

Reaction of *N*-Aryl-3-oxobutanethioamides with 2-Amino-1,3-thiazole and 2-Amino-1,3-benzothiazole

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Abstract—*N*-Aryl-3-oxobutanethioamides react with 2-amino-1,3-thiazole (2-amino-1,3-benzothiazole) in acetic acid to give mixtures of 7-methyl-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-5-thione (2-methyl-4*H*-pyrimido[2,1-*b*][1,3]benzothiazole-4-thione) and 5-arylimino-7-methyl-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidines (4-arylimino-2-methyl-4*H*-pyrimido[2,1-*b*][1,3]benzothiazoles), whose ratio depends on the nature of the aryl substituent in the initial butanethioamide.

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N-Aryl-3-oxobutanethioamides possess several reaction centers and are ambident substrates which can be used as starting materials in synthesis of various heterocycles [1–4]. These compounds can also act as efficient complexing agents toward heavy metal ions [5, 6], herbicides [7], and antitumor agents [8]. In addition, *N*-aryl-3-oxobutanethioamides, as well as β -dicarbonyl and β -thioxocarbonyl compounds, are capable of forming strong intramolecular hydrogen bonds, and they may exist as different tautomers, thus providing convenient models for studying prototropic tautomerism [9–11].

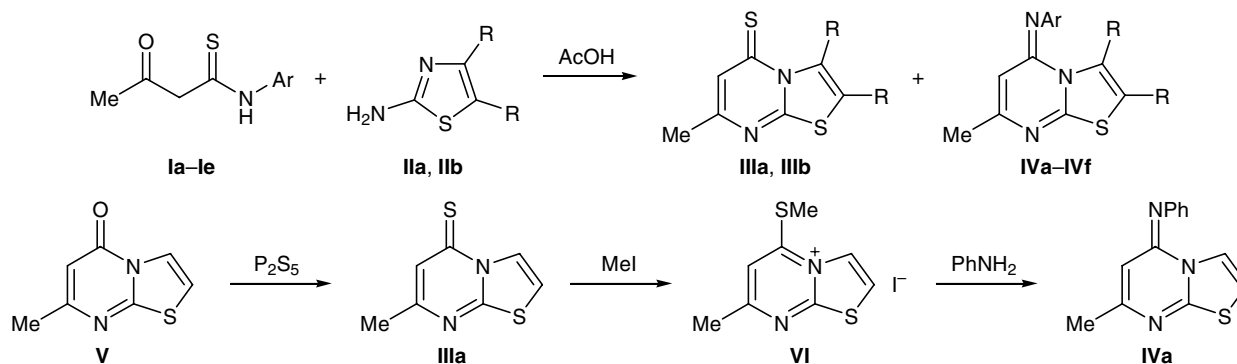
In continuation of our studies on heterocyclizations of *N*-aryl-3-oxobutanethioamides with difunctional 1,3-nucleophiles [12], in the present work we examined their reactions with 2-amino-1,3-thiazole and

2-amino-1,3-benzothiazole. These reactions may be considered to follow [3+3]-cyclocondensation pattern involving three possible reaction centers in *N*-aryl-3-oxobutanethioamides and two centers in 2-aminothiazole; as a result, the products may be four compounds of the thiazolo[3,2-*a*]pyrimidine series.

We found that, unlike reactions of ethyl acetoacetate and its derivatives with 2-aminothiazole and 2-aminobenzothiazole [13, 14], *N*-aryl-3-oxobutanethioamides **Ia–Ie** reacted with the same binucleophiles **IIa** and **IIb** in a nonselective fashion, yielding mixtures of compounds **IIIa** (**IIIb**) and **IVa–IVf** whose ratio depended on the nature of the aryl substituent in the initial thioamide (Scheme 1, see table).

Thiazolo[3,2-*a*]pyrimidine-5(4)-thiones **IIIa** and **IIIb** characteristically showed in the ^1H NMR spectra

Scheme 1.



I, Ar = Ph (**a**), 4-MeOC₆H₄ (**b**), 4-EtOC₆H₄ (**c**), 4-ClC₆H₄ (**d**), 4-O₂NC₆H₄ (**e**); **II**, **III**, R = H (**a**), RR = CH=CH–CH=CH (**b**); **IV**, R = H, Ar = Ph (**a**), 4-MeOC₆H₄ (**b**), 4-ClC₆H₄ (**c**), 4-O₂NC₆H₄ (**d**); RR = CH=CH–CH=CH, Ph (**e**), 4-EtOC₆H₄ (**f**).

Yields of compounds **III** and **IV** in the reactions of *N*-aryl-3-oxobutanethioamides **Ia–Ie** with 2-amino-1,3-thiazole (**IIa**) and 2-amino-1,3-benzothiazole (**IIb**)

Initial reactants	Yield, %	
	III	IV
Ia + IIa	30	35
Ib + IIa	52	20
Id + IIa	15	69
Ie + IIa	–	70
Ia + IIb	16	62
Ic + IIb	31	33

singlets from protons in the 7(2)-Me group and 6(3)-H at δ 2.32–2.35 and 7.23–7.32 ppm, respectively. The spectra of 5(4)-aryliminothiazolopyrimidines **IVa–IVf** contained signals from the 7(2)-Me group and 6(3)-H at δ 2.08–2.17 and 5.90–6.10 ppm. In the IR spectra of **IIIa** and **IIIb** we observed absorption bands belonging to stretching vibrations of the C=N and =C–H bonds at 1570–1580 and 3100 cm^{-1} , respectively, while the corresponding absorption bands in the spectra of **IVa–IVf** were located at 1590–1610, 1630–1650, and 2900–3100 cm^{-1} . However, the IR and ^1H NMR data did not allow us to distinguish between 7-methyl-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-5-thiones and 5-arylimino-7-methyl-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidines, on the one hand, and isomeric 5-methyl-7*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-7-thiones and 7-arylimino-5-methyl-7*H*-[1,3]thiazolo[3,2-*a*]pyrimidines. Therefore, we performed a series of chemical transformations to determine the structure of compounds **III** and **IV**.

By reaction of 2-amino-1,3-thiazole with ethyl acetoacetate according to the procedure described in [13] we synthesized 7-methyl-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidin-5-one (**V**), and treatment of the latter with P_2S_5 in pyridine gave thiazolo[3,2-*a*]pyrimidine **IIIa**. The ^1H NMR spectra of samples of **IIIa** prepared from thioamide **Ia** and 2-amino-1,3-thiazole (**IIa**) and by sulfurization of known thiazolopyrimidinone **V** [13] were fully identical, and their mixture showed no depression of the melting point.

The structure of aryliminothiazolo[3,2-*a*]pyrimidines **IVa–IVf** was confirmed as follows. Alkylation of **IIIa** with methyl iodide gave 7-methyl-5-methylsulfanyl-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidin-4-ium iodide (**VI**). Unlike initial compound **IIIa**, all signals in the ^1H NMR spectrum of **VI** were displaced downfield by 0.35–0.76 ppm (except for the 3-H proton which is also strongly deshielded in the initial compound), indicat-

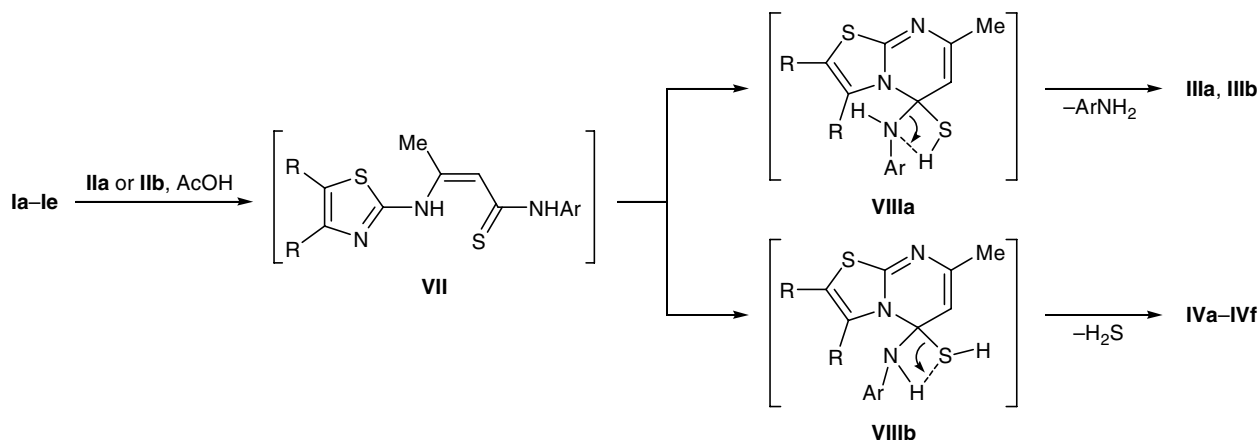
ing reduced electron density in the thiazolopyrimidine ring system of **VI**. Heating of a solution of iodide **VI** in aniline at 150°C resulted in nucleophilic replacement of the methylsulfanyl group by phenylimino with liberation of methanethiol and formation of thiazolo[3,2-*a*]pyrimidine **IVa** (Scheme 1). The ^1H NMR spectra of samples of **IVa** obtained by aminolysis of iodide **VI** and by reaction of thioamide **Ia** with aminothiazole **IIa** were identical, and their mixture showed no depression of the melting point. Thus the structure of compounds **IIIa**, **IIIb**, and **IVa–IVf** was unambiguously proved by independent syntheses.

The results of our study show that, unlike 5-substituted 3-amino-1,2,4-triazoles [12], the exocyclic amino group in aminothiazoles **IIa** and **IIb** is more reactive than the endocyclic imino group N^3H (in the 2-imino tautomer) toward *N*-aryl-3-oxobutanethioamides **Ia–Ie**. The carbonyl group in *N*-aryl-3-oxobutanethioamides **Ia–Ie** is more reactive than the C=S group in reactions with 2-aminothiazoles **IIa** and **IIb**, as in reactions with arylamines [15].

It is known that thioamide **Ia** reacts with aniline and other aromatic amines in acetic acid to give enaminothioamides [15]. Therefore, we expected initial formation of enaminothioamides **VII** by reaction of thioamides **Ia–Ie** with aminothiazoles **IIa** and **IIb** (Scheme 2). As follows from the data in table, the mode of cyclization of enaminothioamides **VII** depends on the nature of the substituent in the benzene ring of *N*-aryl-3-oxobutanethioamide **Ia–Ie**. Electron-donor substituents favor formation of the corresponding thiazolo[3,2-*a*]pyrimidine-5-thione **III**. For example, in going from thioamide **Ia** (Ar = Ph) to **Ib** (Ar = 4-MeOC₆H₄), the yield of compound **IIIa** increases from 30 to 52%, while the yield of alternative product **IV** decreases from 35 (**IVa**) to 20% (**IVb**). By contrast, in the reaction with *p*-nitrophenyl derivative **Ie**, the yield of **IVd** reached 70%, while thiazolopyrimidinethione **IIIa** was not formed at all.

Taking into account that nucleophilic substitution at a carbon atom linked to oxygen or sulfur by a double bond involves formation of a tetrahedral intermediate [16], there are reasons to believe that intramolecular cyclization of enaminothioamides **VII** follows two concurrent pathways: (1) through intermediate **VIIa** with elimination of substituted aniline and formation of thiazolo[3,2-*a*]pyrimidine-5(4)-thione **IIIa** or **IIIb** and (2) through intermediate **VIIb** which loses hydrogen sulfide molecule to give 5(4)-aryliminothiazolo[3,2-*a*]pyrimidines **IVa–IVf**. Presumably, interme-

Scheme 2.



diates **VIIIa** and **VIIIb** are transformed via four-membered cyclic transition states in which a weak hydrogen bond (coordination) exists between the SH proton (NH proton of the *N*-arylamino group) and nitrogen atom of *N*-arylamino group (sulfur atom), depending on the basicity of the *N*-aryl group. The proposed scheme is consistent with the data given in table, which illustrate the effect of the substituent nature in initial thioamides **Ia–Ie** on the ratio of products **III** and **IV**.

Thus 2-amino-1,3-thiazole and 2-amino-1,3-benzothiazole react with *N*-aryl-3-oxobutanethioamides to give mixtures of 7-methyl-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-5-thione (2-methyl-4*H*-pyrimido[2,1-*b*][1,3]benzothiazole-4-thione) and 5-arylimino-7-methyl-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidines (4-arylimino-2-methyl-4*H*-pyrimido[2,1-*b*][1,3]benzothiazoles), whose ratio depends on the nature of the aryl substituent in the initial butanethioamide.

EXPERIMENTAL

The ^1H NMR spectra were recorded from solutions in $\text{DMSO}-d_6$ on a Varian-300 spectrometer (300 MHz) using tetramethylsilane as internal reference. The IR spectra were recorded in KBr on a UR-20 instrument. 7-Methyl-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidin-5-one (**V**) was synthesized by the procedure reported in [13].

Reactions of *N*-aryl-3-oxobutanethioamides **Ia–Ie with 2-amino-1,3-thiazole (**IIa**) and 2-amino-1,3-benzothiazole (**IIb**) (general procedure).** A solution of 10 mmol of *N*-aryl-3-oxobutanethioamide **Ia–Ie** and 10 mmol of 2-amino-1,3-thiazole (**IIa**) or 2-amino-1,3-benzothiazole (**IIb**) in 8 ml of acetic acid was heated for 4 h at 100°C . The mixture was cooled, and the

precipitate of compound **IIIa** or **IIIb** was filtered off. The filtrate was treated with 50 ml of 25% aqueous Na_2CO_3 , the mixture was left to stand for 12 h, and the precipitate of 5-arylimino-7-methyl-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine **IVa–IVd** or 4-arylimino-2-methyl-4*H*-pyrimido[2,1-*b*][1,3]benzothiazole **IVe** or **IVf** was filtered off. The yields of compounds **IIIa, IIIb**, and **IVa–IVf** are given in table.

7-Methyl-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-5-thione (IIIa**).** mp $142\text{--}143^\circ\text{C}$ (from ethanol). IR spectrum, ν , cm^{-1} : 1210, 1310, 1370, 1460, 1580, 3100. ^1H NMR spectrum, δ , ppm: 2.35 s (3H, 7- CH_3), 7.23 s (1H, 6-H), 7.84 d (1H, 2-H, $J = 4.8$ Hz), 8.66 d (1H, 3-H, $J = 4.8$ Hz). Found, %: C 45.86; H 3.03; N 15.18; S 35.30. $\text{C}_7\text{H}_6\text{N}_2\text{S}_2$. Calculated, %: C 46.13; H 3.32; N 15.37; S 35.18.

2-Methyl-4*H*-pyrimido[2,1-*b*][1,3]benzothiazole-4-thione (IIIb**).** mp $181\text{--}183^\circ\text{C}$ (from nitromethane). IR spectrum, ν , cm^{-1} : 1320, 1360, 1450, 1530, 1570, 3100. ^1H NMR spectrum, δ , ppm: 2.32 s (3H, 2- CH_3), 7.32 s (1H, 3-H), 7.52–7.69 m (2H, H_{arom}), 8.11 d (1H, 9-H, $J = 7.8$ Hz), 10.45 d (1H, 6-H, $J = 8.7$ Hz). Found, %: C 57.02; H 3.70; N 11.79. $\text{C}_{11}\text{H}_8\text{N}_2\text{S}_2$. Calculated, %: C 56.87; H 3.47; N 12.06.

***N*-(7-Methyl[1,3]thiazolo[3,2-*a*]pyrimidin-5-ylidene)aniline (**IVa**).** mp $150\text{--}153^\circ\text{C}$ (from nitromethane). IR spectrum, ν , cm^{-1} : 1350, 1370, 1400, 1490, 1510, 1580, 1600, 1650, 3100. ^1H NMR spectrum, δ , ppm: 2.10 s (3H, 7- CH_3), 5.91 s (1H, 6-H), 6.87 m (2H, H_{arom}), 7.00 m (1H, H_{arom}), 7.31 m (2H, H_{arom}), 7.42 d (1H, 2-H, $J = 4.5$ Hz), 8.12 d (1H, 3-H, $J = 4.5$ Hz). Found, %: C 64.89; H 4.32; N 17.19. $\text{C}_{13}\text{H}_{11}\text{N}_3\text{S}$. Calculated, %: C 64.71; H 4.59; N 17.41.

4-Methoxy-*N*-(7-methyl[1,3]thiazolo[3,2-*a*]pyrimidin-5-ylidene)aniline (IVb**).** mp $146\text{--}148^\circ\text{C}$ (from

ethanol). IR spectrum, ν , cm^{-1} : 1350, 1370, 1400, 1440, 1510, 1560, 1610, 1630, 2900–3100. ^1H NMR spectrum, δ , ppm: 2.08 s (3H, 7- CH_3), 3.73 s (3H, CH_3O), 5.90 s (1H, 6-H), 6.78 d (2H, H_{arom} , $J = 8.6$ Hz), 6.85 d (2H, H_{arom} , $J = 8.6$ Hz), 7.37 d (1H, 2-H, $J = 4.3$ Hz), 8.08 d (1H, 3-H, $J = 4.3$ Hz). Found, %: C 61.75; H 5.02; N 15.21. $\text{C}_{14}\text{H}_{13}\text{N}_3\text{OS}$. Calculated, %: C 61.97; H 4.83; N 15.49.

4-Chloro-*N*-(7-methyl[1,3]thiazolo[3,2-*a*]pyrimidin-5-ylidene)aniline (IVc). mp 183–185°C (from nitromethane). IR spectrum, ν , cm^{-1} : 1340, 1370, 1410, 1505, 1570, 1590, 1640, 3000–3100. ^1H NMR spectrum, δ , ppm: 2.12 s (3H, 7- CH_3), 5.91 s (1H, 6-H), 6.79–6.87 m (2H, H_{arom}), 7.03 m (1H, H_{arom}), 7.31 m (1H, H_{arom}), 7.43 d (1H, 2-H, $J = 4.6$ Hz), 8.08 d (1H, 3-H, $J = 4.6$ Hz). Found, %: C 56.45; H 3.37; N 15.49. $\text{C}_{13}\text{H}_{10}\text{ClN}_3\text{S}$. Calculated, %: C 56.62; H 3.66; N 15.24.

***N*-(7-Methyl[1,3]thiazolo[3,2-*a*]pyrimidin-5-ylidene)-4-nitroaniline (IVd).** mp 215–217°C (from DMSO). IR spectrum, ν , cm^{-1} : 1250, 1320, 1410, 1500, 1560, 1590, 1640, 3100. ^1H NMR spectrum, δ , ppm: 2.17 s (3H, 7- CH_3), 6.10 s (1H, 6-H), 7.08 d (2H, H_{arom} , $J = 8.4$ Hz), 7.52 d (1H, 2-H, $J = 4.0$ Hz), 8.16–8.19 m (3H, H_{arom} , 3-H). Found, %: C 54.35; H 3.31; N 19.69. $\text{C}_{13}\text{H}_{10}\text{N}_4\text{O}_2\text{S}$. Calculated, %: C 54.54; H 3.52; N 19.57.

***N*-(2-Methyl-4*H*-pyrimido[2,1-*b*][1,3]benzothiazol-4-ylidene)aniline (IVe).** mp 198–199°C (from DMSO). IR spectrum, ν , cm^{-1} : 1360, 1390, 1460, 1490, 1540, 1590, 1645, 3100. ^1H NMR spectrum, δ , ppm: 2.09 s (3H, 2- CH_3), 5.99 s (1H, 3-H), 6.89 m (2H, H_{arom}), 7.06 m (1H, H_{arom}), 7.35 m (2H, H_{arom}), 7.49 (2H, H_{arom}), 7.96 m (1H, H_{arom}), 9.37 m (1H, H_{arom}). Found, %: C 69.82; H 4.71; N 14.29. $\text{C}_{17}\text{H}_{13}\text{N}_3\text{S}$. Calculated, %: C 70.08; H 4.50; N 14.42.

4-Ethoxy-*N*-(2-methyl-4*H*-pyrimido[2,1-*b*][1,3]benzothiazol-4-ylidene)aniline (IVf). mp 178–181°C (from DMSO). IR spectrum, ν , cm^{-1} : 1290, 1360, 1390, 1520, 1590, 1640, 3000. ^1H NMR spectrum, δ , ppm: 1.36 t (3H, $\text{CH}_3\text{CH}_2\text{O}$, $J = 6.9$ Hz); 2.09 s (3H, 2- CH_3); 3.99 q (2H, CH_2O , $J = 6.9$ Hz); 6.03 s (1H, 3-H); 6.80 d (2H, C_6H_4 , $J = 8.1$ Hz); 6.91 d (2H, C_6H_4 , $J = 8.1$ Hz); 7.48 m (2H), 7.93 (1H), and 9.36 m (1H) (6-H–9-H). Found, %: C 67.81; H 5.32; N 12.72. $\text{C}_{19}\text{H}_{17}\text{N}_3\text{OS}$. Calculated, %: C 68.04; H 5.11; N 12.53.

Sulfurization of 7-methyl-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidin-5-one (V). A solution of 1.66 g (10 mmol) of compound V and 2.22 g (10 mmol) of P_2S_5 in 10 ml of pyridine was heated for 10 h under

reflux. The mixture was cooled, diluted with 30 ml of water, and extracted with chloroform (2×10 ml). The extract was dried over MgSO_4 and evaporated under reduced pressure (water-jet pump), and the residue was recrystallized from ethanol. Yield of compound **IIIa** 0.783 g (43%), mp 142–143°C.

7-Methyl-5-methylsulfanyl-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidin-4-ium iodide (VI). A solution of 0.91 g (5 mmol) of compound **IIIa** and 1.14 g (8 mmol) of methyl iodide in 10 ml of benzene was heated for 8 h at 50°C. The mixture was cooled, and the precipitate was filtered off. Yield 1.085 g (67%), mp 215–216°C. IR spectrum, ν , cm^{-1} : 1310, 1340, 1370, 1430, 1490, 1560, 1585, 2900–3100. ^1H NMR spectrum, δ , ppm: 2.77 s (3H, 7- CH_3), 2.97 s (3H, SCH_3), 7.99 s (1H, 6-H), 8.46 d (1H, 2-H, $J = 4.0$ Hz), 8.65 d (1H, 3-H, $J = 4.0$ Hz). Found, %: C 29.92; H 2.52; N 8.47. $\text{C}_8\text{H}_9\text{IN}_2\text{S}_2$. Calculated, %: C 29.64; H 2.80; N 8.64.

A solution of 0.81 g (2.5 mmol) of iodide VI in 3 ml of aniline was heated for 0.5 h at 150°C. The mixture was cooled, and the precipitate was filtered off, washed in succession with diethyl ether (2×5 ml), 20% aqueous Na_2CO_3 (2×10 ml), and water, and dried. Yield of thiazolopyrimidine **IVa** 0.374 g (62%), mp 150–153°C (from nitromethane).

REFERENCES

1. Britsun, V.N., Borisevich, A.N., Samoilenko, L.S., and Lozinskii, M.O., *Russ. J. Org. Chem.*, 2005, vol. 41, p. 283.
2. Britsun, V.N., Borisevich, A.N., Samoilenko, L.S., and Lozinskii, M.O., *Russ. J. Org. Chem.*, 2005, vol. 41, p. 745.
3. Britsun, V.N., Borisevich, A.N., Samoilenko, L.S., Chernega, A.N., and Lozinskii, M.O., *Izv. Ross. Akad. Nauk, Ser. Khim.*, 2005, p. 757.
4. Britsun, V.N., Bazavova, I.M., Bodnar, V.N., Chernega, A.N., and Lozinskii, M.O., *Khim. Geterotsikl. Soedin.*, 2005, no. 1, p. 120.
5. Ludwig, E., Dietze, F., and Uhleman, E., *Z. Anorg. Allg. Chem.*, 1984, vol. 512, p. 181.
6. Ludwig, E., Uhleman, E., and Glock, N., *Anal. Chim. Acta*, 1982, vol. 140, p. 171.
7. Ishinaki, M., Osaka, S., and Takenata, S., JPN Patent no. 06-179646, 1994; *Chem. Abstr.*, 1994, vol. 122, no. 105446a.
8. Hanna, M.A., Girges, M.M., and Moevad, M.M., *Chem. Pap.*, 1989, vol. 43, no. 5, p. 661; *Chem. Abstr.*, 1990, vol. 113, no. 23827r.

9. Close, G., Ludwig, E., and Uhlemann, E., *Org. Magn. Reson.*, 1977, vol. 10, p. 151.
10. Il'chenko, N.N., Britsun, V.N., and Lozinskii, M.O., *Teor. Eksp. Khim.*, 2005, vol. 41, p. 272.
11. Britsun, V.N., Borisevich, A.N., Samoilenko, L.S., and Lozinskii, M.O., *Ukr. Khim. Zh.*, 2005, vol. 71, no. 8, p. 111.
12. Britsun, V.N., Borisevich, A.N., Samoilenko, L.S., Chernega, A.N., and Lozinskii, M.O., *Russ. J. Org. Chem.*, 2006, vol. 42, p. 1516.
13. Okabe, T., Maekawa, K., and Taniguchi, E., *Agric. Biol. Chem.*, 1973, vol. 17, p. 1197; *Chem. Abstr.*, 1973, vol. 79, no. 53256a.
14. Falch, E. and Natvig, T., *Acta Chem. Scand.*, 1970, vol. 24, p. 1423.
15. Borisevich, A.N. and Pel'kis, P.S., *Zh. Org. Khim.*, 1967, vol. 3, p. 1339.
16. March, J., *Advanced Organic Chemistry. Reactions, Mechanisms, and Structure*, New York: Wiley, 1985. Translated under the title *Organicheskaya khimiya*, Moscow: Mir, 1987, vol. 2, p. 55.