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Studies on Peptides. XXIX.[1] *p*-Methoxybenzyl Mixed Carbonates

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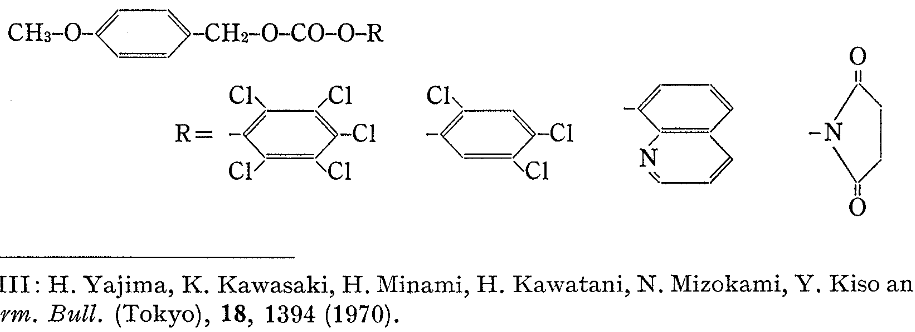
Recently we described the direct route to prepare *p*-methoxybenzyl azidoformate,[3] an important reagent originally introduced by Weygand and Hunger[4] for the preparation of *p*-methoxybenzyloxycarbonylamino acids. This procedure involved the direct action of phosgen to *p*-methoxybenzyl alcohol to form *p*-methoxybenzyl chloroformate followed by addition of sodium azide. Excess phosgen has to be removed from the reaction mixture prior to the addition of the azide compound in order to avoid a possible formation of explosive carbazide.[5] With this precaution, this method seems to be the most convenient route to prepare this important reagent.

We have extended this principle to the direct preparation of *p*-methoxybenzyl mixed carbonates with various phenolic compounds. It is known that *p*-methoxybenzyloxycarbonylamino acids can be prepared alternatively by the aminolysis of *p*-methoxybenzyl mixed carbonates, such as *p*-nitrophenyl,[4] 2,4,5-trichlorophenyl[6] or 1-piperidyl carbonate.[7] The former two compounds were prepared by the reaction of chloroformates of respective phenolic compounds with *p*-methoxybenzyl alcohol. Jones and Young[7] prepared the last compound by the reaction of *p*-methoxybenzyl chloroformate with N-hydroxypiperidine in the presence of aqueous sodium carbonate. Sofuku, *et al.*[8] adopted such a direct route to prepare *p*-methoxybenzyl *p*-nitrophenyl carbonate using sodium *p*-nitrophenolate.

In our present investigation, we slightly modified the procedure of Jones and Young.[7] *p*-Methoxybenzyl chloroformate prepared in cold as described was allowed, without isolation, to react with some phenolic compounds in the presence of triethylamine instead of aqueous sodium carbonate. We prepared new *p*-methoxybenzyl mixed carbonates; *i.e.*, *p*-methoxybenzyl pentachlorophenyl and 8-quinolyl carbonates in satisfactory yields. In addition, *p*-methoxybenzyloxycarbonyl N-hydroxysuccinimide ester was also prepared in the same manner. It was found that *p*-methoxybenzyl 2,4,5-trichlorophenyl carbonate could be prepared by such a direct procedure. Under anhydrous conditions, the reaction of the chloroformate was completed in any case within 2 hr at 0°. Attempt to prepare *p*-methoxybenzyl



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[1] Part XXVIII: H. Yajima, K. Kawasaki, H. Minami, H. Kawatani, N. Mizokami, Y. Kiso and F. Tamura, *Chem. Pharm. Bull.* (Tokyo), **18**, 1394 (1970).

[2] Location: *Sakyo-ku, Kyoto.*

[3] H. Yajima and Y. Kiso, *Chem. Pharm. Bull.* (Tokyo), **17**, 1962 (1969).

[4] F. Weygand and K. Hunger, *Chem. Ber.*, **95**, 1 (1962).

[5] H. Yajima, H. Kawatani and Y. Kiso, *Chem. Pharm. Bull.* (Tokyo), **18**, 860 (1970).

[6] E. Klieger, *Ann.*, **724**, 204 (1969).

[7] J.H. Jones and G.T. Young, *Chem. Ind.*, 1722 (1966).

[8] S. Sofuku, M. Mizumura and A. Hagitani, *Bull. Chem. Soc. Japan*, **42**, 278 (1969); *idem, ibid.*, **43**, 177 (1970).

2,4-dinitrophenyl carbonate was unsuccessful, since it decomposed during the isolation. The high acidity of this phenolic compound (pK 3.5) may be responsible for this phenomenon.

Efficiencies in aminolysis of these mixed carbonates with alanine were compared in the presence of triethylamine. Reactions were performed in 50% aqueous dioxane at room temperature for 48 hr. *p*-Methoxybenzyl pentachlorophenyl and quinolyl carbonates both gave fairly good yields (72 and 81% respectively), but *p*-methoxybenzyloxycarbonyl N-hydroxysuccinimide ester gave the lowest yield. The yields of *p*-methoxybenzyloxycarbonylalanine prepared by *p*-methoxybenzyl piperidyl and trichlorophenyl carbonates were reported as 58% (after reaction at 20° for 3 days)[7] and 79% (after reaction at 50° for 12 hr)[6] respectively. It is noteworthy that relatively high yield in the aminolysis of *p*-methoxybenzyl pentachlorophenyl and quinolyl carbonates could be achieved under similar conditions employed for *p*-methoxybenzyl azidoformate.[4]

When aminolysis of mixed carbonates was performed, difficulties were encountered in the purification of the desired *p*-methoxybenzyloxycarbonylamino acids from phenols liberated during the reaction. The use of triethylamine seems to have some advantage in this respect. After evaporation of the solvent, water was added and the aqueous solution was washed with ether. Phenols were extracted into the organic phase and triethylammonium salt of *p*-methoxybenzyloxycarbonylalanine remained in the aqueous solution. Acidification of the latter with citric acid gave the product in high purity. When magnesium oxide, instead of triethylamine, was used, separation of phenols was difficult. In this respect, *p*-methoxybenzyl quinolyl carbonate and *p*-methoxybenzyloxycarbonyl N-hydroxysuccinimide ester have an advantageous property, since 8-hydroxyquinoline liberated is acid soluble and N-hydroxysuccinimide is water soluble, both can be removed by simple washing procedure. Comparing the rate of aminolysis of these two compounds, the quinolyl carbonate seems to be the most preferable reagent for the preparation of *p*-methoxybenzyloxycarbonylamino acid among those prepared in the present investigation.

For the preparation of *tert*-butoxycarbonylamino acids, various *tert*-butyl mixed carbonates with phenolic compounds are known in the literatures.[9] However, large amounts of these carbonates can only be prepared by the reaction of *tert*-butanol and chloroformates of the phenolic compounds which have to be isolated. It should be mentioned that these procedures form more or less the symmetrical carbonates of phenols employed besides the desired mixed carbonates. In view of obtaining the amino acid derivatives bearing the acid labile amino protecting group equivalent to the *tert*-butoxycarbonyl group, the simple procedure for the preparation of *p*-methoxybenzyl azidoformate described previously and *p*-methoxybenzyl mixed carbonates presented in this paper seems to be of great value and these procedures may contribute further for the application of *p*-methoxybenzyloxycarbonylamino acids in peptide synthesis.

Experimental

***p*-Methoxybenzyl Pentachlorophenyl Carbonate**——The entire operation was performed under cooling with ice–NaCl (−10° to −15°). A solution of *p*-methoxybenzyl alcohol (35 ml, 0.28 mole) in dry ether (100 ml) was added to a solution of phosgen (31 g, 0.30 mole) in ether (40 ml) during a period of 30 min. After stirring was continued for 30 min, dry nitrogen gas was bubbled through the reaction mixture for 30 min and then pentachlorophenol (75.6 g, 0.28 mole) in ether (400 ml) was combined. To this solution, triethylamine (77 ml, 0.56 mole) in ether (70 ml) was added dropwise during a period of 1 hr. The reaction was continued for an additional 1 hr with stirring. After addition of H_2O, the organic phase was washed

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[9] G.W. Anderson and A.C. McGregor, *J. Am. Chem. Soc.*, **79**, 6180 (1957); W. Broadbent, J.S. Morley and B.E. Stone, *J. Chem. Soc.*, (*C*), **1967**, 2632; M. Fujino and C. Hatanaka, *Chem. Pharm. Bull.* (Tokyo), **15**, 2015 (1967); B. Rzeszotarska and S. Wiejak, *Ann.*, **716**, 216 (1968); M. Frankel, D. Ladkany, C. Gilon and Y. Woolman, *Tetrahedron Letters*, **1966**, 4765; W. Klee and M. Brenner, *Helv. Chem. Acta*, **44**, 2151 (1961).

successively with 10% citric acid and a solution of NaCl, dried over Na_2SO_4 and then evaporated. The resulting solid was recrystallized from ether; yield 71.0 g (60%), mp 95—97°. *Anal.* Calcd. for $C_{15}H_9O_4Cl_5$: C, 41.85; H, 2.17; Cl, 41.18. Found: C, 42.07; H, 2.12; Cl, 41.14.

Progress of the reaction was followed by thin-layer chromatography on silica gel (Kieselgel G, Merck) using benzene as a developing solvent.³⁾ Ceric sulfate served to locate *p*-methoxybenzyl alcohol, *Rf* 0.03 and *p*-methoxybenzyl chloroformate, *Rf* 0.61.

***p*-Methoxybenzyl 2,4,5-Trichlorophenyl Carbonate**——The title compound was prepared as described above; yield 89%, mp 108.5—110° (lit.⁶⁾ mp 104—106°). *Anal.* Calcd. for $C_{15}H_{11}O_4Cl_3$: C, 49.82; H, 3.07. Found: C, 49.65; H, 3.01.

***p*-Methoxybenzyl 8-Quinolyl Carbonate**——*p*-Methoxybenzyl alcohol (32.5 ml, 0.26 mole) in dry tetrahydrofuran (THF, 80 ml) was added to a solution of phosgen (29 g, 0.29 mole) in THF (100 ml) during a period of 30 min. After stirring for 30 min, dry nitrogen gas was bubbled through the soultion and then 8-hydroxyquinoline (43.5 g, 0.3 mole) in THF (200 ml) was added. To this solution, a solution of triethylamine (84 ml, 0.6 mole) in THF (100 ml) was added dropwise during a period of 1 hr and stirring was continued for an additional 1 hr. The solvent was evaporated *in vacuo*. AcOEt and H_2O were added to the residue and the organic phase was washed with 0.05N HCl and a saturated solution of NaCl, dried over Na_2SO_4 and then evaporated. Trituration of the residue with petroleum ether (bp 35—65°) gave solid, which was recrystallized from EtOH; yield 68.0 g (85%), mp 94—96°. *Anal.* Calcd. for $C_{18}H_{15}O_4N$: C, 69.89; H, 4.89; N, 4.53. Found: C, 70.01; H, 4.83; N, 4.83.

***p*-Methoxybenzyloxycarbonyl N-Hydroxysuccinimide Ester**——The title compound was similarly prepared as described above. It was recrystallized from THF and ether; yield 62%, mp 113—115°. *Anal.* Calcd. for $C_{13}H_{13}O_6N$: C, 55.91; H, 4.70; N, 5.02. Found: C, 56.17; H, 4.71; N, 4.81.

***p*-Methoxybenzyloxycarbonylalanine [Z(OMe)-Ala-OH]**——Alanine (0.89 g, 0.01 mole) was dissolved in H_2O (25 ml) with the aid of triethylamine (2.8 ml, 0.02 mole). *p*-Methoxybenzyl mixed carbonate (0.012 mole) in dioxane (25 ml) was combined and the mixture was stirred at room temperature (24°) for 48 hr. The solvent was then evaporated and H_2O was added to the residue. The aqueous phase was washed with ether and then acidified with 10% citric acid or 0.1N HCl (in the case of quinolyl carbonate) under ice-cooling. The resulting precipitate was extracted with AcOEt, which after washing with a saturated solution of NaCl, was dried over Na_2SO_4 and then evaporated. Trituration of the residue with petroleum ether gave solid which was recrystallized from AcOEt and petroleum ether; yield and melting point of the products were as follows;

Mixed carbonate	Z(OMe)-Ala-OH %	mp (°C)
Pentachlorophenyl carbonate	72	81.5—82.5
Trichlorophenyl carbonate	56	73—75
Quinolyl carbonate	81	82—82.5
N-Hydroxysuccinimide ester	51	78—81

Anal. Calcd. for $C_{12}H_{15}O_5N$: C, 56.91; H, 5.97; N, 5.53. Found: C, 56.64; H, 6.22; N, 5.28 (lit.⁴⁾ mp 74—75°, lit.⁶⁾ mp 78—79°, lit.⁸⁾ mp 78—81°, lit.¹⁰⁾ mp 80—82°).

When magnesium oxide, instead of triethylamine, was used, yield and melting point of the products were as follows;

Mixed carbonate	Z(OMe)-Ala-OH %	mp (°C)
Pentachlorophenyl carbonate	70	80—82
Trichlorophenyl carbonate	25	below 60
Quinolyl carbonate	77	81.5—82.5
N-Hydroxysuccinimide ester	34	73—76

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10) S. Sakakibara, I. Honda, M. Naruse and M. Kanaoka, *Exp.*, 25, 576 (1969).