

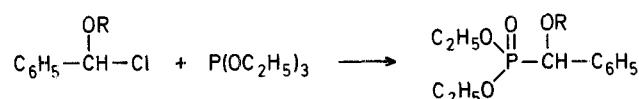
Novel Synthesis of 1-Alkoxy-1-arylmethanephosphonic Acid Esters*

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The demonstration of the synthetic utility of α -hetero-substituted methanephosphonate carbanions in the Wittig-Horner reaction has long been a subject of interest in our laboratory¹. Work in our laboratory utilizing this type of chemistry has resulted in practical synthetic routes to obtain enamines, amidines, substituted vinyl chlorides, acetylenes, diacetylenes, indoles, benzofurans, silyl enol ethers, deoxybenzoins, and quinolines. In continuation of our investigation into the use of this chemistry, a convenient synthesis for 1-alkoxy-1-arylmethanephosphonates or equivalent species was needed. Earlier attempts by us to prepare similar compounds were not satisfactory when the tetrahydropyranyl group was used as the hydroxy-protecting group^{1j} (however, see Ref.²). Thus, diphenyl 1-(2-tetrahydropyranoxy)-1-(4-nitrophenyl)-methanephosphonate was found to be rather unstable though it could be used in a Wittig-Horner type reaction with 4-nitrobenzaldehyde to give the expected 1,2-bis[4-nitrophenyl]-1-(2-tetrahydropyranoxy)-ethylene in excellent yield^{1j}. Attempts to use the trimethylsilyl group as a protecting group led to a rearrangement involving a 1,4-*O,O*-trimethylsilyl migration¹ⁱ.

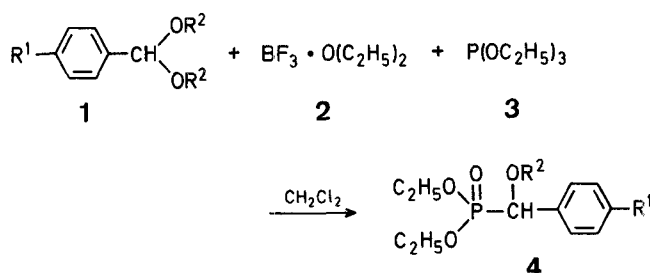
Though the synthesis and use of 1-alkoxymethanephosphonates is well documented^{2,3,4}, the preparation of 1-alkoxy-1-arylmethanephosphonates, first reported by Schaumann and Grabley^{2d}, proved to be more difficult and cumbersome. Their procedure called for the reaction of α -chlorobenzyl alkyl ether with triethyl phosphite in an Arbuzov reaction.



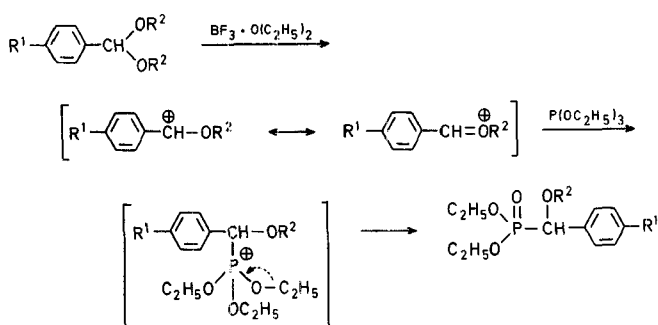
The synthesis of α -chlorobenzyl alkyl ether was accomplished by reacting the benzaldehyde dialkyl acetal with acetyl chloride.

The reaction of arylaldehyde diethyl acetals with triethyl phosphite in the presence of a Lewis acid seems to represent a general and rather convenient approach towards the synthesis of the desired 1-alkoxy-1-(substituted-aryl)-methanephosphonates. The successful preparation of α -amino-methanephosphonates by interaction of α -methoxyurethanes with trialkyl phosphites⁴ also was a good indication that the contemplated approach towards the synthesis of the desired compounds could be accomplished. The advantages of this approach are (1) to eliminate the preparation of the α -chlorobenzyl alkyl ether, an extra step, and (2) to avoid the rather harsh conditions which are required to drive the standard Arbuzov reaction to completion.

As expected, it was found that arylaldehyde diethyl acetals **1** ($\text{R}^2 = \text{C}_2\text{H}_5$) reacted with triethyl phosphite (**3**) in the presence of boron trifluoride diethyl etherate (**2**) cleanly to yield the desired diethyl 1-alkoxy-1-arylmethanephosphonates **4**. Compounds **4** were purified either by Kugelrohr distillation and/or column chromatography and characterized by exact mass determination and their ¹H-N.M.R.-spectra (Table).



Treatment of **1** with the boron trifluoride etherate presumably leads to formation of intermediate oxonium ions. In a subsequent nucleophilic reaction **3** reacts with these ions to yield **4**. The reaction proceeds satisfactorily with electron donating as well as electron withdrawing *para*-substituents on the aromatic moiety of **1**; also, whether the reaction is run with dimethyl or diethyl acetals seems to have little if any influence on the yields (see Table).



I.R. spectra were recorded on a Perkin-Elmer Model number 197 spectrophotometer. ¹H-N.M.R.-spectra were taken using a Varian EM-360A spectrometer. Mass spectral data were obtained from a Perkin-Elmer RMU-F Instrument and/or a Kratos MS80 instrument with a DS-55 data system. Microanalyses were performed by M-H-W Laboratories, Phoenix, Arizona.

All reactants were used as purchased from the Aldrich Chemical Company without any additional purification. All flash chromatography was conducted on silica gel 60 (230–400 mesh).

Arylaldehyde Dialkyl Acetals 1:

All acetals **1a–j** are synthesized in almost quantitative yield from the corresponding aldehyde, according to the method of Ref.⁶. The 10 min reflux period, however, is substituted with stirring for 18 h at ambient temperature. The mixture is then neutralized by stirring with anhydrous sodium carbonate for 5 min. Filtration and evaporation yields a residue which is taken up in anhydrous diethyl ether and gravity filtered. Evaporation produces a mobile oil whose ¹H-N.M.R. is consistent with the proposed structure. No further purification is required or performed.

Dialkyl 1-Alkoxy-1-arylmethanephosphonates 4:

The crude acetal **1** (32.9 mmol) and triethyl phosphite **3** (32.9 mmol) are dissolved in dichloromethane (60 ml) under an inert atmosphere and cooled to –20°C. Boron trifluoride etherate **2** (35.2 mmol) is then added dropwise. The resulting mixture is left to slowly return to ambient temperature over 18 h. The mixture is quenched by adding water (~5–10 ml) and stirring for 5 min. The organic layer is separated, dried with magnesium sulfate, and evaporated to leave a yellow oil. The oil, dissolved in a small amount of chloroform, is applied to a column of silica gel in chloroform. Any unreacted acetal, as the aldehyde, is eluted with chloroform. The desired phosphonate is eluted with 20% ethyl acetate/chloroform and is pure enough for analytical verification of its structure. Kugelrohr distillation produces a pure sample. Temperatures in excess of 140°C, however, result in decomposition.

Table. Dialkyl 1-Alkoxy-1-arylmethanephosphonates 4a-j

Product ^a No.	R ¹	R ²	Yield [%]	b.p. [°C]/torr ^b (Lit. value)	Molecular formula	¹ H-N.M.R. (CDCl ₃ /TMS) δ [ppm]	M.S. m/e (rel. intens. %)	H.R.M.S. m/e (M ⁺) [calc. for M ⁺]
4a	H	C ₂ H ₅	73	138–140°/0.8 (108–110°/0.2) ^{3d}	C ₁₃ H ₂₁ O ₄ P (272.3)	1.25 (t, J = 7 Hz, 9H); 3.62 (q, J = 7 Hz, 2H); 4.2 (qq, J = 7 Hz, 4H); 4.8, 5.0 (2d, J = 15 Hz, 1H); 7.45 (s, 5H)	—	—
4b	H	CH ₃	58	130–135°/0.6 (111–113°/0.3) ^{3d}	C ₁₂ H ₁₉ O ₄ P (258.3)	1.27 (t, J = 7 Hz, 6H); 3.41 (s, 3H); 3.6–4.47 (m, 4H); 4.6, 4.75 (2d, J = 15 Hz, 1H); 7.45 (s, 5H)	—	—
4c	CH ₃	C ₂ H ₅	64	— ^c	C ₁₄ H ₂₃ O ₄ P (286.3)	1.23, 1.27 (2t, J = 7 Hz, 9H); 2.37 (d, J = 2 Hz, 3H); 3.59 (q, J = 7 Hz, 2H); 3.8–4.4 (m, 4H); 4.63 (d, J = 16 Hz, 1H); 7.1–7.6 (m, 4H)	286 (M ⁺ , 15.4); 149 (100); 121 (53.6)	286.1346 [286.1335]
4d	CH ₃	CH ₃	67	— ^c	C ₁₃ H ₂₁ O ₄ P (272.3)	1.22, 1.26 (2t, J = 7 Hz, 6H); 2.36 (d, J = 2 Hz, 3H); 3.4 (s, 3H); 3.72–4.35 (m, 4H); 4.56, 4.66 (2d, J = 15.5 Hz, 1H); 7.1–7.6 (m, 4H)	272 (M ⁺ , 2.1); 135 (100)	272.1195 [272.1178]
4e	OCH ₃	C ₂ H ₅	84	— ^c	C ₁₄ H ₂₃ O ₅ P (302.3)	1.20, 1.25 (2t, J = 2 Hz, 9H); 3.54 (q, J = 7 Hz, 2H); 3.8 (s, 3H); 4.1 (qq, J = 7 Hz, 4H); 4.6 (d, J = 15.5 Hz, 1H); 6.79–7.6 (m, 4H)	302 (M ⁺ , 2.2); 165 (100); 137 (57.3)	302.1301 [302.1284]
4f	OCH ₃	CH ₃	80	— ^c	C ₁₃ H ₂₁ O ₅ P (288.3)	1.22, 1.35 (2t, J = 7 Hz, 6H); 3.4 (s, 3H); 3.83 (s, 3H); 3.9–4.34 (m, 4H); 4.5, 4.63 (2d, J = 15.5 Hz, 1H); 6.82–7.68 (m, 4H)	288 (M ⁺ , 34.5); 165 (88.1); 151 (100); 137 (91.6); 136 (52.9); 135 (90.6)	288.1138 [288.1127]
4g	Cl	C ₂ H ₅	80	130–135°/0.6	C ₁₃ H ₂₀ ClO ₄ P ^d (306.7)	1.22, 1.27 (2t, J = 7 Hz, 9H); 3.6 (q, J = 7 Hz, 2H); 4.06 (qq, 4H); 4.66 (d, J = 16 Hz, 1H); 7.42 (s, 4H)	306 (M ⁺ , 2.9); 171 (29.6); 169 (100); 141 (76.0)	306.0798 [306.0789]
4h	Cl	CH ₃	69	— ^c	C ₁₂ H ₁₈ ClO ₄ P (292.7)	1.26 (t, J = 7 Hz, 6H); 3.41 (s, 3H); 3.5–4.35 (m, 4H); 4.52, 4.63 (2d, J = 16 Hz, 1H); 7.44 (s, 4H)	292 (M ⁺ , 1.0); 171 (48.7); 169 (93.8); 157 (80.0); 155 (100)	292.0594 [292.0632]
4i	NO ₂	C ₂ H ₅	78	— ^c	C ₁₃ H ₂₀ NO ₆ P (317.3)	1.26 (t, J = 7 Hz, 9H); 3.65 (q, J = 7 Hz, 2H); 4.15 (qq, J = 7 Hz, 4H); 4.8 (d, J = 16.5 Hz, 1H); 7.56–8.48 (m, 4H)	317 (M ⁺ , 0.9); 180 (100); 155 (88.8); 127 (50.2); 99 (94.1)	317.1042 [317.1029]
4j	NO ₂	CH ₃	72	— ^c	C ₁₂ H ₁₈ NO ₆ P (303.3)	1.28 (t, J = 7 Hz, 6H); 3.47 (s, 3H); 4.13 (qq, J = 7 Hz, 4H); 4.68 (d, J = 16.5 Hz, 1H); 7.57–8.49 (m, 4H)	303 (M ⁺ , 6.7); 166 (93.9); 150 (51.5); 120 (100)	303.0865 [303.0872]

^a The I.R. spectra of all products show an absorption at $\nu = 1250 \text{ cm}^{-1}$ (s, P = O).

^b Kugelrohr distillation.

^c Isolated by column chromatography.

^d Calc. C 50.90 H 6.57
found 50.80 6.40

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