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Synthesis and Some Reactions of Aryl 4,5-Dichloroisothiazol-3-yl Ketones

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Abstract—By acylation of benzene, toluene, and *p*-xylene with 4,5-dichloroisothiazole-3-carbonyl chloride the corresponding aryl 4,5-dichloroisothiazol-3-yl ketones were obtained. By reaction of 4,5-dichloroisothiasol-3-yl 4-methylphenyl ketone with piperidine, alkyl(aryl) thiolates, sodium alcoholates, and 2,4-dinitrophenylhydrazine were synthesized 4-methylphenyl 5-piperidyl-4-chloroisothiazol-3-yl ketone, 5-alkyl(aryl)sulfanyl-4-chloroisothiazol-3-yl 4-methylphenyl ketones, 5-alkoxy-4-chloroisothiazol-3-yl 4-methylphenyl ketones, and 2,4-dinitrophenylhydrazone of the initial ketone respectively.

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Functional derivatives of isothiazole exhibit a wide range of biological action, and therefore the development is stimulated of studies on the synthesis and properties of this class compounds [1, 2]. Based on isothiazoles were obtained in particular efficient antibacterial drugs [3], highly selective antagonists of 5-HT_{2B} receptors [4], immunosupressants [5], and other pharmaceuticals, quite a number of chemicals for plant protection was also synthesized [6].

In a series of isothiazolyl ketones compounds are known having the keto group in the positions *4* or *5* of the heterocycle that are obtained from 4-iodoisothiazoles [7] and 5-aryl-substituted furans or thiophenes respectively [8]. Some among the ketones obtained exhibit high herbicidal activity [1, 2].

The target of our study was the development of synthetic approach to preparation of previously unknown aryl 4,5-dichloroisothiazol-3-yl ketones with a keto group in the position *3* of isothiazole ring starting with acyl chloride obtained from available 4,5-dichloroisothiazole-3-carboxylic acid (**I**), whose preparation we had described formerly [9].

The synthesis of ketones was performed by acylating arenes with 4,5-dichloroisothiazole-3-carbonyl chloride (**II**) under the Friedel–Krafts reaction conditions in the presence of anhydrous aluminum chloride in dichloromethane at 40°C. Benzene, toluene, and xylene were used as arenes. The reaction completed in 2 h, the yield of the corresponding aryl 4,5-dichloroisothiazol-3-yl ketones **III–V** was 63–86%.

The composition and structure of obtained reaction products **III–V** were established from elemental analysis and IR, ^{1}H NMR, and mass spectra. In the IR spectra of ketones strong absorption bands of the carbonyl group are observed in the region 1659–1672 cm^{-1}, the vibrations of C=C, C=N, and C–C bonds of the isothiazole ring give rise to three characteristic absorption bands in the range 1349–1579 cm^{-1}. In the ^{1}H NMR spectra of compounds **III–V** appear the multiplets of aromatic protons in the region 7.27–8.03 ppm and the signals of methyl substituents at the benzene ring with an appropriate integral intensity. In the mass spectra of ketones **III–V** groups of molecular ion peaks are observed where the intensity ratio of the main isotope components (100:65:1.1) indicates the presence in the ion of two chlorine atoms [10, 11]. The fragmentation of molecules under the electron impact is characteristic for isothiazoles [12, 13] involving the cleavage of the isothiazole ring and elimination of substituents (chlorine and aryl moieties). The fragmentation process unambiguously confirms the structure of the synthesized aryl isothiazolyl ketones.

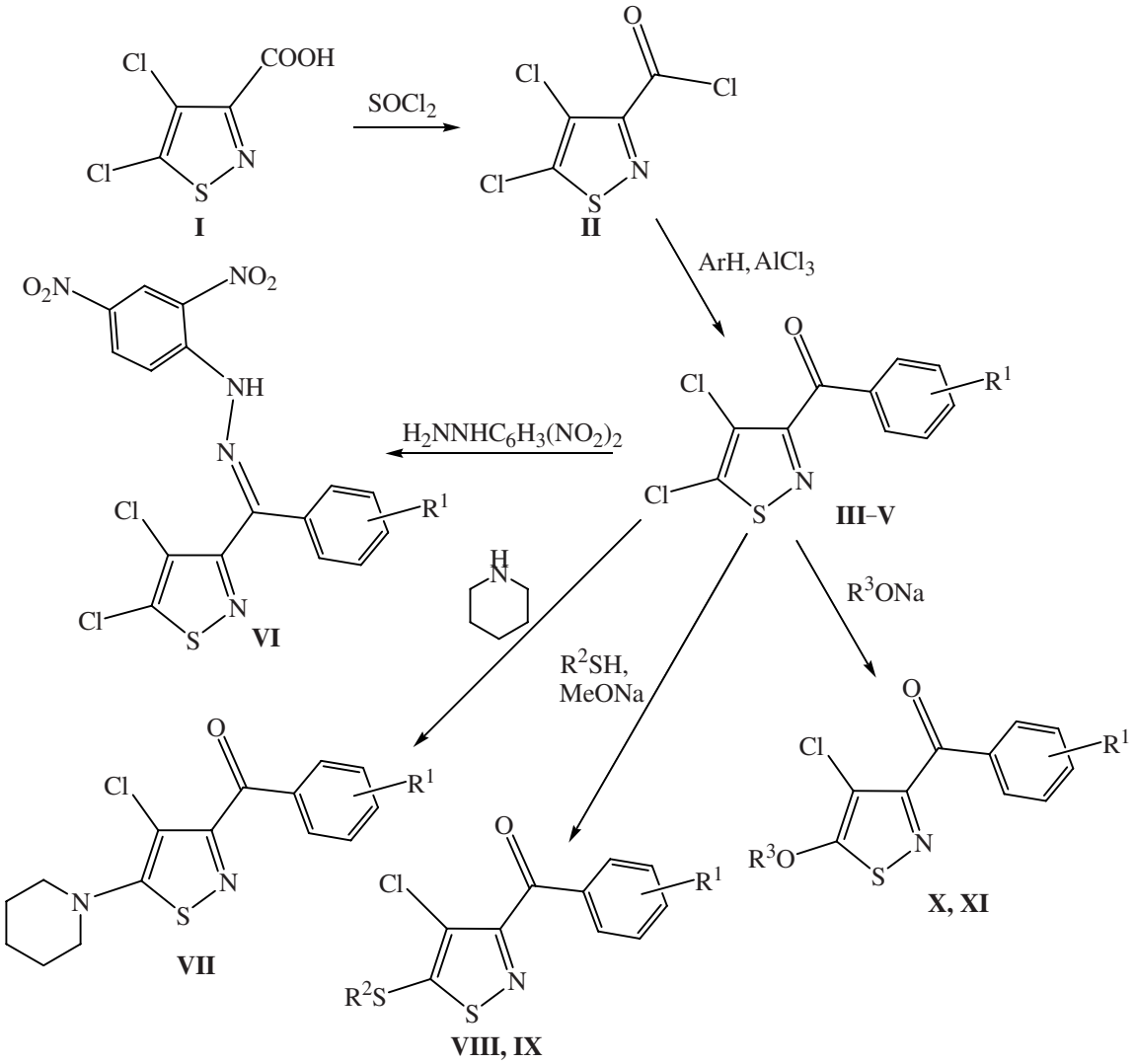
It is known that in chlorine-substituted isothiazoles the most reactive site with respect to nucleophilic reagents is the position *5* of the heterocycle as compared to the low reactive position *4* [2]. The molecules of

ketones obtained contain also a carbonyl group, an additional reactive site. Therefore the synthesized ketones **III–V** are promising compounds for preparation of isothiazole functional derivatives. We studied the behavior of the ketones in reactions with some nucleophiles by an example of 4,5-dichloroisothiazol-3-yl 4-methylphenyl ketone (**IV**). Nucleophiles of various character were applied: 2,4-dinitrophenylhydrazine, piperidine, thiolates, and sodium alcoholate.

The reaction of ketone **IV** with 2,4-dinitrophenylhydrazine in a water-methanol mixture in the presence of sulfuric acid took the "classic" route at the carbonyl group and led to the formation in a preparative yield of 2,4-dinitrophenylhydrazone **VI**. Obtained compound **VI** was identified based on IR and ^{1}H NMR spectra and on elemental analysis. The IR spectrum of compound **VI** lacked the absorption band of the C=O group of the initial ketone in the region 1659 cm^{-1}, and absorption bands appeared characteristic of C=N bond vibrations at 1616 cm^{-1} and of symmetrical and anisymmetrical vibrations of N–O bonds in the nitro groups at 1336 and 1518 cm^{-1}. In the ^{1}H NMR spectrum of compound **VI** a broadened singlet of amino group appears at δ 11.4 ppm.

The reaction of ketone **IV** with piperidine at the ratio ketone:piperidine = 1:2 occurred selectively at the position *5* of the heterocycle with the substitution of chlorine atom and resulted in 4-methylphenyl 5-piperidino-4-chloroisothiazol-3-yl ketone (**VII**) in 85% yield. Piperidine was used in excess to bind the liberated hydrogen chloride.

The reaction of ketone **IV** with butyl- and phenylthioles in methanol in the presence of triethylamine also



R^1 = H (**III**), 4-Me (**IV, VI–XI**), 2,5-Me_2 (**V**); R^2 = Bu (**VIII**), Ph (**IX**); R^3 = Me (**X**), Et (**XI**).

occurred at the position *5* of the heterocycle and led to the formation of the corresponding 4-methylphenyl 5-butylsulfanyl- and 4-methylphenyl 5-phenylsulfanyl-4-chloroisothiazol-3-yl ketones **VIII** and **IX**. However the yields of these reaction products were relatively low, 15 and 36% respectively. We succeeded in increasing the yield to 50–60% by raising the thiols nucleophilicity carrying out the reaction in the presence of equimolar amount of sodium methylate.

Ketone **IV** cleanly reacted with sodium methylate and ethylate in the solution of the corresponding alcohol with substitution of chlorine in the position *5* to provide 5-alkoxy-4-chloroisothiazol-3-yl 4-methylphenyl ketones **X** and **XI** in 70–85% yield. It was established that the reaction should be performed in an anhydrous alcohol for even small quantity of water led to significant tarring.

The composition and structure of compounds **VII–XI** obtained were established from elemental analysis and IR, ^{1}H NMR, and mass spectra. In the IR spectra the vibrations of C=C, C=N, and C–C bonds of the isothiazole ring give rise to three characteristic absorption bands in the range 1300–1577 cm^{-1}, the vibrations of the carbonyl group appear as strong absorption bands in the region 1663–1668 cm^{-1}. The ^{1}H NMR spectra contain the signals of aromatic protons and protons of substituents of an appropriate integral intensity. In the mass spectra of substances **VII–XI** groups of molecular ion peaks are observed where the intensity ratio of the main isotope components (100:33) indicates the presence in the molecules of one chlorine atom [10, 11]. The fragmentation of molecules is characteristic of isothiazoles involving the cleavage of the isothiazole ring [13, 14] and elimination of substituents, and it clearly confirms the structure of compounds **VII–XI**.

Some of ketones synthesized exhibited insecticide activity and presented an interest for testing them as chemicals for plant protection.

EXPERIMENTAL

IR spectra of compounds were recorded on a Fourier spectrophotometer Nikolet Protege-460 from samples pelletized with KBr (substances **IV–VII**, **X**, and **XI**) and from thin films (compounds **III, VIII**, and **IX**). ^{1}H NMR spectra were registered on a spectrometer Tesla BS-567A (100 MHz) in $CDCl_3$, internal reference TMS. Mass spectra were measured on a GC-MS instrument Hewlett-Packard 5890/5972 in an electron impact mode, 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-carboxylic acid (**I**) was prepared by procedure [9], its acyl chloride **II**, by method [14].

Aryl 4,5-dichloroisothiazol-3-yl ketones III–V. To a complex of 30 mmol of acyl chloride **II** and 36 mmol of $AlCl_3$ in 30 ml of anhydrous dichloromethane was added 75 mmol of an appropriate arene, and the reaction mixture was stirred for 2 h at 40°C till the end of HCl evolution, then the mixture was poured into water, the organic layer was separated, washed with a solution of sodium hydrogen carbonate, with water, and dried with magnesium sulfate. On removing the solvent the residue was purified by recrystallization from hexane (compounds **IV** and **V**) or by column chromatography on silica gel 100/160 μ, eluent hexane–ether, 6:1 (ketone **III**).

4,5-Dichloroisothiazol-3-yl phenyl ketone (III). Yield 86%, oily substance. IR spectrum, ν, cm^{-1}: 1672 (C=O), 1598, 1495 (C=C), 1579, 1386, 1351 (isothiazole), 893 (C–Cl). ^{1}H NMR spectrum, δ, ppm: 7.56 m ($3H_{arom}$), 8.03 m ($2H_{arom}$). Found, %: C 46.11; H 1.89; Cl 27.15; N 5.37; S 12.32. $[M]^+$ 257. $C_{10}H_5Cl_2NOS$. Calculated, %: C 46.53; H 1.96; Cl 27.47; N 5.43; S 12.42. *M* 258.12.

4,5-Dichloroisothiazol-3-yl 4-methylphenyl) \ketone (IV). Yield 72%, mp 80–81°C. IR spectrum, ν, cm^{-1}: 1659 (C=O), 1602, 1506 (C=C), 1564, 1383, 1353 (isothiazole), 894 (C–Cl). ^{1}H NMR spectrum, δ, ppm: 2.44 s (3H, CH_3), 7.31 d ($2H_{arom}$, ^3J 7.2 Hz), 7.92 d ($2H_{arom}$, ^3J 7.2 Hz). Found, %: C 48.90; H 2.84; Cl 26.23; N 5.21; S 11.52. $[M]^+$ 271. $C_{11}H_7Cl_2NOS$. Calculated, %: C 48.54; H 2.60; Cl 26.05; N 5.15; S 11.78. *M* 272.15.

2,5-Dimethylphenyl 4,5-dichloroisothiazol-3-yl ketone (V). Yield 63%, mp 37–38°C. IR spectrum, ν, cm^{-1}: 1668 (C=O), 1613, 1498 (C=C), 1568, 1380, 1349 (isothiazole), 927 (C–Cl). ^{1}H NMR spectrum, δ, ppm: 2.35 s (3H, CH_3), 2.45 s (3H, CH_3), 7.27 d ($2H_{arom}$, ^3J 7 Hz), 7.31 br.s ($1H_{arom}$). Found, %: C 50.69; H 3.44; Cl 24.95; N 4.73; S 11.46. $[M]^+$ 285. $C_{12}H_9Cl_2NOS$. Calculated, %: C 50.36; H 3.18; Cl 24.77; N 4.90; S 11.20. *M* 286.18.

4,5-Dichloroisothiazol-3-yl 4-methylphenyl ketone 2,4-dinitrophenylhydrazone (VI). In 15 ml of concn. H_2SO_4 was dissolved 2.97 g (15 mmol) of 2,4-dinitrophenylhydrazine, 20 ml of water and 70 ml of methanol was addede, to the solution obtained in one

portion was poured a solution of 2.72 g (10 mmol) of ketone **IV** in 20 ml of methanol. The mixture was stirred for 2 h, the separated orange precipitate was filtered off, washed with water and with ether, and dried in a vacuum. Yield 4.34 g (96%), orange crystals, mp 206–207°C. IR spectrum, ν, cm^{-1}: 1616 (C=N), 1565, 1370, 1339 (isothiazole), 1518, 1336 (NO_2), 892 (C–Cl). ^{1}H NMR spectrum, δ, ppm: 2.43 s (3H, CH_3), 7.25 d (2H$_{arom}$, ^3J 8 Hz), 7.93 d (2H$_{arom}$, ^3J 8 Hz), 8.18 d (1H$_{arom}$, ^3J 9 Hz), 8.52 d.d (1H$_{arom}$, ^3J 9 Hz), 9.28 d (1H$_{arom}$, ^4J 3 Hz), 11.4 br.s (1H, NH). Found, %: C 45.44; H 2.47; Cl 15.89; N 15.23; S 7.51. $C_{17}H_{11}Cl_2N_5SO_4$. Calculated, %: C 45.14; H 2.46; Cl 15.68; N 15.49; S 7.09.

5-Piperidyl-4-chloroisothiazol-3-yl 4-methylphenyl ketone (VII). A solution of 1.36 g (5 mmol) of ketone **IV** and 0.85 g (10 mmol) of piperidine in 30 ml of ethanol was heated at reflux for 12 h, then the mixture was poured into water, the precipitate was filtered off, washed with water, and dried in a vacuum. After recrystallization from hexane the yield was 1.37 g (85%), mp 112–114°C. IR spectrum, ν, cm^{-1}: 1668 (C=O), 1604, 1572 (C=C), 1524, 1376, 1300 (isothiazole), 895 (C–Cl). ^{1}H NMR spectrum, δ, ppm: 1.70 m (6H, $3CH_2C$), 2.44 s (3H, CH_3), 3.37 m (4H, $2CH_2N$), 7.30 d (2H$_{arom}$, ^3J 8 Hz), 7.94 d (2H$_{arom}$, ^3J 8 Hz). Found, %: C 59.90; H 2.84; Cl 26.23; N 8.53; S 10.14. $[M]^+$ 320. $C_{16}H_{17}ClN_2OS$. Calculated, %: C 59.99; H 2.97; Cl 26.47; N 8.73; S 9.99. *M* 320.86.

5-Butyl(phenyl)sulfanyl-4-chloroisothiazol-3-yl 4-methylphenyl ketones VIII and IX. To a solution of 1.36 g (5 mmol) of ketone **IV** and 5 mmol of an appropriate thiol in 25 ml of anhydrous methanol was added dropwise a solution of 5.5 mmol of sodium methylate in 30 ml of methanol, and the mixture was stirred at 50°C for 15 h. The formed precipitate of sodium chloride was filtered off, the filtrate was diluted with 150 ml of water, extracted with chloroform, and dried over $CaCl_2$. The solvent was removed, the product was purified by column chromatography on silica gel 100/160 μ, eluent hexane–ether, 5:1.

5-Butylsulfanyl-4-chloroisothiazol-3-yl 4-methylphenyl ketone (VIII). Yield 50%, oily substance. IR spectrum, ν, cm^{-1}: 1666 (C=O), 1605 (C=C), 1564, 1380, 1345 (isothiazole), 890 (C–Cl). ^{1}H NMR spectrum, δ, ppm: 0.93 t (3H, CH_3, ^3J 6 Hz), 1.50 m (4H, $2CH_2C$), 2.44 s (3H, CH_3), 2.72 t (2H, CH_2S, ^3J 7 Hz), 7.30 d (2H$_{arom}$, ^3J 8 Hz), 7.93 d (2H$_{arom}$, ^3J 8 Hz). Found, %: C 55.49; H 4.80; Cl 10.97; N 4.35; S 19.50. $[M]^+$ 325. $C_{15}H_{16}ClNOS_2$. Calculated, %: C 55.28; H 4.96; Cl 10.88; N 4.30; S 19.68. *M* 325.89.

4-Methylphenyl 5-phenylthio-4-chloroisothiazol-3-yl ketone (IX). Yield 60%, oily substance. IR spectrum, ν, cm^{-1}: 1665 (C=O), 1604 (C=C), 1577, 1379, 1348 (isothiazole), 892 (C–Cl). ^{1}H NMR spectrum, δ, ppm: 2.45 s (3H, CH_3), 7.40 m (7H$_{arom}$), 7.97 d (2H$_{arom}$, ^3J 8 Hz). Found, %: C 59.28; H 3.76; Cl 10.49; N 4.29; S 18.87. $[M]^+$ 345. $C_{17}H_{12}ClNOS_2$. Calculated, %: C 59.03; H 3.50; Cl 10.25; N 4.05; S 18.54. *M* 345.87.

5-Alkoxy-4-chloroisothiazol-3-yl 4-methylphenyl ketones X and XI. In 50 ml of an appropriate alcohol was dissolved 1.4 g (6 mmol) of sodium metal, 1.36 g (5 mmol) of ketone **IV** was added, and the mixture obtained was stirred at 60°C for 10 h, then it was poured into water, extracted with dichloromethane, and dried over $CaCl_2$. The solvent was removed, the product was purified by recrystallization from hexane.

5-Methoxy-4-chloroisothiazol-3-yl 4-methylphenyl ketone (X). Yield 85%, mp 60–62°C. IR spectrum, ν, cm^{-1}: 1663 (C=O), 1603, 1532 (C=C), 1570, 1378, 1350 (isothiazole), 900 (C–Cl). ^{1}H NMR spectrum, δ, ppm: 2.43 s (3H, CH_3), 4.16 s (3H, CH_3O), 7.29 d (2H$_{arom}$, ^3J 8 Hz), 7.93 d (2H$_{arom}$, ^3J 8 Hz). Found, %: C 53.59; H 4.10; Cl 13.38; N 5.25; S 11.50. $[M]^+$ 267. $C_{12}H_{10}ClNO_2S$. Calculated, %: C 53.83; H 3.77; Cl 13.24; N 5.23; S 11.97. *M* 267.74.

4-Methylphenyl 5-ethoxy-4-chloroisothiazol-3-yl ketone (XI). Yield 70%, mp 69–70°C. IR spectrum, ν, cm^{-1}: 1667 (C=O), 1605, 1527 (C=C), 1568, 1383, 1351 (isothiazole), 895 (C–Cl). ^{1}H NMR spectrum, δ, ppm: 1.60 t (3H, CH_3, ^3J 7 Hz), 2.45 s (3H, CH_3), 4.30 q (2H, CH_2O, ^3J 7 Hz), 7.31 d (2H$_{arom}$, ^3J 8 Hz), 7.94 d (2H$_{arom}$, ^3J 8 Hz). Found, %: C 55.73; H 4.55; Cl 12.69; N 4.78; S 11.44. $[M]^+$ 281. $C_{15}H_{16}ClNOS_2$. Calculated, %: C 55.41; H 4.30; Cl 12.58; N 4.97; S 11.38. *M* 281.77.

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