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Study of Reaction Routes in Sulfoination of 2-Aminothiazoles with Chlorosulfonic Acid

S.N. Lyashchuk, V.I. Enya, T.F. Doroshenko, and Yu.G. Skrypnik

Litvinenko Institute of Physical Organic and Coal Chemistry, National Academy of Sciences of the Ukraine, Donetsk, 83114 Ukraine
e-mail: lyaschuk@skif.net

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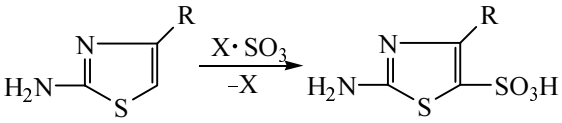
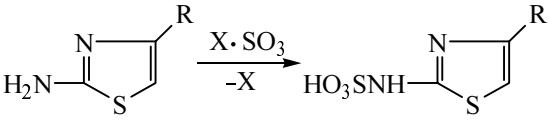
Abstract—The sulfonation of 4-substituted 2-aminothiazoles with chlorosulfonic acid under mild conditions afforded primarily 2-amino-5-thiazolesulfonic acids that at heating in sulfuric acid rearranged into the corresponding stable 2-thiazolesulfamoylic acids.

According to published data [1–5] two routes are presumable for sulfonation of 4-substituted 2-aminothiazoles: into position *5* of the thiazole ring (electrophilic substitution in an aromatic ring) (1), and at the amino group (nucleophilic substitution at a sulfur atom) (2).



(1)



(2)

R = CH_3 (**I, V, IX**), *p*-ClC_6H_4 (**II, VI, X**), *p*-BrC_6H_4 (**III, VII, XI**), *m*-$NO_2C_6H_4$ (**IV, VIII, XII**).

Besides at R = Ar the sulfonation of the aromatic substituent can also occur.

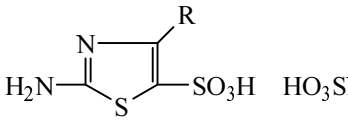
The formulation of the conditions governing these competing processes led to ambiguous conclusions [3–5]. For instance, according to [3, 4], the sulfonation of 2-aminothiazole with the chlorosulfonic acid and oleum in the cold gave rise solely to 2-thiazolesulfamic acid whose high stability against hydrolysis was ascribed to its dipolar structure.

Later Poplavskii *et al*. [5] suggested that the sulfonation of 2-aminothiazole with chlorosulfonic acid might in this case occur in abnormal way into the position *5* of the thiazole ring.

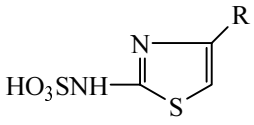
Both Hurd *et al*. and Poplavskii *et al*. regarded the reaction as analogous to the aniline sulfonation where primarily an unstable benzenesulfamoylic acid arose. They studied only the sulfonation of 2-aminothiazole and 2-amino-4-methylthiazole that excluded the possibility to make any general conclusions. Besides no spectral measurements were performed on the reaction products in these works preventing unambiguous identification of the compounds synthesized.

The target of this study was the investigation of the route taken by sulfonation of some 4-substituted 2-aminothiazoles with chlorosulfonic acid and also evaluation of stability and possible rearrangements of the arising sulfonic acids.

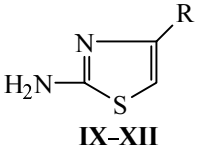
As objects of the study were chosen 4-substituted 2-amino-5-thiazolesulfonic acids (**I–IV**) and 4-substituted 2-thi-azolesulfamoylic acids **V–VIII** prepared from the corresponding 4-substituted 2-aminothiazoles **IX–XII**.



I–IV



V–VIII



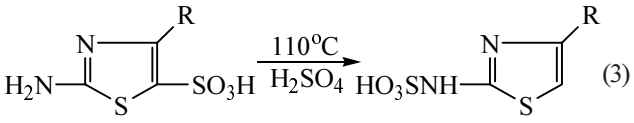
IX–XII

The sulfonation of 2-aminothiazoles substituted in position *4* was carried out by adding them at cooling to excess chlorosulfonic acid.

To avoid the possibility of sulfonation into the aromatic ring of the substituent R we limited the study to compounds with electron-withdrawing substituents on the phenyl for they prevent the electrophilic substitution. With R = C_6H_5 under the reaction conditions a mixture of sulfonation products was obtained significantly complicating the observed pattern.

The analysis of the spectra of the sulfonation products showed that in all cases only the sulfonation of the position *5* in the thiazole ring occurred, and the corresponding 4-substituted 2-amino-5-thiazolesulfonic acids **I–IV** were obtained in good yields. In this case in the ^{1}H NMR spectrum the signal of proton attached to C^5 atom is lacking. The sulfonic acids obtained are stable to hydrolysis: The boiling of their water solution for several hours did not affect the compounds.

At the same time compounds **I–IV** are capable of isomerization into the corresponding 4-substituted 2-thiazolesulfamoylic acids **V–VIII** at heating in sulfuric acid (3).



(3)

Therewith in the ^{1}H NMR spectra of the isomerization products a signal appeared belonging to the proton at the C^5 atom of the thiazole ring. The aryl ring of the substituent did not undergo sulfonation under these conditions.

Thus the aniline sulfonation where first occurs nucleophilic substitution at the sulfur atom of the chlorosulfonic acid affording unstable to heating benzenesulfamoylic acid that then isomerizes at heating into sulfanilic acid cannot be regarded as similar to the process with 2-aminothiazoles. In the 2-aminothiazoles **IX–XII** that we studied the process took the opposite route obviously because of the specific features of their electronic structure.

For instance, quantum-chemical calculations in the semiempirical approximation AM1 revealed the presence of a considerable negative charge on the carbon atom in the position *5* of all compounds under study, and the qualitative pattern of the charge distibution remained unchanged in going to the corresponding protonated and tautomer forms of 2-aminothiazoles (see table). Note that the imine tautomers are approximately by 25–34 kJ mol^{-1} less energetically favorable than the amine forms and thus the fraction of the former in the reaction mixture should

Effective charges on atoms of compounds **IX–XII**

Compd. no.	Heat of formation, kJ mol^{-1}	Charge on atom (a.u.)					
		S^1	C^2	N^3	C^4	C^5	$N^{(NH2)}$
IX	130.3	0.471	–0.174	–0.161	–0.048	–0.485	–0.282
	163.8[a]	0.269	–0.004	–0.278	0.018	–0.433	–0.286
	815.4[b]	0.767	–0.492	–0.050	–0.027	–0.455	0.039
X	239.7	0.489	–0.173	–0.154	–0.017	–0.472	–0.282
	264.4[a]	0.422	–0.041	–0.304	0.035	–0.437	–0.287
	931.0[b]	0.762	–0.489	–0.049	0.024	–0.452	0.038
XI	289.9	0.490	–0.173	–0.153	–0.021	–0.469	–0.282
	314.7[a]	0.425	–0.042	–0.303	0.031	–0.435	–0.286
	982.5[b]	0.764	–0.489	–0.047	0.022	–0.451	0.038
XII	283.2	0.508	–0.172	–0.156	–0.029	–0.466	–0.282
	313.0[a]	0.439	–0.049	–0.295	0.013	–0.422	–0.287
	991.8[b]	0.785	–0.491	–0.046	0.011	–0.448	0.038

[a] Tautomer form of the correcponding compound.
[b] Protonated form of the corresponding compound.

be small. In the highly acidic medium the amine group of the 2-aminothiazoles is virtually completely protonated. At the same time for the nucleophilic substitution at the sulfur atom in the chlorosulfonic acid to occur the presence of nonprotonated form is essential. Under conditions of acidic medium where in the substrate molecule a sufficiently strong nucleophilic center (the carbon atom in position *5*) is present obviously the competing route (2) fails to operate. At the same time the sulfonation of 2-aminothiazoles by sulfur trioxide complexes with pyridine and dioxane when the amino group is not protonated occurs almost completely along equation (1) [1].

The heating of 2-aminothiazole-5-sulfonic acid in the sulfuric acid should intensify the amino group deprotonation, and thus alongside the destabilization of the polar C–S bond should favor process (3) giving more thermodynamically feasible products, the corresponding 2-thiazolesulfamoylic acids. These compounds are fairly stable and do not appreciably hydrolyze even at prolonged boiling in water solutions of mineral acids.

During the aniline sulfonylation with chlorosulfonic acid the process first occurs at the amino group (the charge on the nitrogen atom is –0.326 a.u.) since the effective charge on the carbon atom in the *para*-position (–0.173 a.u.) is small, and only the subsequent heating of the reaction mixture causes a rearrangement of the formed benzenesulfamoylic acid into the more thermodynamically stable sulfanilic acid.

EXPERIMENTAL

IR spectra were recorded on spectrophotometer UR-20 from samples prepared as KBr pellets . ^{1}H NMR spectra of compounds synthesized were registered on spectro-meter Gemini-200 at operating frequency 200 MHz in DMSO-d_6 using TMS as internal reference.

Quantum-chemical calculations and processing of results was performed using software Hyper-Chem 5.02 (trial) [6] on a computer SINTAL CAMEO XL, processor Intel Pentium IV 2.4 GHz, 512 Mb DDR SDRAM of memory. In all cases total geometry optimization of compounds **IX–XII**, their protonated and tautomer forms was carried out.

Initial 2-aminothiazoles **IX–XII** were prepared from the corresponding phenacyl halides by reaction with thiourea [4]. Physical constants of compounds obtained were consistent with the published data.

The solvents used in the study were purified by known procedures [7], the chlorosulfonic acid was twice distilled before use, the middle fraction being collected.

2-Amino-4-(4-chlorophenyl)-5-thiazolesulfonic acid (II). To 35 g (0.3 mol) of chlorosulfonic acid cooled by a bath of ice mixed with salt to –5°C was added by small portions while stirring within 30 min 21 g (0.1 mol) of 4-(4-chlorophenyl)-2-aminothiazole **X**. The solution turned dark, and the hydrogen chloride evolution was observed. After adding the substrate the mixture was stirred at room temperature for 1 h, and then slowly poured on crushed ice. Then thereto a cooled solution of sodium hydroxide was added till neutralization while adding ice to maintain the temperature below 10°C. The precipitate was filtered off, washed with ethanol, with water, and recrystallized from a 10-fold amount of water. Yield 24.5 g (85%), colorless prismatic crystals, mp 205–206°C. IR spectrum, ν, cm^{-1}: 595, 665 (NH_2), 715, 845 Cp, 1020 Cp, 1075 C (SO_2), 1095, 1210 C, 1245 C (SO_2), 1495, 1580 (NH_2), 1645 C (C–H^{Ar}), 3150, 3390. ^{1}H, δ, ppm: 7.28, 7.48 d (4H, H arom), 7.62 C (2H, NH_2), 13.8 br.s (1H, SO_3H). Found, %: C 31.13; H 2.74; N 10.81; S 24.18. $C_7H_7ClN_2O_3S_2$. Calculated, %: C 31.52; H 2.65; N 10.50; S 24.04.

Compounds **I, III**, and **IV** were prepared in the similar way.

2-Amino-4-methyl-5-thiazolesulfonic acida (I). Yield 60%, mp 276–277°C. IR spectrum, ν, cm^{-1}: 475, 590, 660 (NH_2), 735, 815, 1025 s (SO_2), 1110, 1175, 1270 s (SO_2), 1380, 1430, 1595 s (NH_2), 1640, 1670, 3140, 3310. ^{1}H NMR spectrum, δ, ppm: 2.11 s (CH_3), 7.54 s (2H, NH_2), 13.6 br.s (1H, SO_3H). Found, %: C 24.21; H 3.15; N 14.52; S 32.92. $C_4H_6N_2O_3S_2$. Calculated, %: C 24.74; H 3.11; N 14.42; S 33.01.

2-Amino-4-(4-bromophenyl)-5-thiazolesulfonic acida (III). Yield 91%, mp 219–220°C. IR spectrum, ν, cm^{-1}: 470, 590, 660 (NH_2), 845, 1015, 1020, 1075 s (SO_2), 1085, 1205 s, 1240 s (SO_2), 1490, 1585 (NH_2), 1640 s (C–H^{Ar}), 3150, 3320. ^{1}H NMR spectrum, δ, ppm: 7.49 d.d (4H, H arom), 7.60 s (2H, NH_2), 13.7 br.s (1H, SO_3H). Found, %: C 26.81; H 2.34; N 9.24; S 20.73. $C_7H_7BrN_2O_3S_2$. Calculated, %: C 27.02; H 2.27; N 9.00; S 20.61.

2-Amino-4-(3-nitrophenyl)-5-thiazolesulfonic acida (IV). Yield 85%, mp 262–264°C. IR spectrum, ν, cm^{-1}: 565, 600, 665 (NH_2), 750, 810, 840, 915, 1020, 1075 s (SO_2), 1150, 1220 s (SO_2), 1365 s (NO_2), 1535 s (NO_2), 1580 s (NH_2), 1650 s (C–H^{Ar}), 3150, 3370. ^{1}H NMR spectrum, δ, ppm: 7.42 t, 7.83 d, 8.05 d, 8.35 s (4H, H arom), 7.80 s (2H, NH_2), 13.7 br.s (1H, SO_3H). Found, %: C 29.84; H 2.61; N 15.36; S 23.37. $C_7H_7N_3O_5S_2$. Calculated, %: C 30.32; H 2.54; N 15.15; S 23.13.

4-(4-Chlorophenyl)-2-thiazolesulfamoylic acid (VI). To 20 ml of cooled 98% sulfuric acid was added by portiona at stirring 14.5 g (0.05 mol) of sulfonic acid **II**. Then the flask was heated for 3 h on a sand bath maintaining the temperature at 110 ± 5°C. The dark solution obtained was cooled and slowly poured on crushed ice. Then the reaction mixture was neutralized with sodium hydroxide solution, the precipitate was filtered off, washed with 2-propanol and water, and recrystallized from water. Yield 13.3 g (92%), colorless needle-like crystals, mp 222–224°C. IR spectrum, ν, cm^{-1}: 530, 615, 725, 830, 1020, 1040, 1090 s (SO_2), 1160 s (SO_2), 1490, 1590 (NH), 1625 s (C–H^{Ar}), 3400. ^{1}H NMR spectrum, δ, ppm: 7.08 s (1H, C^{5}H), 7.54, 7.72 d (4H, H arom), 8.64 s (1H, NH), 13.5 br.s (1H, SO_3H). Found, %: C 31.24; H 2.73; N 10.71; S 24.10. $C_7H_7ClN_2O_3S_2$. Calculated, %: C 31.52; H 2.65; N 10.50; S 24.04.

Likewise were prepared compounds **V, VII**, and **VIII**.

4-Methyl-2-thiazolesulfamoylic acid (V). Yield 83%, mp 310–312°C. IR spectrum, ν, cm^{-1}: 505, 795, 895, 985, 1025 s (SO_2), 1105, 1200 s (SO_2), 1250 m, 1365, 1410, 1580 s (NH), 1620, 1650, 3105, 3310. ^{1}H NMR spectrum, δ, ppm: 3.08 s (CH_3), 6.48 s (1H, C^{5}H), 8.62 s (1H, NH), 13.3 br.s (1H, SO_3H). Found, %: C 24.44; H 3.19; N 14.57; S 32.97. $C_4H_6N_2O_3S_2$. Calculated, %: C 24.74; H 3.11; N 14.42; S 33.01.

4-(4-Bromophenyl)-2-thiazolesulfamoylic acid (VII). Yield 66%, mp 280–281°C. IR spectrum, ν, cm^{-1}:

510, 615, 735, 765, 840, 1010 s, 1065 s (SO_2), 1120, 1200 s, 1220 s (SO_2), 1460, 1575 (NH), 1645 s (C–H^{Ar}), 3380. ^{1}H NMR spectrum, δ, ppm: 7.11 s (1H, C^5H), 7.58 d.d (4H, H arom), 8.65 s (1H, NH), 13.2 br.s (1H, SO_3H). Found, %: C 26.89; H 2.29; N 9.14; S 20.75. $C_7H_7BrN_2O_3S_2$. Calculated, %: C 27.02; H 2.27; N 9.00; S 20.61.

4-(3-Nitrophenyl)-2-thiazolesulfamoylic acid (VIII). Yield 92%, mp 195–197°C. IR spectrum, ν, cm^{-1}: 460, 580, 725, 880, 1040 s, 1055 s (SO_2), 1190 s, 1210 s (SO_2), 1350 s (NO_2), 1525 s (NO_2), 1560 (NH), 1635 s (C–H^{Ar}), 3130, 3390. ^{1}H NMR spectrum, δ, ppm: 7.31 s (1H, C^5H), 7.76 t, 8.10 d, 8.27 d, 8.53 s (4H, H arom), 8.67 s (1H, NH), 13.2 br.s (1H, SO_3H). Found, %: C 29.80; H 2.64; N 15.25; S 23.21. $C_7H_7N_3O_5S_2$. Calculated, %: C 30.32; H 2.54; N 15.15; S 23.13.

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