SHORT COMMUNICATIONS

A New Reagent for the p-Nitrophenylation of Carboxylic Acids

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(Received May 2, 1964)

The *p*-nitrophenylester of acylamino acid is well known to be a convenient intermediate in peptide synthesis. Bodanszky[1] originally prepared this compound by heating a mixture of *p*-nitrophenol and carbobenzoxy amino acid chloride or mixed anhydride. Since then, Schwyzer et al.[2] have developed two new reagents, di-*p*-nitrophenyl sulfite and tri-*p*-nitrophenyl phosphite, for the *p*-nitrophenylation of carbobenzoxy amino acid. Later, Bodanszky and du Vigneaud[3] prepared the same *p*-nitrophenylesters by using dicyclohexylcarbodiimide as a coupling reagent.

In the present study, it was found that *p*-nitrophenyl trifluoroacetate (I) was a useful reagent for the same purpose. A solution of trifluoroacetic anhydride (62 g., 0.3 mol.) and *p*-nitrophenol (28 g., 0.2 mol.) in dry benzene

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1) M. Bodanszky, *Nature*, **175**, 685 (1955).

2) R. Schwyzer, B. Iselin and P. Sieber, *Helv. Chim. Acta*, **40**, 373 (1957).

3) M. Bodanszky and V. du Vigneaud, *J. Am. Chem. Soc.*, **81**, 5688, 6072 (1959).

TABLE I. FORMATION OF *p*-NITROPHENYLESTERS BY ESTER-EXCHANGE REACTIONS WITH CARBOXYLIC ACIDS

Carboxylic acid	Reagent	Yield %	Melting point, °C		$[\alpha]_D$, *c* 2 in DMF (temp., °C)	
			Found	Cited	Found	Cited
CH_3COOH	$CF_3COOPNP$	80	78～80	79～80[a]		
C_6H_5COOH	$CF_3COOPNP$	90.5	143	142.5[b]		
Z-Gly-OH	$CF_3COOPNP$	93	126～127.5	127.5～128.5[c]		
Z-L-Pro-OH	$CF_3COOPNP$	83.5	94～95.5	94～96[d]	−70.0(22)	−68(20)[d]
Z-L-Phe-OH	$CF_3COOPNP$	85.5	125～126	126～126.5[e]	−24.7(22)	−24.7(25)[e]
Z-L-Glu(NH_2)-OH	$CF_3COOPNP$	63.5	151～153	155～156[d]	−24.0(21.5)	−24(20)[d]
Z-Gly-Gly-OH	$CF_3COOPNP$[f]	89	160～162[g]			
Z-L-Phe-OH	$CH_2ClCOOPNP$[h]	37	124～126	126～126.5[e]	−24.7(20)	−24.7(25)[e]
Z-L-Pro-OH	$CCl_3COOPNP$[h]	57	94～96	94～96[d]	−70.0(22)	−68(20)[d]

a) A. Kaufmann, *Ber.*, **42**, 3482 (1909). b) Beilstein Vol. 9, p. 119. c) M. Bodanszky and V. du Vigneaud, Biochemical preparation Vol. 9, p. 110. d) M. Bodanszky and V. du Vigneaud, *J. Am. Chem. Soc.*, **81**, 5688 (1959). e) M. Bodanszky and V. du Vigneaud, ibid., **81**, 6072 (1959). f) The reaction was carried out for two hours at room temperature. g) Found: C, 55.88; H, 4.36; N, 10.61. Calcd. for $C_{18}H_{17}N_3O_7$: C, 55.81; H, 4.42; N, 10.85%. h) The reaction was carried out by refluxing the pyridine solution for about 10 min.

(Z: Carbobenzoxy; PNP: *p*-nitrophenyl; DMF: dimethyl formamide)

(60 ml.) was refluxed for about 5 hr., and then the solution was concentrated to dryness; the yield of crystalline product I was quantitative (m. p. 37～39°C). This product was used without further purification in the following reactions. A part of the product was subjected to sublimation in vacuo for analysis; m. p. 36～38°. Found: C, 41.11; H, 1.89. Calcd. for $C_8H_4O_4NF_3$: C, 40.86; H, 1.71%. A solution of a carboxylic acid such as carbobenzoxy amino acid (0.005 mol.) in dry pyridine (1.5～3 ml.) was treated with I (0.005 mol.) at room temperature. After about 10 min., water (20 ml.) was added to the reaction mixture to precipitate the resulting *p*-nitrophenylester of the carboxylic acid as crystals. The product was collected by filtration and then recrystallized from a suitable solvent system. The yields and physical constants of the reaction products are listed in Table I. In contrast with this, it was confirmed that the mono-, di- or trichloroacetic acid *p*-nitrophenylester was only reactive with carbobenzoxy amino acids in boiling pyridine, and gave poor yields of the desired products, together with colored by-products.

In carbobenzoxy peptides, however, the ester-exchange reaction of I was slower than that in carbobenzoxy amino acids. In these cases, the heating of the reaction mixture or the prolongation of the reaction time at room temperature was necessary in order to complete the reaction, and the racemization of the *C*-terminal amino acid residues might occur to some extent during the reaction. The advantages of the new method over the Schwyzer method[2] are as follows: 1) Since the reaction occurred within 10 min. at room temperature (with acylamino acids), such undesirable side-reactions as racemization were few. 2) The only co-product of the reaction was trifluoroacetic acid, which can easily be removed from the reaction mixture. Therefore, the product could easily be purified.

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