Chemistry of Heterocyclic Compounds, Vol. 37, No. 10, 2001

HETARYL 1,2,3-THIADIAZOLYL SULFIDES

Yu. Yu. Morzherin, T. A. Pospelova, T. V. Glukhareva, V. S. Berseneva,

Yu. A. Rozin, E. V. Tarasov, and V. A. Bakulev

The synthesis of hetaryl 1,2,4-thiadiazolyl sulfides has been carried out by nucleophilic substitution of the chlorine atom in 5-chloro-1,2,3-thiadiazole by mercaptoheterocycles.

Keywords: hetarylthiols, quantum-chemical calculations, nucleophilic substitution, reactivity.

Derivatives of 1,2,3-thiadiazole possess a wide range of physiological and biological activity [1]. They exhibit pesticidal, anti-inflammatory, hypotensive, antibacterial, antiallergic, antitumor, and anthelminthic properties, and photo- and radio-labile polymers have been prepared based on them [2]. Derivatives of this heterocycle represent themselves a new class of chemical preparations used to increase the immune system of plants [3] and the search is continuing for derivatives which possess various types of biological activity. For example 1,2,3-thiadiazoles containing alkylmercapto group at position 5 exhibit herbicidal [4] and antimicrobial activity [5]. However, 1,2,3-thiadiazolyl-1,2,4-triazoles, which possess antibacterial and herbicidal activity [6], are the only known derivatives of 1,2,3-thiadiazolyl sulfides with a heterocyclic residue at the sulfur atom. The aim of this study is the synthesis of 1,2,3-thiadiazolyl sulfides containing hetaryl substituents at the sulfur atom.

In continuation of our investigation of the synthesis of derivatives of 1,2,3-thiadiazoles [7-11] we have studied the reactivity of 5-chloro-1,2,3-thiadiazoles **1a-d** in the nucleophilic substitution reaction with various S-nucleophiles containing heterocyclic substituents.

The reaction of compound **1** with mercaptoazoles, which have several nucleophilic centers, may occur either at the sulfur atom or at the nitrogen atom of the azole ring [12]. Three hetarylation products can be formed in reaction with 5-mercapto-1,2,3-thiadiazole: sulfide **2**, 2,5'-bi(1,2,3-thiadiazolyl)-5-thione or the zwitterionic strucure 3,5'-bi(1,2,3-thiadiazolyl)-5-thiol (Schemes 1 and 2).

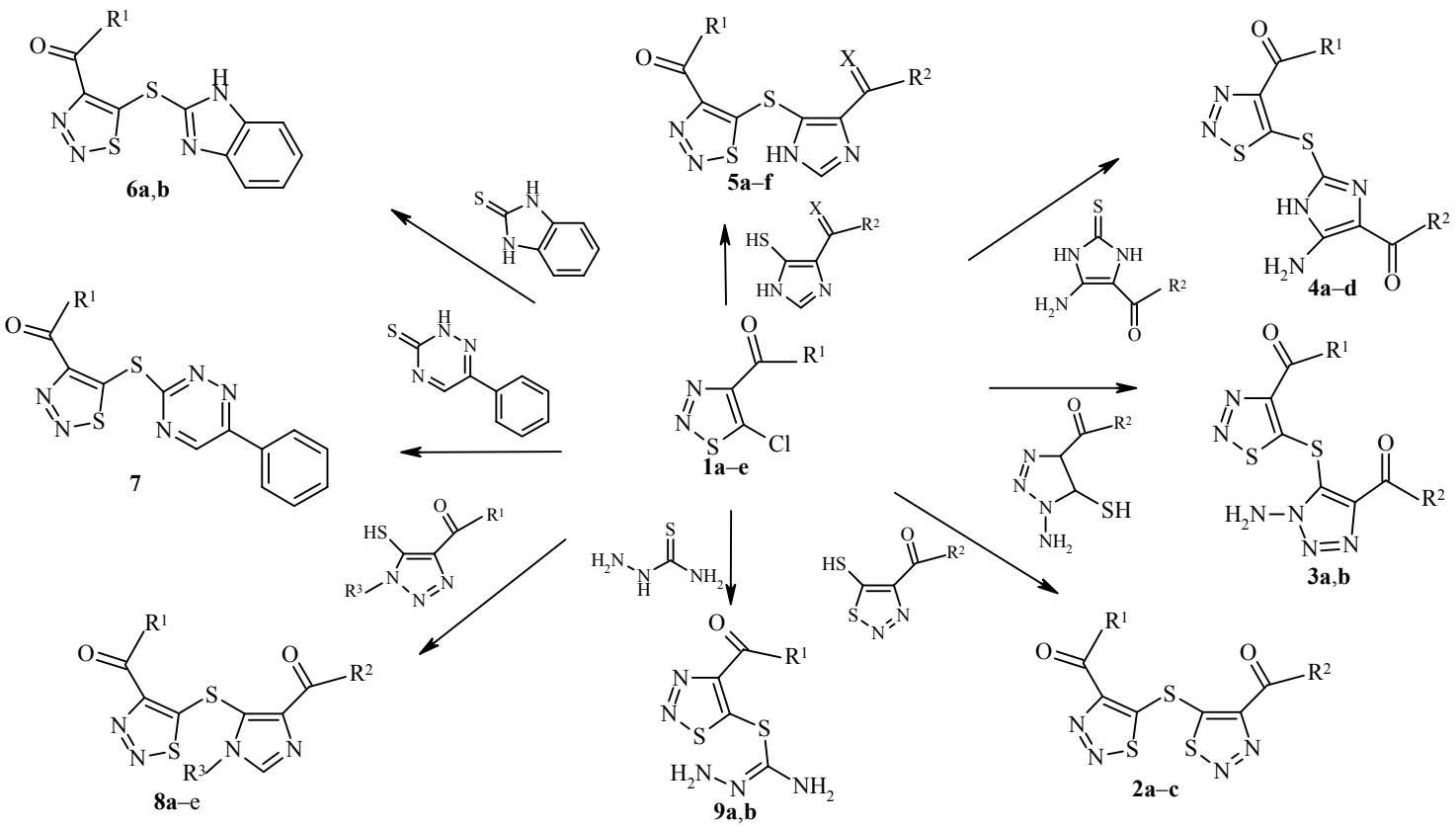
Quantum-chemical calculations of the electronic structures of 5-mercapto-1,2,3-thiadiazoles using the AM1 method [13] with complete optimization of the geometry show that the sulfur atom of the mercapto group (Fig. 1) has considerable electron density which produces an increased contribution to the HOMO (C_{pz}) and also increases the negative charge in the anionic particle. The charge and the index of reactivity (C_{pz}) at the nitrogen atoms of the heterocycle are considerably lower. In the neutral molecule the charge on the sulfur atom is positive which may lead to reaction at the nitrogen atom of the ring.

We have isolated a chromatographically individual product from the reaction. In the ^{1}H NMR spectra of compounds **2a,b**, which contain two identical substituents R^1 and R^2, signals of only one group are observed (Table 1) which indicates that symmetrical product has been obtained – bis(1,2,3-thiadiazolyl-5)sulfide **2a,b**, because hetarylation at nitrogen atom of the ring should give unsymmetrical products.

Ural State Technical University, Ekaterinburg 620002, Russia; e-mail: morjerine@htf.ustu.ru. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, 1388-1395, October, 2001. Original article submitted July 30, 1999.

 0009-3122/01/3710-1270$25.00

Scheme 1



1 a R^1 = OEt, **b** R^1 = NH_2, **c** R^1 = NHMe, **d** R^1 = NHPh, **e** R^1 = NHC_6H_4COMe, **f** R^1 = $NHC_6H_2Cl_3$-2,4,6, **g** R^1 = NHC_6H_4Cl-4. **2 a** R^1 = R^2 = OEt, **b** R^1 = NHMe, **c** R^1 = OEt, R^2 = NHMe. **3 a** R^1 = R^2 = OEt; **b** R^1 = OEt, R^2 = NH_2; **c** R^1 = OEt, R^2 = NHMe; **d** R^1 = C_6H_4Cl-4, R^2 = NH_2. **4 a** R^1 = R^2 = OEt; **b** R^1 = OEt, R^2 = NH_2; **c** R^1 = OEt, R^2 = NHMe; **d** R^1 = C_6H_4Cl-4, R^2 = NH_2. **5 a** R^1 = OEt, R^2 = NH_2, X = O; **b** R^1 = OEt, R^2 = NH_2, X = S; **c** R^1 = R^2 = NH_2, X = O; **d** R^1 = R^2 = NH_2, X = S; **e** R^1 = NHMe, R^2 = NH_2, X = O; **f** R^1 = NHMe, R^2 = NH_2, X = S. **6 a** R = OEt, **b** R = NH_2. **7** R^1 = OEt. **8 a** R^1 = OEt, R^2 = NHMe, R^3 = H; **b** R^1 = NHC_6H_4COMe, R^2 = NHMe, R^3 = H; **c** R^3 = CH_2Ph; **d** R^1 = OEt, R^2 = $NHC_4H_2Cl_3$-2,4,6, R^3 = Me; **e** R^1 = NHMe, R^2 = OEt, R^3 = Me. **9 a** R^1 = OEt, **b** R^1 = NHPh

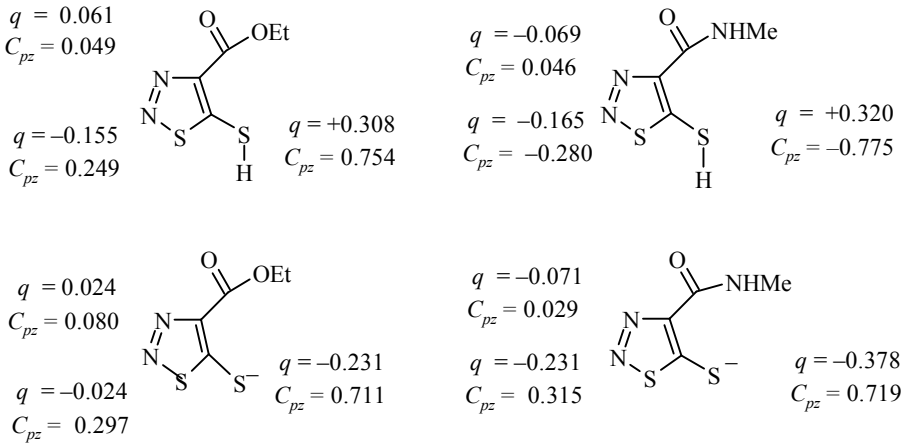
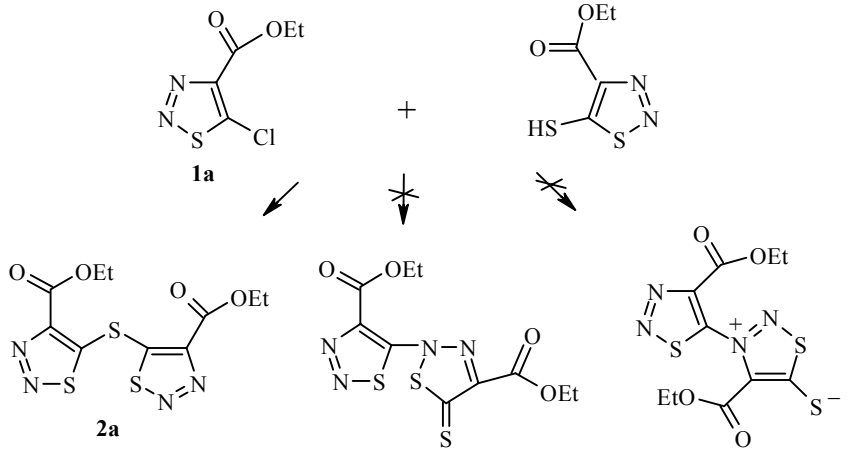


Fig.1. Charges (q) and contributions to the HOMO (C_{pz}) on the atoms of 5-mercapto-1,2,3-thiadiazoles calculated by the AM1 method

Scheme 2



For confirmation we synthesized compounds **2a,b** by an independent synthesis from 5-chloro-1,2,3-thiadiazoles **1a,c** and thiourea. The physicochemical characteristics of the compounds obtained coincided with those of the compounds obtained previously. We have shown therefore that the reaction occurs in just one direction, namely at the "softer" nucleophilic center, the sulfur atom.

Compound **2c**, which contains ester and methylcarboxamide group, was also synthesized by two routes: from the chlorothiadiazoles **1a** and **1c**. The reaction products were identical in all characteristics, which also indicates hetarylation at the sulfur atom.

Scheme 3

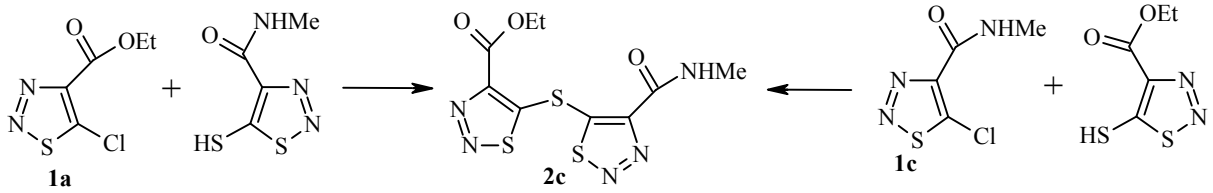
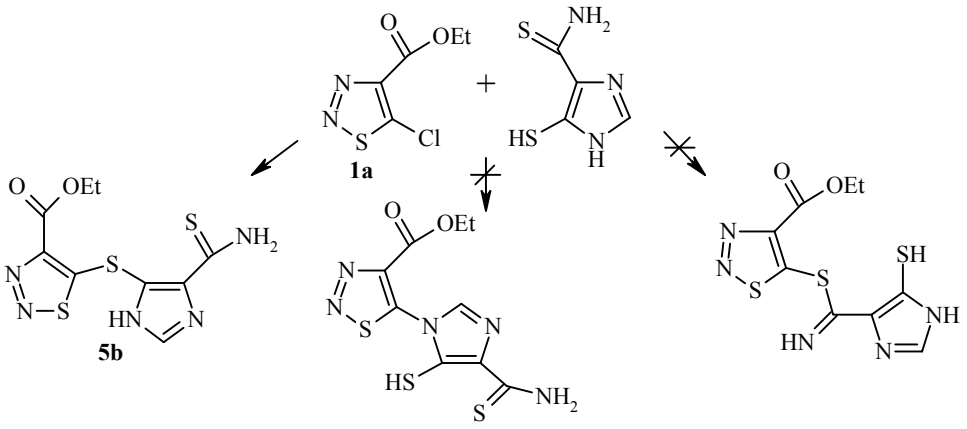


TABLE 1. ^{1}H NMR Spectral Characteristics of the Compounds Synthesized

Compound	δ, ppm, *J*, Hz (DMSO-d_6)
2a	4.48 (2H, q, *J* = 4.9, OCH_2); 1.40 (3H, t, *J* = 4.9, CH_3)
2b	8.95 (1H, t, $NHCH_3$); 2.87 (3H, d, $NHCH_3$)
2c	9.25 (1H, t, $NHCH_3$); 4.50 (2H, q, *J* = 4.7, OCH_2); 2.90 (3H, d, $NHCH_3$); 1.30 (3H, t, *J* = 4.7, CH_3)
3a	8.60 (1H, t, $NHCH_3$); 7.40 (2H, br. s, NH_2); 4.50 (2H, q, *J* = 7.0, OCH_2); 2.73 (3H, d, $NHCH_3$); 1.40 (3H, t, *J* = 7.0, CH_3)
3b	9.05 (1H, t, NH); 8.60 (1H, t, NH); 7.29 (2H, br. s, NH_2); 2.90 (3H, d, $NHCH_3$); 2.80 (3H, d, $NHCH_3$)
4a	12.81 (1H, br. s, NH); 5.97 (2H, br. s, NH_2); 4.46 (2H, q, *J* = 7.1, OCH_2); 4.42 (2H, q, *J* = 7.1, OCH_2); 1.39 (3H, t, *J* = 7.1, CH_3); 1.29 (3H, t, *J* = 7.1, CH_3)
4b	12.36 (1H, br. s, NH); 6.81 (2H, br. s, NH_2); 5.98 (2H, br. s, NH_2); 4.46 (2H, q, *J* = 7.1, OCH_2); 1.39 (3H, t, *J* = 7.1, CH_3)
4c	12.38 (1H, br. s, NH); 7.38 (1H, t, NH); 5.92 (2H, br. s, NH_2); 4.46 (2H, q, *J* = 7.1, OCH_2); 2.74 (3H, d, $NHCH_3$); 1.39 (3H, t, *J* = 7.1, CH_3)
4d	12.35 (1H, br. s, NH); 11.08 (1H, s, NH); 7.92 (2H, d, *J* = 9.0, ArH); 7.43 (2H, d, *J* = 9.0, ArH); 6.84 (2H, br. s, NH_2); 5.98 (2H, br. s, NH_2)
5a	13.20 (1H, br. s, NH); 8.13 (1H, s, CH); 7.53 (2H, br. s, NH_2); 4.46 (2H, q, *J* = 7.0, OCH_2); 1.40 (3H, t, *J* = 7.0, CH_3)
5b	9.62 (1H, s, NH); 8.81 (2H, br. s, NH); 8.20 (1H, s, CH); 4.50 (2H, q, OCH_2); 1.40 (3H, t, CH_3)
5c	13.08 (1H, br. s, NH); 8.29 (1H, s, NH); 8.10 (1H, s, CH); 7.91 (1H, s, NH); 7.48 (2H, s, NH_2)
5e	13.1 (1H, br. s, NH); 8.90 (1H, t, NH); 8.10 (1H, s, CH); 7.47 (2H, s, NH_2); 2.87 (3H, d, $NHCH_3$)
5f	9.5 (1H, br. s, NH); 8.9 (2H, br. s, NH_2); 8.20 (1H, s, CH); 2.85 (3H, d, $NHCH_3$)
6a	13.1 (1H, br. s, NH); 7.60 (2H, ddd, ArH); 7.30 (2H, ddd, ArH); 4.50 (2H, q, *J* = 7.1, OCH_2); 1.40 (3H, t, *J* = 7.1, CH_3)
6b	13.2 (1H, br. s, NH); 8.47 (1H, br. s, NH); 8.10 (1H, br. s, NH); 7.50 (2H, ddd, ArH); 7.30 (2H, ddd, ArH),
7	10.10 (1H, s, CH); 8.40-8.44 (2H, m, Ph); 7.69-7.76 (3H, m, Ph); 4.53 (2H, q, *J* = 7.0, OCH_2); 1.44 (3H, t, *J* = 7.0, CH_3)
8a	10.40 (1H, br. s, NH); 8.60 (1H, t, $NHCH_3$); 4.50 (2H, q, *J* = 7.0, OCH_2); 2.72 (3H, d, $NHCH_3$); 1.40 (3H, t, *J* = 7.0, CH_3)
8b	11.27 (1H, s, NH); 8.63 (1H, t, $NHCH_3$); 8.09 (2H, d, *J* = 9.15, C_6H_4); 7.99 (2H, d, *J* = 9.15, C_6H_4); 2.79 (3H, d, $NHCH_3$); 2.57 (3H, s, CH_3)
8c	11.27 (1H, s, NH); 8.75 (1H, t, $NHCH_3$); 8.07 (2H, d, *J* = 9.0, C_6H_4); 8.00 (2H, d, *J* = 9.0, C_6H_4); 7.20 (5H, s, Ph); 5.81 (2H, s, CH_2); 2.74 (3H, d, $NHCH_3$); 2.57 (3H, s, $COCH_3$)
8d	10.75 (1H, s, NH); 7.76 (2H, s, C_6H_2); 4.48 (2H, q, *J* = 7.0, OCH_2); 4.03 (3H, s, CH_3); 1.39 (3H, t, *J* = 7.0, CH_3)
8e	8.60 (1H, t, $NHCH_3$); 4.39 (2H, q, *J* = 7.0, OCH_2); 3.95 (3H, s, NCH_3); 2.72 (3H, d, $NHCH_3$); 1.30 (3H, t, *J* = 7.0, CH_3)
9a	10.20 (1H, s, NH); 9.94 (1H, s, NH); 8.08 (1H, br. s, NH_2); 4.36 (2H, q, *J* = 7.1, OCH_2); 1.30 (3H, t, *J* = 7.1, CH_3)

Reaction of compound **1** with 1-amino-1,2,3-triazole-5-thiols or 5-aminoimidazole-2-thiols may also occur at the nitrogen atom of the amino groups, however in the reaction conditions used only the S-substitution products **3a,b** and **4a-d** were isolated, which was confirmed by the presence (Table 1) of proton signals characteristic of the amino group in the ^{1}H NMR spectra. So the interaction of 5-chloro-1,2,3-thiadiazoles with mercaptoazoles occurs exclusively at the sulfur atom of the mercapto group. This is in excellent agreement with the suggestion that the sulfur atom is more nucleophilic than the nitrogen atoms of the heterocycle or the amino group.

Scheme 4



The presence of a thioamide group in the molecule of the mercapto compound permits the prediction that reaction might occur concurrently at the sulfur atom of the thioamide group. Quantum-chemical calculations using the AM1 method [13] showed that the charge on the sulfur atom of the thioamide group is greater that on the sulfur atom of the mercapto group, but the reactivity index (C_{pz} in the HOMO) is higher for the sulfur atom of the mercapto group (Fig. 2). Only one of the tautomeric forms was taken into account in the calculations [14]. So the reaction may occur at the sulfur atom of the thioamide group if the reaction is under charge control, but at the sulfur atom of the mercapto group if it is under orbital control. Analysis of the ^{1}H NMR spectra of compounds **5b,e** shows the presence of signals of both the NH protons of the imidazole ring at about 13 ppm and a broad two proton singlet at 8.8-8.9 ppm which is characteristic of the protons of the thioamide group. Thus in this case reaction also occurs at the sulfur atom of the mercapto group.

The results obtained permitted us to develop a series of 1,2,3-thiadiazolyl hetaryl sulfides **2-8**. It was shown that the reactions occur in sufficiently high yields (50-90%) in various solvents (DMF, ethanol, acetonitrile). The use of triethylamine or other bases, e.g., Na_2CO_3, as HCl acceptors, and also carrying out the reaction in protonic solvents considerably reduced the yields of the desired products.

In an attempt to synthesize hetaryl 1,2,3-thiadiazol-5-yl sulfides the reaction of 5-chlorothiadiazoles **1** with thiosemicarbazide was attempted. Products of hetarylation at the sulfur atom **9a,b** were isolated. These compounds give a qualitative reaction for hydrazide group but do not undergo condensation reactions with chloroacetone, acetylacetone, or orthoesters.

So it has been shown that the reactions of 5-chloro-1,2,3-thiadiazoles with mercaptoheterocycles represent a suitable method for the synthesis of hetaryl 1,2,3-thiadiazol-5-yl sulfides. Replacement of chlorine atom at position 5 of the 1,2,3-thiadiazole ring by heterocyclic thiol occurs in high yield under mild conditions in DMF solutions at room temperature or on heating to 40°C. Use of triethylamine, sodium ethoxide, or sodium carbonate leads to decrease in the yield of the desired product, which is probably related to destruction of the 5-chloro-1,2,3-thiadiazole ring under the influence of bases.

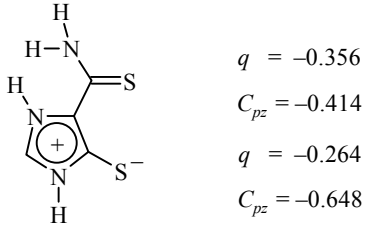


Fig. 2. Charges (q) and reactivity indexes (C_{pz} in the HOMO) for 5-mercaptoimidazole-4-carbothiamide calculated by the AM1 method.

TABLE 2. Characteristics of the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %		IR spectrum, $cm^{-1}(\nu_{C=O})$	mp, °C	Yield, %
		N	S			
2a	$C_{10}H_{10}N_4O_4S_3$	15.80 / 16.17	28.30 / 27.77	1700	167	85
2b	$C_8H_8N_6O_2S_3$	20.90 / 21.13	29.40 / 29.03	1680	183	72
2c	$C_9H_9N_5O_3S_3$	23.40 / 23.78	29.90 / 29.70	1700	145	55
3a	$C_9H_{11}N_7O_3S_2$	26.55 / 26.77	— / 19.47	1705	210 dec.	80
3b	$C_8H_{10}N_8O_2S_2$	35.20 / 35.65	— / 20.40	1690	242-245	89
4a	$C_{11}H_{13}N_4O_3S_2$	20.40 / 20.40	18.48 / 18.68	1690	246-248	85
4b	$C_{11}H_{13}N_4O_3S_2$	26.72 / 26.73	20.57 / 20.40	1685	197-199	68
4c	$C_{10}H_{12}N_6O_3S_2$	25.49 / 25.59	19.31 / 19.53	1695	>280 dec.	60
4d	$C_{13}H_{10}ClN_7O_2S_2 \cdot H_2O$	23.89 / 23.69	14.78 / 15.49	1700	285–287	72
5a	$C_9H_9N_5O_3S_2$	23.62 / 23.41	22.0 / 21.40	1700	281-282	85
5b	$C_9H_9N_5O_2S_3$	22.56 / 22.19	30.90 / 30.50	1680	249-252	25
5c	$C_7H_6N_6O_2S_2$	31.53 / 31.09	23.31 / 23.73	1685	285-290	25
5d	$C_7H_6N_6OS_3$	29.52 / 29.52	— / 33.60	1690	250-253	30
5e	$C_8H_8N_6O_2S_2$	29.42 / 29.58	22.35 / 22.55	1685	290-295	27
5f	$C_8H_8N_6OS_3$	28.50 / 27.96	— / 32.02	1690	243-246	38
6a	$C_{12}H_{10}N_5O_2S_2$	17.67 / 18.29	— / 20.93	1690	121-123	54
6b	$C_{10}H_7N_5OS_2$	24.84 / 25.25	— / 23.12	1695	242 dec.	67
7	$C_{13}H_{11}N_5O_2S_2$	20.71 / 20.29	18.26 / 18.55	1690	235-236	86
8a	$C_9H_{10}N_6O_3S_2$	26.90 / 26.73	— / 20.40	1690	253-255	69
8b	$C_{14}H_{13}N_7O_3S_2$	24.12 / 24.32	15.44 / 15.88	1695	291-293	72
8c	$C_{19}H_{19}N_7O_3S_2$	19.99 / 19.88	13.26 / 12.98	1700	212-213	66
8d	$C_{15}H_{11}Cl_3N_6O_3S_2$	17.46 / 17.02	12.89 / 12.97	1695	207-208	91
8e	$C_{10}H_{12}N_6O_3S_2$	25.80 / 25.59	— / 19.53	1680	215-217	77
9a	$C_6H_9N_5O_2S_2$	28.03 / 28.32	26.4 / 25.93	1680	215-216	62
9b	$C_{10}H_{10}N_6OS_2$	28.42 / 28.55	22.0 / 21.79	1685	125-126	70

The structures of the compounds synthesized were confirmed by elemental analysis, ^{1}H NMR and IR spectroscopy.

EXPERIMENTAL

^{1}H NMR spectra were recorded with TMS as internal standard on Bruker WR-80 (80 MHz) and Bruker 250 (250 MHz) apparatus. IR spectra of KBr tablets were recorded with an IR-75 spectrometer. The course of reactions and the purity of products were monitored by TLC on Silufol UV-254 strips with the following solvent systems: chloroform, ethyl acetate–hexane (3:1), chloroform–ethanol (9:1), and chloroform–ethanol–25% ammonia (60:11:1). Melting points are uncorrected.

The starting 5-chloro-1,2,3-thiadiazoles **1a-e** were synthesized by known methods [8, 11, 15, 16] as were 5-mercapto-1,2,3-thiadiazoles [17] and mercaptoimidazoles [14].

General method for nucleophilic substitution. A. Mercaptoheterocycle (10 mmol) was added to solution of 5-chloro-1,2,3-thiadiazole **1a-e** (10 mmol) in DMF (3 ml). The reaction mixture was stirred magnetically at 20-40°C. The end of the reaction was determined by disappearance of the starting materials by TLC. The product was precipitated with water (100 ml), filtered and recrystallized from ethanol.

B. Mercaptoheterocycle (10 mmol) was added to solution of 5-chloro-1,2,3-thiadiazole (10 mmol) in solution of sodium ethoxide prepared from sodium (230 mg, 10 mmol) in ethanol (50 ml). The reaction mixture was stirred magnetically at 30-70°C. The end of the reaction was determined by disappearance of the starting materials by TLC. The precipitate was filtered off and recrystallized from ethanol.

C. Mercaptoheterocycle (10 mmol) and sodium carbonate (0.84 g, 10 mmol) were added to solution of 5-chloro-1,2,3-thiadiazole **1a-e** (10 mmol) in acetonitrile (80 ml). The reaction mixture was stirred magnetically at 20-40°C. The end of the reaction was determined by disappearance of the starting materials by TLC. The product was precipitated with water (100 ml), filtered off, and recrystallized from ethanol.

D. Mercaptoheterocycle (10 mmol) and triethylamine (0.72 ml, 10 mmol) were added to solution of 5-chloro-1,2,3-thiadiazole **1a-e** (10 mmol) in acetonitrile (80 ml) or ethanol (80 ml). The reaction mixture was stirred magnetically at 20-40°C. The end of the reaction was determined by disappearance of the starting materials by TLC. The reaction mixture was evaporated to dryness and the residue was recrystallized from ethanol.

This work was carried out with financial support from the Russian Fund for Fundamental Research (grant 98-03-33045-a).

REFERENCES

1. Al. Gommaa and M. Selhdar, *Alexandria J. Pharm. Sci.,* **5**, 153 (1991).
2. E. W. Tomas, *Comprehensive Heterocyclic Chemistry,* **2**, Ed. by A. R. Katritzky, C. W. Rees, and E. F. Scriven, **4**, 289 (1996).
3. E. G. Lebel, J. A. Ryals, L. Tharne, S. J. Uknes, and E. R. Ward, US Pat W098 03536; *Chem. Abstr.,* **128**, 137192 (1998).
4. F. Halgand, F. Vives. J.-P. Dumas, R. Cantegril, J. Gagnon, R. Douce, E. Forest, and D. Job, *Biochemistry,* **34**, 4773 (1998).
5. L. C. Blaszczak, C. N. Eid, J. Flokowitsch, G. S. Gregory, S. A. Hitchock, G. W. Huffman, D. R. Mayhuhg, M. J. Nesler, D. A, Preston, and M. Zia-Ebrahimi, *Bioorg. Med. Chem. Lett.,* **7**, 2261 (1997).
6. T. Kobori, T. Hirada, M. Fujita, S. Kondo, T. Asada, S. Ono, and H. Tsuboi, Jpn. Pat. 09249665; *Chem. Abstr.,* **127**, 278196 (1998).
7. Yu. Yu. Morzherin, V. A. Bakulev, E. F. Dankova, and V. S. Mokrushin, *Khim. Geterotsikl. Soedin.,* 548 (1994).

8. E. V. Tarasov, Yu. Yu. Morzherin, N. N. Volkova , and V. A. Bakulev, *Khim. Geterotsikl. Soedin.,* 1124 (1996).
9. V. A. Bakulev, E. V. Tarasov, Yu. Yu. Morzherin. S. Toppet, and W. Dehaen, *Bull. Soc. Chim. Belg.,* **106**, 643 (1997).
10. E. V. Tarasov, Yu. Yu. Morzherin, S. Toppet, W. Dehaen, and V. A. Bakulev, *J. Chem. Res.,* **11**, (S) 396, (M) 2472 (1997).
11. V. A. Bakulev, E. V. Tarasov, Yu. Yu. Morzherin, I. Lutyen, S. Toppet, and W. Dehaen, *Tetrahedron,* **54**, 8501 (1998).
12. G. L'abbe, P. Delbeke, L. Bastin, W. Dehaen, and S. Toppet, *J. Heterocycl. Chem.,* **30**, 301 (1993).
13. M. J. S. Dewar and E. G. Zoebisch, *Theochem.,* **49**, 1 (1988).
14. V. S. Mokrushin, *Diss. Dr. Sc. (Chem.)*, Moscow (1985).
15. J. Goerdeler and G. Gnad, *Chem. Ber.,* **99**, 1618 (1966).
16. Yu. Yu. Morzherin, E. V. Tarasov, and V. A. Bakulev, *Khim. Geterotsikl. Soedin.,* 554 (1994).
17. V. A. Bakulev, *Diss. Dr. Sc. (Chem.)*, Moscow (1990).