New approach to the synthesis of 2-carbamoylbenzothiazoles

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The reactions of substituted anilines with chloroacetamide and sulfur in the presence of triethylamine afforded monothiooxamides. When treated with $K_3Fe(CN)_6$, the latter underwent cyclization to form 2-carbamoylbenzothiazoles. The reactions were accompanied by the formation of the corresponding thiooxanilic acids, which also underwent cyclization to form benzothiazole-2-carboxylic acids.

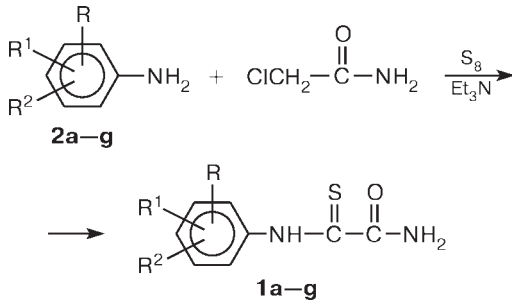
Key words: monothiooxamides, 2-carbamoylbenzothiazoles, thiooxanilic acids, benzothiazole-2-carboxylic acids.

2-Carbamoylbenzothiazoles are used in the synthesis of polycyclic systems. For example, these compounds were used for the preparation of a series of 2-(thiazolyl)benzothiazoles possessing anti-inflammatory activity[1,2] as well as for the synthesis of the natural compound, *viz.*, D(−)-2-(6-hydroxybenzothiazol-2-yl)-4,5-dihydrothiazole-4-carboxylic acid (luciferin),[3,4] and its analogs.[5] It should be noted that procedures for the preparation of 2-carbamoylbenzothiazoles described in the literature are multi-step and laborious and, moreover, afford products in low total yields. The most rational scheme was employed in the studies.[4,5] The first step of the latter process involves the preparation of monothiooxamides from readily accessible anilines followed by cyclization under the action of $K_3Fe(CN)_6$. However, when we started our studies, convenient procedures for the preparation of monothiooxamides were lacking. *N*^{S}-Arylthiooxamides were synthesized[4,5] by the reactions of carbamoylthiocarbonylthioacetic acid with aromatic amines in ethanol performed during three days, and the yields were at most 50%. Carbamoylthiocarbonylthioacetic acid, in turn, was prepared by the reaction of H_2S with trichloroacetamide in ethanol followed by treatment with an aqueous solution of monochloroacetic acid and potassium carbonate. In the present study, we developed a procedure for the synthesis of 2-carbamoylbenzothiazoles.

Results and Discussion

Monothiooxamides **1a—g** were synthesized according to the procedure proposed by us previously,[6] which was based on the reactions of the corresponding anilines with chloroacetamide in the presence of sulfur and triethylamine. For the reactions to proceed, it was necessary to prepare a solution of aniline **2a—g**, sulfur, and triethylamine in DMF followed by the addition of chloroacetamide. When the reagents were mixed in this order, monothiooxamides were obtained in 60—80% yields (Scheme 1).

Scheme 1



	a	b	c	d	e	f	g
R	4-MeO	2-MeO	4-Br	4-Cl	2-MeO	3-MeO	3-Me
R^1	H	H	H	H	5-MeO	4-MeO	5-Me
R^2	H	H	H	H	H	5-MeO	H

The study of cyclization of monothiooxamides **1a—g** under the action of $K_3Fe(CN)_6$ in alkaline solutions demonstrated that the syntheses of 2-carbamoylbenzothiazoles **3a—g** were always accompanied by the formation of the corresponding thiooxanilic acids **4a—g** as by-products (Scheme 2).

The yields and the ratio of the reaction products depend on the nature of the substituents in the phenyl ring. Electron-donating substituents facilitate cyclization, whereas electron-withdrawing substituents inhibit this process, which is indicative of its electrophilic character.

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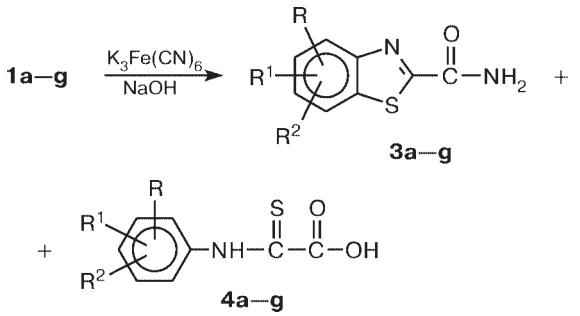
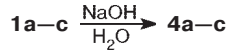
Scheme 2



	R	R^1	R^2		R	R^1	R^2
3a	6-MeO	H	H	**4a**	4-MeO	H	H
3b	4-MeO	H	H	**4b**	2-MeO	H	H
3c	6-Br	H	H	**4c**	4-Br	H	H
3d	6-Cl	H	H	**4d**	4-Cl	H	H
3e	4-MeO	7-MeO	H	**4e**	2-MeO	5-MeO	H
3f	5-MeO	6-MeO	7-MeO	**4f**	3-MeO	4-MeO	5-MeO
3g	5-Me	7-Me	H	**4g**	3-Me	5-Me	H

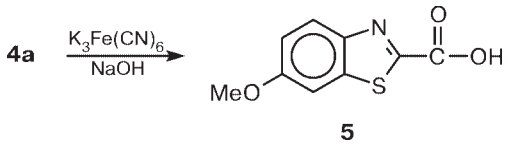
Thus, monothiooxamides **1a,b,e,g** containing the methyl and methoxy groups produced 2-carbamoylbenzothiazoles **3a,b,e,g** in 76—92% yields, whereas chloro and bromo derivatives **1c,d** gave benzothiazoles **3c,d** in low yields (3—10%). The reverse situation was observed in the case of thiooxanilic acids, *viz.*, compounds **1c,d** containing electron-withdrawing substituents were transformed into acids **4c,d** in 60—70% yields, whereas the yields of thiooxanilic acids **4a,b,e,g** bearing electron-donating substituents fell to 2—10%.

It should be noted that saponification of thiooxamides **1** proceeded readily even at ~20 °C to form thiooxanilic acids **4** in 70—80% yields.



However, the above-mentioned fact has only a slight effect on the yields of 2-carbamoylbenzothiazoles because cyclization in the course of oxidation of monothiooxamides with $K_3Fe(CN)_6$ proceeded rather rapidly (15—30 min).

Thiooxanilic acids **4** can also undergo cyclization to benzothiazole-2-carboxylic acids **5** under the action of $K_3Fe(CN)_6$.



This makes it possible to prepare the target products containing the benzothiazole system in the cases where 2-carbamoylbenzothiazoles are formed in low yields.

It should be noted that cyclization of monothiooxamides to give the benzothiazole system was completed in 15—30 min, whereas the duration of the reaction in the case of thiooxanilic acids increased to 48 h.

To summarize, we developed a new approach to the synthesis of 2-carbamoylbenzothiazoles based on cyclization of monothiooxamides, which are prepared by the

Table 1. Yields, melting points, and results of elemental analysis of the compounds

Compound	Yield* (%)	M.p./°C (lit. data)	Found / Calculated (%)				Molecular formula
			C	H	N	S	
1a	80	183—185 (182—185)[4]	—	—	—	—	—
1b	72	129—131	51.62 51.41	4.90 4.79	12.94 13.32	15.07 15.25	$C_9H_{10}N_2O_2S$
1c	65	186—188 (187)[7]	—	—	—	—	—
1d	72	185—186 (184)[7]	—	—	—	—	—
1e	76	118—119	50.17 49.99	5.09 5.03	11.34 11.66	—	$C_{10}H_{12}N_2O_3S$
1f	68	146—147	49.00 48.88	5.26 5.26	10.24 10.36	11.70 11.86	$C_{11}H_{14}N_2O_4S$
1g	76	128—131	57.80 57.67	5.54 5.81	13.62 13.45	15.24 15.39	$C_{10}H_{12}N_2OS$
3a	80	257—258 (258—260)[3]	—	—	—	—	—
3b	76	213—214 (214—215)[5]	—	—	—	—	—

(*to be continued*)

Table 1 (*continued*)

Compound	Yield* (%)	M.p./°C (lit. data)	Found / Calculated (%)				Molecular formula
			C	H	N	S	
3c	10	280—287	36.92 37.37	1.79 1.96	10.68 10.90	12.25 12.47	$C_8H_5BrN_2OS$
3d	3	283—285 (284)[1]	—	—	—	—	—
3e	70	245—247	50.49 50.41	4.23 4.23	11.72 11.76	13.34 13.46	$C_{10}H_{10}N_2O_3S$
3f	16	150—151.5	49.36 49.25	4.48 4.51	10.68 10.44	12.06 11.95	$C_{11}H_{12}N_2O_4S$
3g	92	215—217	58.20 58.23	4.90 4.89	13.57 13.58	15.28 15.54	$C_{10}H_{10}N_2OS$
4a	8 (71)	135—137 (134)[7]	—	—	—	—	—
4b	8 (70)	135—137 (136.5)[7]	—	—	—	—	—
4c	71 (78)	167—169 (171)[8]	—	—	—	—	—
4d	60	133—134 (136)[7]	—	—	—	—	—
4e	8	111—112	49.43 49.78	4.36 4.60	5.56 5.81	12.98 13.29	$C_{10}H_{11}NO_4S$
4f	60	148—149	48.56 48.70	4.62 4.83	4.87 5.16	11.62 11.82	$C_{11}H_{13}NO_5S$
4g	2	116—118	57.63 57.40	5.48 5.30	6.47 6.69	14.97 15.32	$C_{10}H_{11}NO_2S$

* The yields of thioacids prepared by hydrolysis of monothiooxamides are given in parentheses.

reactions of substituted anilines with chloroacetamide and sulfur in the presence of triethylamine, under the action of $K_3Fe(CN)_6$.

Experimental

The ^{1}H NMR spectra were recorded on Bruker AC-200 (200 MHz) and Bruker WM-250 (250 MHz) instruments in DMSO-d_6. The mass spectra were measured on a Varian MAT CH-6 instrument with direct introduction of the samples into the ion source; the energy of ionizing electrons was 70 eV; the controlling voltage was 1.75 kV. The melting points were measured on a Boetius stage and were not corrected. The yields, the melting points, and the results of elemental analysis of the compounds are given in Table 1. The data from ^{1}H NMR spectroscopy and mass spectrometry are listed in Table 2. The commercial reagents were purchased from Aldrich.

Synthesis of *N*^{S}-arylthiooxamides 1a—g (general procedure). Chloroacetamide (0.5 g, 5.3 mmol) was added to a mixture of substituted aniline **2a—g** (5.7 mmol), sulfur (0.7 g), and Et_3N (1 mL) in DMF (5 mL). The reaction mixture was stirred at ~20 °C for 8 h and diluted with water. The precipitate that formed was filtered off, washed with water, and dried. The resulting compound was dissolved in acetone (10 mL) and filtered. The acetone was removed and the residue was crystallized from 95% EtOH.

Synthesis of 2-carbamoylbenzothiazoles 3a—g and thiooxanilic acids 4a—g (general procedure). Monothiooxamide **1a—g** (0.01 mol) was dissolved in a 10% NaOH solution (0.42 mol). The resulting solution was filtered and added dropwise with stirring to a solution of $K_3Fe(CN)_6$ (12.5 g, 0.038 mol) in water (38 mL). The precipitate of amide **3a—g** that formed was filtered off, washed with water, dried, and recrystallized. The filtrate was acidified with HCl. The precipitate of thioacid **4a—g** that formed was filtered off, washed with water, dried, and recrystallized from 95% EtOH.

Synthesis of thiooxanilic acids 4a—c from monothiooxamides (general procedure). Monothiooxamide **1a—c** (0.01 mol) was dissolved in a 10% aqueous solution of NaOH (0.42 mol). The resulting solution was kept at 20 °C for 48 h and then acidified with HCl. The precipitate that formed was filtered off. The resulting acid was dissolved in a 10% aqueous solution of $NaHCO_3$ and acidified with HCl. The precipitate of the corresponding acid that formed was washed with water and recrystallized from 95% EtOH.

6-Methoxybenzothiazole-2-carboxylic acid (5). Thiooxanilic acid **4a** (0.01 mol) was dissolved in a 10% aqueous solution of NaOH and then added with stirring to a solution of $K_3Fe(CN)_6$ (0.038 mol) in water (38 mL) at ~20 °C. The reaction mixture was kept at ~20 °C for 48 h and then acidified with HCl. The

Table 2. ^{1}H NMR spectra and mass spectra of the compounds

Compound	Mass spectrum $[M]^+/m/z$	^{1}H NMR, δ (*J*/Hz)		
		NH (s, 1 H)	NH_2	Other signals
1b	210	11.83	8.21 (br.s, 2 H)	3.90 (s, 3 H, OMe); 7.05 (t, 1 H, *J* = 7.75); 7.20 (d, 1 H, *J* = 8.10); 7.32 (t, 1 H, *J* = 7.75); 8.70 (d, 1 H, *J* = 7.90)
1e	—	11.84	8.25 (s, 1 H); 8.30 (s, 1 H)	3.71 (s, 3 H, OMe); 3.85 (s, 3 H, OMe); 6.89 (d, 1 H, *J* = 8.90); 7.10 (s, 1 H); 8.51 (d, 1 H, *J* = 8.90)
1f	270	11.84	8.05 (s, 1 H); 8.15 (s, 1 H)	3.70 (s, 3 H, OMe); 3.78 (s, 6 H, 2 OMe); 7.60 (s, 2 H)
1g	208	11.87	7.95 (s, 1 H); 8.07 (s, 1 H)	2.30 (s, 6 H, 2 Me); 7.20 (s, 1 H); 7.57 (s, 2 H)
3c	—		8.00 (s, 1 H); 8.40 (s, 1 H)	7.75 (d, 1 H); 8.05 (d, 1 H); 8.51 (s, 1 H)
3e	238		7.90 (s, 1 H); 8.20 (s, 1 H)	3.91 (s, 3 H, OMe); 3.98 (s, 3 H, OMe); 7.03 (s, 2 H)
3f	268		7.95 (br.s, 1 H); 8.13 (br.s, 1 H)	3.87 (s, 3 H, OMe); 3.95 (s, 3 H, OMe); 4.05 (s, 3 H, OMe); 7.41 (s, 1 H)
3g	206		7.11 (br.s, 1 H); 8.71 (br.s, 1 H)	2.55 (s, 3 H, Me); 3.45 (s, 3 H, Me); 7.20 (s, 1 H); 7.70 (s, 1 H)
4e	—	11.60		3.72 (s, 3 H, OMe); 3.85 (s, 3 H, OMe); 6.90 (d, 1 H, *J* = 8.95); 7.10 (d, 1 H, *J* = 8.95); 8.03 (s, 1 H)
4f	—	12.19		3.76 (s, 3 H, OMe); 3.77 (s, 6 H, 2 OMe); 3.47 (s, 2 H)
4g	208	12.09		2.30 (s, 6 H, 2 Me); 7.20 (s, 1 H); 7.51 (s, 2 H)

precipitate that formed was filtered off, washed with water, and dried. The yield was 50%, m.p. 107—109 °C. ^{1}H NMR (acetone-d_6), δ: 3.91 (s, 3 H); 7.17 (d, 1 H); 7.65 (s, 1 H); 8.00 (d, 1 H); 9.07 (s, 1 H).

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