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Synthesis of 2-Carbamoylthieno[3,2-*d*]thiazoles

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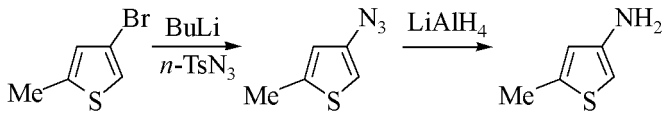
Abstract—A preparation procedure was developed for previously unknown 2-carbamoylthieno[3,2-*d*]-thiazoles consisting in cyclization effected by $K_3Fe(CN)_6$ of monothiooxamides obtained from 2-methyl-4-aminothiophene, chloroacetamides, and sulfur in the presence of triethylamine.

Heterocyclic compounds with an amide function are used in the synthesis of biologically active compounds [1, 2]. We developed formerly a simple procedure for preparation of monothiooxamides [3], and it was demonstrated that they were convenient initial compounds for the synthesis of various difficultly available carbamoyl-containing heterocycles, namely, carbamoylimidazolines [4], carbamoyl-1,2,4-oxadiazoles [5], carbamoyl-1,3,4-oxadiazoles [6], biscarbamoylfuroxanes [6], carbamoyl-1,2,4-triazoles [7], 2-carbamoylbenzothiazoles [8]. The approach we used in the latter case looked promising also for preparation of compounds with fuzed structures, in particular, of previously unknown 2-carbamoylthieno-[3,2-*d*]thiazoles. The published methods of thienothiazoles preparation [9, 10] are scanty, labor-consuming, multistage, and they do not permit the synthesis of thieno[3,2-*d*]thiazoles containing a carbamoyl group. For instance, the overall yield of 2-methylthieno[3,2-*d*]thiazole with respect to the initial thiophene did not exceed 1.5% [10]. The target of this study was a development of a convenient preparation procedure for 2-carbamoylthieno[3,2-*d*]thiazoles.

To the synthesis of 2-carbamoylthieno[3,2-*d*]-thiazoles (**VIa–c**) we applied the approach we had previously used [8] in the preparation of 2-carbamoylbenzothiazoles including the reaction of the corresponding amines with chloroacetamides and sulfur in the presence of triethylamine followed by cyclization of the arising monothiooxamides by the action of $K_3Fe(CN)_6$.

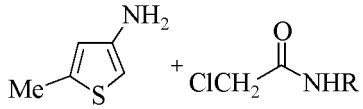
The initial compound, previously unknown 2-methyl-4-aminothiophene (**III**) was synthesized from easily accessible 2-methyl-4-bromothiophene (**I**) by a two-stage procedure we developed [11].

Bromide **I** was treated with BuLi in ether and then at –70°C a *p*-toluenesulfonyl azide was added. The thus forming 2-methyl-4-azidothiophene (**II**) was reduced with $LiAlH_4$ in THF.

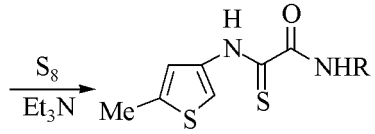


I **II** **III**

Amine **III** was mixed with sulfur and triethylamine in DMF. Then to the mixture was added chloroacetamides **IVa–d** at 20°C, and in 8 h monothiooxamides **Va–d** were isolated in 50–65% yield.



III **IVa–d**



Va–d

R = Ph (**a**), 4-MeC_6H_4 (**b**), CH_2Ph (**c**), 4-FC_6H_4 (**d**).

In the mass spectra of compounds **Va–d** are observed molecular ion peaks. In the ^1H NMR spectra alongside the proton signals of methyl group and aromatic ring appear also singlets from two protons of the thiophene ring (δ 7.35–7.40 and 8.45 ppm), and typical for monothiooxamides proton signals from amide (δ 9.25–10.52 ppm) and thioamide (δ 12.35–12.55 ppm) groups. The composition of compounds **Va–d** is also confirmed by elemental analysis.

The cyclization of monothiooxamides **Va–d** into a thiazole system occurs cleanly at 20°C as with

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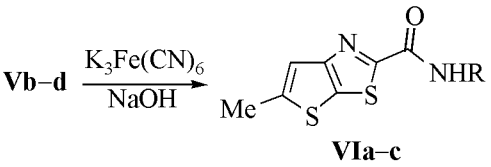
N,*S*-aroylthiooxamides [8]. The target 2-carbamoylthieno[3,2-*d*]thiazoles **VIa–c** were obtained in fair yields.



VIa–c

VI, R = 4-MeC_6H_4 (**a**), CH_2Ph (**b**), 4-FC_6H_4 (**c**).

The structure and composition of compounds **VIa–c** were proved by elemental analyses, mass spectra and ^1H NMR spectra. In the mass spectra of compounds **VIa–c** were present the molecular ion peaks. In the ^1H NMR spectra alongside the signals of the methyl group and the aromatic ring appeared the proton peaks of the thiophene ring (7.35–7.40 ppm), and also of an amino group in the region 9.47–10.75 ppm.

Thus we developed a convenient preparation procedure for 2-carbamoylthieno[3,2-*d*]thiazoles from monothiooxamides obtained by reaction of aminothiophene with chloroacetamides and sulfur in the presence of Et_3N followed by cyclization effected by $K_3Fe(CN)_6$.

EXPERIMENTAL

^1H NMR spectra were registered on spectrometer Bruker AC-300 (operating frequency 300 MHz) from solutions in DMSO-d_6. Mass spectra were measured on Kratos instrument with direct admission of the sample into the ion source, ionizing electrons energy 70 eV, controlling voltage 1.75 kV. In the study were used commercial reagents from Aldrich. Chloroacetamides **IVa–d** were obtained as in [3].

4-Azido-2-methylthiophene (II). To a solution of 5.34 g (0.03 mol) of 4-bromo-2-methylthiophene (**I**) [11] in 80 ml of anhydrous ether at –70°C under argon was added while stirring 60 ml (0.06 mol) of BuLi as 1.6 M solution in hexane. The mixture was stirred for 18 min, and then at –70°C was added dropwise 14.8 g (0.075 mol) of *p*-toluenesulfonyl azide. Therewith separated a yellow precipitate. The reaction mixture was stirred for 5 h at –70°C, then the temperature was slowly (within 1.5 h) raised to –40°C, and to reaction mixture was added a solution of 11.4 g (0.05 mol) of ethylendiaminetetraacetic acid disodium salt in 125 ml of water maintaining the temperature below 0°C. After stirring for 15 min at 0°C the reaction mixture was warmed to the room temperature and stirred for 12 h more. The red-brown ether layer was separated, the water layer was extracted with ether. The combined ether solutions were washed with water, dried with $MgSO_4$, filtered, and evaporated. The red-brown residue obtained was subjected to column chromatography on silica gel (eluent petroleum ether). We obtained 2.0 g (48%) of 4-azido-2-methylthiophene (**II**).

4-Amino-2-methylthiophene (III). In 15 ml of anhydrous THF was dissolved 0.83 g (6 mmol) of 4-azido-2-methylthiophene (**II**), and to the solution was added at stirring dropwise a suspension of 0.41 g (12 mmol) of $LiAlH_4$ in 15 ml of THF under argon at room temperature. After stirring for 2 h at 20°C to the stirred suspension was added dropwise 50 ml of water, the reaction products were extracted into ether, the extract was washed with water, dried with $MgSO_4$, and the solvent was evaporated. The residue (0.64 g of compound **III**), yellow-brown oily substance, was used in further syntheses without additional purification.

Monothiooxamides Va–d. To a preliminary prepared mixture of 0.64 g (5.7 mmol) of 4-amino-2-methylthiophene (**III**), 0.7 g of sulfur, and 1 ml of Et_3N in 5 ml of DMF was added 5.3 mmol of chloroacetamide. The mixture was stirred at 20°C for 8 hand then diluted with water. The separated precipitate was filtered off, washed with water, dried, dissolved in 10 ml of acetone, and filtered. On evaporation of acetone the residue was crystallized from 95% ethanol. The yields are calculated with respect to initial chloroacetamides.

N-Phenyl-2-[(5-methylthien-3-yl)amino]-2-thioxoacetamide (Va). Yield 51%; mp 88–90°C (EtOH). ^1H NMR spectrum, δ, ppm: 2.45 s (3H, CH_3); 7.20 m (1H arom); 7.40 m (1H of thiophene, 2H arom); 7.80 d (2H arom, *J* 7.27); 8.45 s (1H of thiophene); 10.45 s (1H, NH); 12.55 s (1H, NH). Mass spectrum, *m/z*: 276 $[M]^+$. Found, %: C 56.52; H 4.35; N 10.14; S 23.18. $C_{13}H_{12}N_2OS_2$. Calculated, %: C 56.49; H 4.30; N 10.17; S 23.23.

N-(4-Methylphenyl)-2-[(5-methylthien-3-yl)-2-amino]-2-thioxoacetamide (Vb). Yield 60%; mp 154–156°C (EtOH). ^1H NMR spectrum, δ, ppm: 2.30 s (3H, CH_3); 2.45 s (3H, CH_3); 7.20 d (2H arom, *J* 8.13 Hz); 7.35 s (1H of thiophene); 7.70 d (2H arom, *J* 8.32 Hz); 8.45 s (1H of thiophene); 10.35 s (1H, NH); 12.55 s (1H, NH). Mass spectrum, *m/z*: 290 $[M]^+$. Found, %: C 57.93; H 4.83; N 9.65; S 22.07. $C_{14}H_{14}N_2OS_2$. Calculated, %: C 57.94; H 4.74; N 9.72; S 22.14.

***N*-Benzyl-2-[(5-methylthien-3-yl)amino]-2-thioxoacetamide (Vc)**. Yield 65%; mp 120–122°C (EtOH). ^{1}H NMR spectrum, δ, ppm: 2.45 s (3H, CH_3); 4.45 d (2H, CH_2, *J* 6.28 Hz); 7.35 m (1H of thiophene; 5H arom); 8.45 s (1H of thiophene); 9.21 s (1H, NH); 12.35 s (1H, NH). Mass spectrum, *m/z*: 290 $[M]^+$. Found, %: C 57.93; H 4.83; N 9.65; S 22.07. $C_{14}H_{14}N_2OS_2$. Calculated %: C 57.94; H 4.81; N 9.70; S 22.03.

***N*-(4-Fluorophenyl-2-[(5-methylthien-3-yl)-amino]-2-thioxoacetamide (Vd)**. Yield 50%; mp 128–130°C (EtOH). ^{1}H NMR spectrum, δ, ppm: 2.45 s (3 H, CH_3); 7.20 m (1 H arom); 7.35 s (1H of thiophene); 7.85 m (2H arom); 8.45 s (1H of thiophene); 10.52 s (1H, NH); 12.55 s (1H, NH). Mass spectrum, *m/z*: 294 $[M]^+$. Found, %: C 53.06; H 3.74; N 9.52; S 21.77. $C_{13}H_{11}FN_2OS_2$. Calculated, %: C 53.07; H 3.85; N 9.41; S 21.60.

2-Carbamoylthieno[3,2-*d*]thiazoles VIa–c. Monothiooxoamides **Va–d** (0.2 mmol) were dissolved in 10% solution of NaOH (8.4 ml), the solution was filtered, and at stirring thereto was added dropwise 0.44 mol of $K_3Fe(CN)_6$ in 4.4 ml of water. The separated precipitate of thienothiazoles **VIa–c** was filtered off, washed with water, dried, and recrystallized from 95% EtOH. The yields are given with respect to the initial monothiooxamides.

***N*-(4-Methylphenyl)-5-methylthieno[3,2-*d*][1,3]-thiazole-2-carboxamide (VIa)**. Yield 44%; mp 183–184°C (EtOH). ^{1}H NMR spectrum, δ, ppm: 2.30 s (3 H, CH_3); 2.65 s (3 H, CH_3); 7.18 d (2H arom, *J* 8.17 Hz); 7.40 s (1H of thiophene); 7.78 d (2H arom, *J* 8.14 Hz); 10.75 s (1H, NH). Mass spectrum, *m/z*: 288 $[M]^+$. Found, %: C 58.33; H 4.17; N 9.72; S 22.22. $C_{14}H_{12}N_2OS_2$. Calculated, %: C 58.44; H 4.18; N 9.60; S 22.20.

***N*-Benzyl-5-methylthieno[3,2-*d*][1,3]thiazole-2-carboxamide (VIb)**. Yield 51%; mp 149–151°C (EtOH). ^{1}H NMR spectrum, δ, ppm: 2.50 s (3 H, CH_3); 4.50 d (2H, CH_2, *J* 6.29 Hz); 7.35 m (1H of thiophene; 5H arom); 9.47 s (1H, NH). Mass spectrum, *m/z*: 288 $[M]^+$. Found %: C 58.33; H 4.17; N 9.72; S 22.22. $C_{14}H_{12}N_2OS_2$. Calculated %: C 58.40; H 4.20; N 9.65; S 22.18.

***N*-(4-Fluorobenzyl)-5-methylthieno[3,2-*d*][1,3]-thiazole-2-carboxamide (VIc)**. Yield 50%; mp 185–187°C (EtOH). ^{1}H NMR spectrum, δ, ppm: 2.45 s (3H, CH_3); 7.20 m (1H arom); 7.38 s (1H of thiophene); 7.90 s (2H arom); 11.00 s (1H, NH). Mass spectrum, *m/z*: 292 $[M]^+$. Found, %: C 53.42; H 3.08; N 9.59; S 21.92. $C_{13}H_9FN_2OS_2$. Calculated, %: C 53.50; H 3.10; N 9.50; S 21.84.

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