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LETTERS TO THE EDITOR

Synthesis of Aminomethylenediphosphonates and Their Derivatives Containing $PCNH_2$ Fragments

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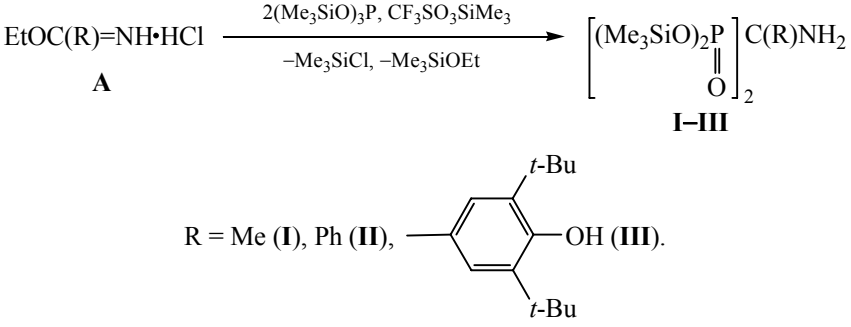
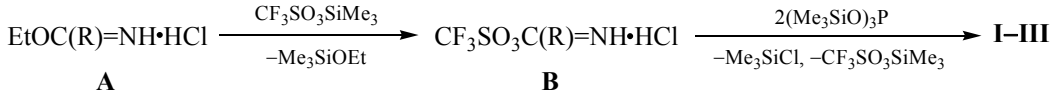
Aminomethylenediphosphonic acids containing free amino group are of interest as promising ligands and biologically active substances with diverse properties [1]. We recently developed several convenient methods for the synthesis of *N*-substituted aminomethylenediphosphonates starting from *N*-substituted formamides and imines [2]. For the synthesis of new trimethylsilyl-containing aminomethylenediphosphonates and their derivatives with $PCNH_2$ fragments we studied the interaction of tris(trimethylsilyl)phosphate with easily accessible hydrochlorides of substituted ethoxymethyleneimines **A** [3] in the presence of trimethylsilyl trifluoromethanesulfonate as a catalyst. Thus, substituted ethoxymethyleneimines hydrochlorides **A** reacted with an excess of tris(trimethylsilyl)phosphite in methylene chloride under mild conditions to form diphosphonates **I–III** with good yields.



A **I–III**

R = Me (**I**), Ph (**II**),

Apparently, mild reaction conditions are caused by activation of the starting imines **A** with silicon triflate, generating a highly reactive intermediate **B** (see [4]).

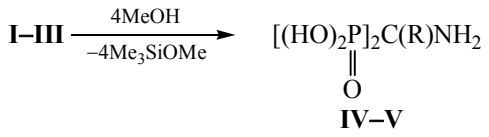


A **B**

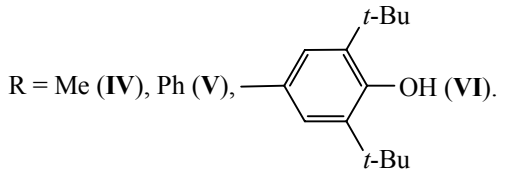
Trimethylsilyl-containing diphosphonates **I–III** reacted with an excess of methanol under mild conditions to form diphosphonic acids **IV–VI**. The latter are white hygroscopic crystalline substances (Scheme 1).

Compounds **I–VI** with unsubstituted amino group are convenient synthons for the preparation of new functionalized aminomethylenediphosphorus-containing substances like diphosphorus-containing peptides. In

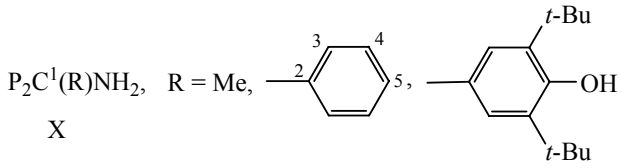
Scheme 1.



IV–V



Scheme 2.



the NMR spectra of compounds **I–VI** there were characteristic signals of the fragments X, whose structure is shown in Scheme 2.

The signals of hydroxy and amino groups of **IV–VI** are broadened due to the proton exchange.

***O,O,O,O*-Tetra(trimethylsilyl)-1-aminoethylidenediphosphonate (I).** To a solution of 10 g of tris(trimethylsilyl)phosphite in 10 mL of methylene chloride was added 1.3 g of 1-ethoxyethylideneimine and then 0.2 mL of trifluoromethanesulfonic acid trimethylsilyl ester. The mixture was refluxed for 1 h, and then the solvent was distilled off. To the residue was added 10 g of bis(trimethylsilyl)amine, and the mixture was refluxed for 1 h. After the solvent removal, the residue was distilled. Yield 3.8 g, 73%, bp 127°C (1 mm Hg). ^{1}H NMR spectrum, δ, ppm: –0.09 d ($2Me_3Si$, $^4J_{PH}$ 2 Hz), –0.08 d ($2Me_3Si$, $^4J_{PH}$ 1.6 Hz), 0.99 t (CH_3, $^3J_{PH}$ 16.8 Hz), 1.13 t (NH_2, $^3J_{PH}$ 12.8 Hz). ^{13}C NMR spectrum, δ_C, ppm: 51.58 t (C^1, $^1J_{PC}$ 152.5 Hz), 20.03 (Me), 0.73 ($2Me_3Si$), 0.78 ($2Me_3Si$). ^{31}P NMR spectrum: δ_P 6.65 ppm. Found, %: C 33.78; H 8.23. $C_{14}H_{41}NO_6P_2Si_4$. Calculated, %: C 34.05; H 8.37.

Diphosphonates **II, III** were prepared similarly.

***O,O,O,O*-Tetra(trimethylsilyl)-1-aminobenzylidenediphosphonate (II).** Yield 72%, bp 152°C (1 mm Hg). ^{1}H NMR spectrum, δ, ppm: –0.24 d ($2Me_3Si$, $^4J_{PH}$ 2.8 Hz), –0.20 d ($2Me_3Si$, $^4J_{PH}$ 2.8 Hz), 1.72 t (NH_2, $^3J_{PH}$ 13 Hz), 6.8–7.6 m (C_6H_5). ^{13}C NMR spectrum, δ_C, ppm: 59.63 t (C^1, $^1J_{PC}$ 147.7 Hz), 135.77 br.s (C^2), 127.18 and 127.25 (C^3, C^4), 126.79 (C^5), 0.45 ($2Me_3Si$), 0.52 ($2Me_3Si$). ^{31}P NMR spectrum: δ_P 2.23 ppm. Found, %: C 40.74; H 7.72. $C_{19}H_{43}NO_6P_2Si_4$. Calculated, %: C 41.06; H 7.80.

***O,O,O,O*-Tetra(trimethylsilyl)-1-amino-1-(3,5-di-*tert*-butyl-4-hydroxyphenyl)methylenediphosphonate (III).** Yield 89%, mp 52°C. ^{1}H NMR spectrum, δ, ppm: 0.06 s ($2Me_3Si$), 0.07 s ($2Me_3Si$), 1.19 br.s (NH_2), 1.34 s (Me_3C), 5.08 br.s (OH), 7.63 s (C_6H_2). ^{13}C NMR spectrum, δ_C, ppm: 59.65 t (C^1, $^1J_{PC}$ 149.3 Hz), 126.42 (C^2), 125.03 (C^3), 139.46 (C^4), 152.31 (C^5), 35.12 ($Me_3\underline{C}$), 30.98 ($\underline{Me}_3C$), 0.68 ($2Me_3Si$), 0.77 ($2Me_3Si$). ^{31}P NMR spectrum: δ_P 3.27 ppm. Found, %: C 47.26; H 8.61. $C_{27}H_{59}NO_7P_2Si_4$. Calculated, %: C 47.41; H 8.69.

1-Aminoethylidenediphosphonic acid (IV). A solution of 3.8 g of diphosphonate **I** in 5 mL of diethyl ether was added to 20 mL of methanol with stirring under cooling to 10°C. The mixture was heated to boiling, and the solvent was distilled off. White crystals were kept in a vacuum (1 mm Hg) for 1 h. Yield 1.5 g, 96%, mp 252°C. ^{1}H NMR spectrum, δ, ppm: 1.12 t (Me, $^3J_{PH}$ 13.2 Hz). ^{13}C NMR spectrum, δ_C, ppm: 51.69 t (C^1, $^1J_{PC}$ 122.2 Hz), 15.64 (Me). ^{31}P NMR spectrum: δ_P 11.15 ppm. Found, %: C 11.58; H 4.47. $C_2H_9NO_6P_2$. Calculated, %: C 11.71; H 4.42.

Acids **V, VI** were prepared similarly.

1-Aminobenzylidenediphosphonic acid (V). Yield 97%, mp 223°C. ^{1}H NMR spectrum, δ, ppm: 6.8–7.6 m (C_6H_5). ^{13}C NMR spectrum, δ_C, ppm: 60.26 t (C^1, $^1J_{PC}$ 120.5 Hz), 131.22 (C^2), 125.52 (C^3), 126.20 (C^4), 124.27 (C^5). ^{31}P NMR spectrum: δ_P 8.54 ppm. Found, %: C 31.32; H 4.19. $C_7H_{11}NO_6P_2$. Calculated, %: C 31.48; H 4.15.

1-Amino-1-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-methylenediphosphonic acid (VI). Yield 98%, mp 183–184°C. ^{1}H NMR spectrum, δ, ppm: 1.30 s (Me_3C), 5.29 br.s (OH), 7.50 s (C_6H_2). ^{13}C NMR spectrum, δ_C, ppm: 62.84 t (C^1, $^1J_{PC}$ 118.2 Hz), 126.89 (C^2), 124.43 (C^3), 138.65 (C^4), 151.09 (C^5), 34.35 ($Me_3\underline{C}$), 30.08 ($\underline{Me}_3C$). ^{31}P NMR spectrum: δ_P 11.06 ppm. Found, %: C 45.43; H 6.94. $C_{15}H_{27}NO_7P_2$. Calculated, %: C 45.57; H 6.88.

NMR spectra were recorded on a Bruker Avance-400 spectrometer in $CDCl_3$ (**I–III**), CD_3OD or C_5D_5N (**IV–VI**), internal reference TMS (^{1}H, ^{13}C) or external reference 85% phosphoric acid solution in D_2O (^{31}P).

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