ISSN 1070-3632, Russian Journal of General Chemistry, 2016, Vol. 86, No. 11, pp. 2558–2561. © Pleiades Publishing, Ltd., 2016.
Original Russian Text © A.A. Prishchenko, R.S. Alekseev, M.V. Livantsov, O.P. Novikova, L.I. Livantsova, V.I. Terenin, V.S. Petrosyan, 2016, published in Zhurnal Obshchei Khimii, 2016, Vol. 86, No. 11, pp. 1919–1922.

LETTERS TO THE EDITOR

Addition of Tris(trimethylsilyl)phosphite to *N*-Formyl Derivatives of Five-Membered Nitrogen Heterocycles

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Received June 23, 2016

Keywords: tris(trimethylsilyl)phosphite, five-membered nitrogen heterocycles, *N*-formyl derivatives

DOI: 10.1134/S1070363216110268

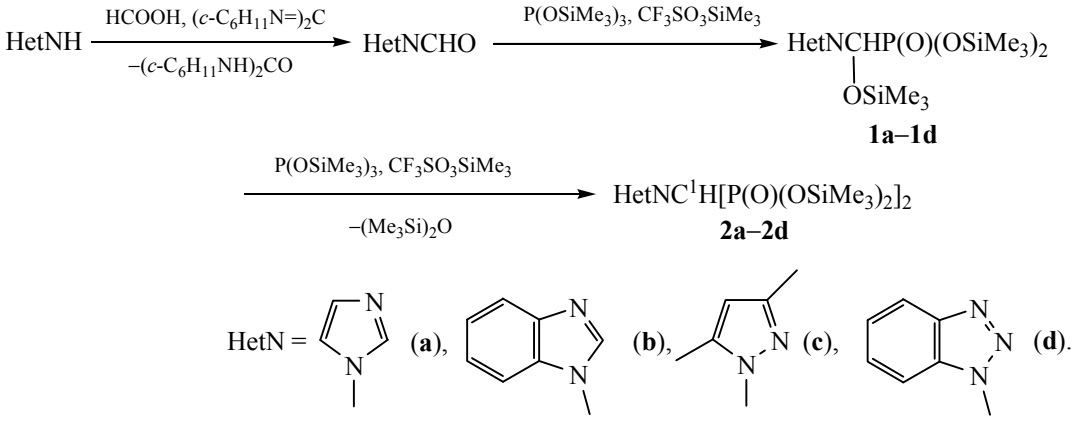
Functionalized phosphonic and methylenediphosphonic acids and derivatives thereof with fragments of nitrogen heterocycles are well known hydroxy(amino)-acids biomimetics and natural pyrophosphates. Some of them, like zoledronic, and minodronic and risedronic acids, are widely used in medicine, as well as are of interest as effective ligands [1, 2]. We have previously developed convenient methods for the synthesis of aminomethylenediphosphorus-containing acids and their derivatives using phosphorous acid trimethylsilyl esters as highly reactive synthons [3, 4]. Here we studied addition of tris(trimethylsilyl) phosphite to easily accessible *N*-formyl derivatives of five-membered nitrogen heterocycles with two or three nitrogen atoms prepared in situ by the known methods [5] using formic acid and *sym*-dicyclohexylcarbodiimide.

The reactions proceeded only in the presence of trimethylsilyl triflate as a catalyst (cf. [4]) in mild conditions and led to the formation of functionalized phosphonates **1** and diphosphonates **2** in various ratios depending on the structure of the starting heterocycle. Thus, in the case of 3,5-dimethyl-1*H*-pyrazole phosphonate **1b** was formed mainly, while diphosphonate **2a** was obtained in a high yield when using imidazole (Scheme 1).

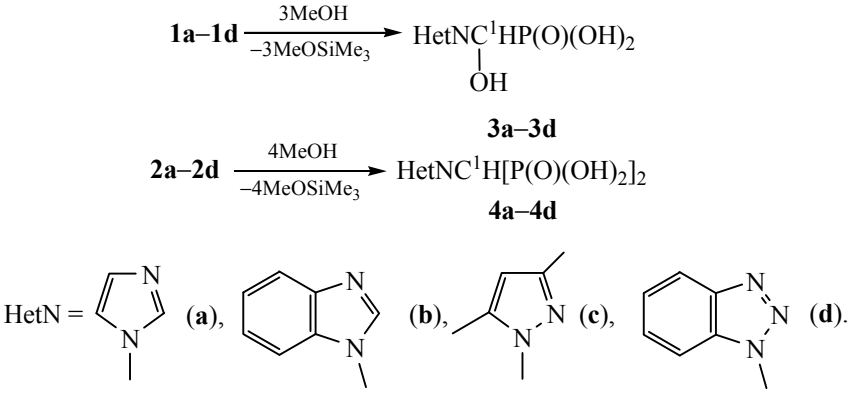
Trimethylsilyl esters **1** and **2** reacted readily with an excess of methanol under mild conditions to form functionalized mono- or diphosphonic acids **3** and **4**, respectively (Scheme 2).

The resulting compound **1**–**4** can be used for the synthesis of new organophosphorus compounds, including both heterocyclic and phosphonic fragments. In addition, they are precursors of highly promising drugs and effective polydentate ligands for mono- and diphosphorus-containing complexes of various metals.

Scheme 1.



Scheme 2.



***O*,*O*-Bis(trimethylsilyl)-1*H*-imidazol-1-yl- (trimethylsiloxy)methylphosphonate (1a) and *O*,*O*,*O*,*O*-tetra (trimethylsilyl)-1*H*-imidazol-1-yl-methylenediphosphonate (2a).** A solution of 14.4 g (0.07 mol) of *sym*-dicyclohexylcarbodiimide in 20 mL of methylene chloride was added with stirring to a mixture of 3.4 g (0.05 mol) of imidazole and 2.8 g (0.06 mol) of formic acid in 50 mL methylene chloride. The mixture was stirred for 6 h and then kept for 12 h. The precipitate was filtered off. To the filtrate were added 44.8 g (0.15 mol) of tris(trimethylsilyl) phosphite and a solution of 2.9 g (0.013 mol) of trimethylsilyl triflate in 10 mL of methylene chloride. The mixture was heated on a boiling water bath until complete distillation of low-boiling compounds, then distilled to yield 1.8 g (9%) of phosphonate **1a** (bp 102°C, 1 mmHg) and 22.0 g (83%) of diphosphonate **2a** (bp 126°C, 1 mmHg).

Phosphonate 1a. ^{1}H NMR spectrum, δ, ppm: –0.38 s (9H, Me_3SiO), –0.24 s (18H, Me_3Si), 5.22 d (1H, C^1H, $^2J_{PH}$ = 4.8 Hz), 6.57 s (2H_{Het}), 7.15 s (1H_{Het}). ^{13}C NMR spectrum, δ_C, ppm: 1.62 (Me_3Si), –0.25 and 0.05 (Me_3Si), 76.47 d (C^1, $^1J_{PC}$ = 213.2 Hz), 106.61 (C_{Het}), 139.80 (C_{Het}), 146.52 (C_{Het}). ^{31}P NMR spectrum: δ_P –4.02 ppm. Found, %: C 39.42. H 7.83. $C_{13}H_{31}N_2O_4PSi_3$. Calculated, %: C 39.57; H 7.92.

Diphosphonate 2a. ^{1}H NMR spectrum, δ, ppm: –0.15 s (18H, Me_3Si), –0.14 s (18H, Me_3Si), 3.55 t (1H, C^1H, $^2J_{PH}$ = 17.2 Hz), 6.57 s (2H_{Het}), 7.15 s (1H_{Het}). ^{13}C NMR spectrum, δ_C, ppm: 0.47 (Me_3Si), 67.80 t (C^1, $^1J_{PC}$ = 168.2 Hz), 121.00 (C_{Het}), 134.69 (C_{Het}). ^{31}P NMR spectrum: δ_P –0.32 ppm. Found, %: C 36.12; H 7.52. $C_{16}H_{40}N_2O_6P_2Si_4$. Calculated, %: C 36.21; H 7.60.

Phosphonates **1b**–**1d** and diphosphonates **2b**–**2d** were prepared similarly.

***O*,*O*-Bis(trimethylsilyl)-1*H*-benzimidazol-1-yl-(trimethylsiloxy)methylphosphonate (1b)**. Yield 30%, bp 110°C (1 mmHg). ^{1}H NMR spectrum, δ, ppm: –0.44 s (9H, Me_3Si), –0.25 s (18H, Me_3Si), 5.58 d (1H, C^1H, $^2J_{PH}$ = 4.4 Hz), 6.70–7.45 m (5H, CH_{Het}). ^{13}C NMR spectrum, δ_C, ppm: –0.22 (Me_3Si), 1.11 (Me_3Si), 75.50 d (C^1, $^1J_{PC}$ = 214.1 Hz), 110.40 (C_{Het}), 120.23 (C_{Het}), 122.51 (C_{Het}), 123.19 (C_{Het}), 139.62 (C_{Het}), 143.28 (C_{Het}), 145.74 (C_{Het}). ^{31}P NMR spectrum: δ_P –3.47 ppm. Found, %: C 45.81; H 7.40. $C_{17}H_{33}N_2O_4PSi_3$. Calculated, %: C 45.92; H 7.48.

***O*,*O*,*O*,*O*-Tetra(trimethylsilyl)-1*H*-benzimidazol-1-ylmethylenediphosphonate (2b)**. Yield 62%, bp 139°C (1 mmHg). ^{1}H NMR spectrum, δ, ppm: –0.38 s and –0.31 s (18H, Me_3Si), –0.16 s (18H, Me_3Si), 3.55 t (1H, C^1H, $^2J_{PH}$ = 16.8 Hz), 6.65–7.55 m (5H, CH_{Ar}). ^{13}C NMR spectrum, δ_C, ppm: 1.10 (Me_3Si), 68.11 d (C^1, $^1J_{PC}$ = 167.3 Hz), 112.46 (C_{Het}), 119.92 (C_{Het}), 122.13 (C_{Het}), 122.75 (C_{Het}), 139.71 (C_{Het}), 141.75 (C_{Het}), 145.46 (C_{Het}). ^{31}P NMR spectrum: δ_P –0.58 ppm. Found, %: C 41.26; H 7.20. $C_{20}H_{42}N_2O_6P_2Si_4$. Calculated, %: C 41.36; H 7.29.

***O*,*O*-Bis(trimethylsilyl)-3,5-dimethyl-1*H*-pyrazol-1-yl(trimethylsiloxy)methylphosphonate (1c)**. Yield 86%, bp 106°C (1 mmHg). ^{1}H NMR spectrum, δ, ppm: –0.38 s and –0.31 s (18H, Me_3Si), –0.16 s (9H, Me_3Si), 1.71 s and 1.99 s (6H, Me), 5.36 s (1H, CH_{Het}), 5.40 d (1H, C^1H, $^2J_{PH}$ = 7.2 Hz). ^{13}C NMR spectrum, δ_C, ppm: –1.62 (Me_3Si), –0.25 and 0.05 (Me_3Si), 10.77 and 12.36 (Me), 81.19 d (C^1, $^1J_{PC}$ = 214.1 Hz), 106.61 (C_{Het}), 139.80 (C_{Het}), 146.52 (C_{Het}). ^{31}P NMR spectrum: δ_P –3.35 ppm. Found, %: C 42.49; H 8.28. $C_{15}H_{35}N_2O_4PSi_3$. Calculated, %: C 42.62; H 8.35.

***O*,*O*,*O*,*O*-Tetra(trimethylsilyl)-3,5-dimethyl-1*H*-pyrazol-1-ylmethylenediphosphonate (2c)**. Yield

7%, bp 129°C (1 mmHg). ^{1}H NMR spectrum, δ, ppm: –0.12 s and –0.16 s (36H, Me_3Si), 1.80 s and 2.01 s (6H, Me), 3.58 t (1H, C^{1}H, $^2J_{PH}$ = 17.2 Hz), 5.36 s (1H, CH_{Het}). ^{13}C NMR spectrum, δ_C, ppm: 0.35 (Me_3Si), 10.80 and 12.40 (6H, Me), 68.09 t (C^1, $^1J_{PC}$ = 168.2 Hz), 106.68 (C_{Het}), 139.86 (C_{Het}), 146.57 (C_{Het}). ^{31}P NMR spectrum: δ_P –0.30 ppm. Found, %: C 38.52; H 7.86. $C_{18}H_{44}N_2O_6P_2Si_4$. Calculated, %: C 38.69; H 7.94.

***O*,*O*-Bis(trimethylsilyl)-1*H*-benzotriazol-1-yl(trimethylsiloxy)methylphosphonate (1d)**. Yield 59%, bp 108°C (1 mmHg). ^{1}H NMR spectrum, δ, ppm: –0.36 s (9H, Me_3Si), –0.05 s (18H, Me_3Si), 6.26 d (1H, C^{1}H, $^2J_{PH}$ = 6.4 Hz), 6.99–7.76 m (4H, C_6H_4). ^{13}C NMR spectrum, δ_C, ppm: –0.93 (Me_3Si), –0.43 (Me_3Si), –0.75 (Me_3Si), 80.73 d (C^1, $^1J_{PC}$ = 213.2 Hz), 113.37 (C_{Het}), 119.20 (C_{Het}), 124.17 (C_{Het}), 127.30 (C_{Het}), 131.84 (C_{Het}), 146.45 (C_{Het}). ^{31}P NMR spectrum: δ_P –4.81 ppm. Found, %: C 43.03; H 7.16. $C_{16}H_{32}N_3O_4PSi_3$. Calculated, %: C 43.12; H 7.24.

***O*,*O*,*O*,*O*-Tetra(trimethylsilyl)-1*H*-benzotriazol-1-ylmethylenediphosphonate (2d)**. Yield 30%, bp 133°C (1 mmHg). ^{1}H NMR spectrum, δ, ppm: –0.11 s (36H, Me_3Si), 3.75 t (1H, C^{1}H, $^2J_{PH}$ = 16.8 Hz), 7.17–7.83 m (4H, C_6H_4). ^{13}C NMR spectrum, δ_C, ppm: 0.01 s (36H, Me_3Si), 67.71 t (C^1, $^1J_{PC}$ = 168.2 Hz), 110.50 s (C_{Het}), 114.55 s (C_{Het}), 119.44 s (C_{Het}), 126.22 s (C_{Het}), 129.93 s (C_{Het}), 140.27 s (C_{Het}). ^{31}P NMR spectrum: δ_P –0.47 ppm. Found, %: C 39.03; H 7.01. $C_{19}H_{41}N_3O_6P_2Si_4$. Calculated, %: C 39.22; H 7.10.

1*H*-Imidazol-1-ylmethylenediphosphonic acid (4a). A solution of 10.6 g (0.02 mol) of diphosphonate **2a** in 15 mL of diethyl ether was added to 40 mL of methanol with cooling to 10°C and stirring. The mixture was heated at reflux and then the solvent was distilled off. The resulting white crystals were heated in a vacuum of 1 mmHg for 1 h. Yield 98% (4.7 g), mp 174–176°C. ^{1}H NMR spectrum, δ, ppm: 3.33 t (1H, C^{1}H, $^2J_{PH}$ = 16.0 Hz), 6.55 s (2H, CH_{Het}), 7.85 s (1H, CH_{Het}). ^{13}C NMR spectrum, δ_C, ppm: 66.26 t (C^1, $^1J_{PC}$ = 139.9 Hz), 117.83 (C_{Het}), 132.43 (C_{Het}). ^{31}P NMR spectrum: δ_P 14.66 ppm. Found, %: C 19.69; H 3.28. $C_4H_8N_2O_6P_2$. Calculated, %: C 19.85; H 3.33.

Acids **3a–3d** and **4b–4d** were prepared similarly.

1*H*-Imidazol-1-yl(hydroxy)methylphosphonic acid (3a). Yield 96%, mp 144–145°C (decomp.). ^{1}H NMR spectrum, δ, ppm: 6.81 d (1H, C^{1}H, $^2J_{PH}$ = 4.2 Hz), 6.57 s (2H_{Het}), 7.92 s (1H_{Het}). ^{13}C NMR spectrum, δ_C, ppm: 78.81 d (C^1, $^1J_{PC}$ = 180.4 Hz), 117.96 (C_{Het}), 132.86 (C_{Het}). ^{31}P NMR spectrum: δ_P 7.47 ppm. Found, %: C 26.86; H 3.88. $C_4H_7N_2O_4P$. Calculated, %: C 26.98; H 3.96.

1*H*-Benzimidazol-1-yl(hydroxy)methylphosphonic acid (3b). Yield 94%, mp 157–159°C (decomp.). ^{1}H NMR spectrum, δ, ppm: 5.15 d (1H, C^{1}H, $^2J_{PH}$ = 6.4 Hz), 7.17 d.d (2H, CH_{Het}, $^3J_{HH}$ = 16.0, $^4J_{HH}$ = 3.2 Hz), 7.47 d.d (2H, CH_{Het}, $^3J_{HH}$ = 16.0, $^4J_{HH}$ = 3.2 Hz), 7.57 s (1H, CH_{Het}). ^{13}C NMR spectrum, δ_C, ppm: 78.85 d (C^1, $^1J_{PC}$ = 170.0 Hz), 114.16 (C_{Het}), 125.86 (C_{Het}), 129.74 (C_{Het}), 138.52 (C_{Het}). ^{31}P NMR spectrum: δ_P 6.88 ppm. Found, %: C 41.97; H 3.91. $C_8H_9N_2O_4P$. Calculated, %: C 42.12; H 3.98.

3,5-Dimethyl-1*H*-pyrazol-1-yl(hydroxy)methylphosphonic acid (3c). Yield 97%, mp 357–359°C (decomp.). ^{1}H NMR spectrum, δ, ppm: 1.86 s and 2.20 s (6H, Me), 4.92 d (1H, C^{1}H, $^2J_{PH}$ = 6.0 Hz), 5.64 s (1H, CH_{Het}). ^{13}C NMR spectrum, δ_C, ppm: 10.47 and 12.44 (Me), 88.18 d (C^1, $^1J_{PC}$ = 191.4 Hz), 103.71 (C_{Het}), 144.05 (C_{Het}). ^{31}P NMR spectrum: δ_P 10.42 ppm. Found, %: C 34.78; H 5.30. $C_6H_{11}N_2O_4P$. Calculated, %: C 34.96; H 5.38.

1*H*-Benzotriazol-1-yl(hydroxy)methylphosphonic acid (3d). Yield 95%, mp 105–107°C (decomp.). ^{1}H NMR spectrum, δ, ppm: 6.43 d (1H, C^{1}H, $^2J_{PH}$ = 7.2 Hz), 7.41 d.d (1H, CH_{Het}, $^3J_{HH}$ = 6.4, $^4J_{HH}$ = 3.2 Hz), 7.89 d.d (2H, CH_{Het}, $^3J_{HH}$ = 6.4, $^4J_{HH}$ = 3.2 Hz). ^{13}C NMR spectrum, δ_C, ppm: 79.96 d (C^1, $^1J_{PC}$ = 187.7 Hz), 114.92 (C_{Het}), 118.84 (C_{Het}), 125.42 (C_{Het}), 126.86 (C_{Het}), 131.87 (C_{Het}), 145.86 (C_{Het}). ^{31}P NMR spectrum: δ_P 10.62 ppm. Found, %: C 36.55; H 3.48. $C_7H_8N_3O_4P$. Calculated, %: C 36.70; H 3.52.

1*H*-Benzimidazol-1-ylmethylenediphosphonic acid (4b). Yield 98%, mp 348–350°C (decomp.). ^{1}H NMR spectrum, δ, ppm: 4.18 t (1H, C^{1}H, $^2J_{PH}$ = 16.0 Hz), 7.18 d.d (1H, CH_{Het}, $^3J_{HH}$ = 6.0 Hz, $^4J_{HH}$ = 3.2 Hz), 7.46 d.d (2H, CH_{Het}, $^3J_{HH}$ = 6.0, $^4J_{HH}$ = 3.2 Hz), 7.56 (1H, CH_{Het}). ^{13}C NMR spectrum, δ_C, ppm: 66.86 d (C^1, $^1J_{PC}$ = 142.1 Hz), 113.79 (C_{Het}), 125.73 (C_{Het}), 129.59 (C_{Het}), 138.88 (C_{Het}). ^{31}P NMR spectrum: δ_P 15.63 ppm. Found, %: C 32.74; H 3.40. $C_8H_{10}N_2O_6P_2$. Calculated, %: C 32.89; H 3.45.

3,5-Dimethyl-1*H*-pyrazol-1-ylmethylenediphosphonic acid (4c). Yield 98%, mp 357–359°C (decomp.). ^{1}H NMR spectrum, δ, ppm: 1.82 s and 2.14 s (6H,

Me), 3.97 t (1H, C^1H, $^2J_{PH}$ = 15.6 Hz), 5.60 s (1H, CH_{Het}). ^{13}C NMR spectrum, δ_C, ppm: 10.44 and 12.34 (Me), 55.57 t (C^1, $^1J_{PC}$ = 181.7 Hz), 105.63 (C_{Het}), 140.83 (C_{Het}). ^{31}P NMR spectrum: δ_P 15.03 ppm. Found, %: C 26.49; H 4.52. $C_6H_{12}N_2O_6P_2$. Calculated, %: C 26.68; H 4.48.

1*H*-Benzotriazol-1-ylmethylenediphosphonic acid (4d). Yield 96%, mp 355–357°C (decomp.). ^1H NMR spectrum, δ, ppm: 3.88 t (1H, C^1H, $^2J_{PH}$ = 17.2 Hz), 8.01 d (1H, CH_{Het}, $^3J_{HH}$ = 8.2 Hz), 8.95 d (1H, CH_{Het}, $^3J_{HH}$ = 8.2 Hz). ^{13}C NMR spectrum, δ_C, ppm: 65.28 t (C^1, $^1J_{PC}$ = 150.2 Hz), 113.61 (C_{Het}), 118.64 (C_{Het}), 124.03 (C_{Het}), 125.42 (C_{Het}), 126.86 (C_{Het}), 138.69 (C_{Het}). ^{31}P NMR spectrum: δ_P 16.41 ppm. Found, %: C 28.56; H 3.14. $C_7H_9N_3O_6P_2$. Calculated, %: C 28.68; H 3.09.

NMR spectra were recorded on a Bruker Avance 400 spectrometers from solutions in $CDCl_3$ (**1**, **2**), $(CD_3)_2SO$, D_2O or C_5D_5N (**3**, **4**), internal reference TMS (^1H, ^{13}C) or external reference 85% H_3PO_4 in D_2O (^{31}P).

ACKNOWLEDGMENTS

This work was financially supported by the Russian Foundation for Basic Research (grants nos. 14-03-00001, 15-03-00002).

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