Nitrosylsulfuric acid as an oxidant in the synthesis of 3,5-diarylisoxazoles*

O. B. Bondarenko,[a]★ A. I. Komarov,[a] L. I. Kuznetsova,[a] S. N. Nikolaeva,[a] A. Yu. Gavrilova,[a] and N. V. Zyk[a,b]

[a] *Department of Chemistry, M. V. Lomonosov Moscow State University, 1 Leninskie Gory, 119992 Moscow, Russian Federation. Fax: +7 (495) 939 4652. E-mail: k527.5msu@gmail.com*
[b] *Institute of Physiologically Active Compounds, Russian Academy of Sciences, 1 Severnyi proezd, Chernogolovka, 142432 Moscow Region, Russian Federation*

By six examples, it was demonstrated that nitrosylsulfuric acid can be successfully used for oxidation of 3,5-diaryl-4,5-dihydroisoxazoles to the corresponding 3,5-diarylisoxazoles. If the starting isoxazolines contain the aromatic substituents activated towards electrophilic substitution, nitration of both newly formed isoxazole and substituted benzene rings occurred.

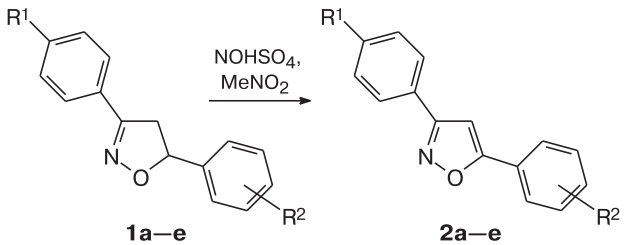
Key words: 3,5-diaryl-4,5-dihydroisoxazoles, nitrosylsulfuric acid, oxidation, 3,5-diarylisoxazoles, nitration.

3,5-Diarylisoxazoles are widely used stable compounds consisting of three conjugated aromatic rings. A scope of application of these compounds is very broad. Due to the presence of isoxazole moiety, 3,5-diarylisoxazoles are of interest for medicine and medicinal chemistry. These compounds exhibit antimicrobial,[1] antituberculosis,[2] antitumor[3] and other types of biological activities[4—7] and are selective estrogen receptor modulators.[8,9] 3,5-Diphenylisoxazole derivatives are the platforms for the design of the liquid-crystal materials[10,11] and light-harvesting systems.[12]

3,5-Diarylisoxazoles could be accessed by two major approaches, namely, by 1,3-dipolar cycloaddition of nitrile oxides to alkynes[13,14] and by condensation of hydroxylamine with either β-diketones or their synthetic equivalents.[15,16] Another method for synthesizing 3,5-diarylisoxazoles is oxidation (dehydrogenation) of 4,5-dihydroisoxazoles (isoxazolines). This method is of particular interest since the construction of the 4,5-dihydroisoxazole ring by the conventional methods is more simple and efficient due to more readily proceeding reactions, higher yields of target heterocycles, and greater variety of the starting compounds. Oxidation of isoxazolines to isoxazoles can be effected with nickel peroxide,[17] chromic acid, potassium permanganate, chloranil, air oxygen,[18] DDQ,[19] and γ-manganese dioxide.[20] In the present work, we applied nitrosylsulfuric acid for the conversion of isoxazolines to isoxazoles. It should be noted that readily available nitrosylsulfuric acid is widely used in organic synthesis. The efficacy of nitrosylsulfuric acid as dehydrogenating agent for the aromatization of hydroaromatic compounds has been reported.[21]

We found that nitrosylsulfuric acid efficiently oxidizes 3,5-diaryl-4,5-dihydroisoxazoles **1a**—**e** to the corresponding 3,5-diarylisoxazoles **2a**—**e** (Scheme 1). The reactions were carried out at room temperature for 15—20 h using a 1.5—2-fold excess of nitrosylsulfuric acid. On the model oxidation of 3,5-diphenylisoxazoline (**1a**), we revealed that the reaction between the equimolar amounts of the starting reagents is very slow. Thus, 5 h after the reaction onset the conversion of isoxazoline **1a** to isoxazole **2a** was only 22% (^{1}H NMR spectral data of the reaction mixture). The reaction conditions and the yields of isoxazoles **2a**—**e** are given in Table 1. From Table 1 follows that the selected conditions gives 3,5-diarylisoxazoles **2** in high yields and high purity.

Scheme 1



Compounds **1** and **2**	R^1	R^2
a	H	H
b	Br	4-Br
c	F	4-F
d	NO_2	H
e	H	2-F

If isoxazoline **1** contains the aromatic substituents activated towards electrophilic substitution (*e.g.*, isoxazoline **1f**), the reaction is accompanied with nitration of

* Dedicated to Academician of the Russian Academy of Sciences I. P. Beletskaya.

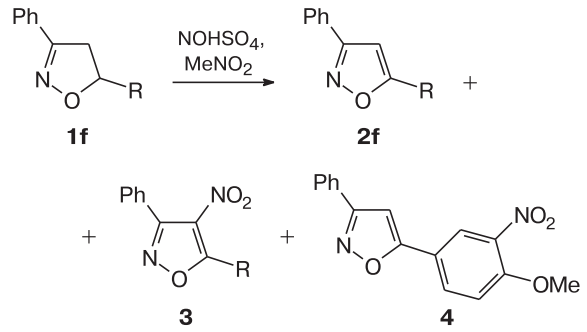
Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 3, pp. 0517—0520, March, 2018.
1066-5285/18/6703-0517 © 2018 Springer Science+Business Media, Inc.

Table 1. Oxidation of isoxazolines **1a—e** to isoxazoles **2a—e** with nitrosylsulfuric acid in nitromethane at 20 °C

Compound **1**	$NOHSO_4$ (equiv.)	Product (yield (%))	M.p./°C
1a	2.0	**2a** (86)	140 (141—143[16,22])
1b	1.5	**2b** (80)	218 (217.5—218.5[11,23])
1c	2.0	**2c** (85)	188 (190[24])
1d	1.5	**2d** (97)	221 (220—221[25])
1e	2.0	**2e** (75)	91—92

both newly formed isoxazole and substituted benzene rings (Scheme 2, Table 2, entry *4*). Spectral and physicochemical properties of isoxazoles **2f** and **3** agree with those published earlier.[22,26] The composition of isoxazole **4** was confirmed by elemental analysis data, its structure was established by ^1H and ^{13}C NMR spectroscopy. The location of the nitro substituent at the *ortho* position for the MeO group is confirmed by a significant upfield shift of the $C(NO_2)$ quaternary carbon atom signal (δ 129.1). Note that nitration of aromatic moieties of compounds on treatment with the nitrosating agents is a well-known fact.[27]

Scheme 2



R = 4-$MeOC_6H_4$

We studied the compositions of the reaction mixtures obtained by oxidation of isoxazoline **1f** under different reaction conditions (see Table 2). It was found that even at 0 °C oxidation of isoxazoline **1f** occurs at a significant rate. At that, by 30 min of the reaction all three isoxazoles (**2f**, **3**, and **4**) were presented in the reaction mixture (see Table 2, entry *1*). The highest selectivity for isoxazole **2f** was achieved by adding equimolar amount of nitrosylsulfuric acid to a cooled nitromethane solution of isoxazoline **1f** (0 °C) and further carrying the reaction at room temperature (see Table 2, entry *3*).

In summary, in the present work we revealed that nitrosylsulfuric acid efficiently oxidizes 3,5-diaryl-4,5-dihydroisoxazoles to the corresponding 3,5-diarylisoxazoles.

Experimental

^1H, ^{13}C, and ^{19}F NMR spectra were recorded with Bruker Avance-400 and Agilent 400-MR spectrometers (working frequencies of 400.13, 100.67, and 376.29 MHz, respectively) in $CDCl_3$. The chemical shifts are given in the δ scale relative to internal standards of hexamethyldisiloxane for ^1H and ^{13}C nuclei and $CFCl_3$ for ^{19}F nucleus. Electron impact mass spectrometry was performed with a Thermo Scientific TSQ 8000 system (Germany) (a capillary column SPB™-5 (15 m×0.25 mm), carrier gas was helium at a flow rate of 1 $mL \cdot min^{-1}$), energy of ionizing electrons was 70 eV); temperature was programmed as follows: maintaining at 70 °C for 2 min, heating with the rate of 20 °C · min^{-1}, maintaining at 280 °C for 5 min. IR spectra were recorded on a Nicolet IR200 FT-IR spectrometer (Thermo Scientific) equipped with an attenuated total reflection (ATR) accessory using ZnSe crystal plate; reflection angle of 45°; spectral resolution of 4 cm^{-1}; 20 scans were collected. Melting points of the synthesized compounds were measured with a Mel-Temp II apparatus and are given uncorrected. The course of the reactions was monitored by TLC on Silufol plates. Nitrosylsulfuric acid was synthesized by the known procedure.[29]

Oxidation of 3,5-diaryl-4,5-dihydroisoxazoles 1a—f (general procedure). A flask equipped with a magnetic stirring bar and a ground glass stopper was charged with 3,5-diaryl-4,5-dihydroisoxazole (**1**) (0.4 mmol), nitromethane (4 mL), and nitrosylsulfuric acid (51 mg, 0.4 mmol) in this order. After 1 h stirring at room temperature, additional portion of nitrosylsulfuric acid (0.2—0.4 mmol) was added and stirring was continued until complete consumption of compound **1**. The products were

Table 2. Composition of the reaction mixtures obtained by oxidation of isoxazoline **1f** depending on the reaction conditions

Entry	$NOHSO_4$ (equiv.)	*T*/°C	*t*/h	Reaction mixture composition (%)[a]			
				1f	**2f**	**3**	**4**
1	1.1	0	0.5	15[b]	45	20	15
2	1.2	0	2	5[c]	—	45	40
3	1.2	0—20	1	—	55	25	20
4	1.2	20	1	—	20	45	35

[a] ^1H NMR data.
[b] Reaction mixture contained *ca.* 5% of 5-(4-methoxy-3-nitrophenyl)-3-phenylisoxazoline.[28]
[c] Reaction mixture contained *ca.* 10% of 5-(4-methoxy-3-nitrophenyl)-3-phenylisoxazoline.

isolated by flash-column chromatography (SiO_2 40/100, elution with chloroform). The obtained isoxazoles were additionally purified by recrystallization from ethanol if required.

3,5-Bis(4-fluorophenyl)isoxazole (2c). ^{1}H NMR, δ: 6.76 (s, 1 H, C(4)H_{is}); 7.20 (m, 4 H, Ar); 7.86 (m, 4 H, Ar). ^{13}C NMR, δ: 97.1 (C(4)H_{is}); 116.0 (d, 2 CH_{Ar}, $^2J_{CF}$ = 22.1 Hz); 116.2 (d, 2 CH_{Ar} ,$^2J_{CF}$ = 22.9 Hz); 123.7 (d, C(1)$_{Ar}$, $^4J_{CF}$ = 3.8 Hz); 125.2 (d, C(1)$_{Ar}$, $^4J_{CF}$ = 3.8 Hz); 127.9 (d, 2 CH_{Ar}, $^3J_{CF}$ = = 9.2 Hz); 128.7 (d, 2 CH_{Ar}, $^3J_{CF}$ = 8.4 Hz); 162.1 (C=N); 163.82 (d, FC(4)$_{Ar}$, $^1J_{CF}$ = 251.8 Hz); 163.84 (d, FC(4)$_{Ar}$, $^1J_{CF}$ = 250.3 Hz); 169.6 (C—O). ^{19}F NMR, δ: −110.4 (m, 1 F); −109.3 (m, 1 F). Found (%): C, 70.18; H, 3.74; N, 5.44. $C_{15}H_9F_2NO$. Calculated (%): C, 70.04; H, 3.53; N, 5.45.

3-(4-Nitrophenyl)-5-phenylisoxazole (2d). ^{1}H NMR, δ: 6.91 (s, 1 H, C(4)H_{is}); 7.53 (m, 3 H, Ar); 8.87 (m, 2 H, Ar); 8.07 (d, 2 H, Ar, ^3J = 8.8 Hz); 8.36 (d, 2 H, Ar, ^3J = 8.8 Hz). MS (EI, 70 eV), *m*/*z* (I_{rel} (%)): 266 $[M]^+$ (40), 207 (50), 105 $[PhCO]^+$ (100), 77 $[Ph]^+$ (57).

5-(2-Fluorophenyl)-3-phenylisoxazole (2e). ^{1}H NMR, δ: 7.05 (d, 1 H, C(4)H_{is}, $^5J_{HF}$ = 3.7 Hz); 7.23 (ddd, 1 H, Ar, $^3J_{HF}$ = = 10.9 Hz, *J* = 7.8 Hz, *J* = 1.0 Hz); 7.31 (dt, 1 H, Ar, *J* = 7.8 Hz, *J* = 1.0 Hz); 7.42—7.47 (m, 1 H, Ar); 7.48—7.50 (m, 3 H, Ar); 7.91 (m, 2 H, Ar); 8.03 (dt, 1 H, Ar, *J* = 7.8 Hz, *J* = 1.7 Hz). ^{13}C NMR, δ: 101.7 (d, C(4)$H_{is,}$ $^4J_{CF}$ = 11.2 Hz); 115.9 (d, C(1)$_{Ar}$, $^2J_{CF}$ = 12.1 Hz); 116.3 (d, C(3)H_{Ar}, $^2J_{CF}$ = 21.7 Hz); 124.7 (d, CH_{Ar}, J_{CF} = 3.2 Hz); 126.9 (2 CH_{Ph}); 127.7 (d, CH_{Ar}, J_{CF} = 2.4 Hz); 129.0 (2 CH_{Ph}); 129.02 (C(1)$_{Ph}$); 130.1 (CH_{Ph}); 131.6 (d, CH_{Ar}, $^3J_{CF}$ = 8.8 Hz); 159.2 (d, C—F, $^1J_{CF}$ = 253.0 Hz); 163.2 (C=N); 164.2 (d, C—O, $^3J_{CF}$ = 3.2 Hz). ^{19}F NMR, δ: −111.7 (m, 1 F). MS (EI, 70 eV), *m*/*z* (I_{rel} (%)): 239 $[M]^+$ (26), 144 $[M - FC_6H_4]^+$ (22), 123 $[FC_6H_4CO]^+$ (100), 95 $[FC_6H_4]^+$ (28), 77 $[Ph]^+$ (16), 76 $[C_6H_4]^+$ (13). Found (%): C, 75.15; H, 4.42; N, 5.66. $C_{15}H_{10}FNO$. Calculated (%): C, 75.30; H, 4.21; N, 5.85.

Oxidation of 4,5-dihydro-5-(4-methoxyphenyl)-3-phenylisoxazole (1f) with nitrosylsulfuric acid. A flask was charged with isoxazoline **1f** (0.25 g, 1 mmol) and nitromethane (15 mL). The obtained solution was cooled to 0 °C, afterwards nitrosylsulfuric acid (0.15 g, 1.2 mmol) was added, and the mixture was stirred at room temperature for 1 h. After the reaction completion, water (10 mL) was added and the aqueous layer was extracted with dichloromethane (3×5 mL). The combined organic layers were dried with sodium sulfate. The solvent was removed *in vacuo* and the residue was subjected to column chromatography (SiO_2 40/100, elution with benzene). The products were eluted in the following order: nitro derivative **3**, compound **2f**, and compound **4**.

5-(4-Methoxyphenyl)-4-nitro-3-phehylisoxazole (3). Yield 0.06 g (19%), R_f 0.65, m.p. 115 °C (*cf*. Ref. 26: m.p. 111—112 °C). IR, ν/cm^{-1}: 2870 (MeOAr), 1618 (C=N), 1600 (C=C), 1530 (NO_2), 1370 (NO_2). ^{1}H NMR, δ: 3.88 (s, 3 H, CH_3O); 7.04 (d, 2 H, Ar, ^3J = 9.0 Hz); 7.50 (m, 3 H, Ar); 7.62 (m, 2 H, Ar); 7.93 (d, 2 H, Ar, ^3J = 9.0 Hz). ^{13}C NMR, δ: 55.5 (CH_3O), 114.4 (2 CH_{Ar}), 116.8 (C(4)$_{is}$), 126.2 (C_{Ar}), 128.3 (C_{Ar}), 128.6 (2 CH_{Ar}), 128.8 (2 CH_{Ar}), 130.7 (CH_{Ar}), 131.0 (2 CH_{Ar}), 158.6 (C—OCH_3), 163.1 (C=N), 168.2 (=C—O). MS (EI, 70 eV), *m*/*z* (I_{rel} (%)): 296 $[M]^+$ (10), 161 $[M - MeOC_6H_4CO]^+$ (5), 135 $[MeOC_6H_4CO]^+$ (100), 119 $[MeOC_6H_4C]^+$ (14), 107 $[MeOC_6H_4]^+$ (14), 103 $[C_6H_5CN]^+$ (94), 92 $[OC_6H_4]^+$ (17), 77 (64), 76 (58), 51 (25), 50 (30). Found (%): C, 64.96; H, 3.95; N, 9.61. $C_{16}H_{12}N_2O_4$. Calculated (%): C, 64.86; H, 4.08; N, 9.46.

5-(4-Methoxyphenyl)-3-phenylisoxazole (2f). Yield 0.13 g (50%), R_f 0.43, m.p. 128 °C (*cf*. Ref. 22 and 26: m.p. 128—129). ^{1}H NMR, δ: 3.83 (s, 3 H, CH_3O); 6.68 (s, 1 H, C(4)H_{is}); 6.97 (d, 2 H, Ar, ^3J = 8.8 Hz); 7.45 (m, 3 H, Ph); 7.75 (d, 2 H, Ar, ^3J = 8.8 Hz); 7.85 (m, 2 H, Ph).

5-(4-Methoxy-3-nitrophenyl)-3-phenylisoxazole (4). Yield 0.04 g (14%), R_f 0.18, m.p. 158 °C. IR, ν/cm^{-1}: 2850 (MeOAr), 1626 (C=N), 1618 (C=C), 1531 (NO_2), 1342 (NO_2). ^{1}H NMR, δ: 4.05 (s, 3 H, CH_3O); 6.85 (s, 1 H, C(4)H_{is}); 7.23 (d, 1 H, Ar, ^3J = 8.8 Hz); 7.50 (m, 3 H, Ar); 7.87 (m, 2 H, Ar); 8.03 (dd, 1 H, Ar, ^3J = 8.8 Hz, ^4J = 2.2 Hz); 8.31 (d, 1 H, Ar, ^4J = 2.2 Hz). ^{13}C NMR, δ: 56.8 (CH_3O), 97.7 (C(4)$_{is}$), 114.1 (HC(5)$_{Ar}$), 120.2 (C(1)$_{Ar}$), 123.3 (HC(2)$_{Ar}$), 126.8 (2 CH), 128.7 (C(1′)$_{Ar}$), 129.0 (2 CH), 129.1 (C(3)$_{Ar}NO_2$), 130.2 (C(6)$_{Ar}$H), 131.2 (HC(4′)$_{Ar}$), 154.0 (C(4)$_{Ar}OCH_3$), 163.2 (C_{is}=N), 167.8 (=C_{is}—O). Found (%): C, 65.26; H, 4.29; N, 9.18. $C_{16}H_{12}N_2O_4$. Calculated (%): C, 64.86; H, 4.08; N, 9.46.

The authors would like to acknowledge Thermo Fisher Scientific Inc., MS Analytica (Moscow, Russia), and personally Prof. A. A. Makarov for providing mass spectrometry equipment for this work. The authors are also grateful to L. G. Saginova for kindly providing 3,5-diaryl-4,5-dihydroisoxazoles used in the present work.

This work was financially supported by the Russian Foundation for Basic Research (Project No. 15-03-04260).

References

1. B. P. Kansagra, H. H. Bhatt, A. R. Parikh, *Indian J. Heterocycl. Chem.*, 2002, **12**, 61.
2. S. G. Kini, A. R. Bhat, R. Bhat, N. Narayanaswamy, *Indian J. Heterocycl. Chem.*, 2008, **17**, 319.
3. V. S. Parmar, N. K. Sharma, M. Husain, A. C. Watterson, J. Kumar, L. A. Samuelson, A. L. Cholli, A. K. Prasad, A. Kumar, S. Malhotra, N. Kumar, A. Jha, A. Singh, I. Singh, Himanshu, A. Vats, N. A. Shakil, S. Trikha, S. Mukherjee, S. K. Sharma, S. K. Singh, A. Kumar, H. N. Jha, C. E. Olsen, C. P. Stove, M. E. Bracke, M. M. Mareel, *Bioorg. Med. Chem.*, 2003, **11**, 913.
4. A. Kumar, S. Rout, C. S. Panda, M. B. V. Raju, B. V. V. Ravikumar, *J. Adv. Pharm. Res.*, 2011, **2**, 94.
5. L. Babar, S. S. Tomar, *Pestic. Res. J.*, 2005, **17**, No. 2, 1.
6. A. Upadhyay, M. Gopal, C. Srivastava, N. D. Pandey, *J. Pestic. Sci.* (*Tokyo, Jpn.*), 2010, **35**, 464.
7. D. A. Patrick, S. A. Bakunov, S. M. Bakunova, E. V. K. Suresh Kumar, R. J. Lombardy, S. K. Jones, A. S. Bridges, O. Zhirnov, J. E. Hall, T. Wenzler, R. Brun, R. R. Tidwill, *J. Med. Chem.,* 2007, **50**, 2468.
8. Pat. WO 2000008001 A1; http://patentscope.wipo.int.
9. T. Haddad, R. Gershman, R. Dilis, D. Labaree, R. B. Hochberg, R. N. Hanson, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 5999.
10. A. A. Vieira, F. R. Bryk, G. Conte, A. J. Bortoluzzi, H. Gallardo, *Tetrahedron Lett.*, 2009, **50**, 905.
11. G. D. Vilela, R. R. da Rosa, P. H. Schneider, I. H. Bechtold, J. Eccher, A. A. Merlo, *Tetrahedron Lett.*, 2011, **52**, 6569.
12. A. Khatyr, H. Maas, G. Calzaferri, *J. Org. Chem.*, 2002, **67**, 6705.
13. M. Tanaka, T. Haino, K. Ideta, K. Kubo, A. Mori, Y. Fukazawa, *Tetrahedron*, 2007, **63**, 652.

14. A. M. Jawalekar, E. Reubsaet, F. P. J. T. Rutjes, F. L. van Delft, *Chem. Commun.*, 2011, **47**, 3198.
15. K. V. G. C. Sekhar, T. V. N. V. T. Sasank, H. N. Nagesh, N. Suresh, K. M. Naidu, A. Suresh, *Chin. Chem. Lett.*, 2013, **24**, 1045.
16. S. Tang, J. He, Y. Sun, L. He, X. She, *Org. Lett.*, 2009, **11**, 3982.
17. C. J. Easton, C. M. Hughes, E. R. T. Tiekink, C. E. Lubin, G. P. Savage, G. W. Simpson, *Tetrahedron Lett.*, 1994, **35**, 3589.
18. C. J. Easton, C. M. M. Hughes, G. P. Savage, G. W. Simpson, *Adv. Heterocycl. Chem.*, 1994, **60**, 261.
19. V. G. Desai, S. G. Tilve, *Synth. Commun.*, 1999, **29**, 3017.
20. A. Barco, S. Bennetti, G. P. Pollini, P. G. Baraldi, *Synthesis,* 1977, 837.
21. M. V. Gorelik, B. L. Lomzakova, *Zh. Org. Khim.* [*Russ. J. Org. Chem.*], 1978, **14**, 1051 (in Russian).
22. U. Türck, H. Behringer, *Chem. Ber.*, 1965, **98**, 3020.
23. O. Dann, H. Fick, B. Pietzner, E. Walkenhorst, R. Fernbach, D. Zeh, *Liebigs Ann. Chem.*, 1975, 160.
24. H.-K. Fun, S. Arshad, S. Samshuddin, B. Narayana, B. K. Sarojini, *Acta Crystallogr.*, *Sect. E*: *Struct. Rep. Online*, 2012, **68**, o1783.
25. D. R. Chrisope, R. A. Keel, A. L. Baumstark, D. W. Boykin, *J. Heterocycl. Chem.,* 1981, **18**, 795.
26. J.-P. Hauff, J. Tuaillon, R. Perrot, *Helv. Chim. Acta*, 1978, **61**, 1207
27. A. D. Kadzhaeva, E. V. Trofimova, R. A. Gazzaeva, A. N. Fedotov, S. S. Mochalov, *Moscow Univ. Chem. Bull.*, 2009, **64**, 28.
28. L. G. Saginova, M. Al-Hamdan, V. S. Petrosyan, *Vestn. MGU, Ser. 2. Khimiya* [*Moscow Univ. Chem. Bull.*], 1999, **40**, 46 (in Russian).
29. *Praktikum po neorganicheskoi khimii: Uchebnoe posobie dlya studentov vysshikh uchebnykh zavedenii* [*Laboratory Course of Inorganic Chemistry: A Textbook for Students of Higher Educational Institutions*], Ed. Yu. D. Tret′yakov, Akademiya, Moscow, 2004, p. 241 (in Russian).

Received December 28, 2017;
in revised form January 16, 2018;
accepted January 18, 2018