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Synthesis of 5-azolyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones and 5-azolyl-1,3,4-thiadiazol-2-amines based on derivatives of 5-arylisoxazole-3-carboxylic and 4,5-dichloroisothiazole-3-carboxylic acids

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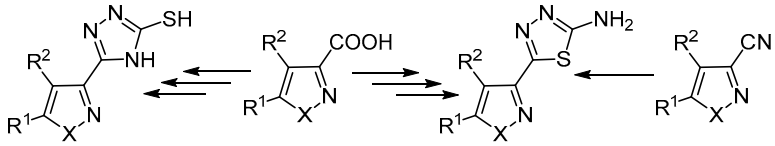


R^1 = Ph, 4-MeC_6H_4, Cl, EtO; R^2 = H, Cl; X = O, S

2-Mercapto-1,3,4-triazoles and 2-amino-1,3,4-thiadiazoles were synthesized by successive transformations of 5-arylisoxazole- and 4,5-dichloroisothiazole-3-carboxylic acids and their derivatives. The amino group of 5-(4,5-dichloroisothiazol-3-yl)-1,3,4-thiadiazol-2-amine was acylated with 5-phenylisoxazole-3-carboxylic acid chloride. Simple approaches to the preparation of previously unknown heterocyclic assemblies containing two or three azole rings with a high potential for biological activity are described.

Keywords: isothiazole, isoxazole, thiadiazoles, thiosemicarbazides, triazoles, heterocyclization.

Thiosemicarbazides are an important class of compounds with a wide spectrum of biological activity. Back in the middle of the XX century, their anti-tuberculosis, antibacterial, antimalarial, antiparasitic, antitumor, antiviral, and antimicrobial properties were discovered.[1] In turn, triazoles containing an exocyclic mercapto group, as well as thiadiazoles with an exocyclic amino group can exhibit various types of biological activity,[2] whereas isoxazole derivatives increase the activity of a number of first-line cytostatics as synergists at the cellular level.[3] In addition, isoxazoles are used in the design of a novel class of complexones – mimics of tweezer ligands.[4] Their sulfur-containing analogs isothiazoles are also used to create a wide range of biologically active compounds and as ligands for metal complexes.[5]

The above data indicates a high relevance of research aimed at developing effective methods for the synthesis of isoxazole(isothiazole)-containing semicarbazides and the corresponding triazoles and thiadiazoles with exocyclic mercapto or amino groups for their subsequent biological screening and use in the design of new materials, in particular, metal complex catalysts.

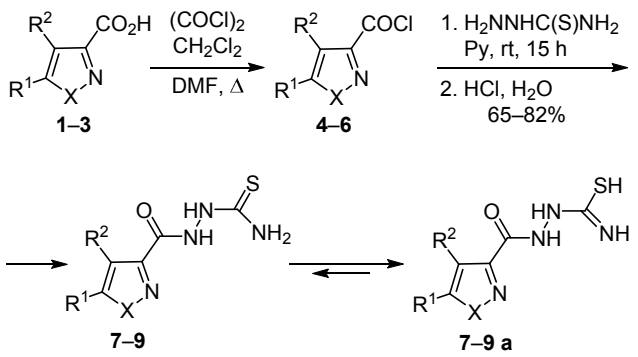
This work continues the series of publications by our team of researchers concerning the transformations of isoxazole and isothiazole derivatives.[6]

One of the widely used methods of obtaining acylated derivatives of thiosemicarbazide is the direct reaction of thiosemicarbazide with acid chlorides of various acids. We have synthesized acyl derivatives of thiosemicarbazides **7**–**9** containing an isoxazole or isothiazole fragment. Despite the apparent simplicity of preparation, these compounds have not been previously described in the literature.

Previously, the reaction of 5-arylisoxazole-3-carboxylic acids **1**, **2**, and 4,5-dichloroisothiazole-3-carboxylic acid (**3**) with $SOCl_2$ in the presence of catalytic amounts of DMF without solvent was used to synthesize acid chlorides

4–**6**.[7,8] In this work, we substituted $SOCl_2$ with $(COCl)_2$ in CH_2Cl_2 solution, which led to an increase in the yields of the target products and a decrease in the reaction time. The reaction of acid chlorides **4**–**6** with thiosemicarbazide in dry pyridine under reflux conditions gave thiosemicarbazide acyl derivatives **7**–**9** (Scheme 1).

Scheme 1



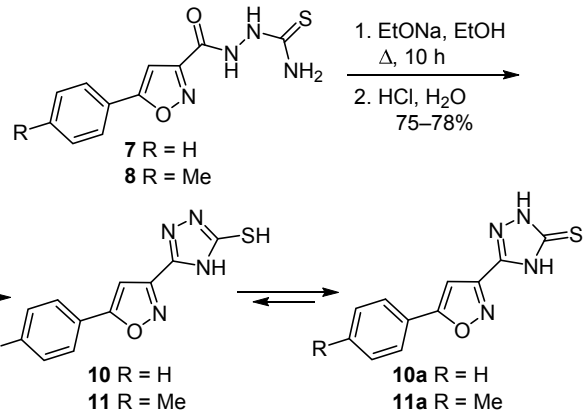
1, **4**, **7** R^1 = Ph, R^2 = H, X = O
2, **5**, **8** R^1 = 4-MeC_6H_4, R^2 = H, X = O
3, **6**, **9** R^1 = Cl, R^2 = Cl, X = S

Acylthiosemicarbazides **7**–**9** can exist in the tautomeric form **7**–**9 a**, which is confirmed by the presence in the ^{1}H NMR spectra of four singlets with the same intensity in the ranges of 7.62–7.75, 7.92–7.96, 9.46–9.51 ppm (3 NH groups) and a downfield signal corresponding to the SH group at 10.64–10.74 ppm, rather than three signals of the NH groups with an integrated intensity of 1:1:2, as would be expected for the thioamide form of compounds **7**–**9**.

The synthesized acyl derivatives of thiosemicarbazide **7**–**9** turned out to be convenient synthons for the preparation of the 1,2,4-triazole ring. We have investigated various approaches to the synthesis of mercaptotriazoles containing an arylisoxazole fragment in the side chain of the triazole ring. It was found that the reaction in 2–10% aqueous alkali proceeds nonselectively (possibly due to the cleavage of the N–O bond in isoxazole)[9] leading to resinification. The treatment of the acylthiosemicarbazide with MeONa in dry MeOH did not result in the formation of the target product – the starting compound was isolated. Replacing MeOH with *i*-PrOH resulted in an inseparable mixture of products. We have found the optimal approach to the preparation of 5-(5-arylisoxazol-3-yl)-2,4-dihydro-3*H*-1,2,4-triazoles **10**, **11**, which involves treatment of acylated thiosemicarbazide derivatives **7**, **8** with EtONa in EtOH under reflux conditions followed by treatment with HCl (Scheme 2). The yields of mercaptotriazoles **10** and **11** were 75–78%.

It was shown that the synthesized thiols **10**, **11** also exist in the tautomeric thioamide form **10**, **11 a**, which is confirmed by the data of IR and NMR spectroscopy. The IR spectra of thioamides **10**, **11 a** contain absorption bands of NH groups in the range of 3195–3317 cm^{-1}, as well as an intense absorption band of the C=S group at 1661–1669 cm^{-1}. The ^{1}H NMR spectra exhibit broadened singlets of two NH groups in the 10.47–10.56 and 13.48–13.54 ppm ranges. The

Scheme 2

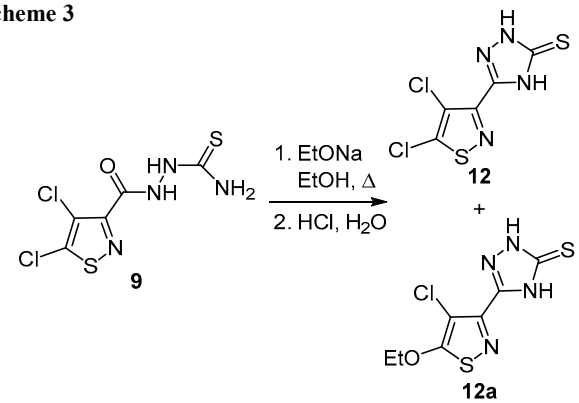


^{13}C NMR spectra exhibit signals at 196.1–196.6 ppm, which also confirms the existence of a tautomeric structure with the C=S fragment.

In contrast to isoxazole derivatives of thiosemicarbazide **7**, **8**, the cyclization of its dichloroisothiazole analog **9** proceeded differently. Treatment of acylthiosemicarbazide **9** with ethanolic EtONa led to the formation of a mixture of two inseparable reaction products 5-(4,5-dichloroisothiazol-3-yl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (**12**) and 5-(4-chloro-5-ethoxyisothiazol-3-yl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (**12a**), the product of substitution of the mobile chlorine atom in position 5 of the isothiazole ring (Scheme 3). The use of a large excess of EtONa and an increase in the time of heating the reaction mixture under reflux did not lead to the selective formation of ethoxy derivative **12a**. It was not possible to isolate it as an individual substance.

The presence of product **12a** in the reaction mixture was confirmed by ^{1}H, ^{13}C NMR spectroscopy and HPLC. The ^{1}H NMR spectrum contains a methyl group triplet at 1.46 ppm and a methylene group quartet at 4.37 ppm. The LC-MS spectra of compounds **12**, **12a** contain groups of molecular ion peaks in which the ratio of the intensities of the isotopic components indicates the presence of two chlorine atoms in molecule **12** with *m*/*z* 253 $[M+H]^+$ (100%) and 275 $[M+Na]^+$ (35%) (intensity ratio 100:98:32:3.5) and four chlorine atoms with *m*/*z* 527 $[2M+H]^+$ (35%) (intensity ratio 77:100:49:11:1.4), and of one chlorine atom with *m*/*z* 263 $[M+H]^+$ (100%), 285

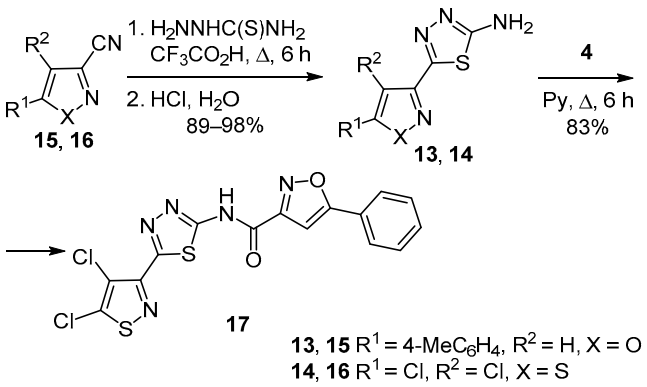
Scheme 3



$[M+Na]^+$ (82%) (intensity ratio 100:33) and two chlorine atoms with *m/z* 547 $[2M+H]^+$ (30%) in molecule **12a**.

Various approaches to the synthesis of aminothiadiazoles are known.[10] We have investigated two approaches to the preparation of aminothiadiazoles comprising the reaction of azolylthiosemicarbazones with anhydrous AcONa in the presence of bromine as an oxidizing agent in glacial AcOH or with K_2CO_3 in the presence of iodine (oxidizer) in 1,4-dioxane. It turned out that the reactions in both cases proceeded indiscriminately and with low yields of the target products. To obtain 5-azolyl-1,3,4-thiadiazol-2-amines **13**, **14**, we used an alternative synthesis method involving the reaction of acid nitriles **15**, **16** with thiosemicarbazide in CF_3CO_2H. The target aminothiadiazoles **13**, **14** were obtained in 89–98% yields. Using aminothiazole **14** as a model, amide **17** was obtained by the reaction with 5-phenylisoxazole-3-carboxylic acid chloride (**4**) in pyridine under reflux (Scheme 4).

Scheme 4



The IR spectra of aminothiadiazoles **13**, **14** contain absorption bands of the NH group in the region of 3134–3445 cm^{-1}. The ^1H NMR spectra of the amines contain singlets of NH_2 groups with chemical shifts of 7.77–7.81 ppm. For compounds **13**, **14**, signals corresponding to aromatic protons are observed, while for aminothiazole **13**, a signal of the methyl group with a chemical shift of 2.36 ppm is also present.

Due to the extremely low solubility of acylated derivative **17** in solvents suitable for recording LC-MS spectra, the mass spectrum of compound **17** could not be recorded. Its structure was confirmed by NMR spectroscopy, and its composition was confirmed by elemental analysis. In the IR spectra of acylated derivative **17**, an absorption band of the amide NH group with a frequency of 3375 cm^{-1} was observed, the vibration of the C=O group corresponded to an absorption band at 1693 cm^{-1}. In addition, a broadened singlet of the amide group NH with a chemical shift of 14.01 ppm was observed in the ^1H NMR spectrum of amide **17**.

In conclusion, a convenient approach to the preparation of 5-azolyl-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones and 5-azolyl-1,3,4-thiadizol-2-amines on the basis of available 5-arylisoxazole-3-carboxylic and 4,5-dichloroisothiazole-3-carboxylic acids and their nitriles was developed.

Experimental

IR spectra were registered on a Thermo Nicolet Protege 460 Fourier transform spectrometer in KBr pellets. ^1H and ^{13}C NMR spectra were acquired on a Bruker Avance 500 spectrometer (500 and 125 MHz, respectively) in DMSO-d_6. The residual solvent signals (2.50 ppm for ^1H nuclei, 40.1 ppm for ^{13}C nuclei) were used as internal standard. The assignment of signals in the ^{13}C NMR spectra was performed using the DEPT technique. Liquid chromatography-mass spectrometry spectra were recorded on an Agilent 1200 LC-MS system with an Agilent 6410 Triple Quad Mass Selective Detector with electrospray ionization in the positive ion registration mode (MS2 scanning mode). An Agilent ZORBAX Eclipse XDB-C18 (4.6 × 50 mm, 1.8 μm) column was used. Mobile phase – MeCN–H_2O + 0.05% HCO_2H, gradient elution from 40 to 90% MeCN in 10 min. 0.5 ml/min flow rate was used. Elemental analysis was performed on a vario MICRO cube CHNS-analyzer. The halogen content was determined by classical microanalysis by a modified Pregl's method.[11] Melting points were determined on a Kofler bench. Monitoring of the reaction progress and assessment of the purity of synthesized compounds were done by TLC on Merck Millipore Silica gel 60 F_{254} plates, eluent Et_2O, visualization by iodine stain.

Reagents and solvents were supplied by Sigma-Aldrich and Merck and used without additional purification. 5-Arylisoxazole-3-carboxylic acids **1**, **2** and 4,5-dichloroisothiazole-3-carboxylic acid (**3**) were synthesized according to previously described procedures.[7,12] Nitriles of *p*-tolylisoxazolecarboxylic acid **15** and dichloroisothiazolecarboxylic acid **16** were accessed according to previously described procedures.[7,13]

Synthesis of acylated thiosemicarbazides 7–9 a (General method). The corresponding acid chloride **4–6**[7,8] (1.54 mmol) was added in portions at 15°C to a suspension of thiosemicarbazide (0.14 g, 1.54 mmol) in dry pyridine (5 ml), and the resulting mixture was stirred for 15 h. The mixture was poured into aqueous NaCl (150 ml) and acidified with HCl to pH ~5. The formed precipitate was filtered off, washed with warm H_2O, and dried under reduced pressure over P_2O_5. The substance did not require further purification.

2-[(5-Phenylisoxazol-3-yl)carbonyl]hydrazine-1-carbimidothionic acid (7a). Yield 0.33 g (82%), light-yellow powder, mp 177–178°C (decomp.). IR spectrum, ν, cm^{-1}: 3438, 3308, 3189, 3152, 3075, 3040, 2976, 1707, 1609, 1571, 1529, 1497, 1469, 1449, 1420, 1301, 1232, 1094, 1070, 948, 870, 768, 690, 672, 567. ^1H NMR spectrum, δ, ppm: 7.43 (1H, s, H-4 isoxazole); 7.53–7.59 (3H, m, H Ar); 7.75 (1H, br. s, NH); 7.90–7.95 (2H, m, H Ar); 7.96 (1H, br. s, NH); 9.51 (1H, br. s, NH); 10.74 (1H, br. s, SH). ^{13}C NMR spectrum, δ, ppm: 100.9 (CH isoxazole); 126.3 (2CH Ar); 130.0 (2CH Ar); 131.5 (CH Ar); 126.8; 158.8; 159.1; 170.7; 182.5. Mass spectrum, *m/z* (I_{rel}, %): 547 $[2M+Na]^+$ (28), 285 $[M+Na]^+$ (71), 263 $[M+H]^+$ (100). Found, %: C 50.21; H 3.96; N 21.44; S 12.27. $C_{11}H_{10}N_4O_2S$. Calculated, %: C 50.37; H 3.84; N 21.36; S 12.22.

2-{[5-(*p*-Tolyl)isoxazol-3-yl]carbonyl}hydrazine-1-carbimidothionic acid (8a). Yield 0.32 g (76%), light-yellow powder, mp 202–204°C (decomp.). IR spectrum, ν, cm^{-1}: 3429, 3294, 3196, 3170, 3051, 3039, 2961, 2922, 2855, 1695, 1614, 1566, 1528, 1506, 1450, 1420, 1297, 1227, 1188, 1097, 1033, 1003, 947, 869, 810, 768, 561, 518. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.36 (3H, s, CH_3); 7.34 (1H, s, H-4 isoxazole); 7.36 (2H, d, *J* = 8.0, H Ar); 7.73 (1H, br. s, NH); 7.81 (2H, d, *J* = 8.0, H Ar); 7.95 (1H, br. s, NH); 9.50 (1H, br. s, NH); 10.71 (1H, br. s, SH). ^{13}C NMR spectrum, δ, ppm: 21.7 (CH_3); 100.3 (CH isoxazole); 126.3 (2CH Ar); 130.5 (2CH Ar); 124.2; 141.5; 158.9; 159.0; 170.9; 182.5. Mass spectrum, *m*/*z* (I_{rel}, %): 575 $[2M+Na]^+$ (40), 299 $[M+Na]^+$ (79), 277 $[M+H]^+$ (100). Found, %: C 52.04; H 4.41; N 20.40; S 11.70. $C_{12}H_{12}N_4O_2S$. Calculated, %: C 52.16; H 4.38; N 20.28; S 11.60.

2-[(4,5-Dichloroisothiazol-3-yl)carbonyl]hydrazine-1-carbimidothionic acid (9a). Yield 0.27 g (65%), light-yellow powder, mp 216–217°C (decomp.). IR spectrum, ν, cm^{-1}: 3438, 3285, 3195, 3145, 3018, 2968, 1691, 1611, 1534, 1484, 1468, 352, 1295, 1213, 1166, 974, 882, 762, 515, 499. ^{1}H NMR spectrum, δ, ppm: 7.62 (1H, br. s, NH); 7.92 (1H, br. s, NH); 9.46 (1H, br. s, NH); 10.64 (1H, br. s, SH). ^{13}C NMR spectrum, δ, ppm: 124.4; 149.8; 156.9; 158.9; 182.5. Mass spectrum, *m*/*z* (I_{rel}, %): 413 $[2M+Na–NHC(S)NH_2]^+$ (34), 392 $[2M+2H–NHC(S)NH_2]^+$ (100), 194 $[M–NHC(S)NH_2]^+$ (47). Found, %: C 22.01; H 1.33; Cl 25.95; N 20.87; S 23.39. $C_5H_4Cl_2N_4OS_2$. Calculated, %: C 22.15; H 1.49; Cl 26.15; N 20.66; S 23.65.

Synthesis of 5-(5-arylisoxazol-3-yl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones 10, 11 a (General method). The corresponding acylthiosemicarbazide **7**, **8** (0.84 mmol) was added at 15°C to a solution of Na (0.1 g, 4.35 mmol) in 96% EtOH (12 ml), and the reaction mixture was heated under reflux with stirring for 10 h. It was then poured into aqueous NaCl (150 ml) and acidified with HCl to pH ~5. The precipitate was filtered off, washed with warm H_2O, dried under reduced pressure over P_2O_5, and recrystallized from EtOH.

5-(5-Phenylisoxazol-3-yl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (10a). Yield 0.16 g (78%), cream-colored powder, mp 194–195°C (decomp.). IR spectrum, ν, cm^{-1}: 3317, 3235, 3063, 2923, 1669, 1608, 1596, 1578, 1548, 1449, 1324, 1295, 1199, 1127, 979, 764, 684. ^{1}H NMR spectrum, δ, ppm: 5.95 (1H, s, H-4 isoxazole); 7.45–7.51 (2H, m, H Ar); 7.54–7.60 (1H, m, H Ar); 7.98–8.04 (2H, m, H Ar); 10.56 (1H, br. s, NH); 13.54 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 100.7 (CH isoxazole); 129.0 (2CH Ar); 129.3 (2CH Ar); 134.0 (CH Ar); 127.9; 136.6; 156.7; 171.4; 196.6. Mass spectrum, *m*/*z* (I_{rel}, %): 245 $[M+H]^+$ (100). Found, %: C 54.01; H 3.49; N 22.91; S 13.02. $C_{11}H_8N_4OS$. Calculated, %: C 54.09; H 3.30; N 22.94; S 13.12.

5-[5-(*p*-Tolyl)isoxazol-3-yl]-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (11a). Yield 0.16 g (75%), cream-colored powder, mp 197–199°C (decomp.). IR spectrum, ν, cm^{-1}: 3313, 3195, 3135, 3073, 3030, 2923, 2765, 1661, 1603, 1570, 1543, 1434, 1320, 1297, 1249, 1213, 1186, 1136, 1008, 977, 802, 725, 629, 586. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.33 (3H, s, CH_3); 5.88 (1H, s, H-4 isoxazole); 7.28 (2H, d, *J* = 7.8, H Ar); 7.89 (2H, d, *J* = 7.8, H Ar); 10.47 (1H, br. s, NH); 13.48 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 21.7 (CH_3); 100.0 (CH isoxazole); 129.1 (2CH Ar); 129.7 (2CH Ar); 126.4; 134.1; 144.3; 156.6; 171.5; 196.1. Mass spectrum, *m*/*z* (I_{rel}, %): 259 $[M+H]^+$ (100). Found, %: C 55.68; H 3.98; N 21.74; S 12.24. $C_{12}H_{10}N_4OS$. Calculated, %: C 55.80; H 3.90; N 21.69; S 12.41.

Synthesis of 5-azolyl-1,3,4-thiadiazol-2-amines 13, 14 (General method). Thiosemicarbazide (1.0 g, 11 mmol) was added at 15°C to a solution of the corresponding nitrile **15**, **16** (10 mmol) in CF_3CO_2H (10 ml), and the resulting mixture was stirred at reflux for 6 h. After cooling, the mixture was poured into aqueous NaCl (150 ml) and acidified with HCl to pH ~5. The precipitate was filtered off, washed with warm H_2O, and dried under reduced pressure over P_2O_5. The substance did not require further purification.

5-[5-(*p*-Tolyl)isoxazol-3-yl]-1,3,4-thiadiazol-2-amine (13). Yield 2.53 g (98%), cream-colored powder, mp 156–158°C. IR spectrum, ν, cm^{-1}: 3406, 3286, 3134, 3025, 2919, 2856, 1611, 1597, 1569, 1535, 1506, 1437, 1404, 1335, 1214, 1184, 1121, 1071, 1053, 1034, 948, 931, 795, 500. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.36 (3H, s, CH_3); 7.35 (2H, d, *J* = 8.1, H Ar); 7.47 (1H, s, H-4 isoxazole); 7.77 (2H, br. s, NH_2); 7.83 (2H, d, *J* = 8.1, H Ar). ^{13}C NMR spectrum, δ, ppm: 21.6 (CH_3); 97.8 (CH isoxazole); 126.4 (2CH Ar); 130.4 (2CH Ar); 124.2; 141.4; 145.6; 157.6; 170.4; 170.9. Mass spectrum, *m*/*z* (I_{rel}, %): 281 $[M+Na]^+$ (21), 259 $[M+H]^+$ (100). Found, %: C 55.79; H 3.78; N 21.84; S 12.48. $C_{12}H_{10}N_4OS$. Calculated, %: C 55.80; H 3.90; N 21.69; S 12.41.

5-(4,5-Dichloroisothiazol-3-yl)-1,3,4-thiadiazol-2-amine (14). Yield 2.25 g (89%), cream-colored powder, mp 192–194°C. IR spectrum, ν, cm^{-1}: 3445, 3312, 3179, 2924, 2853, 1608, 1500, 1388, 1346, 1159, 1121, 1052, 915, 837, 749, 702. ^{1}H NMR spectrum, δ, ppm: 7.81 (2H, s, NH_2). ^{13}C NMR spectrum, δ, ppm: 121.6; 150.1; 151.0; 155.0; 170.6. Mass spectrum, *m*/*z* (I_{rel}, %): 253 $[M+H]^+$ (100). Found, %: C 23.70; H 0.89; Cl 28.19; N 22.02; S 25.42. $C_5H_2Cl_2N_4S_2$. Calculated, %: C 23.73; H 0.80; Cl 28.01; N 22.14; S 25.33.

***N*-[5-(4,5-Dichloroisothiazol-3-yl)-1,3,4-thiadiazol-2-yl]-5-phenylisoxazole-3-carboxamide (17)**. 5-Phenylisoxazole-3-carboxylic acid chloride **4** (0.42 g, 2.0 mmol) was added at 15°C to a solution of 5-(4,5-dichloroisothiazol-3-yl)-1,3,4-thiadiazol-2-amine (**14**) (0.50 g, 2.0 mmol) in dry pyridine (10 ml). The resulting mixture was stirred at reflux for 6 h, poured into aqueous NaCl (150 ml), and acidified with HCl to pH ~5. The precipitate was filtered off, washed with warm H_2O, and dried under reduced pressure over P_2O_5. The product was recrystallized from EtOH. Yield 0.70 g (83%), cream-colored powder, mp 165–167°C (decomp.). IR spectrum, ν, cm^{-1}: 3375, 3149, 3115, 2975, 2885, 2754, 1693, 1609, 1589, 1529, 1496, 1472, 1447, 1390, 1346, 1311, 1215, 1163, 1089, 1006, 948, 920, 878, 840, 797, 762, 689, 677, 635, 615, 524. ^{1}H NMR spectrum, δ, ppm: 7.56–7.61 (3H, m, H Ar); 7.65 (1H, s, H-4

isoxazole); 7.94–7.99 (2H, m, H Ar); 14.01 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 101.0 (CH isoxazole); 126.4 (2CH Ar); 130.0 (2CH Ar); 131.7 (CH Ar); 122.5; 126.6; 151.0; 153.0; 154.6; 158.0; 160.7; 167.5; 171.6. Found, %: C 42.24; H 1.89; Cl 16.90; N 16.44; S 15.25. $C_{15}H_7Cl_2N_5O_2S_2$. Calculated, %: C 42.46; H 1.66; Cl 16.71; N 16.51; S 15.11.

Supplementary information file containing ^{1}H and ^{13}C NMR spectra for compounds **7–11 a**, **13**, **14**, and **17** is available at the journal website at http://link.springer.com/journal/10593.

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