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A new approach to synthesis of 2-carbamoylbenzothiazoles

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Abstract: The reactions of substituted anilines with chloroacetamide and sulfur in the presence of triethylamine afford monothiooxamides, which being treated with K3Fe(CN)6 are cyclized to 2-carbamoylbenzothiazoles. The cyclization is established to be accompanied by the formation of the corresponding thiooxanilic acids, which are also cyclized to benzothiazole-2-carboxylic acids.

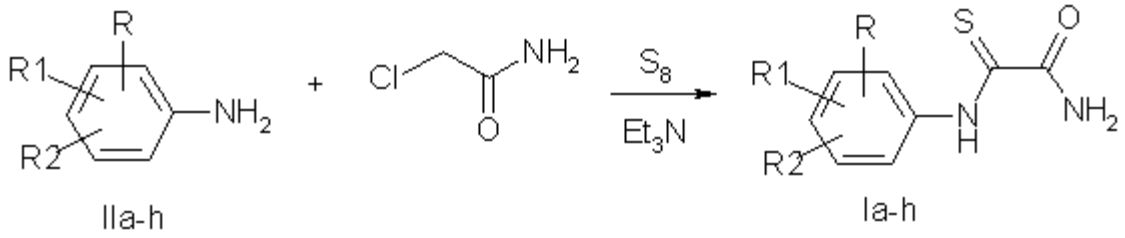
Keywords: Anilines, chloroacetamides, sulfur, monothiooxamides, 2-carbamoylbenzothiazoles, thiooxanilic acids, benzothiazole-2-carboxylic acids.

.Introduction

It is known that 2-carbamoylbenzothiazoles are used in the synthesis of polycyclic systems. For example, a series of 2-(thiazolyl)benzothiazoles with anti-inflammatory activity was obtained.**1,2** The natural compound D(**+**) 2-(6-hydroxybenzothiazolyl-2)-3,4-dihydrothiazole-4-carboxylic acid, "luciferin,"**3,4** and its analogs**5** were synthesized. It is noteworthy that the methods of preparation of 2-carbamoylbenzothiazoles described in the literature are multistage and labor-consuming, and the overall yields are low. The scheme used in Refs. 4 and 5 are the most rational. According to this scheme, monothiooxamides are synthesized from accessible anilines at the first stage, and the monothiooxamides obtained are cyclized under the action of K3Fe(CN)6. However, convenient methods for preparation of monothiooxamides were lacking before the beginning to our studies.

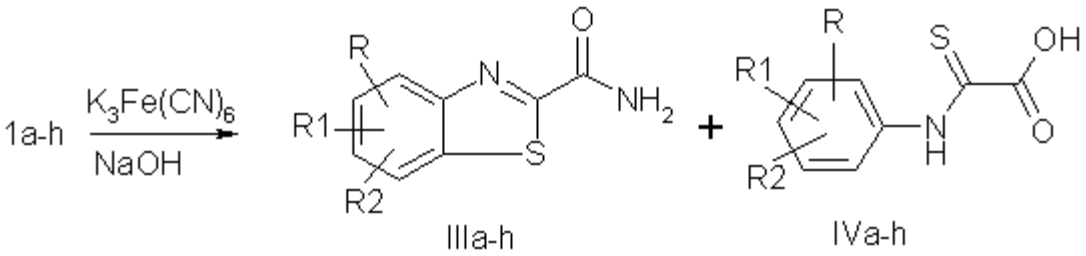
Results and Discussion

In this work, to synthesize monothiooxamides (**Ia–h**), we used the approach suggested by us: the reactions of the corresponding anilines with chloroacetamide in the presence of sulfur and triethylamine. It is established that the reaction occurs successfully when a solution of aniline (**IIa–h**), sulfur, and triethylamine in DMF is preliminary prepared, and then chloroacetamide is added. When this order of mixing the reagents is used, monothiooxamides are formed in 60–80% yield.



I, II a: R = 4-CH 3O; $R_1 = R_2 = H$
b: R = 2-CH3O; $R_1 = R_2 = H$
c: R = 4-Br; $R_1 = R_2 = H$
d: R = 2-Br; $R_1 = R_2 = H$
e: R = 4-Cl; $R_1 = R_2 = H$
f: R = 2-CH 3O; R_1 = 5-CH3O; $R_2 = H$
g: R = 3-CH 3O; R_1 = 4-CH3O; R_2 = 5-CH3O
h: R = 3-CH 3; R_1 = 5-CH3; $R_2 = H$

The study of the cyclization reaction of monothiooxamides **Ia–h** under the action of K3Fe(CN)6 in alkaline solutions shows that in all cases, the corresponding thiooxanilic acid (**IVa–h**) is formed as the by-product along with 2-carbamoylbenzothiazoles (**IIIa–h**).

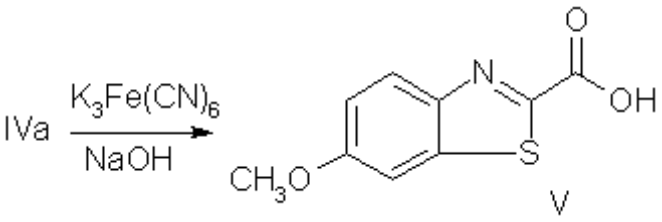


III a: R = 6-CH 3O; $R_1 = R_2 = H$
b: R = 4-CH3O; $R_1 = R_2 = H$
c: R = 6-Br; $R_1 = R_2 = H$
e: R = 6-Cl; $R_1 = R_2 = H$
f: R = 4-CH 3O; R_1 = 7-CH3O; $R_2 = H$
g: R = 5-CH 3O; R_1 = 6-CH3O; R_2 = 7-CH3O
h: R = 5-CH 3; R_1 = 7-CH3; $R_2 = H$

IV a: R = 4-CH 3O; $R_1 = R_2 = H$
b: R = 2-CH3O; $R_1 = R_2 = H$
c: R = 4-Br; $R_1 = R_2 = H$
e: R = 4-Cl; $R_1 = R_2 = H$
f: R = 2-CH 3O; R_1 = 5-CH3O; $R_2 = H$
g: R = 5-CH 3O; R_1 = 6-CH3O; R_2 = 7-CH3O
h: R = 5-CH 3; R_1 = 7-CH3; $R_2 = H$

The yield and ratio of the reaction products depend on the nature of substituents in the phenyl ring, on solubility of the starting monothiooxamides, and the concentration of alkali. Donor substituents favor and electron-acceptor substituents prevent cyclization, which indicates the electrophilic character of this process.

It is noteworthy that the presence of a substituent in the *ortho*-position to the thioamide group in (**Ib**) and (**Id**) results in a decrease in the yield of cyclic products. Correspondingly, the amount of saponification products also increases. It is of interest that thiooxamides (**I**) to thiooxanilic acids (**IV**) are readily saponified already at room temperature. Thiooxanilic acids (**IV**) also can be oxidized to benzothiazole-2-carboxylic acids (**V**), but in lower yields than thiooxamides.



Experimental Part

1H NMR spectra were recorded on Bruker AC-200 (working frequency 200 MHz) and Bruker WM-250 (working frequency 250 MHz) instruments in DMSO-d6. Mass spectra were recorded on a Varian MAT CH-6 instrument with the direct introduction of samples into the radiation source with an ionization energy of 70 eV and a controlling voltage of 1.75 keV. Melting points were measured on a Boetus heating table and were not corrected.

Monothiooxamides **Ia–h** were obtained by the reactions of chloroacetamide with amines **IIa–h** and sulfur in the presence of Et3N according to the known procedure.**6**

Ia N0-(4-Methoxyphenyl)(thiooxamide)

Yield 80%, m.p. 127–129oC with decomp. (ethanol); Ref. 7: m.p. 127–129oC.

Ib N0-(2-Methoxyphenyl)(thiooxamide)

Yield 72%, m.p. 127–131oC (ethanol). Found (%): C, 51,62; H, 4,90; N, 12,94; S, 15,07. $C_9H_{10}N_2O_2S$. Calculated (%): C,51,43; H.4,76; N, 13,33; S, 15,24. 1H NMR (d, ppm): 3,90 (s, 3H); 7,05 (t, 1H); 7,20 (d,1H); 7,35 (t, 1H); 8,21 (s, 2H); 8,70 (d, 1H); 11,85 (s, 1H).. MS, *m/z*:210[M^+]

Ic N0-(4-Bromophenyl)(thiooxamide)

Yield 65%, m.p. 186–188oC (ethanol); Ref. 7: m.p. 187oC.

Id N0-(2-Bromophenyl)(thiooxamide)

Yield 60%, m.p. 133–135oC (ethanol); Ref. 7: m.p. 133oC.

Ie N0-(4-Chlorophenyl)(thiooxamide)

Yield 72%, m.p. 185–186oC (ethanol); Ref. 7: m.p. 184oC.

If N0-(2,5-Dimethoxyphenyl)(thiooxamide)

Yield 76%, m.p. 118–119oC (ethanol). Found (%): C, 50,17; H, 5,09; N, 11,34; S, 13,18. $C_{10}H_{12}N_2O_3S$. Calculated (%): C,50,00; H, 5,00; N, 11,67; S, 13,33. 1H NMR (d, ppm): 3,71 (s,3H); 3,85 (s, 3H); 6,00 (d,1H); 7,10(d,1H); 8,02 (s,1H); 11,60 (s, 1H).).

Ig N0-(3,4,5-Trimethoxyphenyl)(thiooxamide)

Yield 68%, m.p. 128–131oC (ethanol). Found (%): C, 49,00; H, 5,26; N, 10,24; S, 11,70. $C_{11}H_{14}N_2O_4S$. Calculated (%): C, 48,89; H, 5,19; N, 10,37; S, 11,85. MS, *m/z*: 270[M^+]

Ih N0-(3,5-Dimethylphenyl)(thiooxamide)

Yield 76%, m.p. 128–131oC (ethanol). Found (%): C, 57,80; H, 5,54; N, 13,62; S, 15,24. $C_{10}H_{12}N_2OS$. Calculated (%): c, 57,69; h, 5,77; N, 13,46; S, 15,38. 1H NMR (d,ppm): 2,30 (s, 6H); 6,95 (s, 1H); 7,55 (s, 2H); 7,85 (t, 1H); 8,20 (br.d, 2H); 11,80 (s, 1H).). MS, *m/z*: 208[M^+]

Preparation of 2-carbamoylbenzothiazoles. IIIa–h (general procedure

The corresponding monothiooxamide (**Ia–h**) (0.01 mol) was dissolved in a 10% solution of sodium hydroxide (0.42 mol). The mixture was filtered, and K3Fe(CN)6 (0.038 mol) in water (38 mL) was added dropwise with stirring. The precipitate that formed (**IIIa–h**) was filtered off, washed with water, dried in air, and recrystallized. The filtrate was acidified with hydrochloric acid, and the precipitate of thio acid (**IVa–h**) that formed was filtered off, washed with water, dried, and recrystallized.

IIIa 6-Methoxybenzothiazole-2-carboxamide

Yield 80%, m.p. 257–258oC (ethanol). Ref. 8: m.p. 257–258oC.

IVa 4-Methoxy-2-thiooxanilic acid

Yield 8%, m.p. 135–137oC (ethyl acetate) (Ref. 7: 134oC). 1H NMR (d, ppm): 3,70 (s, 3H); 7,00 (d, 2H); 7,82 (d, 2H); 12,08(s, 1H).). MS, *m/z*: 211[M^+]

IIIb 4-Methoxybenzothiazole-2-carboxamide

Yield 3%, m.p. 213–214oC (ethyl acetate) (Ref. : 214–215oC). 1H NMR (d, ppm): 4,01 (s, 3H); 7,13 (d, 1H); 7,50 (t, 1H); 7,71 (d, 1H); 7,01-8,25 (br.d 2H). MS, *m/z*: 208[M^+].

IVb 2-Methoxy-2-thiooxanilic acid

Yield 76%, m.p. 130–133oC (reprecipitation from H2O) (Ref. : 136.5oC). 1H NMR (d, ppm): 3,87 (s, 3H); 7,00 (t, 1H); 7,19 (d, 1H); 7,32 (t, 1H); 8,10 (d, 1H); 11,65 (s, 1H).. MS, *m/z*: 211[M^+].

IIIc 6-Bromobenzothiazole-2-thiooxanilic acid

Yield 10%, m.p. 278–287oC (subl.) (toluene).

IIIe 6-Chlorobenzothiazole-2-carboxamide

Yield 3%, m.p. 283–285oC (toluene) (Ref. : m.p. 284oC).

IVe 4-Chloro-2-thiooxanilic acid

Yield 60%, m.p. 133–134oC (Ref. : m.p. 136oC).

IIIf 4,7-Dimethoxybenzothiazole-2-carboxamide

Yield 70%, m.p. 245–247oC (methanol). Found (%): C, 50,67; H, 4,40; N, 12,01; S 13,28. $C_{10}H_{10}N_2O_3S$. Calculated (%): C, 50,41; H, 4,23; N, 11,76; S, 13,45. 1H NMR (d, ppm): 3,91 (s, 3H); 3,98 (s, 3H); 7,03 (s, 2H); 7,90-8,20 (br.s, 2H)). MS, *m/z*: 238[M^+].

IVf 2,5-Dimethoxy-2-thiooxanilic acid

Yield 8%, m.p. 111–112oC (hexane). 1H NMR (d, ppm): 6,90 (d, 1H); 7,10 (d, 1H); 8,02 (s, 1H); 11,60 (s, 1H).

IIIg 5,6,7-Trimethoxybenzothiazole-2-carboxamide

Yield 16%, m.p. 150.5–151.5oC (ethanol). Found (%): C, 49,36; H, 4,48; N, 4,28; S, 12,06. $C_{11}H_{12}N_2O_4S$. Calculated (%): C,49,24; H, 4,51; N, 10,44; S, 11,95. 1H NMR (d, ppm): 3,70 (s, 3H); 3,78 (s, 3H); 4,05 (,s, 3H); 7,41 (s, 1H) 7,95-8,13 (br.d, 2H). MS, *m/z*: 268[M^+].

IIIh 5,7-Dimethylbenzothiazole-2-carboxamide

Yield 92%, m.p. 215–217oC (methanol). Found (%): C, 58,20; H, 4,90; N, 13,68; S, 15,28. $C_{10}H_{10}N_2OS$. Calculated (%): C,58,25; H, 4,85; N, 13,59; S, 15,53. 1H NMR (d, ppm): 2,45 (s, 3H); 2,55 (s, 3H); 7,20 (s 1H); 7,70 (s, 1H); 7,11-7,71 (,br.d, 2H).). MS, *m/z*: 206[M^+].

IVh 3,5-Dimethylbenzothiazole-2-thiooxanilic acid

Yield 2%, m.p. 116–118oC (hexane). Found (%): C,57,75; H, 4,73; N, 6,91; S, 15,67. $C_{10}H_{10}NO_2S$. Calculated (%): C, 57,69; H, 4,81; N, 6,73; S, 15,38. 1H NMR (d, ppm): 2,30 (s, 6H); 6,97 (s, 1H) 7,50 (s, 2H); 12,09 (s, 1H). MS, *m/z*: 208[M^+]

Preparation of thiooxanilic acid from monothiooxamides (general procedure).

Monothioxamide **Ia–h** (0.01 mol) was dissolved in 10% aqueous NaOH (0.42 mol), and the solution was stored at 20oC for 48 h. Then the solution was acidified by hydrochloric acid, and the precipitate that formed was filtered off. The acid that formed was dissolved in 10% aqueous sodium bicarbonate and acidified with hydrochloric acid. The precipitate that formed was washed and recrystallized.

IVa: Yield 71%, m.p. 135–138oC (from H2O).

IVb: Yield 70%, m.p. 111–112oC (hexane).

IVc: Yield 78%, m.p. 167–169oC (toluene).

Preparation of benzothiazole-2-carboxylic acid V

Thiooxanilic acid (lVa) (0.01 mol) was dissolved in 10% aqueous NaOH and added to an aqueous solution of K3Fe(CN)6 (0.038 mol in 38 mL H2O) with stirring at room temperature. Yield 50%, m.p. 107–109oC. 1H NMR (d, ppm, acetone-D6): 3,91 (s, 3H); 7,17 (d, 1H); 7,65 (s, 1H); 8,00 (d, 1H); 9,07 (s, 1H).

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