Available online at www.sciencedirect.com
ScienceDirect
Mendeleev Commun., 2017, **27**, 90–92
Mendeleev Communications

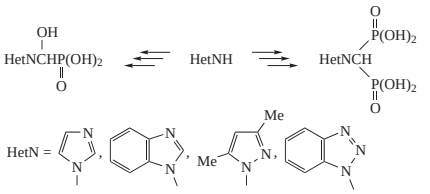
Synthesis of new five-membered N-heterocycle derivatives of mono- and bis-phosphonic acids

Andrey A. Prishchenko,* Mikhail V. Livantsov, Olga P. Novikova, Ludmila I. Livantsova and Valery S. Petrosyan

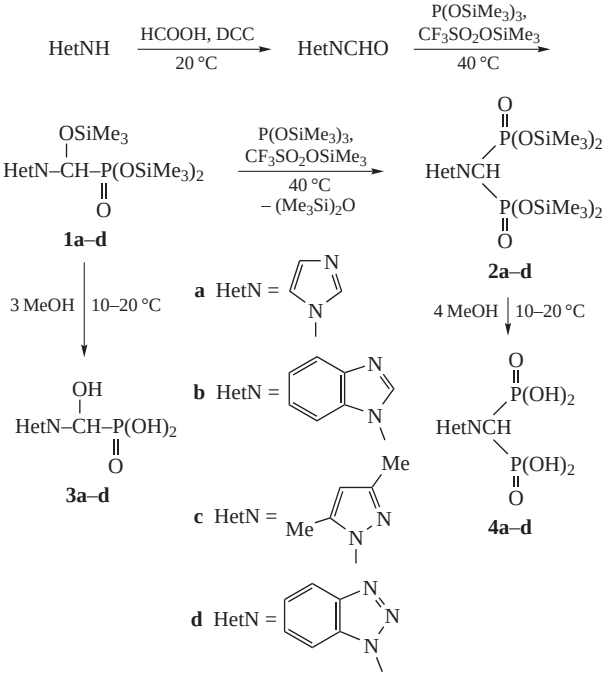
Department of Chemistry, M. V. Lomonosov Moscow State University, 119991 Moscow, Russian Federation. E-mail: aprishchenko@yandex.ru

DOI: 10.1016/j.mencom.2017.01.029

The new functionalized hydroxymethylphosphonic and methylenebis(phosphonic) acids are synthesized *via* reaction of tris(trimethylsilyl) phosphite and *N*-formyl derivatives of five-membered N-heterocycles in the presence of trimethylsilyl triflate.



Methylphosphonic and methylenebis(phosphonic) acids and their derivatives functionalized with N-heterocycle moieties and hydroxyl or amino groups are of interest as promising polydentate ligands and organophosphorus biomimetics of hydroxy or amino acids and natural pyrophosphates with multifactor activity.[1–4] These compounds with stable P–C bonds interfere with various enzymatic processes and possess antibacterial, antiviral, antibiotic, pesticidal, antitumor and enzyme inhibitory properties. Various derivatives of mono- and bis-phosphonic acids are good complexones and promising plant-growth regulators. Bis-phosphonates with hardly hydrolysable P–C–P unit such as zoledronic, risedronic and minodronic acids are used in medicine as regulators of calcium metabolism. Recently we prepared some N-substituted (aminomethylene)bis(phosphonates) by reaction of formamides or their equivalents with trimethylsilyl esters of trivalent organophosphorus acids bearing PH or $POSiMe_3$ moieties.[5–8]



Scheme 1

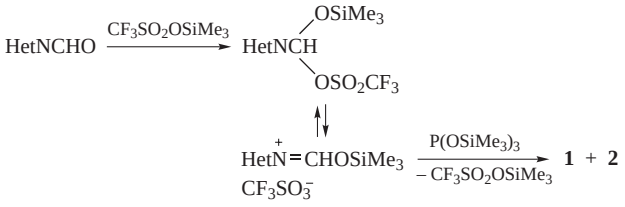
Herein, we propose a convenient access to new five-membered N-heterocycle derivatives of mono- and bis-phosphonic acids by addition of tris(trimethylsilyl) phosphite to readily available N-formylated five-membered N-heterocycles[9] which are obtained *in situ*. This reaction proceeds only in the presence of effective catalyst, trimethylsilyl triflate,[6,10] under mild conditions to give phosphonates **1** and bis-phosphonates **2**, the ratio of products **1**, **2** depending on the structure of N-heterocycle used (Scheme 1). Phosphonate **1c** predominates in case of bulky *N*-formyl-3,5-dimethyl-1*H*-pyrazole. The current version of this reaction yields simultaneously two types of products **1**, **2**. This is superior to similar procedure[6] using phosphites and various alkylformamides affording only (aminomethylene)bis(phosphonates). In the experiment, products **1**, **2** are obtained in one-pot directly from N-heterocycles, formic acid, *symm*-dicyclohexylcarbodiimide (DCC), and tris(trimethylsilyl) phosphite (see Scheme 1).†

Apparently, in the course of the reaction, *N*-formyl derivatives HetNCHO react with tris(trimethylsilyl) phosphite similarly to formamides of simple structure,[6] with the catalytic role of trimethylsilyl triflate being the generation of highly reactive intermediate salts[6] (Scheme 2). The ability of substituted (trimethylsiloxymethyl)phosphonates **1** to remain steady under the process

† Starting trimethylsilyl esters of phosphorous acid were prepared as reported.[12–14]

*Bis(trimethylsilyl) [(1*H*-imidazol-1-yl)(trimethylsiloxy)methyl]phosphonate* **1a** *and tetrakis(trimethylsilyl) (1*H*-imidazol-1-ylmethylene)-bis(phoshonate)* **2a**. A solution of DCC (14.4 g, 0.07 mol) in CH_2Cl_2 (20 ml) was added under stirring to a solution of 1*H*-imidazole (3.4 g, 0.05 mol) and formic acid (2.8 g, 0.06 mol) in CH_2Cl_2 (50 ml). The mixture was stirred for 6 h and left for 12 h. The precipitate was filtered off, the filtrate was added to a solution of tris(trimethylsilyl) phosphite (44.8 g, 0.15 mol), and a solution of trimethylsilyl triflate (2.9 g, 0.013 mol) in CH_2Cl_2 (10 ml) was added to this mixture. The mixture was heated in a boiling water bath to complete the removal of low-boiling compounds and then distilled to give phosphonate (1.8 g) **1a**, yield 9%, bp 102 °C (1 Torr) and bis-phosphonate (22.0 g) **2a**, yield 83%, bp 126 °C (1 Torr).

For **1a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: –0.38 (s, Me_3SiO), –0.24 (s, 2Me_3Si), 5.22 (d, α-CH, $^2J_{PH}$ 4.8 Hz), 6.57 and 7.15 (both s, CH_{Het}). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 1.62 (s, Me_3Si), –0.25 and 0.05 (both s, 2Me_3Si), 76.47 (d, α-C, $^1J_{PC}$ 213.2 Hz), 106.61, 139.80, 146.52 (all s, C_{Het}). ^{31}P NMR (162 MHz, $CDCl_3$) δ: –4.02 (s). Found (%): C, 39.42; H, 7.83. Calc. for $C_{13}H_{31}N_2O_4PSi_3$ (%): C, 39.57; H, 7.92.



Scheme 2

conditions is obviously determined by the size of the heterocyclic moiety which prevents further substitution of trimethylsiloxy group at α-C of phosphonates **1**.

Trimethylsilyl esters **1**, **2** readily react with excess methanol under mild conditions to form water-soluble functionalized mono- or diphosphonic acids **3**, **4**, respectively (see Scheme 1).‡

The resulting compounds **1**–**4** can be used in the synthesis of new types of organophosphorus substances, including both heterocyclic fragments and phosphonic groups.[11] These compounds are promising precursors for multitarget drug discovery, perspective plant-growth regulators as well as effective polydentate ligands for various metal complexes with versatile properties.

In conclusion, we have proposed the convenient methods of synthesis of new functionalized mono- and bis-phosphonic acids equipped with five-membered N-heterocycle moieties *via* the unique reaction of tris(trimethylsilyl) phosphite with N-formylated N-heterocycles catalyzed by trimethylsilyl triflate.

For **2a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: –0.15 (s, 2Me_3Si), –0.14 (s, 2Me_3Si), 3.55 (t, α-CH, $^2J_{PH}$ 17.2 Hz), 6.57 and 7.15 (2 s, CH_{Het}). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 0.47 (s, 4Me_3Si), 67.80 (t, α-C, $^1J_{PC}$ 168.2 Hz), 121.00 and 134.69 (both s, C_{Het}). ^{31}P NMR (162 MHz, $CDCl_3$) δ: –0.32 (s). Found (%): C, 36.12; H, 7.52. Calc. for $C_{16}H_{40}N_2O_6P_2Si_4$ (%): C, 36.21; H, 7.60.

Phosphonates **1b**–**d** and bis-phosphonates **2b**–**d** were prepared similarly.

*Bis(trimethylsilyl) [(1*H*-benzimidazol-1-yl)(trimethylsiloxy)methyl]-phosphonate* **1b**. Yield 30%, bp 110 °C (1 Torr). ^{1}H NMR (400 MHz, $CDCl_3$) δ: –0.44 (s, Me_3Si), –0.25 (s, 2Me_3Si), 5.58 (d, α-CH, $^2J_{PH}$ 4.4 Hz), 6.70–7.45 (m, CH_{Het}). ^{13}C NMR (100 MHz, $CDCl_3$) δ: –0.22 (s, Me_3Si), 1.11 (s, 2Me_3Si), 75.50 (d, α-C, $^1J_{PC}$ 214.1 Hz), 110.40, 120.23, 122.51, 123.19, 139.62, 143.28, 145.74 (all s, C_{Het}). ^{31}P NMR (162 MHz, $CDCl_3$) δ: –3.47 (s). Found (%): C, 45.81; H, 7.40. Calc. for $C_{17}H_{33}N_2O_4PSi_3$ (%): C, 45.92; H, 7.48.

*Bis(trimethylsilyl) [(2,4-dimethyl-1*H*-pyrazol-1-yl)(trimethylsiloxy)-methyl]phosphonate* **1c**. Yield 86%, bp 106 °C (1 Torr). ^{1}H NMR (400 MHz, $CDCl_3$) δ: –0.38 and –0.31 (2 s, 2Me_3Si), –0.16 (s, Me_3Si), 1.71 and 1.99 (2 s, 2Me), 5.36 (s, CH_{Het}), 5.40 (d, α-CH, $^2J_{PH}$ 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: –1.62 (s, Me_3Si), –0.25 and 0.05 (2 s, 2Me_3Si), 10.77 and 12.36 (2 s, 2Me), 81.19 (d, α-C, $^1J_{PC}$ 214.1 Hz), 106.61, 139.80, 146.52 (all s, C_{Het}). ^{31}P NMR (162 MHz, $CDCl_3$) δ: –3.35 (s). Found (%): C, 42.49; H, 8.28. Calc. for $C_{15}H_{35}N_2O_4PSi_3$ (%): C, 42.62; H, 8.35.

*Bis(trimethylsilyl) [(1*H*-benzotriazol-1-yl)(trimethylsiloxy)methyl]-phosphonate* **1d**. Yield 59%, bp 108 °C (1 Torr). ^{1}H NMR (400 MHz, $CDCl_3$) δ: –0.36 (s, Me_3Si), –0.05 (s, 2Me_3Si), 6.26 (d, α-CH, $^2J_{PH}$ 6.4 Hz), 6.99–7.76 (m, C_6H_4). ^{13}C NMR (100 MHz, $CDCl_3$) δ: –0.93 (s, Me_3Si), –0.75 (s, Me_3Si), –0.43 (s, Me_3Si), 80.73 (d, α-C, $^1J_{PC}$ 213.2 Hz), 113.37, 119.20, 124.17, 127.30, 131.84, 146.45 (all s, C_{Het}). ^{31}P NMR (162 MHz, $CDCl_3$) δ: –4.81 (s). Found (%): C, 43.03; H, 7.16. Calc. for $C_{16}H_{32}N_3O_4PSi_3$ (%): C, 43.12; H, 7.24.

*Tetrakis(trimethylsilyl) (1*H*-benzimidazol-1-ylmethylene)bis(phosphonate)* **2b**. Yield 62%, bp 139 °C (1 Torr). ^{1}H NMR (400 MHz, $CDCl_3$) δ: –0.38 and –0.31 (2 s, 2Me_3Si), –0.16 (s, Me_3Si), 3.55 (t, α-CH, $^2J_{PH}$ 16.8 Hz), 6.65–7.55 (m, CH_{Het}). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 1.10 (s, 4Me_3Si), 68.11 (d, α-C, $^1J_{PC}$ 167.3 Hz), 112.46, 119.92, 122.13, 122.75, 139.71, 141.75, 145.46 (all s, C_{Het}). ^{31}P NMR (162 MHz, $CDCl_3$) δ: –0.58 (s). Found (%): C, 41.26; H, 7.20. Calc. for $C_{20}H_{42}N_2O_6P_2Si_4$ (%): C, 41.36; H, 7.29.

*Tetrakis(trimethylsilyl) (2,4-dimethyl-1*H*-pyrazol-1-ylmethylene)bis-(phosphonate)* **2c**. Yield 7%, bp 129 °C (1 Torr). ^{1}H NMR (400 MHz, $CDCl_3$) δ: –0.12 and –0.16 (2 s, 4Me_3Si), 1.80 and 2.01 (2 s, 2Me), 3.58 (t, α-CH, $^2J_{PH}$ 17.2 Hz), 5.36 (s, CH_{Het}). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 0.35 (s, 4Me_3Si), 10.80 and 12.40 (2 s, 2Me), 68.09 (t, α-C, $^1J_{PC}$ 168.2 Hz), 106.68, 139.86, 146.57 (all s, C_{Het}). ^{31}P NMR (162 MHz, $CDCl_3$) δ: –0.30 (s). Found (%): C, 38.52; H, 7.86. Calc. for $C_{18}H_{44}N_2O_6P_2Si_4$ (%): C, 38.69; H, 7.94.

*Tetrakis(trimethylsilyl) (1*H*-benzotriazol-1-ylmethylene)bis(phosphonate)* **2d**. Yield 30%, bp 133 °C (1 Torr). ^{1}H NMR (400 MHz, $CDCl_3$) δ: –0.11 (s, 4Me_3Si), 3.75 (t, α-CH, $^2J_{PH}$ 16.8 Hz), 7.17–7.83 (m, C_6H_4). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 0.01 (s, 4Me_3Si), 67.71 (t, α-C, $^1J_{PC}$ 168.2 Hz), 110.50, 114.55, 119.44, 126.22, 129.93, 140.27 (all s, C_{Het}). ^{31}P NMR (162 MHz, $CDCl_3$) δ: –0.47 (s). Found (%): C, 39.03; H, 7.01. Calc. for $C_{19}H_{41}N_3O_6P_2Si_4$ (%): C, 39.22; H, 7.10.

---

‡ (*1*H*-Imidazol-1-ylmethylene)bis(phosphonic) acid* **4a**. A solution of bis-phosphonate **2a** (10.6 g, 0.02 mol) in diethyl ether (15 ml) was added to methanol (40 ml) under stirring and cooling to 10 °C, the mixture was refluxed, the solvent was removed. White crystals were kept in vacuum (1 Torr) to give 4.7 g of acid **4a**, yield 97%, mp 174–176 °C. ^{1}H NMR (400 MHz, D_2O–pyridine-d_5) δ: 3.33 (t, α-CH, $^2J_{PH}$ 16.0 Hz), 6.55 and 7.85 (2 s, CH_{Het}). ^{13}C NMR (100 MHz, D_2O–pyridine-d_5) δ: 66.26 (t, α-C, $^1J_{PC}$ 139.9 Hz), 117.83 and 132.43 (2 s, C_{Het}). ^{31}P NMR (162 MHz, D_2O–pyridine-d_5) δ: 14.66 (s). Found (%): C, 19.69; H, 3.28. Calc. for $C_4H_8N_2O_6P_2$ (%): C, 19.85; H, 3.33.

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

[(*1*H*-Imidazol-1-yl)(hydroxy)methyl]phosphonic acid* **3a**. Yield 96%, mp 144–145 °C (decomp.). ^{1}H NMR (400 MHz, D_2O–pyridine-d_5) δ: 6.81 (d, α-CH, $^2J_{PH}$ 4.2 Hz), 6.57 and 7.92 (2 s, CH_{Het}). ^{13}C NMR (100 MHz, D_2O–pyridine-d_5) δ: 78.81 (d, α-C, $^1J_{PC}$ 180.4 Hz), 117.96 and 132.86 (2 s, C_{Het}). ^{31}P NMR (162 MHz, D_2O–pyridine-d_5) δ: 7.47 (s). Found (%): C, 26.86; H, 3.88. Calc. for $C_4H_7N_2O_4P$ (%): C, 26.98; H, 3.96.

[(*1*H*-Benzimidazol-1-yl)(hydroxy)methyl]phosphonic acid* **3b**. Yield 94%, mp 157–159 °C (decomp.). ^{1}H NMR (400 MHz, D_2O–pyridine-d_5) δ: 5.15 (d, α-CH, $^2J_{PH}$ 6.4 Hz), 7.17 (dd, $^3J_{HH}$ 16.0 Hz, $^4J_{HH}$ 3.2 Hz), 7.47 (dd, $^3J_{HH}$ 16.0 Hz, $^4J_{HH}$ 3.2 Hz), 7.57 (s, CH_{Het}). ^{13}C NMR (100 MHz, D_2O–pyridine-d_5) δ: 78.85 (d, α-C, $^1J_{PC}$ 170.0 Hz), 114.16, 125.86, 129.74, 138.52 (all s, C_{Het}). ^{31}P NMR (162 MHz, D_2O–pyridine-d_5) δ: 6.88 (s). Found (%): C, 41.97; H, 3.91. Calc. for $C_8H_9N_2O_4P$ (%): C, 42.12; H, 3.98.

[(*2,4-Dimethyl-1*H*-pyrazol-1-yl)(hydroxy)methyl]phosphonic acid* **3c**. Yield 97%, mp 357–359 °C (decomp.). ^{1}H NMR (400 MHz, D_2O–pyridine-d_5) δ: 1.86 and 2.20 (2 s, 2Me), 4.92 (d, α-CH, $^2J_{PH}$ 6.0 Hz), 5.64 (s, CH_{Het}). ^{13}C NMR (100 MHz, D_2O–pyridine-d_5) δ: 10.47 and 12.44 (2 s, 2Me), 88.18 (d, α-C, $^1J_{PC}$ 191.4 Hz), 103.71, 144.05 (all s, C_{Het}). ^{31}P NMR (162 MHz, D_2O–pyridine-d_5) δ: 10.42 (s). Found (%): C, 34.78; H, 5.30. Calc. for $C_6H_{11}N_2O_4P$ (%): C, 34.96; H, 5.38.

[(*1*H*-Benzotriazol-1-yl)(hydroxy)methyl]phosphonic acid* **3d**. Yield 95%, mp 105–107 °C (decomp.). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 6.43 (d, α-CH, $^2J_{PH}$ 7.2 Hz), 7.41 (dd, CH_{Het}, $^3J_{HH}$ 6.4 Hz, $^4J_{HH}$ 3.2 Hz), 7.89 (dd, CH_{Het}, $^3J_{HH}$ 6.4 Hz, $^4J_{HH}$ 3.2 Hz). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 79.96 (d, α-C, $^1J_{PC}$ 187.7 Hz), 114.92, 118.84, 125.42, 126.86, 131.87, 145.86 (all s, C_{Het}). ^{31}P NMR (162 MHz, DMSO-d_6) δ: 10.62 (s). Found (%): C, 36.55; H, 3.48. Calc. for $C_7H_8N_3O_4P$ (%): C, 36.70; H, 3.52.

*(1*H*-Benzimidazol-1-ylmethylene)bis(phosphonic) acid* **4b**. Yield 98%, mp 348–350 °C (decomp.). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 4.18 (t, α-CH, $^2J_{PH}$ 16.0 Hz), 7.18 (dd, CH_{Het}, $^3J_{HH}$ 6.0 Hz, $^4J_{HH}$ 3.2 Hz), 7.46 (dd, CH_{Het}, $^3J_{HH}$ 6.0 Hz, $^4J_{HH}$ 3.2 Hz), 7.56 (s, CH_{Het}). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 66.86 (d, α-C, $^1J_{PC}$ 142.1 Hz), 113.79, 125.73, 129.59, 138.88 (all s, C_{Het}). ^{31}P NMR (162 MHz, DMSO-d_6) δ: 15.63 (s). Found (%): C, 32.74; H, 3.40. Calc. for $C_8H_{10}N_2O_6P_2$ (%): C, 32.89; H, 3.45.

*(2,4-Dimethyl-1*H*-pyrazol-1-ylmethylene)bis(phosphonic) acid* **4c**. Yield 98%, mp 357–359 °C (decomp.). ^{1}H NMR (400 MHz, DMSO-d_6–pyridine-d_5) δ: 1.82 and 2.14 (2 s, 2Me), 3.97 (t, α-CH, $^2J_{PH}$ 15.6 Hz), 5.60 (s, CH_{Het}). ^{13}C NMR (100 MHz, DMSO-d_6–pyridine-d_5) δ: 10.44 and 12.34 (2 s, 2Me), 55.57 (t, α-C, $^1J_{PC}$ 181.7 Hz), 105.63, 140.83 (all s, C_{Het}). ^{31}P NMR (162 MHz, DMSO-d_6–pyridine-d_5) δ: 15.03 (s). Found (%): C, 26.49; H, 4.52. Calc. for $C_6H_{12}N_2O_6P_2$ (%): C, 26.68; H, 4.48.

*(1*H*-Benzotriazol-1-ylmethylene)bis(phosphonic) acid* **4d**. Yield 96%, mp 355–357 °C (decomp.). ^{1}H NMR (400 MHz, DMSO-d_6–pyridine-d_5) δ: 3.88 (t, α-CH, $^2J_{PH}$ 17.2 Hz), 8.01 (d, $^3J_{HH}$ 8.2 Hz), 8.95 (d, $^3J_{HH}$ 8.2 Hz). ^{13}C NMR (100 MHz, DMSO-d_6–pyridine-d_5) δ: 65.28 (t, α-C, $^1J_{PC}$ 150.2 Hz), 113.61, 118.64, 124.03, 125.42, 126.86, 138.69 (all s, C_{Het}). ^{31}P NMR (162 MHz, DMSO-d_6–pyridine-d_5) δ: 16.41 (s). Found (%): C, 28.56; H, 3.14. Calc. for $C_7H_9N_3O_6P_2$ (%): C, 28.68; H, 3.09.

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

References

1 *Aminophosphonic and Aminophosphinic Acids. Chemistry and Biological Activity*, eds. V. P. Kukhar and H. R. Hudson, Wiley, New York, 2000.
2 L. Widler, K. A. Jaeggi, M. Glatt, K. Müller, R. Bachmann, M. Bisping, A.-R. Born, R. Cortesi, G. Guiglia, H. Jeker, R. Klein, U. Ramseier, J. Schmid, G. Schreiber, Y. Seltenmeyer and J. R. Green, *J. Med. Chem.*, 2002, **45**, 3721.
3 O. I. Kolodiazhnyi, *Russ. Chem. Rev.*, 2006, **75**, 227 (*Usp. Khim.*, 2006, **75**, 254).
4 A. Mucha, P. Kafarski and L. Berlicki, *J. Med. Chem.*, 2011, **54**, 5955.
5 A. A. Prishchenko, M. V. Livantsov, O. P. Novikova, L. I. Livantsova and V. S. Petrosyan, *Russ. Chem. Bull., Int. Ed.*, 2016, **65**, 228 (*Izv. Akad. Nauk, Ser. Khim.*, 2016, 228).
6 A. A. Prishchenko, M. V. Livantsov, O. P. Novikova, L. I. Livantsova, I. S. Ershov and V. S. Petrosyan, *Heteroat. Chem.*, 2013, **24**, 355.
7 A. A. Prishchenko, M. V. Livantsov, O. P. Novikova, L. I. Livantsova, I. S. Ershov and V. S. Petrosyan, *Heteroat. Chem.*, 2015, **26**, 101.
8 A. A. Prishchenko, M. V. Livantsov, O. P. Novikova, L. I. Livantsova, G. M. Averochkin and V. S. Petrosyan, *Heteroat. Chem.*, 2015, **26**, 405.
9 A. R. Katriztky, H.-X. Chang and B. Yang, *Synthesis*, 1995, 503.
10 A. D. Dilman and S. L. Ioffe, *Chem. Rev.*, 2003, **103**, 733.
11 A. A. Prishchenko, M. V. Livantsov, O. P. Novikova, L. I. Livantsova, and V. S. Petrosyan, *Russ. Chem. Bull., Int. Ed.*, 2016, **65**, 1846 (*Izv. Akad. Nauk, Ser. Khim.*, 2016, 1846).
12 A. A. Prishchenko, M. V. Livantsov, O. P. Novikova, L. I. Livantsova and V. S. Petrosyan, *Heteroat. Chem.*, 2009, **20**, 319.
13 L. Woźniak and J. Chojnowski, *Tetrahedron*, 1989, **45**, 2465.
14 V. D. Romanenko, M. V. Shevchuk and V. P. Kukhar, *Curr. Org. Chem.*, 2011, **15**, 2774.

Received: 12th May 2016; Com. 16/4969