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Preparation and Properties of 2-Methyl-4-tosyl-1,3-thiazole-5-sulfonyl Chloride

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Abstract—Chlorination of readily available 2-methyl-5-methylsulfanyl-4-tosyl-1,3-thiazole has afforded 2-methyl-4-tosyl-1,3-thiazole-5-sulfonyl chloride. The latter can react with amines to build sulfonamides, efficient electrophilic reagents capable of undergoing nucleophilic substitution reactions. Regiochemistry of the described reactions depends strongly on the nature of nucleophiles, used for regioselective synthesis of some previously unknown trisubstituted 1,3-thiazoles.

Keywords: 1,3-thiazole-5-sulfonyl chloride, 1,3-thiazole-5-sulfonamide, sulfochlorination, regioselective synthesis, anticancer activity

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Thiazole heterocycle is a component of many natural products and synthetic compounds exhibiting a wide range of biological activity [1–10]. Therefore, studies on preparation of novel thiazole derivatives are of definite interest. Acylation of 2-amino-1,3-thiazoles [3] is a most general approach towards introducing the thiazole moiety into the molecule of bioactive compound. An alternative method is to use halothiazoles and acyl- or sulfonyl chloride thiazole derivatives [11]. The latter are particularly important synthetic building blocks, as the pharmacophore sulfonate group is introduced along with thiazole moiety.

Derivatives of 1,3-thiazole-5-sulfonyl chloride have been previously synthesized by sulfochlorination of 5-unsubstituted 1,3-thiazoles [12, 13]. 1,3-Thiazole-5-sulfonic acids chlorides containing hydrogen atom or alkyl and aryl substituents in the position 4 of the ring are usually thus obtained.

In this work we proposed a simple preparative route for synthesis of previously unknown 2-methyl-4-tosyl-1,3-thiazole-5-sulfonyl chlorides and studied their properties.

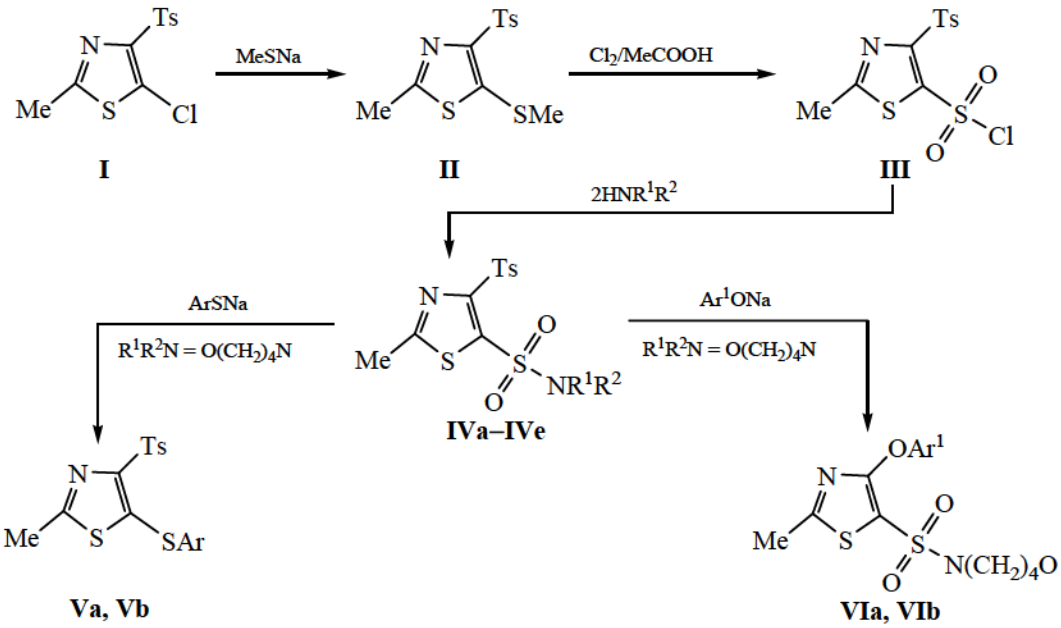
It has been recently shown [14] that reaction of 1-tosyl-2,2-dichloroethenylacetamide **I** with the Lawesson's reagent results in formation of 2-methyl-4-tosyl-5-chloro-1,3-thiazole. The latter contains labile chlorine atom which can be replaced with the residues of highly basic amines, sodium phenolate, or thiophenolate. Extending these studies, we found that refluxing a mixture of compound **I** and NaSMe in MeOH led to the formation of 2-methyl-5-methylsulfanyl-4-tosyl-1,3-thiazole **II** with yield of 76%. Oxidative chlorination (Cl_2, $MeCOOH/H_2O$, 0°C) of the latter gave 2-methyl-4-tosyl-1,3-thiazole-5-sulfonyl chloride **III** in yield of 82%.

Sulfonyl chloride **III** reacted with ammonia, aliphatic and aromatic amines to form the corresponding sulfonamides **IV**a–**IV**e.

Sulfonamides **IV** were electrophilic substrates due to the presence of electron-withdrawing tosyl and sulfonamide groups. They reacted differently with the "soft" and "hard" nucleophiles. The former type of the reagents attacked primarily the C^5 atom, whereas the latter nucleophiles reacted at the C^4 atom. The "soft" arylsulfanyl groups are introduced into position 5 of the thiazole ring, replacing sulfonamide group, and the "hard" aryloxy moieties replaced the tosylate anion at the C^4 atom (see transformations **IV** → **V** and **IV** → **VI**). It should be noted that novel trisubstituted thiazoles **VIa** and **VIb** were difficult to be obtained in other ways (Scheme 1).

Composition and structure of the synthesized compounds were confirmed by elemental analysis

Scheme 1.



R^1R^2N = NH_2 (**IVa**), NHMe (**IVb**), NMe_2 (**IVc**), morpholyl (**IVd**), 4-MeC_6H_4NH (**IVe**); Ar = 4-MeC_6H_4 (**Va**, **VIb**), 4-ClC_6H_4 (**Vb**), Ph (**VIa**); Ts = 4-$MeC_6H_4SO_2$.

(Table 1), IR, ^1H and ^{13}C NMR spectroscopy, and chromato-mass spectrometry methods (Table 2). In particular, IR spectra contained two (**II**, **V**, **VI**) or four (**III**, **IV**) strong absorption bands of the SO_2 groups. ^1H and ^{13}C NMR spectra of the products contained the signals of all of the structural fragments; the GC–MS traces contained peaks of the molecular ions $[M + 1]^+$.

Preliminary evaluation of anticancer activity of 1,3-thiazole-4-sulfonamides **IVa**–**IVe** was performed in the frame of the International Scientific Program of the National Cancer Institute (USA). Screening was performed in vitro with 60 cancer cell lines, the tested substance being taken in concentration of 1×10^{-5} mol/L; and then growth inhibition (GI) of cancer cell lines

Table 1. Yield, melting point, and elemental analysis data of compounds **II**–**VI**

Comp. no.	Yield, %	mp, °C (solvent for recrystallization)	Found, %		Formula	Calculated, %	
			N	S		N	S
II	76	164–165 (EtOH)	4.51	32.35	$C_{12}H_{13}NO_2S_3$	4.68	32.12
III	82	128–130 (C_6H_6)	3.77	27.64	$C_{11}H_{10}ClNO_4S_3$[a]	3.98	27.34
IVa	84	226–228 (EtOH + DMF)	8.67	28.91	$C_{11}H_{12}N_2O_4S_3$	8.43	28.94
IVb	85	190192 (EtOH + DMF)	8.01	27.78	$C_{12}H_{14}N_2O_4S_3$	8.09	27.77
IVc	80	174–175 (EtOH + DMF)	7.54	26.73	$C_{13}H_{16}N_2O_4S_3$	7.77	26.68
IVd	81	158–159 (EtOH + DMF)	6.90	23.89	$C_{15}H_{18}N_2O_5S_3$	6.96	23.90
IVe	77	185–187 (EtOH + DMF)	6.86	22.68	$C_{18}H_{18}N_2O_4S_3$	6.63	22.77
Va	70	138–140[b] (EtOH)	3.58	25.22	$C_{18}H_{17}NO_2S_3$	3.73	25.62
Vb	68	168–170 (EtOH)	3.49	24.04	$C_{17}H_{14}ClNO_2S_3$[c]	3.54	24.30
VIa	72	113–115 (EtOH)	8.07	18.61	$C_{14}H_{16}N_2O_4S_2$	8.23	18.84
VIb	64	173–175 (EtOH)	7.75	17.79	$C_{15}H_{18}N_2O_4S_2$	7.90	18.09

[a] Found Cl, %: 10.20. Calculated Cl, %: 10.07. [b] mp 138–139°C (EtOH) [14]. [c] Found Cl, %: 8.77. Calculated Cl, %: 8.95.

Table 2. Parameters of IR and NMR spectra of compounds **II–VI**

Comp. no.	IR spectrum (KBr), ν, cm^{-1}	^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz)	^{13}C NMR spectrum, δ_C, ppm (DMSO-d_6)	*m/z* $[M+1]^+$
II	1143, 1321 (SO_2); 1421, 1595, 2851, 2918	2.42 s (3H, CH_3), 2.56 s (3H, CH_3), 2.60 s (3H, CH_3), 7.32 d (2H_{Ar}, *J* 8.0), 7.97 d (2H_{Ar}, *J* 8.0)	19.55 (CH_3), 20.07 (CH_3), 21.70 (CH_3), 127.53, 129.31, 137.35, 144.16, 145.11 ($C^5_{thiazole}$), 156.81 ($C^4_{thiazole}$), 168.78 ($C^2_{thiazole}$)	300
III	1155 br; 1335, 1379 (SO_2); 1594	2.40 s (3H, CH_3), 2.61 s (3H, CH_3), 7.35 d (2H_{Ar}, *J* 8.0), 8.02 d (2H_{Ar}, *J* 8.0)	19.45 (CH_3), 21.44 (CH_3), 129.12, 129.68, 135.35, 141.16, 145.81 ($C^5_{thiazole}$), 162.81 ($C^4_{thiazole}$), 171.78 ($C^2_{thiazole}$)	–
IVa	1155 br; 1328, 1357 (SO_2); 1438, 1556, 1594; 3267, 3346 (NH_2)	2.41 s (3H, CH_3), 2.63 s (3H, CH_3), 7.49 d (2H_{Ar}, *J* 8.2), 7.95 d (2H_{Ar}, *J* 8.2), 8.02 s (2H, NH_2)	19.05 (CH_3), 21.42 (CH_3), 128.78, 129.70, 135.25, 141.11, 145.43 ($C^5_{thiazole}$), 162.75 ($C^4_{thiazole}$), 171.61 ($C^2_{thiazole}$)	333
IVb	1149 br; 1325, 1350 (SO_2); 1412, 1438, 1596; 3324 (NH)	2.41 s (3H, CH_3), 2.64 s (3H, CH_3), 2.67 s (3H, CH_3), 7.50 d (2H_{Ar}, *J* 8.0), 7.70 s (1H, NH), 7.94 d (2H_{Ar}, *J* 8.0)	18.80 (CH_3), 21.13 (CH_3), 29.71 (CH_3), 127.41, 129.12, 137.56, 144.23, 145.03 ($C^5_{thiazole}$), 156.76 ($C^4_{thiazole}$), 168.45 ($C^2_{thiazole}$)	347
IVc	1154 br; 1329, 1359 (SO_2); 1420, 1462,1595	2.41 s (3H, CH_3), 2.65 s (3H, CH_3), 2.94 s [6H, $N(CH_3)_2$], 7.49 d (2H_{Ar}, *J* 8.0), 7.89 d (2H_{Ar}, *J* 8.0)	18.80 (CH_3), 21.70 (CH_3), 38.39 [N $(CH_3)_2$], 127.41, 129.12, 137.56, 144.23, 145.69 ($C^5_{thiazole}$), 156.76 ($C^4_{thiazole}$), 168.45 ($C^2_{thiazole}$)	361
IVd	1162, 1208; 1300, 1354 (SO_2); 1491,1518, 2862,	2.42 s (3H, CH_3), 2.61 s (3H, CH_3), 3.25 br.s (4H_{morph}), 3.75 br.s (4H_{morph}) 7.48 d (2H_{Ar}, *J* 8.0), 7.89 d (2H_{Ar}, *J* 8.0)	18.78 (CH_3), 21.67 (CH_3), 46.01 (CN), 69.20 (CO), 128.44, 129.25, 137.34, 144.45, 145.79 ($C^5_{thiazole}$), 156.75 ($C^4_{thiazole}$), 168.46 ($C^2_{thiazole}$)	404
IVe	1169 br, 1328 br (SO_2), 1509, 1579; 3252 (NH)	2.31 s (3H, CH_3), 2.41 s (3H, CH_3), 2.43 s (3H, CH_3), 7.26 d (2H_{Ar}, *J* 7.6), 7.34 d (2H_{Ar}, *J* 7.6), 7.48 d (2H_{Ar}, *J* 8.0), 7.89 d (2H_{Ar}, *J* 8.0), 8.53 s (1H, NH)	19.65 (CH_3), 20.34 (CH_3), 21.12 (CH_3), 118.62, 130.53, 132.32, 133.31, 134.35, 135.34, 137.67, 140.14, 143.15 ($C^5_{thiazole}$), 156.34 ($C^4_{thiazole}$), 168.56 ($C^2_{thiazole}$)	424
Vb	1146, 1325 (SO_2)	2.37 s (3H, CH_3), 2.41 s (3H, CH_3), 7.18 d (2H_{Ar}, *J* 8.0), 7.33 d (2H_{Ar}, *J* 8.4), 7.42 d (2H_{Ar}, *J* 8.0), 8.00 d (2H_{Ar}, *J* 8.4)	20.07 (CH_3), 21.70 (CH_3), 127.34, 130.56, 131.75, 138.34, 139.17, 143.16, 144.22 ($C^5_{thiazole}$), 156.23 ($C^4_{thiazole}$), 168.63 ($C^2_{thiazole}$)	397
VIa	1151, 1322 (SO_2)	2.60 s (3H, CH_3), 3.25 br.s (4H_{morph}), 3.75 br.s (4H_{morph}), 7.09–7.39 m (5H_{Ar})	18.78 (CH_3), 46.10 (CN), 69.16 (CO), 108.44, 115.65, 121.18, 124.51, 132.25, 156.32, 168.74	341
VIb	1133, 1343 (SO_2)	2.40 s (3H, CH_3), 2.66 s (3H, CH_3), 3.44 br.s (4H_{morph}), 3.77 br.s (4H_{morph}) 7.32 d (2H_{Ar}, *J* 8.0), 8.01 d (2H_{Ar}, *J* 8.0)	18.20 (CH_3), 20.24 (CH_3), 46.14 (CN), 69.12 (CO), 108.54, 118.54, 132.95, 133.65, 144.32, 156.35, 168.79	355

was determined in comparison with the reference (100%). The investigated compounds showed low activity in inhibition of tumor cell growth. The most active product was **IVd**, which acted selectively on certain cancer cell lines, in particular renal cell carcinoma (UO-31, GI = 76.53), small cell lung carcinoma (NCI-H522, GI = 75.03), and melanoma (LOX IMVI, GI = 60.23%).

In summary, we developed a preparative method for synthesis of previously unknown 2-methyl-1,3-thiazole-5-sulfonyl chloride and the derived sulfonamides. The sulfonamides obtained were studied in nucleophilic substitution reactions with the "soft" and "hard" agents. The value of the obtained compounds is the presence in their structure of the sulfonamide moiety, which is important in biological screening studies.

EXPERIMENTAL

IR spectra were recorded with a Vertex 70 spectrometer (KBr pellets). ^1H and ^{13}C NMR spectra of the solutions in DMSO-d_6 were obtained using a Bruker AVANCE DRX-500 spectrometer operating at 500 and 125 MHz, respectively; TMS was used as an internal reference. GC–MS spectra were registered using a liquid chromatography–mass spectrometry system of an Agilent 1100 Series chromatograph equipped with a diode array with a mass selective detector Agilent LC\MSD SL. Parameters of GC–MS analysis were as follows: column Zorbax SB-C18 (1.8 mm, 4.6 × 15 mm); solvents MeCN–H_2O, 95 : 5, 0.1% CF_3COOH (A), 0.1% aqueous CF_3COOH (B); eluent feed 3 mL/min; injection volume 1 μL. Melting points were determined with a Fisher-Johns instrument. The reaction progress was monitored with TLC using Silufol UV-254 plates, eluting with a mixture $CHCl_3$–MeOH (9 : 1) and developing with UV irradiation.

Elemental analysis was performed at analytical laboratory of the Institute of Bioorganic Chemistry and Petrochemistry, National Academy of Sciences of Ukraine.

The starting 2-methyl-4-tosyl-5-chloro-1,3-thiazole **I** was prepared according to the procedure described in [14].

2-Methyl-5-methylsulfanyl-4-tosyl-1,3-thiazole (II). 20% aqueous solution of MeSNa (10 mL) was added to a solution of 2.88 g (0.01 mol) of compound **I** in 20 mL of MeOH. The mixture was refluxed for 5 h, and then the solvent was removed in vacuum. Next, 20 mL of water was added to the residue. The precipitate was filtered off and recrystallized.

2-Methyl-4-tosyl-1,3-thiazole-5-sulfonyl chloride (III). Gaseous chlorine was bubbled through a solution of 1.5 g (0.005 mol) of compound **II** in 10 mL of 95% acetic acid under stirring at 0°C during 0.5 h. Then the mixture was poured into 100 mL of cold water. The precipitate was filtered off, dried over P_2O_5 in a desiccator, and recrystallized.

2-Methyl-4-tosyl-1,3-thiazole-5-sulfonamide (IVa). A solution of 0.88 g (0.0025 mol) of sulfonyl chloride **III** in 10 mL of CH_3CN was added to 50 mL of 25% aqueous ammonia solution while stirring and cooling with ice water. The mixture was stirred at 20–25°C for 5 h. Then, the precipitate was filtered off, dried in air, and recrystallized.

***N*,2-Dimethyl-4-tosyl-1,3-thiazole-5-sulfonamide (IVb).** A solution of 0.16 g (0.0051 mol) of methylamine in 10 mL of H_2O was added to a solution of 0.88 g (0.0025 mol) of sulfonyl chloride **III** in 10 mL of CH_3CN. Then the mixture was stirred for 3 h at 20–25°C. After the solvent removal, the residue was treated with water, and the precipitate was filtered off and recrystallized.

***N*,*N*,2-Trimethyl-4-tosyl-1,3-thiazole-5-sulfonamide (IVc)** was prepared similarly from 0.88 g (0.0025 mol) of sulfonyl chloride **III** and 0.23 g (0.0051 mol) of dimethylamine; the reaction time was 5 h.

4-[(2-Methyl-4-tosyl-1,3-thiazol-5-yl)sulfonyl]morpholine (IVd) was prepared similarly from 0.88 g (0.0025 mol) of sulfonyl chloride **III** and 0.44 g (0.0051 mol) of morpholine; the reaction time was 5 h.

2-Methyl-4-tosyl-*N*-(4-methylphenyl)-1,3-thiazole-5-sulfonamide (IVe) was prepared similarly from 0.88 g (0.0025 mol) of sulfonyl chloride **III** and 0.55 g (0.0051 mol) of *p*-toluidine; the reaction time was 5 h.

5-Arylsulfanyl-2-methyl-4-tosyl-1,3-thiazoles (Va, Vb). The corresponding sodium thiophenolate (0.002 mol) was added to a solution of 0.81 g (0.002 mol) of compound **IVd** in 20 mL of THF. The mixture was refluxed for 4 h, and then the solvent was removed in vacuum. Next, 20 mL of water was added to the residue. The precipitate was filtered off and recrystallized. Physico-chemical constants of compound **Va** coincided with those reported in [14].

4-[(4-Aryloxy-2-methyl-1,3-thiazol-5-yl)sulfonyl]-morpholines (VIa, VIb) were prepared similarly from 0.81 g (0.002 mol) of compound **IVd** and 0.002 mol of sodium phenolate or 4-methylphenolate.

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