Studies on Organophosphorus Compounds; LXXV: A Facile Synthesis of 1-(Hydroxyamino)alkyl(or aryl)phosphonic Acids

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Received 25 January 1993; revised 5 April 1993

Reduction of dialkyl 1-(hydroxyimino)alkyl(aryl)phosphonate **1** with borane–pyridine complex proceeds smoothly to give dialkyl 1-(hydroxyamino)alkyl(or aryl)phosphonate **2** which is then easily converted into the corresponding hydroxyaminophosphonic acid **3** by acidic hydrolysis.

1-(Hydroxyamino)alkylcarboxylic acids are a class of important biologically active compounds.[1-3] As expected, the phosphorus analogs of these compounds, namely hydroxyaminoalkylphosphonic acids possess strong antibacterial activity.[4-8] A number of syntheses have been developed with the goal of providing a route to this class of compounds, including the controlled reduction of 1-nitroalkylphosphonates with zinc and ammonium chloride,[9] addition of dialkylphosphite to 1-oxo aldoxime at elevated temperature,[10] the nucleophilic addition of lithium and potassium dialkylphosphite to *N*-glycosyl nitrone followed by glycoside cleavage and hydrolysis.[11] Recently, Elhaddadi et al.[12-14] described a novel synthetic route leading to 1-(hydroxyamino)alkylphosphonic acids based on the condensation of 1-(benzyloxyamino)alkylphosphonic acid with *O*-alkylisourea followed by subsequent treatment with boron tris(trifluoroacetate) (BTFA). Unfortunately, these methods are limited by narrow scope, by competition from other reactions, and difficulties in the preparation of starting materials.

In this paper, we wish to report a facile synthesis of 1-(hydroxyamino)alkyl(or aryl)phosphonic acids by controlled reduction of (hydroxyimino)alkyl(or aryl) phosphonates **1** with borane–pyridine complex.

$$\underset{\mathbf{1}}{R^1C(=NOH)P(O)(OR^2)_2} \xrightarrow[35-90\,\%]{BH_3\text{–}Py} \underset{\mathbf{2}}{R^1CH(NHOH)P(O)(OR^2)_2} \xrightarrow[51-92\,\%]{H^+ \text{ or TMSBr}} \underset{\mathbf{3}}{R^1CH(NHOH)PO_3H_2}$$

Compound **1** is easily obtained in almost quantitative yield by conversion of 1-oxophosphonates into the corresponding hydroxyimino derivatives. Reduction of the oxime to hydroxylamine by borane–pyridine complex in strong acidic medium was reported by Kikugawa et al.[15] However, we observed that in aqueous concentrated hydrochloric acid, no reduction product could be detected upon reaction of **1** with borane–pyridine complex. Transformation of **1** to **2** proceeded smoothly in alcoholic hydrogen chloride with an excess of borane–pyridine complex providing **2** as the crystalline hydrochloride salt. In most cases, borane–trimethylamine complex could be used as reducing agent but usually under more drastic conditions. Compounds **2** could be converted into the corresponding free acids either by hydrolysis with 6 M hydrochloric acid at 90 °C for 4 h in 45–86 % yield or by dealkylation with bromotrimethylsilane (TMSBr) in acetonitrile followed by treatment with aqueous methanol. However, dealkylation is usually conducted under milder conditions with higher yield.

Melting points were uncorrected. IR spectra were recorded on a Perkin-Elmer 983G spectrophotometer. ^{1}H NMR spectra were taken on a Varian EM-360A or a XL-200 spectrometer. $CDCl_3$ was used as solvent for dialkyl hydroxyaminophosphonates, D_2O for the corresponding oxalates and D_2O/NaOD for hydroxyaminophosphonic acids, except where otherwise indicated. TMS was used as the standard in every case. ^{31}P NMR spectra were obtained from a Varian FX-90Q or a Bruker AM-300 spectrometer, 85 % H_3PO_4 was employed as external standard. EIMS were measured on a Finigan MAT-4201 spectrometer. Bromotrimethylsilane, BH_3–Me_3N complex and most of the acyl chlorides were Fluka reagents which were kindly sent as a gift from Ciba-Geigy Ltd. (Switzerland). Triethyl phosphite was purchased from Aldrich Chemical Company (USA). Trimethyl and triisopropyl phosphites were prepared by conventional methods.[17] BH_3–pyridine complex was prepared from sodium borohydride (Merck–Schuchardt) and pyridine hydrochloride by the method proposed by Talor.[18] Anhydrous MeCN was

Table 1. Compounds **2** and **3** Prepared

	R^1	R^2	Yield (%)	mp (°C)	Molecular Formula[b] or Lit. mp (°C)
2a	Me	i-Pr	60	96–97[a]	$C_{10}H_{22}NO_8P$ (315.3)
2b	c-Pr	Et	63	117–118[a]	$C_{10}H_{20}NO_8P$ (313.3)
2c	$PhCH_2$	Et	75	106–107[a]	$C_{14}H_{22}NO_8P$ (363.4)
2d	4-$FC_6H_4CH_2$	Et	47	91–92[a]	$C_{14}H_{21}FNO_8P$ (381.3)
2e	4-$FC_6H_4CH_2$	i-Pr	53	125–127[a]	$C_{16}H_{25}FNO_8P$ (409.4)
2f	Ph	Me	71	104–106	$C_9H_{14}NO_4P$ (231.2)
2g	Ph	Et	91	134–136	$C_{11}H_{18}NO_4P$ (259.3)
2h	Ph	i-Pr	84	102–103	$C_{13}H_{22}NO_4P$ (287.3)
2i	4-MeC_6H_4	Et	66	87–88	$C_{12}H_{20}NO_4P$ (273.3)
2j	2-MeC_6H_4	Et	35	64–66	$C_{12}H_{20}NO_4P$ (273.3)
2k	3-MeC_6H_4	Et	80	67–69	$C_{12}H_{20}NO_4P$ (273.3)
2l	4-FC_6H_4	Et	85	137–138	$C_{11}H_{17}FNO_4P$ (277.3)
2m	4-ClC_6H_4	Et	90	110–112	$C_{11}H_{17}ClNO_4P$ (293.8)
3a	Me	H	55 (81[c])	172–173	$C_2H_8NO_4P$ (141.1)
3b	c-Pr	H	63 (89[c])	186–187	$C_4H_{10}NO_4P$ (167.1)
3c	$PhCH_2$	H	63	170 (dec.)	$C_8H_{12}NO_4P$ (217.2)
3d	4-$FC_6H_4CH_2$	H	51	204 (dec.)	$C_8H_{11}FNO_4P$ (235.2)
3e	Ph	H	45 (92[c])	184–186	182–190[16]
3f	3-MeC_6H_4	H	45 (85[c])	191–192	$C_8H_{12}NO_4P$ (217.2)
3g	4-MeC_6H_4	H	48	184–185	$C_8H_{12}NO_4P$ (217.2)
3h	4-FC_6H_4	H	86	190–191	$C_7H_9FNO_4P$ (221.1)
3i	4-ClC_6H_4	H	52	193–194	$C_7H_9ClNO_4P$ (237.6)

[a] mp of oxalic salt.
[b] Satisfactory microanalyses: C ± 0.38, H ± 0.29, N ± 0.30.
[c] Yield of dealkylation with bromotrimethylsilane.

Table 2. Spectroscopic Data of Compounds **2** and **3**

	IR (ν, cm^{-1}) P=O, P–O–C	^1H NMR (δ, J, Hz)	^{31}P NMR (δ)	MS
2a	1235, 1005	1.24 (d, 12H, J = 6), 1.42 (dd, 3H, J = 6; 20). 3.6–4.1 (m, 1H, CHP), 4.4–5.0 (m, 2H)	22.55	
2b	1225, 1029	0.4–1.0 (m, 5H), 1.2 (t, 6H, J = 6), 3.2 (m, 1H, CHP), 4.2 (m, 4H)	25.29 ($CDCl_3$)	273 (M)
2c	1245, 1051	1.0–1.2 (t, 6H, J = 7), 2.9–3.3 (dd, 2H, J = 7; 15), 3.1–4.3 (m, 5H), 7.2 (s, 5H)		
2d	1236, 1025	0.8–1.4 (t, 6H, J = 6), 3.2 (dd, 2H, J = 7; 16), 3.6–4.4 (m, 5H), 6.8–7.4 (m, 4H)	20.16	
2e	1225, 1010	1.1 (m, 12H), 3.1 (dd, 2H, J = 8; 16), 3.8–4.4 (m, 1H), 6.8–7.4 (m, 4H)	15.99	
2f	1241, 1030	3.5–3.8 (dd, 6H, J = 16; 16), 4.5 (d, 1H, J = 18), 5.8 (br, 2H, NHOH), 7.2–7.6 (m, 5H)		
2g	1236, 1050	(DMSO-d_6) 1.05 (t, 3H, J = 7), 1.17 (t, 3H, J = 7), 3.73–3.87 (m, 2H), 3.91–4.06 (m, 2H), 4.4.35 (d, 1H, J = 20.4), 6.1 (br, 2H), 7.25–7.63 (m, 5H)	20.8	260 (M + 1)
2h	1240, 1041	1.0–1.5 (m, 12H), 4.45 (d, 1H, J = 20), 4.4–5.1 (m, 2H), 7.3–8.0 (m, 7H)	18.34	
2i	1240, 1022	(CD_3OD) 0.8–1.2 (m, 6H), 2.1 (s, 3H), 4.2 (d, 1H, J = 20), 7.0 (m, 4H)	23.41	
2j	1235, 1052	(CCl_4) 1.1 (t, 3H, J = 7), 1.3 (t, 3H, J = 7), 2.4 (s, 3H), 3.5–4.3 (m, 4H), 6.5 (br, 2H), 7.2 (m, 3H), 7.1–7.3 (m, 1H)	21.41 ($CDCl_3$)	
2k	1237, 1052	0.9–1.3 (m, 6H), 3.4–4.3 (m, 4H), 4.3 (d, 1H, J = 18), 6.6–7.4 (m, 4H)	20.41	273 (M)
2l	1240, 1049	1.2 (t, 3H, J = 6), 1.3 (t, 3H, J = 6), 4.1 (m, 4H), 4.5 (d, 1H, J = 18.6), 4.3–4.8 (br, 2H), 7.1 (t, 3H, J = 8.4), 7.45 (m, 2H)	20.26	277 (M)
2m	1240, 1051	1.1–1.3 (m, 6H), 3.8–4.3 (m, 4H), 4.5 (d, 1H, J = 18), 5.7–6.5 (br, 2H), 7.3–7.6 (m, 4H)	14.72	293 (M)
3a	1174, 1000	1.35 (dd, 3H, J = 7; 18), 3.0–3.8 (m, 1H)		
3b	1160, 986	0.3–0.7 (m, 4H), 0.8–1.1 (m, 1H), 1.9–2.5 (m, 1H)	16.38	
3c	1198, 1012	2.8–3.6 (m, 3H), 7.44 (s, 5H)	19.6	
3d	1197, 1014	2.5–3.6 (m, 3H), 6.5–7.2 (m, 4H)	17.58	
3e	1171, 1033	4.1 (d, 1H, J = 19), 7.4 (s, 5H)	19.14	
3f	1205, 1020	2.44 (s, 3H), 5.26 (d, 1H, J = 18), 7.14–7.30 (m, 4H)	7.26	
3g	1165, 1025	2.2 (s, 3H), 3.95 (d, 1H, 18), 7.1 (m, 4H)	12.26	
3h	1216, 1062	4.2 (d, 1H, J = 22), 7.45 (m, 4H)		
3i	1162, 1017	4.1 (d, 1H, J = 21), 7.42 (s, 4H)	7.24	

achieved by distillation from P_2O_5 and then from K_2CO_3 followed by fractional distillation and stored over 4 Å molecular sieves.

Dialkyl 1-(Hydroxyimino)alkyl(or aryl)phosphonates (1):
These compounds were prepared by modification of the method described by Berlin[19] and Breuer.[20] Trialkyl phosphite (0.1 mol) was added dropwise to the acyl chloride (0.1 mol) with stirring under an atmosphere of dry nitrogen, keeping the temperature of the reaction mixture below 40 °C. It was then heated to 60 °C with the outlet open to an atmosphere of dry nitrogen. Then the volatile components were removed thoroughly under reduced pressure with a bath temperature below 80 °C. The residue was dissolved in absolute EtOH (100 mL) and anhydr. hydroxylamine hydrochloride (0.14 mol) was added followed by the addition of dry pyridine (11.9 g, 0.15 mol). The resultant clear solution was stirred at r. t. for 24 h and then concentrated under reduced pressure. The residue was mixed with CH_2Cl_2 (100 mL), washed successively with H_2O (2 × 50 mL), 2 M aq HCl (2 × 50 mL) and brine (50 mL), and dried (Na_2SO_4). After removal of the solvent, **1** was obtained as an oily liquid or an amorphous powder which was then dried in vacuo and could be used directly for reduction without purification.

Dialkyl 1-(Hydroxyamino)alkyl(or aryl)phosphonates (2); General Procedure:
Compound **1** (0.05 mol) and borane–pyridine complex (14 g, 0.15 mol) were dissolved in absolute EtOH (50 mL) and then cooled to 0 °C with an ice-water bath. Ethanolic 30 % HCl (43 g, equivalent to 0.35 mol of HCl) was then added dropwise and the resultant clear solution was stirred at r. t. for 12 h. More than half of the solvent was removed on a rotatory evaporator and the residue was treated with sat. aq Na_2CO_3 with cooling until pH 9 was reached. In this way, **2f–m** crystallized from the solution, and were collected and recrystallized from $CHCl_3$/petroleum ether; **2a–e** were extracted into CH_2Cl_2 (3 × 50 mL). The extracts were combined and dried (Na_2SO_4). Upon removal of solvent, **2a–e** were obtained as viscous liquids which were isolated in the form of oxalates. The yields and spectroscopic data of **2** are listed in Tables 1 and 2.

1-(Hydroxyamino)alkyl(or aryl)phosphonic Acids (3):
Method A *(Hydrolysis with 6 N HCl):*
A solution of **2** (0.02 mol) in 6 M HCl (100 mL) was stirred at 90 °C for 4 h. The solvent and volatile components were removed under reduced pressure with a bath temperature below 90 °C. The residue thus obtained was triturated with EtOH (30 mL). The resultant crystalline products were collected, dried and recrystallized from water/EtOH or, in some cases, from dilute hydrochloric acid.

Method B *(Dealkylation with TMSBr):*
To a stirred solution of **2** (0.01 mol) in anhydr. MeCN (20 mL) was added TMSBr (6.3 g, 0.041 mol) under an atmosphere of dry nitrogen. After being stirred for 12 h at ambient temperature, the volatile components were removed and the residue was dissolved in MeOH (20 mL). While stirring, propylene oxide was added dropwise until pH 5 was obtained. After workup, **3** were obtained as colorless crystalline compounds. The yields and spectroscopic data of **3** are listed in Tables 1 and 2.

This project was supported by the National Natural Science Foundation of China.

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