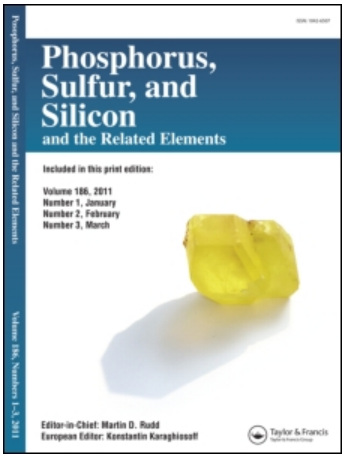

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

STUDIES ON ORGANOPHOSPHORUS COMPOUNDS LXXVI. A CONVENIENT SYNTHESIS OF 1-ALKYL-OR 1-ARYL-1-HYDROXY-2-*N*-HYDROXYLAMINOETHYLPHOSPHONIC ACIDS

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To cite this Article Yuan, Chengye , Wang, Guohong , Feng, Hanzhen , Chen, Jipin and Maier, Ludwig(1993) 'STUDIES ON ORGANOPHOSPHORUS COMPOUNDS LXXVI. A CONVENIENT SYNTHESIS OF 1-ALKYL-OR 1-ARYL-1-HYDROXY-2-*N*-HYDROXYLAMINOETHYLPHOSPHONIC ACIDS', Phosphorus, Sulfur, and Silicon and the Related Elements, 81: 1, 149 — 154
To link to this Article: DOI: 10.1080/10426509308034384
URL: http://dx.doi.org/10.1080/10426509308034384

Phosphorus, Sulfur, and Silicon, 1993, Vol. 81, pp. 149–154
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STUDIES ON ORGANOPHOSPHORUS COMPOUNDS LXXVI. A CONVENIENT SYNTHESIS OF 1-ALKYL- OR 1-ARYL-1-HYDROXY-2-*N*-HYDROXYLAMINOETHYLPHOSPHONIC ACIDS

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(Received March 30, 1993)

A series of 1-alkyl- or 1-aryl-1-hydroxy-2-*N*-hydroxylaminoethylphosphonic acids was prepared by controlled reduction of dialkyl 1-alkyl- or 1-aryl-1-hydroxy-2-nitroethyl phosphonates with aluminum amalgam or stannous chloride followed by subsequent acid hydrolysis or dealkylation via the corresponding trimethylsilyl ester.

Key words: Phosphonic acid; hydroxylamino derivatives; hydroxy derivatives; 1-alkyl(aryl)-1-hydroxy-2-*N*-hydroxylaminoethylphosphonic acids.

INTRODUCTION

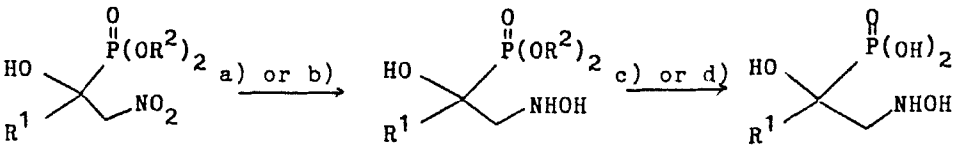
Since the successful isolation of 3-(*N*-acetyl-hydroxylamino)-propionic acid as antibiotics from streptomyces rubellomurinus[1] it was found that some synthetic analogues also possess strong antibacterial activities.[2] It is therefore interesting to synthesize various derivatives of 1-hydroxy-2-*N*-hydroxylaminoethylphosphonic acid for the structure-activity investigations.

Among numerous methods available for the formation of the hydroxylamino moiety, the controlled reduction of a nitro group is one of the convenient synthetic routes.[3,4] However, such reductive conversion is complicated if there are additional functional groups in the substrate which make the molecule unstable under reaction conditions. For example, derivatives of 1-hydroxy-alkylphosphonates are easily degraded through C—C and C—P bond cleavage in the presence of alkali, even with a catalytic amount of organic base.[5]

RESULTS AND DISCUSSION

We found that dialkyl 1-alkyl- or 1-aryl-1-hydroxy-2-nitroethylphosphonates[6] (**1**) can be easily converted to dialkyl 1-alkyl- or 1-aryl-1-hydroxy-2-hydroxylamino-

ethylphosphonates (**2**) by treatment either with aluminum amalgam in ethyl acetate (Method A) or with stannous chloride in hydrochloric acid solution (Method B).



1 2 3

a) Al-Hg(ETOAc), 47-74% b) $SnCl_2$(HCl), 43-75%
c) HCl, 54-84% d) Me_3SiBr, H_2O, 54-78%

The controlled reduction of a nitro group to a hydroxylamino functionality by Al-Hg is one of the traditional synthetic methods.[7,8] Our experimental data reveal that the yield of **2** by this method is very much dependent on the structure of the substrate **1** and the reactivity of Al-Hg. Variation of the steric hindrance of the ester alkyl group in **1** has a dramatic effect on the yield of **2**. The isopropyl ester usually provides higher yields than the corresponding ethyl and methyl esters. This can be explained by the steric effect which hinders the attack of the oxygen atom on phosphorus, and thus prevents the phosphonate-phosphate rearrangement via the formation of a reactive three membered ring oxide species as the result of intramolecular interaction.[9] On the other hand, the presence of a nuclear ortho-substituent in aryl-phosphonates (**1** or **2**) effects significant steric hindrance which depressed the yield of the product. As demonstrated by us,[5] addition of *p*-toluene sulfonic acid can decrease the amount of by-product in the preparation of 1-hydroxy-alkylphosphonates bearing a basic functional group by reductive conversion. In the present case, addition of *p*-toluene sulfonic acid or acetic acid also has similar effect but it requires longer reaction time and gives product **2** contaminated with the amino-compound. During the reaction course we observed that the reactivity of Al-Hg decreased probably due to the formation of a metal oxide coated on the surface of the reagent. In a protic solvent the reducing power of Al-Hg is enhanced. However, this is a favourable condition to form amino-derivatives.

The conversion of the nitro-function into oximido and hydroxylamino group by stannous chloride in hydrochloric acid is well documented.[7,8] Our results indicated that this method (B) usually provides better yields of **2** at low (<10°C) temperature, no matter of the structure of substrate **1**. The conversion yield is up to >95% based on ^{31}P NMR. However, the isolated yield is around 60% due to the interference of the formation of stannous salts and the solubility of the product in water. Both ether and ethyl acetate are good solvents to separate **2** from inorganic salts. Neutralization of the reaction mixture by conc. ammonium hydroxide or sodium bicarbonate powder at low temperature (10°C) to pH 8 is critical. Conversion of **2** to **3** is easily achieved either by acid hydrolysis or by dealkylation through the trimethyl silyl ester in the usual manner.

EXPERIMENTAL

Melting points are not corrected. IR spectra were obtained on a Shimadzu 440 spectrometer. ^1H and ^{31}P NMR spectra were taken with a Varian EM-360A (60 MHz) or FX-90Q (90 MHz) spectrometer

with internal TMS (^1H) or external 85% H_3PO_4 (^{31}P) as standard, and the coupling constants J are given in Hz. The starting material and solvents used were purified by standard procedure prior to use.

Dialkyl 1-alkyl or 1-aryl-1-hydroxy-2-hydroxylaminoethylphosphonates **2**; *General Procedure.* Method A (Al-Hg/EtOAc): To a suspension of Al-Hg, prepared from 1.5 g aluminium foil[10] in EtOAc/ether (1:1/V:V) (100 ml) containing H_2O (2 ml) are added at 0°C dialkyl 1-alkyl- or 1-aryl-1-hydroxy-2-nitroethylphosphonate (30 mmol). The reaction mixture was stirred at a temperature of 25°C and monitored by TLC until no more starting material **1** can be detected. The resultant mixture was centrifuged. The separated solid was extracted with EtOAc (3 × 20 ml) and then discarded. The combined organic solution and extract was dried ($MgSO_4$) and the solvent was evaporated in a rotatory evaporator. The oily residue thus obtained was dissolved in ethanol and treated with oxalic acid (2.7 g, 30 mmol). After removal of the solvent the crystalline oxalate salt was isolated upon addition of anhydrous ether. Recrystallization from ethanol/ether afforded **2**. The results are summarized in Tables I and II.

Method B ($SnCl_2$/HCl): To a solution of $SnCl_2$ (30 g) in conc. HCl (50 ml) was added at 0°C, compound **1** (50 mmol) in small portions. Upon completion of the reaction as indicated by TLC, the reaction mixture was poured into a flask containing EtOAc (200 ml). After cooling in a dry ice alcohol

TABLE I

Compounds **2** prepared[a]

2	R^1	R^2	mp (°C)	Method	Yield (%)	Molecular Formula[b]
a	Me	Et	153–155	A	67	$C_9H_{20}NO_9P$ (317.1)
b	Me	*i*-Pr	148–150	A	71	$C_{11}H_{24}NO_9P$ (345.2)
c	Et	Et	134–136	A	56	$C_{10}H_{22}NO_9P$ (331.2)
d	*i*-Pr	Et	137–139	A	47	$C_{11}H_{24}NO_9P$ (345.2)
e	*c*-C_3H_5	Et	118–120	A	69	$C_{11}H_{22}NO_9P$ (343.2)
f	Bn	Me	118–120	A	61	$C_{11}H_{18}NO_5P$ (275.0)
g	Bn	Et	102–104	A	74	$C_{13}H_{22}NO_5P$ (303.1)
h	$PhCH_2CH_2$	Et	116–118	A	66	$C_{16}H_{26}NO_9P$ (407.3)
i	4-$FC_6H_4CH_2$	Et	102–104	B	62	$C_{15}H_{23}FNO_9P$ (411.2)
j	*c*-C_6H_{11}	*i*-Pr	136–138	B	54	$C_{16}H_{32}NO_9P$ (413.3)
k	Ph	Et	142–144	B	43	$C_{14}H_{22}NO_9P$ (379.0)
l	4-MeC_6H_1	Et	135–136	B	64	$C_{15}H_{24}NO_9P$ (393.2)
m	4-MeC_6H_4	*i*-Pr	162–164	B	75	$C_{17}H_{28}NO_9P$ (421.2)
n	3-MeC_6H_4	Et	120–122	A	47	$C_{15}H_{24}NO_9P$ (393.2)
o	3-MeC_6H_4	*i*-Pr	164–166	A	71	$C_{17}H_{28}NO_9P$ (421.2)
p	4-FC_6H_4	Et	112–114	B	43	$C_{14}H_{21}FNO_9P$ (395.2)
q	4-ClC_6H_4	Et	133–135	B	54	$C_{14}H_{21}ClNO_9P$ (413.7)

[a]All of the compounds were isolated as oxalate salt except **2f** and **2g**.
[b]Satisfactory microanalyses obtained: C ± 0.3, H ± 0.2, N ± 0.3, P ± 0.32.

TABLE II
Spectroscopic data of compounds **2**

Product	IR (KCl) P=O	ν (cm^{-1}) P—O—C	^1H NMR (solvent/TMS ext) δ (ppm)	^{31}P NMR (80% H_3PO_4 int) δ (ppm)
2a	1222	1020	(D_2O) 0.85–1.40 (m, 9H), 3.20–3.60 (m, 2H), 4.05 (m, 4H)	23.15
2b	1224	1002	(D_2O) 1.3–1.5 (m, 15H), 3.70 (br, 2H), 4.40–4.80 (m, 2H)	22.85
2c	1225	1025	(D_2O) 1.20 (t, 3H), 1.38 (dt, 6H), 1.46 (m, 2H), 3.68 (m, 2H), 4.35 (m, 4H)	22.78
2d	1214	1021	(D_2O) 0.95–1.50 (m, 13H), 3.40–3.75 (m, 2H), 4.20 (m, 4H)	25.14
2e	1218	1022	(CD_3OH) 0.20–0.70 (m, 5H), 1.20 (t, 6H), 3.30 (m, 2H), 4.10 (m, 4H)	24.43
2f	1215	1030	(CD_3Cl_3) 2.90–3.30 (m, 4H, CH_2N, $PhCH_2$), 3.70–4.15 (m, 6H), 5.30–5.70 (m, 3H, NHOH, OH), 7.30 (s, 5H)	26.06
2g	1212	1029	($CDCl_3$) 1.30 (t, 6H), 2.90–3.40 (m, 4H, $PhCH_2$, CH_2N), 4.30 (m, 4H), 5.30–5.70 (m, 3H, NHOH, OH), 7.30 (s, 5H)	25.97
2h	1225	1024	(D_2O) 1.18 (m, 6H), 1.50–2.80 (m, 4H), 3.35–4.10 (m, 6H), 7.10 (s, 5H)	24.73
2i	1221	1020	(D_2O) 1.20 (dt, 6H), 3.05 (d, 2H) 3.55 (m, 2H), 4.15 (m, 4H), 6.95–7.40 (m, 4H)	24.14
2j	1218	990	(D_2O) 1.45–1.95 (m, 23H), 3.65 (m, 2H), 4.50–4.85 (m, 2H)	23.99
2k	1216	1013	(D_2O) 1.20 (dt, 6H), 3.60–4.10 (m, 2H, CH_2N), 4.30 (m, 4H), 7.05–7.35 (m, 5H)	21.22
2l	1218	1031	(D_2O) 1.05 (m, 6H), 2.20 (m, 3H), 3.45–4.05 (m, 6H), 7.25 (m, 4H)	21.32
2m	1216	1013	(D_2O) 0.95–1.40 (m, 12H), 2.30 (s, 3H), 3.82–4.10 (m, 2H, CH_2N), 4.30–5.00 (m, 2H), 7.30–7.60 (m, 4H)	21.44
2n	1228	1025	(D_2O) 1.15 (dt, 6H), 2.30 (s, 3H), 3.35–3.45 (m, 2H), 3.60–4.15 (m, 4H), 6.85–7.35 (m, 4H)	21.31
2o	1218	998	(D_2O) 1.15 (m, 12H), 3.65–4.15 (m, 2H, CH_2N), 4.50–5.00 (m, 2H), 7.05–7.60 (m, 4H)	19.51
2p	1227	1021	(D_2O) 1.20 (dt, 6H), 3.60–4.20 (m, 6H), 7.20–7.80 (m, 4H)	21.02
2q	1226	1014	(D_2O) 1.30 (dt, 6H), 3.60–4.35 (m, 6H), 7.25–7.85 (m, 4H)	20.75

bath, the resultant was treated either with dropwise addition of conc. NH_4OH or by neutralization with $NaHCO_3$ powder below $-10°C$ until pH 8 was reached. After that the reaction mixture was warmed to room temperature, centrifuged and the organic layer collected. The separated aqueous layer and solid was extracted with EtOAc (3 × 60 ml). The combined EtOAc solution and extracts were dried over $MgSO_4$ and the solvent evaporated in a rotatory evaporator. The viscous oily liquid thus obtained was treated as described in method A. The results are summarized in Tables I and II.

1-Alkyl- or 1-aryl-1-hydroxy-2-hydroxylaminoethylphosphonic acid **3**; *General Procedure.* Method A (acid hydrolysis): A mixture of the oxalate of **2** (30 mmol) in aqueous HCl (1:1) was heated to 80°C with stirring for 7–12 h. After being cooled, the acidic solution was washed with benzene to remove oxalic acid and other impurities followed by treatment with charcoal. The clear aqueous solution was heated in a rotatory evaporator under reduced pressure. The resultant residue was dissolved in absolute alcohol and treated with propylene oxide until precipition occurred. Recrystallization from $EtOH/H_2O$ afforded compounds **3** summarized in Tables III and IV.

Method B (dealkylation): A suspension of oxalate of **2** (20 mmol) in ether (100 ml) was chilled in a dry ice bath and treated with diluted NH_4OH solution by dropwise addition until a clear solution was

TABLE III

Compounds **3** prepared

3	R	mp (°C)	Method	Yield (%)	Molecular Formula[a]
a	Bn	198–200 (dec)	A	84	$C_9H_{14}NO_5P$ (247.0)
b	$C_6H_5CH_2CH_2$	204–206 (dec)	A	75	$C_{10}H_{16}NO_5P$ (261.2)
c	4-$FC_6H_4CH_2$	210–212 (dec)	B	60	$C_9H_{13}FNO_5P$ (265.1)
d	C_6H_5	192–194 (dec)	B	54	$C_8H_{12}NO_5P$ (233.0)
e	4-MeC_6H_4	170–172	B	78	$C_9H_{14}NO_5P$ (247.1)
f	3-MeC_6H_4	162–164	A	71	$C_9H_{14}NO_5P$ (247.1)
g	4-FC_6H_4	154–158	A	54	$C_8H_{11}FNO_5P$ (251.1)
h	4-ClC_6H_4	193–196	A	62	$C_8H_{11}ClNO_5P$ (267.5)

[a]Satisfactory microanalyses obtained: C ± 0.4, H ± 0.2, N ± 0.3, P ± 0.33.

TABLE IV

Spectroscopic data of compounds **3**

Product	IR (KCl) P=O	IR (KCl) ν (cm^{-1}) P—O—C	^1H NMR (solvent/TMS ext) δ (ppm)	^{31}P NMR (80% H_3PO_4 int) δ (ppm)
3a	3400 3125	1125	(DMSO/TFA) 2.70–3.45 (m, CH_2N, $PhCH_2$), 7.26 (s, 5H)	20.58
3b	3426 3026	1119	(TFA) 1.41–2.80 (m, 4H), 3.45–3.90 (m, 2H), 7.50 (s, 5H)	20.78
3c	3500 3220	1130	(D_2O/TFA) 2.80–3.10 (m, 2H), 3.45–3.75 (m, 2H), 6.50–7.00 (m, 4H)	18.88
3d	3450 3120	1143	(DMSO/TFA) 3.01–3.52 (m, 2H, CH_2N), 6.95–7.90 (m, 5H)	16.90
3e	3450 3030	1162	(D_2O/TFA) 2.0 (m, 3H), 3.30–3.90 (m, 2H), 7.0 (m, 4H)	18.62
3f	3440 3110	1165	(D_2O/TFA) 2.10 (s, 3H), 3.15–3.50 (m, 2H), 6.80–7.30 (m, 4H)	18.97
3g	3460 3050	1161	(D_2O/TFA) 2.85–3.45 (m, 2H), 6.65–7.60 (m, 4H)	18.90
3h	3560 3052	1138	(DMSO/TFA) 3.30–3.90 (m, 2H, CH_2N), 7.20–7.90 (m, 4H)	18.55

formed. The ether layer was collected and the aqueous solution was extracted with ether (3 × 40 ml). The combined etheral solution was washed with brine (2 × 15 ml) dried ($MgSO_4$) and concentrated in vacuo. The residue thus obtained was dissolved in anhydrous CH_2Cl_2 (100 ml). After addition of Me_3SiBr (15.3 g, 100 mmol) the mixture was stirred for 8 h at room temperature. After removal of the solvent and excess reagent in vacuo, the residue was treated with methanol (20 ml) with stirring for 4 h. After evaporation of methanol a mixture of water (20 ml) and conc. HCl (5 ml) was added and the resultant mixture was heated at <60°C for 2 h. After evaporation under reduced pressure the residue was dissolved in a minimum amount of ethanol and treated with propylene oxide until precipitation occurred. Recrystallization from EtOH/H_2O afforded compounds **3** as summarized in Tables III and IV. The data of the elemental analyses are summarized in Table V.

TABLE V
Data of elemental analyses

Product	Calculated (%)				Found (%)			
	C	H	N	P	C	H	N	P
2a	34.07	6.31	4.42	9.78	33.88	6.28	4.28	9.56
2b	38.26	6.95	4.06	8.98	38.02	6.72	4.15	9.01
2c	36.23	6.04	4.22	9.36	36.51	6.11	4.02	9.08
2d	38.26	6.95	4.06	8.98	38.50	7.02	4.15	9.12
2e	38.46	6.41	4.08	9.03	38.24	6.21	4.29	9.33
2f	48.00	6.55	5.09	11.27	48.33	6.58	5.21	11.35
2g	51.47	5.94	4.62	10.23	51.55	5.78	4.86	10.50
2h	47.14	6.38	3.44	7.61	47.34	6.49	3.71	7.72
2i	43.77	5.59	3.40	7.53	43.99	5.69	3.45	7.62
2j	46.46	7.74	3.39	7.50	46.24	7.54	3.29	7.66
2k	44.33	5.80	3.67	8.18	44.55	5.91	3.73	8.32
2l	45.78	6.10	3.56	7.88	45.98	6.32	3.86	7.99
2m	48.43	6.65	3.32	7.36	48.42	6.38	3.02	7.26
2n	45.78	6.10	3.56	7.88	45.98	6.00	3.62	8.12
2o	48.43	6.65	3.32	7.36	48.22	6.73	3.45	7.58
2p	42.51	5.31	3.32	7.84	42.81	5.31	3.23	7.68
2q	40.61	5.08	3.38	7.49	40.48	5.12	3.60	7.66
3a	43.72	5.67	5.67	12.55	43.55	5.78	5.86	12.48
3b	45.94	6.13	5.36	11.87	46.22	6.33	5.26	11.78
3c	40.74	4.90	5.28	11.69	70.34	4.72	5.00	11.52
3d	41.20	5.15	6.01	13.31	41.28	5.15	6.08	13.08
3e	43.71	5.67	5.67	12.55	43.66	5.79	5.37	12.72
3f	43.71	5.67	5.67	12.55	43.78	5.67	5.44	12.33
3g	38.23	4.38	5.58	12.35	38.00	4.52	5.28	12.05
3h	35.88	4.11	5.23	11.59	35.66	4.32	5.44	11.74

ACKNOWLEDGEMENT

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

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