Russian Journal of Organic Chemistry, Vol. 39, No. 8, 2003, pp. 1133–1139. Translated from Zhurnal Organicheskoi Khimii, Vol. 39, No. 8, 2003, pp. 1204–1210.

Synthesis of Oxamic Acids Thiohydrazides and Carbamoyl-1,3,4-thiadiazoles

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Received September 27, 2002

Abstract—A convenient preparation method was developed for oxamic acids thiohydrazides by reaction of α-chloroacetamides with a preliminary prepared solution of elemental sulfur and hydrazines. A series of carbamoyl-1,3,4-thiadiazole derivatives was obtained.

We formerly developed a convenient general method of monothiooxamides synthesis by reaction of available chloroacetamides with a preliminary prepared solution of elemental sulfur in amines [1]. Synthetic approaches basing on modifications of amide and thioamide groups in the monothiooxamides are promising for building up a wide range of various compounds. For instance, we showed that modification of the thioamide group in the monothiooxamides effected with N-nucleophiles provided versatile hetarenecarboxamides [2–7].

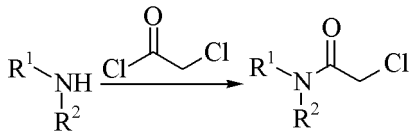
In the present study in extension of our research concerning the use of the products of S-functionalization of organic compounds in the synthesis of S,N-heterocyclic substances we investigated the possibility of preparation of oxamic acids thiohydrazides. The oxamic acids thiohydrazides having in a single molecule thiohydrazide and amide groups possess great synthetic potential and are very interesting for preparation of complexing structures and biologically active compounds [8–10].

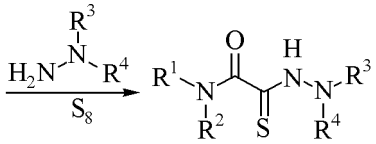
However the known preparation methods for oxamic acids hydrazides with substituents at the terminal nitrogen of the thiohydrazide moiety are laborious [11], and the unsubstituted derivatives are synthesized in three stages starting with chloroacetamides [12].

We studied the possibility to prepare oxamic acids thiohydrazides in one stage by reaction of available α-chloroacetamides with the elemental sulfur and hydrazides.

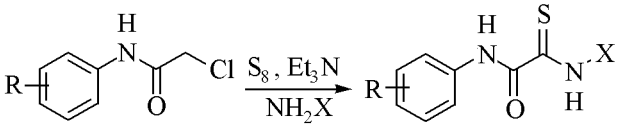
The procedure we proposed was not formerly used for the synthesis of oxamic acids thiohydrazides.

Actually it turned out that simultaneous addition of hydrazines, elemental sulfur, and triethylamine to a solution of α-chloroacetamide in DMF gave rise to the corresponding oxamic acids thiohydrazides. The yields of products **IId, e** were no more than 20–30%.





We investigated the effect of storage time in DMF of a preliminary prepared solution containing elemental sulfur, mono- and disubstituted hydrazines, and triethylamine on the yield of oxamic acids thiohydrazides. We succeeded in increasing the yield of oxamic acids thiohydrazides (**II**) to 60–70% using a sulfur solution obtained by mixing the components for 20–30 min.



Ia, b **IIa–e**

I, R = H (**a**), 4-Cl (**b**); **II**, X = NMe_2: R = H (**a**), 4-Cl (**b**); X = NHPh, R = H (**c**); X = $N(CH_2CH_2)_2N$–CH_3: R = H (**d**), 4-Cl (**e**).

The method is of general character and provides a possibility to prepare among others oxamic acids thiohydrazides containing an α-amino acid fragment.

However we failed to obtain oxamic acids thiohydrazides with unsubstituted thiohydrazide moiety

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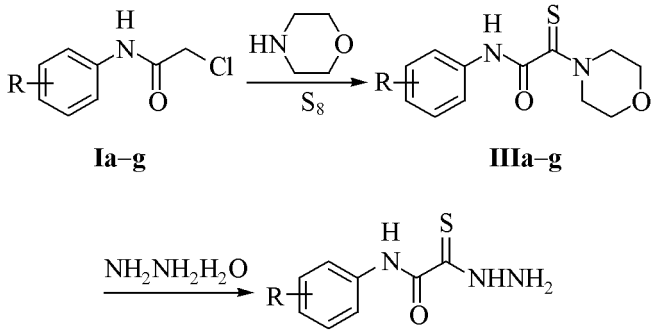
by reaction of α-chloroacetamides with hydrazine hydrate. Apparently hydrazine readily reacted with the elemental sulfur and also reduced the polysulfide bonds in anions arising in the system sulfur–hydrazine decomposing therewith to gaseous nitrogen.

With greater success we applied to the synthesis of unsubstituted thiohydrazides the approach we had developed for preparation of monothiooxamides. It was shown earlier that monothiooxamides cleanly formed in reaction of easily accessible N(S)-morpholino-N(O)-R-thiooxamides with various amines [5]. The application of hydrazine instead of amine in this procedure made possible the preparation of unsubstituted thiohydrazides of oxamic acids (**IV**).

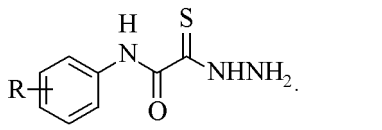


Ia–g **IIIa–g**

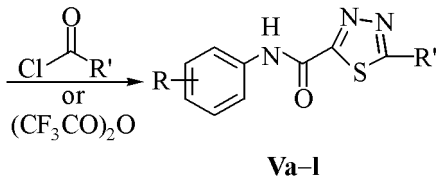
IVa–g

I, III, IV, R = H (**a**), 4-Cl (**b**), 4-MeO (**c**), 4-Br (**d**), 4-F (**e**), 2,3-Me_2 (**f**), 3-Me (**g**).

The oxamic acids thiohydrazides obtained are valuable synthons for preparation of versatile heterocyclic products. We obtained therefrom in particular quite a number of carbamoyl-1,3,4-thiadiazole derivatives that can be interesting for the synthesis of pharmaceuticals and pesticides [13–15]. For instance, in the reaction of thiahydrazides **IV** with haloacetyl chlorides were cleanly obtained carbamoyl-1,3,4-thiadiazoles with halomethyl groups.



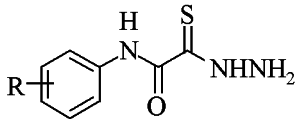
IVa–d, g



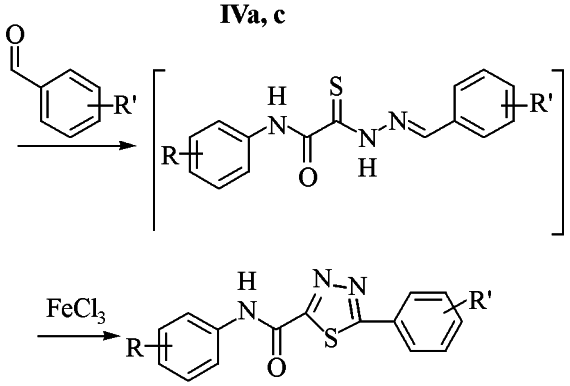
Va–l

V, R' = CF_3: R = H (**a**), 4-Cl (**b**), 4-MeO (**c**), 4-Br (**d**); R' = CCl_3: R = H (**e**), 4-Cl (**f**), 4-MeO (**g**), 2,3-Me_2 (**h**); R' = $CHCl_2$, R = 4-MeO (**i**); R' = CH_2Cl, R = 4-MeO (**j**).

However our attempts to perform heterocyclization by treating with substituted benzoyl chlorides were unsuccessful. Thiadiazoles **VI** with aryl groups were synthesized by oxidation of the corresponding hydrazones with $FeCl_3$.



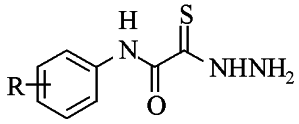
IVa, c



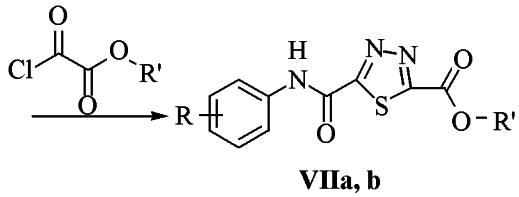
VIa–c

VI, R = H: R' = H (**a**), 4-NO_2 (**b**); R = 4-MeO, R' = H (**c**).

Reactions of thiohydrazides with alkyl oxalyl chlorides furnished the corresponding alkoxycarbonyl derivatives of substituted thiadiazoles **VII**.



IVc



VIIa, b

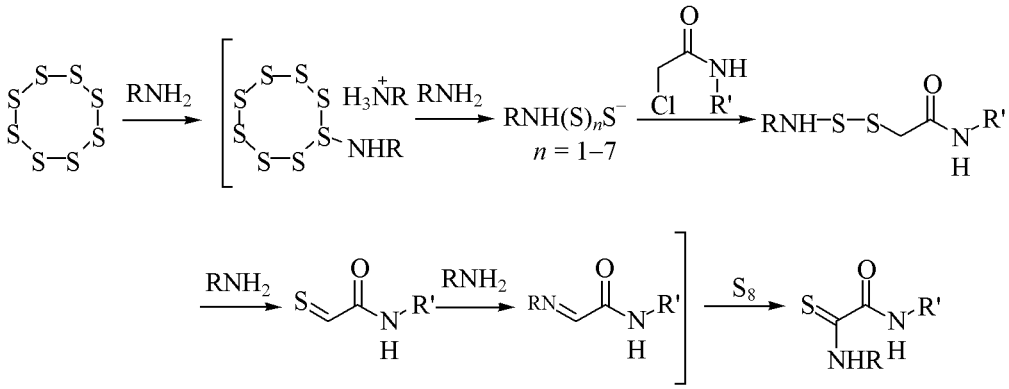
VII, R = 4-MeO: R' = Et (**a**), *t*-Bu (**b**).

Thus we developed a new preparation method for oxamic acids thiohydrazides and synthesized

therefrom derivatives of carbamoyl-1,3,4-thiadiazoles.

We believe that increased yield of oxamic acids thiohydrazides at application of the preliminary prepared solutions of elemental sulfur and hydrazines as compared to the mode of simultaneous addition of reagents is presumably due to reduced possibility of the side reaction (alkylation of hydrazines with chloroacetamides) under these conditions.

It is known that at sufficiently long interaction between amines and elemental sulfur a considerable amount of polysulfide anions accumulates in solution. The anions originate from the cleavage by amines of the eight-membered cycle of the elemental sulfur molecule [16]. Apparently at a sufficiently high concentration just polysulfide anins and not hydrazines predominantly react with the chloroacetamides. From the nucleophilic substitution of chlorine results the corresponding polysulfide where the hydrazine molecules effect simultaneous proton abstraction and sulfide bond cleavage to furnish a thioaldehyde fragment. The thioaldehyde reacts with hydrazine yielding a hydrazone which further suffers oxidation by sulfur into the corresponding thiohydrazide moiety.



Hence at sufficiently high concentration of polysulfide anions generated in the system sulfur–hydrazines apparently a pattern may be realized with participation of intermediate structures which significantly facilitate the thiolation process of the methylene fragment. The monothiooxamides arise from chloroacetamides also along a similar scheme.

Thus we demonstrated that the application of a preliminary prepared sulfur solution in amines or hydrazines is a convenient way of S-functionalization of α-chloroacetamides.

EXPERIMENTAL

^{1}H NMR spectra were registered on spectrometers Bruker WM-200 (200 MHz) and Bruker WM-250 (250 MHz) in DMSO-d_6. Mass spectra were measured on Varian MAT CH-6 instrument with direct admission of a sample into the ion source, ionizing electrons energy 70 eV, and control voltage 1.75 kV. Melting points were measured on Boetius heating block and were reported uncorrected. The analysis of reaction mixtures and checking of the products purity was carried out by TLC on Silufol UV-254 plates, eluent ethyl acetate–hexane, 1 : 1 by volume.

Synthesis of chloroacetanilides Ia–h. Chloroacetanilides were synthesized from appropriate arylamines and chloroacetyl chloride by a known procedure [17].

Simultaneous addition of 1-amino-4-methylpiperazine, elemental sulfur, and triethylamine to α-chloroacetanilide. To 6 mmol of chloroacetanilide **Ia, b** in 5 ml of DMF was added 18 mmol of sulfur, 12 mmol of 1-amino-4-methylpiperazine, and 2 ml of triethylamine. The reaction mixture was stirred at room temperature for 3 h and was left standing for 12 h. Then the mixture was poured into water, the separated precipitate was filtered off and dried. To remove the unreacted sulfur the product was dissolved in acetone, the acetone solution was separated, and the solvent was evaporated in a vacuum. The solid residue was recrystallized from ethanol.

***N*(1)-Phenyl-2-(2-amino-4-methylpiperazino)-2-thiooxacetamide (IId)**. Yield 24%, mp 132–135°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.25 s (3H, CH_3); 3.65 t (2 H, CH_2); 4.1 t (2H, CH_2); 7.1 t (1H, Harom, *J* 7.37); 7.3 t (2H, H arom, *J* 7.61); 7.6 d (2H, Harom, *J* 7.92); 10.55 s (1H, NH). Mass spectrum, *m/z*: 278 $[M]^+$. Found, %: C 56.20; H 6.42;

N 20.16; S 11.45. $C_{13}H_{18}N_4OS$. Calculated, %: C 56.09; H 6.52; N 20.13; S 11.52.

N(1)-(4-Chlorophenyl)-2-(2-amino-4-methylpiperazino)-2-thiooxacetamide (IIe). Yield 36%, mp 128–130°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.25 s (3H, CH_3); 3.65 t (1H, CH_2); 4.1 t (1H, CH_2); 7.3 d (2H, H arom, *J* 8.73); 7.65 d (2H, Harom, *J* 8.72); 10.7 s (1H, NH). Mass spectrum, *m/z*: 312 $[M]^+$. Found, %: C 50.02; H 5.39; Cl 11.40; N 18.03; S 10.34. $C_{13}H_{17}ClN_4OS$. Calculated, %: C 49.91; H 5.48; Cl 11.33; N 17.91; S 10.25.

Synthesis of oxamic acids thiohydrazides IIa–f. A mixture of 18 mmol of sulfur, 12 mmol of hydrazine, and 2 ml of triethylamine in 5 ml of DMF was stirred for 30 min, then a solution of 6 mmol of chloroacetanilide **Ia–c** in 3 ml of DMF was poured thereto. The reaction mixture was stirred at room temperature for 3 h and then was left overnight. Then the mixture was poured into water, the separated precipitate was filtered off and dried. To remove the unreacted sulfur the product was dissolved in acetone, the acetone solution was separated, and the solvent was evaporated in a vacuum. The solid residue was recrystallized from ethanol.

***N*(1)-Phenyl-2-(*N,N*-dimethylhydrazino)-2-thiooxacetamide (IIa)**. Yield 51%, mp 135–137°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.25 d (6H, $HNMe_2$);); 7.1 t (1H, Harom, *J* 7.37); 7.3 t (2H, Harom, *J* 7.61); 7.6 d (2H, Harom, *J* 7.92); 10.40 s (1H, NH). Mass spectrum, *m/z*: 208 $[M-15]^+$. Found, %: C 53.86; H 5.92; N 18.78; S 14.32. $C_{10}H_{13}N_3OS$. Calculated, %: C 53.79; H 5.87; N 18.82; S 14.36.

N(1)-(4-Chlorophenyl)-2-(*N,N*-dimethylhydrazino)-2-thiooxacetamide (IIb). Yield 62%, mp 174–176°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.25 s (6 H, $HNMe_2$); 7.4 d (2H, Harom, *J* 8.73); 7.6 d (2H, Harom, *J* 8.72); 10.65 s (1H, NH). Mass spectrum, *m/z*: 242 $[M-15]^+$. Found, %: C 46.55; H 4.64; Cl 13.81; N 16.20; S 12.40. $C_{10}H_{12}ClN_3OS$. Calculated, %: C 46.60; H 4.69; Cl 13.76; N 16.30; S 12.44.

***N*(1)-Phenyl-2-phenylhydrazino-2-thiooxacetamide (IIc)**. Yield 62%, mp 148–150°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.2 m (3H, Harom); 7.25 m (2H, Harom); 7.35 m (2H, H arom); 7.75 d (2H, Harom); 10.25 s (1H, NH). Mass spectrum, *m/z*: 271 $[M]^+$. Found, %: C 62.06; H 4.79; N 15.37; S 11.98. $C_{14}H_{13}N_3OS$. Calculated, %: C 61.97; H 4.83; N 15.49; S 11.82.

***N*(1)-Phenyl-2-(2-amino-4-methylpiperazino)-2-thiooxacetamide (IId)**. Yield 64%, mp 132–135°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.25 s (3 H, CH_3); 3.65 t (2 H, CH_2); 4.1 t (2H, CH_2); 7.1 t (1H, Harom, *J* 7.37); 7.3 t (2H, Harom, *J* 7.61); 7.6 d (2H, Harom, *J* 7.92); 10.55 s (1H, NH). Mass spectrum, *m/z*: 278 $[M]^+$.

***N*(1)-(4-Chlorophenyl)-2-(2-amino-4-methylpiperazino)-2-thiooxacetamide (IIe)**. Yield 57%, mp 128–130°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.25 s (3H, CH_3); 3.65 t (1H, CH_2); 4.1 t (1H, CH_2); 7.3 d (2H, Harom, *J* 8.73); 7.65 d (2H, Harom, *J* 8.72); 10.7 s (1H, NH). Mass spectrum, *m/z*: 312 $[M]^+$.

Methyl-2-{[(4-methylpiperazin-1-amino)(thiooxo)acetyl]amino}-3-phenylpropanoate (IIf). Yield 68%, mp 168–170°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.5 m (3H, CH_3); 3.00–3.5 m (8H, CH_2); 3.65 m (3H, CH_3); 4.0 m (2H, CH_2); 4.65 m (1H, CH); 7.3 m (5H, Harom); 9.00 d (1H, NH). Mass spectrum, *m/z*: 302 $[M-62]^+$. Found, %: C 56.12; H 6.71; N 15.25; S 8.91. $C_{17}H_{24}N_4O_3S$. Calculated, %: C 56.02; H 6.64; N 15.37; S 8.80.

Synthesis of monothiooxamides IIIa–g. *N*(1)-Aryl-2-morpholino-2-thiooxacetamides were prepared by a published procedure [8]. To a suspension of 3 mmol of sulfur in 30 ml of morpholine was added at stirring a solution of 1 mmol of chloroacetanilide **Ia–g** in 5 ml of DMF. The reaction mixture was stirred for 1 h at room temperature. Then the mixture was poured into water, the separated precipitate was filtered off and dried. To remove the unreacted sulfur the product was dissolved in acetone, the acetone solution was separated, and the solvent was evaporated in a vacuum. The solid residue was recrystallized from ethanol.

Synthesis of unsubstituted thiohydrazides of oxamic acids IVa–g. To a solution of 0.8 mmol of monothiooxamide **IIIa–g** in 2 ml of DMF was added 30 mmol of hydrazine hydrate, and the mixture was left standing at room temperature. On completion of reaction (TLC monitoring) the reaction mixture was poured into 50 ml of water, the solution was acidified by hydrochloric acid to pH 5. The separated precipitate was filtered off and recrystallized from ethanol.

***N*(1)-Phenyl-2-hydrazino-2-thiooxacetamide (IVa)**. Yield 83%, mp 144–147°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz); 7.15 t (1H, Harom, *J* 7.37); 7.4 t (2H, Harom, *J* 7.61); 7.6 d (2H, Harom, *J* 7.92); 10.20 s (1H, NH). Mass spectrum, *m/z*: 195 $[M]^+$. Found, %: C 49.34; H 4.50; N 21.63; S 16.33. $C_8H_9N_3OS$. Calculated, %: C 49.21; H 4.65; N 21.52; S 16.42.

***N*(1)-(4-Chlorophenyl)-2-hydrazino-2-thiooxacetamide (IVb)**. Yield 84.5%, mp 172–174°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.4 d (2H, Harom, *J* 8.73); 7.8 d (2H, Harom, *J* 8.72); 10.30 s (1H, NH). Mass spectrum, *m/z*: 229 $[M]^+$. Found, %: C 41.94; H 3.42; Cl 15.51; N 18.23; S 14.01. $C_8H_8ClN_3OS$. Calculated, %: C 41.83; H 3.51; Cl 15.44; N 18.29; S 13.96.

***N*(1)-(4-Methoxyphenyl)-2-hydrazino-2-thiooxacetamide (IVc)**. Yield 62%, mp 161–163°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.75 s (3H, Harom, *J* 8.83); 7.7 d (2H, Harom, *J* 8.83); 10.1 s (1H, NH). Mass spectrum, *m/z*: 225 $[M]^+$. Found, %: C 47.85; H 4.84; N 18.77; S 14.12. $C_9H_{11}N_3O_2S$. Calculated, %: C 47.99; H 4.92; N 18.65; S 14.23.

***N*(1)-(4-Bromophenyl)-2-hydrazino-2-thiooxacetamide (IVd)**. Yield 60%, mp 164–166°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.50 d (2H, Harom, *J* 8.86, *J* 8.85); 7.75 d (2H, Harom); 10.30 s (1H, NH). Mass spectrum, *m/z*: 274 $[M]^+$. Found, %: C 34.93; H 2.82; Br 29.26; N 15.47; S 11.81. C_8HBrN_3OS. Calculated, %: C 35.05; H 2.94; Br 29.15; N 15.33; S 11.70.

***N*(1)-(4-Fluorophenyl)-2-hydrazino-2-thiooxacetamide (IVe)**. Yield 75%, mp 157–160°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.2 m (2H, Harom); 7.80 t (2H, Harom); 10.20 s (1 H, NH). Mass spectrum, *m/z*: 213 $[M]^+$. Found, %: C 45.16; H 3.85; N 19.62; S 15.12. $C_8H_8FN_3OS$. Calculated, %: C 45.06; H 3.78; N 19.71; S 15.04.

***N*(1)-(2,3-Dimethylphenyl)-2-hydrazino-2-thiooxacetamide (IVf)**. Yield 68%, mp 150–153°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.3 s (6H, CH_3); 7.25 m (1H, Harom); 7.50 m (1H, Harom); 10.10 s (1H, NH). Mass spectrum, *m/z*: 223 $[M]^+$. Found, %: C 53.88; H 5.97; N 18.74; S 14.29. $C_{10}H_{13}N_3OS$. Calculated, %: C 53.79; H 5.87; N 18.82; S 14.36.

***N*(1)-(3-Methylphenyl)-2-hydrazino-2-thiooxacetamide (IVg)**. Yield 71%, mp 156–158°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.2 s (3 H, CH_3); 6.95 d (1H, Harom, *J* 7.4); 7.25 t (1H, Harom, *J* 7.74); 7.25 d (1H, Harom, *J* 8.14); 7.50 s (2H, Harom); 10.05 s (1H, NH). Mass spectrum, *m/z*: 209 $[M]^+$. Found, %: C 51.53; H 5.29; N 20.16; S 15.20. $C_9H_{11}N_3OS$. Calculated, %: C 51.66; H 5.30; N 20.08; S 15.32.

Synthesis of 5-(trifluoromethyl)-1,3,4-thiadiazole-2-carboxamides Va–d. To 10 mmol of oxamic acid thiohydraside **IVa–d** in 5 ml of DMF was added 20 ml of trifluoroacetic anhydride. After 15 min (TLC monitoring, eluent ethyl acetate–hexane, 1 : 2 by volume) the reaction mixture was poured into water, the separated precipitate was filtered off and recrystallized from ethanol.

***N*-Phenyl-5-(trifluoromethyl)-1,3,4-thiadiazole-2-carboxamide (Va)**. Yield 89%, mp 177–180°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.1 t (1H, Harom, *J* 7.37); 7.3 t (2H, Harom, *J* 7.61); 7.6 d (2H, Harom, *J* 7.92); 11.40 s (1H, NH). Mass spectrum, *m/z*: 273 $[M]^+$. Found, %: C 44.05; H 2.14; N 15.42; S 11.81. $C_{10}H_6F_3N_3OS$. Calculated, %: C 43.96; H 2.21; N 15.38; S 11.73

***N*-(4-Chlorophenyl)-5-trifluoromethyl-1,3,4-thiadiazole-2-carboxamide (Vb)**. Yield 51.5%, mp 181–183°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.5 d (2H, Harom, *J* 8.73); 7.9 d (2H, Harom, *J* 8.72); 11.50–11.60 s (1H, NH). Mass spectrum, *m/z*: 307 $[M]^+$. Found, %: C 39.12; H 1.51; Cl 11.63; N 13.60; S 10.33. $C_{10}H_5ClF_3N_3OS$. Calculated, %: C 39.04; H 1.64; Cl 11.52; N 13.66; S 10.42.

***N*-(4-Methoxyphenyl)-5-(trifluoromethyl)-1,3,4-thiadiazole-2-carboxamide (Vc)**. Yield 75%, mp 157–158°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.7 s (3H, CH_3); 6.9 d (2H, Harom, *J* 8.83); 7.80 d (2H, Harom, *J* 8.84); 11.20 s (1H, NH). Mass spectrum, *m/z*: 303 $[M]^+$. Found, %: C 43.49; H 2.74; N 13.95; S 10.44. $C_{11}H_8F_3N_3O_2S$. Calculated, %: C 43.57; H 2.66; N 13.86; S 10.57.

***N*-(4-Bromophenyl)-5-(trifluoromethyl)-1,3,4-thiadiazole-2-carboxamide (Vd)**. Yield 45.2%, mp 183–186°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.5–7.6 d (2H, Harom); 7.80–7.90 d (2H, Harom); 11.50 s (1H, NH). Mass spectrum, *m/z*: 352 $[M]^+$. Found, %: C 34.01; H 1.52; Br 22.56; N 12.01; S 9.05. $C_{10}H_5BrF_3N_3OS$. Calculated, %: C 34.11; H 1.43; Br 22.69; N 11.93; S 9.11.

Synthesis of 5-(trichloromethyl)-1,3,4-thiadiazole-2-carboxamides Ve–h. To 10 mmol of oxamic acid thiohydraside **IVe–h** in 5 ml of DMF was added 20 ml of trichloroacetyl chloride. After 4 h the reaction mixture was poured into water, the separated precipitate was filtered off and recrystallized from ethanol.

***N*-Phenyl-5-(trichloromethyl)-1,3,4-thiadiazole-2-carboxamide (Ve)**. Yield 64%, mp 152– 153°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.1 t (1H, Harom, *J* 7.37); 7.3 t (2H, Harom, *J* 7.61); 7.6 d (2H, Harom, *J* 7.92); 11.40 s (1H, NH). Mass spectrum, *m/z*: 322 $[M]^+$. Found, %: C 37.14; H 1.75; Cl 33.05; N 13.12; S 9.90. $C_{10}H_6Cl_3N_3OS$. Calculated, %: C 37.23; H 1.87; Cl 32.97; N 13.03; S 9.94.

***N*-(4-Chlorophenyl)-5-(trichloromethyl)-1,3,4-thiadiazole-2-carboxamide (Vf)**. Yield 62%, mp 165–167°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.4 d (2H, Harom, *J* 8.73); 7.9 d (2H, Harom, *J* 8.72); 11.40 s (1H, NH). Mass spectrum, *m/z*: 357 $[M]^+$. Found, %: C 33.72; H 1.53; Cl 39.64; N 11.85; S 9.05. $C_{10}H_5Cl_4N_3OS$. Calculated, %: C 33.64; H 1.41; Cl 39.72; N 11.77; S 8.98.

***N*-(4-Methoxyphenyl)-5-(trichloromethyl)-1,3,4-thiadiazole-2-carboxamide (Vg)**. Yield 75%, mp 157–158°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.7 s (3H, CH_3); 6.9 d (2H, Harom, *J* 8.83); 7.80 d (2H, Harom, *J* 8.84); 11.20 s (1H, NH). Mass spectrum, *m/z*: 352 $[M]^+$. Found, %: C 37.34; H 2.20; Cl 30.29; N 12.04; S 9.15. $C_{11}H_8Cl_3N_3O_2S$. Calculated, %: C 37.47; H 2.29; Cl 30.16; N 11.92; S 9.09.

***N*-(2,3-Dimethylphenyl)-5-(trichloromethyl)-1,3,4-thiadiazole-2-carboxamide (Vh)**. Yield 52%, mp 138–140°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.1 s (3H, CH_3); 2.2 s (3H, CH_3); 7.10–7.20 m (3H, Harom); 10.85 s (1H, NH). Mass spectrum, *m/z*: 349 $[M]^+$. Found, %: C 41.21; H 2.95; Cl 30.36; N 11.86; S 9.03. $C_{12}H_{10}Cl_3N_3OS$. Calculated, %: C 41.10; H 2.87; Cl 30.33; N 11.98; S 9.14.

5-(Dichloromethyl)-1,3,4-thiadiazole-2-carboxamide Vi. To 10 mmol of oxamic acid thiohydraside **IVi** in 5 ml of DMF was added 20 ml of dichloroacetyl chloride. After 4 h the reaction mixture was poured into water, the separated precipitate was filtered off and recrystallized from ethanol. Yield 78%, mp 133–135°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.7 s (3H, CH_3); 6.4 s (1H, CH_3); 6.9 d (2H, Harom, *J* 8.83); 7.80 d (2H, Harom, *J* 8.84); 11.20 s (1H, NH). Mass spectrum, *m/z*: 318 $[M]^+$. Found, %: C 41.65; H 2.73; Cl 22.32; N 13.19; S 10.01. $C_{11}H_9Cl_2N_3O_2S$. Calculated, %: C 41.52; H 2.85; Cl 22.28; N 13.21; S 10.08.

5-(Chloromethyl)-1,3,4-thiadiazole-2-carboxamide Vj. To 10 mmol of oxamic acid thiohydraside **IVc** in 5 ml of DMF was added 20 ml of monochloroacetyl chloride. After 4 h the reaction mixture was poured into water, the separated precipitate was filtered off and recrystallized from ethanol. Yield 51%, mp 146–148°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.7 s (3H, CH_3); 6.9 d (2H, Harom, *J* 8.83); 7.80 d (2H, Harom, *J* 8.84); 11.20 s (1H, NH). Mass spectrum, *m/z*: 283 $[M]^+$. Found, %: C 46.44; H 3.46; Cl 12.61; N 14.74; S 11.45. $C_{11}H_{10}ClN_3O_2S$. Calculated, %: C 46.56; H 3.55; Cl 12.49; N 14.81; S 11.30.

Synthesis of 5-aryl-1,3,4-thiadiazole-2-carboxamides VIa–c. A mixture of 1 mmol of thiohydrazide **IVa, c** and 1.1 mmol of aldehyde in 6 ml of ethanol was boiled for 15 min. To the reaction mixture obtained a solution was added of 2 mmol of iron(III) chloride hexahydrate in 5 ml of ethanol, and the mixture was heated for 1.5 h more. Then the reaction mixture was cooled to room temperature, the separated precipitate was filtered off, twice washed with 3 ml of ethanol, with 5 ml of water, and dried in air.

***N*-Phenyl-5-phenyl-1,3,4-thiadiazole-2-carboxamide (VIa)**. Yield 70%, mp 228–230°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.1 t (1H, Harom, *J* 7.37); 7.25 t (1H, Harom, *J* 7.38); 7.6 m (4 H, Harom); 7.8 d (2 H, Harom, *J* 7.92); 8.1 d (2H, Harom, *J* 7.92); 11.0 s (1H, NH). Mass spectrum, *m/z*: 281 $[M]^+$. Found, %: C 63.92; H 4.01; N 15.09; S 11.32. $C_{15}H_{11}N_3OS$. Calculated, %: C 64.04; H 3.94; N 14.94; S 11.40.

***N*-Phenyl-5-(4-nitrophenyl)-1,3,4-thiadiazole-2-carboxamide (VIb)**. Yield 72%, mp 248–250°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.1 t (1H, Harom, *J* 7.92); 7.35 t (2H, Harom, *J* 7.38); 7.65 m (4H, Harom); 8.4 d (2H, Harom, *J* 7.92); 11.0 s (1H, NH). Mass spectrum, *m/z*: 326 $[M]^+$. Found, %: C 55.11; H 3.03; N 17.12; S 9.95. $C_{15}H_{10}N_4O_3S$. Calculated, %: C 55.21; H 3.09; N 17.17; S 9.83.

***N*-(4-Methoxyphenyl)-5-phenyl-1,3,4-thiadiazole-2-carboxamide (VIc)**. Yield 67%, mp 225–226°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.8 s (3H, CH_3); 7.0 d (2H, Harom, *J* 8.83); 7.6 m (3H, Harom); 7.8 m (2H, Harom); 8.1 d (2H, Harom, *J* 7.92); 11.0 s (1H, NH). Mass spectrum, *m/z*: 311 $[M]^+$. Found, %: C 61.64; H 4.33; N 13.39; S 10.43. $C_{16}H_{13}N_3O_2S$. Calculated, %: C 61.72; H 4.21; N 13.50; S 10.30.

Ethyl 5-{[(4-methoxyphenyl)amino]carbonyl}-1,3,4-thiadiazole-2-carboxylate (VIIa). To 10 mmol of oxamic acid thiohydrazide **IVc** in 5 ml of DMF was added 20 mmol of methyl oxalyl chloride. In 4 h the separated precipitate was filtered off and recrystallyzed from methanol. Yield 72%, mp 135–138°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.5 t (3H, CH_3); 4.5 d (2H, CH_2); 3.8 s (3H, CH_3); 6.9 d (2H, Harom, *J* 8.83); 7.80 d (2H, Harom, *J* 8.84); 11.20 s (1H, NH). Mass spectrum, *m/z*: 307 $[M]^+$. Found, %: C 50.92; H 4.14; N 13.73; S 10.55. $C_{13}H_{13}N_3O_4S$. Calculated, %: C 50.81; H 4.26; N 13.67; S 10.43.

***tert*-Butyl 5-{[(4-methoxyphenyl)amino]carbonyl}-1,3,4-thiadiazole-2-carboxylate (VIIb).** To

10 mmol of oxamic acid thiohydrazide **IVc** in 5 ml of DMF was added 20 mmol of *tert*-butyl oxalyl chloride. In 4 h the separated precipitate was filtered off and recrystallyzed from *t*-BuOH. Yield 65%, mp 151–152°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.3 s (9H, CH_3); 3.8 s (3H, CH_3); 6.9 d (2H, Harom, *J* 8.83); 7.80 d (2H, Harom, *J* 8.84); 11.20 s (1H, NH). Mass spectrum, *m/z*: 335 [*M*]+. Found, %: C 53.86; H 5.02; N 13.07; S 10.04. $C_{15}H_{17}N_3O_4S$. Calculated, %: C 53.72; H 5.11; N 12.53; S 9.56.

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