Thiocarbamoylation of amine-containing compounds
2.* The reaction of tetramethylthiuram disulfide with 5-amino-2-mercaptobenzooxazole

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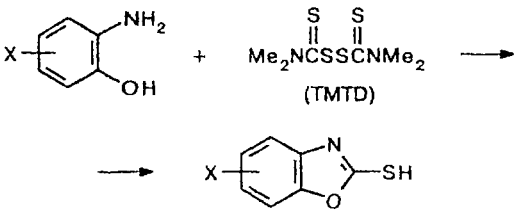
The reaction of 5-amino-2-mercaptobenzooxazole with tetramethylthiuram disulfide afforded *N,N*-dimethylthioureido-2-mercaptobenzooxazole, which was converted into 5-isothiocyanato-2-mercaptobenzooxazole under the action of AcCl, Ac_2O, or HCl. Based on the latter compound, 4-(2-mercaptobenzooxazol-5-yl)thiosemicarbazide was synthesized, whose reactions with aldehydes and ketones yielded the corresponding thiosemicarbazones.

Key words: 5-amino-2-mercaptobenzooxazole, 2-mercaptobenzooxazole, tetramethylthiuram disulfide, *N,N*-dimethylthioureido-2-mercaptobenzooxazole, 5-isothiocyanato-2-mercaptobenzooxazole, 4-(2-mercaptobenzooxazol-5-yl)thiosemicarbazide, 4-(2-mercaptobenzooxazol-5-yl)thiosemicarbazones, thioureas.

2-Mercaptobenzooxazole derivatives exhibit biological activity and can be used as fungicides, bactericides, or insecticides.[2,3] These compounds also find use as poly(vinyl chloride) stabilizers,[4] as components in the synthesis of azo dyes,[5] *etc.* So far, these compounds have been prepared from the corresponding *o*-aminophenols and carbon disulfide or potassium xanthate.[6] These methods are laborious and the yields of the target products were not necessarily satisfactory. Recently, we have developed a convenient preparative procedure for the synthesis of 2-mercaptobenzooxazole and its derivatives.[1] The method is based on the reaction of tetramethylthiuram disulfide (TMTD) with substituted aminophenols (Scheme 1).

Scheme 1



X = H, Alkyl, Hal, Ac, NO_2

This one-stage procedure is characterized by simplicity and high yields of the target products (up to 94%). By virtue of this, almost all derivatives, including 5-amino-2-mercaptobenzooxazole (**1**), become readily accessible. Compound **1** was readily prepared by reduction of the corresponding nitro compound with sodium dithionite according to a procedure reported previously.[7] This compound served as a precursor in the synthesis of 5-isothiocyanato-2-mercaptobenzooxazole (**2**) under study.

5-Isothiocyanato-2-mercaptobenzooxazole (**2**) possesses strong fungicidal properties; however, it remains poorly studied. The synthesis of this compound by treating compound **1** with thiophosgene was described previously[8]; however, the yield was not reported. As part of our continuing studies, in this work we examined the possibility of the use of the reaction of TMTD with aromatic amines, *viz.*, with compound **1**, followed by decomposition of the thiourea (**3**) that formed for the preparative synthesis of compound **2** according to Scheme 2.

5-(*N,N*-Dimethylthioureido)-2-mercaptobenzooxazole (**3**) was synthesized according to a procedure analogous to that developed by us,[9] *viz.*, by the reaction of amine **1** with TMTD in aqueous DMF or in dioxane. The ratio of the reagents affected substantially the yield of **3**. The best results were obtained when amine **1** and TMTD were taken in an equimolar ratio (80.3%).

Decomposition of thiourea **3** to isothiocyanate **2** was performed with the use of HCl, Ac_2O, and AcCl. A comparison of our results caused us to give preference to

* For Part 1, see Ref. 1.

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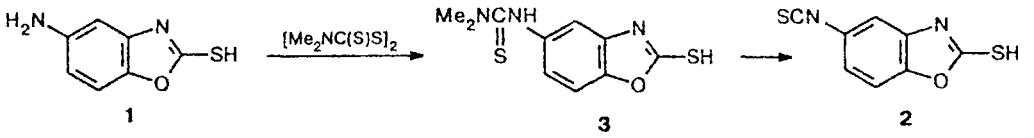
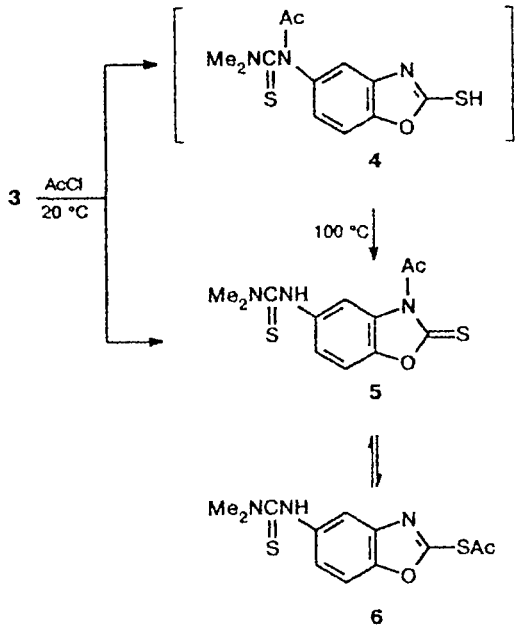
Scheme 2



Scheme 3



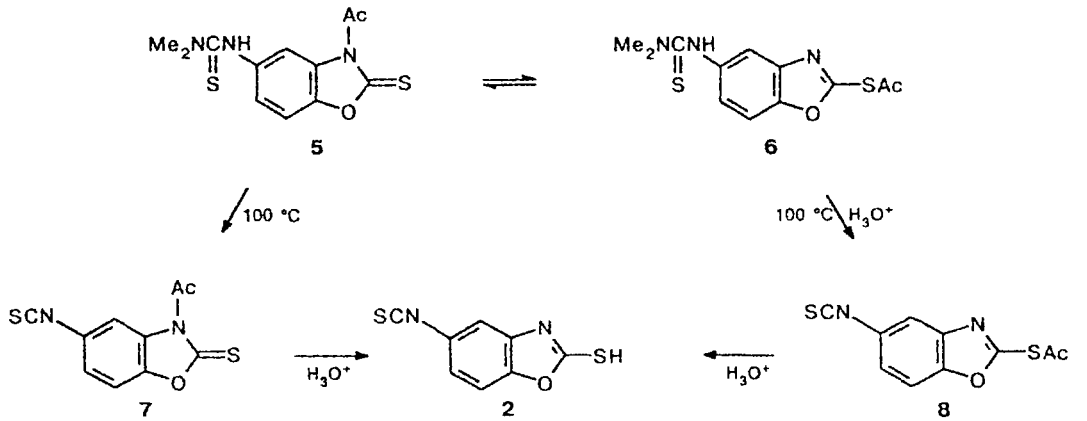
HCl, which made it possible to synthesize isothiocyanate **2** in one stage in 67% yield.

Since the initial thiourea **3** contains three reaction centers that can form *N*- and *S*-acetyl derivatives, the use of AcCl is complicated by the presence of intermediates **4**—**6** even at room temperature. The IR spectra of the latter compounds have ν(>N—C=O) and ν(—S—C=O) stretching absorption bands at 1660 and 1730 cm^{-1}, respectively (Scheme 3).

It should be noted that compound **4** exists only under mild conditions. An increase in the temperature led to rapid conversion of compound **4** into **5** or **6**. At a temperature higher than 100 °C, the latter compounds eliminated the dimethylamino group to form acetyl-substituted isothiocyanatobenzooxazoles **7** or **8**. The IR spectrum of a mixture of acetyl-substituted isothiocyanates **7** and **8** has medium-intensity (ν(—S—C=O) = 1730 cm^{-1}) and very low-intensity (ν(—N—C=O) = 1660 cm^{-1}) bands. The IR spectra of aliquot samples of the mixture, which were drawn at specific intervals, indicate that a ν(—NCS) band appears at 2100 cm^{-1} simultaneously with the disappearance of the ν(NH) band of the dimethylthioureido group at 3320 cm^{-1}. Judging from the ratio of the intensities of the ν(SCO) and ν(NCO) bands, the *S*-acylated product (**8**) dominated over the *N*-acylated compound (**7**). Acid hydrolysis of a mixture of compounds **7** and **8** afforded 5-isothiocyanato-2-mercaptobenzooxazole **2** (Scheme 4).

At room temperature, Ac_2O did not react with compound **3**. However, an increase in the temperature to 100 °C led to the formation of the *S*- and *N*-acetyl derivatives of isothiocyanatobenzooxazoles **7** and **8**, which also gave compound **2** upon acid hydrolysis.

Scheme 4



5-Isothiocyanato-2-mercaptobenzooxazole **2** is an attractive reagent owing to its ability to undergo conversions into compounds of different classes, including derivatives of thiosemicarbazide and thiosemicarbazones, which we prepared according to Scheme 5.

The reaction of isothiocyanate **2** with hydrazine taken in an equimolar ratio under mild conditions afforded 4-(2-mercaptobenzooxazol-5-yl)thiosemicarbazide (**9**). The reaction with an excess of hydrazine gave unidentified products. We failed to prepare thiosemicarbazide **9** from thiourea **3** and hydrazine in dioxane at 100 °C by nucleophilic substitution according to the procedure developed by us previously,[10] due to competitive replacement reactions of the thiol group.

The reactions of thiosemicarbazide **9** with aldehydes and ketones afforded thiosemicarbazones **10**, which we identified by independent synthesis from isothiocyanate **2** and hydrazones **11** (see Scheme 5).

The reactions with hydrazones gave products **10** of higher purity. The characteristics of these products are given in Table 1.

Compounds **2—4**, **9**, and **10** containing the thiol group are soluble in aqueous solutions of alkalis and are precipitated from these solutions with mineral or organic acids. These compounds are poorly soluble in usual organic solvents but are readily soluble in DMF and DMSO.

Scheme 5

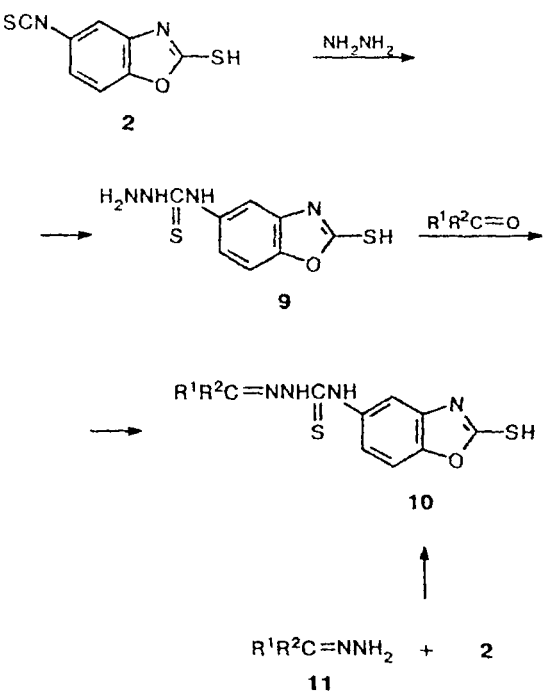
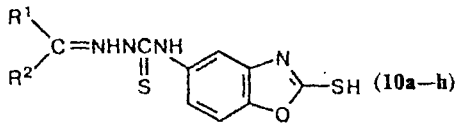


Table 1. Physicochemical characteristics of 4-(2-mercaptobenzooxazol-5-yl)thiosemicarbazones



(10a—h)

Compound	R^1	R^2	M.p./°C	Found / Calculated (%) C	H	N	^{1}H NMR (DMSO-d_6), δ
10a	Me	Me	219	47.14 47.13	4.29 4.31	20.00 19.98	2.05 (s, 6 H, 2 Me); 7.34 (s, 1 H, hetaryl); 7.50 (d, 2 H, hetaryl); 9.73 (s, 1 H, NNH); 10.25 (s, 1 H, NH)
10b	H	Ph	228	54.78 54.86	3.56 3.68	17.17 17.06	7.40 (s, 1 H, hetaryl); 7.55 (d, 2 H, hetaryl); 7.68 (m, Ph); 10.00 (s, 1 H, NNH); 11.75 (s, 1 H, NH); 13.68 (s, 1 H, NH)
10c	H	*o*-C_6H_4OH	205	52.41 52.32	3.49 3.51	16.17 16.27	6.85 (d, 1 H, Ar); 7.07 (t, 2 H, Ar); 7.37 (s, 1 H, hetaryl); 7.50 (d, 2 H, hetaryl); 7.90 (d, 1 H, Ar); 9.95 (s, 1 H, NNH); 11.70 (s, 1 H, NH); 13.60 (s, 1 H, NH)
10d	H	2-Furyl	230	49.16 49.04	3.14 3.17	17.69 17.60	6.55 (m, 1 H, furyl); 7.00 (d, 1 H, furyl); 7.36 (s, 1 H, benzooxazolyl); 7.55 (d, 2 H, benzooxazolyl); 7.72 (d, 1 H, furyl); 9.75 (s, 1 H, NH); 13.63 (s, 1 H, NH)
10e	H	4-Nitro-2-furyl	230 (decomp.)	42.91 42.97	2.36 2.48	19.21 19.28	7.36 (s, 1 H, benzooxazolyl); 7.50 (d, 2 H, benzooxazolyl); 7.55 (d, 2 H, furyl); 8.10 (s, 1 H, =CH); 10.12 (s, 1 H, NNH); 12.19 (s, 1 H, NH); 13.68 (s, 1 H, NH)
10f	Me	*p*-C_6H_4Cl	225	50.81 51.00	3.35 3.45	14.92 14.87	7.38 (s, 1 H, hetaryl); 7.50 (d, 2 H, hetaryl); 7.70 (m, 4 H, Ar); 10.00 (s, 1 H, NNH); 10.55 (s, 1 H, NH)
10g	Me	*p*-$C_6H_4NO_2$	195	49.56 49.61	3.21 3.36	17.09 17.18	7.30 (s, 1 H, hetaryl); 7.45 (d, 2 H, hetaryl); 8.00—8.25 (m, 4 H, Ar); 10.10 (s, 1 H, NNH); 11.75 (s, 1 H, NH)
10h	H	*p*-C_6H_4Br	238	44.35 44.23	2.79 2.70	13.85 13.76	7.40 (s, 1 H, hetaryl); 7.50 (d, 2 H, hetaryl); 7.60 (d, 2 H, Ar); 7.85 (d, 2 H, Ar); 10.05 (s, 1 H, NNH); 11.80 (s, 1 H, NH); 13.65 (s, 1 H, NH)

Experimental

The IR spectra were recorded on a UR-20 spectrometer as 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 carried out 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.

5-(*N,N*-Dimethylthioureido)-2-mercaptobenzooxazole (3). A mixture of 5-amino-2-mercaptobenzooxazole (**1**) (1.5 g, 9 mmol) and TMTD (2.28 g, 9.5 mmol) in water (10 mL) was refluxed for 2 h until elimination of hydrogen sulfide ceased. Then the solvent was distilled off. The residue was treated with a 1 *M* NaOH solution (10 mL). Sulfur and other admixtures were filtered off. The precipitate was washed on a filter with a dilute alkali and the filtrate was acidified with HCl to H 5. The precipitate that formed was filtered off and dried. The yield was 1.81 g (80.3%), m.p. 210 °C (DMF). Found (%): C, 47.45; H, 4.35; N, 16.57. $C_{10}H_{11}N_3OS_2$. Calculated (%): C, 47.41, H, 4.38 N, 16.59. ^{1}H NMR (DMSO-d_6), δ: 3.31 (s, 6 H, NMe_2); 7.23 (d, 2 H, benzooxazolyl); 7.28 (s, 1 H, benzooxazolyl); 8.98 (s, 1 H, NH).

5-Isothiocyanato-2-mercaptobenzooxazole (2). ***A.*** A mixture of mercaptobenzooxazole **3** (0.20 g, 0.8 mmol) and Ac_2O (0.20 g, 2 mmol) in DMF (0.6 mL) was heated at 100 °C for 2 h and then cooled. Water was added dropwise and the precipitate that formed was filtered off and washed with distilled water. The resulting mixture of 3-acetyl-5-dimethylureidobenzooxazole-2-thione (**5**) and 2-acetylthio-5-dimethylthioureidobenzooxazole (**6**) (0.16 g) was subjected to hydrolysis by heating in dioxane (1 mL) with 10% HCl (0.15 mL) for 1 h. The solvent was distilled off and the precipitate was washed with distilled water and dried. 5-Isothiocyanato-2-mercaptobenzooxazole (**2**) was obtained in a yield of 0.10 g (60%), m.p. 248 °C (dioxane). Compound **2** was purified by chromatography on silica gel (benzene as the eluent) after which its m.p. was 250 °C. Found (%): C, 47.67; H, 1.91; N, 3.31. $C_8H_4N_2OS_2$. Calculated (%): C, 47.44; H, 1.94; N, 13.45. ^{1}H NMR (DMSO-d_6), δ: 7.20 (s, 1 H, benzooxazolyl); 7.29 (d, 2 H, benzooxazolyl); 13.87 (s, 1 H, SH).

B. A solution of mercaptobenzooxazole **2** (0.2 g, 0.8 mmol) in dioxane (1 mL) was heated on a water bath and HCl was passed through the reaction mixture for 1 h. Then the solvent was distilled off and the precipitate was worked up as described in method ***A***. Compound **3** was obtained in a yield of 0.11 g (67%).

4-(2-Mercaptobenzooxazol-5-yl)thiosemicarbazide (9). A solution of mercaptobenzooxazole **2** (1.00 g, 4.8 mmol) in dioxane (10 mL) and water (30 mL) was added dropwise with stirring to hydrazine hydrate (0.28 g, 5.5 mmol). The reaction solution was heated at 50 °C for 1 h and acidified with AcOH. The precipitate that formed was filtered off, washed with distilled water, and dried. Thiosemicarbazide **9** was obtained in a yield of 0.84 g (73%), m.p. 178 °C (Pr^iOH—DMF). Found (%): C, 39.80; H, 3.61; N, 22.90. $C_8H_8N_4OS_2$. Calculated (%): C, 39.99; H, 3.46; N, 23.12. ^{1}H NMR (DMSO-d_6), δ: 7.17 (d, 2 H, benzooxazolyl); 7.22 (s, 1 H, benzooxazolyl).

4-(2-Mercaptobenzooxazol-5-yl)thiosemicarbazones (10). ***A.*** Aldehyde or ketone (5 mmol) dissolved in a minimum amount of Pr^iOH was added to a solution of 4-(2-mercaptobenzooxazol-5-yl)thiosemicarbazide (**9**) (1.15 g, 4.8 mmol) in DMF (1.5 mL). The mixture was heated for 1.5 h and then cooled. The precipitate was filtered off and recrystallized from a Pr^iOH—DMF mixture. Thiosemicarbazone **10a** was prepared in the presence of an excess of acetone which was also used as the solvent. The yields of thiosemicarbazones **10a—h** were 85—95%.

B. Hydrazone **11** (0.01 mol) was added dropwise with stirring to a solution of 5-isothiocyanato-2-mercaptobenzooxazole (**2**) (2.08 g, 0.01 mol) in DMF (2 mL). Then the reaction mixture was heated at 50—60 °C for 30 min. The product that precipitated upon cooling was filtered off and washed on a filter with ethanol. An additional amount of thiosemicarbazone **10** was obtained from the filtrate. The total yield was 90—95%. Thiosemicarbazones **10** prepared according to methods ***A*** and ***B*** are characterized by identical R_f values (ethyl acetate as the eluent) and identical IR spectra. The characteristics of compounds **10a—h** are given in Table 1.

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