Thiocarbamoylation of amine-containing compounds

1. The reaction of tetramethylthiuram disulfide with 3-amino-4-methylbenzoic acid

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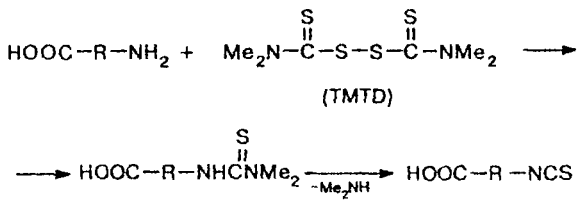
The reaction of 3-amino-4-methylbenzoic acid with tetramethylthiuram disulfide in DMF afforded 3-*N,N*-dimethylthioureido-4-methylbenzoic acid. Thermolysis or treatment of the latter with acidic reagents resulted in elimination of dimethylamine to form 3-isothiocyanato-4-methylbenzoic acid whose reaction with hydrazine yielded substituted thiosemicarbazide. The reactions of the latter with aldehydes and ketones gave thiosemicarbazones, and its reaction with tetramethylthiuram disulfide afforded 3-(2-mercapto-1,3,4-thiadiazol-5-ylamino)-4-methylbenzoic acid.

Key words: aminobenzoic acids, *N,N*-dimethylthioureidomethylbenzoic acids, isothiocyanatobenzoic acids, thiosemicarbazide, thiosemicarbazones, tetramethylthiuram disulfide, (mercaptothiadiazolylamino)benzoic acids.

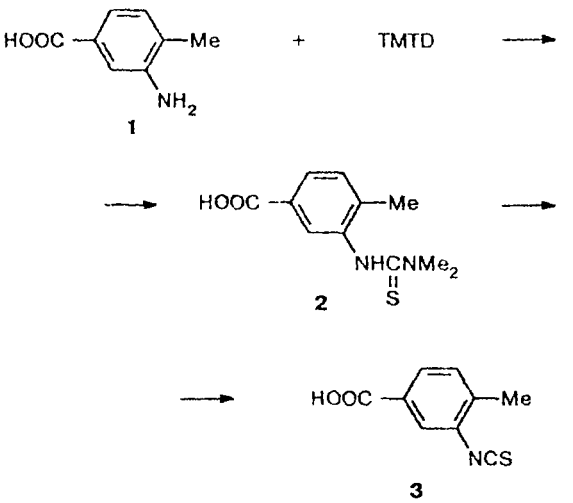
Isothiocyanatobenzoic acids exhibit fungicidal, bactericidal, and nematocidal activity. Their biological properties depend on the nature and positions of substituents in the aromatic ring.[1–3] Derivatives of isothiocyanatobenzoic acids are difficultly accessible and poorly studied. So far, they have been prepared by treating the corresponding aminobenzoic acids with thiophosgene.[4] This procedure is laborious and the yields of the target products were not necessarily satisfactory. Recently, we have reported a new preparative procedure[5] for the synthesis of isothiocyanatocarboxylic acids based on thiocarbamoylation of aminocarboxylic acids with tetramethylthiuram disulfide (TMTD) followed by decomposition of the *N,N*-dimethylthioureido derivatives formed (Scheme 1). The procedure is characterized by simplicity and high yields of target products (> 90%).

Scheme 1



As part of continuing studies, in this work we prepared 3-isothiocyanato-4-methylbenzoic acid and a series of its derivatives (Scheme 2).

Scheme 2



3-*N,N*-Dimethylthioureido-4-methylbenzoic acid (**2**) was synthesized by heating a mixture of 3-amino-4-methylbenzoic acid (**1**) and TMTD in DMF. The ratio of the reagents substantially affected the yield of the product. The best result was obtained when the reagents were taken in an equimolar ratio. A decrease in the **1** : TMTD molar ratio to 1 : 0.5 led to a decrease in the yield of acid **2** to 50%. Thus, the behavior of acid **1** in the reaction with TMTD is analogous to that of

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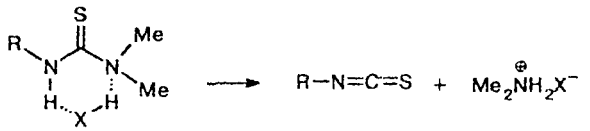
3-aminobenzoic acid.[6] Conversion of acid **2** into 3-isothiocyanato-4-methylbenzoic acid (**3**) was performed in two ways, namely, by thermolysis or by decomposition of acid **2** with acidic reagents. Thermal decomposition of *N,N*-dimethylthioureido derivatives in toluene at the boiling temperature of the reaction mixture proceeded slowly, and the reaction in xylenes at 140 °C led to resinification of the target products due to interaction between the COOH and NCS functional groups.[7] The best results (42%) were obtained when the solvent was continuously distilled off, which excluded return of dimethylamine into the reaction mixture, and the equilibrium shifted toward acid **3**.

The second procedure makes use of acetic anhydride, acetyl chloride, or mineral acids in organic solvents, which favor elimination of dimethylamine in the form of either *N,N*-dimethylacetamide or the corresponding ammonium salt. Boiling (4 h) of a benzene solution of a mixture of acid **2** and acetic anhydride taken in an equimolar ratio afforded acid **3** in 80% yield. When the reaction was carried out in a sealed tube and acetyl chloride was used instead of acetic anhydride, the reaction time was decreased to 2 h with retention of the high yield of the target product. However, mineral acids, which more readily (compared to other reagents) react with the thioureido residue to form cyclic transition states, appeared to be the most efficient reagents (Scheme 3).

Scheme 3



X = Cl, OSO_3H

In this case, dioxane, in which the substrate and mineral acids are readily soluble, is the most suitable solvent. The reaction with hydrogen chloride was carried out in a sealed tube with a twofold excess of the reagent. In the case of H_2SO_4, the optimum molar ratio of the reagents was 1 : 1. In both cases, the yield of acid **3** was 93%.

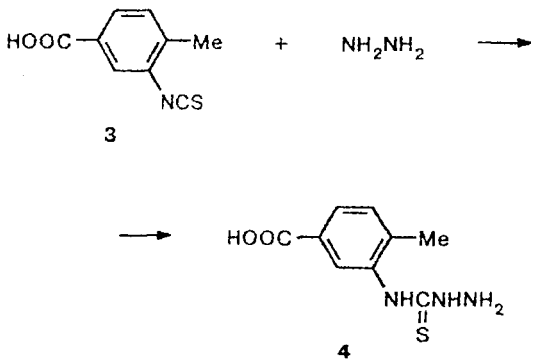
Thus, isothiocyanatobenzoic acids prepared by the method developed by us become inexpensive and available reagents for various synthetic procedures.

4-(5-Carboxy-2-methylphenyl)thiosemicarbazide (**4**) was prepared by the addition of hydrazine to acid **3** (Scheme 4).

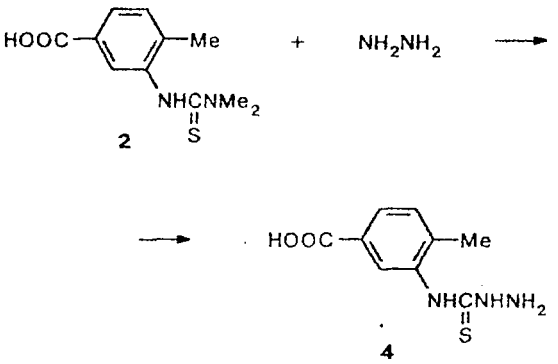
The same thiosemicarbazide **4** was prepared from thioureidobenzoic acid **2** by the reaction with hydrazine according to the procedure which we have developed previously[8] (Scheme 5). Both reactions afforded thiosemicarbazide **4** in 93—94% yields.

Thiosemicarbazide **4** readily reacted with aldehydes and ketones to form thiosemicarbazones **5a—e** (Table 1) and reacted with TMTD to give 3-(5-mercapto-1,3,4-thiadiazol-2-ylamino)-4-methylbenzoic acid (**6**) (Scheme 6). The resulting compounds are potential objects for studying biological activity.

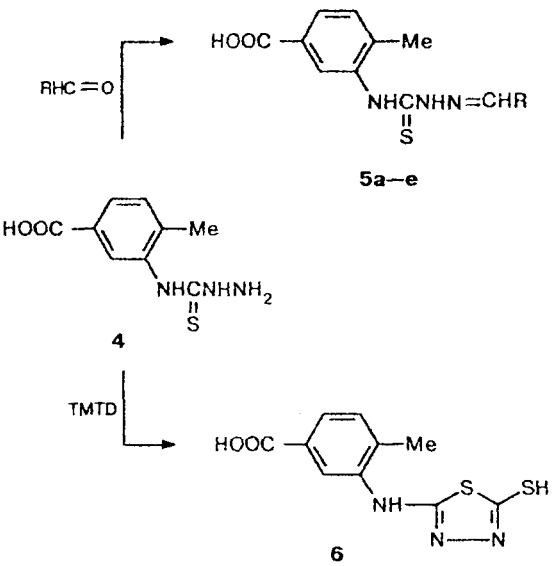
Scheme 4



Scheme 5

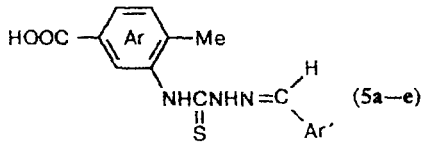


Scheme 6



R = Ph (**a**), *p*-BrC_6H_4 (**b**), *o*-HOC_6H_4 (**c**), 2-furyl (**d**), *p*-$NO_2C_6H_4$ (**e**)

Table 1. Selected characteristics of 4-(5-carboxy-2-methylphenyl)thiosemicarbazones



Compound	Ar'	M.p./°C	Found (%) / Calculated (%)			^{1}H NMR (DMSO-d_6), δ
			C	H	N	
5a	Ph	226—228	61.41 61.32	4.83 4.82	13.56 13.41	2.35 (s, 3 H, Me); 7.54 (d, 2 H, Ar); 7.65 (m, 5 H, Ph); 7.95 (s, 1 H, Ar); 8.17 (s, 1 H, =CH); 9.85 (s, 1 H, NNH); 11.78 (s, 1 H, NH)
5b	*p*-BrC_6H_4	245—247	48.58 48.99	3.68 3.60	10.80 10.71	7.50 (d, 2 H, Ar'); 7.57 (d, 2 H, Ar); 7.85 (d, 2 H, Ar'); 7.90 (s, 1 H, Ar); 8.10 (s, 1 H, =CH); 9.88 (s, 1 H, NNH); 11.78 (s, 1 H, NH)
5c	*o*-HOC_6H_4	225—227	58.32 58.35	4.54 4.59	12.71 12.76	6.80 (s, 1 H, Ar'); 6.87 (t, 1 H, Ar'); 7.17 (t, 1 H, Ar'); 7.55 (d, 2 H, Ar); 7.85 (s, 1 H, Ar'); 7.95 (s, 1 H, Ar); 8.47 (s, 1 H, =CH); 9.63 (s, 1 H, OH); 9.77 (s, 1 H, NNH); 11.70 (s, 1 H, NH)
5d	2-Furyl	231—232	55.46 55.43	4.41 4.32	13.90 13.85	6.55 (m, 1 H, furyl); 6.96 (d, 1 H, furyl); 7.56 (d, 2 H, Ar); 7.69 (d, 1 H, furyl); 8.00 (s, 1 H, Ar); 8.07 (s, 1 H, =CH); 9.55 (s, 1 H, NNH); 11.78 (s, 1 H, NH)
5e	*p*-$NO_2C_6H_4$	178—180	54.78 54.83	4.28 4.33	15.01 15.04	2.37 (s, 3 H, Me); 2.82 (s, 3 H, =CMe); 7.56 (d, 2 H, Ar); 7.93 (s, 1 H, Ar); 8.18 (d, 2 H, Ar'); 8.28 (d, 2 H, Ar'); 10.02 (s, 1 H, NNH); 10.73 (s, 1 H, NH)

Experimental

The IR spectra were recorded on a UR-20 spectrometer (Nujol mulls). The ^{1}H NMR spectra were obtained on a Bruker AM-250 instrument. The chemical shifts were measured relative to $SiMe_4$. The TLC analysis was performed on Silufol UV-254 plates. The plates were inspected under UV light. The reagents used were of "chemically pure" grade. Commercial-grade tetramethylthiuram disulfide was recrystallized from $CHCl_3$, m.p. 154—156 °C.

3-(*N,N*-Dimethylthioureido)-4-methylbenzoic acid (2). A mixture of 3-amino-4-methylbenzoic acid (15.1 g, 0.1 mol) and tetramethylthiuram disulfide (24 g, 0.1 mol) in DMF (20 mL) was heated at 100 °C, diluted with water, and treated with a 5% aqueous solution of NaOH until the reaction became weakly alkaline. Sulfur and insoluble admixtures were filtered off. The filtrate was acidified with 10% HCl. The acid that precipitated was filtered off and washed on a filter with water. Acid **2** was obtained in a yield of 22.6 g (95%), m.p. 185 °C (with decomp., DMF). Found (%): C, 55.50; H, 5.96; N, 11.82. $C_{11}H_{14}N_2SO_2$. Calculated (%): C, 55.44; H, 5.92; N, 11.76. ^{1}H NMR (DMSO-d_6), δ: 2.22 (s, 3 H, Me); 3.28 (s, 6 H, NMe_2); 7.51 (d, 2 H, Ph); 7.65 (s, 1 H, Ar); 8.88 (s, 1 H, NH). IR, ν/cm^{-1}: 1690 (C=O); 3300 (NH).

3-Isothiocyanato-4-methylbenzoic acid (3). ***A.*** A solution of acid **2** (1.19 g, 0.005 mol) in *p*-xylene (150 mL) was boiled with continuous distillation of the solvent (~100 mL) for 1.5 h. The completion of the reaction was determined from the negative test of the last portion of the distillate for the presence of dimethylamine (with phenolphthalein). The remaining solution (~50 mL) was chromatographed on silica gel (*p*-xylene as the eluent). The solvent was distilled off at 60—70 °C *in vacuo*. Acid **3** was obtained in a yield of 0.4 g (42%), m.p. 197 °C (decomp.).

B. A solution of acid **2** (2.38 g, 0.01 mol) and Ac_2O (1.02 mol) in benzene (20 mL) was refluxed for 3 h. The solvent was distilled off *in vacuo*. The residue was filtered off and washed with distilled water. Acid **3** was obtained in a yield of 1.54 g (80%).

C. A solution of acid **2** (2.38 g, 0.01 mol) and AcCl (0.78 g, 0.01 mol) in benzene (20 mL) was heated in a sealed tube at 100 °C for 2 h. The solvent was distilled off. The residue was filtered off and washed with water. The yield of acid **3** was 1.64 g (85%).

D. A solution of acid **2** (2.38 g, 0.01 mol) and concentrated H_2SO_4 (0.98 g) in dioxane (10 mL) was heated at 100 °C for 3 h. Dioxane was distilled off *in vacuo*. The precipitate that formed was filtered off and washed with water. Acid **3** was obtained in a yield of 1.75 g (91%).

Acid **3**, which was prepared according to procedures ***B***, ***C***, and ***D***, was purified by recrystallization from benzene or by chromatography on silica gel (benzene as the eluent). Its decomposition temperature coincides with the decomposition temperature of the acid prepared according to method ***A***.

Found (%): C, 67.28; H, 4.18; N, 19.76. $C_9H_7NO_2S$. Calculated (%): C, 67.08; H, 4.38; N, 19.86. ^{1}H NMR (DMSO-d_6), δ: 2.43 (s, 3 H, Me); 7.68 (d, 2 H, Ph); 7.90 (s, 1 H, Ph). IR, ν/cm^{-1}: 1700 (COOH); 2100 (NCS).

4-(5-Carboxy-2-methylphenyl)thiosemicarbazide (4). ***A.*** Acid **3** (1.79 g, 0.01 mol) was added portionwise with stirring to a 10% aqueous solution of hydrazine (11 mL). The completion of the reaction was determined from the disappearance of the absorption band of the NCS group in the IR spectrum. The

resulting solution was filtered off and acidified to pH 4—5. The precipitate that formed was filtered off and washed on a filter with water. Compound **4** was obtained in a yield of 2.09 g (93%), decomp. point 239 °C (DMF—ethanol).

B. A solution of acid **2** (1.19 g, 0.005 mol) and hydrazine hydrate (0.5 g, 0.01 mol) in pyridine (6 mL) was heated at 100 °C for 30 min and then the solvent was distilled off *in vacuo*. Distilled water (5 mL) was added to the precipitate and the mixture was acidified with HCl to pH 5. Compound **4** was obtained in a yield of 1.05 g (94%).

Found (%): C, 55.90; H, 5.71; N, 21.61. $C_9H_{11}N_3O_2$. Calculated (%): C, 55.95; H, 5.74; N, 21.75. ^{1}H NMR (DMSO-d_6), δ: 2.30 (s, 3 H, Me); 7.48 (d, 2 H, Ph); 8.12 (s, 1 H, Ph).

The acids which were prepared according to procedures ***A*** and ***B*** are characterized by identical ^{1}H NMR spectra and decomposition points (239 °C).

4-(5-Carboxy-2-methylphenyl)thiosemicarbazones (5a—e). ***A.*** A solution of carbonyl compound in a minimum amount of ethanol was added dropwise to a mixture of thiosemicarbazide **4** (1.12 g, 0.005 mol) and DMF (1 mL) at 40—50 °C. The mixture was heated for 1 h. The crystals that precipitated upon cooling were filtered off and recrystallized from an EtOH—DMF mixture. Thiosemicarbazones **5a—e** were obtained in 90—95% yields.

B. A solution of a carbonyl compound hydrazone in ethanol (0.005 mol) was added dropwise to a solution of acid **3** (0.96 g, 0.005 mol) in DMF (1 mL) at 50 °C. The reaction mixture was heated (10—30 min) and then cooled. The crystals that precipitated were filtered off. Thiosemicarbazones **5a—e** were obtained in 87—92% yields.

The thiosemicarbazones which were prepared according to procedures ***A*** and ***B*** are characterized by identical ^{1}H NMR spectra and melting points. The characteristics of the thiosemicarbazones synthesized are given in Table 1.

3-(5-Mercapto-1,3,4-thiadiazol-2-ylamino)-4-methylbenzoic acid (6). A mixture of thiosemicarbazide **4** (1.12 g, 0.005 mol) and TMTD (1.2 g, 0.005 mol) in DMF (3 mL) was heated at 80 °C for 1 h. The mixture was treated with an aqueous solution of $NaHCO_3$ until acid **6** dissolved. A precipitate of sulfur was separated by filtration and the filtrate was acidified to pH 5. The precipitate was filtered off, washed with water, and dried. Acid **6** was obtained in a yield of 1.93 g **6** (92%), decomp. point ~245 °C. Found (%): C, 44.86; H, 3.29; N, 15.81. $C_{10}H_9N_3O_2S_2$. Calculated (%): C, 44.94; H, 3.37; N, 15.73. ^{1}H NMR (DMF-d_7), δ: 2.23 (s, 3 H, Me); 7.40 (d, 2 H, Ph); 8.35 (s, 1 H, Ph); 9.19 (s, 1 H, NH); 13.40 (s, 1 H, SH).

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