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SHORT COMMUNICATIONS

Synthesis of Thieno[2,3-*d*]thiazole-2-carboxamides

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Heterocyclic compounds containing an amide group are used in the synthesis of biologically active substances [1, 2]. We previously developed a simple procedure for the preparation of monothiooxamides [3] and showed that they are convenient starting compounds for the synthesis of various difficultly accessible heterocyclic carboxamides, e.g., dihydroimidazolecarboxamides [4], 1,2,4-oxadiazolecarboxamides [5], 1,3,4-oxadiazolecarboxamides [6], furoxandicarboxamides [6], and 1,2,4-triazolecarboxamides [7]. We also showed that oxidation of compounds in which monothiooxamide fragments are linked to a benzene ring or heteroring results in formation of fused heterocycles in good yields. Benzothiazolecarboxamides were synthesized just in such a way [8]. Using 4-amino-2-methylthiophene as initial compound, we obtained previously unknown thieno[3,2-*d*]thiazole-2-carboxamides [9] (Scheme 1).

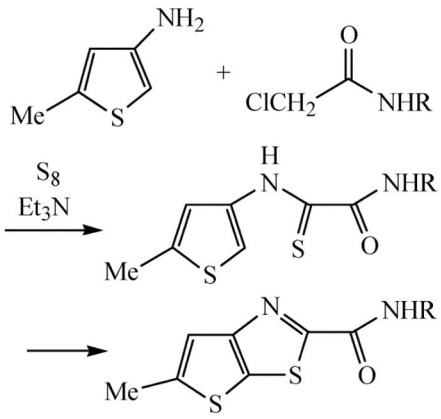
It should be emphasized that known methods for the synthesis of thienothiazoles [10, 11] are very laborious; they include many steps and cannot be applied to the preparation of thieno[3,2-*d*]thiazoles having a carb-amoyl group. For example, the overall yield of 2-methylthieno[3,2-*d*]thiazole did not exceed 1.5%, calculated on the initial thiophene [10].

In the present communication we report on a new convenient synthesis of thieno[2,3-*d*]thiazole-2-carboxamides, which is based on the reaction of the corresponding amine with chloroacetamides and sulfur in the presence of triethylamine, followed by cyclization of intermediate monothiooxamides by the action of $K_3Fe(CN)_6$.

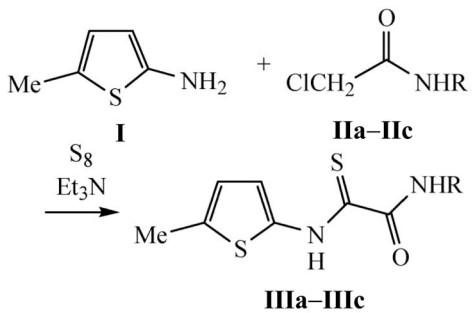
The starting compound, 5-amino-2-methylthiophene, was synthesized from accessible 5-methylthiophene-2-carboxylic acid by the procedure described in [12]. The amine was mixed with sulfur and triethylamine in DMF, chloroacetamide **IIa**–**IIc** was then added at 20°C, and (after 8 h) monothiooxamides **IIIa**–**IIIc** were isolated in 51–60% yield (Scheme 2).

The mass spectra of **IIIa**–**IIIc** contained peaks from the molecular ions. In the ^{1}H NMR spectra of these compounds we observed signals from protons of the 5-methyl group, aromatic protons, protons in the thiophene ring (as two singlets at δ 6.70–6.72 and 7.08–7.12 ppm), and also protons of the amide and thioamide groups at

Scheme 1.



Scheme 2.



II, **III**, R = H (**a**), 4-ClC_6H_4 (**b**), 4-FC_6H_4 (**c**).

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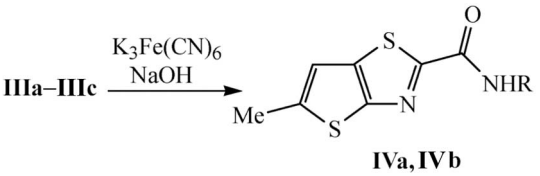
Scheme 3.



δ 10.10–10.15 and 11.65–11.78 ppm, which are typical of monothiooxamides. The elemental analyses of compounds **IIIa**–**IIIc** were consistent with the assumed structure.

The cyclization of monothiooxamides **IIIb** and **IIIc** to thienothiazoles, respectively, **IVa** and **IVb**, occurred at 0°C in a 2% solution of sodium hydroxide (Scheme 3). Products **IVa** and **IVb** were isolated in satisfactory yields.

The structure of N-substituted thieno[2,3-*d*]thiazoles **IVa** and **IVb** was confirmed by the data of elemental analysis, ^{1}H NMR spectroscopy, and mass spectrometry. Compounds **IVa** and **IVb** showed the molecular ion peaks in the mass spectra. In the ^{1}H NMR spectra of **IVa** and **IVb**, signal from the thiophene ring proton (6-H) appeared at δ 6.50 ppm, and the amide proton signal was observed at δ 8.90–9.00 ppm; also, signals from protons of the methyl group and aromatic ring were present.

Monothiooxamides IIIa–IIIc (*general procedure***).** Appropriate chloroacetamide, 5.3 mmol, was added to a mixture of 0.64 g (5.7 mmol) of 2-amino-5-methylthiophene (**I**), 0.7 g of elemental sulfur, and 1 ml of triethylamine in 5 ml of DMF [3]. The mixture was stirred for 8 h at 20°C and diluted with water, and the precipitate was filtered off, washed with water, dried, and dissolved in 10 ml of acetone. The undissolved material was filtered off, the filtrate was evaporated, and the residue was recrystallized from 95% ethanol. The yields were calculated on the initial chloroacetamide.

2-(5-Methyl-2-thienylamino)-2-thioxoacetamide (IIIa). Yield 55%, mp 155–157°C. Mass spectrum: *m*/*z* 200 [*M*]$^+$. ^{1}H NMR spectrum, δ, ppm: 2.50 s (3H, CH_3), 5.78 s (1H, NH_2), 6.70 d (1H, thiophene, J = 3.85 Hz), 7.08 d (1H, thiophene, J = 3.74 Hz), 8.00 s (1H, NH_2), 11.65 s (1H, NH). Found, %: C 42.03; H 3.95; N 14.05; S 31.97. $C_7H_8N_2OS_2$. Calculated, %: C 42.00; H 4.00; N 14.00; S 32.00.

***N*-(4-Chlorophenyl)-2-(5-methyl-2-thienylamino)-2-thioxoacetamide (IIIb).** Yield 60%, mp 184–186°C. Mass spectrum: *m*/*z* 310 [*M*]$^+$. ^{1}H NMR spectrum, δ, ppm: 2.49 s (3H, CH_3), 6.72 s (1H, thiophene), 7.12 s (1H, thiophene), 7.40 d (2H, H_{arom}, J = 7.97 Hz), 7.73 d (2H, H_{arom}, J = 6.10 Hz), 10.15 s (1H, NH), 11.75 s (1H, NH). Found, %: C 50.26; H 3.50; N 9.04; S 20.62. $C_{13}H_{11}ClN_2OS_2$. Calculated, %: C 50.24; H 3.54; N 9.02; S 20.61.

***N*-(4-Fluorophenyl)-2-(5-methyl-2-thienylamino)-2-thioxoacetamide (IIIc).** Yield 51%, mp 175–177°C. Mass spectrum: *m*/*z* 294 [*M*]$^+$. ^{1}H NMR spectrum, δ, ppm: 2.50 s (3H, CH_3), 6.70 s (1H, thiophene), 7.10 m (3H, $2H_{arom}$ + thiophene), 7.70 m (2H, H_{arom}), 10.10 s (1H, NH), 11.78 s (1H, NH). Found, %: C 53.07; H 3.85; N 9.41; S 21.60. $C_{13}H_{11}FN_2OS_2$. Calculated, %: C 53.06; H 3.74; N 9.52; S 21.77.

Thieno[2,3-*d*]thiazole-2-carboxamides IVa and IVb (*general procedure***).** Monothiooxamide **IIIb** or **IIIc**, 0.2 mol, was dissolved in a 2% solution of sodium hydroxide (1.68 mol), the solution was filtered and was added dropwise under stirring at 0°C to a solution of 0.44 mol of $K_3Fe(CN)_6$ in 4.4 ml of water. The mixture was stirred for 2 h at 0°C and allowed to warm up to room temperature. The precipitate was filtered off, washed with water, dried, and recrystallized from 95% ethanol.

***N*-(4-Chlorophenyl)-5-methylthieno[2,3-*d*][1,3]-thiazole-2-carboxamide (IVa).** Yield 41%, mp 156–158°C. Mass spectrum: *m*/*z* 308 [*M*]$^+$. ^{1}H NMR spectrum, δ, ppm: 2.50 s (3H, CH_3), 6.50 s (1H, 6-H), 7.37 m (2H, H_{arom}), 7.68 m (2H, H_{arom}), 8.90 s (1H, NH). Found, %: C 50.50; H 3.00; N 9.06; S 20.78. $C_{13}H_9ClN_2OS_2$. Calculated, %: C 50.57; H 2.92; N 9.08; S 20.75.

***N*-(4-Fluorophenyl)-5-methylthieno[2,3-*d*]-[1,3]thiazole-2-carboxamide (IVb).** Yield 40%, mp 190–192°C. Mass spectrum: *m*/*z* 292 [*M*]$^+$. ^{1}H NMR spectrum, δ, ppm: 2.50 s (3H, CH_3), 6.50 s (1H, 6-H), 7.10 m (2H, H_{arom}), 7.70 m (2H, H_{arom}), 9.00 s (1H, NH). Found, %: C 53.50; H 3.10; N 9.50; S 21.84. $C_{13}H_9FN_2OS_2$. Calculated, %: C 53.42; H 3.08; N 9.59; S 21.92.

The ^{1}H NMR spectra were recorded on a Bruker AC-300 spectrometer at 300 MHz using $CDCl_3$ as solvent. The mass spectra (70 eV) were obtained on a Kratos instrument with direct sample admission into the ion source (accelerating voltage 1.75 kV). Commercial reagents (from Acros) were used.

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