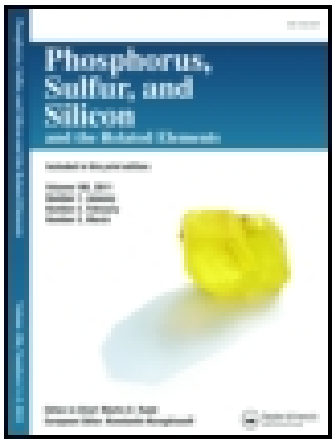

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SYNTHESIS OF ALKYL- AND ARYLPHOSPHONIC ACID MONOESTERS BY DIRECT ESTERIFICATION OF DIBASIC PHOSPHONIC ACIDS IN THE PRESENCE OF AN ARSONIC ACID CATALYST

Michael D. Crenshaw [a]

[a] Battelle Memorial Institute , Columbus, Ohio, USA

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SYNTHESIS OF ALKYL- AND ARYLPHOSPHONIC ACID MONOESTERS BY DIRECT ESTERIFICATION OF DIBASIC PHOSPHONIC ACIDS IN THE PRESENCE OF AN ARSONIC ACID CATALYST

Michael D. Crenshaw
Battelle Memorial Institute, Columbus, Ohio, USA

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Partial hydrolysis of a diester, hydrolysis of the monochloro monoester, or alcoholysis of a phosphonic acid anhydride generally is used to prepare monoesters of alkyl- and arylphosphonic acids. Limited cases have been reported for the esterification of a dibasic phosphonic acid to yield the monoester, and none of these methods are as simple as the analogous method for preparing carboxylic acid esters, in which the carboxylic acid is esterified with an alcohol in the presence of an acid catalyst. Described is a method for preparing monoesters of alkyl- and arylphosphonic acids by direct esterification with an alcohol in the presence of a catalytic amount of phenylarsonic acid. The water formed during the reaction is removed azeotropically. For example, methylphosphonic acid was esterified in good yield to give its isopropyl, butyl, cyclohexyl, bornyl, and octadecyl monoesters. Similarly prepared are the ethyl, butyl, hexyl, and 2-(ethylthio)ethyl monoesters of phenylphosphonic acid, as well as 2-isopropoxyethyl hydrogen ethylphosphonate and 2-methoxyethyl hydrogen benzylphosphonate.

Keywords: Alkylphosphonic acid monoester; arylphosphonic acid monoester; catalysis; esterification; phenylarsonic acid

INTRODUCTION

Monoesters of alkyl- and arylphosphonic acids are generally prepared by partial hydrolysis of a diester,[1–4] hydrolysis of the monochloro monoester,[5,6] or alcoholysis of a phosphonic acid anhydride or dioxophosphorane.[7–10] In 1999, Pienaar et al. found the alcoholysis of the anhydride preferable to alkaline hydrolysis for the preparation

NMR spectra were acquired by Sue Harsh. Exact mass measurements were obtained by Edwin Quinones and Dr. Aaron Frank.

Address correspondence to Michael D. Crenshaw, Battelle Memorial Institute, 505 King Avenue, Columbus, OH 43201, USA. E-mail: crenshaw@battelle.org

of monoalkyl esters of alkylphosphonic acids.[11] Other, less-often used methods include the thermolysis or photolysis of phosphonyl peroxides,[12,13] oxidation of a phosphonite with chlorine or nitrogen dioxide,[14,15] and alcoholysis of a tetrachlorophosphorane.[16]

More recently, additional methods have been developed. Cleavage of alkylphosphonate diesters with NaI in acetone or 2-butanone yields the monoesters,[17] while methylphosphonic acid monoesters have been prepared by methanolysis of the alkyl trimethylsilyl diester.[18]

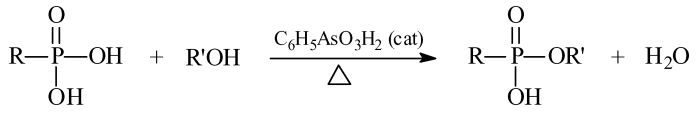
Three methods have been reported in which the monoester was derived directly from the dibasic phosphonic acid. These three are the reaction of a phosphonic acid with one-half molar equivalent of carbodiimide followed by addition of alcohol,[19] reaction of the phosphonic acid with trichloroacetonitrile and ethanol,[20] and *O*-alkylation of a phosphonic acid bis(tetramethylammonium) salt.[21] However, none of these methods for preparing the monoesters of phosphonic acids are as simple as the analogous method for preparing carboxylic acid esters, in which the acid is esterified with an alcohol in the presence of an acid catalyst.

RESULTS AND DISCUSSION

Reported here is a simple preparative method, analogous to the Fischer esterification reaction, for the direct monoesterification of alkyl- and arylphosphonic acids with alcohols. This reaction is performed in the presence of an arsenic catalyst, phenylarsonic acid at 3 mol%, while azeotropically removing the water formed. In the absence of the arsonic acid catalyst, or when it is substituted by *p*-toluenesulfonic acid, no esterification occurs. As listed in Table I, the monoesters of both alkylphosphonic and arylphosphonic acids were prepared in good-to-excellent yield in this manner. This method was demonstrated to be successful for the formation of the monoesters from both primary and secondary alcohols, although the yields were greater with primary alcohols. Excess alcohol was required to obtain good yields when the boiling point of the alcohol was less than that of the solvent. The higher-boiling solvents, toluene and tetrachloroethylene, were found to give yields of the monoesters superior to those from the lower-boiling solvents, trichloroethylene and nitromethane.

Samples of isopropyl hydrogen methylphosphonate (**1**), butyl hydrogen methylphosphonate (**2**), and cyclohexyl hydrogen methylphosphonate (**4**) prepared as described here were found to be identical to authentic samples prepared by the method of Petrov et al.[7] ^{1}H- and ^{31}P-NMR (nuclear magnetic resonance) spectra for **1**,[1,11,18] **2**,[1,18] **4**,[1,10,11,18] **7**,[5] and **8**[13,22] agree well with those reported.

TABLE I Reaction Conditions for the Preparation of Phosphonic Acid Monoesters

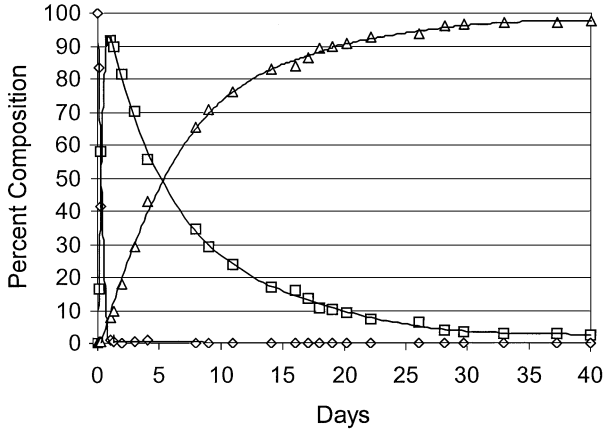


No.	R	R'OH	Equiv. R'OH	Solvent	Duration (h)	Yield[a] (%)
1	Me	Isopropanol	6.0	C_2Cl_4	76	64
			3.0	Toluene	76	26
			1.6	Toluene	28	18
2	Me	Butanol	1.5	Toluene	28	90
			1.5	C_2HCl_3	28	50[b]
3	Me	Octadecanol	1.1	Toluene	28	86
4	Me	Cyclohexanol	1.2	Toluene	28	39
5	Me	[(1 *S*)-endo]-(-)-Borneol	1.1	Toluene	97	59
6	Et	2-Isopropoxyethanol	1.2	Toluene	28	87
7	Ph	Ethanol	6.1	C_2Cl_4	76	89
8	Ph	Butanol	1.5	Toluene	28	98
			1.5	C_2Cl_4	28	96
			1.5	C_2HCl_3	28	63[b]
			1.5	CH_3NO_2	28	58[b]
9	Ph	Hexanol	1.2	Toluene	28	98
10	Ph	2-(Ethylthio)ethanol	1.3	Toluene	19	76
11	$PhCH_2$	2-Methoxyethanol	1.2	Toluene	28	74

[a]Isolated and purified yields unless stated otherwise.
[b]Yields based on ^{31}P-NMR analysis in D_2O.

To determine the extent that the diester could be produced under these conditions, phenylphosphonic acid was reacted with 3.2 equivalents of butanol and 3% arsenic catalyst (As_2O_5) in toluene. The reaction was monitored, and the relative proportions of phenylphosphonic acid, butyl hydrogen phenylphosphonate, and dibutyl phenylphosphonate were determined. Figure 1 shows the results from analysis of this reaction. Phenylphosphonic acid is quickly consumed, and butyl hydrogen phenylphosphonate is produced in greater than 90% in 24 h. Dibutyl phenylphosphonate is formed more slowly, and greater than 5 days are required for it to comprise more than 50% of the reaction mixture, and about 20 days are required for it to reach 90%.

At this time, the mechanism of this reaction is not known. Clearly, the arsonic acid is not acting as an acid catalyst. It seems likely that one of two mechanisms is involved. In the first, the arsonic acid is esterified with the alcohol, and then through transesterification the phosphonate ester is formed, leaving the arsonic acid to become esterified again. The



Phenylphosphonic acid (◊), butyl hydrogen phenylphosphonate (□), dibutyl phenylphosphonate (Δ)

FIGURE 1 Reaction composition from esterification of phenylphosphonic acid with butanol as function of time.

second mechanism involves the formation of the mixed phosphonic-arsonic anhydride, which then undergoes alcoholysis to yield the phosphonate ester and the arsonic acid. Investigations to determine the role of the arsonic acid in the mechanism of this esterification reaction are ongoing, as are studies to further the application of this reaction to other phosphorus acids and the preparation of their aryl esters.

EXPERIMENTAL

All chemicals were purchased from Sigma-Aldrich (Milwaukee, WI, USA), Pfaltz & Baur (Waterbury, CT, USA), or Lancaster Synthesis (Windham, NH, USA). NMR spectra were obtained using a Varian Gemini NMR spectrometer operating at 300 MHz for ^{1}H and 121.5 MHz for ^{31}P. ^{1}H-NMR are expressed in ppm relative to the internal standard, tetramethylsilane, and ^{31}P-NMR are expressed in ppm relative to the external standard, 85% H_3PO_4. ^{31}P-NMR spectra are decoupled with respect to protons. Prior to analysis by GC/MS, the monoesters were methylated with trimethylsilyldiazomethane in the presence of methanol to give the corresponding mixed alkyl methyl diester as described below. Mass spectra (+EI) were obtained using a Shimadzu QP-5000 GC/MS system. HRMS data was obtained from a VG 70S or a VG AutoSpec Ultima S170 magnetic sector instrument.

Procedure for the Preparation of Monoesters of Alkyl- or Arylphosphonic Acids

In 200 ml of solvent were mixed alkyl- or arylphosphonic acid (0.063 mol), phenylarsonic acid (3 mol%), and the selected alcohol (0.069 to 0.38 mol). The mixture was heated to reflux under an atmosphere of dry nitrogen and the water/solvent azeotrope collected in a Dean-Stark or similar receiver. After cooling, the solvent and any remaining volatile alcohol were removed using a rotary evaporator. With the exception of octadecyl methylphosphonic acid, the residue was mixed with water and the pH adjusted to 13–14 with 2.5N NaOH. The alkaline solution was then extracted with $CHCl_3$. Concentrated HCl was then added to the aqueous portion until the pH was 1. This acidic solution was extracted with $CHCl_3$. The combined $CHCl_3$ extracts were dried over Na_2SO_4, filtered, and the solvent removed using a rotary evaporator. Residual solvent was removed under high vacuum (1 mmHg). Oils were not further purified, while solids were recrystallized. Octadecyl methylphosphonic acid was purified by removing the reaction solvent and recrystallizing the residue. Purity of the products was found to be greater than 95% based on ^{1}H- and ^{31}P-NMR analyses. 2-(Ethylthio)ethyl phenylphosphonic acid was determined to be 92% pure initially but degraded to about 70% after six months of storage at 4°C.

Procedure for Preparing Methyl Esters of the Phosphonic Acids[23]

About 4 mg of phosphonic acid was dissolved in one milliliter of acetone and then 100 μL of this solution was added to 700 μL of benzene and 200 μL of methanol. Addition of 20 μL of a 2.0 M solution of trimethylsilyldiazomethane in THF (tetrahydrofuran) at ambient temperature completed the methylation.

Isopropyl Hydrogen Methylphosphonate (1)

^{1}H-NMR ($CDCl_3$) ppm: 1.33 (6H, d, $J = 6.2$ Hz), 1.48 (3H, d, $J = 17.9$ Hz), 4.66 (1H, dsept, $J = 8.3$, 6.2 Hz), 11.49 (1H, s); ^{31}P-NMR ($CDCl_3$) ppm: 33.07; MS (EI) of the methyl ester of **1** m/z 152 ($[M]^{+\cdot}$, absent), 137 (31.11), 111 (87.46), 93 (100.00), 79 (25.96).

Butyl Hydrogen Methylphosphonate (2)

^{1}H-NMR ($CDCl_3$) ppm: 0.94 (3H, t, $J = 7.3$ Hz), 1.41 (2H, m), 1.50 (3H, d, $J = 17.9$ Hz), 1.66 (2H, m), 4.01 (2H, dt, $J = 7.3$, 6.6 Hz), 11.94 (1H, s); ^{31}P-NMR ($CDCl_3$) ppm: 34.02; MS (EI) of the methyl ester of **2** m/z 166 ($[M]^{+\cdot}$, absent), 137 (6.26), 111 (100.00), 93 (72.95), 79 (17.27).

Octadecyl Hydrogen Methylphosphonate (3)

m.p., 71–73°C (isooctane); ^{1}H-NMR (C_6D_6) ppm: 0.92 (3H, t, J = 6.7 Hz), 1.18–1.38 (33H, m) overlapping 1.23 (d, J = 17.7 Hz), 1.54 (2H, m), 4.00 (2H, dt, J = 6.6, 7.3 Hz), 10.10 (1H, s); ^{31}P-NMR (C_6D_6) ppm: 34.64; MS (EI) of the methyl ester of **3** *m/z* 362 ($[M]^{+\cdot}$, absent), 111 (100.00), 93 (9.51), 57 (14.49), 55 (21.96), 43 (35.76).

Cyclohexyl Hydrogen Methylphosphonate (4)

m.p., 37–39°C (isooctane) [lit.[7] m.p., 45–48°C]; ^{1}H-NMR ($CDCl_3$) ppm: 1.31 (3H, m), 1.45–16.0 (6H, m) overlapping 1.49 (d, J = 17.9 Hz), 1.75 (2H, m), 1.94 (2H, m), 4.37 (1H, m), 11.38 (1H, s). ^{31}P-NMR ($CDCl_3$) ppm: 33.19; MS (EI) of the methyl ester of **4** *m/z* 192 ($[M]^{+\cdot}$, 0.03), 111 (100.00), 93 (41.27), 79 (13.63), 67 (21.31), 55 (17.34), 54 (22.73), 41 (37.66); HRMS: *m/z*: calc. for methyl ester of **4** ($C_8H_{17}O_3P$): 192.0915. Found: 192.0894.

Bornyl Hydrogen Methylphosphonate (5)

m.p., 132–133°C (isooctane) [lit.[24] m.p., 129–131°C]; ^{1}H-NMR ($CDCl_3$) ppm: 0.87 (6H, s, br), 0.88 (3H, s), 1.25 (3H, m), 1.49 (3H, d, J = 17.9 Hz), 1.66 (1H, m), 1.74 (1H, m), 1.95 (1H, m), 2.29 (1H, m), 4.55 (1H, m), 11.81 (1H, s); ^{31}P-NMR ($CDCl_3$) ppm: 34.10; MS (EI) of the methyl ester of **5** *m/z* 246 ($[M]^{+\cdot}$, absent), 137 (38.77), 136 (30.33), 121 (32.98), 111 (70.34), 95 (30.95), 93 (100.00), 79 (25.74).

2-(Isopropoxy)ethyl Hydrogen Ethylphosphonate (6)

^{1}H-NMR ($CDCl_3$) ppm: 1.17 (6H, d, J = 6.1 Hz), 1.18 (3H, dt, J = 20.4, 7.7 Hz), 1.79 (2H, dq, J = 18.7, 7.7 Hz), 3.63 (3H, m), 4.13 (2H, m), 11.36 (1H, s); ^{31}P-NMR ($CDCl_3$) ppm: 37.56; MS (EI) of the methyl ester of **6** *m/z* 210 ($[M]^{+\cdot}$, absent), 151 (35.16), 138 (31.29), 125 (85.84), 110 (79.86), 107 (50.59), 79 (61.28), 58 (45.75), 43 (100.00).

Ethyl Hydrogen Phenylphosphonate (7)

^{1}H-NMR ($CDCl_3$) ppm: 1.29 (3H, dt, J = 7.0, 0.5 Hz), 4.07 (2H, dq, J = 7.8, 7.0 Hz), 7.43 (2H, m), 7.53 (1H, m), 7.81 (2H, m), 12.18 (1H, s); ^{31}P-NMR ($CDCl_3$) ppm: 21.04; MS (EI) of the methyl ester of **7** *m/z* 200 ($[M]^{+\cdot}$, 20.50), 173 (19.44), 172 (39.77), 171 (31.79), 155 (41.53), 141 (46.98), 91 (77.51), 79 (27.31), 78 (79.58), 77 (100.00); HRMS: *m/z*: calc. for methyl ester of **7** ($C_9H_{13}O_3P$): 200.0602. Found: 200.0596.

Butyl Hydrogen Phenylphosphonate (8)

^{1}H-NMR ($CDCl_3$) ppm: 0.86 (3H, t, J = 7.3 Hz), 1.36 (2H, m), 1.61 (2H, m), 3.99 (2H, dt, J = 6.9, 6.7 Hz), 7.42 (2H, m), 7.51 (1H, m), 7.79 (2H, m), 11.66 (1H, s); ^{31}P-NMR ($CDCl_3$) ppm: 21.82; MS (EI) of the

methyl ester of **8** *m/z* 228 ($[M]^{+\cdot}$, 0.79), 173 (100.00), 155 (52.80), 141 (28.33), 91 (19.11), 78 (23.88), 77 (55.66); HRMS: *m/z*: calc. for methyl ester of **8** ($C_{11}H_{17}O_3P$): 228.0915. Found: 228.0905.

Hexyl Hydrogen Phenylphosphonate (9)

^{1}H-NMR ($CDCl_3$) ppm: 0.86 (3H, t, $J = 6.7$ Hz), 1.28 (6H, m), 1.64 (2H, m), 3.90 (2H, dt, $J = 7.0$, 6.7 Hz), 7.43 (2H, m), 7.53 (1H, m), 7.80 (2H, m), 12.22 (1H, s); ^{31}P-NMR ($CDCl_3$) ppm: 21.08; MS (EI) of the methyl ester of **9** *m/z* 256 ($[M]^{+\cdot}$, 0.80), 173 (100.00), 155 (42.50), 141 (25.61), 77 (42.48); HRMS: *m/z*: calc. for methyl ester of **9** ($C_{13}H_{21}O_3P$): 256.1228. Found: 256.1222.

2-(Ethylthio)ethyl Hydrogen Phenylphosphonate (10)

^{1}H-NMR ($CDCl_3$) ppm: 1.18 (3H, t, $J = 7.4$ Hz), 2.49 (2H, q, $J = 7.4$ Hz), 2.74 (2H, t, $J = 7.1$ Hz), 4.08 (2H, dt, $J = 7.9$, 7.1 Hz), 7.43 (2H, m), 7.52 (1H, m), 7.80 (2H, m), 11.96 (1H, s); ^{31}P-NMR ($CDCl_3$) ppm: 20.55; MS (EI) of the methyl ester of **10** *m/z* 260 ($[M]^{+\cdot}$, absent), 173 (58.65), 155 (17.14), 88 (83.25), 77 (36.98), 60 (100.00).

2-(Methoxy)ethyl Hydrogen Benzylphosphonate (11)

^{1}H-NMR ($CDCl_3$) ppm: 3.07 (2H, d, $J = 22.3$ Hz), 3.32 (3H, s), 3.45 (2H, m), 3.91 (2H, m), 7.26 (5H, m), 11.27 (1H, s); ^{31}P-NMR ($CDCl_3$) ppm: 30.20; MS (EI) of the methyl ester of **11** *m/z* 244 ($[M]^{+\cdot}$, 14.50), 187 (17.69), 186 (38.09), 153 (22.49), 109 (22.96), 104 (32.19), 91 (100.00), 65 (41.47); HRMS: *m/z*: calc. for methyl ester of **11** ($C_{11}H_{17}O_4P$): 244.0864. Found: 244.0853.

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