Synthesis of Activated Esters of *N*-Protected Amino-acids

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A simplified method for the synthesis of activated esters of *N*-protected amino-acids is described. The synthesis proceeds through the aminolysis of various active esters of t-butyl or benzyl carbonate, and the leaving group displaced in this process becomes reincorporated by the addition of dicyclohexylcarbodi-imide to the reaction mixture, to give the desired compound.

THE aminolysis of various diaryl and alkyl aryl carbonates is well known and has been used for the preparation of various aryloxycarbonyl- and alkoxycarbonyl-amino-acid derivatives, *e.g.*, benzyloxycarbonyl derivatives by aminolysis of benzyl phenyl carbonate [1] or benzyl 1-piperidyl carbonate,[2] 4-nitrobenzyloxycarbonyl derivatives by aminolysis of 4-nitrobenzyl 1-piperidyl carbonate,[2] 4-methoxybenzyloxycarbonyl derivatives by aminolysis of 4-methoxybenzyl *p*-nitrophenyl carbonate,[3] and t-butoxycarbonyl derivatives by aminolysis of t-butyl *p*-nitrophenyl carbonate.[4]

Recently we described the synthesis of various benzyloxycarbonyl- and t-butoxycarbonyl-amino-acid *N*-hydroxysuccinimide esters by treating benzyl or t-butylsuccinimido carbonate with the sodium salt of the desired amino-acid, followed by acidification and addition of 1 equivalent of dicyclohexylcarbodi-imide to the reaction mixture.[5] This reaction can be summarised by the following equations (where R^1 = a or b and R^2 = a).

$$R^1O{\cdot}CO{\cdot}R^2 + NH_2{\cdot}CHR^3{\cdot}CO_2^- \longrightarrow R^1O{\cdot}CO{\cdot}NH{\cdot}CHR^3{\cdot}CO_2^- + R^2H$$

$$R^1O{\cdot}CO{\cdot}NH{\cdot}CHR^3{\cdot}CO_2H + R^2H \xrightarrow{DCCI} R^1O{\cdot}CO{\cdot}NH{\cdot}CHR^3{\cdot}CO{\cdot}R^2$$

R^1 a = CH_2Ph; b = CMe_3

R^2 a = O·succinimido; b = $O{\cdot}C_6H_4{\cdot}NO_2$-*p*; c = SPh; d = $O{\cdot}C_6H_2(Cl_3$-2,4,5); e = $O{\cdot}C_6H_2(Cl_3$-2,4,6); f = $O{\cdot}C_6Cl_5$

We have found that the reaction can be used generally for the synthesis of activated esters of aryloxycarbonyl- and alkoxycarbonyl-amino-acids. Aminolysis of various aryl benzyl carbonates (R^1 = a, R^2 = b, c, d, e, or f) yields the corresponding benzyloxycarbonylamino-acids. Addition of dicyclohexylcarbodi-imide to the reaction mixture gave the corresponding activated esters of benzyloxycarbonylamino-acids in 65—80% yield (based on the free amino-acids). The compounds obtained were identical with authentic samples prepared according to the literature.

Although the preparation of t-butoxycarbonylamino-acids by aminolysis of t-butyl *p*-nitrophenyl carbonate was reported some time ago [4] it did not gain wider use, obviously because of the necessity for the elaborate purification procedure of the reaction products from *p*-nitrophenol. This problem is eliminated once the t-butoxycarbonylamino-acid *p*-nitrophenyl esters are obtained without isolation of the free t-butoxycarbonylamino-acids. Various t-butoxycarbonylamino-acid *p*-nitrophenyl esters were prepared in 70—75% yield by the aminolysis of t-butyl *p*-nitrophenyl carbonate (R^1 = b, R^2 = b).

The aryl benzyl esters were synthesised in 65—80% yield by treating the corresponding phenols with benzyl chloroformate in the presence of 1 equivalent of quinoline. While employing this procedure, benzyl *p*-nitrophenyl carbonate becomes available in 80% yield. We obtained this compound, in 30% yield only, by the reaction of *p*-nitrophenyl chloroformate with benzyl alcohol in the presence of 1 equivalent of quinoline. Similarly, while the benzyl *S*-phenyl thiocarbonate was prepared in 20% yield on treating phenyl chlorothiolformate with benzyl alcohol in the presence of base,[6] we were able to obtain the same compound in over 80% yield by the action of benzyl chloroformate on thiophenol in the presence of 1 equivalent of quinoline.

TABLE 1

Benzyl aryl carbonates

Ester	Method	Yield (%)	M. p. or b. p./mm.	Cryst. from	Found (%) C	H		Formula	Required (%) C	H	
p-$NO_2{\cdot}C_6H_4$	A	83	79—80°	Benzene–petrol.	61·3	4·0	N, 4·9	$C_{14}H_{11}NO_5$	61·55	4·05	N, 5·15
	B	30	79	Benzene–petrol.	61·6	3·95	N, 5·3				
PhS	A	82	58—59 [a]	Benzene–petrol.	68·7	5·1	S, 13·3	$C_{14}H_{12}O_2S$	68·85	4·95	S, 13·1
(2,4,6-Cl_3)C_6H_2 ...	A	78	185—188/4		51·05	3·1	Cl, 31·7	$C_{14}H_9Cl_3O_3$	50·7	2·75	Cl, 32·1
(2,4,5-Cl_3)C_6H_2 ...	A	65	86—87	Petrol.	50·9	2·7	Cl, 32·3	$C_{14}H_9Cl_3O_3$	50·7	2·75	Cl, 32·1
C_6Cl_5	A	78	115—116 [b]	Toluene	42·15	1·55	Cl, 44·0	$C_{14}H_7Cl_5O_3$	42·0	1·75	Cl, 44·25

[a] Lit.,[6] 59—60°. [b] M. p. 116° was reported (Beilstein, vol. 6, p. 437).

EXPERIMENTAL

Melting points were determined in a Fisher-Johns apparatus and are uncorrected.

Benzyl p-*Nitrophenyl Carbonate.*—(a) *Using benzyl chloroformate.* To a solution of *p*-nitrophenol (6·95 g., 0·05 mole)

[1] H. Zahn and H. R. Falkenburg, *Annalen*, 1960, **636**, 117.
[2] B. O. Handford, J. H. Jones, G. T. Young, and T. F. N. Johnson, *J. Chem. Soc.*, 1965, 6814.
[3] F. Weygand and K. Hunger, *Chem. Ber.*, 1962, **95**, 1.
[4] G. W. Anderson and A. C. McGregor, *J. Amer. Chem. Soc.*, 1957, **79**, 6180.
[5] M. Frankel, D. Ladkany, C. Gillon, and Y. Wolman, *Tetrahedron Letters*, 1966, 4765.
[6] J. L. Kice, R. A. Bartsch, M. A. Dankleff, and S. L. Schwartz, *J. Amer. Chem. Soc.*, 1965, **87**, 1734.

TABLE 2

Activated esters of benzyloxycarbonyl- and t-butoxycarbonyl-amino-acids

	Yield (%)	M. p.	Lit., m. p.
Benzyloxycarbonyl derivatives			
Glycine *p*-nitrophenyl ester	78	126°	130° [a]
L-Alanine *p*-nitrophenyl ester	75	76—78	79 [b]
L-Phenylalanine *p*-nitrophenyl ester	81	126	126—127 [b]
S-Benzyl-L-cysteine *p*-nitrophenyl ester	80	89	91—92 [b]
Glycine phenylthio ester	60	73	72 [a]
S-Benzyl-L-cysteine phenylthio ester	64	100—101	100 [c]
Glycine 2,4,6-trichlorophenyl ester	78	101—103	103—104 [d]
L-Phenylalanine 2,4,6-trichlorophenyl ester	80	126—127	128 [e]
Glycine 2,4,5-trichlorophenyl ester	77	102—104	107—108 [e]
L-Phenylalanine 2,4,5-trichlorophenyl ester	79	140—141	142 [e]
Glycine pentachlorophenyl ester	72	180—182	186—187 [f]
L-Phenylalanine pentachlorophenyl ester	78	159—160	158 [e]
t-Butoxycarbonyl derivatives			
Glycine *p*-nitrophenyl ester	74	66—68	70—71 [g]
L-Alanine *p*-nitrophenyl ester	72	81—82	83 [g]
L-Phenylalanine *p*-nitrophenyl ester	75	129—130	132 [g]
N^{ϵ}-t-Butoxycarbonyl-L-lysine *p*-nitrophenyl ester	78	124—125	127 [g]
γ-Benzyl-L-glutamate α-*p*-nitrophenyl ester	71	122—123	123 [g]

[a] T. Wieland and B. Heinke, *Annalen*, 1958, **615**, 185. [b] M. Goodman and K. C. Stueben, *J. Amer. Chem. Soc.*, 1959, **81**, 3980. [c] K. C. Hooper, H. N. Rydon, J. A. Schofield, and G. S. Heaton, *J. Chem. Soc.*, 1956, 3148. [d] G. Kupryszewski and M. Kaczmarek, *Roczniki Chem.*, 1961, **35**, 931. [e] J. Pless and R. A. Boissonnas, *Helv. Chim. Acta*, 1963, **46**, 1609. [f] G. Kupryszewski and M. Formela, *Roczniki Chem.*, 1961, **35**, 1533. [g] Ed. Sandrin and R. A. Boissonnas, *Helv. Chim. Acta*, 1963, **46**, 1637.

and quinoline (6·45 g., 0·05 mole) in methylene chloride (100 ml.) benzyl chloroformate (8·5 g., 0·05 mole) was added dropwise during 15 min. The reaction mixture was kept overnight, washed with 1N-hydrochloric acid (2 × 50 ml.), 0·5N-sodium hydrogen carbonate (4 × 50 ml.), and water (2 × 50 ml.), and dried (Na_2SO_4), and the solvent was removed *in vacuo*. The *product* crystallised from benzene–light petroleum (11·2 g., 83%), m. p. 79—80°.

Other benzyloxycarbonyl active esters were prepared similarly (see Table 1).

(b) *Using* p-*nitrophenyl chloroformate*. To a solution of benzyl alcohol (5·5 g., 0·05 mole) and quinoline (6·45 g., 0·05 mole) in methylene chloride (100 ml.) *p*-nitrophenyl chloroformate [4] (10·1 g., 0·05 mole) was added in portions during 15 min. The mixture was kept overnight, and worked up as in (a), to give the *product* (4·2 g., 30%), m. p. 79°.

Benzyloxycarbonylglycine p-*Nitrophenyl Ester*.—A solution of benzyl *p*-nitrophenyl carbonate (546 mg., 2 mmoles) in dioxan (10 ml.) was added to an aqueous solution (10 ml.) of glycine sodium salt (2 mmoles, prepared from 150 mg. of glycine and 168 mg. of sodium hydrogen carbonate). After heating the combined reaction mixture at 100° for 3 hr. 1N-hydrochloric acid (2 ml., 2 mmoles) was added in the cold, followed by a solution of dicyclohexylcarbodiimide (406 mg., 2 mmoles) in dioxan (3 ml.). After 30 min. in an ice-bath and 2 hr. at room temperature, dicyclohexylurea was removed by filtration, dioxan was removed *in vacuo*, and the ester was extracted with ethyl acetate (3 × 15 ml.). The combined organic layers were washed with 0·5N-sodium hydrogen carbonate (4 × 10 ml.) and water (4 × 10 ml.), dried (Na_2SO_4), and the solvent was removed *in vacuo*, to give a yellow oil. The compound crystallised upon the addition of light petroleum and was recrystallised from ethyl acetate–light petroleum to yield the *product* (540 mg., 78%), m. p. 126—127°.

Other activated esters of benzyloxycarbonyl- and t-butoxycarbonyl-amino-acids were prepared similarly by treating the corresponding benzyl or t-butyl aryl carbonates with the desired amino-acid (see Table 2).

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