[Chem. Pharm. Bull. 22(2) 468—470 (1974)]

UDC 547.558.04

A Convenient Method for the Preparation of Alkyl Phenyl Phosphates[1]

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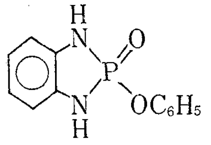
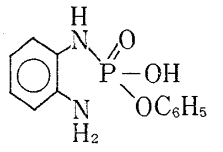
(Received July 26, 1973)

During the course of our study on the preparation and the reaction of 2-phenoxy-1,3-dihydro-2*H*-1,3,2-benzodiazaphosphole-2-oxide (I), we noticed that phenyl hydrogen N-(2-aminophenyl)phosphoramidate (II) reacts with methanol to give a crystalline *o*-phenylenediamine salt of methyl phenyl phosphate in a good yield and indicated that II might be useful as a phosphorylating reagent of alcohols.[3] This paper describes the results along this line and presents a convenient method for the preparation of alkyl phenyl phosphates.



I



II

Before the application to various alcohols, the reaction of II with ethanol has been undertaken by the following procedure. Ten millimoles of II was heated with 1 mole of ethanol under reflux for twenty-four hours. After the reaction excess ethanol was removed *in vacuo* and the residue was recrystallized from benzene to give colorless needles of *o*-phenylenediammonium ethyl phenyl phosphate (mp 109—110°) in 95% yield. The almost quantitative yield of the product again strongly suggested the use of II for the phosphorylation of alcohols. Although the mechanistic study might be an object of further investigations,[4] we are much interested in the scope and limitation of the reaction and explored the reaction with the representative alcohols.

As a general procedure, a mixture of 5—10 millimoles of phenyl hydrogen N-(2-aminophenyl)phosphoramidate II and 100 millimoles to 1 mole of a certain alcohol has been heated under reflux unless otherwise stated. After 24 hours, excess alcohol was evaporated *in vacuo* and the residue was recrystallized from benzene to give *o*-phenylenediamine salt of the corresponding alkyl phenyl phosphate. The results are summarized in Table I. As is clear from Table I, primary and secondary alcohols yield alkyl phenyl phosphate derivatives in good yields. In the case of tertiary butyl alcohol, however, the expected reaction was not observed and the starting materials were recovered unchanged. Accordingly, this method affords a good preparation of primary and secondary alkyl esters of phenyl phosphate starting from primary and secondary alcohols. It may be appropriate at this stage to compare the present method with those previously reported.[5,6] The yields obtained by the present method are comparable to and in some cases are better. Furthermore, the present method has several advantages over the previous methods. For example, Takaku and Shimada[6] recently introduced an elegant method for the preparation of alkyl phenyl phosphate by the reaction of phenyl 8-quinolyl phosphate with alcohols. However, the experimental problem with their

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[1] A part of this study was presented at the 93rd Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, April, 1973.

[2] Location: *Gofuku, Toyama.*

[3] T. Koizumi, Y. Arai, and E. Yoshii, *Chem. Pharm. Bull.* (Tokyo), **21**, 202 (1973).

[4] Following two mechanisms may be considered for the reaction. *a*) The protonation of the amide nitrogen and nucleophilic attack by alcohols on the electron deficient P atom. *b*) Unimolecular decomposition of II to give phenyl metaphosphate and the subsequent reaction with alcohols.

[5] W. Kampe, *Chem. Ber.*, **98**, 1038 (1965).

[6] H. Takaku and Y. Shimada, *Chem. Pharm. Bull.* (Tokyo), **21**, 445 (1973).

Table I. Reaction of Phenyl Hydrogen N-(2-Aminophenyl)phosphoramidate with Alcohols

Alcohol (R)	Reaction conditions		Product					
	Temp. (°C)	Time (hr)	Yield (%)[a]	mp (°C)	Formula	Analysis (%) Calcd. (Found)		
						C	H	N
CH_3[b]	66	24	82	155—157	$C_{13}H_{17}O_4N_2P$	52.75 (52.60)	5.79 (5.82)	9.46 (9.56)
C_2H_5	78	24	95	109—110	$C_{14}H_{19}O_4N_2P$	54.24 (54.07)	6.18 (6.08)	9.04 (8.87)
n-C_3H_7	97	24	82	132—133	$C_{15}H_{21}N_2O_4P$	55.60 (55.36)	6.53 (6.50)	8.65 (8.40)
iso-C_3H_7	83	24	70	128—130	$C_{15}H_{21}O_4N_2P$	55.60 (55.32)	6.53 (6.47)	8.65 (8.64)
n-C_4H_9	116	24	69	143—145	$C_{16}H_{23}O_4N_2P$	56.85 (56.61)	6.86 (7.11)	8.29 (8.39)
iso-C_4H_9	108	24	88	154—155	$C_{16}H_{23}O_4N_2P$	56.85 (56.63)	6.86 (6.84)	8.29 (8.02)
sec-C_4H_9[c]	99	24	74	180—182	$C_{16}H_{28}O_4NP$	58.41 (58.57)	8.58 (8.83)	4.25 (4.27)
tert-C_4H_9	83	120	0					
$C_6H_5CH_2$	80—90	24	64	155—156	$C_{19}H_{21}O_4N_2P$	61.34 (61.13)	5.69 (5.66)	7.53 (7.64)
CH_2=CH-CH_2	97	4.5	61	101—102	$C_{15}H_{19}O_4N_2P$ (+½H_2O)	54.43 (54.59)	6.09 (5.83)	8.46 (8.14)

a) The yield was calculated from phenyl hydrogen N-(2-aminophenyl)phosphoramidate-monohydrate employed.
b) literature 3
c) isolated as a cyclohexylammonium salt

method is that the phenyl 8-quinolyl phosphate is a viscous oily material, and should be purified by a column chromatography. Our compound, phenyl hydrogen N-(2-aminophenyl)-phosphoramidate II, is a crystalline compound which is easily prepared in a fair yield and is quite stable, practically unchanged for a long period of time without any protection from moisture. These advantages together with good yield of products and the simple work-up procedure to give crystalline products make the present method as a convenient way of preparing alkyl phenyl phosphates. The application to complex alcohols is now being investigated.

Experimental

Material——Phenyl hydrogen N-(2-aminophenyl)phosphoramidate-monohydrate II was prepared by the reaction of *o*-phenylenediamine with phenyl phosphorodichloridate and working up according to the procedure reported previously.[3] The monohydrate was employed without drying. Alcohols employed were purified by distillation.

Preparation of *o*-Phenylenediammonium Ethyl Phenyl Phosphate——Ten m moles of II were heated under reflux with 1 mole of ethanol for 24 hr. The excess EtOH was evaporated to dryness and the residue was recrystallized from benzene to give needles of mp 109—110° in 95% yield. *Anal.* Calcd. for $C_{14}H_{19}O_4N_2P$: C, 54.24; H, 6.18; N, 9.04. Found: C, 54.07; H, 6.08; N, 8.87. IR ν_{max}^{KBr} cm^{-1}: 3360, 3040, 2850, 2600, 1630, 1595, 1220, 1095, 1080, 1070.

General Procedure for the Reaction of II with Alcohols——II (10 m moles) was suspended in 100 m moles—1 mole of a certain alcohol and heated under reflux (or around 80°). After 24 hr, excess alcohol was evaporated *in vacuo* and the residue was recrystallized from benzene to give crystalline *o*-phenylenediammonium alkyl phenyl phosphate. When crystalline *o*-phenylenediammonium salt is not obtained easily, the crude product was dissolved in dilute HCl and the solvent was evaporated *in vacuo*. The residue was extracted with ether and to the ether solution was added cyclohexylamine to give cyclohexylammonium salt.

The results are summarized in Table I.

Product——The elemental analysis, mp, and the yield of the products are listed in Table I. The representative infrared (IR) bands and recrystallization solvent will be described below.

o-Phenylenediammonium *n*-Propyl Phenyl Phosphate——Obtained from *n*-PrOH according to the general procedure as needles of mp 132—133° (from benzene). IR ν_{max}^{KBr} cm^{-1}: 3440, 3200, 3100—2400, 1625, 1570, 1220, 1100, 1050.

o-Phenylenediammonium Isopropyl Phenyl Phosphate——Obtained as needles of mp 128—130° (from benzene). IR ν_{max}^{KBr} cm^{-1}: 3360, 3240, 2850, 2600, 1633, 1595, 1220, 1070, 1050.

o-Phenylenediammonium *n*-Butyl Phenyl Phosphate——Obtained as needles of mp 143—145° (from benzene). IR ν_{max}^{KBr} cm^{-1}: 3350, 3200, 2850, 2600, 1620, 1595, 1210, 1190, 1070.

o-Phenylenediammonium Isobutyl Phenyl Phosphate——Obtained as needles of mp 154—155° (from benzene). IR ν_{max}^{KBr} cm^{-1}: 3440, 3240, 2960, 2600 (shoulder), 1210, 1100, 1050.

Monocyclohexylammonium *sec*-Butyl Phenyl Phosphate——Obtained from *sec*-BuOH as needles of mp 180—182° (from benzene-acetone). IR ν_{max}^{KBr} cm^{-1}: 2920, 2600 (sh), 1630—1590, 1220, 1130—1010.

o-Phenylenediammonium Allyl Phenyl Phosphate——Obtained as needles of mp 101—102° (from benzene). IR ν_{max}^{KBr} cm^{-1}: 3380, 3240, 2880, 2600, 1635, 1590, 1220, 1195, 1080, 1045.

o-Phenylenediammonium Benzyl Phenyl Phosphate——Obtained as needles of mp 155—156° (from benzene). IR ν_{max}^{KBr} cm^{-1}: 3400, 2880, 2600, 1630, 1600, 1570, 1230, 1080, 1060.

Acknowledgement This work was supported in part by a Grant-in-Aid from the Ministry of Education, which is gratefully acknowledged. Thanks are due to Mr. M. Morikoshi and Mr. H. Hori of this faculty for measurement of NMR and elemental analyses.