ISSN 1070-4272, Russian Journal of Applied Chemistry, 2011, Vol. 84, No. 2, pp. 230−235. © Pleiades Publishing, Ltd., 2011.
Original Russian Text © V.M. Chernyshov, G.V. Kozlenko, V.A. Taranushich, 2011, published in Zhurnal Prikladnoi Khimii, 2011, Vol. 84, No. 2, pp. 234−239.

ORGANIC SYNTHESIS AND INDUSTRIAL ORGANIC CHEMISTRY

Regioselective Single-Reactor Synthesis of Arylsulfonyl Derivatives of 3,5-Diamino-1,2,4-triazole

V. M. Chernyshov, G. V. Kozlenko, and V. A. Taranushich

South-Russian State Technical University (Novocherkassk Polytechnic Institute), Novocherkassk, Rostov-on-Don oblast, Russia

Received March 23, 2010

Abstract—Arylsulfonylation of 1-acetyl-3,5-diamino-1,2,4-triazole with arylsulfonyl chlorides in pyridine, with the subsequent hydrolysis of the acetyl group, was studied; a new regioselective method for synthesis of *N*-(5-amino-1*H*-1,2,4-triazol-3-yl)arylsulfonamides was developed.

DOI: 10.1134/S107042721102011X

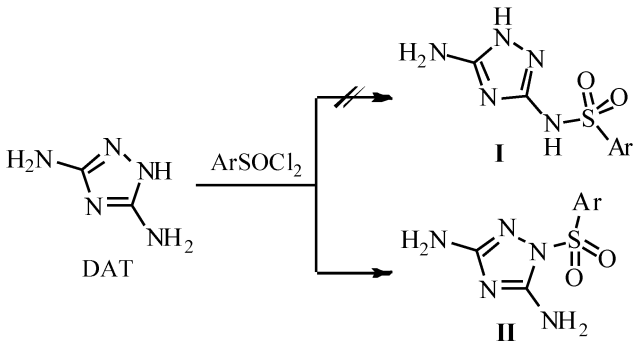
Arylsulfonyl derivatives of 3,5-diamino-1,2,4-triazole of general formula **I** are key starting substances in syntheses of effective herbicides: *N*-([1,2,4]triazolo[1,5-*a*]pyrimidin-2-yl)- and ([1,2,4]triazolo[1,5-*a*][1,3,5]triazin-2-yl)arylsulfonamides [1–5]. Some representatives of this group of compounds exhibit anti-HIV and antitumor activity [6]. Methods for synthesis of compounds **I**, described until now, include construction of an aminotriazole fragment bonded to the arylsulfamide group by reactions of condensation of *N*-(arylsulfonyl)-*N*'-cyanoimidothiocarbamates with derivatives of hydrazine [1, 2, 4, 5] or S,S-dimethyl-*N*-(arylsulfonyl)carbodithioimidates with aminoguanidine hydrocarbonates [3]. The main disadvantages of these methods are the high cost of starting substances and poor yield of target products [4].

A promising method for synthesis of compounds might become arylsulfonylation of 3,5-diamino-1,2,4-triazole (DAT). However, the high nucleophilicity of the endocyclic nitrogen, compared with the exocyclic amino group, results in that this reaction yields 1-arylsulfonyl-3,5-diamino-1,2,4-triazoles **II**, rather than compound **I** [7] (Scheme 1).

The goal of our study was to develop a method for synthesis of compound **I** from the available 3,5-diamino-1,2,4-triazole derivatives.

According to published data [8, 9], 1-substituted 3,5-diamino-1,2,4-triazoles are selectively sulfonylated by arylsulfonyl chlorides at the amino group in position *3*

Scheme 1.



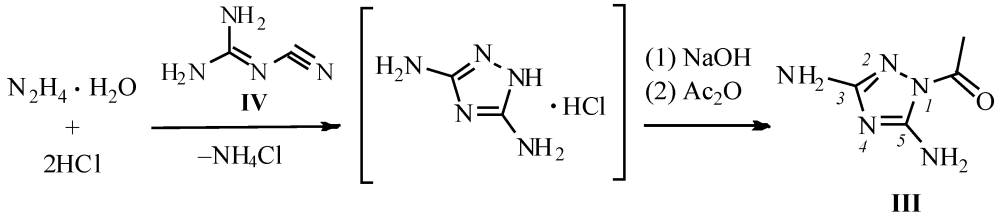
under heating in acetone in the presence of pyridine. This suggests that sulfonylation of 3,5-diamino-1,2,4-triazole having a protective group in position *1* of the triazole ring upon removal of the protective group will yield compound **I**. A suitable compound for arylsulfonylation, which has an easily removable protective group, might become 1-acetyl-3,5-diamino-1,2,4-triazole (**III**). Compound **III** can be easily obtained by single-reactor synthesis from accessible starting substances: hydrazine hydrate, *N*-cyanoguanidine [dicyandiamide (IV)], and acetic anhydride in accordance with Scheme 2.

A detailed analysis of the process of arylsulfonylation of compound **III** was made for the example of the reaction with 4-methylbenzenesulfonyl chloride (TsCl). Attempts to perform arylsulfonylation in acetonitrile–pyridine mixtures failed because of the poor solubility of compound **III**. However, the interaction of compound **III** and TsCl in pure boiling pyridine led to fast dissolution of compound **III** to give arylsulfonylation products. An analysis of unpurified reaction products by ^{1}H NMR spectroscopy demonstrated that their composition depends on the synthesis duration (see the table). First, *N*-(5-amino-1-acetyl-1*H*-1,2,4-triazol-3-yl)-4-methylbenzene sulfonamide (**V**) is formed during several minutes. Then the content of compound **VI** in the reaction products gradually decreases, so that *N*-(5-{[(4-methylphenyl)sulfonyl]amino}-1*H*-1,2,4-triazol-3-yl)acetamide (**VI**) and *N*-(5-amino-1*H*-1,2,4-triazol-3-yl)-4-methylbenzene sulfonamide (**VII**) become the main components in 2 h. Thus, the protective acetyl group precludes endocyclic sulfonylation and the reaction involves an amino group in position *3* (amino group in position *5* has a reduced nucleophilicity [8–10] and, therefore, is not sulfonylated). Compound **V** is gradually rearranged into a thermodynamically more stable isomer **VI** similarly to other 1-acyl-5-amino-1,2,4-triazoles [11–13]. Compound **VII** is presumably formed via hydrolysis of compound **V** because of atmospheric moisture finding its way into the reaction mixture (Scheme 3).

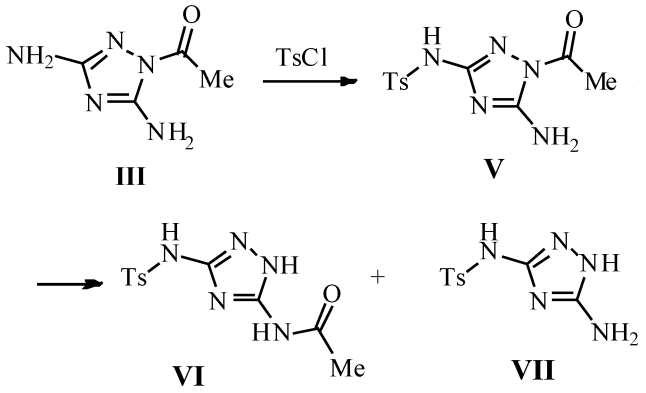
The structure of compounds **V**–**VII** was confirmed by spectroscopic data and elemental analysis. The direction of the sulfonylation reaction at the amino group in position *3* is confirmed by the chemical shift of protons of the free amino group (7.57 ppm) in compound **V**, which is typical of 1-acyl-5-amino-1,2,4-triazoles (7.2–8.3 ppm in DMSO-d_6) [7, 11–13].

An alkaline hydrolysis of both the acetyl derivative

Scheme 2.



Scheme 3.



Composition of products formed in arylsulfonylation of 1-acetyl-3,5-diamino-1,2,4-triazole (**III**) with 4-methylbenzenesulfonyl chloride in pyridine

Synthesis duration, min	Composition of products, mol %			
	III	**V**	**VI**	**VII**
1	27	73	0	0
3	0	100	0	0
6	0	96	4	0
20	0	66	26	8
40	0	52	33	15
120	0	14	63	23

V and acetamide **VI** leads to the desired product **VII** at however, different rates. Compound **V** is very easily hydrolyzed when boiled in an aqueous solution of NaOH for about 5 min at a **V** : NaOH molar ratio of 1 : 2, with a nearly quantitative yield of compound **VII**. However, hydrolysis of acetamide **VI** requires a pronounced excess of the alkali and heating for about 8 h. Therefore, compound **V** is a more suitable starting compound for synthesis of compound **VII**, than acetamide **VI**. It was found that compound **V** can be conveniently converted to compound **VII** without preliminary isolation from the reaction mixture after sulfonylation of compound **III**, i.e., in a single-reactor synthesis (Scheme 4).

However, to provide a high yield and purity of the target product, the duration of the first stage of synthesis, sulfonylation of acetyl derivatives **III**, must be 3–5 min. Making the synthesis duration shorter leads to a decrease in the yield, and making it longer, to a poorer purity of the target product because an admixture of a difficultly hydrolyzable compound **VI** is formed.

Using TsCl and arylsulfonyl chlorides **VIII–XI**, we obtained arylsulfonyl derivatives **VII** and **XII–XV** in 53–82% yield. We could not obtain *ortho*- and *para*-nitrobenzenesulfonyl derivatives by this method because strong tarring of the reaction mixture occurred in sulfonylation and individual substances could not be eventually recovered from the mixture.

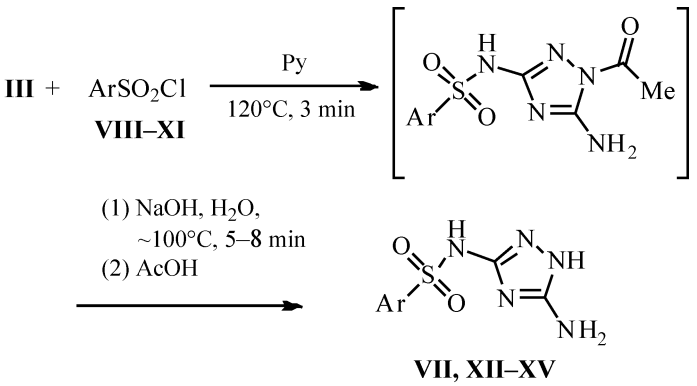
Thus, we developed a selective single-reactor method for synthesis of arylsulfonyl derivatives of 3,5-diamino-1,2,4-triazole. The applicability of the method is limited to arylsulfonyl chlorides containing no substituents capable of chemical transformation under synthesis conditions.

EXPERIMENTAL

^{1}H NMR spectra were recorded with a VARIAN UNITY-300 spectrometer (300 MHz for 1H and 75 MHz for ^{13}C, solvent DMSO-d_6, internal standard TMS). Mass spectra were obtained with a Finnigan MAT Incos 50 instrument with direct introduction of a sample into the ionic emission source with an ionization energy of 70 eV. The elemental analysis was made with a Perkin–Elmer 2400 analyzer. The melting points were determined in sealed capillaries in a PTP instrument.

1-Acetyl-3,5-diamino-1,2,4-triazole (III). To 25 g (0.5 mol) of hydrazine hydrate we added under vigorous agitation and cooling 121.7 g (1.0 mol) of 30% hydrochloric acid, making sure that the temperature of the reaction mixture was not higher than 50°C. Then we

Scheme 4.



VII, XII–XV

Ar = 4-MeC_6H_4 (TsCl) (**VII**); Ph (**VIII**), (**XII**); 4-ClC_6H_4 (**IX**), (**XIII**); 4-MeOC_6H_4 (**X**), (**XIV**); naphthyl-2 (**XI**), (**XV**).

added 42 g (0.5 mol) of *N*-cyanoguanidine (**IV**) to the resulting solution under agitation at a temperature of 40–50°C in the course of 30 min. The reaction mixture was kept at 45–50°C for 1 h, and then 100 ml of a 5 M KOH solution was added dropwise. The resulting mixture was cooled to 10°C and 63.8 g (0.625 mol) of acetic anhydride was poured in under vigorous agitation in the course of 15–25 min, with the temperature maintained within the range 10–20°C. The mixture was additionally agitated for 30 min at a temperature of 10°C, and the resulting precipitate was filtered off, washed with 100 ml of cold water, and dried at 50°C. We obtained 49.4 g (70%) of compound **III** sufficiently pure for further syntheses. If necessary, compound **III** can be purified by recrystallization from water. The properties of the product obtained are identical to those described in [14].

The effect of the synthesis duration on the yield of compounds **V**–**VII** was studied as follows. A solution of 1.71 g (9 mmol) of TsCl in 5 ml of pyridine was heated to 115°C under vigorous agitation, then 1.41 g (10 mmol) of thoroughly ground compound **III** was added, and time reckoning was started. In the process, the mixture warmed up to boiling. The reaction mixture was boiled with a reflux for a required time (see the table) and then was cooled to 20°C and diluted with 15 ml of cold water. The resulting precipitate was filtered off, washed with 30 ml of cold water, and dried in a vacuum at 50°C. The content of compounds **V**–**VII** in the products obtained was determined using ^{1}H NMR spectroscopy.

***N*-(5-Amino-1-acetyl-1*H*-1,2,4-triazol-3yl)-4-methylbenzenesulfonamide (V).** A solution of 1.71 g (9 mmol) of TsCl in 5 ml of pyridine was heated to 115°C under vigorous agitation and then 1.41 g (10 mmol) of thoroughly ground compound **III** was added. The resulting mixture was boiled with a reflux for 3 min, cooled to 20°C, and 15 ml of cold water was poured in. The resulting precipitate was filtered off and washed successively with 30 ml of water and 20 ml of ethanol. We obtained 1.7 g (64%) of unpurified compound **V**, with the content of the main substance of 95% and more (according to ^{1}H NMR data). The product was purified by heating its suspension in ethanol to boiling (3 × 6 ml), to give 1.22 g (46%) of a white crystalline substance, mp 290–293°C. ^{1}H NMR spectrum, δ, ppm: 2.36 s (6H, $2CH_3$), 7.37 d ($2H_{arom}$, J = 8.2 Hz), 7.57 br.s (2H, NH_2), 7.81 d ($2H_{arom}$, J = 8.2 Hz), 11.24 br.s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 20.9, 22.8, 127.4, 129.2, 137.1, 143.3, 154.2, 156.2, 170.5. Mass-spectrum, *m/z* (I_{rel}, %): 295 (9) [M^+], 253 (48), 189 (13), 155 (12), 99 (10), 98 (94), 91 (67), 43 (100). Found (%): S 44.51, N 4.42, N 23.92. $C_{11}H_{13}N_5O_3S$. Calculated (%): S 44.74, N 4.44, N 23.71; M 295.32.

***N*-(5-{[(4-Methylphenyl)sulfonyl]amino}-1*H*-1,2,4-triazol-3-yl)acetamide (VI).** A mixture of 1.41 g (10 mmol) of thoroughly ground compound **III**, 5 ml of pyridine, and 1.71 g (9 mmol) of TsCl was boiled with a reflux under agitation for 2 h and then was cooled to 20°C and diluted with 15 ml of ethanol. The resulting precipitate was filtered off, washed with 30 ml of ethanol, twice recrystallized from DMFA, and dried in a vacuum at 120°C. We obtained 1.1 g (40%) of a white crystalline substance, mp 292–293°C. ^{1}H NMR spectrum, δ, ppm: 2.02 s (3H, CH_3), 2.34 s (3H, CH_3), 7.34 d ($2H_{arom}$, J = 8.0 Hz), 7.73 d ($2H_{arom}$, J = 8.0 Hz), 10.83 s (1H, NH), 11.47 s (1H, NH), 12.87 s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 20.9, 22.7, 125.6, 126.8, 129.3, 137.7, 143.0, 147.6, 168.9. Mass-spectrum, *m/z* (I_{rel}, %): 295 (5) [M^+], 253 (21), 231 (18), 189 (24), 155 (11), 99 (6), 98 (24), 91 (63), 43 (100). Found (%): S 44.68, H 4.43, N 23.56. $C_{11}H_{13}N_5O_3S$. Calculated (%): S 44.74, N 4.44, N 23.71; M 295.32.

Synthesis of *N*-(5-amino-1*H*-1,2,4-triazol-3-yl-4-methylbenzenesulfonamide (VII) by hydrolysis of compounds **V** and **VI**. a. A mixture of 1.0 g (3.39 mmol) of a thoroughly ground compound **V**, 5 ml of water, and 0.27 g (6.77 mmol) of NaOH was boiled with a reflux for 5 min and then was neutralized with glacial acetic acid and cooled to 20°C. The resulting precipitate of compound **VII** was filtered off, washed with water, and dried at 120°C. Yield 0.84 g (98%), light yellow crystals, mp 314–315°C with decomposition (mp 314–315°C [3]). ^{1}H NMR spectrum, δ, ppm: 2.38 s (3H, CH_3), 5.82 br.s (2H, NH_2), 7.23 d ($2H_{arom}$, J = 8.1 Hz), 7.67 d ($2H_{arom}$, J = 8.1 Hz), 11.27 br.s (1H, NH), 11.64 br.s (1H, NH). Mass-spectrum, *m/z* (I_{rel}, %): 253 (24) [M^+], 189 (10), 155 (12), 99 (13), 98 (79), 92 (23), 91 (100), 89 (10), 77 (12). Found (%): C 42.63, H 4.40, N 27.68. $C_9H_{11}N_5O_2S$. Calculated (%): C 42.68, H 4.38, N 27.65; M 253.28.

b. A mixture of 0.5 g (1.69 mmol) of a thoroughly ground compound **VI**, 3 ml of water, and 0.54 g (13.5 mmol) of NaOH was boiled with a reflux for 8 h and then was neutralized with glacial acetic acid and cooled to 20°C. The resulting precipitate of compound **VII** was filtered off, washed with water, and dried at 120°C. Yield 0.26 g (61%); the properties of the compound are identical to those of the product synthesized by the

procedure described above.

General procedure for single-reactor synthesis of *N*-(5-amino-1*H*-1,2,4-triazol-3-yl)arylsulfonamides VII and XII–XV. A solution of 90 mmol of the corresponding arylsulfonyl chloride (TsCl, **VIII**–**XI**) in 50 ml of pyridine was heated to 110–115°C under vigorous agitation and 14.1 g (100 mmol) of thoroughly ground compound **III** was added. The mixture was boiled with a reflux under agitation for 3 min and then 150 ml of a 2M NaOH solution was poured in and the mixture was boiled for additional 5–8 min. The resulting solution was neutralized with glacial acetic acid and cooled to 20°C. The precipitate formed was filtered off, recrystallized from DMFA, and dried in a vacuum at 120°C. Compounds **VII** and **XII**–**XV** were obtained.

***N*-(5-Amino-1*H*-1,2,4-triazol-3-yl)-4-methylbenzenesulfonamide (VII).** Yield 15.23 g (60%), the properties of the compound are identical to those of the product obtained by hydrolysis of compound **V**.

***N*-(5-Amino-1*H*-1,2,4-triazol-3-yl)benzenesulfonamide (XII).** Yield 14.62 g (61%), white crystals, mp 293–294°C with decomposition (mp 293–294°C [3]). ^{1}H NMR spectrum, δ, ppm: 5.83 br.s (2H, NH_2), 7.40–7.45 m (3H_{arom}), 7.77–7.80 m (2H_{arom}), 11.29 br.s (1H, NH), 11.70 br.s (1H, NH). Mass-spectrum, *m/z* (I_{rel}, %): 239 (34) [M^+], 99 (11), 98 (100), 78 (18), 77 (82). Found (%): C 40.18, H 3.81, N 29.18.

$C_8H_9N_5O_2S$. Calculated (%): C 40.16, H 3.79, N 29.27; M 239.25.

***N*-(5-Amino-1*H*-1,2,4-triazol-3-yl)-4-chlorobenzenesulfonamide (XIII).** Yield 14.50 g (53%), light yellow crystals, mp 305–306°C with decomposition (mp 299°C [2]). ^{1}H NMR spectrum, δ, ppm: 5.86 br.s (2H, NH_2), 7.57 d (2H_{arom}, J = 8.5 Hz), 7.78 d (2H_{arom}, J = 8.5 Hz), 11.58 br.s (1H, NH), 11.94 br.s (1H, NH). Mass-spectrum, *m/z* (I_{rel}, %): 273 (22) [M^+], 209 (12), 113 (18), 112 (16), 111 (60), 99 (23), 98 (100), 91 (12), 75 (39). Found (%): C 35.18, H 3.01, N 25.47. $C_8H_8ClN_5O_2S$. Calculated (%): C 35.11, H 2.95, N 25.59; M 273.70.

***N*-(5-Amino-1*H*-1,2,4-triazol-3-yl)-4-methoxybenzenesulfonamide (XIV).** Yield 17.51 g (65%), light yellow crystals, mp 288–290°C with decomposition (mp 294°C [2]), ^{1}H NMR spectrum, δ, ppm: 3.78 s (3H, OCH_3), 5.81 br.s (2H, NH_2), 7.01 d (2H_{arom}, J = 9.0 Hz), 7.71 d (2H_{arom}, J = 9.0 Hz), 11.40 br.s (1H, NH), 11.73 br.s (1H, NH). Mass-spectrum, *m/z* (I_{rel}, %): 269 (33) [M^+], 205 (39), 171 (67), 155 (26), 123 (46), 108 (29), 107 (82), 99 (31), 98 (82), 92 (58), 78 (14), 77 (82), 43 (100). Found (%): C 40.19, H 4.16, N 25.89. $C_9H_{11}N_5O_3S$. Calculated (%): C 40.14, H 4.12, N 26.01; M 269.28.

***N*-(5-Amino-1*H*-1,2,4-triazol-3-yl)naphthalene-2-sulfonamide (XV).** Yield 23.72 g (82%), yellowish crystals, mp 305–308°C with decomposition (mp 308–309°C [2]), ^{1}H NMR spectrum, δ, ppm: 5.85 br.s (2H, NH_2), 7.59–7.66 m (2H_{arom}), 7.80 m (1H_{arom}), 7.97–8.07 m (3H_{arom}), 8.42 s (1H_{arom}), 11.55 br.s (1H, NH), 11.88 br.s (1H, NH). Mass-spectrum, *m/z* (I_{rel}, %): 289 (9) [M^+], 225 (15), 127 (100), 99 (15), 98 (33). Found (%): C 49.55, H 3.75, N 24.16. $C_{12}H_{11}N_5O_2S$. Calculated (%): C 49.82, H 3.83, N 24.21; M 289.31.

CONCLUSIONS

(1) Introduction of an acetyl group into position *1* of the triazole ring can serve as a way to protect endocyclic nitrogen atoms and amino groups in position *5* of 5-amino-1,2,4-triazoles in reactions involving arylsulfonyl chlorides.

(2) Sulfonylation of 1-acetyl-3,5-diamino-1,2,4-triazole with arylsulfonyl chlorides in pyridine, followed by hydrolysis of the acetyl group, enables regioselective synthesis of *N*-(5-amino-1*H*-1,2,4-triazol-3-yl) arylsulfonamides.

ACKNOWLEDGMENTS

The study was financially supported by the RF Federal Agency for Education in the framework of the Federal Target Program “Scientific and scientific-pedagogical personnel of the innovative Russia,” State Contract P302, project NK-109P/2.

REFERENCES

1. Kleschick, W.A., Dunbar, J.E., Snider, S.W., and Vinogradoff, A.P., *J. Org. Chem.,* 1988, vol. 53, no. 13, pp. 3120–3122.
2. US Patent 4822404.
3. Maybhate, S.P., Rajamohanan, P.P., and Rajappa, S., *Synthesis*, 1991, no. 3, pp. 220–222.
4. Chibale, K., Dauvergne, J., and Wyatt, P.G., *Synthesis*, 2002, no. 2, pp. 185–190.
5. US Patent 4685958.
6. Kuo, C.-L., Assefa, H., Kamath, Sh., et al., *J. Med. Chem*.,

2004, vol. 47, no. 2, pp. 385–399.

7. Chernyshev, V.M., Gaidukova, G.V., Zemlyakov, N.D., and Taranushich, V.A., *Zh. Prikl. Khim*., 2005, vol. 78, no. 5, pp. 790–795.
8. Chernyshev, V.M., Rakitov, V.A., Taranushich, V.A., and Blinov, V.V., *Chem. Heterocycl. Compd*., 2005, vol. 41, no. 9, pp. 1139–1146.
9. Chernyshev, V.M., Kosov, A.E., Gladkov, E.S., et al., *Izv. Akad. Nauk, Ser. Khim*., 2006, no. 2, pp. 329–334.
10. Kofman, T.P. and Namestnikov, V.I., *Zh. Org. Khim*., 2003, vol. 39, no. 4, pp. 616–620.
11. Reiter, J., Pongo, L., and Dvortsak, P., *J. Heterocycl. Chem*., 1987, vol. 24, pp. 127–142.
12. Dzygiel, A., Masiukiewicz, E., and Rzeszotarska, B., *J. Agric. Food Chem*., 2002, vol. 50, no. 6, pp. 1383–1388.
13. Abdel-Megeed, A.M., Abdel-Rahmana, H.M., Alkaramanya, G.-E.S., and El-Gendy, M.A., *Eur. J. Med. Chem*., 2009, vol. 44, no. 1, pp. 117–123.
14. Pevzner, M.S., Gladkova, N.V., and Kravchenko, T.A., *Zh. Org. Khim*., 1996, vol. 32, no. 8, pp. 1230–1233.