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Synthesis of Functionalized 2-Trimethylsiloxy-Substituted *O*-Trimethylsilyl Alkylphosphonites, Their Analogues, and Derivatives

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ABSTRACT: *Nucleophilic addition of trimethylsilyl esters of tricoordinate organophosphorus acids to several functionalized alkylene oxides is proposed as convenient methods for the synthesis of new 2-trimethylsiloxysubstituted alkylphosphonites, their analogues, and derivatives. Also the new functionalized derivatives of these phosphonites, including amino, carboxy, or sulfo groups as well as certain properties of these compounds, which may be the important precursors of new functionalized 2-hydroxyalkylorganophosphorus acids, are presented.* © 2008 Wiley Periodicals, Inc. Heteroatom Chem 19:450–454, 2008; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20453

INTRODUCTION

There are only a few reported examples of the reaction of trimethylsilyl phosphites with epoxides, involving phosphorus-carbon formation [1]. Heterosubstituted derivatives of propylene oxide, especially a well-known epichlorohydrin and readily available *O,O*-diethyl-2,3-epoxypropylphosphonate [2], as well as cyclohexene oxide are promising compounds for organic synthesis [3,4]. Recently, we have synthesized the new 1-trimethylsiloxysubstituted alkylphosphonites and their derivatives with aryl, heterocyclic, and organoelement fragments in high yields via nucleophilic addition of trimethylsilyl esters of trivalent organophosphorus acids to various functionalized aldehydes [5]. Also the functionalized derivatives of 2-hydroxyalkylorganophosphorus acids containing aryl and heterocyclic fragments and various hydroxyl, amino, or amido groups present great interest as promising-polydentate ligands and biologically active compounds as organophosphorus biomimetics of hydroxyl and amino acids [6,7]. In the present work, with purpose of synthesis new functionalized 2-trimethylsiloxyalkylphosphonates and phosphinates including 3-heteropropyl or cyclohexene fragments, we have studied reaction of trimethylsilyl esters of trivalent phosphorus acids with epichlorohydrin, 2,3-epoxypropylphosphonate, and cyclohexene oxide. These reactions provide a convenient synthetic route to new precursors of interesting functionalized 2-hydroxyalkylorganophosphorus acids (cf. [5]).

RESULTS AND DISCUSSION

In the present work, we have shown that esters of trivalent phosphorus acids containing $POSiMe_3$

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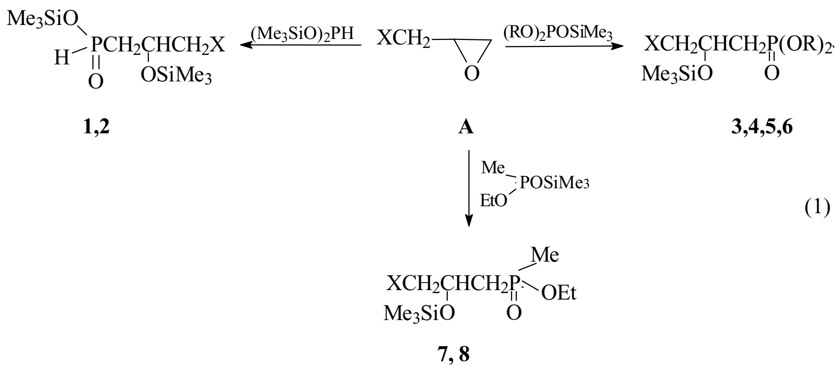
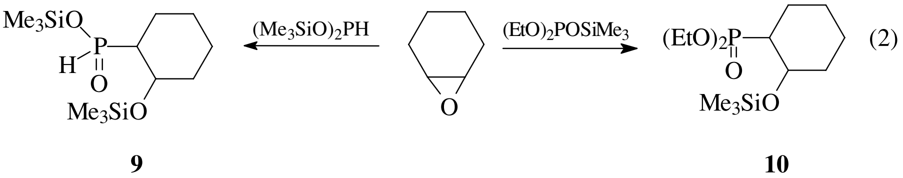
fragment add to epichlorohydrin and *O*,*O*-diethyl-2,3-epoxypropylphosphonate **A** at 130°C in the presence of zinc chloride, with selective opening of the epoxide ring and formation of 3-heterosubstituted 2-trimethylsiloxypropylphosphonites **1,2**; phosphonates **3–6**, and phosphinates **7,8** in high yields (Eq. (1)), (cf. [3]).



(1)

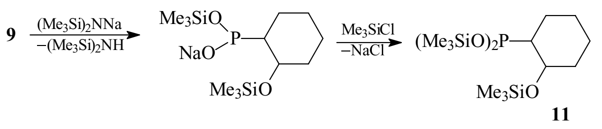
$R = Et$ (**3,4**), Me_3Si (**5,6**);
$X = Cl$ (**1,3,5,7**), $(EtO)_2P(O)$ (**2,4,6,8**)

Under the same conditions, cyclohexene oxide easily reacts with bis(trimethylsilyloxy)phosphine and diethyl trimethylsilyl phosphite to give 2-trimethylsilyloxycyclohexylphosphonite **9** or phosphonate **10**, respectively (Eq. (2)).



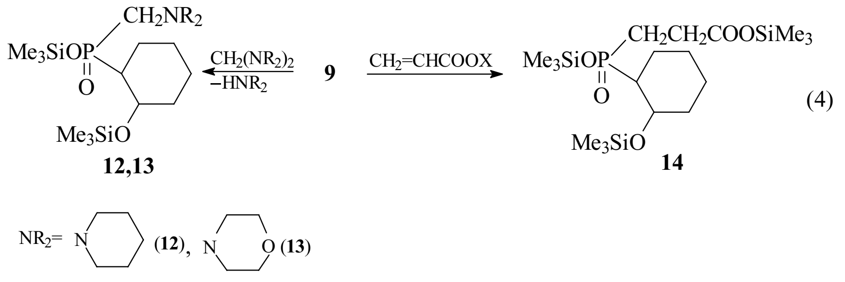
(2)

Using phosphonite **9**, we have devised a convenient method for preparing bis(trimethylsilyl)2-trimethylsiloxycyclohexylphosphonite **11**, which was obtained in high yield by successive treatment of phosphonite **9** with sodium bis(trimethylsilyl)amide and chlorotrimethylsilane. Contrary to that, prolonged boiling of a mixture of phosphonite **9** with bis(trimethylsilyl)amine in the presence of chlorotrimethylsilane gave no more than traces of phosphonite **11** detected by ^{31}P NMR in the reaction mixture (Eq. (3)).



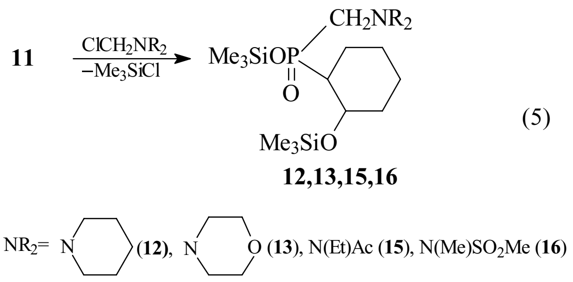
(3)

Phosphonites **9,11** are the convenient synthons for preparing functionalized phosphinates including cyclohexane fragments that attract attention as potential ligands and biologically active compounds. Thus, the aminomethylation of phosphonite **9** with aminals at 130°C in the presence of zinc chloride (cf. [8]) gives aminomethylphosphinates **12,13** and the addition of phosphonite **9** to trimethylsilyl acrylate proceeds to form phosphinate **14** with propionate fragment (Eq. (4); cf. [9]).

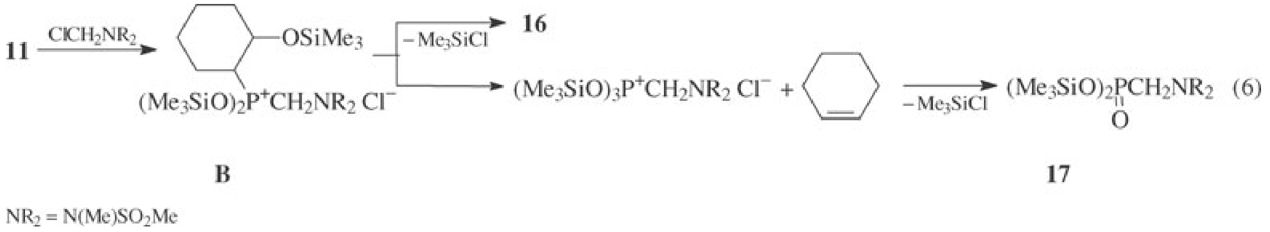


(4)

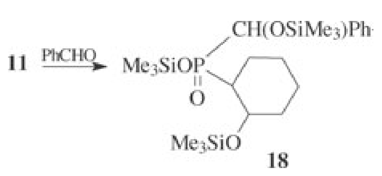
Phosphonite **11** is a key compound for preparing various aminomethyl 2-trimethylsiloxycyclohexylphosphinates **12,13,15,16** by aminomethylation with various *N*-chloromethylamines under mild conditions (Eq. (5); cf, [8]).



Phosphinates **12,13,15** were prepared in high yields, and the yield of phosphinate **16** was as low as 35%. The second reaction product in the latter case was phosphonate **17** isolated in 40% yield. This reaction's result is explained by the decomposition of intermediate quasiphosphonium adduct **B** in two directions. The usual Arbuzov reaction leads to phosphinate **16**, whereas 1,2-elimination in adduct **B** proceeds with liberation of cyclohexene and subsequent formation of phosphonate **17**, which was obtained by us earlier (Eq. (6)).



Phosphonite **11** under mild conditions readily reacts with benzaldehyde to give unsymmetrical phosphinate **18** as a promising precursor of interesting substituted 1-hydroxymethyl (2-hydroxycyclohexyl) phosphinic acid (Eq. (7); cf. [5]).



(7)

The constants and NMR data of new functionalized 2-trimethylsiloxyalkylphosphonites, their analogues and derivatives **1–18** are presented in Tables 1 and 2. The elemental analysis data of synthesized compounds are summarized in Table 3.

EXPERIMENTAL

The ^1H, ^{13}C, and ^{31}P NMR spectra were registered on the Varian VXR-400 and Bruker Avance-400 spectrometers (400, 100, and 162 MHz, respectively) in $CDCl_3$ (**1–18**) against TMS (^1H, ^{13}C) and 85% H_3PO_4 in D_2O (^{31}P). All reactions were carried out under dry argon in anhydrous solvents.

*O-Trimethylsilyl-3-chloro-2-trimethylsiloxypropylphosphonite (***1***)*. A mixture of 16 g bis(trimethylsiloxy)phosphine, 5 g of epichlorohydrin, and 0.2 g of zinc chloride was heated at 110–130°C for 2 h and then distilled in a vacuum to give 13.3 g phosphonite **1**.

The compounds **2–10** were prepared similarly.

*O,O-Bis(trimethylsilyl)-2-trimethylsiloxycyclohexylphosphonite (***11***).* To a solution of 15.4 g of phosphonite **9** in 50 mL of diethyl ether, a solution of 10.1 g of sodium bis(trimethylsilyl)amide in 15 mL of ether was added dropwise, with stirring, at 10°C. The mixture was stirred for 0.5 h, and then a solution of 6.5 g of chlorotrimethylsilane in 20 mL of ether was added. The mixture was left to stand for 24 h, the precipitate that formed was filtered off, the solvent was removed, and the residue was distilled in a vacuum to give 14.9 g of phosphonite **11**.

*O-Trimethylsilyl(N-piperidinomethyl) 2-trimethylsiloxycyclohexylphosphinate (***12***)*

a. A mixture of 10 g of phosphonite **9**, 5.5 g of bis(*N*-piperidino)methane, and 0.2 g of zinc chloride was heated at 130°C for 1 h and then distilled to obtain 10.8 g of phosphinate **12**.

   Phosphinate **13** was prepared similarly.

b. To a solution of 9.4 g of phosphonite **11** in 50 mL of methylene chloride, a solution of 3.3 g of *N*-(chloromethyl)piperidine in 20 mL of methylene chloride was added dropwise with stirring at 10°C. The solvent was then removed, and the

TABLE 1 Yields, Product Constants and NMR Spectral Data for the $P^1C^1H_2C^2HC^3H_2X$ fragments[a] (δ, ppm; J, Hz) of Compounds **1–8**[a]

No	*Yield* (%)	*Bp (°C)* (*p, mmHg*)	n_D^{20}	$\delta(C^1)$ *d/d. d*	$^1J_{PC}$	$^3J_{PC}$	$\delta(C^2)$ *s*	$\delta(C^3)$ *d/d. d*	$^1J_{PC}$	$^3J_{PC}$	$\delta(P^1)$ *s*[b]	$\delta(P^2)$ *s*[b]
1[c]	81	115 (1)	1.4468	37.66	96.1	—	68.69	49.77	—	14.8	18.89	—
				37.77	93.9	—	68.89	49.25	—	10.3	18.11	—
2[c]	78	150 (1)	1.4435	40.71	95.6	4.1	64.48	36.38	135.0	12.1	19.40	23.89
				40.07	93.7	4.9	64.53	35.45	134.2	7.8	19.05	24.16
3	76	142 (4)	1.4410	32.67	137.9	—	68.72	49.72	—	9.6	24.14	—
4	83	165 (1)	1.4415	35.34	136.4	7.9	64.32	35.34	136.4	7.9	25.07	25.07
5	81	136 (4)	1.4372	34.66	143.1	—	67.63	48.36	—	6.9	5.51	—
6	80	142 (0.5)	1.4421	37.87	141.1	10.6	63.48[d]	36.06	137.5	4.4	5.96	25.27
7[e]	85	160 (6)	1.4528	34.46	93.5	—	67.40[d]	47.93	—	9.1	47.93	—
				34.71	92.0	—	67.52[d]	48.33	—	12.5	48.80	—
8[e]	72	155 (1)	1.4520	36.87	92.4	4.0	62.69	33.28	134.9	7.3	48.60	24.30
				36.57	90.8	4.9	62.64	34.45	135.2	11.1	48.34	23.84

[a] All signals of alkyl and trimethylsilyl groups are in the standard area. The ^1H NMR signals of the protons of the groups $C^1H_2C^2HC^3H_2$ are multiplets. According to the NMR spectra, compounds **1,2,7.8** are mixtures of two stereoisomers. Their ratio was determined from the ^1H NMR and ^{31}P NMR spectra as 70:30 for **1** and as 55:45 for **2,7,8**. The spectral parameters of the major isomer are given first.

[b] Data of $^{31}P\{^1H\}$ spectra.

[c] In ^1H NMR spectra, PH fragments, d, $^1J_{PH}$, **1**: 7.12, 553.2 and 7.15, 553.4; **2**: 7.17, 549.6 and 7.24, 552.4.

[d] d, $^2J_{PC}$, **6**, 3.8; **7**, 3.0 and 3.8.

[e] Fragments PCH_3. In ^1H NMR spectra, d, $^2J_{PH}$, **7**: 1.06, 14.4, and 1.07, 14.4; **8**: 0.86, 14.4, and 0.88, 14.8. In ^{13}C NMR spectra, d, $^1J_{PC}$, **7**: 15.13, 93.6 and 15.19, 94.2; **8**: 15.08, 92.5 and 15.19, 92.7.

TABLE 2 Yields, Product Constants, and NMR Spectral Data for the $PC^1HC^2(C^3H_2)C^2$ HO, PC^4H_2 N, $PC^4H_2C^5H_2C^6{=}O$, and PC^4 HO fragments[a] (δ, ppm; *J*, Hz) of Compounds **9–18**[a]

No	*Yield* (%)	*Bp (°C)* (*p, mmHg*), (*mp,* °*C*)	n_D^{20}	*Ratio* (%)	$\delta(C^1)d$	$^1J_{PC}$	$\delta(C^2)s/d$	$^2J_{PC}$	$\delta(C^3)s/d$	$^2J_{PC}$	$\delta(C^4)d$	$^1J_{PC}$	$\delta(P)s$[b]
9[c]	78	105 (1)	1.4512	80	46.75	101.3	70.64	—	35.97	—	—	—	24.52
				20	45.93	100.3	71.01	—	35.86	—	—	—	24.27
10	83	110 (2)	1.4548	85	45.50	137.7	70.31	4.2	35.97	11.6	—	—	28.01
				15	43.86	136.5	68.98	5.7	35.47	15.2	—	—	29.43
11	78	93 (1)	1.4497	100	54.54	27.3	70.54	13.3	35.68	—	—	—	158.82
12	89	160 (1),	—	60	44.15	94.0	71.11	3.9	36.13	11.8	59.91	109.2	42.85
		(42)		40	43.91	91.7	71.95	4.9	36.27	15.3	59.51	109.2	40.61
13	86	164 (1)	1.4705	60	43.86	95.1	70.79	3.8	35.79	11.9	59.18	107.8	42.02
				40	43.28	92.9	71.80	5.6	36.05	15.5	58.80	109.8	39.93
14[d]	83	164 (2)	1.4565	70	44.90	97.2	70.95	3.6	35.96	11.8	27.52	96.3	46.11
				30	44.68	94.6	72.04	5.5	36.29	15.4	27.09	96.6	45.34
15[e]	68	158 (2)	1.4698	70	45.57	97.6	71.13	4.2	35.89	11.6	43.47	101.7	40.10
				30	45.79	93.0	71.73	5.3	35.99	9.9	44.38	102.2	39.65
16	35	175 (1)	1.4675	55	45.11	94.4	70.81	—	34.45	4.2	50.07	102.3	38.54
				45	45.01	96.6	71.47	—	33.45	5.8	50.01	102.3	38.20
18[f]	87	148 (0.5)	—	70	41.72	92.7	71.67	—	36.00	11.8	74.64	105.7	39.01
		(34)		30	40.48	93.5	72.40	—	36.57	12.1	74.30	109.6	40.95

[a] All signals of alkyl, phenyl, and trimethylsilyl groups are in the standard area. The ^1H NMR spectra of products fragments show expected signals that look like as overlapping multiplets. According to the NMR spectra, all compounds except **11** are mixtures of two stereoisomers. Their ratio was determined from the ^1H and ^{31}P NMR spectra. The spectral parameters of the major isomer are given first. Phosphonate **17**, yield 40%, bp 152°C (2 mmHg), mp 49°C. Fragment PCH_2 N: δ_H 3.12d, $^2J_{PH}$10.8; δ_C 46.52d, $^2J_{PC}$ 169.8; δ_H –0.05 s (cf. [10]).

[b] Data of $^{31}P\{^1H\}$ spectra.

[c] In ^1H NMR, PH fragments, d, $^1J_{PH}$: 7.08, 557.6, and 7.07, 558.1.

[d] In ^{13}C NMR, C^5, s; $C^6{=}O$, d, $^3J_{PC}$: 29.26 and 29.08; 172.91, 15.6, and 172.73, 15.3.

[e] In ^{13}C NMR, NC=O, s: 169.18 and 169.82.

[f] In ^1H NMR, C^4 H, d, $^2J_{PH}$, 5.03, 6.4 and 5.14, 7.2.

TABLE 3 Elemental Analyses Data of Synthesized Compounds[a]

			Calcd. (%)		*Found (%)*	
No	*Empirical Formula*	*Formula Weight*	*C*	*H*	*C*	*H*
1	$C_9H_{24}ClO_3PSi_2$	302.89	35.69	7.99	35.52	7.86
2	$C_{13}H_{34}O_6P_2Si_2$	404.53	38.60	8.47	38.41	8.28
3	$C_{10}H_{24}ClO_4PSi$	302.81	39.67	7.99	39.49	7.83
4	$C_{14}H_{34}O_7P_2Si$	404.45	41.57	8.47	41.32	8.39
5	$C_{12}H_{32}ClO_4PSi_3$	391.07	36.86	8.25	36.54	8.02
6	$C_{16}H_{42}O_7P_2Si_3$	492.71	39.00	8.59	38.78	8.47
7	$C_9H_{22}ClO_3PSi$	272.78	39.63	8.13	39.51	7.98
8	$C_{13}H_{32}O_6P_2Si$	374.42	41.70	8.61	41.53	8.50
9	$C_{12}H_{29}O_3PSi_2$	308.51	46.72	9.47	46.49	9.39
10	$C_{13}H_{29}O_4PSi$	308.42	50.62	9.48	50.54	9.52
11	$C_{15}H_{37}O_3PSi_3$	380.69	47.33	9.80	47.12	9.65
12	$C_{18}H_{40}NO_3PSi_2$	405.65	53.29	9.94	53.01	9.87
13	$C_{17}H_{38}NO_4PSi_2$	407.64	50.09	9.40	49.78	9.35
14	$C_{18}H_{41}O_5PSi_3$	452.74	47.75	9.13	47.59	8.98
15	$C_{17}H_{38}NO_4PSi_2$	407.64	50.09	9.40	49.86	9.28
16	$C_{15}H_{36}NO_5PSSi_2$	429.67	41.93	8.44	41.74	8.28
18	$C_{22}H_{43}O_4PSi_3$	486.81	54.28	8.90	54.01	8.79

[a] The elemental analysis of phosphonate **17** was made in [10].

residue was distilled in a vacuum to give 7.9 g of phosphinate **12**, yield 79%.

The compounds **13** (yield 74%), **15–17** were prepared similarly.

O-Trimethylsilyl-2-(trimethylsiloxycarbonyl)ethyl-(2-trimethylsiloxycyclohexyl)phosphinate (**14**). To a solution of 5.2 g of phosphonite **9** in 50 mL of methylene chloride, 3.5 g of trimethylsilyl acrylate and 2 mL triethylamine were added, then the solvent was distilled off on a water bath, the residue heated at 100°C for 1 h, and then distilled in a vacuum to give 6.3 g of compound **14**.

O-Trimethylsilyl-1-(trimethylsiloxy)benzyl(2-trimethylsiloxycyclohexyl)phosphinate (**18**). To a solution of 13.5 g of phosphonite **11** in 30 mL of methylene chloride, a solution of 3.7 g of benzaldehyde in 10 mL of methylene chloride was added, dropwise with stirring, at 10°C. The reaction mixture was stirred for 0.5 h and heated to boil. The solvent was removed, and the residue distilled in a vacuum to give 14.8 g of phosphinate **18** (cf. [5]).

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