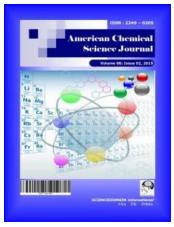

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Synthesis and Biological Activity of Novel 5-(Alkylthio)-1,3,4-thiadiazol-2(3*H*)-thione Derivatives

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Authors' contributions

This work was carried out in collaboration between all authors. Authors APY and ENH planned the study, managed the literature searches, analyzed the spectral data of obtained compounds and wrote the manuscript. Authors ASV and AAG performed the experiments. All authors read and approved the final manuscript.

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ABSTRACT

Some nonfused biheterocyclic system derivatives containing a combination of 1,3,4-thiadiazole and pharmacophores such as 1,3,4-oxadiazole and/or pyrazoles in the same molecule were obtained based on 2-((5-(alkylthio)-1,3,4-thiadiazol-2-yl)thio)acetohydrazide. The synthesized compounds show pronounced plant growth stimulant properties.

Keywords: 5-(alkylthio)-1,3,4-thiadiazole-2(3H)-thiones derivatives; heterocyclization; nonfused biheterocyclic systems; 1,3,4-oxadiazole; pyrazole; plant growth stimulant properties.

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1. INTRODUCTION

To obtain consistently high yields of crops, intensive cultivation technologies based on application of fertilizers and pesticides are used. At the same time, problems arise concerning human and environment safety, which is related to pollution of soil, water and the accumulation of their residues or degradation products in food. Another disadvantage of plant protection chemicals is that harmful organisms acquire resistance towards them. These undesirable phenomena makes it necessary to regularly replenish the arsenal of pesticides with new environmentally friendly compounds having different mechanisms of action.

In the last two decades 1,3,4-thiadiazole derivatives, which exhibit a broad spectrum of biological activity have received considerable attention from scientific researchers.The compounds based on this heterocycle are widely used not only in medicinal practice, but also in agriculture as plant protection chemicals [1]. The search for new medicines and pesticides is continuing in the new series of 1,3,4-thiadiazole derivatives. Among them the new substances with anticonvulsant, antimicrobial, anti-inflammatory, anesthetic, antituberculosis, anti-depressant, anxiolitic, antifungal, antiproliferative [2-12] and pescididal [13,14] activities have been discovered.

Taking into consideration the pesticidal activity of some compounds, which were earlier synthesized in the series of 1,3,4-thiadiazole-2-thione S-substituted derivatives, and the availability and high yield of 1,3,4-thiadiazol-2,5-dithiones [15,16] it would be useful to continue the search for new active compounds, based on this heterocyclic system. Therefore the aim of this research was the synthesis of new 2-S-substituted 5-alkylthio-1,3,4-thiadiazol-2-thiones, as well as compounds with a combination of 1,3,4-thiadiazole and other pharmacophoric heterocycles – 1,3,4-oxadiazole and pyrazole in the same molecule, as their derivatives are also the object of attention of researchers in the search for new pesticides ([17-21] and [22-31], respectively).

2. EXPERIMENTAL DETAILS

2.1 General

^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded at 30 ^{0}C on Mercury-300 spectrometer (Varian, USA) with standard pulse sequences operating in the mixture of solvents DMSO-d_6 and CCl_4 (1:3) using tetramethylsilane (0.0 ppm) as internal standard. The NMR multiplicities br s, s, d, t, q, and m stand for broad singlet, singlet, doublet, triplet, quartet and multiplet, respectively. The reaction progress and purity of the obtained substances were checked by using the TLC method on “Silufol UV-254” plates and acetone/hexane mixture (2:1) as eluent. All melting points were determined in open capillaries and are uncorrected.

2.2 Methyl 2-((5-(methylthio)-1,3,4-thiadiazol-2-yl)thio)acetate (2a)

To a solution of NaOH (0.01 mol) in 10 mL of water, 0.01 mol of 5-(alkylthio)-1,3,4-thiadiazole-2(3*H*)-thione (**1a**) and then catalitic amount of TEBAC were added. The mixture was stirred, 0.01 mol of $NaI\cdot 2H_2O$ was added, and then at cooling with cold water 0.01 mol of methyl 2-chloroacetate was slowly added. The mixture was stirred at 35 ^{0}C for 2-3 h and cooled. The precipitate was filtered off, washed with cold water and dried. Yield: 88%, M.p.: 68-69^{0}C. ^{1}H NMR δ (ppm): 2.78 (s, 3H, SCH_3); 3.77 (s, 3H, OCH_3); 4.12 (s, 2H, SCH_2). Analysis for $C_6H_8N_2O_2S_3$ (188) Calculated : C: 30.49%, H: 3.41%, N: 11.85%, S: 40.70%. Found: C: 30.21%, H: 3.27%, N: 11.55%, S: 40.58%.

2.2.1 Methyl 2-((5-(ethylthio)-1,3,4-thiadiazol-2-yl)thio)acetate (2b)

Was obtained as an oily liquid, was not isolated from the reaction medium, and at once was used to synthesize compound **3b**.

2.2.2 2-((5-(Methylthio)-1,3,4-thiadiazol-2-yl)thio)acetohydrazide (3a)

To a mixture of compound **2a** (0.005 mol) in 8 mL of isopropanol, at cooling with cold water 0.0056 mol of hydrazine hydrate (70%) was added. The mixture was stirred for 0.5 h, heated at 35ºC for 1.5-2 h and cooled. To a mixture, 5-10 mL of cold water was added and the precipitate was filtered off and dried. Yield: 85%, M.p.: 135-137ºC. ^{1}H NMR δ (ppm): 2.77 (s, 3H, SCH_3); 3.90 (s, 2H, SCH_2); 4.10 (brs, 2H, NH_2); 9.28 (brs, 1H, NH). Analysis for $C_5H_8N_4OS_3$(236.33) Calculated: C: 25.41; H, 3.41; N: 23.71; S:40.70. Found: C:25.35; H, 3.44; N: 23.55; S:40.49.

2.2.3 2-((5-(Ethylthio)-1,3,4-thiadiazol-2-yl)thio)acetohydrazide (3b)

In a solution of NaOH (0.01 mol) in 10 mL of water, 0.01 mol of compound **1a** was dissolved. To this solution catalitic amount of TEBAC and 0.01 mol of $NaI \cdot 2H_2O$ were added. After cooling with cold water, 0.012 mol of methyl 2-chloroacetate was slowely added. The mixture was stirred at 35-40ºC for 2-3 h and allowed to stand overnight. The oil layer was separated and the aqueous layer extracted with ether. From the joined ether extracts the ether was removed, to the residue 6.7 mL of isopropanol was added and at cooling with cold water slowly 0.01 mol of hydrazin hydrate (70%) was added. The mixture was stirred for 0.5 h and heated at 35-40ºC for 1-2 h. After cooling, 10 mL of cold water was added and the precipitate was filtered off, washed and dried. Yield: 72%, M.p.: 68-70ºC. ^{1}H NMR δ (ppm): 1.44 (t, J=7.1, 3H, $SCH_2\mathit{CH_3}$); 3.26 (q, J=7.1, 2H, $S\mathit{CH_2}CH_3$); 3.90 (s, 2H, SCH_2); 9.28 (brs, 1H, NH). Analysis for $C_6H_{10}N_4OS_3$ (250.35) Calculated: C: 28.79%, H: 4.03%, N: 22.38%, S:38.42%. Found: C: 28.62%, H: 3.95%, N: 22.56%, S:38.20%.

2.3 General Procedure for the Synthesis of Compounds 4a, b

To a solution of 85% KOH (0.005 mol) in 7-8 mL of abs. ethanol, 0.005 mol of hydrazide **3**, then 0.6 mL (0.01 mol) of CS_2 were added and the mixture was boiled at 80-90ºC for 5-6 h. After solvent evaporation the residue was processed with 7-8 mL of cold water and acidified with acetic acid. The precipitate was filtered off, washed with water and dried. For purification compounds **4** were again dissolved in KOH aqueous solution and acidified with acetic acid.

2.3.1 5-(((5-(Methylthio)-1,3,4-thiadiazol-2-yl)thio)methyl)-1,3,4-oxadiazole-2(3*H*)-thione (4a)

Yield: 78%, M.p.: 177-178 ^{0}C. ^{1}H NMR δ (ppm): 2.78 (s, 3H, SCH_3); 4.60 (s, 2H, SCH_2); 14.25 (brs, 1H, NH). Analysis for $C_6H_6N_4OS_4$(278.38) Calculated: C: 25.89%, H: 2.17%, N: 20.13%, S: 46.07%. Found: C: 25.71%, H: 2.13%, N: 19.85%, S: 46.02%.

2.3.2 5-(((5-(Ethylthio)-1,3,4-thiadiazol-2-yl)thio)methyl)-1,3,4-oxadiazole-2(3*H*)-thione (4b).

Yield: 69%, M.p.: 129-130ºC. ^{1}H NMR δ (ppm): 1.47 (t, J=7.3, 3H, $SCH_2\mathit{CH_3}$); 3.31 (q, J=7.3, 2H, $S\mathit{CH_2}CH_3$); 4.60 (s, 2H, SCH_2); 14.26 (brs, 1H, NH). Analysis for $C_7H_8N_4OS_4$ (292,41) Calculated: C: 28.75%, H: 2.76%, N: 19.16%, S: 43.86%. Found: C: 28.71%, H: 2.73%, N: 18.85%, S: 43.65%.

2.4 General Procedure for the Synthesis of Compounds 5a-d

To a solution of 85% KOH (0.005 mol) in 10 mL of water at continuous stirring, one after another 0.005 mol of compound **4** and 0.005 mol of DMS or 2-chloroacetamide at cooling with icy water were added. The mixture was stirred for 0.5-1 h and allowed to stand overnight at room temperature. The precipitate was filtered off, washed with dilute solution of KOH, then with water and dried.

2.4.1 2-(Methylthio)-5-(((5-(methylthio)-1,3,4-thiadiazol-2 -yl)thio)methyl)-1,3,4-oxadiazole (5a)

Yield: 76 %, M.p.: 67-69ºC. ^{1}H NMR δ ppm: 2.68 and 2.74 [ss, 6H, $2\times SCH_3$]; 4.77 (s, 2H, SCH_2). ^{13}C NMR δ (ppm): 14.15, 16.39, 27.26, 161.54, 164.01, 165.12, 168.62. Analysis for $C_7H_8N_4OS_4$(294.41) Calculated: C: 28.75%, H: 2.76%, N: 19.16%, S: 43.86%. Found: C: 28.78%, H: 2.77%, N: 19.21%, S: 43.89%.

2.4.2 2-(((5-(Ethylthio)-1,3,4-thiadiazol-2-yl)thio)methyl)-5-(methylthio)-1,3,4-oxadiazole (5b)

Yield: 80%, M.p.: 66-68ºC. ^{1}H NMR δ (ppm): 1.47 (t, J=7.3, 3H, $SCH_2\mathit{CH_3}$); 2.71 (s, 3H, SCH_3); 3.31 (q, J=7.3, 2H, $S\mathit{CH_2}CH_3$); 4.72 (s, 2H, SCH_2). Analysis for $C_8H_{10}N_4OS_4$ (306.44): C: 31.36%, H: 3.29%, N: 18.28%, S: 41.85%. Found: C: 31.38%, H: 3.31%, N: 18.31%, S:41.89%.

2.4.3 2-((5-(((5-(methylthio)-1,3,4-thiadiazol- 2-yl)thio)methyl)-1,3,4-oxadiazol-2-yl)thio)acetamide (5c)

Yield: 71%, M.p.:159-160ºC. ^{1}H NMR δ (ppm): 2.74 (s, 3H, SCH_3); 4.03 (s, 2H, SCH_2CO); 4.78 (s, 2H, SCH_2); 7.31 and 7.71 (brs, 2H, NH_2). ^{13}C NMR δ (ppm): 16.41, 27.20, 35.91, 161.56, 163.97, 164.14, 167.56, 168.57). Analysis for $C_8H_9N_5O_2S_4$ (335.43) Calculated: C: 28.65%, H: 2.70%, N: 20.88%, S: 38.23%. Found: C: 28.58%, H: 2.51%, N: 20.61%, S: 38.19%.

2.4.4 2-((5-(((5-(Ethylthio)-1,3,4-thiadiazol-2 -yl)thio)methyl)-1,3,4-oxadiazol-2-yl)thio)acetamide (5d)

Yield: 85%, M.p.: 126-128ºC. ^{1}H NMR δ (ppm): 1.45 (t, J=7.3, 3H, SCH_2CH_3); 2.76 (s, 3H, SCH_3); 3.32 (q, J=7.3, 2H, SCH_2CH_3); 4.05 (s, 2H, SCH_2CO); 4.76 (s, 2H, SCH_2); 7.25 and 7.66 (brs, 2H, NH_2). Analysis for $C_8H_{10}N_4OS_4$(349.46) Calculated : C: 30.9%, H: 3.17%, N: 20.04%, S: 36.70%. Found: C: 30.88%, H: 3.11%, N: 20.01%, S: 36.69%.

2.5 General Procedure for the Synthesis of Compounds 6a, b

To 0.001 mol of compound **3**, at cooling with cold water 1 mL of $POCl_3$ then 0.0022 mol of benzoic acid were added. The mixture was stirred for 2-3 h and allowed to stand overnight at room temperature. To a mixture 3-4 mL of cold water was added, and neutralized with concentrated solution of NaOH. The precipitate was filtered off, washed with water and dried.

2.5.1 2-(((5-(Methylthio)-1,3,4-thiadiazol-2 -yl)thio)methyl)-5-phenyl-1,3,4-oxadiazole (6a)

Yield: 69%, M.p.: 110-112ºC. ^{1}H NMR δ (ppm): 2.76 (s, 3H, SCH_3); 4.81(s, 2H, SCH_2); 7.51-8.01 (m, 5H, C_6H_5). Analysis for $C_{12}H_{10}N_4OS_3$ (322.42) Calculated: C: 44.70%, H: 3.13%, N: 17.38%, S: 29.83%. Found: C: 44.88%, H: 3.16;%, N: 17.41%, S: 29.89%.

2.5.2 2-(((5-(Ethylthio)-1,3,4-thiadiazol-2 yl)thio)methyl)-5-phenyl-1,3,4-oxadiazole (6b)

Yield: 71%, M.p.: 103-105ºC. ^{1}H NMR δ (ppm): 1.46 (t, J=7.3, 3H, SCH_2CH_3); 3.32 (q, J=7.3, 2H, SCH_2CH_3); 4.81 (s, 2H, SCH_2); 7.50-8.02 (m, 5H, C_6H_5). Analysis for $C_{13}H_{12}N_4OS_3$ (336.45) Calculated: C:46.41%, H: 3.60%, N: 16.65%, S:28.59%. Found: C: 46.38%, H: 3.56%, N: 16.61%, S: 28.55%.

2.5.3 2-Chloro-N'-(2-((5-(methylthio)-1,3,4-thiadiazol-2-yl)thio)acetyl)acetohydrazide (7)

To 0.001 mol of compound **3a**, at cooling with icy water 0.5 mL of $POCl_3$ then 0.0011 mol of chloroacetic acid were added. The mixture was stirred at room temperature for 2-3 h and allowed to stand for 24-26 h. To a mixture, 3-4 mL of cold water was addded and at cooling with icy water it was neutralized with concentrated solution of Na_2CO_3. Obtained precipitate was filtered off, washed with dilute solution of HCl, then with water and dried. Yield: 67%, M.p.: 174-176ºC. ^{1}H NMR δ (ppm): 2.76 (s, 3H, SCH_3); 4.03 and 4.04 (ss, 4H, SCH_2 and CH_2Cl); 10.54 (s, 2H, NHNH). Analysis for $C_7H_9ClN_4O_2S_3$ (312.80) Calculated: C: 26.88%, H: 2.90%, Cl: 11.33%, N: 17.91%, S: 30.75%. Found: C: 26.83%, H: 2.88%, Cl: 11.29%, N: 17.89%, S: 30.71%.

2.5.4 N'-Acetyl-2-((5-(methylthio)-1,3,4-thiadiazol-2-yl)thio)acetohydrazide (8)

The mixture of 0.001 mol of compound **3a** and 1 mL of acetanhydride (or 1 mL of glacial acetic acid) was stirred at room temperature for 2-3 h and allowed to stand overnight. 2-3 mL of icy water was added to mixture and obtained precipitate was filtered off, washed with water and dried. Yield: 85%, M.p.: 183-184ºC. ^{1}H NMR δ (ppm): 1.89 (s, 3H, $COCH_3$); 2.76 (s, 3H, SCH_3); 4.05 (s, 2H, SCH_2CO); 9.97 (s, 1H, NH); 10.20 (s, 1H, NH). Analysis for $C_7H_{10}N_4O_2S_3$(312.80) Calculated: C: 30.20%, H: 3.62%, N: 20.13%, S: 34.55%. Found: C: 30.28%, H: 3.66%, N: 20.16%, S: 34.57%.

2.6 General Procedure for the Synthesis of Compounds 9a, b

a) A mixture of compound **3** (0.0025 mol), 1 mL of pentane-2,4-dione and 2 mL of 1,4-dioxane was heated at 65-70ºC for 7-8 h. After evaporation of solvent the residue was processed with water, filtered off, washed with dilute solution of HCl, then with water and dried.

b) A mixture of compound **3** (0.0025 mol), 1.2 mL of pentane-2,4-dione in 1 mL of glacial acetic acid was allowed to stand at room temperature overnight. To a mixture, 3-4 mL of cold water was added, the precipitate was filtered off and dried.

2.6.1 1-(3,5-Dimethyl-1H-pyrazol-1-yl)-2-((5-(methylthio)-1,3,4-thiadiazol-2-yl)thio)ethan-1-one (9a)

Yield: 80%, M.p.: 110-111ºC. ^{1}H NMR δ (ppm): 2.23 (s, 3H, 3-CH_3-pyraz.); 2.53 (s, 3H, 5-CH_3-pyraz.); 2.77 (s, 3H, SCH_3); 4.85 (s, 2H, SCH_2); 6.08 (s, 1H, CH-pyraz.). ^{13}C NMR δ (ppm): 13.20, 13.55, 15.87, 37.40, 102.68, 143.32, 151.60, 162.16, 165.55, 166.07. Analysis for $C_{10}H_{12}N_4OS_3$ (300.41) Calculated: C: 39.98%, H:

4.03%, N: 18.65%, S: 32.02%. Found: C: 40.03%, H: 3.88%, N: 18.47%, S: 31.86%.

2.6.2 1-(3,5-Dimethyl-1H-pyrazol-1-yl)-2-((5-(ethylthio)-1,3,4-thiadiazol-2 yl)thio)ethan-1-one (9b)

Yield: 81%, M.p.: 100-102ºC. ^{1}H NMR δ (ppm): 1.46 (t, J=7.3, 3H, SCH_2CH_3); 2.22 (s, 3H, 3-CH_3-pyraz.); 2.55 (s, 3H, 5-CH_3-pyraz.); 3.29 (q, J=7.3, 2H, SCH_2CH_3); 4.86 (s, 2H, SCH_2); 6.07 (s, 1H, CH-pyraz.). Analysis for $C_{11}H_{14}N_4OS_3$ (314.44) Calculated: C: 42.02%, H: 4.49%, N: 17.82%, S: 30.59%. Found: C: 41.83%, H: 4.40%, N: 17.61%, S: 30.29%.

2.7 General Procedure for the Synthesis of Compounds 10a, b

The mixture of compound **3** (0.0025 mol) and 1 mL of ethyl 3-oxobutanoate in 0.5 mL of glacial acetic acid was stirred for 2-3 h and allowed to stand at room temperature for 14-16 h. 2-3 mL of icy water was added and obtained precipitate was filtered off. Compounds **10** were recrystallized from ethanol.

2.7.1 Ethyl2-(2-(2-((5-(methylthio)-1,3,4-thiadiazol-2-yl)thio)acetyl)hydrazono)propanoate (10a)

Yield: 86%, M.p.:109-111ºC. ^{1}H NMR δ (ppm): 1.28 (t, J=7.1, 3H, OCH_2CH_3); 1.95 (s, 3H, CH_3); 2.76 (s, 3H, SCH_3); 4.15 (q, J=7.1, 2H, OCH_2CH_3); 4.38 (s, 2H, SCH_2); 10.07 (s, 1H, NH). Analysis for $C_{10}H_{14}N_4O_3S_3$ (334.43) Calculated: C: 35.92%, H: 4.22%, N: 16.75%, S: 28.76%. Found: C: 35.88%, H: 4.18%, N: 16.71% S: 28.66%.

2.7.2 Ethyl 2-(2-(2-((5-(ethylthio)-1,3,4-thiadiazol-2-yl)thio)acetyl)hydrazono)propanoate (10b)

Yield: 90%, M.p.: 99-100ºC. ^{1}H NMR δ (ppm): 1.28 (t, J=7.1, 3H, OCH_2CH_3); 1.46 (t, J=7.3, 3H, SCH_2CH_3); 1.95 (s, 3H, CH_3); 2.76 (s, 3H, SCH_3); 3.28 (q, J=7.3 Гц, 2H, SCH_2CH_3); 4.14 (q, J=7.1, 2H, OCH_2CH_3); 4.39 (s, 2H, SCH_2); 10.72 (s, 1H, NH). Analysis for $C_{11}H_{16}N_4O_3S_3$ (348.45) Calculated: C: 37.92%, H: 4.63%, N: 16.08%, S: 27.60%. Found: C: 37.88%, H: 4.58%, N: 16.11%, S: 27.66%.

2.8 General Procedure for the Synthesis of Compounds 11a, b

To a mixture of compound **3** (0.002 mol) and $NaNO_2$ (0.0056 mol) in 3-4 mL of water, at cooling with ice 0.0056 mol of glacial acetic acid was added dropwise. The mixture was stirred for 3 h, the precipitate was filtered off and dried.

2.8.1 2-((5-(Methylthio)-1,3,4-thiadiazol-2-yl)thio)acetyl azide (11a)

Yield: 86%, m.p. 75-77ºC. ^{1}H NMR δ (ppm): 2.77 (s, 3H, SCH_3); 4.17 (s, 2H, SCH_2). Analysis for $C_5H_5N_5OS_3$ (247.31) Calculated: C: 24.28%, H: 2.04%, N: 28.32%, S: 38.89%. Found: C: 24.25%, H: 2.01%, N: 28.21%, S: 38.66%.

2.8.2 2-((5-(Ethylthio)-1,3,4-thiadiazol-2-yl)thio)acetyl azide (11b)

Yield: 80%, M.p.: 72-73ºC. ^{1}H NMR δ (ppm): 1.46 (t, J=7.3, 3H, SCH_2CH_3); 3.29 (q, J=7.3, 2H, SCH_2CH_3); 4.18 (s, 2H, SCH_2). Analysis for $C_6H_7N_5OS_3$ (261.34) Calculated: C: 27.58%, H: 2.07%, N: 26.80%, S: 36.80%. Found: C:27.55%, H: 2.04%, N: 26.78%, S: 36.76%.

2.9 General Procedure for the Synthesis of Compounds 12a, b

To a mixture of compound **11** (0.001 mol) and aniline (0.001 mol) in 2-3 mL of abs. toluene, one drop of pyridine was added, and heated at 90-100ºC for 5-6 h. Toluene was removed, the recidue was processed with hexane, filtered off and dried.

2.9.1 2-((5-(Methylthio)-1,3,4-thiadiazol-2-yl)thio)-N-phenylacetamide (12a)

Yield: 72%, M.p.: 120-121ºC (ethanol). ^{1}H NMR δ (ppm): 2.76 (s, 3H, SCH_3); 4.18 (s, 2H, SCH_2); 6.98-7.60 (m, 5H, C_6H_5); 10.11 (s, 1H, NH). ^{13}C NMR δ (ppm): 15.96, 38.17,118.93, 122.88, 128.02, 138.50, 163.24, 164.18, 165.61. Analysis for $C_{11}H_{11}N_3OS_3$ (297.41) Calculated: C: 44.42%, H: 3.73%, N: 14.13%, S: 32.34%. Found: N: 14.14%, S: 32.32%.

This compound was also obtained via reaction of potassium salt of compound **1** with 2-chloro-N-phenylacetamide.

2.9.2 2-((5-(Ethylthio)-1,3,4-thiadiazol-2-yl)thio)-N-phenylacetamide (12b)

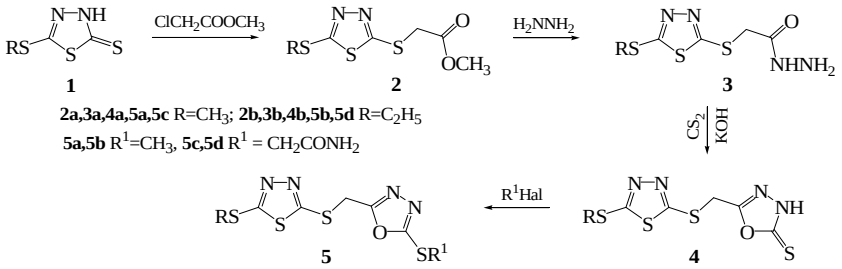
Yield: 68%, M.p.: 76-78ºC. ^{1}H NMR δ (ppm): 1.46 (t, J=7.3, 3H, SCH_2CH_3); 3.30 (q, J=7.3, 2H, SCH_2CH_3); 4.18 (s, 2H, SCH_2); 6.97-7.61 (m, 5H, C_6H_5); 10.11 (s, 1H, NH). Analysis for $C_{12}H_{13}N_3OS_3$ (311.44) Calculated: C: 46.28%, H: 4.21%, N: 13.49%, S: 30.88%. Found: C: 46.25%, H: 4.18%, N: 13.31%, S:30.86%.

3. RESULTS AND DISCUSSION

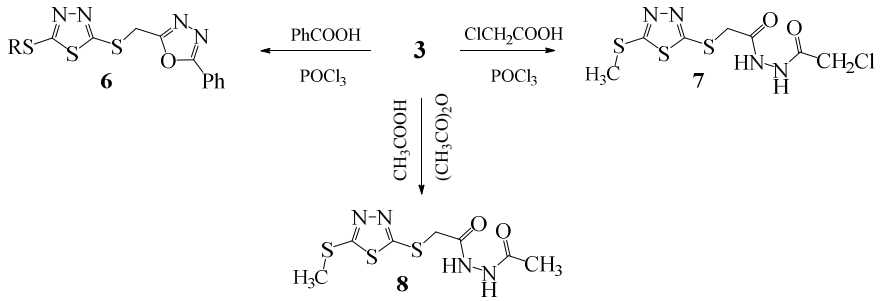
The reaction of starting 5-(alkylthio)-1,3,4-thiadiazole-2(3*H*)-thiones (**1**) with methyl chloroacetate occurs in an aqueous medium in the presence of an equimolar amount of NaOH and catalytic amounts of triethyl benzyl ammonium chloride (TEBAC). The hydrazinolysis of obtained esters (**2**) takes place exclusively in the medium of isopropyl alcohol with an equimolar amount of hydrazine hydrate and afforded hydrazide **3**. The heterocyclization of the latter with carbon disulfide in the presence of KOH takes place in absolute ethanol by refluxing the reactants in a molar ratio of 1:1:2 (hydrazide : KOH : CS_2) and leads to corresponding 5-(((5-(alkylthio)-1,3,4-thiadiazol-2-yl)thio)methyl)-1,3,4-oxadiazole-2(3H)-thiones (**4**). These compounds react with caustic bases to form the corresponding salts, which then react with various alkylating agents and afford the corresponding 2-alkylthio-oxadiazoles (**5**) (Scheme 1).

The reaction of hydrazides **3** with carboxylic acids was studied. The reactions with benzoic and chloroacetic acids occured in $POCl_3$ medium at room temperature. In the first case the heterocyclization process afforded 5- phenyl substituted 1,3,4-oxadiazoles (**6**), the reaction of the same hydrazides with chloroacetic acid led to acyclic chloroacetylhydrazides (**7**). Appropriate acetylhydrazides (**8**) were formed by treatment of compounds **3** with acetic acid or acetic anhydride (Scheme 2).

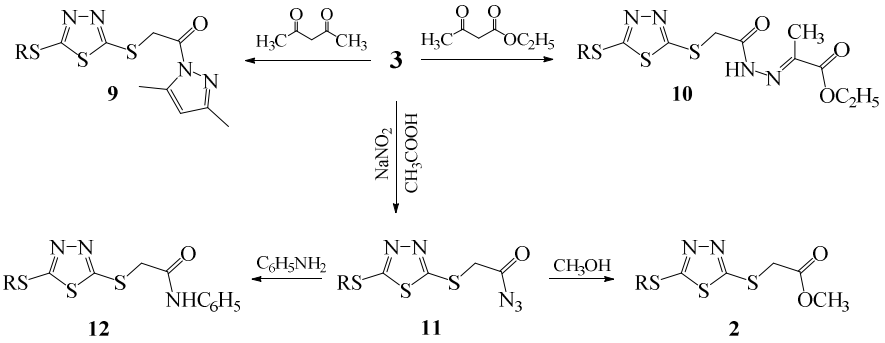
The reaction of hydrazides **3** with carbonyl compounds (acetylacetone and acetoacetic ester) were carried out. When compounds **3** reacted with acetylacetone the heterocyclization was occurred, which led to the corresponding 1-(3,5-Dimethyl-1H-pyrazol-1-yl)-2-((5-(alkylthio)-1,3,4-thiadiazol-2-yl)thio)ethan-1-ones (**9**). The reaction proceeds in dioxane with heating at 60-70ºC for 5-6 hours. It is shown that the formation of compounds **9** also took place in glacial acetic acid at room temperature for 12-14 hours. At the same time the reaction of hydrazides **3** with acetoacetic ester afforded acyclic condensation products (**10**) (Scheme 3).



Scheme 1. Synthesis of acetohydrazides 3 and thier heterocyclization



Scheme 2. Transformations of 2-((5-(alkylthio)-1,3,4-thiadiazol-2-yl)thio)acetohydrazides 3



Scheme 3. Heterocyclization and transformations of acetohydrazides 3

Hydrazides **3** reacted with $NaNO_2$ in the presence of acetic acid and formed the corresponding 2-((5-(alkylthio)-1,3,4-thiadiazol-2-yl)thio)acetyl azides (**11**). Some transformations of resulting azides (**12**), in particular, the reactions with methanol and aniline were studied. It is found that this reactions proceeds abnormally, and instead of the expected derivatives of urea and urethanes by Curtius, the starting esters (**2**) and anilides (**12**) were obtained. Compounds **12** were also synthesized by reaction of compound **1** with 2-chloro-N-phenylacetamide.

3.1 Biological Properties

At preliminary screening the synthesized compounds did not posses noticeable herbicidal or fungicidal properties, but they showed the pronounced plant growth stimulant activity. The object of study were the seeds and seedlings of common bean (*Phaseolus vulgaris* L.). The activity of obtained compounds solutions (25 and 50 mg/L) were determined in comparison with corresponding solutions of IAA (in %). The plant growth stimulant activity of synthesized derivatives was in the range of 56-90%. The most effective preparations were selected for deeper study and further field trials.

4. CONCLUSION

Simple and convenient high yield methods for the synthesis of novel 5-(alkylthio)-1,3,4-thiadiazole-2(3H)-thiones acyclic and nonfused biheterocyclic system derivatives that incorporate 1,3,4-thiadiazole with 1,3,4-oxadiazole and pyrazoles in the same molecules have been described.

The synthesized compounds have shown the pronounced plant growth stimulant properties. Seven compounds having high activity (70-90%, compared with heteroauxin) were selected for deeper study and further field trials. These results of the study indicate that the new obtained derivatives can be of interest for the search of new plants growth stimulators.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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