SYNTHESIS AND SOME TRANSFORMATIONS OF HETEROCYCLIC SUBSTITUTED DERIVATIVES OF THIOGLYCOLIC ACID

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The methods have been developed for the preparation of diheterocyclic systems of a new structure, such as pyrazolo- and 1,3,4-oxadiazolo-1,2,4-triazoles, based on S-substituted thioglycolic acid derivatives.

Keywords: 1,2,4-triazoles, oxadiazol, pyrazolo-1,2,4-triazoles.

Introduction. We have previously summarized the high biological activities of substituted triazoles and their wide spectrum of action [X]. Individual derivatives of 1,2,4-triazoles exhibit moderate and high antiviral [1], antimicrobial [2, 3], antibacterial [4, 5], anticancer [6, 7], anticonvulsant [8, 9], antifungal [10, 11] activity. Among the numerous developments of recent years, we note the synthesis of condensed systems [12, 13], bis-tetrazolo-1,2,4-triazoles [14], triazino- [15], pyrimidino- [16], pyrido- [17], triazolino- [18], C-glycopyranosyl-1,2,4-triazoles [19], etc.

Obviously, the synthesis and research of new representatives of 1,2,4-triazoles are relevant and appropriate. In order to create new heterocyclic systems and identify the useful properties of the synthesized substances, 3,4-disubstituted-1,2,4-triazole-5-thiols (1a–e) were selected as starting compounds, since the synthesis of the latter allows substituents to be introduced into the triazole molecule of various nature, which in turn will allow us to draw conclusions both about the reactivity of the obtained compounds, and about the relationship between structure and biological activity.

It was previously shown that, depending on the structure of the reagent, in the presence of bases, products of either S-substitution or Michael N-addition are formed on the basis of compounds 1. This is explained by the fact that compounds 1 in the solution are in a thione-thiol equilibrium state. It was also shown that under certain conditions, reactions proceed chemoselectively, with the formation of individual products [20].

Based on the foregoing, this paper presents the results of studies on the synthesis of S-derivatives of 5-mercapto-1,2,4-triazoles (1) and their further transformations. To achieve this goal, triazoles 1 were alkylated with chloroacetic

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acid ethyl ester. The reaction was found to proceed smoothly with the formation of 2-[(4,5-disubstituted-4H-1,2,4-triazole-3-yl)sulfanyl]ethyl acetate (2a-e) [20].

By the known method, the compounds 2 were subjected to hydrazinolysis, resulting in a high yield of aceto hydrazides of 2-[(4,5-disubstituted-4H-1,2,4-triazole-3-yl)sulfanyls] (3a-e), which are good raw materials for various heterocyclic systems. To achieve this goal, some transformations were carried out according to the scheme below.

It was shown that the interaction of 3a–d with a carbon disulfide in the presence of caustic potassium as a result of the further intramolecular cyclization promoted by the latter leads to the formation of triazolo-1,3,4-oxadiazoles 5-

Experimental Part. 1H and 13C NMR spectra were recorded on a Varian Mercury-300 MHz spectrometer in DMSO–CCl₄ mixture (1:3) (300 1H and 75 13C). TLC analysis was performed on “Silufol UV-254” plates. Melting points were determined on a “Boetius” micro-heating stage. The starting compounds 1a–d and 2a–d were synthesized according to known methods [17, 20].
**General Method for Preparation of Hydrazides 2-(f5-Substituted-4-phenyl-4H-1,2,4-triazole-3-yl)thio)acetates (3a–d).** To a mixture of 9.5 mmol of the corresponding ester 2a–d in 20 mL of ethanol was added 5.2 mL of an 85% solution of hydrazine hydrate, left for 2 h at room temperature and heated for 4 h at 75–80°C. After cooling, the mixture was diluted with water, the precipitate was filtered off, washed with water, dried and re-crystallized.

2-{(5-(4-Bromphenyl)-4-phenyl-4H-1,2,4-triazole-3-yl)thio}acetohydrazide (3a).

Yield 90%, m.p. 230–232°C (ethanol:water=1:4), Rf 0.55 (ethanol:benzene=1:5) [20].

2-{
5-(4-Tolyl)-4-phenyl-4H-1,2,4-triazole-3-yl}thio]acetohydrazide (3b).

Yield 80%, m.p. 136–137°C (ethanol:water=1:1), Rf 0.54 (ethanol:benzene=1:5). 1H NMR, δ, ppm: 2.33 s (3H, CH₃); 3.85 s (2H, SCH₂); 4.10 br.s (2H, NH₂); 7.03–7.11 m (2H, CHarom.); 7.17–7.26 m (2H, CHarom.); 7.27–7.38 m (2H, CHarom.); 7.46–7.57 m (2H, CHarom.). 13C NMR, δ, ppm: 33.6; 60.5; 117.0; 120.9; 126.9; 127.4; 128.5; 129.4; 131.9; 132.7; 148.7; 150.0; 153.8; 167.2. Found, %: C 60.20, H 5.13, N 20.68, S 9.48. C₁₇H₁₇N₅OS. Calculated, %: C 60.16, H 5.05, N 20.63, S 9.45.

2-{(4-Allyl-5-(2-methoxyphenyl)-4H-1,2,4-triazole-3-yl)thio}acetohydrazide (3c).

Yield 90%, m.p. 85°C (ethanol:water=2:3), Rf 0.56 (ethanol:benzene=1:6) [20].

2-{
5-(Furan-2-yl)-4-phenyl-4H-1,2,4-triazole-3-yl}thio]acetohydrazide (3d).

Yield 90%, m.p. 111–113°C (ethanol:water=1:1), Rf 0.50 (ethanol:benzene=1:7) [20].

2-{
5-(3-Hydroxypropyl)-4-phenyl-4H-1,2,4-triazole-3-yl}thio]acetohydrazide (3e).

Yield 70%, m.p. 149–150°C (ethanol:water=3:2), Rf 0.50 (ethanol:benzene=1:7). 1H NMR, δ, ppm: 2.58 t (2H, J=7.54 Hz, CH₂); 3.36–3.49 m (2H, CH₂); 3.93 s (2H, CH₂); 4.14 q (2H, J=7.14 Hz, CH₂); 4.18 br.s (1H, OH); 6.10 d (1H, J=3.17 Hz, NH₂); 6.29 d (1H, J=5.55 Hz, NH₂); 7.28–7.49 m (2H, CHarom.); 7.49–7.73 m (3H, CHarom.); 9.28 br.s (1H, NH). Found, %: C 50.75, H 5.65, N 22.85, S 10.53. C₁₃H₁₇N₅O₂S. Calculated, %: C 50.80, H 5.57, N 22.78, S 10.43.

**General Method for Preparation of 5-{(4,5-disubstituted-4H-1,2,4-triazole-3-yl)methyl}-1,3,4-oxadiazole-2(3H)-thiones (4a–d).** To a mixture of 9 mmol of the corresponding hydrazide 3a–d and 6.5 mL of ethanol were added 5.4 mL of carbon disulfide and, after 15 min, 0.0225 mmol of potassium. The mixture was stirred at room temperature for 15 min and 3 h at 75–80°C. After cooling, the mixture was diluted with a 15% solution of hydrogen chloride to pH 3–4, the precipitate was filtered off, washed with water, dried and re-crystallized.

5-{(5-(4-Bromphenyl)-4-phenyl-4H-1,2,4-triazole-3-yl)methyl}-1,3,4-oxadiazole-2(3H)-thione (4a).

Yield 94%, m.p. 210–211°C (ethanol:water=10:1), Rf 0.50 (ethanol:benzene=1:7). 1H NMR, δ, ppm: 4.01 s (2H, SCH₂); 7.23–7.31 m (3H, CHarom.); 7.32–7.48 m (2H, CHarom.); 7.49–7.61 m (4H, CHarom.); 13.02 br.s (1H, NH). 13C NMR, δ, ppm: 33.9; 123.3; 124.2; 124.7; 125.4; 127.1; 129.2; 129.6; 131.1; 133.4; 138.8; 151.7; 152.9; 180.4. Found, %: C 44.80, H 2.59, N 17.60, S 14.40. C₁₇H₁₂BrN₅OS₂. Calculated, %: C 44.74, H 2.63, N 17.54, S 14.35.

5-{(5-(4-Methylphenyl)-4-phenyl-4H-1,2,4-triazole-3-yl)methyl}-1,3,4-oxadiazole-2(3H)-thione (4b).

Yield 71%, m.p. 200–201°C (ethanol:water=10:1), Rf 0.58 (ethanol:benzene=1:2). 1H NMR, δ, ppm: 2.33 s (3H, CH₃); 4.46 s (2H, SCH₂); 7.00–7.14 m (2H, CHarom.); 7.18–7.27 m (2H, CHarom.); 7.28–7.37 m (2H, CHarom.); 7.45–7.57 m (3H, CHarom.); 13.62 br.s (1H, NH). 13C NMR, δ, ppm: 13.7; 33.8 (CH₂); 123.1; 125.5; 127.1 (2CH); 129.1 (2CH); 129.5 (CH, CH); 131.1 (2CH); 133.5;
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151.6; 152.8. Found, %: C 58.80, H 3.29, N 19.10, S 17.50. C_{18}H_{13}N_{5}O_{2}S_{2}. Calculated, %: C 58.85, H 3.54, N 19.07, S 17.44.

5-\{[(5-(2-Methoxyphenyl)-4-allyl-4H-1,2,4-triazole-3-yl)thio]methyl\}-1,3,4-oxadiazole-2(3H)-thione (4c). Yield 70%, m.p. 171–172°C (ethanol:water=4:1), R_{f} 0.53 (ethanol:benzene=1:4). \textsuperscript{1}H NMR, δ, ppm: 3.81–3.87 s (3H, ОСН\textsubscript{3}); 3.98 s (2H, SCH\textsubscript{2}); 4.39–4.49 m (2H, NCH\textsubscript{2}); 4.86–4.88 m (1H, =CH\textsubscript{2}); 5.10–5.12 m (1H, =CH\textsubscript{2}); 5.70 s (1H, СН=); 7.00–7.14 m (2H, CH arom.); 7.33–7.35 m (2H, CH\textsubscript{arom.}); 7.47–7.49 m (1H, CH\textsubscript{arom.}); 13.11 br.s (1H, NH). \textsuperscript{13}C NMR, δ, ppm: 12.9; 13.5; 25.8; 123.1; 124.6; 127.0 (2CH); 129.1 (2CH); 129.5(CH); 131.4; 133.5; 151.6; 152.8.

Found, %: C 48.50, H 4.79, N 22.00, S 17.30. C\textsubscript{15}H\textsubscript{15}N\textsubscript{5}O\textsubscript{2}S\textsubscript{2}. Calculated, %: C 48.52, H 4.84, N 21.56, S 17.25.

5-\{[(Furan-2-yl)-4-phenyl-4H-1,2,4-triazole-3-yl\}thio)methyl\}-1,3,4-oxadiazole-2(3H)-thione (4d). Yield 60%, m.p. 218°C (ethanol:water=5:1), R_{f} 0.42 (ethanol:benzene=2:5). \textsuperscript{1}H NMR, δ, ppm: 4.45 s (2H, SCH\textsubscript{2}); 6.22 d (1H, J=4.0Hz, CH\textsubscript{furyl}); 6.40 d (1H, J=5.5 Hz, CH\textsubscript{furyl}); 7.36–7.44 m (2H, CH arom.); 7.53 s (1H, CH\textsubscript{furyl}); 7.56–7.63 m (3H, CH arom.); 14.20 br.s (1H, NH). \textsuperscript{13}C NMR, δ, ppm: 26.1; 110.9; 110.9; 127.2; 129.4; 129.9; 132.9; 140.9; 143.8; 147.3; 159.1; 177.8.

Found, %: C 50.40, H 3.06, N 19.66, S 17.98. C\textsubscript{15}H\textsubscript{11}N\textsubscript{5}O\textsubscript{2}S\textsubscript{2}. Calculated, %: C 50.42, H 3.08, N 19.61, S 17.93.

General Method for Preparation of (3,5-dimethyl-1H-pyrazol-1-yl)-2-(4,5-disubstituted-4H-1,2,4-triazole-3-yl)thio)ethan-1-ones (5а–b). To a mixture of 9 mmol of the corresponding hydrazide 3d–e and 6.5 mL of ethanol were added 9 mmol of acetyl acetone and, after 15 min, 0.2 mL of concentrated hydrochloric acid. The mixture was stirred at room temperature for 15 min and 6 h at 80–85°C. After cooling, the mixture was diluted with water, the precipitate was filtered off, washed with water, dried and re-crystallized.

1-(3,5-Dimethyl-1H-pyrazol-1-yl)-2-\{[(furan-2-yl)-4-phenyl-4H-1,2,4-triazole-3-yl\}thio)ethan-1-one (5a). Yield 60%, m.p. 113–115°C (ethanol:water=1:1); R_{f} 0.50 (ethanol:benzene=1:6). \textsuperscript{1}H NMR, δ, ppm: 2.10 t (3H, CH\textsubscript{3}); 2.46 t (3H, CH\textsubscript{3}); 4.45 s (2H, SCH\textsubscript{2}); 6.10–6.12 m (1H, CH\textsubscript{furyl}); 6.22 d (1H, J=4.0Hz, CH\textsubscript{furyl}); 6.40 d (1H, J=5.5 Hz, CH\textsubscript{furyl}); 7.36–7.44 m (2H, CH arom.); 7.53 s (1H, CH\textsubscript{furyl}); 7.56–7.63 m (3H, CH arom.). \textsuperscript{13}C NMR, δ, ppm: 12.9; 13.5; 25.3; 29.8; 38.4; 60.4; 110.3; 129.1; 145.9; 146.9; 151.8; 157.7; 162.6. Found, %: C 60.12, H 4.42, N 18.50, S 8.50. C\textsubscript{19}H\textsubscript{17}N\textsubscript{5}O\textsubscript{2}S. Calculated, %: C 60.14, H 4.52, N 18.46, S 8.45.

1-(3,5-Dimethyl-1H-pyrazol-1-yl)-2-\{[(3-hydroxypropyl)-4-phenyl-4H-1,2,4-triazole-3-yl\}thio)ethan-1-one (5b). Yield 67%, m.p. 70–71°C (ethanol:water=1:1), R_{f} 0.40 (ethanol:benzene=1:7). \textsuperscript{1}H NMR, δ, ppm: 2.10 t (3H, CH\textsubscript{3}); 2.46 t (3H, CH\textsubscript{3}); 2.58 t (2H, J=7.5 Hz, CH\textsubscript{2}); 3.36–3.49 m (2H, CH\textsubscript{2}); 3.93 s (2H, SCH\textsubscript{2}); 4.14 qw (2H, J=7.1 Hz, CH\textsubscript{2}); 4.18 br.s (1H, OH); 6.10–6.12 m (1H, CH); 7.28–7.49 m (2H, CH arom.); 7.49–7.73 m (3H, CH arom.). \textsuperscript{13}C NMR, δ, ppm: 12.9; 13.5; 25.3; 29.8; 38.4; 60.4; 110.3; 129.1; 132.0; 142.3; 147.7; 148.2; 149.4; 151.8; 162.3. Found, %: C 37.80, H 4.28, N 8.99. C\textsubscript{19}H\textsubscript{17}N\textsubscript{5}O\textsubscript{2}S. Calculated, %: C 37.99, H 4.48, N 18.46, S 8.44.

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