) Dicyclohexylammonium salt.

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3) Pentachlorophenyl chloroformate was easily prepared in a stable crystalline from by allowing pentachlorophenol (commercial, 90% pure) to react with excess phosgen in a benzene-tetrahydrofuran solution in the presence of triethylamine, m.p. 58°.
4) Amino acid (0.1 mole) was dissolved in cooled 4*N*-sodium hydroxide (25 ml.).
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The aminolysis of the carbonate (40 g., 0.12 mol.) with sodium salt[4] of amino acid (0.10 mol.) was carried out in a mixture of dimethylformamide (100 ml.) and chloroform (50 ml.) in the presence of triethylamine (14 ml.) at room temperature for 24 hours. Chloroform (200 ml.) was added to the reaction mixture and then the sodium salt of the resulting BOC-amino acid was extracted with water. The aqueous extract was washed with ethyl acetate and then acidified with *N*-hydrochloric acid (200 ml.) under cooling and immediately extracted with ethyl acetate. From the ethyl acetate solution, BOC-amino acid was isolated by a usual manner. The yields and physical constants of the BOC-amino acids so synthesized were listed in Table I.

For the racemization test, BOC-isoleucine (listed in Table I) wes deacylated with trifluoroacetic acid and then subjected to the amino acid analyzer (Beckman 120B) : Isoleucine, 101±5%. Alloisoleucine, not detected.

Therefore the use of this reagent for usual BOC-amino acid synthesis must be safe against their racemization.

Incidentally, *tert*-amyloxycarbonyl (AOC-) amino acids[5] were prepared by the same procedures as described above, employing *tert*-amyl pentachlorophenyl carbonate (m.p. 88~90°, 83% yield) which was obtained by reacting pentachlorophenyl chloroformate with *tert*-amyl alcohol. The yields and physical constants of the AOC-amino acids thus obtained were also listed in Table I.

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Chemical Research Laboratories
Research and Development Division
Takeda Chemical Ind., Ltd.
Juso, Higashiyodogawa-ku, Osaka

Masahiko Fujino (藤野政彦)
Chitoshi Hatanaka (畑中千年)

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