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Synthesis of 5-Alkyl(aryl)sulfanyl-4-chloro-3-trichloromethyl-1,2-thiazoles and 5-Alkyl(aryl)sulfanyl-4-chloro-1,2-thiazole-3-carboxylic Acids

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Abstract—Butane-, phenylmethane-, and benzenethiols reacted with 4,5-dichloro-3-trichloromethyl-1,2-thiazole in the presence of sodium ethoxide to give the corresponding 5-alkyl(aryl)sulfanyl-4-chloro-3-trichloromethyl-1,2-thiazoles. The reaction of 4,5-dichloro-1,2-thiazole-3-carboxylic acid with the same thiols under similar conditions resulted in the formation of sodium 4,5-dichloro-1,2-thiazole-3-carboxylate, while in the presence of pyridine 5-alkyl(aryl)sulfanyl-4-chloro-1,2-thiazole-3-carboxylic acids were obtained.

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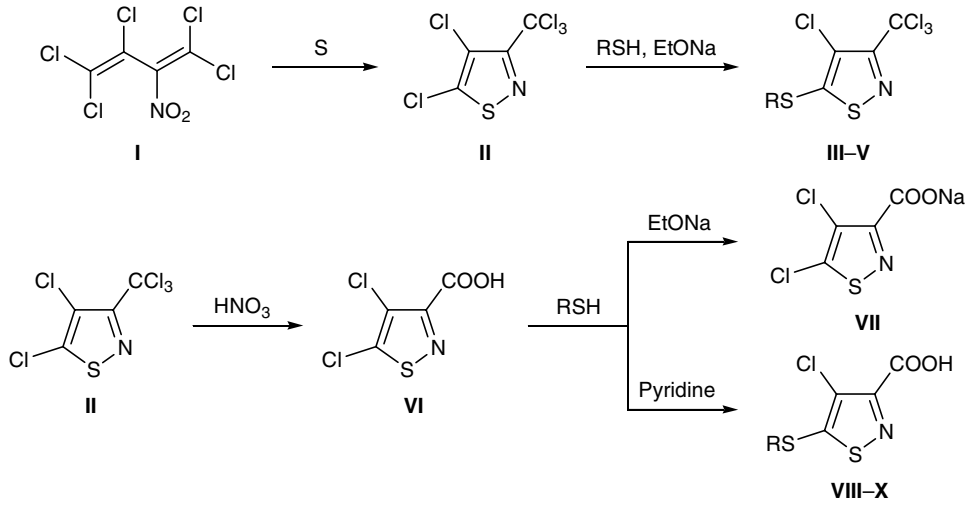
The chemistry of isothiazole is extensively developed due to high biological activity revealed in the recent years for a number of isothiazole derivatives. For example, these compounds were shown to be promising for the treatment of Alzheimer's disease; they also exhibited antiphlogistic, antithrombotic, and anticonvulsant activity; some isothiazole derivatives are capable of interacting with glutamate receptors, while the others may be used as chemical means for plant protection. In addition, some isothiazole derivatives showed a synergistic effect and were therefore included into pesticide compositions to enhance their efficiency [1, 2].

We previously described a new and convenient procedure for building up isothiazole ring starting from accessible 2-nitropentachlorobuta-1,3-diene (**I**); its reaction with molecular sulfur leads to the formation of 4,5-dichloro-3-trichloromethyl-1,2-thiazole (**II**) [3]. Molecule **II** possesses several reaction centers, specifically a trichloromethyl group and a labile chlorine

Scheme 1.



III, **VIII**, R = Bu; **IV**, **IX**, R = Bzl; **V**, **X**, R = Ph.

atom in the 5-position of the heteroring; therefore, it attracts interest from the viewpoint of further functionalization. It is known that isothiazole **II** is capable of reacting with alkali metal alkoxides to give the corresponding 5-alkoxy derivatives as a result of replacement of the 5-chlorine atom [4]. In the present work we examined reactions of compound **II** and 4,5-dichloro-1,2-thiazole-3-carboxylic acid with various thiols with the goal of obtaining alkyl(aryl)sulfanyl-substituted isothiazoles.

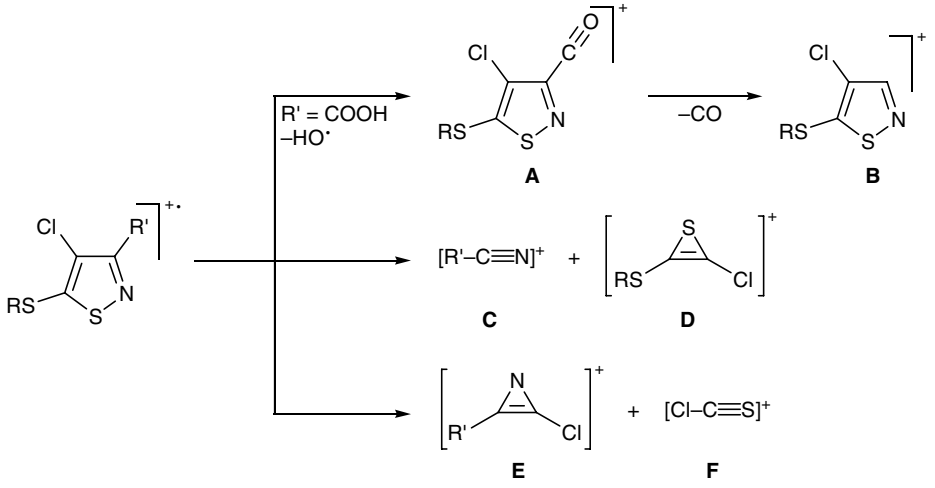
Dichlorotrichloromethylisothiazole **II** reacted with equimolar amounts of butane-, phenylmethane-, and benzenethiols in ethanol in the presence of sodium ethoxide to produce the corresponding 5-alkyl(aryl)-sulfanyl-4-chloro-3-trichloromethyl-1,2-thiazoles **III–V** in 54–61% yield via selective replacement of one chlorine atom in position *5* of the heteroring (Scheme 1). We previously showed [4] that the trichloromethyl group in compound **II** is readily converted into carboxy group by the action of anhydrous nitric acid; 4,5-dichloro-1,2-thiazole-3-carboxylic acid (**VI**) is isomeric to dichloroisothiazolecarboxylic acids possessing a strong pesticide activity [5, 6]. We made an attempt to synthesize 5-sulfanyl-substituted derivatives of acid **VI**. By treatment of **VI** with equimolar amounts of the above thiols in the presence of sodium ethoxide we obtained the corresponding sodium salt **VII** in quantitative yield. The properties of salt **VII** coincided with those reported previously [7]. The reactions of acid **VI** with thiols in diethyl ether in the presence of pyridine followed a different pathway. As with isothiazole **II**, the reactions involved replacement of the 5-chlorine atom with formation of the corresponding 5-alkyl(aryl)sulfanyl-4-chloro-1,2-thiazole-3-carboxylic acids **VIII–X** in 52–65% yield (Scheme 1). No reaction occurred in the absence of pyridine even on prolonged heating of the reaction mixture.

The structure of compounds **III–X** was determined on the basis of their elemental compositions and IR, ^{1}H NMR, and mass spectra. In the IR spectra of **III–V** and **VIII–X**, absorption bands in the region 1350–1500 cm^{-1} were assigned to vibrations of the isothiazole ring. Strong bands at 735–782 cm^{-1} in the spectra of **III–V** belong to stretching vibrations of the C–Cl bonds in the trichloromethyl group. Carboxylic acids **VIII–X** characteristically displayed a strong absorption band at 1661–1673 cm^{-1} due to stretching vibrations of the carbonyl group.

In the ^{1}H NMR spectra of **III–V** and **VIII–X** we observed signals from protons in the R-sulfanyl group, whose intensities were consistent with the assumed structures. The acid COOH proton signal appeared in the spectra of **VIII–X** as a broadened singlet at δ 8.75–8.80 ppm.

The structure of the obtained sulfanyl-substituted isothiazole derivatives was convincingly proved by analysis of their mass spectra. All compounds **III–V** and **VIII–X** showed in the mass spectra peaks from the molecular ions with an intensity ratio of isotope peaks of 77 : 100 : 49 : 10 for **III–V** and 100 : 33 for **VIII–X**; these data indicate the presence of four chlorine atoms in molecules **III–V** and one chlorine atom in **VIII–X** [8, 9]. The molecular ions of these compounds undergo fragmentation along several pathways, including decomposition of the carboxy group in **VIII–X** to give ions **A** and **B** [10], elimination of chlorine, hydrocarbon, and alkyl(aryl)sulfanyl groups, and decom-

Scheme 2.



position of the heteroring with formation of ions **C**–**F**, which is typical of isothiazoles [11, 12] (Scheme 2).

The main fragmentation pathways of isothiazoles **III**–**V** are elimination of chlorine to give $[M - Cl]^+$ ions (this ion is the most abundant in the spectrum of **V**) and elimination of the alkyl (aryl) or alkyl(aryl)sulfanyl group; therefore, peaks from ions **C**–**F** formed as a result of fragmentation of the isothiazole ring are characterized by low intensities. In the mass spectra of compounds **III**–**V** ion peaks from the trichloromethyl fragment were present (*m*/*z* 117 for ^{35}Cl), indicating that the CCl_3 group in **II** is not involved in the reaction with thiols.

Alkyl(aryl)sulfanyl-substituted isothiazolecarboxylic acids **VIII**–**X** displayed in the mass spectra peaks of ions **A** arising from elimination of hydroxyl radical from the molecular ions; ion **A** then loses CO molecule to give ion **B**. The latter can also be formed directly from the molecular ion via elimination of $[HOC{\equiv}O]^+$. Strong peaks in the mass spectra of **VIII**–**X** correspond to elimination of hydrocarbon fragments from the molecular ions and ions **A**. Ions **C**–**F** resulting from decomposition of the isothiazole ring in **VIII**–**X** give rise to weak peaks in the mass spectra.

In all cases, the reaction mixtures contained the corresponding alkyl(aryl) disulfides which were detected by gas chromatographic–mass spectrometric analysis.

It is known that chlorine-containing isothiazolecarboxylic acids and their derivatives, as well as 5-alkylsulfanyl-substituted isothiazole-4-carbonitriles, exhibit strong biological activity [1, 2]; therefore, alkyl(aryl)sulfanyl derivatives of 3-trichloromethylisothiazole and isothiazole-3-carboxylic acids synthesized in the present work attract interest from the viewpoint of studying their biological activity.

EXPERIMENTAL

The IR spectra of were recorded on a Nicolet Protege-460 spectrophotometer with Fourier transform; samples were examined as KBr pellets (**VIII**–**X**) or thin films (**III**–**V**). The ^1H NMR spectra were recorded on a Tesla BS-567A spectrometer (100 MHz) from solutions in $CDCl_3$ (**III**, **IV**) or DMSO-d_6 (**V**, **VIII**–**X**) using tetramethylsilane as internal reference. The mass spectra (electron impact, 70 eV) were obtained on a Hewlett–Packard HP 5972 mass-selective detector coupled with an HP 5890 gas chromatograph (HP-5MS capillary column, 30 m×0.25 mm, film thickness 0.25 μm, 5% of phenylmethylsilicone; injector temperature 250°C). The components were identified using the NBS75k library of mass spectra.

4,5-Dichloro-3-trichloromethyl-1,2-thiazole (**II**) and 4,5-dichloro-1,2-thiazole-3-carboxylic acid (**VI**) were synthesized by the procedures described in [4].

5-Alkyl(aryl)sulfanyl-4-chloro-3-trichloromethyl-1,2-thiazoles III–V (*general procedure*)**.** A solution of 4 mmol of sodium ethoxide in 20 ml of ethanol was added dropwise under stirring at 20–25°C to a solution of 1.08 g (4 mmol) of 4,5-dichloro-3-trichloromethyl-1,2-thiazole (**II**) and 4 mmol of the corresponding thiol in 30 ml of ethanol. The mixture was stirred for 1 h, the precipitate of sodium chloride was filtered off, the filtrate was diluted with 150 ml of water and extracted with chloroform, and the extract was dried over $CaCl_2$ and evaporated. The residue was purified by column chromatography on silica gel (100–160 μm) using hexane–diethyl ether (4:1) as eluent.

5-Butylsulfanyl-4-chloro-3-trichloromethyl-1,2-thiazole (III). Yield 54%, oily substance. IR spectrum, ν, cm^{-1}: 782 (CCl_3); 1357, 1380, 1500 (isothiazole). ^1H NMR spectrum, δ, ppm: 0.99 t (3H, CH_3, ^3J = 6 Hz), 1.20–1.85 m (4H, CH_2), 3.08 t (2H, CH_2S, ^3J = 8 Hz). Mass spectrum, *m*/*z* (I_{rel}, %): 323 (12) $[M]^+$, 288 (19), 267 (10), 234 (20), 190 (6), 180 (5), 143 (9), 133 (10), 117 (11), 57 (100). Found, %: C 29.78; H 2.99; Cl 43.66; N 4.47; S 19. 55. $C_8H_9Cl_4NS_2$. Calculated, %: C 29.55; H 2.80; Cl 43.62; N 4.31; S 19.72. *M* 325.10.

5-Benzylsulfanyl-4-chloro-3-trichloromethyl-1,2-thiazole (IV). Yield 58%, oily substance. IR spectrum, ν, cm^{-1}: 781 (CCl_3); 1355, 1413, 1495 (isothiazole). ^1H NMR spectrum, δ, ppm: 4.50 s (2H, CH_2S), 7.34–7.47 m (5H, C_6H_5). Mass spectrum, *m*/*z* (I_{rel}, %): 357 (6) $[M]^+$, 322 (17), 267 (7), 234 (10), 214 (7), 190 (11), 167 (9), 143 (14), 117 (16), 91 (100). Found, %: C 36.90; H 2.09; Cl 39.76; N 4.05; S 17.63. $C_{11}H_7Cl_4NS_2$. Calculated, %: C 36.79; H 1.97; Cl 39.49; N 3.90; S 17.86. *M* 359.11.

4-Chloro-5-phenylsulfanyl-3-trichloromethyl-1,2-thiazole (V). Yield 61%, oily substance. IR spectrum, ν, cm^{-1}: 735 (CCl_3); 1365, 1439, 1480 (isothiazole). ^1H NMR spectrum, δ, ppm: 7.21–7.36 m (5H, C_6H_5). Mass spectrum, *m*/*z* (I_{rel}, %): 343 (42) $[M]^+$, 308 (100), 273 (10), 234 (11), 200 (14), 190 (9), 153 (16), 143 (12), 117 (19), 109 (44), 90 (49). Found, %: C 34.99; H 1.65; Cl 41.32; N 4.14; S 18.53. $C_{10}H_5Cl_4NS_2$. Calculated, %: C 34.80; H 1.46; Cl 41.09; N 4.06; S 18.58. *M* 345.08.

5-Alkyl(aryl)sulfanyl-4-chloro-1,2-thiazole-3-carboxylic acids VIII–X (*general procedure*)**.** Pyri-

dine, 0.8 g (10 mmol), was added dropwise under stirring at 20–25°C to a solution of 1.98 g (10 mmol) of isothiazolecarboxylic acid **VI** and 10 mmol of the corresponding thiol in 90 ml of anhydrous diethyl ether. The mixture was stirred for 3 h, and the precipitate was filtered off, washed with 0.1 N hydrochloric acid, cold water (3×50 ml), and a 1:3 diethyl ether–hexane mixture, dried under reduced pressure, and recrystallized from acetone–hexane (1:1).

5-Butylsulfanyl-4-chloro-1,2-thiazole-3-carboxylic acid (VIII). Yield 57%, mp 150–152°C. IR spectrum, ν, cm^{-1}: 1352, 1380, 1475 (isothiazole); 1661 (C=O). ^1H NMR spectrum, δ, ppm: 1.04 t (3H, CH_3, ^3J = 6 Hz), 1.22–1.90 m (4H, CH_2), 3.11 t (2H, CH_2S, ^3J = 8 Hz). Mass spectrum, *m/z* (I_{rel}, %): 251 (63) $[M]^+$, 234 (4), 206 (4), 194 (100), 180 (36), 177 (80), 149 (11), 133 (3), 118 (25), 83 (15), 71 (10), 57 (94). Found, %: C 38.33; H 4.45; Cl 14.23; N 5.19; S 25.69. $C_8H_{10}ClNO_2S_2$. Calculated, %: C 38.16; H 4.01; Cl 14.08; N 5.56; S 25.47. *M* 251.76.

5-Benzylsulfanyl-4-chloro-1,2-thiazole-3-carboxylic acid (IX). Yield 65%, mp 157–159°C. IR spectrum, ν, cm^{-1}: 1350, 1405, 1498 (isothiazole); 1670 (C=O). ^1H NMR spectrum, δ, ppm: 4.53 s (2H, CH_2S), 7.37–7.50 m (5H, C_6H_5). Mass spectrum, *m/z* (I_{rel}, %): 285 (30) $[M]^+$, 268 (22), 250 (9), 240 (8), 214 (10), 194 (70), 177 (70), 167 (7), 149 (9), 118 (19), 91 (100), 71 (20). Found, %: C 46.54; H 3.07; Cl 12.58; N 5.11; S 22.73. $C_{11}H_8ClNO_2S_2$. Calculated, %: C 46.23; H 2.83; Cl 12.41; N 4.90; S 22.44. *M* 285.77.

4-Chloro-5-phenylsulfanyl-1,2-thiazole-3-carboxylic acid (X). Yield 52%, mp 107–109°C. IR spectrum, ν, cm^{-1}: 1356, 1415, 1490 (isothiazole); 1673 (C=O). ^1H NMR spectrum, δ, ppm: 7.24–7.43 m (5H, C_6H_5). Mass spectrum, *m/z* (I_{rel}, %): 271 (40) $[M]^+$, 254 (11), 236 (57), 226 (17), 200 (24), 194 (76), 177 (57), 153 (10), 149 (14), 118 (20), 83 (18), 77 (100). Found, %: C 44.47; H 2.50; Cl 13.22; N 5.31; S 23.88. $C_{10}H_6ClNO_2S_2$. Calculated, %: C 44.20; H 2.23; Cl 13.05; N 5.16; S 23.60. *M* 271.74.

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