

A ONE-POT PROCEDURE FOR THE PREPARATION OF PHOSPHONIC ACIDS FROM ALKYL HALIDES

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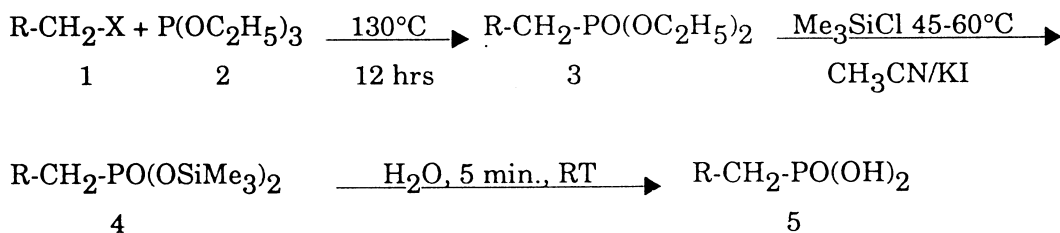
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In connection with other work in our laboratory, it became necessary to prepare a series of phosphonic acids from alkyl halides. A sequence of three individual steps for such a transformation is well known: (i) the Arbuzov procedure for the preparation of dialkyl phosphonates,^{1,2} (ii) the conversion of dialkyl phosphonates into bis-trimethylsilyl phosphonates,^{3,4,5,6} and (iii) their hydrolysis to phosphonic acids.^{3,5} However, there is no previous report of a one-pot method for the preparation of phosphonic acids from alkyl halides and triethyl phosphite. We now report such a rapid and efficient one-pot procedure for the preparation of phosphonic acids. (Direct hydrolysis of alkyl phosphonates to phosphonic acids is well known to be very difficult, hence the necessity for the trimethylsilyl intermediates).

Arylmethyl chlorides or phenacyl bromide derivatives of type **1** were transformed to the respective diethyl phosphonates **3** by treatment with triethyl phosphite (**2**) in a typical Michaelis-Arbuzov reaction.

SCHEME 1



The formation of phosphonates **3** could be monitored by $^1\text{H-NMR}$ analysis based on the disappearance of the $\text{R-CH}_2\text{X}$ signals as well as on the formation of signals for RCH_2P group. This first step was completed within 12 hrs at $120\text{-}130^\circ\text{C}$. The crude reaction mixture was then dissolved in anhydrous acetonitrile and three equivalents of chlorotrimethylsilane and the same molar amount of sodium or potassium iodide was added (fume hood: evolution of ethyl chloride). The second reaction was completed in a yield of 100% usually after 2.5-5.0 hrs, as shown by $^1\text{H-NMR}$. The sodium chloride precipitate was filtered off, and acetonitrile was evaporated under reduced pressure.

TABLE 1. Preparation of Phosphonic Acids $\text{RCH}_2\text{PO}(\text{OH})_2$ (**5a-h**) from the Halides $\text{RCH}_2\text{X}^{\text{a}}$ (**1a-h**)

Compd No	R	Reaction time step II	yield ^b (%)	m.p($^\circ\text{C}$)	
				found	lit.
5a	C_6H_5	3	87	168-170(w)	169-171 ³
5b	4-ClC ₆ H ₄	3	81	165-166(w)	166-170 ¹²
5c	4-CH ₃ OC ₆ H ₄	2.5 ^c	72	204-205(E)	204-206 ⁷
5d ^r	4-tBuC ₆ H ₄	5	86	193-194(w)	... ^d
5e	2,5-diMeC ₆ H ₄	5	84	207-209(Ew)	... ^e
5f	$\text{C}_6\text{H}_5\text{CO}$	3	67	134-136 ^f	135 ⁸
5g	1-C ₁₀ H ₇	5	78	212-213(w)	212 ⁹
5h	2-C ₁₀ H ₇	5	86	229-230(Ew)	229-230 ¹⁰

a) In all experiments X = Cl; except that phenethyl bromide **1f** was used b) Yield is for isolated NMR clean products. c) Reaction was carried out at 45°C ; dealkylation of the ethereal bond did not proceed at this temperature. ¹¹ d) Anal. Calcd C, 57.89; H, 7.51. Found C, 57.41; H, 7.52. e) Anal. Calcd C, 54.00, H 6.55. Found C, 53.66; H, 6.56. f) crude product was washed with diisopropyl ether (E) recrystallized from EtOH; (w) recrystallized from water; (Ew) recrystallized from mixture EtOH:H₂O.

TABLE 2. ^{13}C -NMR Spectra^a of Phosphonic Acids **5**

Compd No	Aromatic Signals ^b					CH_2PO ($J_{\text{P-C}}$ [Hz])	
5a	134.14	129.95	128.20	126.17			36.59(132)
	133.97	129.83	128.15	126.11			33.95
5b	133.35	131.69	128.09	130.96			35.90(131)
	133.17	131.56	128.04	130.88			33.27
5c ^c	125.97	130.72	113.54	157.72			35.59(133)
	125.79	130.60	113.49	157.66			32.93
5d ^d	128.93	129.58	125.27	149.34			34.77(135)
	128.74	129.46	125.32	149.31			32.06
5e	134.25	133.49	132.37	131.21	129.80	126.74	33.95(131)
	134.19	133.36	132.19	131.10	129.74	126.67	31.32
5f	136.18	129.51	128.65	133.42			42.25 ^e
5g	133.68	132.08	130.82	128.45 ^f	126.96	125.92	34.55(145)
	133.63	131.98	130.63		126.89		31.65
	125.75 ^f	125.27					
5h	131.22	129.85	129.73	129.50	126.64	126.17	34.85(132) ^f
	131.16	129.81			126.50	126.01	32.20
	125.50	125.46	124.06	123.45			

a) Spectra were registered in DMSO- d_6 , b) Aromatic signals for compounds **5a-d** and **5f** are given in carbon ring number order; for compounds **5e** and **5g-h** are given from downfield to up field order. c) OCH_3 Signal; 55.03. d) t-Bu Signals; 34.26, 31.23($3\times\text{CH}_3$). e) overlapping signal with solvent; in D_2O CH_2PO : 40.56, 38.09 ($J_{\text{P-C}} = 123$). f) overlapping signals.

The crude bis-silyl esters **4** were hydrolyzed by treatment with water at 20°C to yield the corresponding solid phosphonic acids of type **5**. Benzoylmethylphosphonic acid (**5f**) was separated after evaporation of water. Phosphonic acids **5a-c** and **5f-h** are known compounds and were identified by ¹H-NMR and ¹³C-NMR. p-t-Butylphenylmethylphosphonic acid (**5d**) and 2,5-dimethylphenylmethylphosphonic acid (**5e**) are new compounds and were identified by spectroscopic method and by elemental analysis.

EXPERIMENTAL SECTION

Melting points were determined on a hot stage microscope and are uncorrected. Proton and carbon NMR spectra were recorded on a Varian XL 200 (200 or 50 MHz) instrument in deuteriochloroform and dimethyl sulfoxide-d₆ using tetramethylsilane as the standard for proton and the solvent signals as the standard for carbon spectra, as reference. Combustion analyses were carried out using a Carlo Erba 1106 elemental analyzer under the supervision of Dr. D. Powell.

TABLE 3. ¹H-NMR Spectra of phosphonic Acids **5**

Compd No	Aromatic Signals	CH ₂ PO (J _{P-H} [Hz])		Solvent
		1Hs	1Hs	
5a	7.25 (5H,br,s)	3.02; 2.91 (6.6)		DMSO-d ₆
5b	7.50 (4H,br,s)	3.25; 2.85 (24)		DMSO-d ₆
5c	7.60-7.20 (2H,m)	3.20; 2.80 (24)		CDCl ₃
	7.20-6.80 (2H,m)	3.80; 3H,s-OCH ₃		
5d	7.50 (4H,br,s)	3.30; 2.90 (24)		CDCl ₃ +D ₂ O
		1.40, 9H,s-3xCH ₃		
5e	7.05 (3H,br,s)	3.10; 2.70 (24)		DMSO-d ₆
		2.15, 6H,s-2xCH ₃		
5f	8.20-7.50 (5H,m)	3.80; 3.45 (21)		D ₂ O
5g	8.20-7.35 (7H,m)	3.55; 3.40 (9)		DMSO-d ₆
5h	8.00-7.30 (7H,m)	3.15; 3.05 (6)		DMSO-d ₆

General Procedure.- The mixture of 0.1 mol of the appropriate arylmethyl chloride **1a-e**, **1g-h** or phenacyl bromide **1f**, and 0.12 mol of triethyl phosphite **2** were heated at 120-130°C for 12 hrs and the crude diethyl phosphonates of type **3** were dissolved in 50 ml of anhydrous acetonitrile. Then 0.3 mol of chlorotrimethylsilane and 0.3 mol of sodium or potassium iodide were added. The reaction mixture was heated at 60°C for 2.5-5 hrs (see Table 1). Precipitated sodium chloride was filtered off, the low boiling materials were distilled off, and the residue was treated with 50 ml of distilled water. The phosphonic acids **5a-e** and **5g-h** precipitated after 5 min. at 25°C. The solid products were filtered off and purified by recrystallization from the solvent given in Table 1. The phosphonic acid **5f** was isolated after evaporation of water under reduced pressure and the solid was washed with diisopropyl ether. The yields of the isolated phosphonic acids are given in Table 1. (Note: this procedure should be carried out in a good hood).

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