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Reaction of 1-Tosyl-2,2-dichloroenamines with the Lawesson's Reagent

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Abstract—In the reaction of the available 1-tosyl-2,2-dihlorenamides with the Lawesson's reagent the derivatives of 4-tosyl-1,3-thiazole were shown to form containing a labile chlorine atom at the C^5 position. This fact was used for the synthesis of a number of the previously unknown bifunctionally substituted 4,5-thiazoles.

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Previously we studied the reaction of the enamides of type **I** with the highly basic amines [1] and sodium hydrosulfide [2], which leads to the derivatives of 5-amino-5-mercaptooxazole, the agonists of 5-NT6 receptors [3].

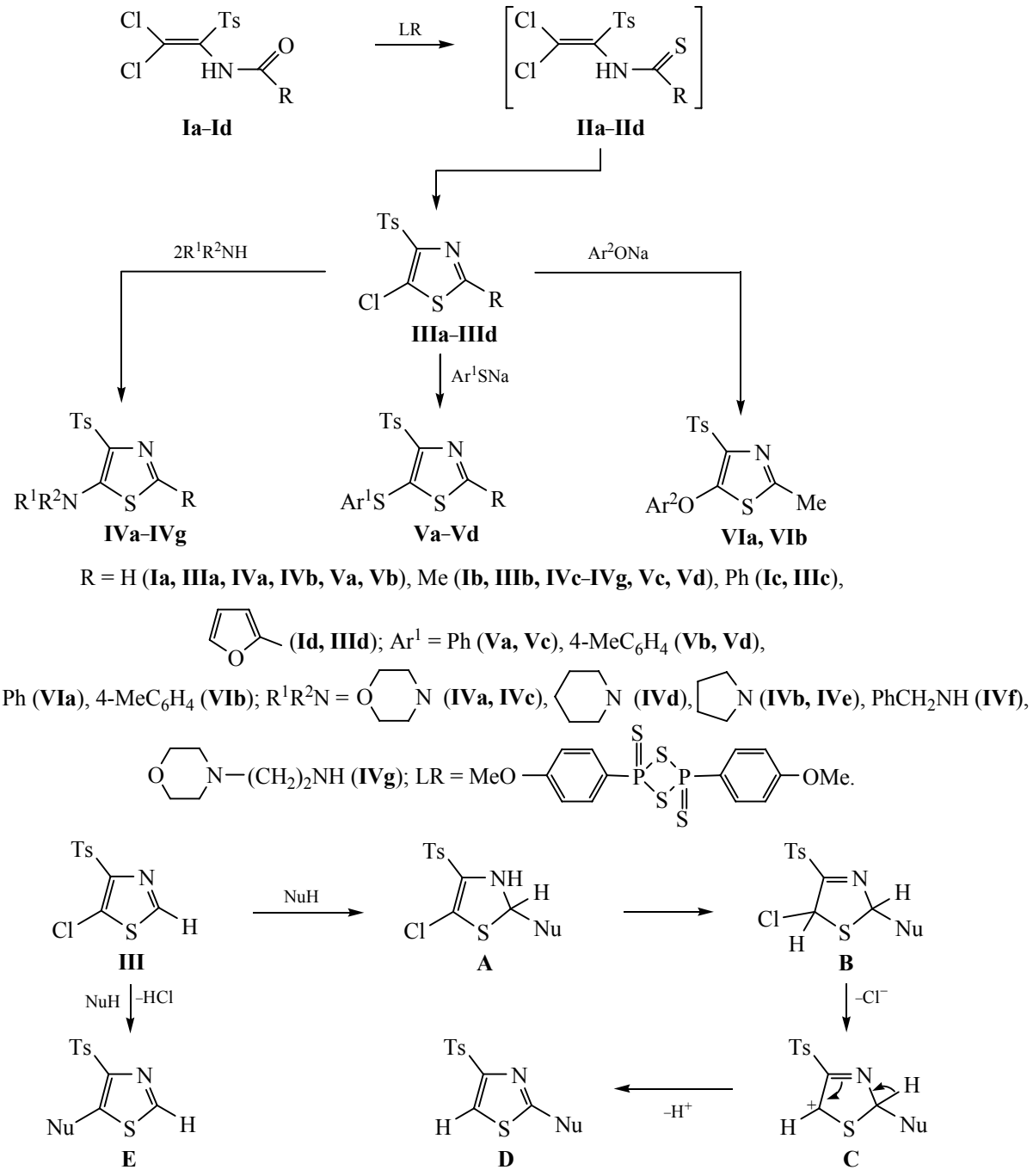
In this work we for the first time studied the interaction of the enamides **I** with the Lawesson's reagent leading to the 2-R-4-tosyl-5-chloro-1,3-thiazole derivatives **III**. The chlorine atom in compounds **III** shows significant lability towards the action of the highly basic amines, sodium phenolate, and thiophenoxides, undoubtedly due to the influence of electron-acceptor groups in the vicinal position to the halogen atom. The nature of the agent used as a rule does not affect the course of this reaction, the reaction products **IV–VI** can be isolated in a high yield (Scheme 1).

Note that at the interaction of the thiazole **IIIa** unsubstituted in 2 position with the secondary amines and sodium tiophenoxides the replacement of the halogen atom occurs under the milder conditions and in a shorter time, but with lower yields. The interaction of compound **IIIa** with the highly basic primary amines is also complicated. The result of these reactions is apparently due not only to the nucleophilic substitution of the chlorine atom. The reaction includes obviously some other processes that in the case of primary amines result in a mixture of unidentified products, so this reaction requires more detailed study. In addition, analysis of the published data [4] suggests that in such systems a nucleophile can attack the C^2 center of the heterocycle. In this case, a possible mechanism involves a sequence of reactions: addition of the nucleophile to the activated double bond of the heterocycle (**A**), prototropic transformation (**B**), and cleavage of the chloride anion (**C**) and proton (**D**).

The choice between two alternative structures (**D** and **E**) by means of NMR spectroscopy is difficult. We failed to accomplish identification also using the nuclear Overhauser effect, because the spatial arrangement of the tozyl group in the 4 and 5 sites and the rest of the nucleophile does not lead to the interaction between them in the NOE experiment, no effect was observed. Therefore, to prove the structure of the compounds **IV–VI** unambiguously, one of them (**Va**) was studied by the method of X-ray diffraction. The general view of the molecule **Va** and its main geometric parameters are shown in the figure.

Bond lengths in the central thiazole heterocycle are close to usual for such compounds. Thus, the CS bonds distances are equal, and the length of the C^1N^1 bond is close to that of the standard C=N double bond 1.28 Å, despite the conjugation in the heterocycle. The $C–S^1$ bonds are equal within experimental error, while the bonds $C–S^3$ are markedly not equivalent (see caption to the figure), apparently, because of a more efficient conjugation of the lone electron pair of the S^3 atom with the aromatic π-system of the thiazole ring. The thiazole ring is planar within 0.004 Å, and the atoms S^1 and S^3 deviate from this plane at –0.059 and –0.023 Å, respectively. Phenyl rings $C^{4–9}$ and $C^{11–16}$ are turned by

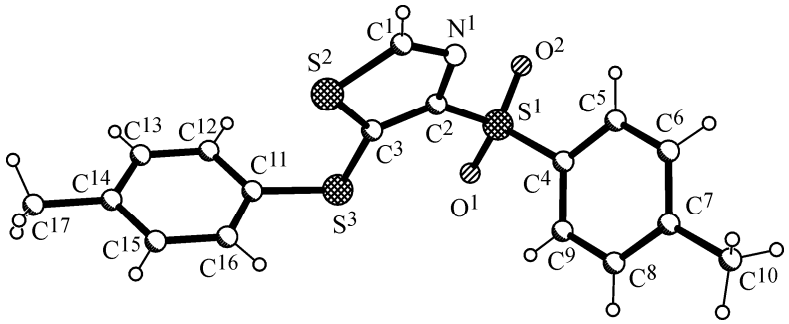
Scheme 1.



96.6° and 95.4°, respectively, with respect to the thiazole mean plane. No other special features were found in the structure of the molecule.

For the introduction of alkylthio group to the 5 position of the thiazole ring it is more convenient to use the approach shown by Scheme 2. Thus, initially compound **IIIb** under the action of excess sodium hydrogen sulfide is transformed into 5-mercaptothiazole derivative **VII**, which is regioselectively alkylated at the sulfur atom to form thiazoles **VIII**.

The structure of the compounds shown in Schemes 1 and 2 not only directly follow from the method of their synthesis, but also were confirmed by elemental analysis (Table 1), and ^{1}H NMR spectra (Table 2). Thus, the reaction of compounds **I** with the Lawesson's reagent actually proceeds with the participation



General view of the molecule **Va** and selected bond lengths and angles: C^1S^2 1.723(3), C^3S^2 1.723(2), C^1N^1 1.299(3), C^2N^1 1.385(3), C^2C^3 1.371(3), C^2S^1 1.754(2), C^4S^1 1.759(2), C^3S^2 1.723(2), $C^{11}S^3$ 1.779(3) Å; $C^1S^2C^3$ 89.75(13), $N^1C^1S^2$ 115.9(2), $C^3C^2N^1$ 117.0(2), $C^1N^1C^2$ 109.0(2), $C^2C^3S^2$ 108.24(18), $C^2S^1C^4$ 103.21(11), $C^3S^3C^{11}$ 101.47(12)°.

of acylamino residues, as evidenced by the disappearance of the NH group signal characteristic of the starting materials. In addition, the data of the elemental analysis on sulfur, chlorine and nitrogen are indicative. Also compound **IIIc** was synthesized previously by another method [5], which leaves no doubt in its structure. Introduction of R^1R^2N, ArS, AlkS, and ArO to the C^5 center of the thiazole ring at the formation of compounds **IV–VIII** is confirmed by the presence in the ^1H NMR spectra of appropriate signals with the corresponding integral intensity.

Thus, the method we developed for the synthesis of substituted thiazoles **III–VIII** not only supplements, but also simplifies the well-known one [5, 6], which involves the use of 1-aryl-3-tosyl-1,4,4-trichloro-2-aza-1,3-dienes less accessible than compounds **I** and does not allow the introduction of a hydrogen atom, alkyl, and heterocyclic substituents in 2 position of the thiazole ring. Another recent publication [7] on the synthesis of 4-tosyl-5-chloro-1,3-thiazoles also concerns only the compounds with aryl substituents at the 2 position of the thiazole ring.

Table 1. Yields, constants, and elemental analysis data of compounds **III–VIII**

Comp. no.	Yield, %	mp, °C [a]	Found, %		Formula	Calculated, %	
			Cl(N)	S		Cl(N)	S
IIIa	76	164–165	12.91	23.35	$C_{10}H_8ClNO_2S_2$	12.95	23.42
IIIb	82	130–131	12.37	22.12	$C_{11}H_{10}ClNO_2S_2$	12.32	22.28
IIIc	87	150–151 [b]	10.01	18.26	$C_{16}H_{12}ClNO_2S_2$	10.13	18.33
IIId	79	142–143	10.32	18.63	$C_{14}H_{10}ClNO_3S_2$	10.43	18.87
IVa	63	174–175	(8.73)	19.64	$C_{14}H_{16}N_2O_3S_2$	(8.63)	19.77
IVb	65	158–159	(8.89)	20.72	$C_{14}H_{16}N_2O_2S_2$	(9.08)	20.79
IVc	59	140–141	(8.11)	18.79	$C_{15}H_{18}N_2O_3S_2$	(8.28)	18.95
IVd	70	138–140	(8.24)	19.12	$C_{16}H_{20}N_2O_2S_2$	(8.33)	19.06
IVe	68	136–138	(8.57)	19.73	$C_{15}H_{18}N_2O_2S_2$	(8.69)	19.89
IVf	60	113–115	(7.65)	17.75	$C_{18}H_{18}N_2O_2S_2$	(7.81)	17.89
IVg	64	145–146	(10.89)	16.76	$C_{17}H_{23}N_3O_3S_2$	(11.01)	16.81
Va	62	145–146	(3.97)	27.54	$C_{16}H_{13}NO_2S_3$	(4.03)	27.68
Vb	64	179–180	(3.76)	26.58	$C_{17}H_{15}NO_2S_3$	(3.87)	26.61
Vc	59	120–121	(3.65)	26.57	$C_{17}H_{15}NO_2S_3$	(3.87)	26.61
Vd	61	138–139	(3.61)	25.65	$C_{18}H_{17}NO_2S_3$	(3.73)	25.61
VIa	68	101–103	(3.79)	18.22	$C_{17}H_{15}NO_3S_2$	(4.05)	18.56
VIb	75	118–119	(3.79)	17.79	$C_{18}H_{17}NO_3S_2$	(3.90)	17.84
VII	54	100–104 [c]	(4.83)	33.91	$C_{11}H_{11}NO_2S_3$	(4.91)	33.70
VIIIa	85	158–159	(3.59)	25.24	$C_{18}H_{17}NO_2S_3$	(3.73)	25.61
VIIIb	87	145–106	(3.32)	24.43	$C_{19}H_{19}NO_2S_3$	(3.60)	24.69

[a] After recrystallization from ethanol. [b] Corresponds to published data [5]. [c] Without further purification.

Table 2. ^{1}H NMR spectra of the synthesized compounds **III–VIII**

Comp. no.	δ, ppm ($CDCl_3$)
IIIa	2.45 s (3H, CH_3); 7.37 d, 7.99 d (4H, C_6H_4, J_{HH} 8.0 Hz), 8.63 s (1H, $CH_{thiaz.}$)
IIIb	2.45 s (3H, CH_3), 2.63 s (3H, CH_3); 7.36 d, 7.98 d (4H, C_6H_4, J_{HH} 8.0 Hz)
IIId	2.44 s (3H, CH_3), 6.54 s (1H_{furan}), 7.10 d (1H_{furan}, J_{HH} 4.0 Hz); 7.36 d, 8.00 d (4H C_6H_4, J_{HH} 8.5 Hz), 7.50 s (1H_{furan})
IVa	2.44 s (3H, CH_3), 3.19 s (4H, 2CH_2), 3.90 s (4H, 2CH_2); 7.33 d, 7.94 d (4H, C_6H_4, J_{HH} 7.0 Hz), 8.33 s (1H, $CH_{thiaz.}$)
IVb	2.04 s (4H, 2CH_2), 2.43 s (3H, CH_3), 3.57 s (4H, 2CH_2), 7.32 d, 7.89 d (4H, C_6H_4, J_{HH} 8.0 Hz), 7.85 s (1H, $CH_{thiaz.}$)
IVc	2.43 s (3H, CH_3), 2.58 s (3H, CH_3), 3.05 s (4H, 2CH_2), 3.85 s (4H, 2CH_2); 7.31 d, 7.95 d (4H, C_6H_4, J_{HH} 8.0 Hz)
IVd	1.57 m (2H, CH_2), 1.73 m (4H, 2CH_2), 2.42 s (3H, CH_3), 2.57 s (3H, CH_3), 2.98 m (4H, 2CH_2); 7.30 d, 7.95 d (4H, C_6H_4, J_{HH} 8.0 Hz)
IVe	1.99 s (4H, 2CH_2), 2.42 s (3H, CH_3), 2.46 s (3H, CH_3), 3.48 s (4H, 2CH_2); 7.29 d, 7.88 d (4H, C_6H_4, J_{HH} 8.0 Hz)
IVf	2.42 s (3H, CH_3), 2.56 s (3H, CH_3), 4.38–4.40 m (2H, CH_2), 7.18–7.84 m (9H, C_6H_5,C_6H_4)
IVg	2.42 s (3H, CH_3), 2.46 s (3H, CH_3), 2.57–2.78 m (6H, 3CH_2), 3.27 s (2H CH_2, 3.80 s (4H, 2CH_2); 7.30 d, 7.88 d (4H, C_6H_4, J_{HH} 8.0 Hz)
Va	2.45 s (3H, CH_3), 7.36–7.38 m (2$H_{arom.}$), 7.42–7.50 m (3$H_{arom.}$); 7.60 d, 8.04 d (4H, C_6H_4, J_{HH} 8.0 Hz), 8.45 s (1H, $CH_{thiaz.}$)
Vb	2.41 s (3H, CH_3), 2.46 s (3H, CH_3); 7.25 d, 7.37 d, (4H, C_6H_4, J_{HH} 8.0 Hz) 7.50 d, 8.05 d (4H, C_6H_4, J_{HH} 8.0 Hz), 8.41 s (1H,$CH_{thiaz.}$)
Vc	2.45 s (3H, CH_3), 2.50 s (3H, CH_3), 7.36–8.04 m (9H, C_6H_5, C_6H_4)
Vd	2.40 s (3H, CH_3), 2.45 s (3H, CH_3), 2.48 s (3H, CH_3), 7.22–8.04 m (8H, 2C_6H_4, J_{HH} 8.0 Hz)
VIa	2.44 s (3H, CH_3), 2.56 s (3H, CH_3), 7.30–7.38 m (5$H_{arom.}$); 7.32 d, 7.97 d (4H, C_6H_4, J_{HH} 8.0 Hz)
VIb	2.36 s (3H, CH_3), 2.44 s (3H, CH_3), 2.56 s (3H, CH_3); 7.00 d, 7.16 d (4H, C_6H_4, J_{HH} 8.0 Hz), 7.32 d, 7.97 d (4H, C_6H_4, J_{HH} 8.0 Hz)
VIIIa	2.44 s (3H, CH_3), 2.56 s (3H, CH_3), 4.18 c (2H, CH_2), 7.29–7.98 m (9H, C_6H_5,C_6H_4)
VIIIb	2.29 s (3H, CH_3), 2.39 s (3H, CH_3), 2.55 s (3H, CH_3), 4.29 s (2H, CH_2), 7.11–7.80 m (9H, C_6H_5, C_6H_4)

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Varian Mercury-400 spectrometer from $CDCl_3$ solution with internal reference TMS.

The X-ray diffraction study of a single crystal of compound **Va** with linear dimensions 0.06×0.23×0.25 mm was carried out at room temperature on a Bruker Smart Apex II diffractometer (λMoK_a radiation, graphite monochromator, θ_{max} 28.66°, a segment of the sphere $-16 \le h \le 16$, $-10 \le k \le 10$, $-21 \le l \le 22$). Totally 16933 reflections were collected, of which 4267 were independent (the averaging R-factor is 0.0658). The structure was solved by the direct method and refined by full-matrix least-squares in an anisotropic approximation using the programs SHELXS97 and SHELXL97 [8,9]. The correction for the extinction was introduced with the program SADABS by the multi-scanning method (T_{min}/T_{max} = 0.8955/0.9734). Hydrogen atoms were revealed and refined isotropically, except for the hydrogen atoms in the C^{10} methyl, which were localizd geometrically and their positions were refined by a *rider* model together with the carbon atom. In the refinement 2828 reflections were used with $I > 2\sigma(I)$, (256 refined parameters, number of reflections per parameter 11.0, a weight scheme was used, $\omega = 1/[\sigma^2(Fo^2) + (0.0420P)^2 + 0.5034P]$ where $P = (Fo^2 + 2Fc^2)/3$, the ratio of maximum (average) shift to the error in the final cycle is 0.001(0.000). The final divergence factors $R_1(F)$ = 0.0484, $wR_2(F^2)$ = 0.1002 for reflections with $I > 2\sigma(I)$, $R_1(F)$ = 0.0863, $wR_2(F^2)$ = 0.1151, GOF = 1.031 for all independent reflections. Residual electron density from the difference Fourier series after the final refinement cycle is 0.40 and –0.39 e Å^{-3}.

A complete set of X-ray data for compound **Va** is deposited in the Cambridge Structural Database (CCDC 812149).

4-Tosyl-5-chloro-1,3-thiazole (IIIa). To a solution of 0.0035 mol of compound **Ia** [1] in 50 ml of dioxane was added 0.0035 mol of Lawesson's reagent. The mixture was heated for 8 h at 100°C, the solvent was removed in a vacuum, to the residue was added 100 ml of saturated solution of sodium hydrogen carbonate, and the mixture was kept for 3 h at 20°C. The precipitated compound **IIIa** was filtered off and purified by recrystallization.

2-Methyl(phenyl, furan-2-yl)-4-tosyl-5-chloro-1,3-thiazoles IIIb–IIId were obtained like **IIIa** from the corresponding enamides **Ib–Id**.

5-Morpholino(pyrrolidino)-4-tosyl-1,3-thiazoles (IVa, IVb). To a solution of 0.001 mol of compound **IIIa** in 20 ml of THF was added 0.003 mol of morpholine (or pyrrolidine), the mixture was heated for 2 h at 60°C, the solvent was removed in a vacuum, to the residue was added 10 ml of water and the precipitated compound **IVa** or **IVb** was filtered off and purified by recrystallization.

2-Methyl-5-morpholino[piperidino, pyrrolidino, benzylamino, (4-morpholino)-2-ethylamino]-4-tosyl-1,3-thiazoles (IVc–IVg). To a solution of 0.001 mol of compound **IIIb** in 20 ml of *n*-butanol was added 0.005 mol of the corresponding nitrogen base, and the mixture was heated for 24 h at 120°C. Then the solvent was removed in a vacuum, to the residue 10 ml of water was added, the precipitate was filtered off. Compounds **IVc–IVg** were purified by recrystallization.

4-Tosyl-5-[phenyl(or *p*-tolyl)sulfanyl]-1,3-thiazoles (Va, Vb). To a solution of 0.001 mol of compound **IIIa** in 20 ml of THF was added 0.0011 mol of the corresponding sodium thiophenolate, and the mixture was left for 3 h at 20–25°C. Then the solvent was removed in a vacuum and 10 ml of water was added to the residue. The formed precipitate was filtered off, compounds **Va** and **Vb** thus obtained were purified by recrystallization.

2-Methyl-4-tosyl-5-[phenyl(or *p*-tolyl)sulfanyl]-1,3-thiazoles (Vc, Vd). To a solution of 0.0035 mol of compound **IIIb** in 20 ml of THF was added 0.0039 mol of the corresponding sodium thiophenolate and the mixture was heated for 4 h at 60°C. Then the solvent was removed in a vacuum and 10 ml of water was added to the residue. The formed precipitate of a compound **Vc** or **Vd** was filtered off and then purified by recrystallization.

2-Methyl-5-phenoxy(or *p*-tolyloxy)-4-tosyl-1,3-thiazoles (VIa, VIb). To a solution of 0.0035 mol of compound **IIIb** in 20 ml of THF was added 0.0039 mol of the corresponding sodium phenolate and the mixture was heated for 15 h at 60°C. Then the solvent was removed in a vacuum and to the residue was added 10 ml of water. The precipitste of a compound **VIa** or **VIb** formed was filtered off and purified by recrystallization.

2-Methyl-5-mercapto-4-tosyl-1,3-thiazole (VII). To a solution of 0.0035 mol of compound **IIIb** in 20 ml of methanol was added 0.007 mol of sodium hydrogen sulfide and the mixture was heated for 3 h at 60°C. Then the solvent was removed in a vacuum, and 10 ml of water was added to the residue; the mixture was acidified with concentrated hydrochloric acid to pH ~2. The precipitate formed (compound **VII**) was filtered off and used for further transformations without purification.

5-[Benzyl(or 3-methylbenzyl)sulfanyl]-2-methyl-4-tosyl-1,3-thiazoles (VIIIa, VIIIb). To a solution of 0.0035 mol of compound **VII** in 20 ml of methanol was added 0.0035 mol of sodium methilate and 0.0038 mol of the corresponding benzyl chloride. The mixture was stirred for 3 h at 20°C, then the solvent was removed in a vacuum and 10 ml of water was added to the residue. The precipitate formed (compounds **VIIIa, VIIIb**) was filtered off and purified by recrystallization.

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