[Chem. Pharm. Bull. 15(5) 593~595 (1967)]

UDC 542.951.3 : 547.27'18 : 547.568.1.04

71. Yuichi Kanaoka, Kazutaka Tanizawa, Eisuke Sato, Osamu Yonemitsu, and Yoshio Ban : Polyphosphate Ester as a Synthetic Agent. Ⅳ.*1 A Novel Preparation of Aryl Esters.*2

(*Faculty of Pharmaceutical Sciences, Hokkaido University**3)

Aryl esters are formed from various free carboxylic acids and phenols by means of polyphosphate ester (PPE) under mild conditions.

(Received September 8, 1966)

Aryl esters are not obtained by conventional process of esterification of carboxylic acid. Because of their relatively low nucleophilicity, phenols are usually not acylated with carboxylic acids under acidic catalysts.[1] Thus aryl esters have generally been prepared by acting certain activated derivatives of carboxylic acid such as acid halide or anhydride upon phenol.[2~4] Several condensation processes have also been developed in connection with the "active ester method" along with the recent advance in peptide synthesis.[5,6]

In our earlier works, it has been shown that polyphosphate ester (PPE) is an efficient agent for various condensation reactions.*1,[7a~e] In the course of the extensive study of the application of PPE, it was found that aryl esters are formed from free carboxylic acids and phenols with PPE as a condensing agent under mild conditions.

A solution of equimolar amounts of benzoic acid and phenol in chloroform was mixed with excess of PPE, and the mixture was refluxed for 30 min., or stood at room temperature for 24 hr. to afford phenyl benzoate (Ⅰ) in 83 or 90% yield, respectively. In a similar manner, *p*-nitrophenol, the most widely used component of "active ester," gave the benzoate (Ⅱ). Pentachlorophenol, which recently received attention in the synthesis of polypeptides with known repeating sequence,[8a,b] also formed the corresponding benzoate (Ⅲ) with PPE. As illustrations of thiophenol, thiophenyl (Ⅳ) and *p*-nitrothiophenyl benzoate (Ⅴ) were prepared by this method.

Likewise, acetic acid afforded corresponding phenyl (Ⅵ), *p*-nitrophenyl (Ⅶ), and pentachlorophenyl acetate (Ⅷ), thus demonstrating that this procedure is applicable to aliphatic carboxylic acid as well.

Experimental data are summarized in Table I, which include phenylacetic acid, and several benzoic acid derivatives carrying nitro or hydroxyl group as a substituent. These results prove that this procedure provides a general method for the preparation of aryl esters from various carboxylic acids and phenols.

---

*1 Part Ⅲ: Y. Kanaoka, M. Machida, O. Yonemitsu, Y. Ban: This Bulletin, **13**, 1065 (1965).

*2 Preliminary communication: Chem. & Ind. (London), **1964**, 2102.

*3 Kita-15, Nishi-7, Sapporo (金岡祐一, 谷沢和隆, 佐藤英助, 米光 宰, 伴 義雄).

1) D. P. N. Satchell: Quart. Rev., **17**, 175 (1963).

2) R. B. Wagner, H. D. Zook: "Synthetic Organic Chemistry," 481 (1953), J. Wiley & Sons, N. Y.

3) H. Henecka: "Houben-Weyl; Methoden der Organischen Chemie (E. Müller, ed.)," 8, 543 (1952), Georg Thiene V., Stuttgart.

4) P. H. Groggins: "Unit Processes in Organic Synthesis," 715; 717 (1958), McGraw-Hill, N. Y.

5) J. P. Greenstein, M. Winitz: "Chemistry of the Amino Acids," 1027 (1961), J. Wiley & Sons, N. Y.

6) N. F. Albertson: "Organic Reactions," **12**, 222 (1962), J. Wiley & Sons, N. Y.

7) Y. Kanaoka, *et al.*: *a*) This Bulletin, **12**, 773 (1964). *b*) Tetrahedron Letters, **1964**, 2417. *c*) Chem. & Ind. (London), **1965**, 473. *d*) This Bulletin, **14**, 934 (1966). *e*) *Ibid.*, **15**, 101 (1967).

8*a*) J. Kovacs, B. J. Johnson: J. Chem. Soc., **1965**, 6777. *b*) J. Kovacs, R. Giannotti, A. Kapoor: J. Am. Chem. Soc., **88**, 2282 (1966).

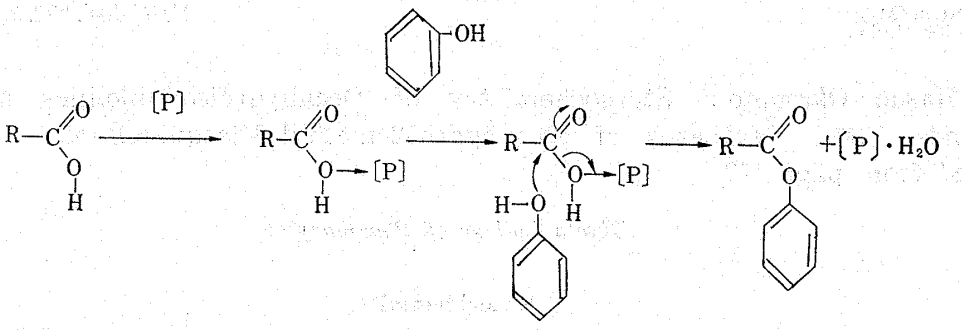
Table I. Preparation of Aryl Esters

Product		Yield (%) A	Yield (%) B	m.p. (°C)[a]		IR (C=O)[b] (cm^{-1})
Phenyl benzoate	I	83	90	70～71 (70)[9]	colorless needles (E)	1730
p-Nitrophenyl benzoate	II	78	65	140～142 (142)[10]	colorless powder (E)	1740
Pentachlorophenyl benzoate	III	88	—	156～157[c] (159)[11]	colorless needles (E)	1775
Thiophenyl benzoate	IV	91	80	56～57 (56)[12]	colorless powder (aq. isopropanol)	1670
p-Nitrothiophenyl benzoate	V	78	73	118～120 (126～127)[13]	pale yellow powder (E)	1675
Phenyl acetate	VI	80	81	b.p_5 50～53 (b.p_8 75～76)[14]	colorless oil	1770
p-Nitrophenyl acetate	VII	73	69	76～78 (81～82)[14]	pale yellow prisms (E)	1770
Pentachlorophenyl acetate	VIII	89	—	144～145 (150～151)[15]	colorless needles (E)	1780
p-Nitrophenyl phenylacetate	IX	78	81	62～63 (65～66)[16]	pale yellow fine needles (E)	1760
Phenyl *p*-nitrobenzoate	X	63	—	126～127 (129～130)[13]	pale yellow fine needles (E)	1740
p-Nitrophenyl *p*-nitrobenzoate	XI	46	—	154～157 (160～162)[13]	pale yellow needles (E)	1750
Phenyl *m*-nitrobenzoate	XII	49	—	95～96 (100)[17]	pale yellow prisms (E)	1740
Phenyl salicylate	XIII	63	—	40～42 (42.5)[18]	colorless prisms (aq. E)	1680
p-Nitrophenyl ester of N-phthaloyl-β-alanine	XIV	87	87	203～205	〃 (AcOEt)	1770, 1715
p-Nitrophenyl ester of N-benzoyl-β-alanine	XV	44	76	158～159	pale yellow leaflets (benzene)	1760, 1630
Pentachlorophenyl ester of N-phthaloyl-β-alanine	XVI	90	—	186～187	colorless needles (AcOEt)	1775
p-Nitrophenyl ester of N-phthaloyl-DL-alanine	XVII	64	16	128～129	colorless leaflets (E)	1770, 1720

a) Solvent of recrystallization: E, ethanol.
b) Nujol
c) Identical with the authentic specimen prepared from benzoic acid and pentachlorophenol by means of DCC.

The course of the reaction may presumably involve the activation of carboxylic group by PPE, which is considered to be a reagent of Lewis-acid type, followed by nucleophilic attack of phenol on carboxylic carbon atom as outlined in the equation, where [P] represents PPE. Detailed mechanism is, however, still uncertain since phenol is also capable of reacting with PPE using its active proton to form a possible activated intermediate.

9) J. Stenhouse: Ann., **53**, 91 (1845).
10) H. Hübner: *Ibid.*, **210**, 379 (1881).
11) S. A. Brazier, H. McCombie: J. Chem. Soc., **101**, 968 (1912).
12) H. Böhme, H. Schran: Chem. Ber., **82**, 453 (1949).
13) G. Cilento: J. Am. Chem. Soc., **75**, 3748 (1953).
14) A. Spassow: Ber., **75**, 779 (1942).
15) C. J. Pennino: J. Org. Chem., **20**, 530 (1955).
16) A. Fukura, T. Szell: Acta Univ. Szegediensis, Acta Phys. et Chem., **6**, 122 (1960); C. A., **55**, 14376[i] (1961).
17) G. S. Saharia, B. R. Sharma: J. Indian Chem. Soc., **33**, 788 (1956).
18) C. Graebe, A. Eichengrün: Ann., **269**, 324 (1892).



Nakazawa, *et al.* showed that polyphosphoric acid (PPA) can effect the Fries reaction of aryl esters under mild conditions. For example, when warmed with PPA for 15 min., phenyl benzoate (I) was readily converted to *p*-hydroxybenzophenone.[19] In contrast to this, the above results in this paper indicated that aryl esters are rather stable under PPE treatment. In order to confirm this distinction, I was refluxed in chloroform solution in the presence of PPE for 0.5~2 hr. and the ester was recovered unchanged in a good yield. Thus it may be concluded that no appreciable rearrangement takes place under the conditions of this preparation of aryl esters.

In view of usefulness of the active ester method in peptide chemistry, preparation of *p*-nitrophenyl or pentachlorophenyl ester of N-protected amino acid was examined. As listed in Table I, N-phthaloyl and N-benzoyl-β-alanine gave corresponding esters by the PPE method. However, attempted conversion of N-protected α-amino acid to aryl ester was in general fruitless though N-phthaloyl-DL-alanine, for example, gave *p*-nitrophenyl ester in a low yield.

Experimental*4

General Procedure for the Preparation of Aryl Esters——Finely powdered, equimolar amounts of carboxylic acid and phenol were mixed with the solution of PPE (15 equivalents; EtO_2P, taken as an equivalent) in $CHCl_3$ (50 w/w%), and the solution was refluxed for 30 min. (Procedure A) or stood at room temp. for 24 hr. (Procedure B). After the reaction, the mixture was evaporated *in vacuo* at room temp. and ice-water and powdered $NaHCO_3$ were added to the residue and then stirred to effect decomposition of the excess of PPE (ca. 0.5 hr.). The whole was extracted with $CHCl_3$ and the extract was washed with cold satd. aq. $NaHCO_3$, water, and dried (Na_2SO_4). Removal of the solvent left a crude aryl ester, which was purified by recrystallization or distillation as listed in Table I.

The Test for the Fries Rearrangement——A solution of phenyl benzoate (496 mg.) and PPE (2.5 g.) in $CHCl_3$ (10 ml.) was refluxed for 30 min. After cooling, solvent was evaporated *in vacuo* at room temp., and to this mixture ice-water was added followed by stirring for 3 hr. The whole was extracted with benzene, and the extract was washed with 5% NaOH, and then water, and dried (Na_2SO_4). Removal of the solvent *in vacuo* left colorless solid, which was recrystallized from *n*-hexane to give colorless prisms of m.p. 67~68° (435 mg. or 88%); identical with the starting material by mixed m.p. and IR comparison. The above alkaline extract was combined with water washings and the whole was acidified with 10% HCl and extracted with benzene. On removal of the solvent, no appreciable amount of *p*-hydroxybenzophenone was isolated. By prolonged heating (2 hr.), 83% of purified ester were recovered similarly.

***p*-Nitrophenyl Ester of N-Phthaloyl-β-alanine (XIV)**——*Anal.* Calcd. for $C_{17}H_{12}O_6N_2$ (XIV): C, 60.06; H, 3.55; N, 8.23. Found: C, 59.99; H, 3.44; N, 8.19.

***p*-Nitrophenyl Ester of N-Benzoyl-β-alanine (XV)**——*Anal.* Calcd. for $C_{16}H_{14}O_5N_2$ (XV): C, 61.14; H, 4.49; N, 8.91. Found: C, 61.34, H, 4.42, N, 9.22.

Pentachlorophenyl Ester of N-Phthaloyl-β-alanine (XVI)——*Anal.* Calcd. for $C_{17}H_8O_4NCl_5$ (XVI): C, 43.67; H, 1.72; N, 3.00. Found: C, 43.58; H, 1.74; N, 2.72.

***p*-Nitrophenyl Ester of N-Phthaloyl-DL-alanine (XVII)**——*Anal.* Calcd. for $C_{17}H_{12}O_6N_2$ (XVII): C, 60.06; H, 3.55; N, 8.23. Found: C, 59.81; H, 3.54; N, 7.99.

We are indebted to Mrs. T. Toma and Miss A. Maeda for elemental analysis. This work was supported in part by a grant from the Ministry of Education, which is gratefully acknowledged.

*4 All melting points are uncorrected.

19) K. Nakazawa, S. Matsuura: Yakugaku Zasshi, **74**, 69 (1954).