PRO EXPERIMENTIS

A Convenient Preparation of some Alkyl Carbazates, Useful Intermediates for Amino-Protection

The *t*-butyloxycarbonyl-(*t*-BOC-) group[1,2] is frequently utilized as a useful amino-protecting group in peptide chemistry, because of the mild conditions required for its removal[3].

Several methods were reported for the introduction of *t*-BOC-group[3], but only *t*-butyl azidoformate was used practically for this purpose. The azide is commonly prepared from *t*-butyl phenyl carbonate[4], *t*-butyl *p*-nitrophenyl carbonate[5], or *t*-butyl S-methyl thiolcarbonate[6]; these methods, however, are inconvenient because of distillation required for purification in each steps.

We wish to report a convenient method for the preparation of *t*-butyl carbazate via *t*-butyl pentachlorophenyl carbonate. Generally pentachlorophenyl derivatives crystallize well, so that all intermediates prepared were used as pure products for the next step without any purification (see below). The obvious merit of this preparation lies in its simplicity as compared with other methods. A typical example is as follows. A suspension of pentachlorophenol (161 g) in dry benzene (250 ml) was added all at once to a well-stirred phosgene solution (73 g in 450 ml of dry benzene), and then pyridine (47.4 g) was dropped into this suspension within $^1/_2$ h at 10–15 °C. The reaction mixture was stirred for 2 h at room temperature and then allowed to stand overnight. After filtration to remove pyridine hydrochloride and the sparingly soluble by-product, di-pentachlorophenyl carbonate, the filtrate was concentrated in vacuo to give a crystalline mass of pentachlorophenyl chloroformate (130 g, 65%), which was contaminated with a trace of di-pentachlorophenyl carbonate, but was used for the next step without purification.

A solution of pentachlorophenyl chloroformate (77.2 g) in dry benzene (100 ml) was added dropwise to a stirred solution of *t*-butanol (20.8 g) and pyridine (22.2 g) in dry benzene (100 ml) within 1 h at 0–5 °C. The reaction mixture was stirred for 2 h at room temperature and allowed to stand overnight. After filtration to remove pyridine hydrochloride, the filtrate was washed with N-hydrochloric acid, water, saturated sodium bicarbonate solution, and brine, and dried over magnesium sulphate adding decolorizing charcoal. Evaporation left pale brown needles, which were washed with ethanol, filtered, and dried; m.p. 116–117 °C, 60.6 g (72%). This product can be used without purification. Recrystallization from ethyl acetate-ethanol gave the *t*-butyl pentachlorophenyl carbonate as white needles of m.p. 117–118 °C. Anal. Calculated for $C_{11}H_9O_3Cl_5$: C, 36.05; H, 2.48; Cl, 48.37. Found: C, 36.18; H, 2.46; Cl, 48.04. The mixture of *t*-butyl pentachlorophenyl carbonate (22.0 g), hydrazine hydrate (12.5 ml) and benzene (25 ml) was allowed to react for 3 h. An exothermic reaction ensued, producing a clear hot solution; occasional cooling was required at the initial stage. The formed solid mass was crushed and extracted with ether several times. The extracts separated from the residue by decantation were combined and dried over magnesium sulphate. Evaporation gave a pale yellow oil of *t*-butyl carbazate, which solidified on cooling; m.p. 34–36 °C, 8.0 g (98%). The product was distilled at 4 mmHg; b.p. 75–76 °C (m.p. 40–41 °C). The literature value is m.p. 40–42 °C[6].

Crude *t*-butyl carbazate was converted to *t*-butyl azidoformate by known method[4] in 75–80% yield. *t*-Amyl-[7], benzhydryl-[8], and *p*-methoxybenzyl carbazate[9] were also prepared as described above (Table).

Because pentachlorophenol (pK = 5.2) is more acidic than *p*-nitrophenol (pK = 7.2), it was expected that the *t*-butyl pentachlorophenyl carbonate would more easily give *t*-BOC-amino acids by direct aminolysis than the corresponding *p*-nitrophenyl derivative. However, it was found that both reactivities were almost similar. Details will be published elsewhere.

Alkyl pentachlorophenyl carbonates and alkyl carbazates[a]

R	$ROCOOC_6Cl_5$		$ROCON_2H_3$	
	m.p. (°C)	Yield (%)	m.p. or b.p. (°C)	Yield (%)
t-Butyl	116–117 (117–118)[b]	72(—)	34–36 (40–41)[c]	98 (—)
t-Amyl	90–91 (90–92)[b]	68 (—)	—(b.p. 89–90/7.5 mmHg)[d]	93 (79)
Benhydryl	120–122 (121–123)[b]	58 (—)	98–101 (102–104)[e,f]	91 (—)
p-Methoxybenzyl	92–94 (93–94.5)[b]	57 (50)	74–76 (76.5–78)[g,h]	93 (89)

[a] The values of purified products are shown in parentheses. [b] Recrystallization from ethyl acetate-ethanol. [c] Lit. m.p. 40–42 °C[6]. [d] Lit. b.p. 85–86 °C/5 mmHg[7]. [e] Recrystallization from ethanol-water. [f] Lit. m.p. 101–102 °C[8]. [g] Recrystallization from ethyl acetate-petroleum ether. [h] Lit. m.p. 71–74 °C[9].

Zusammenfassung. Eine einfache Methode zu Herstellung einiger Alkyloxycarbonylhydrazide via Alkyl-pentachlorophenylcarbonate wird beschrieben.

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[1] F. C. McKay and N. F. Albertson, J. Am. chem. Soc. *79*, 4686 (1957).
[2] G. W. Anderson and A. C. McGregor, J. Am. chem. Soc. *79*, 6180 (1957).
[3] E. Schröder and K. Lübke, *The Peptides* (Academic Press, New York 1965), vol. 1, p. 36.
[4] L. A. Carpino, C. A. Giza and B. A. Carpino, J. Am. chem. Soc. *81*, 955 (1959).
[5] K. Inouye, M. Kanayama and H. Otsuka, J. chem. Soc. Japan *85*, 599 (1964).
[6] L. A. Carpino, J. Am. chem. Soc. *82*, 2725 (1960).
[7] I. Honda, Y. Shimonishi and S. Sakakibara, 4th Symposium on Peptide Chemistry. Institute for Protein Research, Osaka University, 3rd December 1965; *The 4th Symposium on Peptide Chemistry* (1965), p. 24.
[8] R. G. Hisky and J. B. Adams, jr., J. Am. Chem. Soc. *87*, 3969 (1965).
[9] F. Weygand and K. Hunger, Chem. Ber. *95*, 1 (1962).