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Synthesis of the New Types of *N*-Unsubstituted Aminomethylenebisorganophosphorus Acids and Their Derivatives

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ABSTRACT: *The interaction of trimethylsilyl esters of trivalent organophosphorus acids containing PH and $POSiMe_3$ groups with hydrochlorides of ethoxymethylene imines is a convenient method for the synthesis of new trimethylsilyl esters of N-unsubstituted aminomethylenebisorganophosphorus acids with three and four coordinated phosphorus. Also trimethylsilyl trifluoromethanesulfonate as effective catalyst is used for the similar interaction of hydrochlorides of ethoxymethylene imines with tris(trimethylsilyl)phosphite. The corresponding bisorganophosphorus acids and their derivatives are presented.* © 2014 Wiley Periodicals, Inc. Heteroatom Chem. 26:101–105, 2015; View this article online at wileyonlinelibrary.com. DOI 10.1002/hc.21220

INTRODUCTION

The numerous aminomethylenebisorganophosphorus acids and their derivatives containing aromatic and heterocyclic moieties as well as unsubstituted amino groups are interesting organophosphorus biomimetics of amino acids and natural pyrophosphates and widely used as effective polydentate ligands and prospective biologically active compounds with the multifunctional mode of action [1–9]. Recently, we developed the convenient synthetic methods for the preparation of the some bisorganophosphorus compounds of the similar structure using various formamides and their derivatives [10–12].

In the present work, we report the results of the interaction of the trimethylsilyl esters of trivalent organophosphorus acids including PH and $POSiMe_3$ groups with various hydrochlorides of ethoxymethylene imines (Pinner compounds) [13] resulting in the formation of the new trimethylsilyl esters of *N*-unsubstituted aminomethylenebisorganophosphorus acids with three and four coordinated phosphorus.

RESULTS AND DISCUSSION

So the excess of most reactive bis(trimethylsiloxy)phosphine smoothly reacts with substituted hydrochlorides of ethoxymethylene imines in methylene chloride to give diphosphonites **1a–d**. Evidently, there are three simultaneous reactions of the transformation of the NH·HCl moiety into the imino group, the addition to C(R)=N moiety, and the substitution of the ethoxy group in course of this process. Diphosphonites **1a–d** are easily silylated by bis(trimethylsilyl)amine in the presence of trimethylchlorosilane to form diphosphonites **2a–d** in good yields, and diphosphonites **3a-d** with $NHSiMe_3$ groups are observed by NMR spectra only as by-products of slow trimethylsilylation of amino groups (Eq. (1)). Note that the route of formation of

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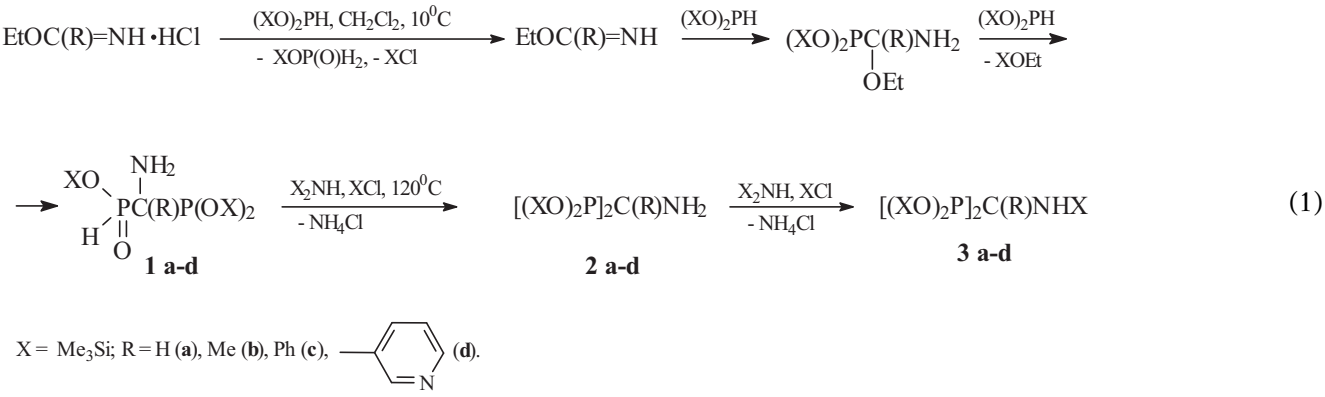
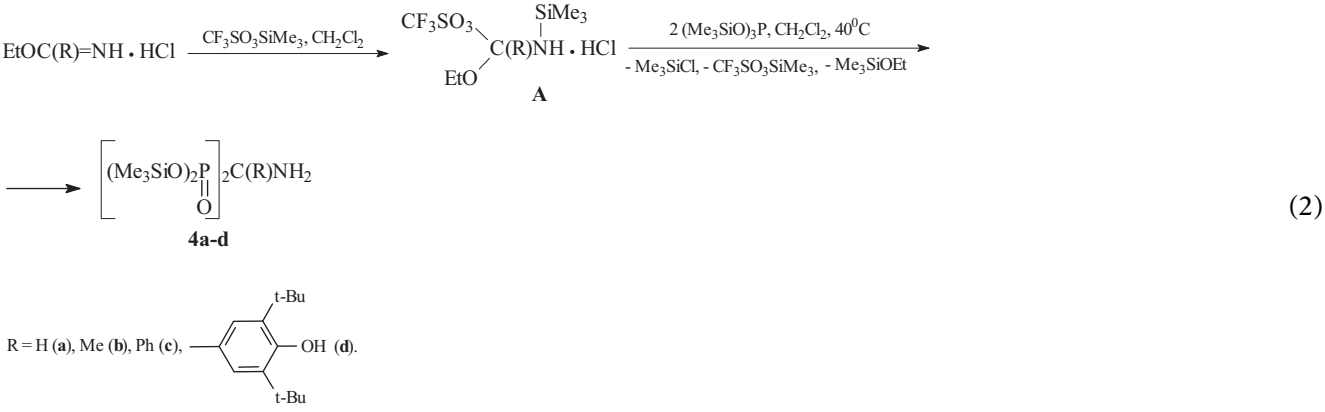
compounds **1–3** is similar to the routes, which are proposed by us recently (cf [10–12]).



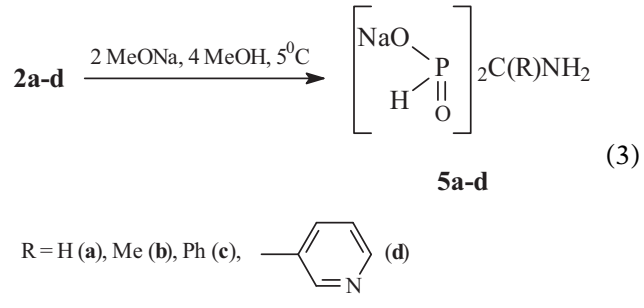
(1)

Also hydrochlorides of ethoxymethylene imines react with an excess of tris(trimethylsilyl)phosphite under the same conditions only in the presence of trimethylsilyl trifluoromethanesulfonate as a catalyst to give diphosphonates **4a–d** in good yields. Evidently the catalytic effect of trimethylsilyl trifluoromethanesulfonate is based on activation of the C=N groups via generation of electrophilic adducts **A** in the course of this reaction (Eq. (2)) (cf [12, 14]).



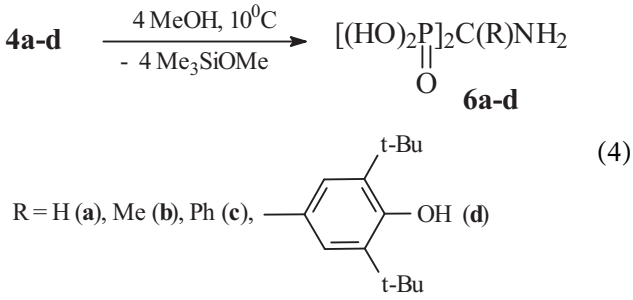
(2)

The treatment of diphosphonites **2a–d** with a dilute solution of sodium methylate in methanol results in the formation of the water-soluble disodium diphosphonites **5a–d** as white hygroscopic crystals in high yields (Eq. (3)).



(3)

Under similar conditions, diphosphonates **4a–d** are easily transformed to corresponding diphosphonic acids **6a–d** via treatment with methanol excess in high yields (Eq. (4)).



(4)

The structures of obtained bisphosphorus acids and their derivatives **1–6** are confirmed by the ^{1}H, ^{13}C, and ^{31}P NMR spectra, which show characteristic signals of the $P_2CR(NH_2)$ moieties whose

TABLE 1 Yields, Products Constants, and NMR Spectral Data (δ (ppm), J (Hz)) for Diphosphonites **1a–d**[a] with the $P^1C^1(R)P^2(O)H$ Groups

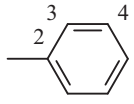
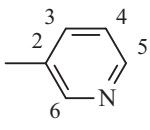
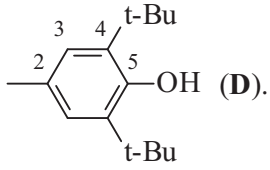
Number	Yield (%)	Bp (°C) (p (mm Hg))	Ratio (%)	δ_H (PH) d	$^1J(P^2H)$	$\delta(C^1)$t	$^1J(P^1C)$	$^1J(P^2C)$	$\delta(P^1)$d	$\delta(P^2)$ d	$^2J_{PP}$
1a	78	122 (1)	60	6.91	551.2	59.24	38.2	91.0	147.25	23.88	39.7
			40	6.92	551.2	59.90	40.1	94.1	146.32	25.58	50.2
1b[b]	68	121 (0.5)	35	6.58	550.8	55.81	34.3	67.0	145.83	30.74	53.6
			30	6.64	551.2	56.15	34.7	68.7	146.34	29.05	51.5
			20	6.57	545.2	55.47	32.7	66.3	145.39	28.14	41.6
			15	6.54	546.8	54.73	34.3	71.1	144.97	31.91	55.4
1c	[a]	[a]	80	–	–	–	–	–	142.45	28.88	65.4
			20	–	–	–	–	–	141.04	24.96	71.4
1d	[a]	[a]	70	–	–	–	–	–	142.15	27.51	61.4
			30	–	–	–	–	–	141.24	23.61	65.4

[a]Diphosphonites **1a–d** are the mixtures of stereoisomers, their ratio is determined by the ^{31}P NMR spectra, and diphosphonites **1c,d** are observed only as intermediates by ^{31}P NMR spectra. The data of $^{31}P–\{^1H\}$ spectra are presented. In ^1H NMR spectra, the signals of Me_3Si, NH_2, CH_3C^1, C_6H_5, C_5H_4N, and C^1H groups are overlapping multiplets in the standard area.
[b]In ^{13}C NMR spectra for the **Me**C^1 group of compound **1b**, δ_C, d ($^2J_{PC}$): 15.8 (19.1), 15.29 (18.3), 14.04 (22.4), and 13.61 (20.8)—for each stereoisomer.

TABLE 2 Yields, Products Constants, and NMR Spectral Data (δ (ppm), J (Hz)) for Compounds **2a–d**, **3a–d**, and **4a–d**[a] with the $P_2C^1(R)NH_2$ Groups

Number	Yield (%)	Bp (°C) (p (mm Hg)) (mp (°C))	$\delta(H)$ NH_2 t	$^3J_{PH}$	$\delta(H)$ $SiMe_3$ s	$\delta(C^1)$t	$^1J_{PC}$	$\delta(C)SiMe_3$ s	$\delta(P)$s
2a	84	126 (1)	2.21[b]	6.2[b]	0.10, 0.11	68.98	38.0	1.37	153.83
2b	88	124 (0.5)	0.92	10.2	0.01, 0.02	60.30	32.8	1.24	154.54
2c	74	144 (1)	1.60	7.6	–0.16, 0.04	70.35	41.5	0.92, 1.35	149.74
2d	72	145 (1)	1.42	9.6	–0.28, –0.13	69.16	41.5	0.80, 1.14	148.07
4a	69	139 (2)	1.19[b]	13.6[b]	–0.02, 0.01	50.66	155.1	0.72, 0.87	3.43
4b	73	127 (1)	1.13	12.8	–0.08[c], 0.09[c]	51.58	152.5	0.73, 0.78	6.65
4c	72	152 (1)	1.72	13.0	–0.24[c], –0.20[c]	59.63	147.7	0.45, 0.52	2.23
4d	89	(52)	1.20	br. s	0.06, 0.07	59.65	149.3	0.68, 0.77	3.27

[a]In ^1H NMR spectra, C^1H groups for compounds: **2a**, δ_H 2.6–2.7 m; **4a**, δ_H 2.6–2.9 m. In NMR spectra, the **CH_3** group for compounds: **2b**, δ_H 0.76 t, $^3J_{PH}$ 12.4, δ_C 14.55 t, $^2J_{PC}$ 17.6; **4b**, δ_H 0.99 t, $^3J_{PH}$ 16.8, δ_C 20.03 s; group **B** for compounds: **2c**, δ_H 6.9–7.4 m, δ_C 138.75 t (C^2, $^2J_{PC}$ 10.4), 126.73 t (C^3, $^3J_{PC}$ 8.8), 127.43 s (C^4), 125.26 s (C^5); **4c**, δ_H 6.8–7.6 m, δ_C 135.77 br. s (C^2), 127.18 s and 127.25 s (C^3, C^4), 126.79 s (C^5); group **C** for compound: **2d**, δ_H 6.92 dd (C^4H, $^3J_{HH}$ 4.8 and 8), 7.52 d (C^3H, $^3J_{HH}$ 8), 8.10 d (C^5H, $^3J_{HH}$ 4.8), 8.48 s (C^6H), δ_C 151.61 s (C^2), 134.05 t (C^3, $^3J_{PC}$ 7.2), 135.03 s (C^4), 146.07 s (C^5), 148.28 t (C^6, $^3J_{PC}$ 9.6); group **D** for compound: **4d**, δ_H 1.34 s (Me_3C), 5.08 br. s (OH), 7.63 s (C_6H_2); δ_C 126.42 s (C^2), 125.03 (C^3), 139.46 s (C^4), 152.31 s (C^5), 35.12 s (Me_3**C**), 30.98 s (**Me_3**C); by-products, for: **3a**, δ_P 151.33 s; **3b**, δ_C 62.36 t (C^1, $^1J_{PC}$ 33.5), 13.09 t (Me, $^2J_{PC}$ 19.2), δ_P 151.21; **3c**, δ_P 141.14 s; **3d**, δ_P 141.18 s.

Groups:  (**B**),  (**C**),  (**D**).

[b]dt, $^3J_{HH}$ for compounds: **2a**, 12; **4a**, 8.
[c]d, $^4J_{PH}$ for compounds: **4b**, 2 and 1.6; **4c**, 2.8 and 2.8.

parameters are presented in Tables 1–3. The elemental analysis data of synthesized compounds are summarized in Table 4.

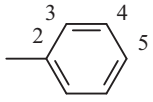
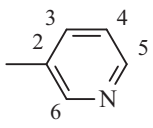
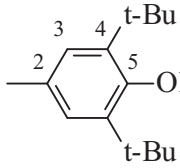
CONCLUSIONS

So the facile synthetic routes to *N*-unsubstituted aminomethylenebisorganophosphorus acids and their derivatives starting from trimethylsilyl esters of trivalent organophosphorus acids containing PH and $POSiMe_3$ groups and hydrochlorides of ethoxymethylene imines were developed. Also the synthesized compounds **1–6** containing some reactive groups (NH_2, POSi, PH) are the promising synthons for the preparation of various functionalized aminomethylenebisphosphorus-containing substances such as bisphosphorus-containing peptides. Also these compounds are perspective polydentate ligands and biologically active substances with versatile properties.

TABLE 3 Yields, Products Constants, and NMR Spectral Data (δ (ppm), J (Hz)) for Salts **5a–d** and Acids **6a–d**[a] with the $P_2C^1(R)NH_2$ Groups

Number	*Yield (%)*	*Mp (°C)*	*δ(H)PH d*	*$^1J_{PH}$*	*δ (C^1)t*	*$^1J_{PC}$*	*δ (P)[b]s*
5a	95	[c]	6.90	528.8	53.20	84.6	22.40
5b	97	[c]	6.67	524.0	51.99	89.4	29.45
5c	96	[c]	6.92	538.4	60.62	85.4	27.10
5d	94	[c]	6.82	541.2	60.34	75.9	27.84
6a	96	159	–	–	54.89	147.4	15.83
6b	96	252	–	–	51.69	122.2	11.15
6c	97	223	–	–	60.26	120.5	8.54
6d	98	184	–	–	62.84	118.2	11.06

[a]In ^{1}H NMR spectra, C^1H groups for compounds: **5a**, δ_H 2.67 t, $^2J_{PH}$ 15.6; **6a**, δ_H 3.82 t, $^2J_{PH}$ 19.2; there is a rapid exchange of OH and NH_2 protons. The signals of C_6H_5 and C_5H_4N groups are multiplets in the standard area; fragment C_6H_2 of acid **6d**, δ_H 7.50 s. In NMR spectra, CH_3 groups for compounds: **5b**, δ_H 1.07 t, $^3J_{PH}$ 16, δ_C 15.26 s; **6b**, δ_H 1.12 t, $^3J_{PH}$ 13.2, δ_C 15.64 s; group **B** for compounds: **5c**, δ_C 135.93 s (C^2), 126.15 s (C^3), 128.55 s (C^4), 127.04 s (C^5); **6c**, δ_C 131.22 s (C^2), 125.52 s (C^3), 126.20 s (C^4), 124.27 s (C^5); group **C** for compound: **5d**, δ_C 151.59 s (C^2), 135.90 s (C^3), 136.14 s (C^4), 146.30 s (C^5), 147.43 s (C^6); group **D** for compound: **6d**, δ_H 1.30 s (t-Bu), 5.30 br. s (OH), δ_C 126.89 s (C^2), 124.43 (C^3), 138.65 s (C^4), 151.09 s (C^5), 34.35 s (Me_3**C**), 30.08 s (**Me$_3$**C).

Groups:  (**B**),  (**C**),  (**D**).

[b]The data of ^{31}P–{^{1}H} spectra are presented.
[c]The compounds are decomposed by heating at 100°C.

TABLE 4 Elemental Analyses Data of Compounds **4b–d, 5a–d,** and **6a–d**[a]

			Calculated (%)		*Found (%)*	
Number	*Empirical Formula*	*Formula Weight*	*C*	*H*	*C*	*H*
4b	$C_{14}H_{41}NO_6P_2Si_4$	493.77	34.05	8.37	33.78	8.23
4c	$C_{19}H_{43}NO_6P_2Si_4$	555.85	41.06	7.80	40.74	7.72
4d	$C_{27}H_{59}NO_7P_2Si_4$	684.07	47.41	8.69	47.26	8.61
5a	$CH_5NNa_2O_4P_2$	203.07	5.91	2.48	5.79	2.52
5b	$C_2H_7NNa_2O_4P_2$	217.02	11.07	3.25	10.88	3.13
5c	$C_7H_9NNa_2O_4P_2$	279.09	30.13	3.25	29.98	3.28
5d	$C_6H_8N_2Na_2O_4P_2$	280.07	25.73	2.88	25.59	2.97
6a	$CH_7NO_6P_2$	191.03	6.29	3.70	6.12	3.74
6d	$C_2H_9NO_6P_2$	205.05	11.71	4.42	11.58	4.47
6c	$C_7H_{11}NO_6P_2$	267.13	31.48	4.15	31.32	4.19
6d	$C_{15}H_{27}NO_7P_2$	395.34	45.57	6.88	45.43	6.94

[a]The air-sensitive compounds **1a–d, 2a–d, 3a–d,** and **4a** were analyzed as their air-stable derivatives **5a–d** and **6a–d**.

EXPERIMENTAL

The ^{1}H, ^{13}C, and ^{31}P NMR spectra were registered on a Bruker Avance-400 spectrometer (400, 100, and 162 MHz, respectively) in $CDCl_3$ (**1–4**), D_2O (**5**), or a mixture of CD_3OD and C_5D_5N (**6**) against tetramethylsilane (^{1}H and ^{13}C) and 85% H_3PO_4 in D_2O (^{31}P). All reactions were carried out under dry argon in anhydrous solvents. The starting trimethylsilyl esters of trivalent phosphorus acids were prepared as described in [15, 16], and the starting hydrochlorides of ethoxymethylene imines were discussed in Ref. [13].

*O,O,O-Tris(trimethylsilyl) 1-Aminoethylidenediphosphonite (**1b**)*

A solution of bis(trimethylsiloxy)phosphine (13.0 g, 62.0 mmol) in 15 mL of methylene chloride was added to a mixture of hydrochloride of 1-ethoxyethylidene imine (2.5 g, 20.0 mmol) under stirring at 10°C. The mixture was stirred for 1 h, then the solvent was removed, and 20 mL of bis(trimethylsilyl)amine was added to the mixture. The mixture was refluxed, the solvent was removed, and the residue was distilled to give 5.4 g of diphosphonite **1b**. According to NMR spectra,

diphosphonite **2b** was observed as a by-product (10%).

Diphosphonite **1a** was prepared similarly, and diphosphonites **1c,d** were observed only by ^{31}P NMR spectra as intermediates in the course of preparation of diphosphonites **2c,d**.

*O,O,O,O-Tetra(trimethylsilyl) 1-Aminoethylidenediphosphonite (**2b**)*

A mixture of diphosphonite **1b** (5.4 g, 14.0 mmol), bis(trimethylsilyl)amine (20 mL) and chlorotrimethylsilane (5.0 g, 46.0 mmol) was refluxed to complete ammonium chloride sublimation. The excess of bis(trimethylsilyl)amine was removed, and the residue was distilled to obtain 5.6 g of diphosphonites **2b**. According to NMR spectra, diphosphonite **3b** was observed as a by-product (15%).

Diphosphonites **2a,c,d** were prepared similarly, and diphosphonites **3a,c,d** were observed as a by-products (5–10%).

*O,O,O,O-Tetra(trimethylsilyl) 1-Aminoethylidenediphosphonate (**4b**)*

Trimethysilyl trifluoromethanesulfonate (0.3 g, 1.3 mmol) was added with stirring to a mixture of tris(trimethylsilyl)phosphite (10.0 g, 33.5 mmol) and hydrochloride of 1-ethoxyethylidene imine (1.3 g, 10.5 mmol) in 10 mL of methylene chloride. The mixture was refluxed for 1 h, the solvent was removed, and bis(trimethylsilyl)amine (15 mL) was added to the residue. The mixture was refluxed to complete sublimation of ammonium chloride, and the residue was distilled to obtain 3.8 g of diphosphonate **4b**.

Diphosphonates **4a,c** were obtained similarly. Diphosphonate **4d** was crystallized from the mixture by the addition of 5 mL of diethyl ether and 10 mL of hexane. The crystals of diphosphonate **4d** were kept in a vacuum (1 mm Hg) for 1 h.

*Disodium 1-Aminoethylidenediphosphonite (**5b**)*

A solution of diphosphonite **2b** (5.6 g, 12.0 mmol) in 15 mL of ether was added with stirring at 5°C to a solution of sodium methylate (1.3 g, 24.0 mmol) in 30 mL of methanol. The resulting mixture was heated to boiling, the solvent was removed, and residue was kept in a vacuum for for 1 h (1 mm Hg) to give 2.5 g of salt **5b**. The salts **5a,c,d** were prepared similarly.

*1-Aminoethylidenediphosphonic Acid (**6b**)*

A solution of diphosphonate **4b** (3.8 g, 7.7 mmol) in ether (10 mL) was added with stirring in 20 mL of methanol cooled to 10°C. The mixture was heated to boiling. The solvent was removed, and white crystals were kept in a vacuum (1 mm Hg) for 1 h to give 1.5 g of acid **6b**. Acids **6a,c,d** were prepared similarly.

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