ISSN 1070-4280, Russian Journal of Organic Chemistry, 2008, Vol. 44, No. 8, pp. 1211–1214. © Pleiades Publishing, Ltd., 2008.
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Reaction of 4,5-Dichloro-3-trichloromethylisothiazole with Heterocyclic Amines

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Received March 14, 2008

Abstract—4,5-Dichloro-3-trichloromethylisothiazole reacted with piperidine, morpholine, pyrrolidine, and piperazine in DMF to give 81–96% of the corresponding 5-amino-4-chloro-3-trichloromethylisothiazoles as a result of selective nucleophilic replacement of the 5-chlorine atom. Acylation of 4-chloro-5-(piperazin-1-yl)-3-trichloromethylisothiazole with acetyl chloride gave 4-chloro-5-(4-acetylpiperazin-1-yl)-3-trichloromethylisothiazole.

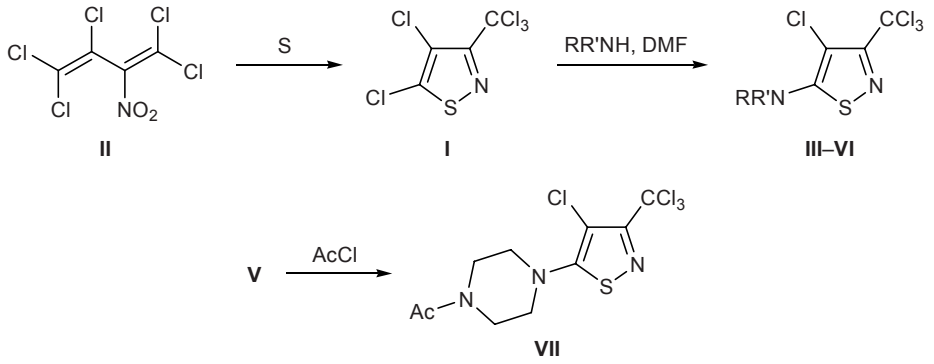
DOI: 10.1134/S1070428008080186

Broad spectrum of biological activity of isothiazole derivatives stimulated extensive studies in the field of isothiazole chemistry [1]. Some amino-substituted isothiazoles were recently shown to be active against Gram-positive bacteria that are resistant to other medical agents; they can also be used in the synthesis of antibiotics active against drug-resistant bacteria [2, 3].

We previously developed a convenient procedure for the synthesis of 4,5-dichloro-3-trichloromethylisothiazole (**I**) by high-temperature heterocyclization of accessible 2-nitropentachloro-1,3-butadiene (**II**) with sulfur; compound **II** is obtained from commercial trichloroethylene via a sequence of readily performable transformations [4]. The chlorine atom in position *5* of the isothiazole ring in **I** is capable of being replaced by nucleophilic groups, as we demonstrated in [5] using reactions with alkoxides and thiolates as examples [5]. However, while studying reactions of isothiazole **I** with amines in alcoholic medium we succeeded in obtaining only the product of its reaction with strongly basic piperidine, 4-chloro-5-piperidino-3-trichloromethylisothiazole (**III**, yield 85%) [6]. Compound **I** failed to react with other amines even on prolonged heating of the reaction mixture. Laboratory experiments showed that 5-piperidinoisothiazole **III** exhibits a synergistic effect in compositions with some pesticides; for instance, it considerably enhances the activity of the known cotton defoliant Tsitodef.

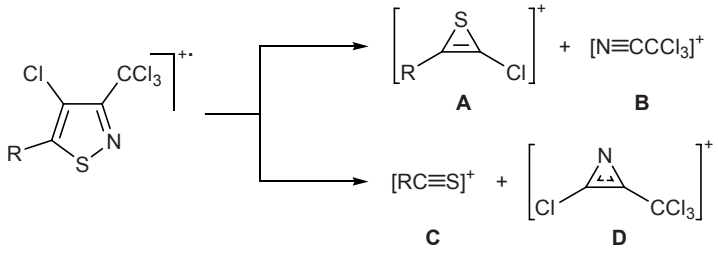
The goal of the present work was to find conditions for the preparation of 4-chloro-3-trichloromethyliso-

Scheme 1.



III, RR′N = piperidino; **IV**, RR′N = morpholino; **V**, RR′N = piperazin-1-yl; **VI**, RR′N = pyrrolidin-1-yl.

Scheme 2.



thiazoles containing cyclic secondary amine residues in the 5-position. It is known that dipolar aprotic solvents enhance the reactivity of amines in S_N2 and S_NAr processes and that the nature of aprotic solvent insignificantly affects the reaction rate [7]. Taking this into account, we used dimethylformamide as solvent for nucleophilic replacement of the 5-chlorine atom in isothiazole **I** by the action of piperidine, morpholine, piperazine, and pyrrolidine.

Isothiazole **I** smoothly reacted with the above cyclic amines at a ratio of 1:2 in DMF at room temperature to produce 81–96% of the corresponding 5-substituted derivatives **III**–**VI** (Scheme 1). The amine was taken in excess to bind hydrogen chloride liberated during the process. In the reaction with piperidine, the yield of substitution product **III** increased from 85% (boiling methanol) to 96% (23°C, DMF). The reaction with piperazine involved only one amino group in the nucleophile molecule, so that we were able to brought piperazin-1-yl-substituted isothiazole **V** into further transformations. For example, treatment of **V** with acetyl chloride gave 78% of 5-(4-acetylpiperazin-1-yl)-4-chloro-3-trichloromethylisothiazole (**VII**) (Scheme 1). Nucleophilic substitution of the 5-chlorine atom in molecule **I** by the above amines occurred with high selectivity: the chlorine atom in position *4* and the trichloromethyl group remained intact. This is consistent with generally accepted views on the reactivity of isothiazoles [8].

The structure of aminoisothiazole derivatives **IV**–**VII** was confirmed by the IR, ^{1}H and ^{13}C NMR, and mass spectra. The physical constants and spectral parameters of compound **III** coincided with those reported in [6]. The IR spectra of **IV**–**VII** contained absorption bands in the region 1265–1556 cm^{-1} due to stretching vibrations of the C=C, C=N, and C–S bonds in the isothiazole ring, vibrations of the trichloromethyl group gave rise to strong absorption bands at 778–789 cm^{-1}, and absorption in the region 2827–3020 cm^{-1} was assigned to stretching vibrations of C–H bonds in methylene groups of the cyclic amine residue. Compound **V** displayed in the IR spectrum N–H absorption band at 3352 cm^{-1}. The carbonyl group in *N*-acetyl derivative **VII** was characterized by a strong absorption band at 1645 cm^{-1}.

In the ^{1}H NMR spectra of **IV**–**VII** we observed signals from methylene protons in the heterocyclic amine residues in the region δ 2.04–3.89 ppm. The NH proton in **V** resonated as a broadened singlet at δ 1.79 ppm, and the acetyl methyl group in **VII** gave a singlet at δ 2.14 ppm. The CCl_3 signal of **IV**–**VII** appeared in the ^{13}C NMR spectra at δ_C 92.07–92.98 ppm, quaternary carbon atoms in the isothiazole ring gave three signals in the region δ_C 98.09–174.97 ppm. Couples of signals in the region δ_C 26.28–66.74 ppm were assigned to methylene carbon atoms in the amine residues of compounds **IV**–**VI**. Acetyl derivative **VII** displayed three signals at δ_C 40.75, 45.69, and 50.55 ppm, the first two of which correspond to the CH_2N groups neighboring to the isothiazole ring, and the downfield signal belongs to two equivalent methylene carbon atoms in the $CH_2N(Ac)$-CH_2 fragment. The ^{13}C signals were assigned using DEPT pulse sequence.

Exhaustive proofs for the assumed structure of the synthesized isothiazole derivatives were obtained by GC–MS. In the mass spectra of compounds **III**–**VII** the isotope intensity ratio in the molecular ion cluster was 77:100:49:10, indicating the presence of four chlorine atoms in their molecules [9, 10]. Peaks from ions **A**–**D** formed by cleavage of the heteroring typical of isothiazoles [11, 12] had low intensity (I_{rel} 3–5%), for they underwent subsequent decomposition with loss of the amine residue (R) and trichloromethyl group (Scheme 2). This follows from the presence in the mass spectra of more intense peaks from ions with *m*/*z* 117 $[CCl_3]^+$, 91 $[\mathbf{A} - R]^+$, 73 $[\mathbf{D} - CCl_3]^+$, and 44 $[\mathbf{C} - R]^+$ (I_{rel} 8–12%; hereinafter, *m*/*z* values and relative intensities are given for ions containing only ^{35}Cl isotope). The main fragmentation pathway of the molecular ions of **IV**–**VII** is elimination of chlorine atom with formation of $[M - Cl]^+$ ions which are the most

abundant in the spectra of most products. The spectra of all the examined isothiazole derivatives contained $[R]^+$ ion peaks corresponding to the amine residue.

Functionally substituted isothiazole derivatives **III**–**VII** attract interest as potential biologically active substances.

EXPERIMENTAL

The IR spectra were recorded in KBr on a Nicolet Protégé-460 spectrometer with Fourier transform. The ^1H and ^{13}C NMR spectra were measured on a Bruker Avance-500 spectrometer from solutions in $CDCl_3$ using TMS (^1H) and $CDCl_3$ (^{13}C, δ_C 77.0 ppm) as internal references. 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 capilary column, 30 m× 0.25 mm, stationary phase 5% phenylmethylsilicone, film thickness 0.25 μm; injector temperature 250°C).

Initial 4,5-dichloro-3-trichloromethylisothiazole (**I**) was synthesized by heterocyclization of 2-nitropentachlorobuta-1,3-diene (**II**) with sulfur according to the procedure described in [4].

5-Amino-4-chloro-3-trichloromethylisothiazoles III–VI (*general procedure*). Compound **I**, 10 mmol, was dissolved in 20 ml of anhydrous DMF, 20 mmol of the corresponding cyclic secondary amine was added at 20°C, and the mixture was stirred for 8 h and poured into 100 ml of a saturated solution of sodium chloride. The precipitate was filtered off, washed with water, dried under reduced pressure, and recrystallized from ethanol.

4-Chloro-5-morpholino-3-trichloroisothiazole (IV). Yield 81%, mp 92–93°C. IR spectrum, ν, cm^{-1}: 2970, 2919, 2856 (C–H); 1521, 1411, 1265 (C=C, C=N, isothiazole); 781 (CCl_3). ^1H NMR spectrum, δ, ppm: 3.39 t (4H, CH_2N), 3.89 t (4H, CH_2O). ^{13}C NMR spectrum, δ_C, ppm: 51.24 (CH_2N); 66.74 (CH_2O); 92.98 (CCl_3); 105.99, 161.02, and 174.60 (C^3, C^4, C^5). Found, %: C 30.04; H 2.68; Cl 44.31; N 9.05; S 10.18. $[M]^+$ 320. $C_8H_8Cl_4N_2OS$. Calculated, %: C 29.84; H 2.50; Cl 44.04; N 8.70; S 9.96. *M* 322.04.

4-Chloro-5-(piperazin-1-yl)-3-trichloromethylisothiazole (V). Yield 84%, mp 73–75°C. IR spectrum, ν, cm^{-1}: 3352 (NH); 2946, 2921, 2827 (C–H); 1516, 1411, 1323 (C=C, C=N, isothiazole); 782 (CCl_3). ^1H NMR spectrum, δ, ppm: 1.79 br.s (NH), 3.06 t (4H, CH_2NH), 3.36 t (4H, CH_2N). ^{13}C NMR spectrum, δ_C, ppm: 45.99 (CH_2NH); 52.23 (NCH_2); 92.56 (CCl_3); 105.37, 160.86, and 174.97 (C^3, C^4, C^5). Found, %: C 30.08; H 2.55; Cl 44.54; N 13.19; S 10.25. $[M]^+$ 319. $C_8H_9Cl_4N_3S$. Calculated, %: C 29.93; H 2.83; Cl 44.17; N 13.08; S 9.99. *M* 321.05.

4-Chloro-5-(pyrrolidin-1-yl)-3-trichloromethylisothiazole (VI). Yield 89%, mp 116–118°C. IR spectrum, ν, cm^{-1}: 2973, 2955, 2879 (C–H); 1556, 1438, 1336 (C=C, C=N, isothiazole); 778 (CCl_3). ^1H NMR spectrum, δ, ppm: 2.04 m (4H, CH_2CH_2), 3.60 t (4H, CH_2N). ^{13}C NMR spectrum, δ_C, ppm: 26.28 (CH_2CH_2); 52.04 (CH_2N); 92.91 (CCl_3); 98.09, 160.32, and 169.75 (C^3, C^4, C^5). Found, %: C 31.67; H 2.84; Cl 46.13; N 9.25; S 10.26. $[M]^+$ 304. $C_8H_8Cl_4N_2S$. Calculated, %: C 31.40; H 2.63; Cl 46.34; N 9.15; S 10.48. *M* 306.04.

5-(4-Acetylpiperazin-1-yl)-4-chloro-3-trichloromethylisothiazole (VII). A solution of 0.80 g (11 mmol) of acetyl chloride in 20 ml of diethyl ether was added dropwise to a solution of 3.40 g (10 mmol) of compound **V** and 0.87 g (11 mmol) of pyridine in 80 ml of diethyl ether. The mixture was stirred for 5 h at 20–23°C, the precipitate was filtered off, the filtrate was washed with water and dried over sodium sulfate, the solvent was removed, and the solid residue was purified by recrystallization from alcohol. Yield 2.80 g (78%), mp 120–121°C. IR spectrum, ν, cm^{-1}: 3020, 2893, 2859 (C–H); 1645 (C=O); 1519, 1416, 1366 (C=C, C=N, isothiazole); 789 (CCl_3). ^1H NMR spectrum, δ, ppm: 2.14 s (3H, CH_3), 3.35 d (4H, CH_2N), 3.74 d [4H, $C\mathbf{H}_2N(Ac)C\mathbf{H}_2$]. ^{13}C NMR spectrum, δ_C, ppm: 21.49 (CH_3); 40.75 (CH_2N); 45.69 (CH_2N); 50.55 (CH_2NCH_2); 92.07 (CCl_3); 106.42, 160.48, 169.22, 173.61 (C^3, C^4, C^5, C=O). Found, %: C 33.23; H 3.18; Cl 39.43; N 11.69; S 8.97. $[M]^+$ 361. $C_{10}H_{11}Cl_4N_3SO$. Calculated, %: C 33.08; H 3.06; Cl 39.06; N 11.57; S 8.83. *M* 363.10.

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

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