ISSN 1070-4280, Russian Journal of Organic Chemistry, 2009, Vol. 45, No. 4, pp. 555–558. © Pleiades Publishing, Ltd., 2009.
Original Russian Text © V.I. Potkin, Yu.S. Zubenko, 2009, published in Zhurnal Organicheskoi Khimii, 2009, Vol. 45, No. 4, pp. 568–572.

# Synthesis of 3-Amino-4,5-dichloroisothiazole

**V. I. Potkin and Yu. S. Zubenko**

*Institute of Physical Organic Chemistry, National Academy of Sciences of Belarus,*
*ul. Surganova 13, Minsk, 220072 Belarus*
*e-mail: potkin@ifoch.bas-net.by*

Received June 9, 2008

**Abstract**—4,5-Dichloro-1,2-thiazol-3-amine was synthesized starting from accessible 4,5-dichloro-1,2-thiazole-3-carbonyl azide and -3-carboxamide via Curtius and Hofmann rearrangements, respectively. The procedure involving Curtius rearrangement was found to be more advantageous from the preparative viewpoint.

**DOI:** 10.1134/S1070428009040149

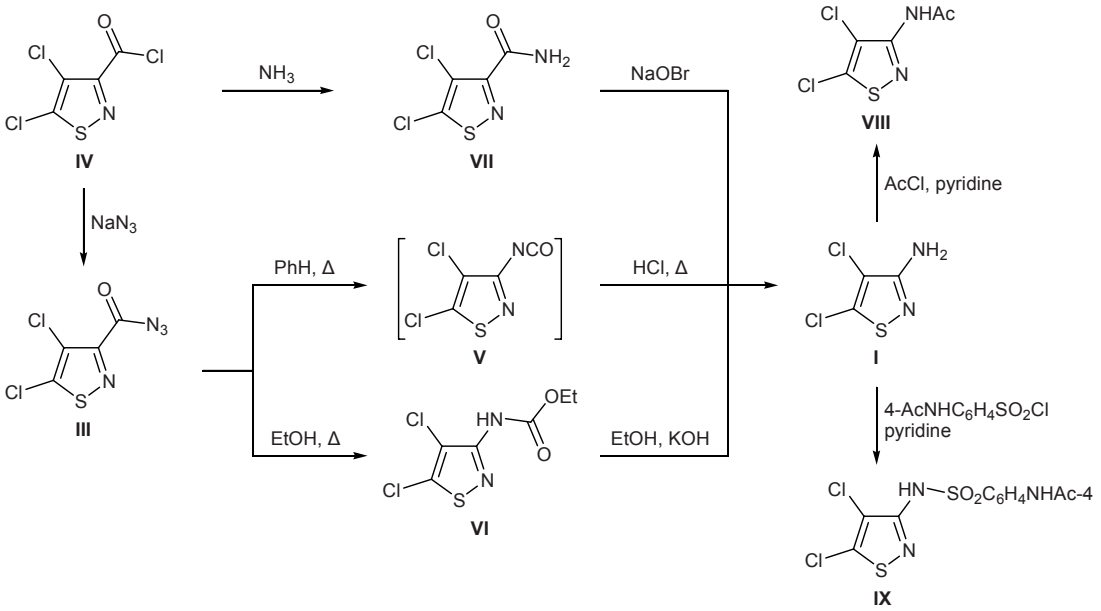
Aminoisothiazoles and their derivatives possess versatile biological activity, and they can be used as effective pesticides in agriculture, kinase inhibitors and highly selective 5-$HT_{2B}$ receptor antagonists in pharmacology, as well as biocides for protection of various materials from biological damage [1–4]. Studies on the development of convenient methods for preparation of these compounds and on their biological activity are extensively progressing [5–7].

The goal of the present study was to develop synthetic routes to previously unknown 3-amino-4,5-dichloroisothiazole (**I**) starting from derivatives of accessible 4,5-dichloroisothiazole-3-carboxylic acid (**II**); a convenient procedure for the preparation of acid **II** was reported by us previously [8]. Known and widely used synthetic approaches to amines are based on the Curtius and Hofmann rearrangements of carboxylic acid azides and amides, respectively, with loss of one carbon atom; also, some modifications of these methods were reported [9]. We examined two versions of the Curtius approach. Here, the key starting compound was 4,5-dichloro-1,2-thiazole-3-carbonyl azide (**III**) which was prepared in 79% yield by treatment of 4,5-dichloro-1,2-thiazole-3-carbonyl chloride (**IV**) with sodium azide and was identified on the basis of its elemental composition and IR and $^{13}C$ NMR spectra. Compound **III** displayed in the IR spectrum an absorption band at 2158 $cm^{-1}$, which is typical of azido group, and the carbonyl group in **III** gave a strong band at 1692 $cm^{-1}$. The $^{13}C$ NMR spectrum of azide **III** contained four signals at $\delta_C$ 126.53, 152.31, 154.99, and 166.22 ppm; among these, the first three correspond to the endocyclic carbon atoms, and the latter belongs to the carbonyl carbon atom.

Azide **III** was converted into aminoisothiazole **I** in two ways. According to the first of these, heating of azide **III** in anhydrous benzene gave the corresponding isocyanate **V**, and hydrolysis of the latter in concentrated hydrochloric acid afforded 3-amino-4,5-dichloroisothiazole (**I**) in 80% yield (calculated on the initial azide **III**; Scheme 1). Intermediate isocyanate **V** was not isolated as individual substance. Azide **III** was completely converted into isocyanate **V** during GC–MS analysis, and compound **V** was reliably identified by the mass spectrum. The second version involved intermediate carbamic acid derivative, ethyl 4,5-dichloro-1,2-isothiazol-3-ylcarbamate (**VI**), which was obtained in 94% yield by heating azide **III** in boiling anhydrous ethanol. Treatment of compound **VI** with alkali in boiling ethanol gave amine **I**. The yield of the latter was 98% calculated on carbamate **VI** and 92% calculated on azide **III**. Thus the second version ensured higher yield of the target product. As in the first version, azide **III** can also be converted into aminoisothiazole **I** without isolation of intermediate carbamate **VI**.

The structure of amine **I** and ethyl 4,5-dichloro-1,2-thiazol-3-ylcarbamate (**VI**) was determined by elemental analysis, IR and $^1H$ and $^{13}C$ NMR spectroscopy, and mass spectrometry. In the IR spectrum of **VI**, vibrations of the N–H group were characterized by absorption bands at 3243 and 1556 $cm^{-1}$, and stretching vibrations of the carbonyl group had a frequency of 1716 $cm^{-1}$. In the $^1H$ NMR spectrum of **VI**, protons in the ethoxy group resonated as a triplet ($CH_3$) and quartet ($CH_2$) at δ 1.33 and 4.29 ppm, respectively. The NH proton gave a singlet at δ 7.27 ppm. The $^{13}C$ NMR spectrum of **VI** contained signals at $\delta_C$ 15.02 and

**Scheme 1.**



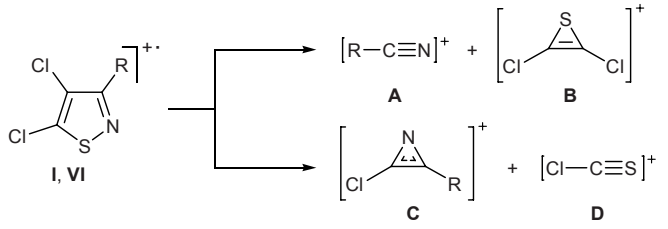

63.05 ppm from the ethoxy group, signals at $\delta_C$ 148.36 and 113.94 ppm were assigned to two carbon atoms in the isothiazole ring, and the third carbon atom in the isothiazole ring and the carbonyl carbon atom gave only one signal at $\delta_C$ 152.08 ppm.

In the IR spectrum of amine **I** we observed absorption bands at 3389 and 3299 $cm^{-1}$ due to stretching vibrations of the N–H bonds, which are typical of primary aromatic amines; bending vibrations of the amino group were characterized by absorption bands at 1630 and 1616 $cm^{-1}$. The $NH_2$ protons gave a broadened singlet at δ 4.88 ppm in the $^1H$ NMR spectrum. The $^{13}C$ NMR spectrum of **I** contained three signals at $\delta_C$ 159.82, 146.63, and 111.16 ppm from carbon atoms in the heteroring, while no signal assignable to exocyclic carbon atom was present.

Exhaustive proofs in support of the assumed structure of compounds **I** and **VI** were obtained by mass spectrometry. The mass spectra of **I** and **VI** contained molecular ion clusters with *m*/*z* values of 168 and 240, respectively (hereinafter, *m*/*z* values are given for ions containing $^{35}Cl$ isotope). The intensity ratio of isotope peak (100 : 65 : 10) is consistent with the presence of two chlorine atoms in molecules **I** and **VI** [10, 11]. The fragmentation patterns of the molecular ions of **I** and **VI** are typical of isothiazoles [12, 13], and they include cleavage of the isothiazole ring with formation of ions **A**–**D** (Scheme 2), subsequent decomposition of these ions, and elimination of substituents.

In the mass spectrum of amine **I**, the molecular ion peak has the maximal intensity (*m*/*z* 168, $I_{rel}$ 100%); next follows ion **B** with *m*/*z* 126 ($I_{rel}$ 33%). The relative intensities of peaks from ions **C** (*m*/*z* 89) and **D** (*m*/*z* 79) are 11 and 9%, respectively, while ion **A** contributes little to the total ion current (*m*/*z* 42, $I_{rel}$ 4%). The relative intensity of the molecular ion peak in the mass spectrum of **VI** is 24%, while the most abundant ion is that with *m*/*z* 168 ($I_{rel}$ 100%). The latter corresponds to amine **I** ion formed as a result of elimination of the COOEt group from the molecular ion. Also, ions

**Scheme 2.**




**I**, R = $NH_2$; **VI**, R = EtOC(O)NH.

**B** (*m*/*z* 126, $I_{rel}$ 17%), **C** (*m*/*z* 161, $I_{rel}$ 3%), and **D** (*m*/*z* 79, $I_{rel}$ 13%) were detected. No peak of ion **A** was observed, but those corresponding to its decomposition were present.

With a view to find optimal procedure for the preparation of amine **I**, we tried to synthesize it via Hofmann rearrangement of previously described 4,5-dichloro-1,2-thiazole-3-carboxamide (**VII**) [14]. In fact, amine **I** was formed in 78% yield by treatment of amide **VII** with a freshly prepared aqueous solution of sodium hypobromite. The reaction was complete in 0.5 h at 95°C, and the product was identical to that obtained via Curtius rearrangement. Comparison of the results showed that the synthesis of 4,5-dichloro-1,2-thiazol-3-amine (**I**) from azide **III** through intermediate carbamate **VI** is more advantageous from the preparative viewpoint, for it ensures the highest yield of the target product.

Aminoisothiazole **I** was subjected to acylation with acetyl chloride and 4-acetylaminobenzenesulfonyl chloride. The reaction of **I** with acetyl chloride was carried out in diethyl ether, and it smoothly afforded 87% of *N*-(4,5-dichloro-1,2-thiazol-3-yl)acetamide (**VIII**) (Scheme 1). Treatment of **I** with 4-acetylaminobenzenesulfonyl chloride resulted in the formation of the corresponding sulfonamide, *N*-[4-(4,5-dichloro1,2-thiazol-3-ylsulfamoyl)phenyl]acetamide (**IX**), in 63% yield. Compounds **VIII** and **IX** were identified on the basis of their elemental compositions and IR and $^1$H NMR spectra. The presence of a carboxamide moiety in molecule **VIII** followed from the IR spectrum which contained amide I band at 1683 cm$^{-1}$ (νC=O) and amide II band at 1617 cm$^{-1}$ (δN–H). Absorption bands at 1172 and 1312 cm$^{-1}$ in the IR spectrum of sulfonamide **IX** corresponded to vibrations of the S=O bonds. Broadened absorption bands in the region 3190–3386 cm$^{-1}$ were assigned to stretching vibrations of N–H bonds in **VIII** and **IX**. Compounds **VIII** and **IX** showed in the $^1$H NMR spectra singlets at δ 2.41 and 1.99 ppm, respectively, from the methyl protons in the acetyl groups, and signals from the NH protons appeared as broadened singlets in the region δ 8.03–10.21 ppm. The mass spectrum of **VIII** contained the molecular ion peak with *m*/*z* 210 ($I_{rel}$ 7%), whereas no molecular ion peak was present in the mass spectrum of sulfonamide **IX**.

## EXPERIMENTAL

The IR spectra were recorded in KBr on a Nicolet Protégé-460 spectrometer with Fourier transform. The $^1$H and $^{13}$C NMR spectra were measured from solutions in $CDCl_3$ on a Bruker Avance-500 spectrometer; the chemical shifts were determined relative to TMS ($^1$H) or solvent signal ($CDCl_3$, $\delta_C$ 77.0 ppm). The mass spectra (electron impact, 70 eV) were obtained on a Hewlett–Packard 5890/5972 GC–MS system (HP-5MS capillary column, 30 m × 0.25 mm, stationary phase 5% of phenylmethylsilicone, film thickness 0.25 μm; injector temperature 250°C).

4,5-Dichloro-1,2-thiazole-3-carbonyl chloride (**IV**) and 4,5-dichloro-1,2-thiazole-3-carboxamide (**VII**) were synthesized as described in [14].

**4,5-Dichloro-1,2-thiazol-3-amine (I).** *a*. A solution of 0.67 g (3 mmol) of azide **III** in 20 ml of anhydrous benzene was heated for 20 min under reflux, 50 ml of concentrated hydrochloric acid was added, and the mixture was heated for 1 h more at the boiling point. The aqueous phase was separated and neutralized with potassium hydroxide, and the precipitate was filtered off, washed with water, and dried under reduced pressure. Yield 0.40 g (80%), mp 121–122°C (from hexane). IR spectrum, ν, cm$^{-1}$: 3389, 3299, 1630, 1616 (NH), 1540, 1466, 1409 (isothiazole), 999, 824 (C–Cl). $^1$H NMR spectrum: δ 4.88 ppm, br.s (1H, NH). $^{13}$C NMR spectrum, $\delta_C$, ppm: 111.16, 146.63, 159.82. Found, %: C 21.50; H 1.61; Cl 41.45; N 16.29; S 18.94. $[M]^+$ 168. $C_3H_2Cl_2N_2S$. Calculated, %: C 21.32; H 1.19; Cl 41.95; N 16.58; S 18.97. *M* 169.03.

*b*. A mixture of 0.30 g (12 mmol) of azide **III** and 30 ml of anhydrous ethanol was heated for 3 h under reflux, a solution of 2.67 g of potassium hydroxide in 30 ml of ethanol was added, and the mixture was heated for an additional 1 h under reflux. It was then poured into water, and the precipitate was filtered off, washed with water, and dried under reduced pressure. Yield 1.82 (92%). The product was identical to a sample of amine **I** prepared as described above in *a*.

*c*. A solution of 1.20 g (30 mmol) of sodium hydroxide in 50 ml of water was cooled to 0°C, 0.3 ml (6 mmol) of bromine was added, and the mixture was stirred for 10 min at 0°C. Powdered amide **VII**, 0.98 g (5 mmol), was added in one portion, the mixture was stirred until it turned homogeneous, heated to 95°C, stirred for 30 min at that temperature, and cooled to 0°C, and the precipitate was filtered off, washed with water, and dried under reduced pressure. Yield 0.65 g (78%). The product was identical to samples of amine **I** prepared as described above in *a* and *b*.

**4,5-Dichloro-1,2-thiazole-3-carbonyl azide (III).** A solution of 2.16 g (10 mmol) of acid chloride **IV** in 25 ml of acetone was cooled to 0°C, a solution of

0.97 g (15 mmol) of sodium azide in 3 ml of water was added dropwise under stirring, the cooling bath was removed, and the mixture was stirred for 20 min and diluted with 100 ml of water. The precipitate was filtered off and dried under reduced pressure over $P_2O_5$. Yield 1.77 g (79%), decomposition point 50°C. IR spectrum, ν, $cm^{-1}$: 2158 ($N_3$); 1692 (C=O); 1402, 1349, 1217 (C=C, C=N); 940, 871 (C–Cl). $^{13}C$ NMR spectrum, $\delta_C$, ppm: 126.53, 152.31, 154.99 (4C); 166.22 (C=O). Found, %: C 21.32; Cl 31.57; N 25.19; S 14.43. $C_4Cl_2N_4OS$. Calculated, %: C 21.54; Cl 31.79; N 25.13; S 14.37.

**Ethyl 4,5-dichloro-1,2-thiazole-3-ylcarbamate (VI).** A suspension of 0.30 g (12 mmol) of azide **III** in 30 ml of anhydrous ethanol was heated for 3 h under reflux. The solvent was removed, and the residue was purified by recrystallization from hexane. Yield 0.31 g (94%), mp 70–72°C. IR spectrum, ν, $cm^{-1}$: 3243, 1556 (N–H); 1716 (C=O); 1518, 1427, 1367 (C=C, C=N); 998, 820 (C–Cl). $^1H$ NMR spectrum, δ, ppm: 1.33 t (3H, Me, $^3J$ = 7 Hz), 4.29 q (2H, $CH_2O$, $^3J$ = 7 Hz), 7.27 br.s (1H, NH). $^{13}C$ NMR spectrum, $\delta_C$, ppm: 152.08 (C=O, $C_{quat}$); 148.36, 113.94 (2C); 63.05 ($CH_2$); 15.02 ($CH_3$). Found, %: C 29.57; H 2.33; Cl 29.27; N 11.73; S 13.45. $[M]^+$ 240. $C_6H_6Cl_2N_2O_2S$. Calculated, %: C 29.89; H 2.51; Cl 29.41; N 11.62; S 13.30. *M* 241.09.

***N*-(4,5-Dichloro-1,2-thiazole-3-yl)acetamide (VIII).** A solution of 0.24 g (3 mmol) of acetyl chloride in 5 ml of diethyl ether was added dropwise under stirring to a solution of 0.51 g (3 mmol) of amine **I** and 0.24 g (3 mmol) of pyridine in 10 ml of diethyl ether. The mixture was stirred for 20 min, the precipitate was filtered off, and the filtrate was washed with 3% hydrochloric acid, dried over $Na_2SO_4$, and evaporated. Yield 0.55 g (87%), mp 147–150°C. IR spectrum, ν, $cm^{-1}$: 3386, 3292, 1617 (N–H); 1683 (C=O); 1539, 1506, 1409 (C=C, C=N); 998, 821 (C–Cl). $^1H$ NMR spectrum, δ, ppm: 2.41 s (3H, $CH_3$), 8.03 br.s (1H, NH). Found, %: C 28.43; H 1.55; Cl 33.89; N 13.74; S 14.98. $[M]^+$ 210. $C_3H_2Cl_2N_2S$. Calculated, %: C 28.45; H 1.91; Cl 33.59; N 13.27; S 15.19. *M* 211.07.

***N*-[4-(4,5-Dichloro-1,2-thiazol-3-ylsulfamoyl)-phenyl]acetamide (IX).** 4-Acetylaminobenzenesulfonyl chloride, 1.5 g (6.5 mmol), was added dropwise to a solution of 1.02 g (6 mmol) of amine **I** in 5 ml of pyridine, and the mixture was stirred for 1 h at 20°C, heated to 50°C, and stirred for 1 h at 50°C. The mixture was then cooled, 10 ml of water and 20 ml of 10% hydrochloric acid were added, and the precipitate was filtered off, washed with water, and dried under reduced pressure. Yield 1.49 g (63%), mp 156–158°C. IR spectrum, ν, $cm^{-1}$: 3260, 3190 (N–H); 1415, 1494, 1582, 1600 (C=C, C=N); 1172, 1312 (S=O); 819 (C–Cl). $^1H$ NMR spectrum, δ, ppm: 1.99 s (3H, $CH_3$), 7.50 d (2H, $H_{arom}$, $^3J$ = 8.5 Hz), 7.55 d (2H, $H_{arom}$, $^3J$ = 8.5 Hz), 7.9 br.s (1H, $SO_2NH$), 10.21 br.s (1H, AcN**H**). Found, %: C 36.48; H 2.50; Cl 17.67; N 10.96; S 16.37. $C_{12}H_9Cl_2N_3O_4S_2$. Calculated, %: C 36.56; H 2.30; Cl 17.98; N 10.66; S 16.26.

This study was performed under partial financial support by the Byelorussian Republican Foundation for Basic Research (project no. Kh07M-025).

## REFERENCES

1. Samaritoni, J.G., Babcock, J.M., Schlenz, M.L., and Johnson, G.W., *J. Agric. Food Chem*., 1999, vol. 47, p. 3381.
2. El Abdellaoui, H., Varaprasad, C.V., Barawkar, D., Chakravarty, S., Maderna, A., Tam, R., Chen, H., Allan, M., Wu, J.Z., Appleby, T., Yan, S., Zhang, W., Lang, S., Yao, N., Hamatake, R., and Hong, Z., *Bioorg. Med. Chem. Lett*., 2006, vol. 16, p. 5561.
3. Forbes, I.T., Ham, P., Booth, D.H., Martin, R.T., Thompson, M., Baxter, G.S., Blackburn, T.P., Glen, A., Kennet, G.A., and Wood, M.D., *J. Med. Chem*., 1995, vol. 38, p. 2524.
4. Cocco, M.T., Congiu, C., Maccioni, A., Onnis, V., Schivo, M.L., and De Logu, A., *Farmaco*, 1994, vol. 49, p. 137.
5. Regiec, A., Machoń, Z., Miedzybrodzki, R., and Szymaniec, S., *Arch. Pharm*., 2006, vol. 339, p. 401.
6. Kaberdin, R.V. and Potkin, V.I., *Usp. Khim*., 2002, vol. 71, p. 764.
7. Hamad Elgazwy, A.-S.S., *Tetrahedron*, 2003, vol. 59, p. 7445.
8. Kaberdin, R.V., Potkin, V.I., and Ol'dekop, Yu.A., *Zh. Org. Khim*., 1990, vol. 26, p. 1560.
9. Vatsuro, K.V. and Mishchenko, G.L., *Imennye reaktsii v organicheskoi khimii* (Name Reactions in Organic Chemistry), Moscow: Khimiya, 1976.
10. Takhistov, V.V., *Prakticheskaya mass-spektrometriya organicheskikh soedinenii* (Practical Mass Spectrometry of Organic Compounds), Leningrad: Leningr. Gos. Univ., 1977, p. 265.
11. Takhistov, V.V., Rodin, A.A., and Maksimova, B.N., *Usp. Khim*., 1991, vol. 60, p. 2143.
12. Poite, J.C., Vivaldi, R.V., and Bonzom, A., *C. R. Acad. Sci., Ser. C*, 1969, vol. 268, p. 12.
13. Naito, T., *Tetrahedron*, 1968, vol. 24, p. 6237.
14. Nechai, N.I., Dikusar, E.A., Potkin, V.I., and Kaberdin, R.V., *Russ. J. Org. Chem*., 2004, vol. 40, p. 1009.