Phosphorylation *via* Oxidation of Phosphites. I. Preparation of Dialkyl Phosphites by the Reaction of Alcohols with Ethyl N-Phenylimino Phosphite and Benzaldehyde

Oyo Mitsunobu and Teruaki Mukaiyama

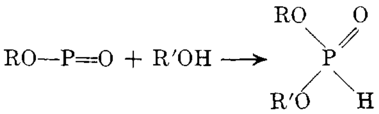
Laboratory of Organic Chemistry, Tokyo Institute of Technology, Ookayama, Meguro-ku, Tokyo, Japan

Received February 7, 1964

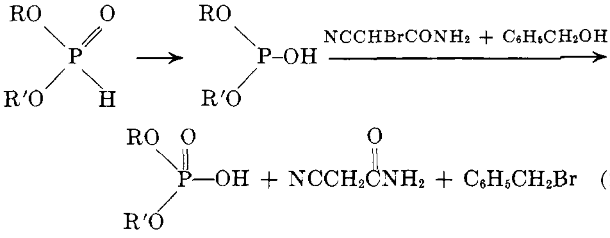
Dialkyl phosphites were prepared in good yields by the reaction of alcohols with 2 moles of ethyl N-phenylimino phosphite and 1 mole of benzaldehyde. The mechanism of their formation is also discussed.

A considerable number of phosphorylation methods have been investigated and successfully applied to the synthesis of various naturally occurring phosphates. When monoesters of phosphoric acid are employed, the phosphorylation reaction is generally believed to proceed through initial formation of metaphosphate ($RO-PO_2$) which in turn reacts with alcohols or phosphates to give the corresponding diesters of phosphoric acid or pyrophosphates.[1]

In a similar manner, metaphosphites ($RO-P{=}O$) would be expected to react with alcohols to give diesters of phosphorous acid (eq. 1). The diesters of phosphorous acid have recently been found to be oxidized under mild conditions to diesters of phosphoric acid by such reagents as monobromocyanoacetamide and benzyl alcohol[2] (eq. 2), or nitrogen oxide.[3]



(1)

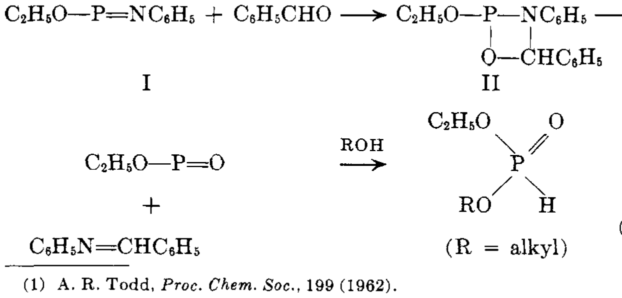


(2)

(R, R′ = alkyl)

Thus, as demonstrated by Todd and co-workers,[4-6] this kind of phosphorylation method, namely, preparation of phosphites and subsequent oxidation to phosphates, offers one route of phosphate synthesis.

The present study was made with a view to producing diesters of phosphorous acid *via* a metaphosphite intermediate under the assumption that the intermediate might be generated by reacting ethyl N-phenylimino phosphite with benzaldehyde, in a manner analogous to the Wittig reaction (shown in eq. 3).



(3)

(R = alkyl)

Ethyl N-phenylimino phosphite (I) was prepared from 1 mole of ethyl phosphorodichloridite and 3 moles of aniline in 50% yield.

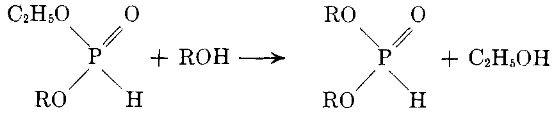
When I was treated with an equimolar amount of benzaldehyde in the presence of a small excess of ethanol in toluene at 100° for 4 hr., a 47% yield of diethyl phosphite and a 45% yield of benzylideneaniline were obtained. Diethyl phosphite was identified by paper chromatography.

When 1 mole of I was reacted with 2 moles of benzaldehyde in the presence of *n*-butyl alcohol, a 48% yield of ethyl *n*-butyl phosphite and a 49% yield of benzylideneaniline were obtained by fractionation, and 47% of the benzaldehyde was recovered.

In both cases, about 40% of I was recovered and the yield of diethyl phosphite showed practically no fluctuations even when the reaction time was prolonged to 7 hr.

On the other hand, when 2 moles of I was treated with 1 mole of benzaldehyde in the presence of a small excess of ethanol, the yield of diethyl phosphite and benzylideneaniline increased to 75 and 66%, respectively, but 59% of I was still recovered unchanged.

In a similar fashion, when 1.5 mole of *n*-butyl alcohol was treated with 2 moles of I and 1 mole of benzaldehyde, ethyl *n*-butyl phosphite (70%), a small amount of di-*n*-butyl phosphite, and benzylideneaniline (68%) were obtained. Similarly, the reaction of *n*-propyl alcohol with 2 moles of I and benzaldehyde gave an 82% yield of ethyl *n*-propyl phosphite which was contaminated with two symmetrical dialkyl phosphites, diethyl and di-*n*-propyl phosphite. The formation of these symmetrical dialkyl phosphites is probably due to an exchange reaction of the resulting unsymmetrical dialkyl phosphite in the presence of an alcohol (eq. 4). The results are summarized in Table I.



(4)

In continuing the investigation, an attempt was made to confirm the existence of metaphosphite. Unexpectedly, when a toluene solution of equimolar amounts of I and benzaldehyde in the absence of an alcohol was refluxed for 6 hr., starting materials I and benzaldehyde were recovered in yields of 77 and 57%, respectively, and no benzylideneaniline could be obtained.

These results suggest that the following mechanism is preferable to the metaphosphite intermediate reaction

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[1] A. R. Todd, *Proc. Chem. Soc.*, 199 (1962).

[2] This has been submitted for publication.

[3] D. Samuel and D. B. Silver, *J. Org. Chem.*, **28**, 2089 (1963).

[4] N. S. Corby, G. W. Kenner, and A. R. Todd, *J. Chem. Soc.*, 3669 (1952).

[5] G. W. Kenner, A. R. Todd, and F. J. Weymouth, *ibid.*, 3675 (1952).

[6] D. M. Brown and P. R. Hammond, *ibid.*, 4229 (1960).

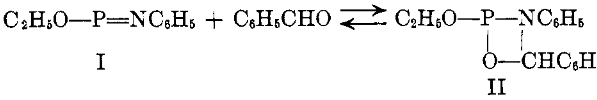
TABLE I

REACTION OF ETHYL N-PHENYLIMINO PHOSPHITE AND BENZALDEHYDE IN THE PRESENCE OR ABSENCE OF ALCOHOLS

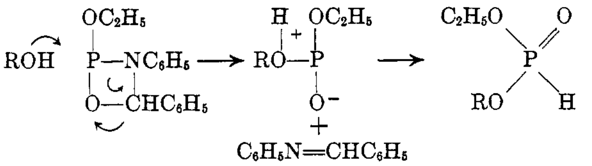
Alcohol	Molar ratio	Reaction	Products					Recovered			
			$C_2H_5O(RO)P(O)H$			$C_6H_5CH{=}NC_6H_5$		$C_2H_5OP{=}NC_6H_5$		C_6H_5CHO	
R	I:C_6H_5CHO	time, hr.	R	%	B.p., °C. (mm.)	%	B.p., °C. (mm.)	%	B.p., °C. (mm.)	%	B.p., °C. (mm.)
Ethyl	1:1	4	C_2H_5	51	80–85 (21)	55	109–113 (0.15)	35	135–150 (0.18)		
Ethyl	1:1	7	C_2H_5	55	78–84 (22)	30	86 (0.014)	43	140–145 (0.018)		
n-Butyl	1:2	3	n-C_4H_9	48	78–89 (2.5)	49	90–94 (0.05)	41	130–147 (0.07)	47	76–86 (25)
Ethyl	2:1	5	C_2H_5	75	72–75 (13)	66	96–105 (0.1)	59	145–147 (0.1)		
n-Propyl	2:1	5	n-C_3H_7	82[a]	84–87 (13)	58	95–105 (0.1)	64	145–155 (0.1)		
n-Butyl	2:1	3	n-C_4H_9	70	90–95 (11)	68	98–105 (0.12)	63	145–155 (0.13)		
n-Amyl	2:1	3	n-C_5H_{11}	46	105–112 (12)	57	105–112 (0.6)	67	145–155 (0.55)		
Isopropyl	2:1	3	i-C_3H_7			28	99–109 (0.1)	77	134–143 (0.12)	68	58–63 (11)
None	1:1	6						77	134–136 (0.015)	57	55–57 (12)

[a] This fraction was contaminated with diethyl phosphite and di-*n*-propyl phosphite.

mechanism assumed earlier in this paper. The formation of II is considered to be reversible and II does not decompose into metaphosphite and benzylideneaniline. When an alcohol is present, II decomposes giving dialkyl phosphite and benzylideneaniline as shown in eq. 6.



$$\underset{\text{I}}{C_2H_5O{-}P{=}NC_6H_5} + C_6H_5CHO \rightleftarrows \underset{\text{II}}{C_2H_5O{-}\underset{O-CHC_6H_5}{P}{-}NC_6H_5} \quad (5)$$



(6)

This mechanism is, of course, purely speculative and the relation between the yield of dialkyl phosphite and the molar ratio of reacting species is still unexplained.

Finally, it is interesting to note that when a secondary alcohol, such as isopropyl alcohol, was used in the place of the primary alcohol in the above experiment, ethyl isopropyl phosphite could not be isolated but 68% of crude benzaldehyde and 77% of I were recovered. At the same time, a small amount of white crystalline solid (m.p. 180–182°) was obtained whose elemental analysis agreed with the formula of II.

Experimental

All melting points and boiling points are uncorrected.

Alcohols and solvents were purified and dried by ordinary procedures. Authentic diethyl phosphite,[7] ethyl *n*-butyl phosphite,[8] and di-*n*-butyl phosphite[8] were prepared by literature procedures. Ethyl *n*-propyl phosphite was prepared by a method analogous to that reported by Kosolapoff.[8]

Preparation of Ethyl N-Phenylimino Phosphite.—A solution of aniline (186 g., 2 moles) in 200 ml. of benzene was added dropwise for a period of 1.5 hr. to a solution of ethyl phosphorodichloridite (98 g., 0.67 mole) in 600 ml. of benzene cooled in a water bath under vigorous stirring. Stirring was continued for 1.5 hr. and the mixture was refluxed for an additional 20 min. After storage of the mixture overnight at room temperature, aniline hydrochloride was removed by filtration and the solvent was removed from the filtrate under reduced pressure. The residue was cooled in a Dry Ice box. Then a small amount of white precipitate was removed and the viscous filtrate was distilled giving 56 g. (50%) of ethyl N-phenylimino phosphite, b.p. 164–175° (0.35 mm.). Redistillation gave 50 g. of pure sample, b.p. 145–147° (0.08 mm.).

Anal. Calcd. for $C_8H_{10}NOP$: N, 8.38. Found: N, 8.23.

Reaction of Ethanol with Ethyl N-Phenylimino Phosphite (I) and Benzaldehyde.—A solution of ethanol (1 ml.) in 5 ml. of toluene was added dropwise to a solution of I (1.67 g., 0.01 mole) and benzaldehyde (1.06 g., 0.01 mole) in 5 ml. of toluene heated at 100°. Heating was continued at 100° for 4 hr. After the solvent had been removed under reduced pressure, the residue was distilled giving crude diethyl phosphite (0.71 g., 51%, b.p. 80–85° at 21 mm.), benzylideneaniline (0.81 g., 45%, b.p. 109–113° at 0.15 mm., m.p. and m.m.p. 45–48°), and 0.59 g. (35%) of recovered I, b.p. 135–150° (0.18 mm.). Diethyl phosphite was shown to be identical with the authentic sample by comparison of gas chromatographic retention times, infrared spectra, and R_f values (0.67, solvent system *n*-propyl alcohol–concentrated NH_4OH-H_2O, 6:3:1).

Reaction of *n*-Butyl Alcohol with Ethyl N-Phenylimino Phosphite (I) and Benzaldehyde.—A solution of *n*-butyl alcohol (1.10 g., 0.015 mole) in 3 ml. of toluene was added dropwise to a solution of I (3.34 g., 0.02 mole) and benzaldehyde (1.06 g., 0.01 mole) in 7 ml. of refluxing toluene. The solution was refluxed for 3 hr. After removal of the solvent, ethyl *n*-butylphosphite (1.17 g., 70%, b.p. 90–95° at 11 mm., lit.[8] 99–100° at 13 mm.), di-*n*-butyl phosphite (0.17 g., b.p. 103–110° at 11 mm., lit.[8] 110–115° at 11 mm.), and benzylideneaniline (1.23 g., 68%, b.p. 98–105° at 0.12 mm.) were obtained and 2.10 g. (63%) of I (b.p. 145–155 at 0.13 mm.) was recovered.

Similarly, diethyl phosphite, ethyl *n*-propyl phosphite, or ethyl *n*-amyl phosphite was prepared by the reaction of ethanol, *n*-propyl alcohol, or *n*-amyl alcohol with benzaldehyde and 2 moles of I. The phosphites were identical with authentic samples by comparison of gas chromatographic retention times and/or infrared absorption spectra. The results are shown in Table I.

Reaction of Isopropyl Alcohol with Ethyl N-Phenylimino Phosphite (I) and Benzaldehyde.—One gram of isopropyl alcohol was treated with 1.10 g. (0.01 mole) of benzaldehyde and 3.34 g. (0.02 mole) of I as described above. After removal of the solvent, the residue was kept standing for 1 hr. and the white precipitate was filtered (0.15 g., m.p. 170–176°; after recrystallization from ethyl acetate, the melting point rose to 180–182°).

Anal. Calcd. for $C_{15}H_{16}NO_2P$: N, 5.12. Found: N, 5.11.

From the filtrate, 0.56 g. (28%) of benzylideneaniline was obtained but 0.75 g. (68%) of benzaldehyde (b.p. 58–63° at 11 mm.) and 2.56 g. (77%) of I (b.p. 135–143° at 0.12 mm.) were recovered. The benzaldehyde fraction was contaminated with a phosphite as indicated by the infrared spectrum (P–H, 2400 cm.$^{-1}$; P=O, 1260 cm.$^{-1}$).

Acknowledgment.—The authors wish to express their hearty thanks to Miss Toshiko Aoyagi for her microanalyses.

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[7] H. McCombie, B. C. Saunders, and G. J. Stacey, *J. Chem. Soc.*, 380 (1945).

[8] G. M. Kosolapoff, *J. Am. Chem. Soc.*, **73**, 4989 (1951).