## SHORT COMMUNICATIONS

A New Reagent for the p-Nitrophenylation of Carboxylic Acids

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The *p*-nitrophenylester of acylamino acid is well known to be a convenient intermediate Bodanszky<sup>1)</sup> originally in peptide synthesis. prepared this compound by heating a mixture of p-nitrophenol and carbobenzoxy amino acid chloride or mixed anhydride. Since then, Schwyzer et al.<sup>2)</sup> 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<sup>3)</sup> prepared the same *p*-nitrophenylesters by using dicyclohexylcarbodiimide as a coupling reagent.

In the present study, it was found that pnitrophenyl 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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<sup>2)</sup> R. Schwyzer, B. Iselin and P. Sieber, Helv. Chim. Acta, 40, 373 (1957).

<sup>3)</sup> M. Bodanszky and V. du Vigneaud, J. Am. Chem. Soc., 81, 5688, 6072 (1959).

Carboxylic acid	Reagent	Yield %	Melting point, °C		$[\alpha]_{D}, c 2 \text{ in DMF}$ (temp., °C)	
			Found	Cited	Found	Cited
CH₃COOH	<b>CF</b> <sub>3</sub> COOPNP	80	$78 \sim 80$	79~80 <sup>a</sup> )		
C <sub>6</sub> H <sub>5</sub> COOH	<b>CF</b> <sub>3</sub> COOPNP	90.5	143	142.5 <sup>b</sup> )		
Z-Gly-OH	<b>CF</b> <sub>3</sub> COOPNP	93	126~127.5	127.5~128.5°)		
Z-l-Pro-OH	CF <sub>3</sub> COOPNP	83.5	94~95.5	94~96 <sup>d</sup> )	-70.0(22)	$-68(20)^{d}$
Z-L-Phe-OH	CF <sub>3</sub> COOPNP	85.5	125~126	126~126.5 <sup>e</sup> )	-24.7(22)	$-24.7(25)^{e}$
$Z-L-Glu(NH_2)-OH$	<b>CF</b> <sup>3</sup> COOPNP	63.5	151~153	155~156d)	-24.0(21.5)	$-24(20)^{d}$
Z-Gly-Gly-OH	CF <sub>3</sub> COOPNP <sup>f</sup> )	89	160~162 <sup>g</sup> )			
Z-L-Phe-OH	CH <sub>2</sub> ClCOOPNPh)	37	124~126	126~126.5 <sup>e)</sup>	-24.7(20)	-24.7(25)e>
Z-l-Pro-OH	CCl <sub>3</sub> COOPNPh)	57	94~96	94~96 <sup>d</sup> )	-70.0(22)	$-68(20)^{d}$

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

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  $C_{18}H_{17}N_{3}O_{7}$ : 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 This product was used (m. p.  $37 \sim 39^{\circ}$ C). 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 $\sim$ 3 ml.) was treated with I (0.005 mol.) at room After about 10 min., water (20 temperature. 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 vields 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 esterexchange 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 Cterminal amino acid residues might occur to some extent during the reaction. The advantages of the new method over the Schwyzer method<sup>2)</sup> are as follows: 1) Since the reaction occurred within 10 min. at room temperature (with acylamino acids), such undesirable sidereactions 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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