Synthesis of monothiooxamides of the thiazole series

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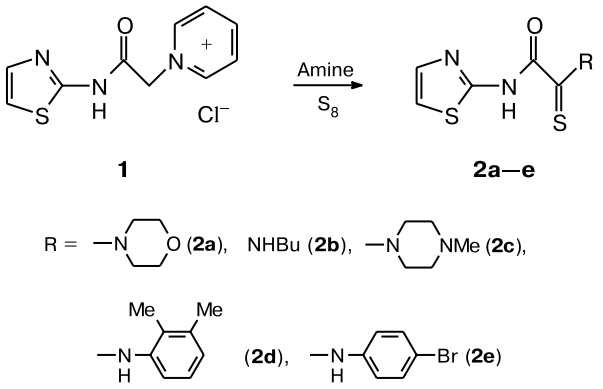
A convenient method for the synthesis of previously inaccessible monothiooxamides of the thiazole series was developed. The method is based on the reaction of pyridinium salts obtained from 2-(chloroacetylamino)thiazole and pyridine with a solution of elemental sulfur and amines prepared beforehand.

Key words: 2-aminothiazole, chloroacetamides, pyridine, sulfur, amines, monothiooxamides.

Previously,[1] we showed that chloroacetamides react with amines in the presence of sulfur to give monothiooxamides. This general and convenient method is suitable for preparing diverse monothiooxamides in good yields.[2,3] It is also known that 2-aminothiazole derivatives are biologically active.[4,5] However, monothiooxamides based on respective chloroacetamide, 2-(chloroacetylamino)thiazole, cannot be prepared by the reported procedure.[2] In this work, we found (Scheme 1) that monothiooxamides **2a—e** are formed in good yields upon the reaction of the pyridinium salt **1** with a preliminarily prepared solution of the required amine and sulfur in excess amine or in DMF at room temperature.

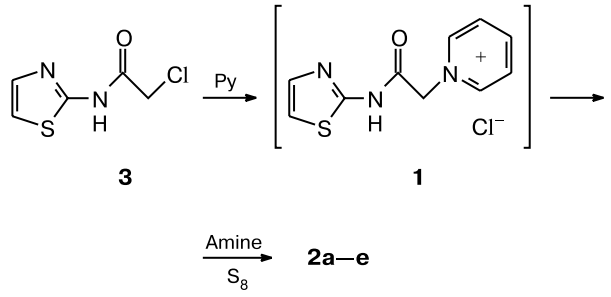
Scheme 1



When less basic aromatic amines are used, triethylamine must be added to the reaction mixture. In this case, the resulting monothiooxamides **2d,e** are formed in good yields.

It was expedient to attempt to prepare monothiooxamides **2a—e** in one step by the reaction of chloroacetamide **3** with a solution of elemental sulfur in pyridine used as the solvent. In this reaction, the pyridinium salt **1** is formed *in situ*. Indeed, if chloroacetamide **3** is added at room temperature to a preliminarily prepared solution of sulfur and amine in pyridine, the corresponding monothiooxamides are formed in good yields **2a—e** (Scheme 2).

Scheme 2



Thus, we developed a method for the synthesis of previously inaccessible monothiooxamides of the 2-aminothiazole series, which are of interest as potential biologically active compounds.

Experimental

^{1}H NMR spectra were recorded on a Bruker AM-300 instrument in DMSO-d_6. Melting points were measured on a Boetius hot stage and were not corrected. Mass spectra were run on a Kratos instrument (70 eV) with direct sample injection into the ion source. Chloroacetamide **3** was synthesized by a known method.[2] The pyridinium salt **1** was prepared by mixing chloroacetamide **3** with pyridine. The salt **1**, which precipitated after some period, was filtered off, dried, and used without further purification.

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Synthesis of monothiooxamides 2a—c (general procedure A). The chloroacetamide pyridinium salt **1** (5.0 mmol) was added to a solution prepared preliminarily from amine (5.5 mmol) and sulfur (0.7 g) in 10 mL of DMF. The reaction mixture was stirred for 8 h at ≈20 °C, cooled, and diluted with water. The precipitate was filtered off, washed with water, and dried. The product was dissolved in acetone (10 mL) and the solution was filtered. The residue after removal of acetone was crystallized from 95% ethanol.

***N*-(Thiazol-2-yl)-2-morpholino-2-thioxoacetamide (2a).** Yield 58%, m.p. 270—271 °C. Found (%): C, 41.96; H, 4.35; N, 16.28. $C_9H_{11}N_3O_2S_2$. Calculated (%): C, 42.02; H, 4.28; N, 16.34. ^{1}H NMR, δ: 3.65, 3.70, 3.80, 4.15 (all m, 2 H each, morpholine H); 7.45 (d, 1 H, thiazole H, J = 3.62 Hz); 7.65 (d, 1 H, thiazole H, J = 3.49 Hz); 12.70 (s, 1 H, NH). MS, m/z: 257 $[M]^+$.

***N*(S)-Butyl-*N*(O)-(thiazol-2-yl)thioxacetamide (2b).** Yield 48%, m.p. 121—122 °C. Found (%): C, 44.96; H, 5.39; N, 17.38. $C_9H_{13}N_3OS_2$. Calculated (%): C, 44.44; H, 5.35; N, 17.28. ^{1}H NMR, δ: 0.90 (t, 3 H, CH_3, J = 7.76 Hz); 1.35, 1.65, 3.65 (all m, 2 H each, CH_2); 7.35 (d, 1 H, thiazole H, J = 3.58 Hz); 7.60 (d, 1 H, thiazole H, J = 3.55 thiazole); 11.05, 11.90 (both s, 1 H each, NH). MS, m/z: 243 $[M]^+$.

***N*-(Thiazol-2-yl)-2-(4-methylpiperazin-1-yl)-2-thiooxacetamide (2c).** Yield 62%, m.p. 197—200 °C. Found (%): C, 44.62; H, 5.13; N, 20.63. $C_{10}H_{14}N_4OS_2$. Calculated (%): C, 44.42; H, 5.22; N, 20.70. ^{1}H NMR, δ: 2.28 (s, 3 H, CH_3); 2.55 (m, 4 H, piperazine H); 3.60, 4.12 (both m, 2 H each, piperazine H); 7.30 (d, 1 H, thiazole H, J = 3.37 Hz); 7.55 (d, 1 H, thiazole H, J = 3.41 Hz); 12.55 (s, 1 H, NH). MS, m/z: 270 $[M]^+$.

Synthesis of monothiooxamides (general procedure B). The chloroacetamide pyridinium salt **1** (5.0 mmol) was added to a preliminarily prepared mixture of aromatic amine (5.5 mmol), sulfur (0.7 g), and triethylamine (1 mL) in 5 mL of DMF. The mixture was subsequently worked-up as described in procedure **A**.

***N*(S)-(2,3-Dimethylphenyl)-*N*(O)-(thiazol-2-yl)thiooxamide (2d).** Yield 64%, m.p. 198—201 °C. Found (%): C, 53.62; H, 4.87; N, 14.63. $C_{13}H_{13}N_3OS_2$. Calculated (%): C, 53.61; H, 4.47; N, 14.43. ^{1}H NMR, δ: 2.10, 2.33 (both s, 3 H each, CH_3); 7.15 (m, 3 H, H arom.); 7.40 (d, 1 H, thiazole H, J = 3.55 Hz); 7.60 (d, 1 H, thiazole H, J = 3.54 Hz); 12.33, 12.36 (both s, 1 H each, NH). MS, m/z: 291 $[M]^+$.

***N*(S)-(4-Bromophenyl)-*N*(O)-(thiazol-2-yl)thiooxamide (2e).** Yield 56%, m.p. 181—183 °C. Found (%): C, 38.45; H, 2.48; Br, 23.57; N, 12.04. $C_{11}H_8BrN_3OS_2$. Calculated (%): C, 38.61; H, 2.36; Br, 23.35; N, 12.28. ^{1}H NMR, δ: 7.40 (d, 1 H, thiazole H, J = 3.61 Hz); 7.60 (d, 1 H, thiazole H, J = 3.53 Hz); 7.65 (d, 2 H, arom H, J = 8.74 Hz); 7.95 (d, 2 H, H arom., J = 8.72 Hz); 12.30, 12.55 (both s, 1 H each, NH). MS, m/z: 341, 343 $[M]^+$.

Synthesis of monothiooxamides (general procedure C). Chloroacetamide **3** (5.0 mmol) was added to a preliminarily prepared mixture of amine (5.5 mmol) and sulfur (0.7 g) in 10 mL of pyridine (when using aromatic amines, 1 mL of triethylamine was added). Then the mixture was worked-up according to procedure **A** to give thiooxamides **2a** (yield 52%), **2b** (yield 43%), **2c** (yield 57%), **2d** (yield 60%), and **2e** (yield 49%), which were identical (judging by melting points) to those described above.

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