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Synthesis of Functionally Substituted Isoxazoles from 5-(2,5-Dimethylphenyl)-1,2-oxazole-3-carbonitrile

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Abstract—Successive transformations of 5-(2,5-dimethylphenyl)-1,2-oxazole-3-carbonitrile, including Curtius rearrangement, led to the formation of 5-(2,5-dimethylphenyl)-1,2-oxazol-3-amine. Sulfonamides and urea derivative containing 5-(2,5-dimethylphenyl)isoxazole fragments were synthesized.

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The chemistry of isoxazole derivatives extensively develops due to their wide application in the synthesis of various organic compounds [1–3] and biological activity of numerous representatives of this class of heterocycles [4–6]. Functionalization of isoxazole ring is one of the most practical ways of obtaining new compounds that may be promising as potential biologically active substances. Among functionally substituted isoxazoles, their amino derivatives attract strong interest as starting compounds for the synthesis of various fused heterocyclic systems, as well as of cytostatic agents, anticonvulsants, fungicides, herbicides, and other bioactive products [7–9]. Development of new synthetic approaches to substituted aminoisoxazoles and search for convenient starting compounds for their synthesis constitute important problems.

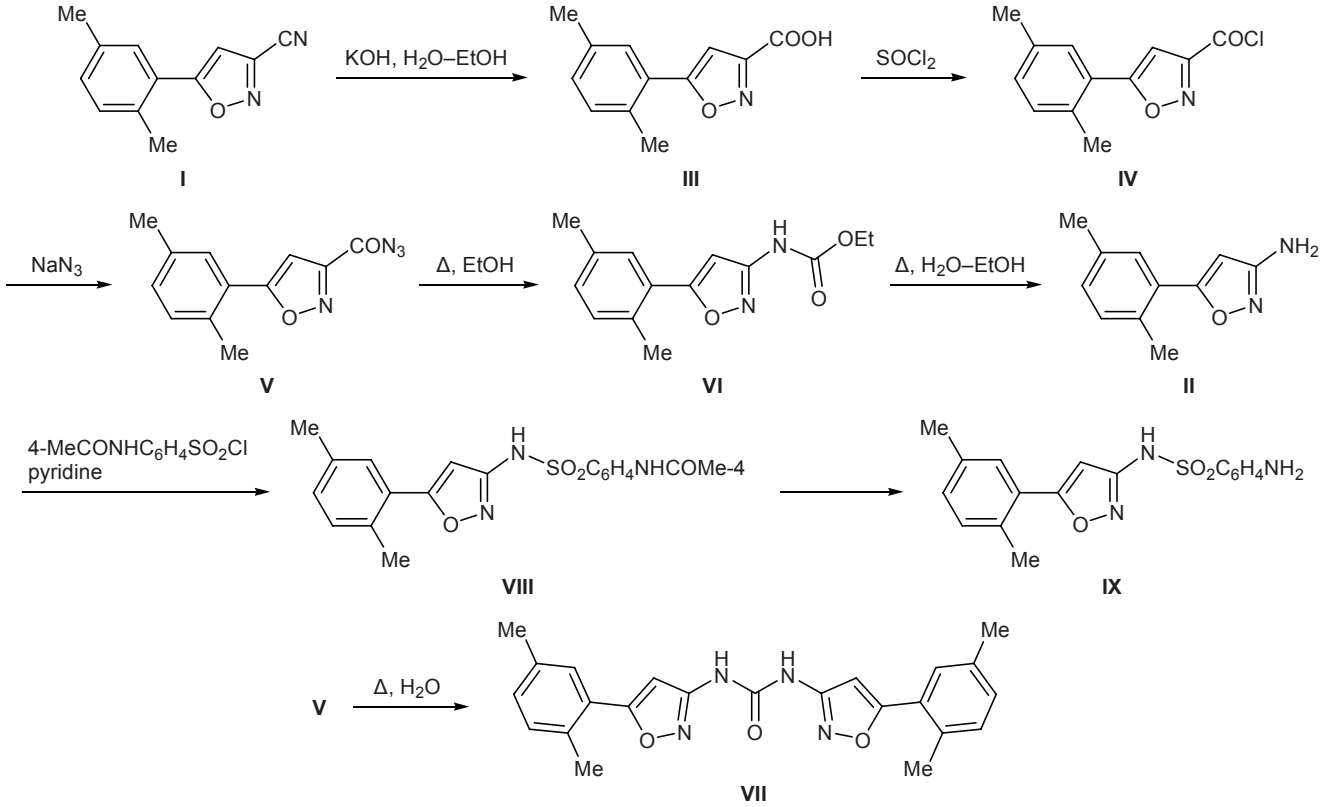
We recently developed a procedure for the synthesis of 5-(2,5-dimethylphenyl)-1,2-oxazole-3-carbonitrile (**I**) [10] from 5-(2,5-dimethylphenyl)-1,2-oxazole-3-carbaldehyde oxime which was prepared in turn by condensation of accessible 1-(2,5-dimethylphenyl)-3,4,4-trichlorobut-3-en-1-one with hydroxylamine [11]. Isoxazole **I** molecule possesses a reactive cyano group whose transformations could lead to various derivatives [12].

The goal of the present work was to synthesize 5-(2,5-dimethylphenyl)-1,2-oxazol-3-amine (**II**), its precursors, and some derivatives starting from compound **I**. We planned to obtain aminoisoxazole **II** via Curtius rearrangement of the corresponding carboxylic acid azide, which is accompanied by loss of one carbon atom [13]. The required 5-(2,5-dimethylphenyl)-1,2-oxazole-3-carboxylic acid (**III**) was synthesized in 90% yield by alkaline hydrolysis of the cyano group in compound **I** on heating in aqueous–alcoholic alkali. Carboxylic acid **III** was converted into isoxazole-3-carbonyl chloride **IV** by treatment with thionyl chloride (yield 85%; Scheme 1). The structure of acid **III** and acid chloride **IV** was determined on the basis of their elemental analyses and IR, ^{1}H and ^{13}C NMR, and mass spectra. The IR spectra of **III** and **IV** lacked absorption band typical of stretching vibrations of the cyano group in initial nitrile **I** (2253 cm^{-1}), and a strong absorption band due to stretching vibrations of the carbonyl group appeared at 1708 (**III**) or 1766 cm^{-1} (**IV**). The electron impact mass spectra of compounds **III** and **IV** contained the molecular ion peaks and fragment ion peaks which were consistent with the assumed structures.

Acid chloride **IV** was treated with sodium azide to obtain 81% of 5-(2,5-dimethylphenyl)-1,2-oxazole-3-carbonyl azide (**V**). The presence of an azido group in compound **V** was confirmed by the IR spectrum which characteristically contained an absorption band at 2171 cm^{-1}; carbonyl stretching vibrations gave rise to a strong band at 1690 cm^{-1}. No molecular ion was observed in the mass spectrum of **V**; instead, an ion peak with m/z 214 $[M - N_2]^+$ (base peak) was present together with ion peaks corresponding to its fragmentation products.

Azide **V** was converted into target aminoisoxazole **II** through carbamate **VI** which was obtained by heating compound **V** for 4 h in boiling anhydrous ethanol. Ethyl 5-(2,5-dimethylphenyl)-1,2-oxazol-3-ylcarba-

Scheme 1.



mate (**VI**) was isolated in 79% yield. The use of anhydrous ethanol was crucial; heating of azide **V** in water for 1 h at 70°C resulted in the formation of 89% of *N*,*N*′-bis[5-(2,5-dimethylphenyl)-1,2-oxazol-3-yl]-urea (**VII**) (Scheme 1). Treatment of carbamate **VI** with alkali in aqueous alcohol at 75°C afforded 92% of 5-(2,5-dimethylphenyl)-1,2-oxazol-3-amine (**II**).

The structure of aminooxazole **II**, carbamate **VI**, and substituted urea **VII** was confirmed by elemental analyses and IR, ^{1}H and ^{13}C NMR, and mass spectra. Compound **VI** displayed in the IR spectrum absorption bands due to stretching vibrations of the N–H bond (3256 cm^{-1}) and C=O group (1737 cm^{-1}, strong band). In the ^{1}H NMR spectrum of **VI**, protons in the ethoxy group resonated as a triplet at δ 1.33 ppm (CH_3) and a quartet at δ 4.29 ppm (CH_2), and the NH proton appeared as a broadened singlet at δ 8.02 ppm. The ^{13}C NMR spectrum of **VI** contained signals from carbon atoms in the ethoxy group (δ_C 14.57, 62.29 ppm) and carbonyl carbon atom (δ_C 152.08 ppm). The molecular ion peak (*m*/*z* 260) in the mass spectrum of **VI** had the maximal intensity.

In the IR spectrum of aminoisoxazole **II** we observed absorption bands at 3398 and 3316 cm^{-1}, typical of stretching vibrations of a primary amino group in aromatic compounds, and a band at 1629 cm^{-1} due to bending vibrations of the NH_2 group. The latter gave rise to a broadened singlet at δ 3.76 ppm in the ^{1}H NMR spectrum. Compound **II** showed in the ^{13}C NMR spectrum two signals from methyl groups, six signals from carbon atoms in the benzene ring, and three signals at δ_C 95.27, 163.52, and 169.96 ppm, which were assigned to the C^4, C^3, and C^5 atoms in the isoxazole ring, by analogy with the spectrum of structurally related aminoisoxazole [14]. The mass spectrum of **II** contained the molecular ion peak.

Urea derivative **VII** was characterized by IR absorption bands at 3253 (N–H) and 1701 cm^{-1} (C=O). Two isoxazole fragments in compound **VII** gave only one set of proton signals in the ^{1}H NMR spectrum, indicating symmetric structure of its molecule.

Compound **II** was subjected to acylation with sulfanilic acid chloride in which the amino group was preliminarily protected by acetylation. The reaction was carried out in pyridine at 80°C, and the product was the corresponding sulfonamide, *N*-{4-[5-(2,5-dimethylphenyl)-1,2-oxazol-3-ylsulfamoyl]phenyl}acetamide (**VIII**, yield 85%). The acetyl protection was removed by treatment of compound **VIII** with aqueous potassium hydroxide, and 4-amino-*N*-[5-(2,5-dimeth-

ylphenyl)-1,2-oxazol-3-yl]benzenesulfonamide (**IX**) was isolated in 90% yield (Scheme 1).

The formation of sulfonamides **VIII** and **IX** was confirmed by the presence in their IR spectra of absorption bands in the regions 1154–1165 and 1320–1325 cm^{-1}, corresponding to stretching vibrations of the sulfonyl group. Stretching vibrations of the N–H bonds gave rise to broad absorption bands in the region 3323–3486 cm^{-1}. In addition, the IR spectrum of *N*-acetyl derivative **VIII** contained carbonyl absorption band at 1677 cm^{-1}; no analogous band was present in the IR spectrum of **IX**. In the ^1H and ^{13}C NMR spectra of **VIII** and **IX** we observed signals from protons and carbon atoms in the isoxazole and sulfanilic acid fragments, as well as from the acetyl group in the spectra of compound **VIII**.

Sulfonamides **VIII** and **IX** are structural analogs of bactericidal agents like Sulfamethoxazole [15], and they attract interest from the viewpoint of their biological activity.

EXPERIMENTAL

The IR spectra were recorded in KBr on a Nicolet Protégé-460 spectrometer with Fourier transform. The ^1H and ^{13}C NMR spectra were measured on a Bruker Avance-500 instrument from solutions in $CDCl_3$ (compounds **II** and **IV**–**VI**), acetone-d_6 (**III**), or DMSO-d_6 (**VII**–**IX**). The ^1H chemical shifts were determined relative to tetramethylsilane, and the ^{13}C chemical shifts were determined relative to the corresponding deuterated solvent signals. The mass spectra (electron impact, 70 eV) were obtained on a Hewlett–Packard 5890/5972 GC–MS system (HP-5MS capillary column, 30 m×0.25 mm, stationary phase 5% of phenylmethylsilicone, film thickness 0.25 μm; injector temperature 250°C).

5-(2,5-Dimethylphenyl)-1,2-oxazole-3-carbonitrile (**I**) was synthesized according to the procedure described in [5].

5-(2,5-Dimethylphenyl)-1,2-oxazole-3-carboxylic acid (III). A solution of 1.3 g of potassium hydroxide in 20 ml of water was added to a solution of 2.15 g (10.85 mmol) of cyanoisoxazole **I** in 30 ml of ethanol, and the mixture was heated to the boiling point, stirred on heating under reflux until ammonia no longer evolved (~10 h), poured into water, and acidified with hydrochloric acid to pH 3. The precipitate was filtered off, washed with water, dried under reduced pressure, and recrystallized from chloroform. Yield 2.13 g (90%), mp 151–153°C. IR spectrum, ν, cm^{-1}: 1708 (C=O); 1573 (C=N); 1613, 1503 (C=C). ^1H NMR spectrum, δ, ppm: 2.37 s (3H, Me), 2.48 s (3H, Me), 6.99 s (1H, 4-H), 7.25 d (1H, H_{arom}, ^3J = 8 Hz), 7.27 d (1H, H_{arom}, ^3J = 8 Hz), 7.60 s (1H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 21.13 (Me), 21.55 (Me), 104.29 (C^4), 129.98, 132.52, 132.67 (CH_{arom}), 127.27, 134.45, 137.22, 158.22, 161.68 (C_{quat}), 172.80 (C=O). Found, %: C 66.62; H 5.37; N 6.18. *m*/*z* 173 $[M - CO_2]^+$. $C_{12}H_{11}NO_3$. Calculated, %: C 66.35; H 5.10; N 6.45. *M* 217.22.

5-(2,5-Dimethylphenyl)-1,2-oxazole-3-carbonyl chloride (IV). Thionyl chloride, 8.94 g (75.12 mmol), was added to a suspension of 3.23 g (14.87 mmol) of acid **III** in 30 ml of anhydrous carbon tetrachloride, and the mixture was heated for 6 h under reflux. The solvent and excess thionyl chloride were removed under reduced pressure, and the solid residue was recrystallized from hexane. Yield 2.98 g (85%), mp 46–47°C. IR spectrum, ν, cm^{-1}: 1766 (C=O); 1569 (C=N); 1613, 1506 (C=C). ^1H NMR spectrum, δ, ppm: 2.40 s (3H, Me), 2.48 s (3H, Me), 6.87 s (1H, 4-H), 7.23 br.s (2H, H_{arom}), 7.55 br.s (1H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 21.51 (Me), 21.55 (Me), 102.86 (C^4), 129.58, 132.24, 132.57 (CH_{arom}), 125.92, 134.03, 136.85, 159.78, 161.52 (C_{quat}), 174.28 (C=O). Found, %: C 61.05; H 4.22; Cl 15.35; N 5.88. *m*/*z* 235 $[M]^+$. $C_{12}H_{10}ClNO_2$. Calculated, %: C 61.16; H 4.28; Cl 15.04; N 5.95. *M* 235.66.

5-(2,5-Dimethylphenyl)-1,2-oxazole-3-carbonyl azide (V). A solution of 2.36 g (10 mmol) of acid chloride **IV** in 25 ml of anhydrous acetone was cooled to 0°C, a solution of 0.78 g (12 mmol) of sodium azide in 3 ml of water was added dropwise under stirring, the cooling bath was removed, the mixture was stirred for 20 min and diluted with 100 ml of water, and the precipitate was filtered off and dried under reduced pressure. Yield 1.96 g (81%), mp 77–78°C. IR spectrum, ν, cm^{-1}: 2171 (N_3); 1690 (C=O); 1590, 1573, 1557, 1500 (C=C, C=N). ^1H NMR spectrum, δ, ppm: 2.39 s (3H, Me), 2.48 s (3H, Me), 6.87 s (1H, 4-H), 7.22 br.s (2H, H_{arom}), 7.57 br.s (1H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 21.01 and 21.12 (Me), 102.57 (C^4), 129.08, 131.64, 131.79 (CH_{arom}), 125.68, 133.44, 136.25, 157.12, 166.14 (C_{quat}), 172.79 (C=O). Found, %: C 59.14; H 4.39; N 23.42. *m*/*z* 214 $[M - N_2]^+$. $C_{12}H_{10}N_4O_2$. Calculated, %: C 59.49; H 4.16; N 23.13. *M* 242.24.

Ethyl 5-(2,5-dimethylphenyl)-1,2-oxazole-3-ylcarbamate (VI). A solution of 3.63 g (15 mmol) of azide **V** in 30 ml of anhydrous ethanol was heated for 4 h under reflux. The solvent was removed, and the

residue was recrystallized from hexane. Yield 3.08 g (79%), mp 103–104°C. IR spectrum, ν, cm^{-1}: 3256 (NH); 1737 (C=O); 1632, 1613, 1547, 1491 (C=C, C=N). ^1H NMR spectrum, δ, ppm: 1.37 t (3H, Me, ^3J = 7 Hz), 2.38 s (3H, Me), 2.50 s (3H, Me), 4.30 q (2H, CH_2O, ^3J = 7 Hz), 7.01 s (1H, 4-H), 7.18 m (2H, H_{arom}), 7.55 s (1H, H_{arom}). 8.02 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 14.57 (Me), 21.01 (Me), 21.10 (Me), 62.29 (CH_2), 96.17 (C^4), 129.01, 131.09, 131.46 (CH_{arom}), 126.80, 132.38, 135.90, 153.13, 158.61 (C_{quat}), 170.55 (C=O). Found, %: C 64.55; H 6.58; N 10.64. *m*/*z* 260 $[M]^+$. $C_{14}H_{16}N_2O_3$. Calculated, %: C 64.60; H 6.20; N 10.76. *M* 260.29.

5-(2,5-Dimethylphenyl)-1,2-oxazol-3-amine (II). Potassium hydroxide, 10 g, was added to a solution of 1.3 g (5 mmol) of compound **VI** in 20 ml of 80% aqueous alcohol, and the mixture was stirred for 8 h at 75°C. The mixture was then poured into water, and the precipitate was filtered off, washed with water, and dried under reduced pressure. Yield 0.86 g (92%), mp 153–155°C. IR spectrum, ν, cm^{-1}: 3398, 3316, 1629 (NH); 1599, 1515, 1500 (C=C, C=N). ^1H NMR spectrum, δ, ppm: 2.36 s (3H, Me), 2.45 s (3H, Me), 3.76 br.s (2H, NH_2), 6.00 s (1H, 4-H), 7.15 d (1H, H_{arom}, ^3J = 8.5 Hz), 7.17 d (1H, H_{arom}, ^3J = 8.5 Hz), 7.50 s (1H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 21.02 (Me), 21.09 (Me), 95.27 (C^4), 128.93, 130.83, 131.34 (CH_{arom}), 127.12, 133.15, 135.83 (C_{quat}), 163.52 (C^3), 169.96 (C^5). Found, %: C 70.39; H 6.58; N 14.79. *m*/*z* 188 $[M]^+$. $C_{11}H_{12}N_2O$. Calculated, %: C 70.19; H 6.43; N 14.89. *M* 188.23.

***N*,*N*′-Bis[5-(2,5-dimethylphenyl)-1,2-oxazol-3-yl]-urea (VII).** A suspension of 1.21 g (5 mmol) of azide **V** in 20 ml of water was stirred for 1 h at 70°C. The precipitate was filtered off, washed with water, and dried under reduced pressure. Yield 0.89 g (89%), mp 217–220°C. IR spectrum, ν, cm^{-1}: 3253 (NH); 1701 (C=O); 1624, 1606, 1561 (C=C, C=N). ^1H NMR spectrum, δ, ppm: 2.30 s (6H, Me), 2.40 s (6H, Me), 7.03 s (2H, 4-H), 7.19 d (2H, H_{arom}, ^3J = 8 Hz), 7.24 d (2H, H_{arom}, ^3J = 8 Hz), 7.52 s (2H, H_{arom}), 9.79 br.s (2H, NH). ^{13}C NMR spectrum, δ_C, ppm: 20.93 (2C, Me), 21.13 (2C, Me), 96.93 (2C, C^4), 128.86, 131.57, 132.01 (6C, CH_{arom}), 126.68, 133.20, 136.21, 151.07, 158.99 (10C, C_{quat}), 169.57 (1C, C=O). Found, %: C 68.53; H 5.77; N 13.85. $C_{23}H_{22}N_4O_3$. Calculated, %: C 68.64; H 5.51; N 13.92.

***N*-{4-[5-(2,5-Dimethylphenyl)-1,2-oxazol-3-ylsulfamoyl]phenyl}acetamide (VIII).** 4-Acetylaminobenzenesulfonyl chloride, 2.33 g (10 mmol), was added to a solution of 1.88 g (10 mmol) of aminoisoxazole **II** in 10 ml of pyridine, and the mixture was stirred for 8 h at 80°C. The mixture was cooled, poured into 100 ml of water, and acidified with 15 ml of 10% hydrochloric acid. The precipitate was filtered off, washed with water, and dried under reduced pressure. Yield 3.27 g (85%), mp 124–126°C. IR spectrum, ν, cm^{-1}: 3413, 3323 (NH); 1677 (C=O); 1588, 1541, 1514, 1494 (C=C, C=N); 1325, 1165 (S=O). ^1H NMR spectrum, δ, ppm: 2.04 s (3H, Me), 2.27 s (3H, Me), 2.32 s (3H, Me), 6.56 s (1H, 4-H), 7.18 d (1H, H_{arom}, ^3J = 8 Hz), 7.21 d (1H, H_{arom}, ^3J = 8 Hz), 7.45 s (1H, H_{arom}), 7.74 d (2H, H_{arom}, ^3J = 8.5 Hz), 7.82 d (2H, H_{arom}, ^3J = 8.5 Hz), 10.37 br.s and 11.51 br.s (1H each, NH). ^{13}C NMR spectrum, δ_C, ppm: 20.89 (Me), 21.00 (Me), 24.69 (Me), 96.76 (C^4), 119.22 (2C, CH_{arom}), 128.80 (2C, CH_{arom}), 128.97, 131.73, 131.99 (CH_{arom}), 126.35, 133.23, 133.28, 136.19, 144.20, 158.36, 169.74 (C_{quat}), 170.13 (C=O). Found, %: C 59.44; H 5.23; N 10.76; S 8.48. $C_{19}H_{19}N_3O_4S$. Calculated, %: C 59.20; H 4.97; N 10.90; S 8.32.

4-Amino-*N*-[5-(2,5-dimethylphenyl)-1,2-oxazol-3-yl]benzenesulfonamide (IX). Sulfonamide **VIII**, 3.85 g (10 mmol), was added to a solution of 1.2 g (21 mmol) of potassium hydroxide in 20 ml of water, and the mixture was kept for 2 days at 25°C, diluted with water to a volume of 100 ml, and neutralized with 20% hydrochloric acid. The precipitate was filtered off, washed with water, and dried under reduced pressure. Yield 3.10 g (90%), mp 181–182°C. IR spectrum, ν, cm^{-1}: 3486, 3384, 1626 (NH); 1596, 1573, 1506, 1494 (C=C, C=N); 1320, 1154 (S=O). ^1H NMR spectrum, δ, ppm: 2.28 s (3H, Me), 2.32 s (3H, Me), 6.52 s (1H, 4-H), 6.57 d (2H, H_{arom}, ^3J = 8.5 Hz), 7.18 d (1H, H_{arom}, ^3J = 8 Hz), 7.22 d (1H, H_{arom}, ^3J = 8 Hz), 7.45 s (1H, H_{arom}), 7.50 d (2H, H_{arom}, ^3J = 8.5 Hz), 11.12 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 20.90 (Me), 21.190 (Me), 96.72 (C^4), 113.24 (2C, CH_{arom}), 129.58 (2C, CH_{arom}), 128.90, 131.66, 131.99 (3C, CH_{arom}), 124.48, 126.44, 133.20, 136.20, 153.84, 158.73, 169.76 (C_{quat}). Found, %: C 59.76; H 5.37; N 12.21; S 9.55. $C_{17}H_{17}N_3O_3S$. Calculated, %: C 59.46; H 4.99; N 12.24; S 9.34.

REFERENCES

1. Khripach, V.A., Zhabinskii, V.N., Ol'khovik, V.K., Zavadskaya, M.I., Drachenova, O.A., and Khripach, N.B., *Russ. J. Org. Chem*., 1996, vol. 32, p. 805.
2. Dondoni, A., Giovannini, P.P., and Massi, A., *Org. Lett*., 2004, vol. 6, p. 2929.

3. Jeon, S.L., Kim, J.K., Son, J.B., Kim, B.T., and Jeong, I.H., *J. Fluorine Chem*., 2007, vol. 128, p. 153.
4. Yamamoto, T., Fujita, K., Asari, S., Chiba, A., Kataba, Y., Ohsumi, K., Ohmuta, N., Iida, Y., Ijichi, C., Iwayama, S., Fukuchi, N., and Shoji, M., *Bioorg. Med. Chem. Lett*., 2007, vol. 17, p. 3736.
5. Wankhede, K.S., Vaidya, V.V., Sarang, P.S., Salunkhe, M.M., and Trivedi, G.K., *Tetrahedron Lett*., 2008, vol. 49, p. 2649.
6. Dallanoce, C., Frigerio, F., De Amici, M., Dorsch, S., Klotz, K.N., and De Micheli, C., *Bioorg. Med. Chem*., 2007, vol. 15, p. 2533.
7. Li, W.-T., Hwang, D.R., Chen, Ch.-P., Shen, Ch.-W., Huang, C.-L., Chen, T.-W., Lin, C.-H., Chang, Y.-L., Chang, Y.-Y., Chang, Y.-K., Lo, Y.-K., Tseng, H.-Y., Lin, C.-C., Song, J.-S., Chen, S.-J., Wu, S.-H., and Chen, C.-T., *J. Med. Chem*., 2003, vol. 46, p. 1706.
8. Eddington, N., Cox, D.S., Roberts, R.R., Butcer, R.J., Edafiogho, I.O., Stables, J.P., Cook, N., Goodwin, A.M., Smith, C.A., and Scott, K.R., *Eur. J. Med. Chem*., 2002, vol. 37, p. 635.
9. Matysiak, J., Krajewska-Kulak, E., Karczewski, J., and Niewiadomi, A., *J. Agric. Food Chem*., 2001, vol. 49, p. 5251.
10. Potkin, V.I., Petkevich, S.K., and Kurman, P.V., *Russ. J. Org. Chem*., 2009, vol. 45, p. 551.
11. Petkevich, S.K., Potkin, V.I., and Kaberdin, R.V., *Russ. J. Org. Chem*., 2004, vol. 40, p. 1146.
12. Zil'berman, E.N., *Reaktsii nitrilov* (Reactions of Nitriles), Moscow: Khimiya, 1972, p. 104.
13. Vatsuro, K.V. and Mishchenko, G.L., *Imennye reaktsii v organicheskoi khimii* (Name Reactions in Organic Chemistry), Moscow: Khimiya, 1976.
14. Lesiv, A.V., Ioffe, S.L., Strelenko, Y.A., Bliznets, I.V., and Tartakovsky, V.A., *Mendeleev Commun*., 2002, no. 3, p. 99.
15. Mashkovskii, M.D., *Lekarstvennye sredstva* (Drugs), Moscow: Novaya Volna, 2005, p. 823.