Russian Journal of General Chemistry, Vol. 72, No. 11, 2002, pp. 1709–1713. Translated from Zhurnal Obshchei Khimii, Vol. 72, No. 11, 2002, pp. 1813–1817.

Dedicated to the centenary of Academician A.V. Kirsanov's birthday

A Convenient Route to New 4,5-Dimercapto-1,3-thiazole Derivatives

S. B. Babii, V. S. Zyabrev, and B. S. Drach

Institute of Bioorganic and Petroleum Chemistry, National Academy of Sciences of Ukraine, Kiev, Ukraine

Received January 8, 2002

Abstract — A series of 2-X-4-tosyl-5-chloro-1,3-thiazoles (X = OH, OAlk, SH, SAlk, NH_2, NHAlk, $NAlk_2$, NHAr, etc.) were prepared from accessible 1-tosyl-2,2-dichloroethenyl isothiocyanate. Only some of these compounds containing a moderately labile hydrogen atom peculiarly react with thiophenols in the presence of triethylamine to give 4,5-di(arylthio)-2-(hydroxy- or arylamino)-1,3-thiazoles, which are difficult to prepare by other routes. It is quite possible that, in the course of nucleophilic substitution of the chlorine atom and tosyl residue by the corresponding arylthio groups, a significant role is played by nonaromatic tautomeric forms of functionally 2-substituted 1,3-thiazoles formed by proton transfer to positions 3 and 5 of the heteroring.

We have shown recently that the accessible polycentered electrophilic agent, 1-tosyl-2,2-dichloroethenyl isothiocyanate **I**, is an indispensable synthetic precursor of a number of 4-tosyl-5-chloro-1,3-thiazole derivatives containing various functional groups in position 2 (compounds **II**–**V** in Scheme 1). A systematic study of the lability of chlorine and tosyl group in these compounds with respect to substitution by arylthiolate ions suggested the possibility of formation of eight types of 4,5-dimercapto-1,3-thiazole derivatives, **VI**–**XIII**; however, only five of them (**VII**, **VIII**, and **X**–**XII**) were actually prepared. It should be primarily noted that, among diverse 2-amino-4-tosyl-5-chloro-1,3-thiazole derivatives **II**, only some of compounds containing aryl residues at the exocyclic nitrogen atom readily react with thiophenols on heating in ethanol in the presence of triethylamine. The regioselective transformation **II** → **VI** could be performed in none of the cases, as at the equimolar ratio of the reactants only 2-arylamino-4,5-di(arylthio)-1,3-thiazoles **X** were obtained, though in a low yield. Similar results were obtained with 2-hydroxy-4-tosyl-5-chloro-1,3-thiazole for which the 3*H*-thiazolone tautomer **III** is major. Its reaction with thiophenols in the presence of triethylamine at the reactant molar ratios of 1 : 1 : 1 and 1 : 2 : 2 yielded exclusively compounds **VII**. It is interesting that compound **IV,** which is the *N*-methyl analog of **III**, reacts with thiophenols differently. Even with an excess of thiophenols, only the chlorine atom is substituted, and the tosyl group is not involved (cf. transformations **III** → **VII** and **IV** → **VIII**).

The structure of **VII** and **VIII** is confirmed by the ^{1}H NMR spectra (Table 1) and by the transformations **VIIa** → **XIa** → **XII** and **IV** → **VIIIa** → **XII**, which led to the same product, 3-methyl-4,5-ditosyl-1,3-thiazol-2(3*H*)-one (Scheme 1).

It should be noted that, in contrast to **III**, its thione analog **V** does not react under mild conditions with arylthiolate anions and is therefore unsuitable for preparing 2,4,5-trimercapto-1,3-thiazole derivatives **IX** and **XIII**.

Thus, the applicability of the new route to 4,5-dimercapto-1,3-thiazole derivatives is apparently limited owing to specific features of nucleophilic substitution of readily leaving groups at the C^4 and C^5 centers of the thiazole ring. To interpret these features, it is useful to consider not only the aromatic tautomer $\mathbf{A^1}$ of the starting compounds but also their nonaromatic forms $\mathbf{B^1}$ and $\mathbf{C^1}$ (Scheme 2).

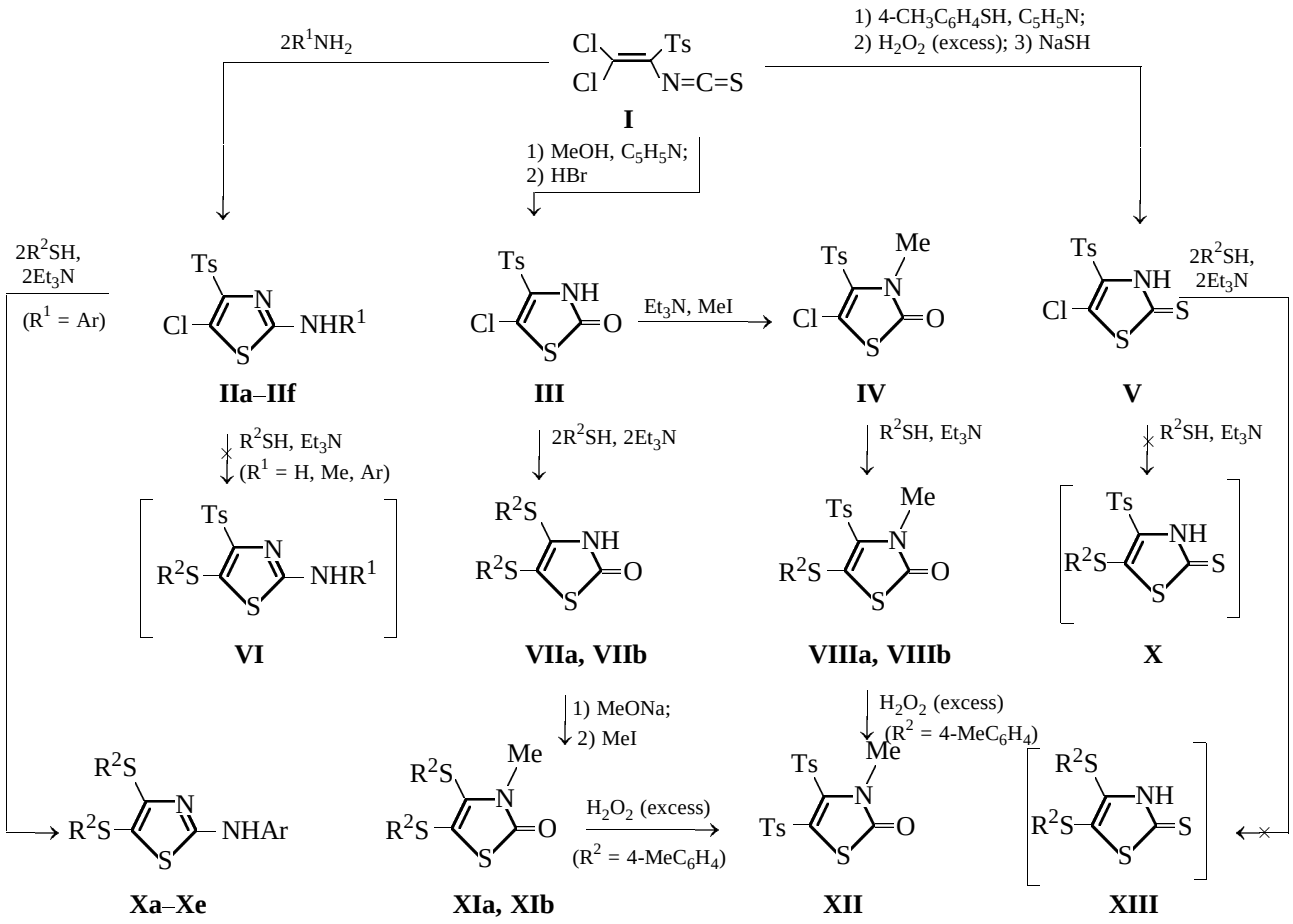
The nucleophilic substitution of chlorine at the C^5 center can hardly occur by the $\mathbf{A^1} \rightarrow \mathbf{A^2}$ pathway, as similar compounds ($\mathbf{A^3}$) with X = O, S, and PhN appeared to be relatively inert toward arylthiolate ions. The fairly low reactivity of the $\mathbf{C^5}$ center in the related structures $\mathbf{A^1}$ and $\mathbf{A^3}$ is apparently due to the conjugation of this center with the lone electron pairs of the exocyclic O, S, or N atom at the 2-position of the ring. The activating effect of the tosyl group at the adjacent $\mathbf{C^4}$ center is undoubtedly less pronounced. At the same time, in the cyclamide tautomer $\mathbf{B^1}$, identified in many cases [2], the C^5 atom exhibits pronounced electrophilic properties; therefore, the nucleo-

1070-3632/02/7211-1709 $27.00 © 2002 MAIK "Nauka/Interperiodica"

Table 1. IR and ^{1}H NMR data for new 1,3-thiazole derivatives **II, IV, VII, VIII**, and **X**–**XII**

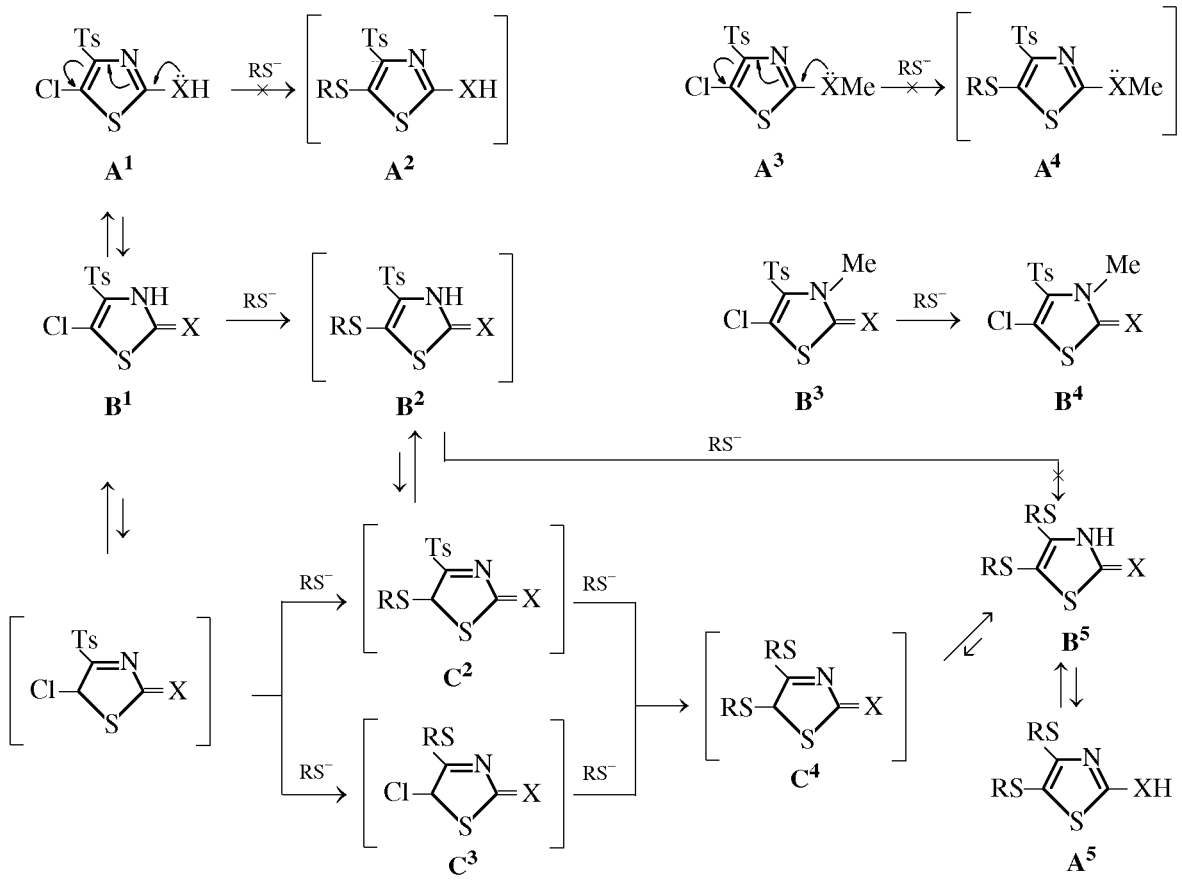
Comp. no.	IR spectrum, ν, cm^{-1}	^{1}H NMR spectrum, δ, ppm (solvent)
IIc	1150, 1325 (SO_2), 3390 (NH)	2.42 s (3H, CH_3), 7.53–8.25 m (8H, ArH), 11.33 s (1H, NH) (DMSO-d_6)
IV	1160, 1340 (SO_2), 1690 (CO)	2.48 s (3H, C$H_3C_6H_4$), 3.47 s (3H, CH_3N), 7.40 d (2H, ArH), 7.85 d (2H, ArH) ($CDCl_3$)
VIIa	1690 (CO), 3390 (NH)	2.34 s (3H, CH_3), 2.36 s (3H, CH_3), 7.12–7.34 m (8H, ArH), 7.93 s (1H, NH) ($CDCl_3$)
VIIIa	1150, 1325 (SO_2), 1685 (CO)	2.39 s (3H, C$H_3C_6H_4$), 2.48 s (3H, C$H_3C_6H_4$), 3.35 s (3H, CH_3N), 7.20–7.47 m (6H, ArH), 7.93 d (2H, ArH) ($CDCl_3$)
Xa	3400 (NH)	2.30 s (6H, CH_3), 7.03–7.33 m (13H, ArH), 7.77 s (1H, NH) ($CDCl_3$)
Xd	3400 (NH)	2.28 s (3H, CH_3), 2.37 s (3H, CH_3), 7.19–7.56 m (10H, ArH), 8.04 d (2H, ArH), 11.15 s (1H, NH) (DMSO-d_6)
XIa	1660 (CO)	2.32 s (3H, C$H_3C_6H_4$), 2.33 s (3H, C$H_3C_6H_4$), 3.25 s (3H, CH_3N), 7.07–7.28 m (8H, ArH) ($CDCl_3$)
XII	1130, 1320 (SO_2), 1660 (CO)	2.43 s (3H, C$H_3C_6H_4$), 2.46 s (3H, C$H_3C_6H_4$), 3.26 s (3H, CH_3N), 7.49–7.92 m (8H, ArH) (DMSO-d_6)

Scheme 1.



R^1 = C_6H_5 (**IIa**), 4-$CH_3C_6H_4$ (**IIb**), 4-$NO_2C_6H_4$ (**IIc**), 2-naphthyl (**IId**), CH_3 (**IIe**), H (**IIf**); R^2 = 4-$CH_3C_6H_4$ (**VIIa, VIIIa, Xa, Xd, Xe, XIa**), 4-ClC_6H_4 (**VIIb, VIIIb, Xb, Xc, XIb**); Ar = C_6H_5 (**Xa, Xb**), 4-$CH_3C_6H_4$ (**Xc**), 4-$NO_2C_6H_4$ (**Xd**), 2-naphthyl (**Xe**).

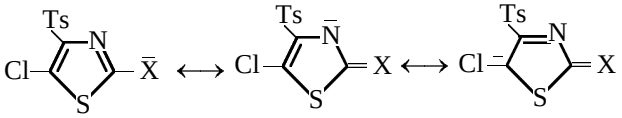
Scheme 2.



X = O, S, NH, AlkN, ArN, NAc.

philic substitution of chlorine by the pathway $\mathbf{B^1} \rightarrow \mathbf{B^2}$ should occur even under mild conditions, which was proved experimentally by the model transformation $\mathbf{B^3} \rightarrow \mathbf{B^4}$. It should be noted that, in structure $\mathbf{B^3}$ and hence in $\mathbf{B^1}$, the tosyl group at C^4 shows no noticeable lability; therefore, to account for ready elimination of this group, we should give attention to tautomers $\mathbf{C^1}$ and $\mathbf{C^2}$, usually disregarded when considering tautomeric equilibria in functionally 2-substituted 1,3-thiazoles (cf. [2]). On the contrary, in cyclic enamides, such *N*-acylimine forms have been identified, and their significant role in manifestation of specific properties of secondary enamides is beyond doubt [3]. Since the $\mathbf{B^1}$ structure contains an enamide fragment, the equilibrium $\mathbf{B^1} \rightleftarrows \mathbf{C^1}$ is quite possible, though it is, apparently, strongly shifted toward $\mathbf{B^1}$. Since the $\mathbf{C^1}$ form is highly electrophilic, even its small content can be sufficient for the occurrence of nucleophilic substitution of the labile tosyl group at the C=N bond. Indeed, such a substitution was recently proved for acyclic analogs of $\mathbf{C^1}$ [4]. The choice between the alternative pathways $\mathbf{C^1} \rightarrow \mathbf{C^2} \rightarrow \mathbf{C^4}$ and $\mathbf{C^1} \rightarrow \mathbf{C^3} \rightarrow \mathbf{C^4}$ cannot be made without special studies, since both the tosyl residue and the chlorine atom at the $\mathbf{C^4}$ and $\mathbf{C^5}$ centers of $\mathbf{C^1}$ should be highly nucleophilic.

Thus, the prototropy plays, apparently, an important role in the complex transformation $\mathbf{A^1} \rightarrow \ldots \rightarrow \mathbf{A^5}$. At the same time, too high acidity of $\mathbf{A^1}$ can have an adverse effect on its reactivity. Although formation of tautomers $\mathbf{B^1}$ and $\mathbf{C^1}$ remains possible, the action of a base can result in formation of a stable mesomeric anion (see below) whose reactivity toward nucleophilic agents is low.



It is quite probable that this fact is responsible for different behavior toward arylthiolate anions of similar representatives of $\mathbf{A^1}$ and $\mathbf{B^1}$ with X = O, S, NAr,

Table 2. Yields, melting points, and elemental analyses of new 1,3-thiazole derivatives **II, IV, VII, VIII**, and **X**–**XII**

Comp. no.	Yield, %	mp, °C (solvent for recrystallization)	Found, %		Formula	Calculated, %	
			Cl	S		Cl	S
IIc	85	220–222 (ethanol–acetonitrile)	8.62	15.63	$C_{16}H_{12}ClN_3O_4S_2$	8.65	15.65
IId	95	140–142 (ethanol)	8.50	15.39	$C_{20}H_{15}ClN_2O_2S_2$	8.54	15.46
IV	65	120–122 (ethanol)	11.65	21.04	$C_{11}H_{10}ClNO_3S_2$ [a]	11.67	21.11
VIIa	36	154–155 (ethanol)	–	27.72	$C_{17}H_{15}NOS_3$	–	27.84
VIIb	53	177–178 (ethanol)	18.20	24.83	$C_{15}H_9Cl_2NOS_3$	18.35	24.90
VIIIa	91	169–170 (ethanol–acetonitrile)	–	24.52	$C_{18}H_{17}NO_3S_3$	–	24.57
VIIIb	88	156–158 (acetonitrile)	8.64	23.38	$C_{17}H_{14}ClNO_3S_3$	8.61	23.35
Xa	93	110–112 (ethanol)	–	22.83	$C_{23}H_{20}N_2S_3$	–	22.87
Xb	75	134–136 (acetonitrile)	15.30	20.86	$C_{21}H_{14}Cl_2N_2S_3$	15.37	20.85
Xc	96	150–151 (ethanol)	15.00	20.28	$C_{22}H_{16}Cl_2N_2S_3$	14.91	20.23
Xd	70	198–200 (ethanol–acetonitrile)	–	20.70	$C_{23}H_{19}N_3O_2S_3$ [b]	–	20.66
Xe	69	126–127 (acetonitrile)	–	20.37	$C_{27}H_{22}N_2S_3$	–	20.44
XIa	65	88–89 (ethanol)	–	26.80	$C_{18}H_{17}NOS_3$	–	26.76
XIb	77	94–96 (ethanol)	17.70	23.98	$C_{16}H_{11}Cl_2NOS_3$ [c]	17.71	24.03
XII	79[d]	215–216 (acetonitrile)	–	22.74	$C_{18}H_{17}NO_5S_3$ [e]	–	22.71

[a] Found, %: C 43.76; H 3.39. Calculated, %: C 43.49; H 3.32. [b] Found N, %: 9.07. Calculated N, %: 9.03. [c] Found, %: C 48.60; H 2.80. Calculated, %: C 48.00; H 2.77. [d] Yield by the reaction **VIIIa** → **XII**; yield by the reaction **XIa** → **XII** 50%. [e] Found, %: C 51.11; H 4.10. Calculated, %: C 51.04; H 4.05.

NAc (see Experimental). All these features appreciably limit the applicability of the suggested route to new 4,5-dimercapto-1,3-thiazole derivatives; nevertheless, its application sphere is wider than shown in Scheme 1.

EXPERIMENTAL

The IR spectrum of **XII** was taken on a UR-20 spectrometer (KBr pellet), and those of the other compounds, on a Specord IR-71 spectrometer (CH_2Cl_2 solutions). The ^1H NMR spectra were recorded on a Varian VXR-300 spectrometer, internal reference TMS. The yields, melting points, and analytical data for the new compounds are given in Table 2.

1-Tosyl-2,2-dichloroethenyl isothiocyanate I, 2-amino(methylamino, *p*-tolylamino, phenylamino)-4-tosyl-5-chloro-1,3-thiazoles IIa, IIb, IIe, and IIf, 4-tosyl-5-chloro-1,3-thiazol-2(3*H*)-one III, and 4-tosyl-5-chloro-1,3-thiazole-2(3*H*)-thione V were prepared as described in [1, 5].

2-*p*-Nitrophenylamino-4-tosyl-5-chloro-1,3-thiazole IIc. A mixture of 10 mmol of isothiocyanate **I**, 20 mmol of *p*-nitroaniline, and 10 ml of acetonitrile was stirred at 20–25°C for 48 h; the precipitate was filtered off and washed with ethanol.

2-(2-Naphthylamino)-4-tosyl-5-chloro-1,3-thiazole IId. A solution of 20 mmol of 2-naphthylamine in 5 ml of ethanol was added with stirring over a period of 10 min to a suspension of 10 mmol of **I**, cooled to 10–15°C. The mixture was stirred at 20–25°C for 24 h, and the precipitate was filtered off and washed with ethanol.

3-Methyl-4-tosyl-5-chloro-1,3-thiazol-2(3*H*)-one IV. Methyl iodide, 7.1 mmol, was added to a solution of 7.1 mmol of **III** and 7.1 mmol of triethylamine in 16 ml of methanol. The mixture was stirred at 20–25°C for 72 h, and the precipitate was filtered off.

4,5-Di(arylthio)-1,3-thiazol-2(3*H*)-ones VIIa and VIIb. A mixture of 3.4 mmol of **III**, 6.9 mmol of *p*-thiocresol or *p*-chlorothiophenol, and 10.5 mmol of triethylamine in 10 ml of ethanol was refluxed for 6 h and then cooled to 20–25°C; 1 ml of concentrated HCl was added, and the precipitate was filtered off and washed with water and ethanol.

3-Methyl-4-tosyl-5-arylthio-1,3-thiazol-2(3*H*)-ones VIIIa and VIIIb. A mixture of 1.1 mmol of **IV**, 1.1 mmol of appropriate thiol, and 1.1 mmol of triethylamine in 4 ml of ethanol was refluxed for 1 h and then cooled to 20–25°C; the precipitate was filtered off and washed with ethanol.

Action of thiols on 2-amino(methylamino, arylamino)-4-tosyl-5-chloro-1,3-thiazoles II. A mixture of 1.3 mmol of **IIa**–**IId**, 2.6 mmol of *p*-thiocresol or

p-chlorothiophenol, and 2.6 mmol of triethylamine in 5 ml of ethanol was refluxed for 6 h and then cooled to 20–25°C; the precipitate was filtered off and washed with ethanol. 2-Arylamino-4,5-di(arylthio)-1,3-thiazoles **Xa**–**Xe** were obtained. The reactions of **IIe** and **IIf** with excess *p*-thiocresol yielded no expected products **VI** and **X**.

Reactions of *p*-thiocresol with 2-methoxy-4-tosyl-5-chloro-1,3-thiazole [1], 2-methylthio-4-tosyl-5-chloro-1,3-thiazole [1], and 2-[methyl(phenyl)amino]-4-tosyl-5-chloro-1,3-thiazole [1]. A mixture of 1.3 mmol of one of the above 1,3-thiazole derivatives, 2.6 mmol of *p*-thiocresol, and 2.6 mmol of triethylamine in 5 ml of ethanol was refluxed for 6 h and then cooled to 20–25°C; the starting compounds were recovered in 60–80% yields.

Acetylation of 2-amino-4-tosyl-5-chloro-1,3-thiazole IIf and reaction of the acetylation product with *p*-thiocresol. A mixture of 5 mmol of **IIf** and 5 ml of acetic anhydride was refluxed for 1 h and then cooled to 20°C; the precipitate was filtered off and dried at 100°C. Analytically pure 2-acetylamino-4-tosyl-5-chloro-1,3-thiazole was obtained; yield 83%, mp 228°C. IR spectrum (KBr), ν, cm^{-1}: 1670 (CO), 3160 (NH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.13 s (3H, CH_3CO), 2.41 s (3H, $CH_3C_6H_4$), 7.48 d (2H, ArH), 7.83 d (2H, ArH), 12.85 s (1H, NH). Found, %: C 43.46; H 3.41; Cl 10.70; S 19.35. $C_{12}H_{11}ClN_2O_3S_2$. Calculated, %: C 43.57; H 3.35; Cl 10.72; S 19.39.

A solution of 2 mmol of this compound and 2 mmol of *p*-thiocresol in 3 ml of pyridine was refluxed for 1 h and then cooled to 20–25°C; the starting 2-acetylamino-4-tosyl-5-chloro-1,3-thiazole was recovered in 62% yield.

Reaction of *p*-thiocresol with 4-tosyl-5-chloro-1,3-thiazole-2(3*H*)-thione V. A solution of 2 mmol of **V**, 4 mmol of *p*-thiocresol, and 4 mmol of triethylamine in 5 ml of ethanol was refluxed for 6 h and then cooled to 20–25°C; 1 ml of concentrated HCl was added. The starting compound **V** was recovered in 55% yield.

3-Methyl-4,5-di(arylthio)-1,3-thiazol-2(3*H*)-ones XIa and XIb. Methyl iodide, 1 mmol, was added to a solution of 1 mmol of **VIIa** and **VIIb** and 1 mmol of sodium methylate in 10 ml of methanol. The mixture was stirred for 72 h at 20–25°C, 3 ml of water was added, and the precipitate was filtered off and washed with water.

3-Methyl-4,5-ditosyl-1,3-thiazol-2(3*H*)-one XII. A mixture of 1.2 mmol of **VIIIa** or **XIa**, 1 ml of 30% aqueous hydrogen peroxide, and 5 ml of acetic acid was refluxed for 2 h and then cooled to 20–25°C. The precipitate was filtered off and washed with water and ethanol.

REFERENCES

1. Babii, S.B., Zyabrev, V.S., and Drach, B.S., *Zh. Obshch. Khim.*, 2002, vol. 72, no. 11, p. 1834.
2. Elguero, J., Marzin, C., Katritzky, A.R., and Linda, P., *The Tautomerism of Heterocycles*, New York: Academic, 1976, pp. 359–361, 396–400, 425–429.
3. Shainyan, B.A. and Mirskova, A.N., *Usp. Khim.*, 1979, vol. 48, no. 2, p. 201.
4. Babii, S.B., Zyabrev, V.S., and Drach, B.S., *Zh. Obshch. Khim.*, 2001, vol. 71, no. 4, p. 688.
5. Kharchenko, A.V., Seferov, S.O., Zyabrev, V.S., Chervonyi, V.A., Vdovenko, S.I., and Drach, B.S., *Ukr. Khim. Zh.*, 1993, vol. 59, no. 6, p. 637.