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Heterocyclization of *N*-Hetaryl-*N*′-(prop-2-en-1-yl)thioureas by the Action of Sulfuryl Chloride

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Abstract—Cyclization of *N*-hetaryl-*N*′-(prop-2-en-1-yl)thioureas by the action of sulfuryl chloride leads to the formation of the corresponding 2-hetarylimino-5-chloromethylthiazolidine hydrochlorides which are converted into the free bases by treatment with aqueous sodium sulfite.

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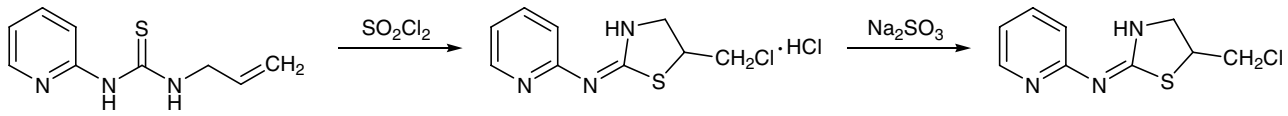
Halocyclization of functionally substituted ethylenes and acetylenes underlies an important method for the synthesis of nitrogen-, oxygen-, and sulfur-containing heterocycles [1]. The cyclizations are usually performed using iodine or bromine as reagents. Highly reactive chlorine promotes formation of a number of by-products; therefore, it is not generally used in such syntheses.

We were the first to use sulfuryl chloride as reagent to effect halocyclization of *N*-hetaryl-*N*′-(prop-2-en-1-yl)thiourea. We found that *N*-(pyridin-2-yl)-*N*′-(prop-2-en-1-yl)thiourea (**I**) reacts with SO_2Cl_2 in chloroform at room temperature (18–25°C) to give 5-(chloromethyl)-2-(pyridin-2-ylimino)-1,3-thiazolidine hydrochloride (**II**) in almost quantitative yield. Treatment of the latter with an aqueous solution of sodium sulfite afforded the corresponding free base **III** (Scheme 1).

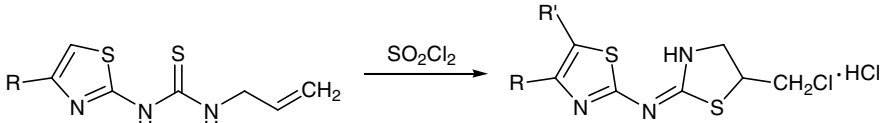
Under analogous conditions, reactions of *N*-(1,3-thiazol-2-yl)-*N*′-(prop-2-en-1-yl)thioureas **IV** and **V** with an equimolar amount of SO_2Cl_2 lead to the formation of 5-chloromethylthiazolidine hydrochlorides **VIa** and **VIIa**, respectively, in high yield (Scheme 2). In the

Scheme 1.

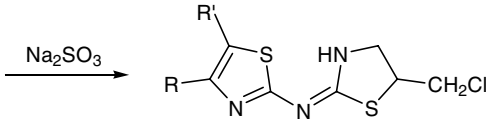


I **II** **III**

Scheme 2.



IV, **V** **VIa**, **VIb**, **VIIa**, **VIIb**



VIIIa, **VIIIb**, **IXa**, **IXb**

IV, **VI**, **VIII**, R = $EtOCOCH_2$; **V**, **VII**, **IX**, R = Ph; R′ = H (**a**), Cl (**b**).

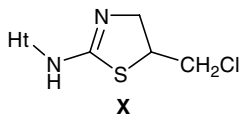
Heterocyclization of *N*-allyl-*N*′-hetarylthioureas by the action of sulfuryl chloride (chloroform, 18–25°C)

Initial compound no.	*N*-Allylthiourea, g (mmol)	Sulfuryl chloride, ml (mmol)	Product no.	Yield, g (%)
I	0.290 (1.50)	0.121 (1.50)	**II**	0.376 (95)
IV	0.300 (1.05)	0.085 (1.05)	**VIa**	0.259 (69)
IV	0.300 (1.05)	0.255 (3.15)	**VIb**	0.309 (75)
V	0.300 (1.09)	0.090 (1.11)	**VIIa**	0.321 (85)
V	0.300 (1.09)	0.180 (2.22)	**VIIb**	0.362 (87)

presence of excess sulfuryl chloride, the cyclization was accompanied by chlorination of the thiazole ring to give compounds **VIb** and **VIIb** (Scheme 2, see table). Our results are very consistent with the data of [2], according to which *N*-(pyridin-2-yl)-1,3-thiazol-2-amine readily undergoes bromination at the 5-position of the thiazole ring under mild conditions; here, the pyridine ring remains intact. By treatment of hydrochlorides **VIa**, **VIb**, **VIIa**, and **VIIb** with an aqueous solution of sodium sulfite we obtained free bases **VIIIa**, **VIIIb**, **IXa**, and **IXb**.

Participation of the double bond in the cyclization is confirmed by the ^{1}H NMR spectra of the products, which lack signals of the allyl fragment present in initial compounds **I**, **IV**, and **V**; instead, two multiplets appear in the δ region 3.71–4.19 ppm due to diastereotopic protons of two methylene groups (C^4H_2 in the thiazolidine ring and CH_2Cl), and a multiplet at δ 4.14–4.44 ppm is present (3-H, thiazolidine).

However, the ^{1}H NMR spectra did not allow us to choose between alternative 2-iminothiazolidine and 2-aminodihydrothiazole **X** structures.



X

Therefore, the structure of cyclization product **III** was unambiguously proved by X-ray analysis. The general view of molecule **III** and principal bond lengths and bond angles therein are given in Fig. 1. The five-membered ring $S^1C^6C^7C^8N^3$ is not planar: deviations of atoms from the mean-square plane reach 0.145 Å (*envelope* conformation); the bond system $S^1C^6N^3C^7$ is planar within 0.013 Å, and it forms a dihedral angle of 22.6° with the $S^1C^8C^7$ plane. The pyridine ring $N^1C^1C^2C^3C^4C^5$ is approximately coplanar to the $S^1C^6C^7C^8N^3$ heteroring: the corresponding dihedral angle is 15.3°. The N^3 atom has a planar–trigonal bond configuration (within experimental error); the sum of the bond angles at that atom is 358.6°. Molecules **III** in crystal are linked to centrosymmetric dimers via medium-strength [3] intermolecular hydrogen bonds N^3–H···N^2 with the following parameters: $N^3\cdots N^2$ 2.966(5) Å, $\angle N^3HN^2$ 174(5)° (Fig. 2).

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Varian VXR-300 spectrometer (300 MHz) from solutions in DMSO-d_6 using tetramethylsilane as internal reference. The X-ray diffraction data for a single crystal of **III**, 0.03×0.39×0.48 mm, were acquired at room temperature on a Bruker Apex II automatic CCD diffractometer (MoK_α irradiation, λ = 0.71069 Å, θ_{max} = 23°, $-16 \le h \le 16$, $-6 \le k \le 5$, $-19 \le l \le 24$). Total of 3560 reflections were measured, 1357 of which were independent (R_{int} = 0.029). Monoclinic crystals with the

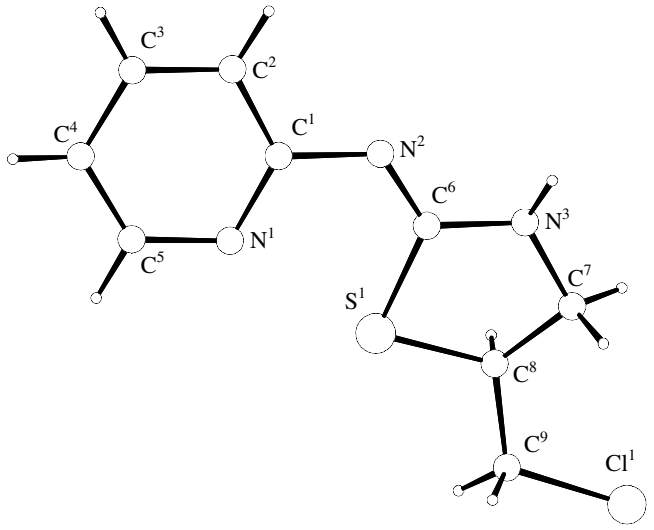


Fig. 1. Structure of the molecule of *N*-(5-chloromethyl-1,3-thiazolidin-2-ylidene)pyridin-2-amine (**III**) according to the X-ray diffraction data. Principal bond lengths (Å) and bond angles (deg): C^1–N^2 1.397(5), N^2–C^6 1.299(6), N^3–C^6 1.330(5), N^3–C^7 1.435(6), S^1–C^6 1.767(5), S^1–C^8 1.825(5), C^7–C^8 1.487(7); $C^6S^1C^8$ 90.9(2), $C^1N^2C^6$ 122.0(4), $C^6N^3C^7$ 117.6(4).

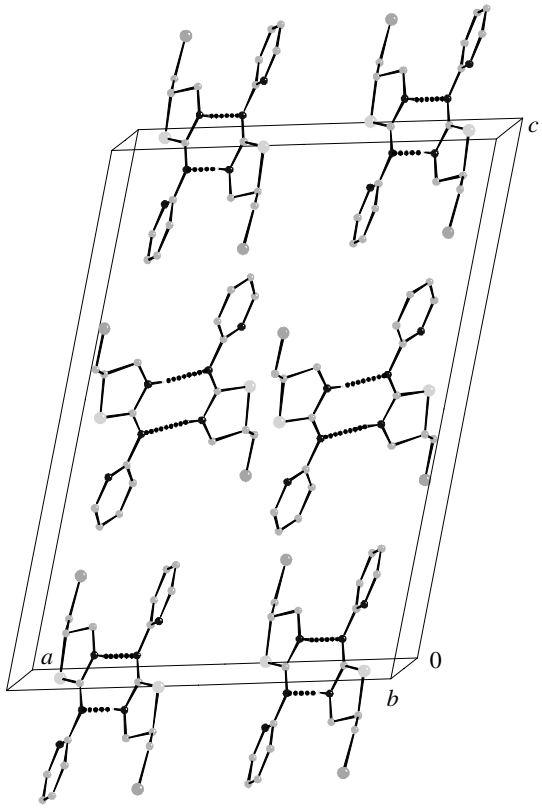


Fig. 2. Crystal packing of *N*-(5-chloromethyl-1,3-thiazolidin-2-ylidene)pyridin-2-amine (**III**). Intermolecular hydrogen bonds N^3–H···N^2 are shown with dotted lines.

following unit cell parameters: a = 15.700(1), b = 6.076(6), c = 22.414(2) Å; β = 104.210(5)°; V = 2072.8(3) Å^3; M 227.72; Z = 8; d_{calc} = 1.46 g/cm^3; μ = 5.32 cm^{-1}; F(000) = 944; space group $C2c$ (no. 15). The structure was solved by the direct method and was refined by the least-squares procedure in full-matrix anisotropic approximation using CRYSTALS software package [4]; 822 reflections with $I > 3\sigma(I)$ were used in the refinement (130 refined parameters, 6.3 reflections per parameter). All hydrogen atoms were visualized by the difference synthesis of electron density and were included into the refinement procedure with fixed positional and thermal parameters. A three-parameter Chebyshev's weight scheme [5] was applied (1.65, 0.89, 1.29). The final divergence factors were R = 0.041 and R_W = 0.048, GOF 1.074; the residual electron density from the Fourier difference series was –0.22 and 0.48 e/Å^3. The complete set of crystallographic data for compound **III** was deposited to the Cambridge Crystallographic Data Center (entry no. CCDC 626858).

***N*-(Prop-2-en-1-yl)-*N′*-(pyridin-2-yl)thiourea (I)** [6]**.** Pyridin-2-amine, 4.70 g (0.05 mol), was dissolved in 5 ml of ethanol at 40–50°C, the solution was cooled to 25–30°C, 5.00 ml (0.051 mol) of allyl isothiocyanate was added, and the mixture was heated for 1 h under reflux. After cooling, the crystalline product was filtered off, washed in succession with a small amount of ice-cold ethanol and diethyl ether, and recrystallized from ethanol. Yield 7.92 g (82%), mp 100–101°C. ^{1}H NMR spectrum, δ, ppm: 4.33 m (2H, C**H**$_2$-CH=CH$_2$), 5.18 d (1H, =CH$_2$, J = 10.3 Hz), 5.26 d (1H, =CH$_2$, J = 17.3 Hz), 5.98 m (1H, CH$_2$C**H**=CH$_2$), 7.07 m (1H, pyridine), 7.20 m (1H, pyridine), 7.81 (1H, pyridine), 8.25 m (1H, pyridine), 10.70 br.s (1H, NH), 11.83 br.s (1H, NH). Found, %: C 55.61; H 5.59; N 21.42; S 16.29. $C_9H_{11}N_3S$. Calculated, %: C 55.93; H 5.74; N 21.74; S 16.59.

***N*-(5-Chloromethyl-1,3-thiazolidin-2-ylidene)-pyridin-2-amine hydrochloride (II).** A solution of 0.121 ml (1.5 mmol) of SO_2Cl_2 in 5 ml of chloroform was added over a period of 2 h under stirring at 18–25°C to a solution of 0.290 g (1.5 mmol) of thiourea **I** in 10 ml of chloroform. After 20 h, the solvent was removed under reduced pressure (~15 mm), the residue was ground with a few drops of acetone or chloroform, and the finely crystalline product was filtered off and washed with pentane. Yield 0.376 g (95%), mp 78–81°C. ^{1}H NMR spectrum, δ, ppm: 3.20–3.65 br.s (HCl, H$_2$O), 3.99–4.19 m (4H, 4′-H, CH$_2$Cl), 4.37 m (1H, 5′-H), 7.30–7.41 m (2H, pyridine), 7.95–8.01 m (1H, pyridine), 8.41 m (1H, pyridine), 10.55–12.55 br.s (NH). Found, %: C 40.79; H 4.34; Cl 26.60; N 15.75; S 11.93. $C_9H_{11}Cl_2N_3S$. Calculated, %: C 40.92; H 4.20; Cl 26.84; N 15.91; S 12.14.

***N*-(Prop-2-en-1-yl)-*N′*-(1,3-thiazol-2-yl)thioureas IV and V (*general procedure*).** A mixture of 0.03 mol of 4-phenyl-1,3-thiazol-2-amine or ethyl 2-amino-1,3-thiazol-4-ylacetate and 5.89 ml (0.06 mol) of allyl isothiocyanate was heated on a boiling water bath for 2 h in the synthesis of **IV** or 6–7 h in the synthesis of **V**. After cooling, the crystalline product was washed with cold ethanol and recrystallized from ethanol.

Ethyl {2-[3-(prop-2-en-1-yl)thioureido]thiazol-4-yl}acetate (IV). Yield 6.58 g (77%), mp 108–109°C. ^{1}H NMR spectrum, δ, ppm: 1.19 t (3H, CH$_3$, J = 7.0 Hz), 3.68 s (2H, CH$_2$CO), 4.09 q (2H, OCH$_2$, J = 7.0 Hz), 4.23 m (2H, C**H**$_2$CH=CH$_2$), 5.15 d (1H, =CH$_2$, J = 10.5 Hz), 5.22 d (1H, =CH$_2$, J = 17.4 Hz), 5.86–5.99 m (1H, C**H**=CH$_2$), 6.91 s (5-H), 9.56 br.s (1H, NH), 11.70 br.s (1H, NH). Found, %: C 46.17; H 5.17; N 14.53; S 22.62. $C_{11}H_{15}N_3O_2S_2$. Calculated, %: C 46.30; H 5.30; N 14.72; S 22.47.

***N*-(4-Phenyl-1,3-thiazol-2-yl)-*N*′-(prop-2-en-1-yl)-thiourea (V).** [7]. Yield 5.69 g (69%), mp 177–178°C. ^{1}H NMR spectrum, δ, ppm: 4.29 m (2H, C**H**$_2$CH=CH$_2$), 5.22 d (1H, =CH$_2$, *J* = 10.2 Hz), 5.31 d (1H, =CH$_2$, *J* = 17.1 Hz), 5.94–6.07 m (1H, C**H**=CH$_2$), 7.31–7.46 m (3H, H$_{arom}$), 7.55 s (5-H), 7.86–7.88 m (2H, H$_{arom}$), 9.62 br.s (1H, NH), 11.78 s (1H, NH). Found, %: C 56.59; H 4.61; N 15.09; S 23.35. $C_{13}H_{13}N_3S_2$. Calculated, %: C 56.70; H 4.76; N 15.26; S 23.29.

Heterocyclization of *N*-allylthioureas IV and V by the action of sulfuryl chloride (*general procedure*). A solution of a required amount of SO_2Cl_2 in 5 ml of chloroform was added over a period of 2 h under stirring at 18–25°C to a solution of 300 mg of compound **IV** or **V** in 20 ml of chloroform. After 20 h, the solvent was removed under reduced pressure. The residue was a light yellow solid which was transformed in 20–40 min into a thick oily material. It was ground with a few drops of acetone or chloroform to obtain a finely crystalline substance which was washed with pentane and dried. The yields of hydrochlorides **VIa**, **VIb**, **VIIa**, and **VIIb** are given in table.

Ethyl [2-(5-chloromethyl-1,3-thiazolidin-2-ylideneamino)-1,3-thiazol-4-yl]acetate hydrochloride (VIa). mp 85–87°C. ^{1}H NMR spectrum, δ, ppm: 1.22 t (3H, CH$_3$, *J* = 7.2 Hz), 3.65–4.25 br.s (HCl, H$_2$O), 3.74–3.83 m (2H) and 3.91–4.01 m (2H) (4′-H, CH$_2$Cl), 3.79 s (2H, CH$_2$CO), 4.13 q (2H, OCH$_2$, *J* = 7.2 Hz), 4.44 m (1H, 5′-H), 7.13 s (5-H), 8.36 s (NH). Found, %: C 36.96; H 4.31; Cl 19.72; N 11.78; S 17.96. $C_{11}H_{15}Cl_2N_3O_2S_2$. Calculated, %: C 37.08; H 4.24; Cl 19.90; N 11.79; S 18.00.

Ethyl [5-chloro-2-(5-chloromethyl-1,3-thiazolidin-2-ylideneamino)-1,3-thiazol-4-yl]acetate hydrochloride (VIb). mp 73–75°C. ^{1}H NMR spectrum, δ, ppm: 1.21 t (3H, CH$_3$, *J* = 7.2 Hz), 3.68 s (2H, CH$_2$CO), 3.73–3.80 m (2H) and 3.86–3.95 m (2H) (4′-H, CH$_2$Cl), 4.12 q (2H, OCH$_2$, *J* = 7.2 Hz), 4.23 m (1H, 5′-H), 6.20–7.30 br.s (HCl, H$_2$O), 8.33 s (NH). Found, %: C 33.76; H 3.72; Cl 27.05; N 10.63; S 16.25. $C_{11}H_{14}Cl_3N_3O_2S_2$. Calculated, %: C 33.81; H 3.61; Cl 27.22; N 10.75; S 16.41.

***N*-(5-Chloromethyl-1,3-thiazolidin-2-ylidene)-4-phenyl-1,3-thiazol-2-amine hydrochloride (VIIa).** mp 111–114°C. ^{1}H NMR spectrum, δ, ppm: 3.79–3.99 m (4H, 4′-H, CH$_2$Cl), 4.27–4.30 m (1H, 5′-H), 4.40–5.40 br.s (HCl, H$_2$O), 7.34–7.48 m (3H, H$_{arom}$), 7.67 s (5-H), 7.94–7.96 m (2H, H$_{arom}$), 8.35 s (NH). Found, %: C 44.96; H 3.89; Cl 19.69; N 12.02; S 18.45. $C_{13}H_{13}Cl_2N_3S_2$. Calculated, %: C 45.09; H 3.78; Cl 20.48; N 12.13; S 18.52.

5-Chloro-*N*-(5-chloromethyl-1,3-thiazolidin-2-ylidene)-4-phenyl-1,3-thiazol-2-amine hydrochloride (VIIb). mp 137–140°C. ^{1}H NMR spectrum, δ, ppm: 3.71–3.92 m (4H, 4′-H, CH$_2$Cl), 4.14 m (1H, 5′-H), 4.35–5.10 br.s (HCl, H$_2$O), 7.40–7.51 m (3H, H$_{arom}$), 7.92–7.95 m (2H, H$_{arom}$), 8.33 s (NH). Found, %: C 40.88; H 3.29; Cl 27.75; N 10.89; S 16.72. $C_{13}H_{12}Cl_3N_3S_2$. Calculated, %: C 41.01; H 3.18; Cl 27.93; N 11.04; S 16.84.

***N*-(5-Chloromethyl-1,3-thiazolidin-2-ylidene)-pyridin-2-amine (III) and *N*-(5-chloromethyl-1,3-thiazolidin-2-ylidene)-1,3-thiazol-2-amines VIIIa, VIIIb, IXa, and IXb (*general procedure*).** A solution of 0.5 g of hydrochloride **II**, **VIa**, **VIb**, **VIIa**, or **VIIb** in 30 ml of dimethyl sulfoxide was cooled in an ice bath, and 40–60 ml of a 10% aqueous solution of sodium sulfite was added in small portions under stirring and cooling over a period of 3 h. After 2–5 h, the finely crystalline product was filtered off, thoroughly washed with water, and recrystallized from acetone (**III**) or ethanol (**VIIIa**, **VIIIb**, **IXa**, **IXb**).

***N*-(5-Chloromethyl-1,3-thiazolidin-2-ylidene)-pyridin-2-amine (III).** Yield 0.39 g (90%), mp 134–135°C. ^{1}H NMR spectrum, δ, ppm: 3.68–3.81 m (4H, 4′-H, CH$_2$Cl), 3.89–3.97 m (1H, 5′-H), 6.91 m (1H, pyridine), 7.15 m (1H, pyridine), 7.64 m (1H, pyridine), 8.23 m (1H, pyridine), 9.02 br.s (NH). Found, %: C 47.30; H 4.31; Cl 15.48; N 18.28; S 13.91. $C_9H_{10}ClN_3S$. Calculated, %: C 47.47; H 4.43; Cl 15.57; N 18.45; S 14.08.

Ethyl [2-(5-chloromethyl-1,3-thiazolidin-2-ylideneamino)-1,3-thiazol-4-yl]acetate (VIIIa). Yield 0.202 g (45%), mp 100–101°C. ^{1}H NMR spectrum, δ, ppm: 1.20 t (3H, CH$_3$, *J* = 7.2 Hz), 3.62 s (2H, CH$_2$CO), 3.65–3.88 m (4H, 4′-H, CH$_2$Cl), 4.07–4.15 m (1H, 5′-H), 4.10 q (2H, OCH$_2$, *J* = 7.2 Hz), 6.84 s (5-H), 8.52 br.s (NH). Found, %: C 41.25; H 4.29; Cl 11.01; N 13.02; S 19.93. $C_{11}H_{14}ClN_3O_2S_2$. Calculated, %: C 41.31; H 4.41; Cl 11.08; N 13.14; S 20.05.

Ethyl [5-chloro-2-(5-chloromethyl-1,3-thiazolidin-2-ylideneamino)-1,3-thiazol-4-yl]acetate (VIIIb). Yield 0.231 g (51%), mp 112–113°C. ^{1}H NMR spectrum, δ, ppm: 1.20 t (3H, CH$_3$, *J* = 7.2 Hz), 3.62 s (2H, CH$_2$CO), 3.65–3.90 m (4H, 4′-H, CH$_2$Cl), 4.07–4.15 m (1H, 5′-H), 4.11 q (2H, OCH$_2$, *J* = 7.2 Hz), 8.85 br.s (NH). Found, %: C 37.15; H 3.62; Cl 19.95; N 11.79; S 18.02. $C_{11}H_{13}Cl_2N_3O_2S_2$. Calculated, %: C 37.29; H 3.70; Cl 20.01; N 11.86; S 18.10.

***N*-(5-Chloromethyl-1,3-thiazolidin-2-ylidene)-4-phenyl-1,3-thiazol-2-amine (IXa).** Yield 0.350 g (79%), mp 159–160°C. ^{1}H NMR spectrum, δ, ppm: 3.62–3.89 m (4H, 4′-H, CH_2Cl), 4.06–4.13 m (1H, 5′-H), 7.29–7.33 m (1H, H_{arom}), 7.40–7.45 m (2H, H_{arom}), 7.52 s (5-H), 7.91–7.94 m (2H, H_{arom}), 8.60 br.s (NH). Found, %: C 49.54; H 3.79; Cl 11.30; N 13.47; S 20.55. $C_{13}H_{12}ClN_3S_2$. Calculated, %: C 50.39; H 3.90; Cl 11.44; N 13.56; S 20.70.

5-Chloro-*N*-(5-chloromethyl-1,3-thiazolidin-2-ylidene)-4-phenyl-1,3-thiazol-2-amine (IXb). Yield 0.382 g (84%), mp 175–176°C. ^{1}H NMR spectrum, δ, ppm: 3.63–3.87 m (4H, 4′-H, CH_2Cl), 4.08–4.13 m (1H, 5′-H), 7.40–7.52 m (3H, H_{arom}), 7.93–7.96 m (2H, H_{arom}), 8.86 br.s (NH). Found, %: C 45.19; H 3.11; Cl 20.43; N 12.09; S 18.47. $C_{13}H_{11}Cl_2N_3S_2$. Calculated, %: C 45.35; H 3.22; Cl 20.60; N 12.20; S 18.63.

REFERENCES

1. Gevaza, Yu.I., Staninets, V.I., and Zefirov, N.S., *Elektrofil'naya vnutrimolekulyarnaya tsiklizatsiya olefinov* (Electrophilic Intramolecular Cyclization of Olefins), Kiev: Naukova Dumka, 1990; Orysyk, V.V., Zborovskii, Yu.L. Staninets, V.I., Dobosh, A.A., and Khripak, S.M., *Khim. Geterotsikl. Soedin*., 2003, p. 739; Zborovskii, Yu.L., Orysyk, V.V., Dobosh, A.A., Staninets, V.I., Pirozhenko, V.V., and Chernega, A.N., *Khim. Geterotsikl. Soedin*., 2003, p. 1255; Zborovskii, Yu.L., Orysyk, V.V., Staninets, V.I., Nadtochii, S.N., Boguslavskii, A.Yu., Sagach, V.F., Dmitrieva, A.V., and Chernega, A.N. *Zh. Org. Farm. Khim*., 2003, vol. 1, p. 80.
2. Bodeker, J., Hauser, S., Selle, U., and Koppel, H., *J. Prakt. Chem*., 1974, vol. 6, p. 881.
3. Kuleshova, L.N. and Zorkii, P.M., *Acta Crystallogr., Sect. B*, 1981, vol. 37, p. 1363.
4. Watkin, D.J., Prout, C.K., Carruthers, J.R., and Betteridge, P.W., *Crystals. Issue 10*, Chemical Crystallography Laboratory, Univ. of Oxford, 1996.
5. Carruthers, J.R. and Watkin, D.J., *Acta Crystallogr., Sect. A*, 1979, vol. 35, p. 698.
6. Karanov, E. and Vasil'ev, G., *Dokl. Akad. Nauk SSSR*, 1964, vol. 156, p. 957.
7. Sahu, M., Garnaik, B.K., and Behera, R.K., *Indian J. Chem., Sect. B*, 1987, vol. 26, p. 779.