Synthesis of new aryl-substituted methylphosphonic and methylenediphosphonic acids and their derivatives

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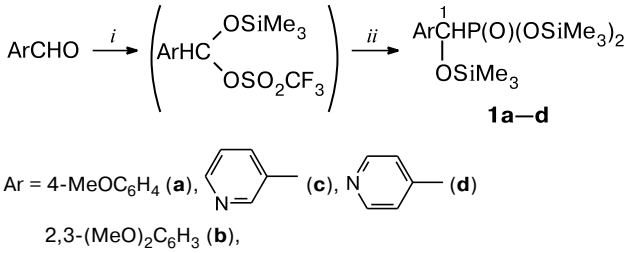
Simple and versatile synthetic procedures towards new aryl-substituted hydroxymethylphosphonic and methylenediphosphonic acids *via* reactions of either aromatic aldehydes or their derivatives with phosphites were elaborated.

Key words: aryl-substituted hydroxymethyl phosphonates, methylene diphosphonates, trimethylsilyl phosphites, trimethylsilyl trifluoromethanesulfonate.

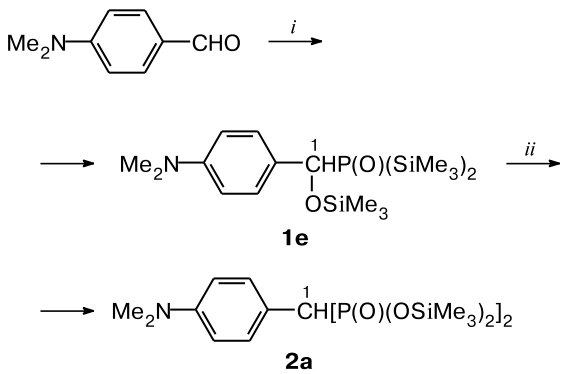
Functionalized (hydroxymethyl)phosphonates, (methylene)diphosphonates, and their derivatives are widely used in organic synthesis. These compounds are of significant interest as efficient ligands and promising biologically active substances.[1,2] Reactions of trimethylsilyl esters of trivalent phosphorus acids with different carbonyl compounds constitute a convenient approach to a series of functionalized hydroxymethyl organophosphorus compounds, for instance, structural biomimetics of α-hydroxyalkyl carboxylic acids.[3—7] In the present work, we performed a detail study of the reactions of diethyltrimethylsilyl and tris(trimethylsilyl) phosphites with different aromatic aldehydes and their functional derivatives catalyzed by trimethylsilyl triflate, zinc chloride, and cadmium iodide. This approach is interesting as a plausible direct pathway towards new aryl-substituted (methylene)diphosphonates, important structural analogs of natural pyrophosphates. It was found that trimethylsilyl triflate noticeably accelerates an exothermic addition of tris(trimethylsilyl) phosphite to the carbonyl group of aromatic aldehydes. The reactions produce phosphonates **1** in high yields (Scheme 1). Apparently, the reaction proceeds *via* intermediate adducts, *i.e.*, electrophilic sulfonyl acetals (*cf.* Ref. 8).

Scheme 1



Reagents and conditions: *i.* $CF_3SO_3SiMe_3$, CH_2Cl_2, 40 °C; *ii.* $(Me_3SiO)_3P$, $-CF_3SO_3SiMe_3$.

Scheme 2



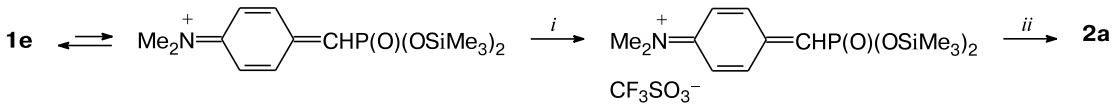
Reagents and conditions: *i.* $(Me_3SiO)_3P$, CH_2Cl_2, 40 °C; *ii.* $(Me_3SiO)_3P$, $CF_3SO_3SiMe_3$, $-(Me_3Si)_2O$.

It is of note that high isolated yield of phosphonate **1e** can be achieved only under catalyst-free reaction conditions. Reaction carried out in the presence of trimethylsilyl triflate unexpectedly gives high yield of diphosphonate **2a** instead of **1e** (Scheme 2). Under these conditions, phosphonate **1e** was detected by NMR ^1H, ^{13}C, and ^{31}P spectroscopy only in trace amounts (5%) and only before distillation of the reaction mixture.

Indeed, the easy substitution of trimethylsilyloxy group of phosphonate **1e** is a result of the activating effect exerted by the dimethylamino group in *para*-position to the trimethylsilyloxymethyl group, which facilitates formation of highly reactive intermediate methylene quinone (Scheme 3).

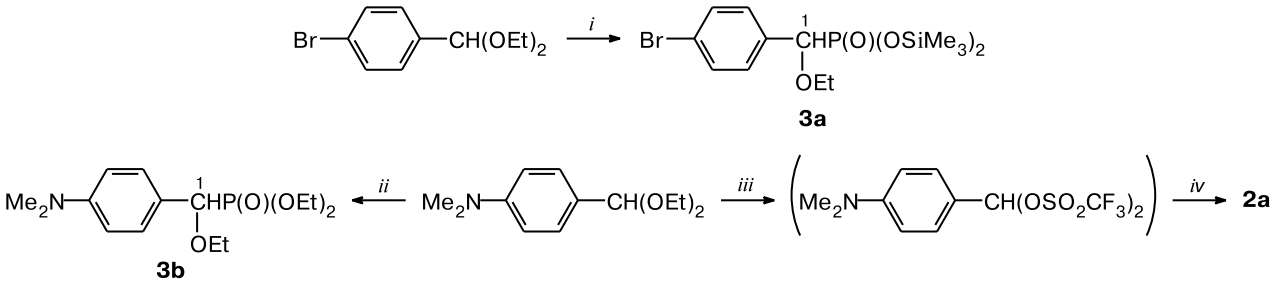
Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 2, pp. 0336—0341, February, 2017.

Scheme 3



Reagents and conditions: *i*. $CF_3SO_3SiMe_3$, $-(Me_3Si)_2O$; *ii*. $(Me_3SiO)_3P$, $-CF_3SO_3SiMe_3$.

Scheme 4



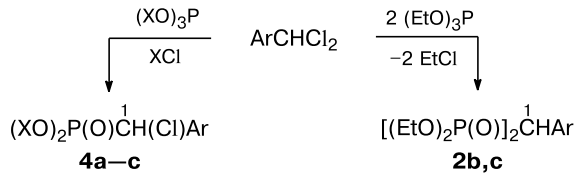
Reagents and conditions: *i*. $(Me_3SiO)_3P$, $CF_3SO_3SiMe_3$, 100 °C; *ii*. $(EtO)_2POSiMe_3$, CdI_2, $ZnCl_2$, 150 °C; *iii*. 2 $CF_3SO_3SiMe_3$, CH_2Cl_2, 40 °C; *iv*. $(Me_3SiO)_3P$.

Readily available diethyl acetals of aromatic aldehydes[9] react with trimethylsilyl phosphites similarly to aldehydes only when heated at 100—150 °C. Under these conditions, the reaction gives ethoxymethyl phosphonates **3** in high yields. For the synthesis of phosphonate **3b**, it is necessary to use cadmium iodide and zinc chloride as the catalysts, since the use of trimethylsilyl triflate is accompanied with replacement of the ethoxysilyl groups at the phosphorus atom by the trimethylsilyl groups leading to a complex product mixture. Note that 4-dimethylaminobenzaldehyde diethyl acetal reacts with tris(trimethylsilyl) phosphite similarly to the corresponding aldehyde producing high yield of diphosphonate **2a** in an exothermic reaction (Scheme 4). Enhanced reactivity of this acetal as compared with the corresponding aldehyde apparently can be explained by the formation of more electrophilic intermediate disulfonyl acetal.

For the reaction of readily available benzal chlorides[10] with triethyl phosphites and tris(trimethylsilyl) phosphites to occur, harsh conditions are required, *i.e.*, heating at 150—160 °C and zinc chloride as a catalyst. The reaction follows the Arbuzov reaction mechanism and produces either aryl-substituted chloromethyl phosphonates **4** or methylene diphosphonates **2b**,**c** depending on the starting phosphite structure (Scheme 5).

Thus, the direction of this reaction is determined by both the electronic effects of the substituents at the benzene ring of the starting benzal chlorides and the size of substituents in phosphites. Electronic effects of *o*- and *p*-substituents in the aromatic fragment also facilitate formation of highly reactive intermediates, *o*- and *p*-methylene quinones (Scheme 6).

Scheme 5



2: Ar = 4-$MeOC_6H_4$ (**b**), 2,5-$(MeO)_2C_6H_3$ (**c**)

4	X	Ar
a	Et	4-FC_6H_4
b	Et	2,3-$(MeO)_2C_6H_4$
c	Me_3Si	4-$MeOC_6H_4$

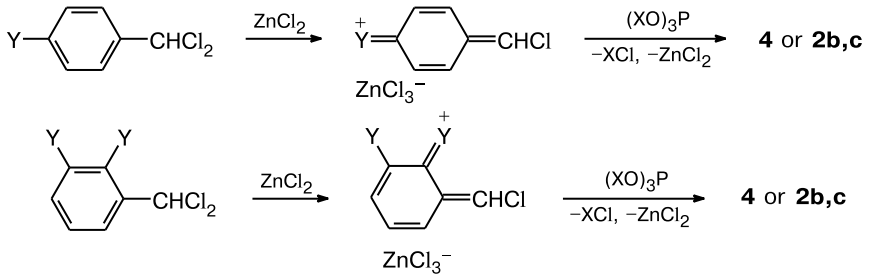
Conditions: 150—160 °C, $ZnCl_2$.

Diethyl trimethylsilyl phosphite non-selectively reacts with anisal chloride under similar conditions to give a mixture of diphosphonates **2b**,**d** in a 1 : 1 ratio. Subsequent treatment of the mixture of diphosphonates **2b**,**d** with concentrated hydrochloric acid and bis(trimethylsilyl)amine produces diphosphonate **2e** in high yield (Scheme 7).

Reaction of unsubstituted benzal chloride with excess triethylphosphite under severe conditions follows complex redox pattern to afford a mixture of benzyl phosphonate, pyrophosphate, and resinous products (Scheme 8).

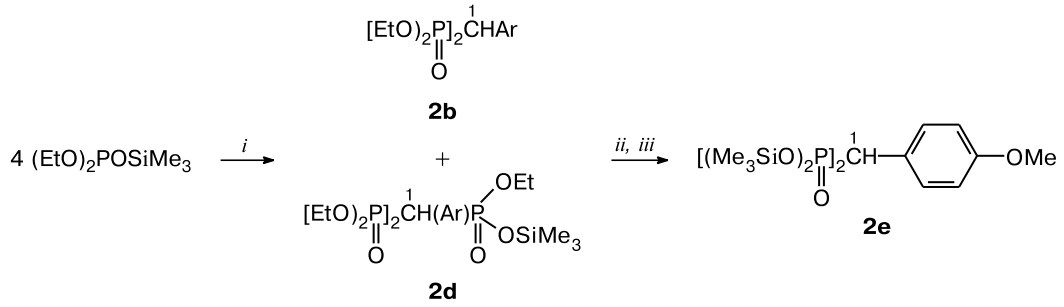
Compounds **1**—**3** are efficient building blocks for the synthesis of the corresponding aryl-substituted methylphosphonic acids. The latter compounds can serve as the polydentane ligands and show a wide range of biological activities. Thus, trimethylsilyl esters **1** and **2** smoothly react with excess methanol under mild conditions giving

Scheme 6



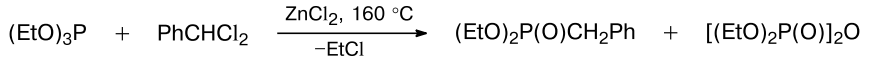
Y = F, MeO; X = Et, Me_3Si

Scheme 7



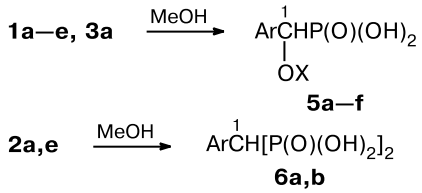
Reagents and conditions: *i*. 2 $ArCHCl_2$, −EtCl, −3 Me_3SiCl, $ZnCl_2$, 160 °C; *ii*. HCl, H_2O, 100 °C; *iii*. $(Me_3Si)_2NH$, 120 °C.

Scheme 8



functionalized mono- and diphosphonic acids **5** and **6**, respectively (Scheme 9).

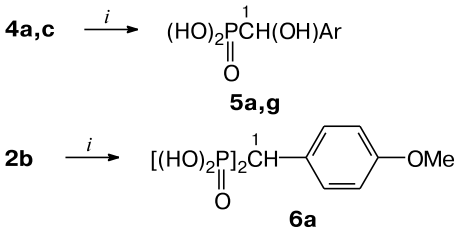
Scheme 9



Compound	Ar	X	Compound	Ar	X
5a	4-$MeOC_6H_4$	H	**5e**	4-$Me_2NC_6H_4$	H
5b	2,3-$(MeO)_2C_6H_3$	H	**5f**	4-BrC_6H_4	Et
5c	3-Py	H	**6a**	4-$MeOC_6H_4$	—
5d	4-Py	H	**6b**	4-$Me_2NC_6H_4$	—

Chloromethyl phosphonates **4a**,**c** and diphosphonate **2b** readily hydrolyze to hydroxymethylphosphonic (**5a**,**g**) and diphosphonic (**6a**) acids by refluxing with hydrochloric acid. Note that these conditions also bring about the C—Cl bond cleavage (Scheme 10).

Scheme 10



Ar = 4-$MeOC_6H_4$ (**5a**), 4-FC_6H_4 (**5g**)

Reagents and conditions: *i*. H_2O, HCl, 100 °C.

In summary, we elaborate simple and versatile synthetic procedures to access new aryl-substituted hydroxymethylphosphonic and methylenediphosphonic acids and their derivatives. The synthesized compounds **1**—**6**

are of interest as promising polydentate ligands and valuable biologically active substances.

Experimental

^1H, $^{13}C\{^1H\}$, and $^{31}P\{^1H\}$ NMR spectra were recorded with a Bruker Avance 400 instrument at working frequencies of 400, 100, and 162 MHz, respectively. The chemical shifts are given in the δ scale relative to Me_4Si (^1H, $^{13}C\{^1H\}$) and a 85% solution of H_3PO_4 in D_2O ($^{31}P\{^1H\}$). All reactions were carried out under dry argon in anhydrous solvents. The starting acetals of aromatic aldehydes,[9] substituted benzal chlorides,[10] and trimethylsilyl esters of trivalent phosphorus acids[3,4] were synthesized by the known procedures.

Bis(trimethylsilyl) 4-methoxyphenyl(trimethylsilyloxy)methylphosphonate (1a). To a stirred solution of tris(trimethylsilyl) phosphite (30 g, 0.10 mol) and *p*-anisaldehyde (5.5 g, 0.04 mol) in dichloromethane (40 mL), trimethylsilyl trifluoromethanesulfonate (0.6 g, 003 mol) was added. After an exothermic reaction ceased, the mixture was refluxed for 1 h and concentrated *in vacuo*. Vacuum distillation of the residue afforded 15.1 g (86%) of phosphonate **1a**, b.p. 144 °C (2 Torr). Found (%): C, 46.72; H, 8.02. $C_{17}H_{35}O_5PSi_3$. Calculated (%): C, 46.97; H, 8.12. ^1H NMR ($CDCl_3$), δ: −0.17 (s, Me_3Si); −0.06 (s, 2 Me_3Si); 3.56 (s, MeO); 4.62 (d, C(1)H, $^2J_{P,H}$ = 12.0 Hz); 6.62 (d, 2 CH_{Ph}, $^3J_{P,H}$ = 8.0 Hz); 7.08 (d, 2 CH_{Ph}, $^3J_{P,H}$ = 8.0 Hz). $^{13}C\{^1H\}$ NMR ($CDCl_3$), δ: −0.26 (s, Me_3Si); 0.49 (s, 2 Me_3Si); 54.89 (s, MeO); 71.76 (d, $^1J_{P,C}$ = 180.0 Hz); 113.14 (s), 128.32 (d, $^3J_{P,C}$ = 7.0 Hz); 129.92 (s), 159.20 (s, C_{Ph}). $^{31}P\{^1H\}$ NMR ($CDCl_3$), δ: −3.96 (s) (*cf.* Ref. 5).

Phosphonates **1b—e** were synthesized similarly; the only exception was a catalyst-free reaction in the case of **1e**.

Bis(trimethylsilyl) 2,3-dimethoxyphenyl(trimethylsilyloxy)methylphosphonate (1b). Yield 84%, b.p. 143 °C (0.5 Torr), m.p. 29 °C. Found (%): C, 46.26; H, 7.94. $C_{18}H_{37}O_6PSi_3$. Calculated (%): C, 46.52; H, 8.02. ^1H NMR ($CDCl_3$), δ: −0.21 (s, Me_3SiOC); −0.02 (s, 2 Me_3Si); 3.56 (s, MeO); 3.63 (s, MeO); 5.17 (d, C(1)H, $^2J_{P,H}$ = 14.4 Hz); 6.55—6.90 (m, C_6H_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$), δ: −0.31 (s, Me_3Si); 0.52 (s, 2 Me_3Si); 55.44 (s, MeO); 60.25 (s, MeO); 65.16 (d, $^1J_{P,C}$ = 182.8 Hz); 111.93 (s), 120.41 (d, $^3J_{P,C}$ = 3.2 Hz); 123.34 (s), 130.96 (s), 145.94 (d, $^3J_{P,C}$ = 8.0 Hz); 151.89 (s, C_{Ph}). $^{31}P\{^1H\}$ NMR ($CDCl_3$), δ: 3.71 (s).

***O,O*-Bis(trimethylsilyl) pyridine-3-yl(trimethylsilyloxy)methylphosphonate (1c).** Yield 89%, b.p. 152 °C (1 Torr). Found (%): C, 44.26; H, 7.89. $C_{15}H_{32}NO_4PSi_3$. Calculated (%): C, 44.41; H, 7.95. ^1H NMR ($CDCl_3$), δ: −0.11 (s, Me_3Si); −0.10 (s, Me_3Si); 0.02 (s, Me_3Si); 4.72 (d, C(1)H, $^2J_{P,H}$ = 15.2 Hz); 7.09—7.13 (m, CH_{Py}); 7.65 (d, CH_{Py}, $^3J_{H,H}$ = 8.0 Hz); 8.32—8.34 (m, CH_{Py}); 8.43 (s, CH_{Py}). $^{13}C\{^1H\}$ NMR ($CDCl_3$), δ: −0.26 (s, Me_3Si); 0.62 (s, Me_3Si); 0.74 (s, Me_3Si); 69.90 (d, C(1), $^1J_{P,C}$ = 179.3 Hz); 123.05 (s), 134.32 (s), 135.37 (d, $^3J_{P,C}$ = 4.6 Hz); 147.85 (d, $^3J_{P,C}$ = 6.5 Hz); 148.39 (s, C_{Py}). $^{31}P\{^1H\}$ NMR ($CDCl_3$), δ: 2.43 (s).

***O,O*-Bis(trimethylsilyl) pyridin-4-yl(trimethylsilyloxy)methylphosphonate (1d).** Yield 86%, b.p. 149 °C (1 Torr). Found (%): C, 44.28; H, 7.86. $C_{15}H_{32}NO_4PSi_3$. Calculated (%): C, 44.41; H, 7.95. ^1H NMR ($CDCl_3$), δ: −0.09 (s, Me_3Si); −0.07 (s, Me_3Si); 0.06 (s, Me_3Si); 4.68 (d, C(1)H, $^2J_{P,H}$ = 17.2 Hz); 7.18 (d, 2 CH_{Py}, $^3J_{H,H}$ = 5.6 Hz); 8.35 (d, 2 CH_{Py}, $^3J_{H,H}$ = 5.6 Hz). $^{13}C\{^1H\}$ NMR ($CDCl_3$), δ: −0.70 (s, Me_3Si); 0.15 (s, Me_3Si); 0.38 (s, Me_3Si); 70.59 (d, C(1), $^1J_{P,C}$ = 174.7 Hz); 121.45 (s, C_{Py}), 147.21 (br.s, C_{Py}); 148.54 (d, C_{Py}, $^3J_{P,C}$ = 2.0 Hz). $^{31}P\{^1H\}$ NMR ($CDCl_3$), δ: 1.85 (s).

Bis(trimethylsilyl) 4-dimethylaminophenyl(trimethylsilyloxy)methylphosphonate (1e). Yield 89%, b.p. 164 °C (1 Torr.), m.p. 55 °C. Found (%): C, 48.03; H, 8.49. $C_{18}H_{38}NO_4PSi_3$. Calculated (%): C, 48.29; H, 8.55. ^1H NMR ($CDCl_3$), δ: −0.29 (s, Me_3Si); −0.19 (s, Me_3Si); −0.16 (s, Me_3Si); 2.59 (s, Me_2N); 4.64 (d, C(1)H, $^2J_{P,H}$ = 16.0 Hz); 6.43 (d 2 CH_{Ph}, $^3J_{H,H}$ = 7.2 Hz); 6.93 (d, 2 CH_{Ph}, $^3J_{H,H}$ = 7.2 Hz). $^{13}C\{^1H\}$ NMR ($CDCl_3$), δ: −0.68 (s, Me_3Si); 0.12 (s, Me_3Si); 40.47 (s, Me_2N); 71.40 (d, C(1), $^1J_{P,C}$ = 181.4 Hz); 112.22 (s), 127.79 (d, $^3J_{P,C}$ = 6.0 Hz); 130.52 (s), 148.76 (s, C_{Ph}). $^{31}P\{^1H\}$ NMR ($CDCl_3$), δ: 4.44 (s) (*cf.* Ref. 5).

Tetrakis(trimethylsilyl) (4-dimethylaminophenyl)methylenediphosphonate (2a). To a solution of 4-dimethylaminobenzaldehyde diacetal (3.4 g, 0.015 mol) and tris(trimethylsilyl) phosphite (18.0 g, 0.060 mol) in dichloromethane (15 mL), a solution of trimethylsilyl trifluoromethanesulfonate (0.9 g, 0.004 mol) in dichloromethane (5 mL) was added. After an exothermic reaction ceased, the reaction mixture was kept at 20 °C for 24 h and concentrated *in vacuo*. The precipitate formed was collected and washed with chilled hexane to afford 8.6 g (96%) of diphosphonate **2a**, m.p. 144 °C. Found (%): C, 43.06; H, 8.06. $C_{21}H_{47}NO_6P_2Si_4$. Calculated (%): C, 43.20; H, 8.11. ^1H NMR ($CDCl_3$), δ: 0.07 (s, 4 Me_3Si); 3.22 (s, Me_2N); 3.48 (t, C(1)H, $^2J_{P,H}$ = 25.2 Hz); 7.53 (d, 2 $C_{Ph}H$, $^3J_{H,H}$ = 8.4 Hz); 7.65 (d, 2 $C_{Ph}H$, $^3J_{H,H}$ = 8.4 Hz). $^{13}C\{^1H\}$ NMR ($CDCl_3$), δ: 0.32 (s, 2 Me_3Si); 46.82 (s, Me_2N); 48.33 (t, C(1), $^1J_{P,C}$ = 135.9 Hz); 120.28 (s), 132.12 (t, $^3J_{P,C}$ = 5.9 Hz); 135.42 (t, $^3J_{P,C}$ = 8.5 Hz); 141.60 (s, C_{Ph}). $^{31}P\{^1H\}$ NMR ($CDCl_3$), δ: −1.47 (s).

Bis(trimethylsilyl) 4-bromophenyl(ethoxy)methylphosphonate (3a). To a solution of 4-bromobenzaldehyde diethylacetal (3.9 g, 0.015 mol) and tris(trimethylsilyl) phosphite (19.0 g, 0.08 mol) in dichloromethane (15 mL), a solution of trimethylsilyl trifluoromethanesulfonate (1.0 g, 0.0045 mol) in dichloromethane (5 mL) was added. The reaction mixture was heated (a boiling water bath) for 2 h with simultaneous distillation off of dichloromethane. Vacuum distillation of the residue afforded 5.0 g (74%) of phosphonate **3a**, b.p. 104 °C (2 Torr). Found (%): C, 40.86; H, 6.33. $C_{15}H_{28}BrO_4PSi_2$. Calculated (%): C, 41.00; H, 6.42. ^1H NMR ($CDCl_3$), δ: 0.07 (s, 2 Me_3Si); 1.05 (t, CH_3, $^3J_{H,H}$ = = 7.2 Hz); 3.30—3.40 (m, CH_2O); 4.43 (d, C(1)H, $^2J_{P,H}$ = 7.2 Hz); 7.15 (d, 2 CH_{Ph}, $^2J_{H,H}$ = 8.0 Hz); 7.30 (d, 2 CH_{Ph}, $^2J_{H,H}$ = 8.0 Hz). $^{13}C\{^1H\}$ NMR ($CDCl_3$), δ: 0.67 (s, 2 Me_3Si); 15.03 (s, Me); 66.38 (d, CH_2O, $^3J_{P,C}$ = 13.8 Hz); 78.11 (d, C(1), $^1J_{P,C}$ = 175.6 Hz); 121.89 (d, $^2J_{P,C}$ = 4.6 Hz); 129.49 (d, $^2J_{P,C}$ = 5.6 Hz); 131.16 (s), 134.70 (s, C_{Ph}). $^{31}P\{^1H\}$ NMR ($CDCl_3$), δ: 0.65 (s).

Diethyl 4-dimethylaminophenyl(ethoxy)methylphosphonate (3b). A mixture of 4-dimethylaminobenzaldehyde diethylacetal (3.4 g, 0.015 mol), diethyl trimethylsilyl phosphite (12.6 g, 0.060 mol), cadmium iodide (0.1 g, 0.0003 mol), and zinc chloride (0.1 g, 0.0004 mol) was heated at 140 °C until complete distillation off of ethoxytrimethylsilane (b.p. 74 °C). Vacuum distillation of the residue afforded 4.2 g (86%) of phosphonate **3b**, b.p. 195 °C (2 Torr). Found (%): C, 56.94; H, 8.26. $C_{15}H_{26}NO_4P$. Calculated (%): C, 57.13; H, 8.31. ^1H NMR ($CDCl_3$), δ: 0.97 (t, CH_3, $^3J_{H,H}$ = 7.2 Hz); 0.98 (t, CH_3, $^3J_{H,H}$ = 7.2 Hz); 1.05 (t, CH_3, $^3J_{H,H}$ = 6.8 Hz); 2.72 (s, Me_2N); 3.20—3.35 (m, CH_2O); 3.60—3.90 (m, 2 CH_2O); 4.29 (d, C(1)H, $^2J_{P,H}$ = 15.2 Hz); 6.47 (d, 2 CH_{Ph}, $^3J_{H,H}$ = 8.8 Hz); 7.08 (d, 2 CH_{Ph}, $^2J_{H,H}$ = 8.8 Hz). $^{13}C\{^1H\}$ NMR ($CDCl_3$), δ: 14.93 (s, Me); 16.17 (d, Me, $^3J_{P,C}$ = = 5.5 Hz); 40.15 (s, Me_2N); 62.37 (d, CH_2O, $^3J_{P,C}$ = 6.5 Hz);

62.58 (d, CH_2O, $^2J_{P,C}$ = 6.4 Hz); 65.39 (d, CH_2O, $^3J_{P,C}$ = 14.7 Hz); 77.99 (t, C(1), $^1J_{P,C}$ = 171.0 Hz); 111.84 (s), 121.87 (s), 128.86 (d, $^3J_{P,C}$ = 5.5 Hz); 150.33 (s, C_{Ph}). $^{31}P\{^1H\}$ NMR ($CDCl_3$), δ: 19.97 (s).

Diethyl (4-fluorophenyl)chloromethylphosphonate (4a). A mixture of 4-fluorobenzaldehyde (3.0 g, 0.017 mol), triethyl phosphite (7.0 g, 0.042 mol), and zinc chloride (0.1 g, 0.0007 mol) was heated at 150—160 °C for 2 h. Vacuum distillation of the reaction mixture afforded 3 g (64%) of phosphonate **4a**, b.p. 152 °C (2 Torr). Found (%): C, 46.89; H, 5.26. $C_{11}H_{15}ClFO_3P$. Calculated (%): C, 47.07; H, 5.39. ^1H NMR ($CDCl_3$), δ: 4.75 (d, 1 H, C(1)H, $^2J_{P,H}$ = 12.0 Hz); 6.82 (d, CH_{Ph}, $^3J_{H,H}$ = 8.0 Hz); 7.32 (d, CH_{Ph}, $^3J_{H,H}$ = 8.0 Hz). $^{13}C\{^1H\}$ NMR ($CDCl_3$), δ: 52.52 (d, C(1), $^1J_{P,C}$ = 160.0 Hz); 115.26 (d, C_{Ph}, $^2J_{F,C}$ = 22.0 Hz); 130.16 (t, C_{Ph}, $^2J_{P,C}$ = 3.5 Hz, $^4J_{F,C}$ = 3.5 Hz); 130.69 (dd, C_{Ph}, $^3J_{P,C}$ = 6.0 Hz, $^3J_{F,C}$ = 8.0 Hz); 162.68 (d, C_{Ph}, $^1J_{F,C}$ = 248.0 Hz). $^{31}P\{^1H\}$ NMR ($CDCl_3$), δ: 16.89 (s).

Compounds **4b**,**c** and **2b**,**c** were synthesized similarly.

Diethyl (2,3-dimethoxyphenyl)chloromethylphosphonate (4b). Yield 68%, b.p. 184 °C (2 Torr). Found (%): C, 48.23; H, 6.16. $C_{13}H_{20}ClO_5P$. Calculated (%): C, 48.38; H, 6.25. ^1H NMR ($CDCl_3$), δ: 5.35 (d, 1 H, C(1)H, $^2J_{P,H}$ = 16.0 Hz); 3.60 and 3.65 (both s, 6 H, 2 MeO); 6.64—7.17 (m, 3 CH_{Ph}). $^{13}C\{^1H\}$ NMR ($CDCl_3$), δ: 45.63 (d, C(1), $^1J_{P,C}$ = 163.0 Hz); 55.52 and 55.73 (both s, 2 MeO); 112.81 (d, $^3J_{P,C,}$ = 3.0 Hz); 117.97 (s), 121.56 (d, $^2J_{P,C}$ = 4.0 Hz); 124.04 (s), 146.59 (d, $^3J_{P,C}$ = 9.0 Hz); 152.04 (s, C_{Ph}). $^{31}P\{^1H\}$ NMR ($CDCl_3$), δ: 17.96 (s).

Bis(trimethylsilyl) (4-methoxyphenyl)chloromethylphosphonate (4c). Yield 81%, b.p. 166 °C (1 Torr), m.p. 65 °C. Found (%): C, 43.98; H, 6.81. $C_{14}H_{26}ClO_4PSi_2$. Calculated (%): C, 44.14; H, 6.88. ^1H NMR ($CDCl_3$), δ: 0.09 and 0.19 (both s, Me_3Si); 4.71 (d, C(1)H, $^2J_{P,H}$ = 12.0 Hz); 3.72 (s, MeO); 6.80 (d, CH_{Ph}, $^3J_{H,H}$ = 8.0 Hz); 7.36 (d, CH_{Ph}, $^3J_{H,H}$ = 8.0 Hz). $^{13}C\{^1H\}$ NMR ($CDCl_3$), δ: 0.63 and 0.79 (both s, Me_3Si); 54.63 (d, C(1), $^1J_{P,C}$ = 168.2 Hz); 55.21 (s, MeO); 113.75 (s), 126.90 (t, $^2J_{P,C}$ = = 3.0 Hz); 130.21 (d, $^3J_{P,C}$ = 6.0 Hz); 159.94 (s, C_{Ph}). $^{31}P\{^1H\}$ NMR ($CDCl_3$), δ: –0.79 (s).

Tetraethyl (4-methoxyphenyl)methylenediphosphonate (2b). Yield 78%, b.p. 202 °C (2 Torr). Found (%): C, 48.59; H, 7.05. $C_{16}H_{28}O_7P_2$. Calculated (%): C, 48.73; H, 7.16. ^1H NMR ($CDCl_3$), δ: 3.47 (t, C(1)H, $^2J_{P,H}$ = 24.0 Hz); 3.54 (s, MeO); 6.63 (d, CH_{Ph}, $^3J_{H,H}$ = 8.0 Hz); 7.17 (d, CH_{Ph}, $^3J_{H,H}$ = 8.0 Hz). $^{13}C\{^1H\}$ NMR ($CDCl_3$), δ: 44.37 (t, C(1), $^1J_{P,C}$ = 132.5 Hz); 54.89 (s, MeO); 113.69 (s); 121.66 (t, $^2J_{P,C}$ = 8.0 Hz); 131.29 (t, $^3J_{P,C}$ = 6.5 Hz); 158.90 (s, C_{Ph}). $^{31}P\{^1H\}$ NMR ($CDCl_3$), δ: 18.74 (s).

Tetraethyl (2,5-dimethoxyphenyl)methylenediphosphonate (2c). Yield 76%, b.p. 212 °C (2 Torr). Found (%): C, 48.02; H, 7.06. $C_{17}H_{30}O_8P_2$. Calculated (%): C, 48.11; H, 7.13 ^1H NMR ($CDCl_3$), δ: 3.52 and 3.55 (both s, MeO); 4.35 (t, C(1)H, $^2J_{P,H}$ = = 26.0 Hz); 6.45—6.60 (m), 7.18 (s, 4 CH_{Ph}). $^{13}C\{^1H\}$ NMR ($CDCl_3$), δ: 35.48 (t, C(1), $^1J_{P,C}$ = 133.0 Hz); 55.29 and 56.30 (both s, OMe); 111.78 (s), 113.94 (s), 116.21 (t, $^3J_{P,C}$ = 4.5 Hz); 119.28 (t, $^2J_{P,C}$ = 8.0 Hz); 150.78 (t, $^3J_{P,C}$ = 7.0 Hz); 153.08 (s, C_{Ph}). $^{31}P\{^1H\}$ NMR ($CDCl_3$), δ: 19.05 (s).

4-Methoxyphenyl(hydroxymethyl)phosphonic acid (5a). A solution of phosphonate **1a** (10.6 g, 0.025 mol) in diethyl ether (15 mL) was added to methanol (40 mL) with stirring under cooling to 10 °C. The mixture was heated to reflux and concentrated. The obtained white crystals were dried *in vacuo* (1 Torr) to give 4.7 g (96%) of acid **5a**, m.p. 78 °C. Found (%): C, 43.96; H, 5.01. $C_8H_{11}O_5P$. Calculated (%): C, 44.05; H, 5.08. ^1H NMR (D_2O), δ: 3.44 (s, MeO); 4.71 (d, C(1)H, $^2J_{P,H}$ = 12.0 Hz); 6.67 (d, 1 H, CH_{Ph}, $^3J_{H,H}$ = 8.0 Hz); 7.12 (d, CH_{Ph}, $^3J_{H,H}$ = 8.0 Hz). $^{13}C\{^1H\}$ NMR (D_2O), δ: 55.16 (s, MeO); 69.77 (d, C(1), $^1J_{P,C}$ = = 160.0 Hz); 113.87 (s), 128.52 (d, $^3J_{P,C}$ = 6.0 Hz); 129.02 (s), 158.29 (s, C_{Ph}). $^{31}P\{^1H\}$ NMR (D_2O), δ: 20.76 (s) (*cf*. Ref. 5).

Acids **5b—f** and **6a,b** were synthesized similarly.

2,3-Dimethoxyphenyl(hydroxymethyl)phosphonic acid (5b). Yield 95%, heavy oil. Found (%): C, 43.46; H, 5.30. $C_9H_{13}O_6P$. Calculated (%): C, 43.56; H, 5.18. ^1H NMR (CD_3OD), δ: 3.84 (s, 3 H, MeO); 3.88 (s, MeO); 5.47 (d, C(1)H, $^2J_{P,H}$ = 12.8 Hz); 6.98 (d, CH_{Ph}, $^3J_{H,H}$ = 8.0 Hz); 7.12 (t, CH_{Ph}, $^3J_{H,H}$ = 8.0 Hz); 7.28 (d, CH_{Ph}, $^3J_{H,H}$ = 8.0 Hz). $^{13}C\{^1H\}$ NMR (CD_3OD), δ: 55.14 (s, MeO); 60.15 (s, MeO); 63.89 (d, C(1), $^1J_{P,C}$ = 164.5 Hz); 112.13 (s), 120.37 (d, $^3J_{P,C}$ = 2.7 Hz); 123.83 (s, 131.57 (s), 146.52 (d, $^3J_{P,C}$ = 7.4 Hz); 152.29 (s, C_{Ph}). $^{31}P\{^1H\}$ NMR (CD_3OD), δ: 21.26 (s).

3-Pyridyl(hydroxy)methylphosphonic acid (5c). Yield 94%, m.p. 219 °C (decomp.). Found (%): C, 37.89; H, 4.15. $C_6H_8NO_4P$. Calculated (%): C, 38.11; H, 4.26. ^1H NMR (D_2O—C_5D_5N), δ: 4.40 (d, C(1)H, $^2J_{P,H}$ = 13.6 Hz); 6.53 (br.s, CH_{Py}); 7.38 (br.s, CH_{Py}); 7.42 (br.s, CH_{Py}); 7.96 (br.s, CH_{Py}). $^{13}C\{^1H\}$ NMR (D_2O—C_5D_5N), δ: 69.12 (d, C(1), $^1J_{P,C}$ = 148.3 Hz); 122.91 (s), 136.54 (s), 136.07 (s), 144.17 (s), 144.46 (d, $^3J_{P,C}$ = 3.0 Hz); all C_{Py}. $^{31}P\{^1H\}$ NMR (D_2O—C_5D_5N), δ: 14.72 (s).

4-Pyridyl(hydroxy)methylphosphonic acid (5d). Yield 96%, m.p. 239 °C (decomp.). Found (%): C, 37.99; H, 4.12. $C_6H_8NO_4P$. Calculated (%): C, 38.11; H, 4.26. ^1H NMR (D_2O—C_5D_5N), δ: 6.69 (br.s, C(1)H); 7.20 (d, CH_{Py}, $^3J_{H,H}$ = 5.2 Hz); 7.87 (d, CH_{Py}, $^3J_{H,H}$ = 5.2 Hz). $^{13}C\{^1H\}$ NMR (D_2O—C_5D_5N), δ: 71.26 (d, C(1), $^2J_{P,C}$ = 141.4 Hz); 122.03 (d, $^3J_{P,C}$ = 3.5 Hz); 145.50 (s), 152.96 (s, C_{Py}). $^{31}P\{^1H\}$ NMR (D_2O—C_5D_5N), δ: 13.77 (s).

4-Dimethylaminophenyl(hydroxy)methylphosphonic acid (5e). Yield 96%, m.p. 152 °C. Found (%): C, 46.64; H, 6.16. $C_9H_{14}NO_4P$. Calculated (%): C, 46.46; H, 6.10. ^1H NMR (D_2O—C_5D_5N), δ: 1.85 (s, 2 CH_3); 4.30 (d, C(1)H, $^2J_{P,H}$ = = 11.6 Hz); 5.85 (d, CH_{Ph}, $^3J_{H,H}$ = 8.0 Hz); 6.73 (d, CH_{Ph}, $^3J_{H,H}$ = 8.0 Hz). $^{13}C\{^1H\}$ NMR (D_2O—C_5D_5N), δ: 40.07 (s, 2 Me); 71.08 (d, C(1); $^1J_{P,C}$ = 152.4 Hz); 113.06 (s), 127.36 (d, $^3J_{P,C}$ = = 4.9 Hz); 129.67 (s), 147.82 (s, C(Ph)). $^{31}P\{^1H\}$ NMR (D_2O—C_5D_5N), δ: 17.22 (s).

4-Bromophenyl(ethoxy)methylphosphonic acid (5f). Yield 96%, heavy oil. Found (%): C, 36.52; H, 4.03. $C_9H_{12}BrO_4P$. Calculated (%): C, 36.64; H, 4.10. ^1H NMR (CD_3OD), δ: 1.21 (t, Me, $^3J_{H,H}$ = 7.2 Hz); 3.53 (q, CH_2O, $^3J_{H,H}$ = 7.2 Hz); 4.62 (d, C(1)H, $^2J_{P,H}$ = 16.4 Hz); 7.40 (d, CH_{Ph}, $^3J_{H,H}$ = 7.2 Hz); 7.50 (d, CH_{Ph}, $^3J_{H,H}$ = 7.2 Hz). $^{13}C\{^1H\}$ NMR (CD_3OD), δ: 14.56 (s, Me); 66.50 (d, CH_2O, $^2J_{P,C}$ = 12.8 Hz); 78.01 (d, C(1), $^1J_{P,C}$ = 164.5 Hz). $^{31}P\{^1H\}$ NMR (CD_3OD), δ: 17.82 (s).

4-Methoxyphenylmethylenediphosphonic acid (6a). Yield 96%, b.p. 92 °C. Found (%): C, 33.94; H, 4.38. $C_8H_{12}O_7P_2$. Calculated (%): C, 34.06; H, 4.29. ^1H NMR (D_2O), δ: 3.59 (t, C(1)H, $^2J_{P,H}$ = 26.2 Hz); 3.57 (s, MeO); 6.65 (d, CH_{Ph}, $^3J_{P,H}$ = 8.0 Hz); 7.20 (d, CH_{Ph}, $^3J_{P,H}$ = 8.0 Hz). $^{13}C\{^1H\}$ NMR (D_2O), δ: 45.06 (t, C(1), $^1J_{P,C}$ = 126.5 Hz); 54.74 (s, MeO); 114.72 (s); 124.96 (t, $^2J_{P,C}$ = 7.5 Hz); 131.08 (t, $^3J_{P,C}$ = 6.0 Hz); 157.76 (s, C_{Ph}). $^{31}P\{^1H\}$ NMR (D_2O), δ: 17.92 (s).

4-Dimethylaminophenylmethylenediphosphonic acid (6b). Yield 98%, m.p. 147 °C. Found (%): C, 36.52; H, 5.06. $C_9H_{15}NO_6P_2$. Calculated (%): C, 36.62; H, 5.12. ^1H NMR (D_2O), δ: 2.45 (s, Me_2N); 3.75 (t, C(1)H, $^2J_{P,H}$ = 23.2 Hz); 6.26

(d, CH_{Ph}, $^2J_{P,H}$ = 6.8 Hz); 7.40 (d, CH_{Ph}, $^3J_{H,H}$ = 6.8 Hz). $^{13}C\{^1H\}$ NMR (D_2O), δ: 40.76 (s, Me_2N); 48.21 (t, $^1J_{P,C}$ = = 117.2 Hz); 113.14 (s), 125.62 (t, $^2J_{P,C}$ = 6.5 Hz); 131.33 (s), 147.55 (s, C_{Ph}). $^{31}P\{^1H\}$ NMR (D_2O), δ: 16.96 (s).

4-Fluorophenyl(hydroxymethyl)phosphonic acid (5g). A mixture of phosphonate **4a** (3 g, 0.011 mol) and concentrated hydrochloric acid (20 mL) was heated at 100 °C (a boiling water bath) for 4 h and then concentrated to dryness under vacuum (7 Torr). The residue was co-evaporated with water (30 mL) to give 2 g (92%) of acid **5g**, m.p. 69 °C. Found (%): C, 49.52; H, 3.94. $C_7H_8FO_4P$. Calculated (%): C, 40.79; H, 3.91. ^1H NMR (D_2O), δ: 4.72 (q, C(1)H, $^2J_{P,H}$ = 12.0 Hz); 7.10—7.15 and 7.41—7.44 (both m, CH_{Ph}). $^{13}C\{^1H\}$ NMR (D_2O), δ: 70.10 (d, C(1), $^1J_{P,C}$ = 160.0 Hz); 114.69 (d, $^2J_{F,C}$ = 21.0 Hz), 129.66 (s), 136.71 (s), 161.76 (d, $^1J_{F,C}$ = 244.0 Hz); all C_{Ph}. $^{31}P\{^1H\}$ NMR (D_2O), δ: 18.52 (s), (*cf.* Ref. 11).

Acids **5a** and **6a** were synthesized similarly.

This work was financially supported by the Russian Foundation for Basic Research (Projects Nos. 14-03-00001, 15-03-00002, and 17-03-00169).

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Received June 21, 2016;
in revised form October 12, 2016