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Synthesis of 4,5-Dichloro-3-cyanoisothiazole and Its Functional Derivatives

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Abstract—By treating with phosphorus pentoxide the 4,5-dichloroisothiazole-3-carboxamide 4,5-dichloro-3-cyanoisothiazole was synthesized whose reactions with piperidine, phenyl- and benzylthiols occurred with replacement of the chlorine atom in the position *5* by the residue of the corresponding nucleophile. Reactions with sodium thiobytylate and also with sodium methylate in methanol led to the formation both of the products of chlorine substitution by BuS or MeO groups respectively and of addition products of methanol to the cyano group. The reaction of butanethiol with cyanoisothiazole in 2-propanol in the presence of sodium 2-propylate was more selective and resulted in the replacement of the chlorine atom in the position *5* by the residue of the butanethiol.

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The stable interest to the synthesis of functionally-substituted isothiazole is stimulated by the high biological activity of many among these compounds. A large part of recent publications consists of patent on preparation and application of isothiazoles as agricultural reagents and pharmaceuticals of versatile range of application [1, 2].

The functionalization of isothiazole ring is one of the most reasonable ways to the synthesis of new compounds promising for testing their biological action. Functional derivatives of isothiazoles possessing a cyano group in the position *4* of the heterocycle are known to exhibit fungicidal, insecticide, and bactericidal activity [3–5]. No published data are available on the preparation and properties of 3-cyano-substituted isothiazoles.

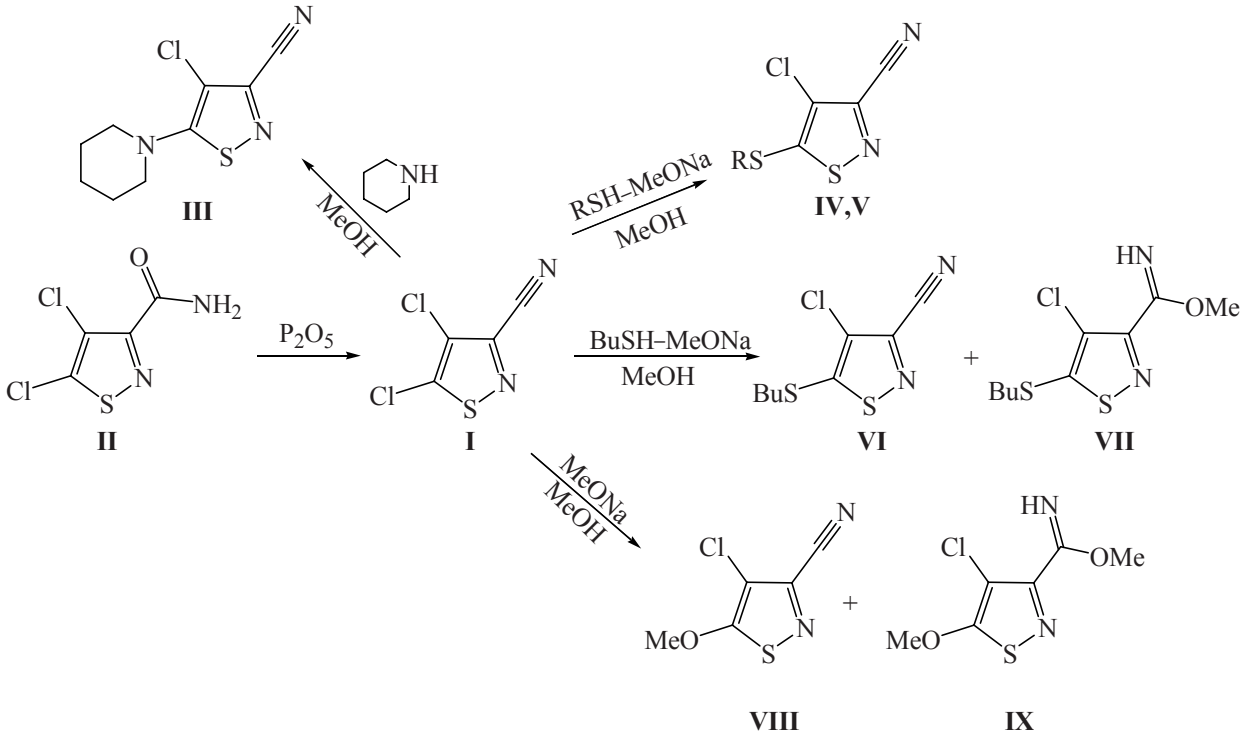
The target of our research consisted in the development of preparation procedure of 4,5-dichloro-3-cyanoisothiazole (**I**) and its heteroatomic derivatives. We chose as an initial compound the available 4,5-dichloroisothiazole-3-carboxamide (**II**) [6]. 4,5-Dichloroisothiazole-3-carboxylic acid is the reioisomer we have formerly synthesized of 3,4-dichloroisothiazole-5-carboxylic acid whose derivatives are endowed with a wide range of pesticide action [7, 8].

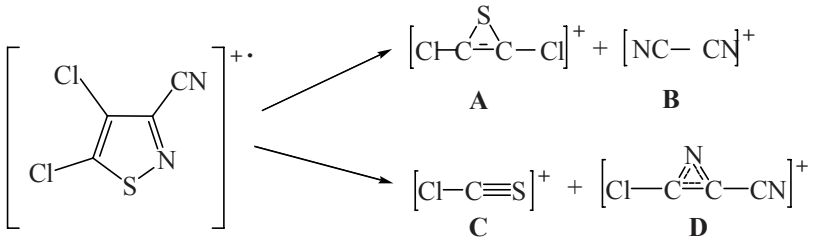
The synthesis of cyanoisothiazole **I** was performed by treating amide **II** with phosphorus pentoxide. It was established that the reaction could be carried out both by heating the reagents without solvent at 110–120°C and by boiling the reagents mixture in perchloroethylene. In both cases the process was completed in 1 h, and the yield of nitrile **I** was 95%.

A popular procedure for nitriles preparation by treating amides with the thionyl chloride in DMF in our case proved to be less acceptable: The reaction proceeded slowly, was accompanied with considerable tarring, and the yield of nitrile **I** did not exceed 50%.

The formation in the reaction of cyanoisothiazole **I** was confirmed by the presence in its IR spectrum of the characteristic absorption band of the C≡N group at 2246 cm^{-1}. In the ^{13}C NMR spectrum of compound **I** lacked the signal of the carbon atom of the amide group of the initial compound **II** at 161.2 ppm and appeared the signal of cyano group at δ 111.8 ppm and also three signals with the chemical shifts 128.3, 139.7, and 151.7 ppm belonging to carbon atoms of the heterocycle.

The exhaustive proofs of the nitrile structure were obtained by mass spectrometry. The mass spectrum of compound **I** contained a group of molecular ion peaks where the intensity ratio of isotope components (100:65:10) indicated the presence in the molecule of two chlorine atoms [9, 10]. The fragmentation of the molecular ion occurred in the way characteristic of

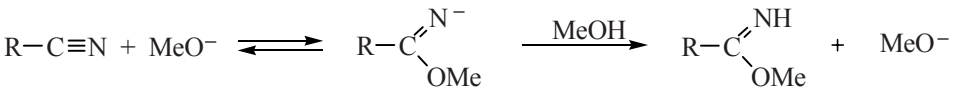




isothiazoles by decomposition of the heterocycle to give ions **A**–**D** [11, 12]. The most abundant were in the spectrum the molecular ion peaks (*m/z* 178, I_{rel} 100%), those of the sulfur-containing ions **A** (*m/z* 126, I_{rel} 44%) and **C** (*m/z* 79, I_{rel} 64%), and also of products of chlorine elimination from these ions. The peaks of nitrogen-containing ions **B** and **D** are of low intensity. (Here and hereinafter the *m/z* values for the chlorine-containing ions are given for the components with the isotope ^{35}Cl).

We investigated the reactions of synthesized nitrile **I** with nucleophiles of different character. The reaction of nitrile **I** with a double excess of piperidine in methanol at 40°C occurred with the substitution of the chlorine atom in the position *5* of the heterocycle and resulted in 5-piperidin-1-yl-4-chloro-3-cyanoisothiazole (**III**) in 53% yield. The piperidine excess served for bonding the evolved hydrogen chloride.

The reaction with phenyl- and benzylthiols in methanol in the presence of sodium methylate at the equimolar reagenta ratio at room temperature also proceeded at the position *5* of the isothiazole molecule and led to the formation of the corresponding 5-(phenylthio)- and 5-(benzylthio)-4-chloro-3-cyanoisothiazoles (**IV** and **V**) in 64–67% yields.



R = Ph (**IV**), Bn (**V**).

The direction of nitrile **I** reaction with butanethiol strongly depended on the nature of alcohol and alcoholate whereas for phenyl- and benzylthiols this was insignificant. For instance, the reaction of butanethiol with nitrile **I** in methanol solution in the presence of sodium methylate occurred nonselectively giving a mixture of products where alongside the expected product of chlorine replacement, 5-(butylthio)-4-chloro-3-cyanoisothiazole (**VI**) methyl 5-(butylthio)-4-chloroisothiazol-3-imidocarboxylate (**VII**) was identified. Overall yield of compounds **VI** and **VII** was 54%, and their ratio in the mixture was ~ 1:2. The reaction of butanethiol with nitrile **I** in 2-propanol solution in the presence of sodium 2-propanolate proceeded relatively selectively and provided in 68% yield 5-(butylthio)-4-chloro-3-cyanoisothiazole (**VI**) isolated in an individual state. Compounds **VI** and **VII** obtained in methanol were not separated, and their formation was confirmed by the data of GC-MS, IR, and ^{1}H NMR spectra of the reaction mixture after its vacuum distillation, and also by comparison of the sprctra of mixture with those of individual compound **VI**. In the mass spectrum of the mixture appeared the peaks of molecular ions with *m/z* 232 and 264 corresponding to compounds **VI** and **VII** respectively. The intensity ratio of the isotope peaks of molecular ions equal 100:33 confirmed the presence in the molecules of a single chlorine atom [9, 10]. In IR spectrum of compounds **VI** and **VII** mixture alongside the absorption band of cyano group of compound **VI** at 2246 cm^{-1} absorption bands were present of N–H bonds (3425 cm^{-1}) and C=N (1637 cm^{-1}) of ester **VII**. In the ^{1}H NMR spectrum of the mixture alongside the signals of the butyl groups a broadened singlet was observed at 7.15 ppm and a singlet at δ 4.10 ppm belonging respectively to imido and methoxy groups of compound **VII**.

The formation of the addition product of MeOH to the cyano group in the reaction of nitrile **I** with butanethiol is apparently due to the higher basicity of anion BuS$^-$ compared with anions PhS$^-$ and BnS$^-$ [13] resulting in higher concentration of methoxy anions in the mixture and catalyzing the methanol reaction at the cyano group occurring through primary reversible addition of the methylate anion to the C≡N bond and giving finally imidoester **VII** [14].

The effect of the alcohol nature on the mode of the nitrile reaction with butanethiol may be ascribed to the difference in the acid-base properties of the alcohols. In 2-propanol possessing considerably smaller autoprotolysis constant and larger proton affinity than methanol [15] the content of anions *i*-PrO$^-$ in the reaction mixture is significantly lower and consequently the content of thiobutylate anions higher favoring the replacement of chlorine and impeding the reaction at the cyano group.

The composition and structure of obtained compounds **III–VI** were established from elemental analyses, IR, ^{1}H NMR, and mass spectra. In the IR spectra of the compounds the C≡N group gave rise to the absorption band in the region 2240–2247 cm^{-1}, the C=C and C=N of isothiazole ring, to three characteristic bands in the range 1313–1528 cm^{-1}. In the ^{1}H NMR spectra of compounds **III–VI** the signals of hydrogen-containing fragments of the molecules appeared with the appropriate multiplicity and integral intensity. The mass spectra of compounds **III–VI** contained the molecular ion peaks with the ratio of isotope components (100:33) corresponding to the presence in the molecules of a single chlorine atom [9, 10]. The fragmentation of molecular ions under the electron impact proceeded in a complex way with elimination of substituents, their fragments, and with the cleavage of the isothiazole ring. The maximum abundance in the spectra of alkyl(aryl)thio derivatives **IV–VI** have the molecular ion peaks with *m/z* 252, 266, and 232 respectively. In the mass spectrum of compound **III** the most abundant peak corresponded to the piperidine residue (*m/z* 84), and the intensity of the molecular ion peak with *m/z* 227 was 65%.

We presumed that the reaction of nitrile **I** with sodium methylate in methanol should also occur not only with the substitution of a chlorine atom, but also with methanol addition to the C≡N bond. Actually, the reaction of nitrile **I** with MeONa in methanol solution resulted in the formation of two main products: 5-methoxy-4-chloro-3-cyanoisothiazole (**VIII**) and methyl 5-methoxy-4-chloroisothiazol-3-imidocarboxylate (**IX**) in a ratio 1:3 and overall yield 40%. Compounds **VIII** and **IX** were identified by GC-MS method, and also based on IR and ^{1}H NMR spectra of the reaction mixture after its vacuum distillation.

In the mass spectra of the mixture resulting from the reaction molecular ion peaks of compounds **VIII** and **IX** were present with *m/z* 174 and 206 respectively and the ratio of isotope components (100:33), corresponding to the presence of a single chlorine atom in the molecule. The ^{1}H NMR spectrum of the mixture contained three singlets at 4.35, 4.25, and 3.92 ppm where the first one belonged to MeO group of compound **VIII**, and the other

two, to methoxy groups of imidoester **IX**. The integral intensities of singlets at 4.25 and 3.92 ppm are equal, and the intensity of the singlet at δ 4.35 ppm is three times less than each of them in agreement with the data of GC-MS analysis. The presence of =NH group in the structure of compound **IX** is confirmed by the appearance in the ^{1}H NMR spectrum of a broadened singlet at δ 8.5 ppm. In the IR spectrum of the products mixture alongside the absorption bands of the isothiazole ring in the region 1313–1532 cm^{-1} the absorption bands are observed of C=N (1621 cm^{-1}) and NH (3456 cm^{-1}) bonds characterizing the molecular fragments of imidoester **IX**. The presence in the mixture of methoxy-substituted nitrile **VIII** is confirmed by the weak absorption band of C≡N bond in the region 2248 cm^{-1}.

Some of compounds obtained show insecticide activity and are interesting for further investigation as chemical agents for plant protection.

EXPERIMENTAL

IR spectra of compounds were recorded on a Fourier-spectrophotometer Nikolet Protégé-460 from samples pelletized with KBr. ^{1}H and ^{13}C NMR spectra were registered on a spectrometer Avance-500 in $CDCl_3$. Chemical shifts of protons were measured with respect to TMS, of carbon atoms, related to $CDCl_3$ signal (δ 77.0 ppm). Mass spectra were obtained on a GC-MS instrument Hewlett Packard 5890/5972 in the electron impact mode at ionizing electrons energy 70 eV; capillary column HP-5MS 30 m × 0.25 mm, stationary phase (5% PhMe Silicone) 0.25 μm, vaporizer temperature 250°C.

4,5-Dichloroisothiazole-3-carboxamide (**II**) was prepared by procedure [6].

4,5-Dichloro-3-cyanoisothiazole (I). A mixture of 2 g (10 mmol) of dichloroisothiazole-3-carboxamide (**II**) and 1.42 g (10 mmol) of phosphorus pentoxide was heated for 1 h at 110–120°C, then the reaction mixture was cooled to room temperature and extracted with dichloromethane. The extract was washed with water, dried with $CaCl_2$, the solvent was removed, the solid reaction product was purified by sublimation in a vacuum (1 mm Hg). Yield 1.71 g (95%), mp 43–44°C. IR spectrum, ν, cm^{-1}: 2246 (C≡N), 1482, 1377, 1351 (C=C, C=N of isothiazole), 972 (C–Cl). ^{13}C NMR spectrum, δ, ppm: 111.79 (C≡N), 128.25, 139.72, 151.67 (carbon atoms of heterocycle). Mass spectrum, *m/z* (I_{rel}, %): 178 (100) $[M]^+$, 126 (44), 99 (4), 91 (53), 79 (64), 64 (5), 56 (17), 52 (5).

5-Piperidyl-4-chloro-3-cyanoisothiazole (III). A solution of 0.9 g (5 mmol) of nitrile **I** and 0.93 g (11 mmol) of piperidine in 20 ml of methanol was stirred at 40°C for 10 h, then it was poured on ice, the precipitate was filtered off, washed with water, and dried in a vacuum. After recrystallization from a mixture ether–hexane, 1:3, yield was 0.61 g (53%), mp 103–104°C. IR spectrum, ν, cm^{-1}: 2240 (C≡N), 1528, 1390, 1313 (C=C, C=N of isothiazole). ^{1}H NMR spectrum, δ, ppm: 1.8–2.1 m (6H, $3CH_2C$), 3.3–3.6 m (4H, $2CH_2N$). Found, %: C 47.83; H 4.58; Cl 15.85; N 18.29; S 14.02. $[M]^+$ 227. $C_9H_{10}ClN_3S$. Calculated, %: C 47.47; H 4.43; Cl 15.57; N 18.45; S 14.08. *M* 228.

5-[Phenyl(benzyl)thio]-4-chloro-3-cyanoisothiazoles IV and V. To a solution of 0.9 g (5 mmol) of nitrile **I** and 5 mmol of an appropriate thiol in 20 ml of methanol was added dropwise 0.27 g (5 mmol) of sodium methylate in 15 ml of methanol; the mixture was stirred for 8 h at 20–25°C. The precipitate was filtered off, the filtrate was evaporated in a vacuum to dryness and washed with water. The obtained reaction product was purified by recrystallization from a mixture ether–hexane, 1:3.

5-(Phenylthio)-4-chloro-3-cyanoisothiazole (IV). Yield 67%, mp 75–76°C. IR spectrum, ν, cm^{-1}: 2242 (C≡N), 1441, 1378, 1356 (C=C, C=N of isothiazole). ^{1}H NMR spectrum, δ, ppm: 7.4–7.6 m (5H, Ph). Found, %: C 47.70; H 1.84; Cl 14.32; N 11.17; S 25.31. $[M]^+$ 252. $C_{10}H_5ClN_2S_2$. Calculated, %: C 47.52; H 1.99; Cl 14.03; N 11.09; S 25.37. *M* 252.73.

5-(Benzylthio)-4-chloro-3-cyanoisothiazole (V). Yield 64%, mp 63–64°C. IR spectrum, ν, cm^{-1}: 2247 (C≡N), 1452, 1380, 1347 (C=C, C=N of isothiazole). ^{1}H NMR spectrum, δ, ppm: 4.55 s (2H, CH_2S), 7.4–7.6 m (5H, Ph). Found, %: C 49.83; H 2.89; Cl 13.32; N 11.17; S 25.31. $[M]^+$ 266. $C_{11}H_7ClN_2S_2$. Calculated, %: C 49.52; H 2.65; Cl 13.29; N 10.50; S 24.04. *M* 266.76.

5-(Butylthio)-4-chloro-3-cyanoisothiazole (VI) was prepared similarly but the nitrile reaction with butanethiol was carried out in 2-propanol in the presence of sodium 2-propylate for 12 h. Yield 68%, mp 165–167°C. IR spectrum, ν, cm^{-1}: 2246 (C≡N), 1486, 1383, 1353 (C=C, C=N of iso-thiazole). ^{1}H NMR spectrum, δ, ppm: 0.97 t (3H, CH_3), 1.48–1.53 m (2H), 1.73–1.77 d.t (2H, CH_2C), 3.06 t (2H, CH_2S, ^3J 7.5 Hz). Found, %: C 41.56; H 4.15; Cl 15.42; N 12.11; S 27.62. $[M]^+$ 232. $C_8H_9ClN_2S_2$. Calculated, %: C 41.28; H 3.90; Cl 15.23; N 12.04; S 27.55. *M* 232.74.

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