ISSN 1070-4280, Russian Journal of Organic Chemistry, 2010, Vol. 46, No. 5, pp. 685–688. © Pleiades Publishing, Ltd., 2010.
Original Russian Text © E.E. Klen, F.A. Khaliullin , 2010, published in Zhurnal Organicheskoi Khimii, 2010, Vol. 46, No. 5, pp. 694–697.

Reactions of 1,2,4-Triazole Derivatives with a "Model" Thiirane

E. E. Klen and F. A. Khaliullin

Bashkir State Medical University, Ufa, 450000, Russia
e-mail: khaliullin_ufa@yahoo.com

Received May 20, 2009

Abstract—Reactions of 3-mono- and 3,5-disubstituted 1,2,4-triazoles with a "model" thiirane, 8-bromo-1,3-dimethyl-7-(thiiran-2-ylmethyl)-3,7-dihydro-1*H*-purine-2,6-diones proceed at the positions $N^1$and N^2 of the triazole ring and yield 7-(5-R-3-R'-1,2,4-triazol-1-yl)methyl- and/or 7-(5-R'-3-R-1,2,4-triazol-1-yl)methyl-1,3-dimethyl-6,7-dihydro[1,3]thiazolo[2,3-f]-purine-2,4-(1*H*,3*H*)-diones. 3-Methylsulfonyl-1,2,4-triazole reacted regiospecifically at the position N^1 forming 1,3-dimethyl-7-[(3-methyl-sulfonyl-1,2,4-triazole-1-yl)-methyl]-6,7-dihydro[1,3]thiazolo-[2,3-*f*]purine-2,4(1*H*,3*H*)-dione.

DOI: 10.1134/S1070428010050155

Reactions of 1,2,4-triazole derivatives with thiiranes are virtually unstudied mainly due to the polymerization proceeding at the reaction of thiiranes with nucleophilic reagents [1].

We investigated the reactions of 3-mono- and 3,5-disubstituted 1,2,4-triazoles with thiiranes by an example of a "model" thiirane suggested by us [2], 8-bromo-1,3-dimethyl-7-(thiiran-2-ylmethyl)-3,7-dihydro-1*H*-purine-2,6-dione (**I**), whose application made it possible to obtain monomer products in reactions with nucleophiles owing to the intramolecular heterocyclization affording derivatives of 6,7-dihydro[1,3]thiazolo[2,3-*f*]purine-2,4(1*H*,3*H*)-dione (Scheme 1).

The reaction of 3-nitro-1,2,4-triazole with oxiranes is known to proceed at the position N^1 of the triazole [3], whereas the 3-azido-1,2,4-triazole gave with oxiranes a mixture of reaction products at positions N^1 and N^2 [4]. The products of reaction at the position N^4 were not mentioned in [3, 4]. We also did not found a product of the reaction at the position N^4 in treating with thiirane **I** the unsubstituted 1,2,4-triazole [2].

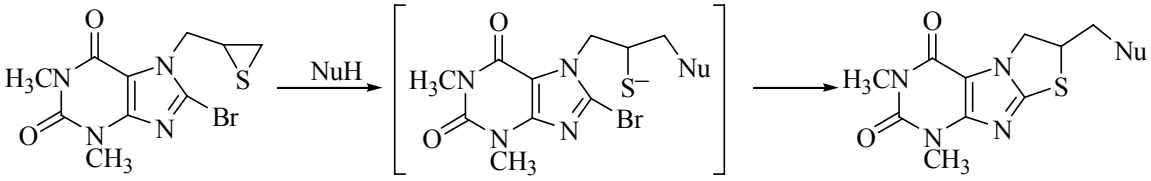
The reactions of thiirane **I** with 1,2,4-triazole **IIa–IIe** were carried out in the presence of KOH in boiling ethanol over 3–5 h (Scheme 2).

The reaction of symmetric 3,5-dibromo-1*H*-1,2,4-triazole (**IIa**) with thiirane **I** led to the formation of 7-[(3,5-dibromo-1*H*-1,2,4-triazol-1-yl)methyl]-1,3-dimethyl-6,7-dihydro[1,3]-thiazolo[2,3-*f*]purine-2,4(1*H*,3*H*)-dione (**III**) (Scheme 2) in 77% yield.

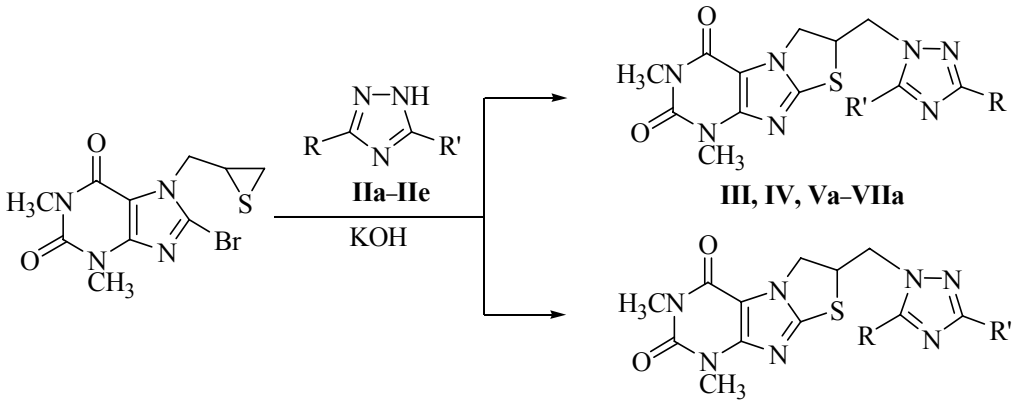
^{1}H NMR spectrum of compound **III** confirmed the formation of the fused system of the dihydrothiazolopurine: characteristic multiplets appeared in the regions 4.62–4.74 and 4.96–5.06 ppm, corresponding to the protons of NCH_2 and SCH groups of the dihydrothiazole ring respectively [5, 6].

The ^{13}C NMR spectrum of compound **III** contained the signals of carbon atoms of dihydrothiazolopurine [4, 5]. The signals at 132.11 and 139.54 ppm belonged to atoms C^5 and C^3 of the triazole ring respectively. Their magnetic nonequivalence showed that the reaction occurred at the position N^1 (N^2) of triazole **IIa**.

Scheme 1.



Scheme 2.



R = R' = Br (**IIa, III**); R = SO_2CH_3, R' = H (**IIb, IV**); R = SCH_3, R' = H (**IIc, Va, Vb**); R = piperidin-1-yl, R' = Br (**IId, VIa, VIb**); R = $NHCH_2C_6H_5$, R' = Br (**IIe, VIIa, VIIb**).

The reaction of thiirane **I** with unsymmetrical 3-methylsulfonyl-1*H*-1,2,4-triazole (**IIb**) proceeded regiospecifically at the position N^1 of the triazole ring (Scheme 2). 1,3-Dimethyl-7-[(3-methylsulfonyl-1*H*-1,2,4-triazol-1-yl)methyl]-6,7-dihydro[1,3]thiazolo-[2,3-*f*]purine-2,4(1*H*,3*H*)-dione (**IV**) formed in 86% yield.

The ^{1}H NMR spectrum of compound **IV** alongside the signals of protons of the fused system of dihydrothiazolopurine and of 7-CH_2 group contained a singlet from the protons of the methylsulfonyl group at 3.34 ppm. The singlet from the proton =CH of the triazole ring at 8.98 ppm confirmed the formation of 3-methylsulfonyl isomer **IV** [4, 7].

The reaction of thiirane **I** with 3-methylsulfanyl-1*H*-1,2,4-triazole (**IIc**) afforded two compounds (Scheme 2). On cooling the reaction mixture 1,3-dimethyl-7-[(5-methylsulfanyl-1*H*-1,2,4-triazol-1-yl)methyl]-6,7-dihydro-[1,3]thiazolo[2,3-*f*]purine-2,4-(1*H*,3*H*)-dione (**Vb**) precipitated in 32% yield. 3-Methylsulfanyl isomer (**Va**) was isolated after evaporation of the filtrate also in 32% yield.

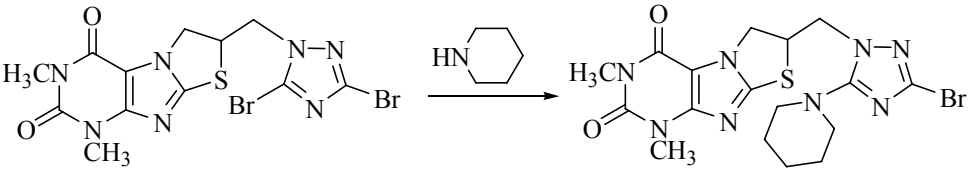
In the ^{1}H NMR spectra of compounds **Va** and **Vb** the singlet of the proton =CH of the triazole ring of 5-methylsulfanyl isomer **Vb** appeared at 7.88 ppm, and the singlet of 3-methylsulfanyl isomer **Va** in a weaker field, at 8.62 ppm, in agreement with the published data [4].

In the ^{13}C NMR spectrum of 5-methylsulfanyl isomer **Vb** the signal at 155.02 ppm belonged to the atom C^5 of the triazole, and the upfield signal at 151.96 ppm, to atom C^3, also in agreement with the published data [7].

The reaction of 5-bromo-3-(piperidin-1-yl)-1*H*-1,2,4-triazole (**IId**) with thiirane **I** also yielded two products (Scheme 2). 7-[(5-Bromo-3-piperidin-1-yl-1*H*-1,2,4-triazole-1-yl)methyl]-1,3-dimethyl-6,7-dihydro[1,3]-thiazolo[2,3-*f*]purine-2,4(1*H*,3*H*)-dione (**VIa**) precipitated in 54% yield. 5-Piperidinyl isomer **VIb** was isolated after evaporation of the filtrate in 31% yield.

Inasmuch as compounds **VIa, VIb** unlike compounds **Va, Vb** do not contain protons in the triazole ring, their assignment to the 3- and 5-piperidinyl isomers is difficult. Therefore we performed an independent synthesis of 5-piperidinyltriazole **VIb** by reaction of triazole **III** with piperidine (Scheme 3). As known, in the presence of a substituent in the position of N^1 of the 1,2,4-triazole the nucleophilic substitution of bromine occurs in the position C^5 [8]. The reaction was carried out by boiling the reagents in BuOH for 5 h to obtain compound **Vb** in 95% yield.

Scheme 3.



The mixed samples of compound **Vb** obtained in different ways melted without depression of the melting points, and their ^{1}H NMR spectra were totally identical.

The ^{1}H NMR spectra of compounds **VIa**, **VIb** contained the proton signals corresponding to the skeleton of dihydrothiazolopurine, to the 7-CH_2 group, and to the piperidine fragment. The multiplet of the protons of $N(CH_2)_2$ group from the piperidine residue of the 3-piperidinyl isomer **VIa** is shifted by 0.25 ppm downfield compared with the analogous signal in the spectrum of 5-piperidinyl isomer **VIb**.

The reaction of 3-benzylamino-5-bromo-1*H*-1,2,4-triazole (**IIe**) with thiirane **I** also furnished two isomers **VIIa** and **VIIb** (Scheme 2). 7-{[3-(Benzylamino)-5-bromo-1*H*-1,2,4-triazol-1-yl]methyl}-1,3-dimethyl-6,7-dihydro[1,3]thiazolo[2,3-*f*]purine-2,4(1*H*,3*H*)-dione (**VIIa**) precipitated in 36% yield. 5-Benzylamino isomer **VIIb** we failed to obtain in an individual state. The overall yield of the reaction products was 83%.

In the ^{1}H NMR spectrum of the mixture of compounds **VIIa** and **VIIb** a double set of signals was observed from the protons of NCH_3 group of the purine residue, of $NHCH_2$ and $NHCH_2$ protons of the benzylamine fragment; therefore we were able to conclude on the formatiom of 3- and 5-benzylamino isomers **VIIa** and **VIIb** in a ratio 3:2 (according to the integral intensities of the signals).

In the ^{1}H NMR spectrum of compound **VIIa** the signal of protons of $NHCH_2$ of the benzylamine fragment appears as a doublet at 4.42 ppm, in a weaker field as compared with the similar signal of 5-benzylamino isomer **VIIb** (at 4.34 ppm in the spectrum of the mixture), indicating as in the event of compound **VIa** the formation of 3-benzylamino isomer.

Thus the reactions of 1,2,4-triazoles with thiirane **I** proceed nonselectively at positions N^1 and N^2except for 3-methylsulfonyl-1*H*-1,2,4-triazole (**IIb**) that reacts regioselectively at the position N^1. As a result form isomeric 7-(5-R-3-R'-1,2,4-triazol-1-yl)methyl- **Va–VIIa** and 7-(5-R'-3-R-1,2,4-triazol-1-yl)methyl-1,3-dimethyl-6,7-dihydro[1,3]thiazolo[2,3-*f*]purine-2,4(1*H*,3*H*)-diones **Vb–VIIb** whose ratio depends on the character of substituents in the positions C^3 and C^5 of the triazole ring. From symmetric 3,5-dibromo-1*H*-1,2,4-triazole (**IIa**) formed a single compound **III**, no reaction products at the position N^4 were detected.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were registered on a spectrometer Bruker AM-300 at operating frequency 300 and 75 MHz respectively. The signals of solvents served as internal references. TLC was performed on Silufol plates using as eluent ethanol or the mixture hexane–ethanol, 3:2, development in the iodine vapor.

7-[(3,5-Dibromo-1*H*-1,2,4-triazol-1-yl)methyl]-1,3-dimethyl-6,7-dihydro[1,3]-thiazolo[2,3-*f*]purine-2,4(1*H*,3*H*)-dione (III). A solution of 0.56 g (10 mmol) of KOH, 2.26 g (10 mmol) of triazole (**IIa**), 1.66 g (5 mmol) of thiirane **I** in 100 ml of ethanol was boiled for 2 h. On cooling the reaction mixture the separated precipitate was filtered off and washed with a solution of KOH and water. Yield 77%, mp 267–269°C (dioxane–water). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.21 s (3H, 3-CH_3), 3.36 s (3H, 1-CH_3), 4.48– 4.57 m (2H, 7-CH_2), 4.62–4.74 m (2H, NCH_2), 4.96–5.06 m (1H, SCH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 27.47 (3-CH_3), 29.57 (1-CH_3), 48.76 (NCH_2), 51.94 (7-CH_2), 52.20 (SCH), 106.61 (C^{4a}), 132.11 ($C^5_{triazole}$), 139.54 ($C^3_{triazole}$), 150.69 (C^{9a}), 151.61 (C^2), 152.79 (C^4), 154.26 (C^{8a}). Found, %: C 30.11; H 2.37; N 20.65. $C_{12}H_{11}Br_2N_7O_2S$. Calculated, %: C 30.21; H 2.32; N 20.55.

1,3-Dimethyl-7-[(3-methylsulfonyl-1*H*-1,2,4-triazol-1-yl)methyl]-6,7-dihydro-[1,3]-thiazolo[2,3-*f*]-purine-2,4(1*H*,3*H*)-dione (IV) was obtained similarly. Yield 86%, mp 215–217°C (H_2O). ^{1}H NMR spectrum (DMF-d_7), δ, ppm: 3.23 s (3H, 3-CH_3), 3.34 s (3H, SO_2CH_3), 3.38 s (3H, 1-CH_3), 4.63 d.d (1H, NCH_2, ^2J 11.9, ^3J 7.5 Hz), 4.73 d.d (1H, NCH_2, ^2J 11.9, ^3J 2.8 Hz), 4.98–5.12 m (2H, 7-CH_2) 5.15–5.26 m (1H, SCH), 8.98 s (1H, $H^{5'}$). Found, %: C 39.41; H 3.62; N 24.58. $C_{13}H_{15}N_7O_4S_2$. Calculated, %: C 39.29; H 3.80; N 24.67.

1,3-Dimethyl-7-[(3-methylsulfanyl-1*H*-1,2,4-triazol-1-yl)methyl]-6,7-dihydro-[1,3]thiazolo[2,3-*f*]-purine-2,4(1*H*,3*H*)-dione (Va) and 1,3-dimethyl-7-[(5-methylsulfanyl-1*H*-1,2,4-triazol-1-yl)methyl]-6,7-dihydro[1,3]thiazolo[2,3-*f*]purine-2,4-(1*H*,3*H*)-dione (Vb). A solution of 1.12 g (20 mmol) of KOH, 2.30 g (20 mmol) of triazole **IIc**, 3.31 g (10 mmol) of thiirane **I** in 100 ml of ethanol was boiled for 4.5 h. On cooling the reaction mixture the separated precipitate was filtered off and washed with a solution of KOH and water. We obtained compound **Vb**. Yield 32%, mp 229–230°C (*i*-PrOH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.71 s (3H, SCH_3), 3.37 s (3H, 3-CH_3), 3.54 s (3H, 1-CH_3), 4.37–4.48 m [3H, NCH_2 (1H), 7-CH_2], 4.55 d.d (1H, NCH_2, ^2J 11.9, ^3J 3.4 Hz), 4.77–4.92 m (1H, SCH),

7.88 C (1H, $H^{3'}$). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 15.63 (SCH_3), 27.92 (3-CH_3), 29.93 (1-CH_3), 48.95 (NCH_2), 50.83 (7-CH_2), 51.11 (SCH), 107.27 (C^{4a}), 151.26 (C^{9a}), 151.96 ($C^{3}_{triazole}$), 152.53 (C^{2}), 153.56 (C^{4}), 154.03 (C^{8a}), 155.02 ($C^{5}_{triazole}$). Found, %: C 42.66; H 4.18; N 26.78. $C_{13}H_{15}N_7O_2S_2$. Calculated, %: C 42.73; H 4.14; N 26.83.

The filtrate was evaporated in a vacuum to dryness, the residue was washed with the solution of KOH, water, and filtered off to obtain compound **Va**. Yield 32%, mp 177–178°C (toluene). ^1H NMR spectrum (DMF-d_7), δ, ppm: 2.53 s (3H, SCH_3), 3.23 s (3H, 3-CH_3), 3.39 s (3H, 1-CH_3), 4.47–4.72 m (2H, NCH_2), 4.72–4.92 m (2H, 7-CH_2), 5.03–5.23 m (1H, SCH), 8.62 s (1H, $H^{5'}$). Found, %: C 42.63; H 4.21; N 26.91. $C_{13}H_{15}N_7O_2S_2$. Calculated, %: C 42.73; H 4.14; N 26.83.

7-[(5-Bromo-3-piperidin-1-yl-1*H*-1,2,4-triazol-1-yl)methyl]-1,3-dimethyl-6,7-dihydro-[1,3]thiazolo-[2,3-*f*]purine-2,4(1*H*,3*H*)-dione (VIa) and 7-[(3-bromo-5-piperidin-1-yl-1*H*-1,2,4-triazole-1-yl)-methyl]-1,3-dimethyl-6,7-dihydro[1,3]thiazolo-[2,3-*f*]purine-2,4(1*H*,-3*H*)-dione (VIb). A solution of 0.28 g (5 mmol) of KOH, 1.16 g (5 mmol) triazole **IId**, 0.83 g (2.5 mmol)of thiirane **I** in 25 ml of ethanol was boiled for 3 h. On cooling the reaction mixture the separated precipitate was filtered off and washed with water to obtain compound **VIa**. Yield 54%, mp 200–202°C (BuOH). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.52–1.68 m [6H, $(CH_2)_3$], 3.25–3.45 m [4H, $N(CH_2)_2$], 3.39 s (3H, 3-CH_3), 3.55 s (3H, 1-CH_3), 4.34 d (2H, 7-CH_2, ^3J 7.1 Hz), 4.44 d.d (1H, NCH_2, ^2J 12.0, ^3J 7.4 Hz), 4.59 d.d (1H, NCH_2, ^2J 12.0, ^3J 3.7 Hz), 4.76–4.90 m (1H, SCH). Found, %: C 42.51; H 4.34; N 23.17. $C_{17}H_{21}BrN_8O_2S$. Calculated, %: C 42.42; H 4.40; N 23.28.

a. The filtrate was evaporated in a vacuum to dryness, the residue was washed with the solution of KOH, water, and filtered off to obtain compound **VIb**. Yield 31%, mp 221–223°C (dioxane–water). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.50–1.63 m [6H, $(CH_2)_3$], 3.02–3.16 m [4H, $N(CH_2)_2$], 3.40 s (3H, 3-CH_3), 3.54 s (3H, 1-CH_3), 4.28 d (2H, 7-CH_2, ^3J 7.2 Hz), 4.46 d (2H, NCH_2, ^3J 5.5 Hz), 4.86–4.97 m (1H, SCH). Found, %: C 42.51; H 4.34; N 23.17. $C_{17}H_{21}BrN_8O_2S$. Calculated, %: C 42.42; H 4.40; N 23.28.

b. A solution of 1.43 g (3 mmol) of triazole **III** and 1.27 g (15 mmol) of piperidine in 50 ml of BuOH was boiled for 5 h. The reaction mixture was evaporated in a vacuum to dryness, the residue was washed with water and filtered off. Yield 95%, mp 223–225°C (BuOH). Found, %: C 42.48; H 4.44; N 23.33. $C_{17}H_{21}BrN_8O_2S$. Calculated, %: C 42.42; H 4.40; N 23.28.

7-{[3-(Benzylamino)-5-bromo-1*H*-1,2,4-triazol-1-yl]methyl}-1,3-dimethyl-6,7-dihydro[1,3]thiazolo-[2,3-*f*]purine-2,4(1*H*,3*H*)-dione (VIIa) and 7-{[5-(benzylamino)-3-bromo-1*H*-1,2,4-triazol-1-yl]-methyl}-1,3-dimethyl-6,7-dihydro[1,3]thiazolo-[2,3-*f*]purine-2,4-(1*H*,3*H*)-dione (VIIb). A solution of 0.17 g (3 mmol) of KOH, 0.76 g (3 mmol) of triazole **IIe**, 0.50 g (1.5 mmol) of thiirane I in 25 ml of EtOH was boiled for 3 h. The reaction mixture was evaporated in a vacuum to dryness, the residue was washed with the solution of KOH, water, and filtered off. Yield of the mixture 83%, mp 128–144°C. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 3.18 s [3H, 3-CH_3 (**VIIb**)], 3.30 s [3H, 1-CH_3 (**VIIb**)], 3.39 s [3H, 3-CH_3 (**VIIa**)], 3.55 C [3H, 1-CH_3 (**VIIa**)], 4.28–4.62 m (6H, 2-CH_2, NCH_2, $NHCH_2$), 4.65 t [1H, $NHCH_2$, ^3J 6.0 Hz (**VIIa**)], 4.77–4.93 m (1H, SCH), 5.57 t [1H, $NHCH_2$, ^3J 5.6 Hz (**VIIb**)], 7.24–7.47 m (5H, $5CH_{arom}$). Found, %: C 45.27; H 3.77; N 22.40. $C_{19}H_{19}BrN_8O_2S$. Calculated, %: C 45.33; H 3.80; N 22.26.

Compound **VIIa** was obtained similarly to compound **VIa**. Yield 36%, mp 177–179°C (*i*-PrOH). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 3.39 s (3H, 3-CH_3), 3.55 s (3H, 1-CH_3), 4.34 d (2H, 7-CH_2, ^3J 7.1 Hz), 4.38–4.48 m [3H, $NHCH_2$, NCH_2 (1H)], 4.60 d.d (1H, NCH_2, ^2J 12.1, ^3J 3.7 Hz), 4.65 t (1H, $NHCH_2$, ^3J 6.0 Hz), 4.77–4.88 m (1H, SCH), 7.26–7.44 m (5H, $5CH_{arom}$). Found, %: C 45.38; H 3.75; N 22.32. $C_{19}H_{19}BrN_8O_2S$. Calculated, %: C 45.33; H 3.80; N 22.26.

REFERENCES

1. Fokin, A.V. and Kolomiets, A.F., *Khimiya tiiranov* (Thiirane Chemistry), Moscow: Nauka, 1978, p. 344.
2. Khaliullin, F.A. and Klen, E.E., *Zh. Org. Khim.,* 2009, vol. 45, 1703.
3. Kofman, T.P. and Kartseva, G.Yu., *Zh. Org. Khim.,* 2001, vol. 37, 744.
4. Kofman, T.P. and Krasnov, K.N., *Zh. Org. Khim.,* 2004, vol. 40, 1699.
5. Khaliullin, F.A., *Cand. Sci. (Farm.) Dissertation*, Ufa., 1998, 428 p.
6. Khaliullin, F.A., Strokin, Yu.V., and Kataev, V.A., *Khim. Geterotsikl. Soedin.,* 1991, p. 840.
7. Saraev, V.V., Kanakina, T.P., Pevzner, M.S., Golod, E.L., Ugrak, B.I., and Kachala, V.V., *Khim. Geterotsikl. Soedin.,* 1996, p. 1078.
8. Zumbrunn, A., *Synthesis,* 1998, p. 1357.