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Synthesis of Phosphonic Acids from Alcohols via Sulfonate Esters[1,2]

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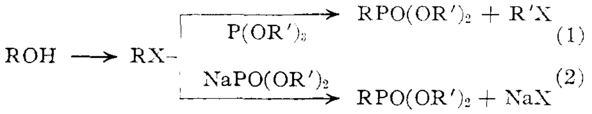
Treatment of a *p*-toluenesulfonic or methanesulfonic acid ester of a primary or secondary alcohol with sodium diethyl phosphite in tetrahydrofuran or dioxane solution effects smooth displacement of the sulfonate group with the formation of the corresponding diethyl alkylphosphonate. This reaction provides a convenient route for the conversion of alcohols into phosphonic acids. When heated with a catalytic amount of ethyl *p*-toluenesulfonate, triethyl phosphite is converted into diethyl ethylphosphonate.

In connection with studies of phosphonate analogs of biologically important phosphate compounds, the need developed for a synthetic method by which a hydroxyl group of an organic compound could be replaced by a phosphonic acid group under mild conditions. The only general procedures[3] heretofore available for the synthesis of phosphonic acids from alcohols require conversion of the alcohol to the corresponding alkyl halide, with subsequent displacement of the halogen by treatment either with a trialkyl phosphite at elevated temperature (equation 1) or with the sodium salt of a dialkyl phosphite (equation 2). This paper describes the direct replacement of the carbon–oxygen bond by a carbon–phosphorus bond by treatment of the *p*-toluenesulfonic or methanesulfonic acid ester of the alcohol with sodium diethyl phosphite. Acid hydrolysis of the resulting phosphonate ester yields the free phosphonic acid.



$$\mathrm{ROH} \longrightarrow \mathrm{RX}\begin{cases} \xrightarrow[\mathrm{P(OR')_3}]{} \mathrm{RPO(OR')_2} + \mathrm{R'X} & (1) \\ \xrightarrow{\mathrm{NaPO(OR')_2}} \mathrm{RPO(OR')_2} + \mathrm{NaX} & (2) \end{cases}$$

The experimental conditions for the facile conversion of simple alcohols to their sulfonate esters are well established.[4] When an alkyl *p*-toluenesulfonate (tosylate) is treated with sodium diethyl phosphite in tetrahydrofuran or dioxane solution,[5] the sodium salt of *p*-toluenesulfonic acid gradually precipitates leaving in solution the diethyl ester of the corresponding phosphonic acid (equation 3).

$$\mathrm{ROTs} + \mathrm{NaPO(OEt)_2} \longrightarrow \mathrm{RPO(OEt)_2} + \mathrm{NaOTs} \quad (3)$$
$$\mathrm{Ts} = \mathrm{CH_3C_6H_4SO_2}$$

With esters of primary alcohols, such as ethyl or butyl tosylates, the reaction occurs smoothly at room temperature although gentle warming is desirable to insure completion of the reaction. Methanesulfonic esters (*e.g.*, *n*-butyl mesylate) react similarly with sodium diethyl phosphite except that gentle warming is required. Under these conditions the yield of phosphonate is excellent.

Tosylate esters of secondary alcohols (*e.g.*, isopropyl tosylate) react satisfactorily with sodium diethyl phosphite but the yield of phosphonate is not as high as that obtained with primary tosylates. Cyclohexyl tosylate reacts only slowly with sodium diethyl phosphite in boiling tetrahydrofuran (65°). Reaction takes place at 85° in dioxane, but under these conditions the yield of diethyl cyclohexylphosphonate is rather low due to the competing elimination reaction to form cyclohexene. This behavior of cyclohexyl tosylate is in agreement with the known low reactivity of cyclohexyl halides[6] in displacement reactions of the S$_N$2 type.

Sodium diethyl phosphite reacts with phenyl tosylate at 90° and with *p*-nitrophenyl tosylate at room temperature. However, the reaction with these aromatic compounds appears to take a course different from that of equation 3, and its exact nature is being investigated.

When heated with trialkyl phosphites, alkyl tosylates undergo a reaction (equation 4) similar to the so-called Michaelis–Arbuzov reaction observed with alkyl halides (equation 1). In analogy with the well-characterized reaction of trialkyl phosphites with alkyl halides,[3,7] the reaction with an alkyl tosylate probably involves the intermediate formation of the quaternary phosphonium tosylate which then eliminates a molecule of alkyl tosylate to yield the phosphonate ester.

$$\mathrm{ROTs} + \mathrm{P(OR')_3} \longrightarrow \mathrm{RP(OR')_3}^{+}\mathrm{OTs}^{-} \longrightarrow \mathrm{RPO(OR')_2} + \mathrm{R'OTs} \quad (4)$$

When R and R′ are identical, the over-all reaction constitutes a simple isomerization of the trialkyl phosphite; since it is regenerated, only a catalytic amount of the alkyl tosylate is required. Thus, on warming in the presence of a small amount of ethyl tosylate, triethyl phosphite is converted to diethyl ethylphosphonate in practically quantitative yield. When R and R′ are not identical the reaction is somewhat more complicated, and its application for synthesis is under investigation.

Experimental

Materials.—Diethyl phosphite, triethyl phosphite, ethyl tosylate and *n*-butyl tosylate, obtained from commercial sources,[8] were redistilled before use. The following sul-

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(3) G. M. Kosolapoff, "Organophosphorus Compounds," John Wiley and Sons, Inc., New York, N. Y., 1950, Chap. 7.

(4) (a) R. S. Tipson, *J. Org. Chem.*, **9**, 235 (1944); (b) R. S. Tipson, M. A. Clapp and L. H. Cretcher, *ibid.*, **12**, 133 (1947); (c) V. C. Sekera and C. S. Marvel, THIS JOURNAL, **55**, 345 (1933).

(5) Because of the high solubility of sodium diethyl phosphite and the insolubility of sodium *p*-toluenesulfonate in tetrahydrofuran or dioxane, these compounds are excellent media in which to carry out sodium diethyl phosphite reactions. Moreover, these solvents are superior to diethyl ether or aromatic hydrocarbons for the reaction of alkyl halides with sodium diethyl phosphite.

(6) J. B. Conant and R. E. Hussey, THIS JOURNAL, **47**, 476 (1925).

(7) W. Gerrard and W. J. Green, *J. Chem. Soc.*, 2550 (1951); A. N. Pudovik, *Doklady Akad. Nauk S. S. S. R.*, **84**, 519 (1952).

(8) The authors are grateful to the Virginia Carolina Co., and to the Monsanto Chemical Co., for generous samples of diethyl and triethyl phosphites.

fonates were prepared by reaction of the alcohol with a 10% excess of the sulfonyl chloride in pyridine solution

	Conditions Hr.	°C.	Yield, %	M.p. or b.p., °C.
Isopropyl tosylate[a]	2	25	76	18–20 from hexane-ether
Cyclohexyl tosylate[b]	24	25	50	43.5–44.50 from hexane
n-Butyl mesylate[c]	3	0	79	80 (0.8 mm.) n^{25}D 1.4250

[a] Reference 4b. [b] S. Winstein, E. Grunwald, R. E. Buckles and C. Hanson, THIS JOURNAL, **70**, 816 (1948). [c] Reference 4c.

Sodium diethyl phosphite was prepared by adding an equivalent amount of metallic sodium to a solution of diethyl phosphite in dry tetrahydrofuran; several hours was required for the dissolving of the sodium.

Diethyl *n*-Butylphosphonate from Butyl Tosylate.—To a stirred solution of *n*-butyl *p*-toluenesulfonate (24.7 g., 0.11 mole) in dry tetrahydrofuran (50 ml.) there was added 82 ml. (0.12 mole) of a 1.5 *M* solution of sodium diethyl phosphite in tetrahydrofuran. After stirring at room temperature for one-half hour a copious white precipitate began to separate. After six hours the reaction mixture was heated at reflux for several hours longer. It was then cooled, and the precipitated sodium *p*-toluenesulfonate (20 g., 0.10 mole) was removed by filtration. The filtrate was evaporated at reduced pressure and the residual oil distilled *in vacuo*. The yield of diethyl *n*-butylphosphonate was 17.3 g., 82% (b.p. 53–55° (0.1 mm.), n^{25}D 1.4213; reported[9] b.p. 74° (1 mm.), n^{17}D 1.4244).

A portion of the product was hydrolyzed by heating in concentrated hydrochloric acid to yield *n*-butylphosphonic acid which, after recrystallization from hexane, melted at 105.5–107° (reported[10] m.p. 105–106°).

Diethyl *n*-Butylphosphonate from Butyl Mesylate.—*n*-Butyl methanesulfonate (7.6 g., 0.05 mole) was treated with sodium diethyl phosphite (0.06 mole) in tetrahydrofuran (50 ml.) in a manner similar to that described above. In this case precipitation of sodium methanesulfonate did not occur within 20 hours at room temperature but took place within a few minutes after the mixture was heated to reflux. After six hours at reflux temperature, the mixture was cooled, and 50 ml. of hexane and 1 ml. of acetic acid were added; the precipitate was removed by centrifugation and washed with 1:1 hexane–tetrahydrofuran. The combined supernatant and washings were concentrated under reduced pressure, and the residual oil was distilled to yield diethyl *n*-butylphosphonate, 8.4 g., 87% (b.p. 60.5–61.5° (0.35 mm.), n^{25}D 1.4207).

Diethyl Ethylphosphonate.—Ethyl *p*-toluenesulfonate was allowed to react with sodium diethyl phosphite in tetrahydrofuran solution in a manner similar to that described for butyl tosylate except that an excess of sodium diethyl phosphite was not employed and the reaction mixture was not warmed above room temperature. Under these conditions the reaction did not proceed entirely to completion in 24 hours. Twenty-four per cent. of the ethyl tosylate was recovered unchanged, and the yield of diethyl ethylphosphonate was 54% of theory (b.p. 58–60° (2 mm.), n^{25}D 1.4142; reported[9] b.p. 62° (2 mm.), n^{18}D 1.4172).

Diethyl Isopropylphosphonate.—To a stirred solution of sodium diethyl phosphite (24.8 g., 0.1 mole) in tetrahydrofuran (55 ml.) there was added isopropyl *p*-toluenesulfonate (21.4 g., 0.1 mole) in tetrahydrofuran (40 ml.). A solid soon began to precipitate. Stirring was continued at room temperature for 24 hours and then at reflux temperature for 17 hours. An equal volume of pentane was added to the reaction mixture, and the sodium tosylate was removed by filtration. The filtrate was concentrated and the residual oil distilled *in vacuo* to yield diethyl isopropylphosphonate, 9.3 g., 51% (b.p. 45–47° (0.2 mm.), n^{25}D 1.4150).

Anal. Calcd. for $C_7H_{17}O_3P$: C, 46.65; H, 9.51; P, 17.19. Found: C, 46.40; H, 9.49; P, 17.06.

Hydrolysis with concentrated hydrochloric acid yielded isopropylphosphonic acid which, after recrystallization from carbon disulfide, melted at 71.5–73.5° (reported[10] m.p. 74–75°).

Diethyl Cyclohexylphosphonate.—The reaction of cyclohexyl *p*-toluenesulfonate with sodium diethyl phosphite did not take place at room temperature, nor was precipitation of sodium *p*-toluenesulfonate complete after 7 days in boiling tetrahydrofuran. When a mixture of cyclohexyl tosylate (25.4 g., 0.10 mole) and sodium diethyl phosphite (0.11 mole) in an approximately equal mixture of tetrahydrofuran and dioxane was heated to 80–90°, sodium *p*-toluenesulfonate began to separate within one-half hour. After 48 hours at this temperature the reaction mixture was cooled, and the precipitate (19.8 g., theory 19.4 g.) was removed by filtration. The solvent was distilled from the filtrate; this contained considerable cyclohexene as indicated by its reaction with bromine. Distillation of the residue yielded crude diethyl cyclohexylphosphonate (7.6 g., 35%) which boiled over the range of 50 to 90° (0.1 mm.); some solid residue remained. By refluxing with concentrated hydrochloric acid, the crude ester was converted directly into cyclohexylphosphonic acid, which, after two recrystallizations from water, melted at 165–166° (reported[11] m.p. 166–167°).

Reaction of Triethyl Phosphite with Ethyl Tosylate.—Triethyl phosphite (16.6 g., 0.10 mole) and ethyl *p*-toluenesulfonate (5.0 g., 0.025 mole) were mixed and heated to 150° for two hours, and then the mixture was allowed to remain overnight at 120°. Distillation of the reaction mixture at reduced pressure yielded diethyl ethylphosphonate, 15.8 g., 95% (b.p. 52–54° (1.5 mm.), n^{25}D 1.4138; reported[9] b.p. 62° (2 mm.), n^{18}D 1.4172). This material, unlike triethyl phosphite, did not decolorize neutral potassium permanganate in aqueous acetone.

A portion of the product was hydrolyzed by heating in concentrated hydrochloric acid to yield ethylphosphonic acid, m.p. 51–54°. Two recrystallizations from carbon disulfide raised the melting point to 58–60° (reported[12] m.p. 61–62°).

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[9] A. H. Ford-Moore and J. H. Williams, *J. Chem. Soc.*, 1465 (1947).

[10] P. C. Crofts and G. M. Kosolapoff, THIS JOURNAL, **75**, 3379 (1953).

[11] J. C. Clayton and W. L. Jensen, THIS JOURNAL, **70**, 3880 (1948).

[12] G. M. Kosolapoff, *ibid.*, **67**, 1180 (1945).