Activation of Dithiocarbamate by 2-Halothiazolium Salts

Hirohiko Sugimoto, Itsuo Makino, and Kentaro Hirai*

Shionogi Research Laboratories, Shionogi & Co., Ltd., Fukushima-ku, Osaka 553, Japan

Received August 4, 1987

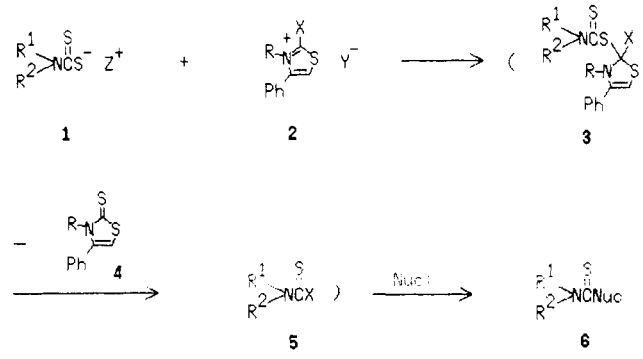
Activation of dithiocarbamate salts with 2-halo-3-alkyl-4-phenylthiazolium salt and subsequent one-pot nucleophilic reaction with N, S, and O nucleophiles provided substituted thioureas, dithiocarbamates, and thiocarbamates or amides, respectively, under very mild conditions. A useful thiocarbonyl-transfer reaction is also described that consists of activation of imidazolodithiocarbamate and a subsequent one-pot nucleophilic reaction. (Thiocarbonyl)diimidazole is generated in situ.

Activation of carboxylic acids followed by nucleophilic reaction with alcohol or amine to give esters or amides, respectively, is a fundamental synthetic strategy. Thioureas, thiocarbamates, and dithiocarbamates have generally been prepared by initial preparation of the thiocarbamoyl chloride (eq 1).

$$R_2NH + CSCl_2 \rightarrow R_2NC(=S)Cl \xrightarrow{Nuc:} R_2NC(=S)Nuc \quad (1)$$

We have now found that activation of the dithiocarbamate **1** with a 2-halothiazolium salt **2** can be followed by reaction in the same flask with a nucleophile to give thiocarbamoyl derivatives **6** (Scheme I).

Scheme I



Results and Discussion

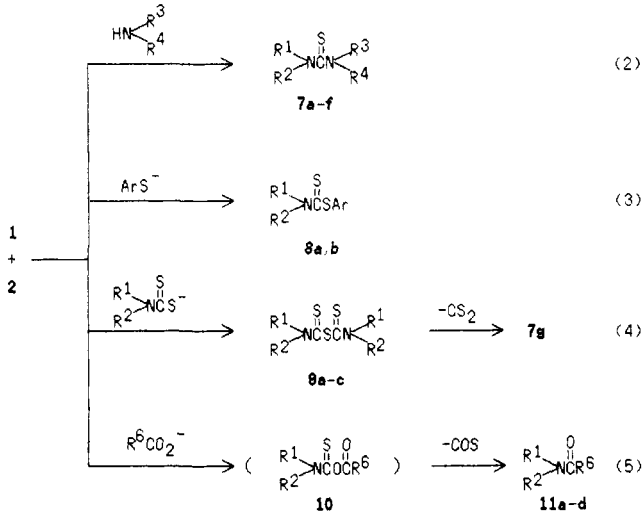
Preparation of 2-Halo-3-alkyl-4-phenylthiazolium Salts. Activation of carboxylate by the onium salt of heterocyclic azoles that bear a halogen substituent adjacent to the quaternized nitrogen atom has been used to prepare esters and amides.[1] We chose readily available 2-halothiazolium salts **2**, which were prepared in good yield by quaternization of 2-halo-4-phenylthiazole[2] with the Meerwein reagent or magic methyl in refluxing CH_2Cl_2.

Activation of N,N-Disubstituted Dithiocarbamate. Secondary amines were converted into their corresponding dithiocarbamate salt in the presence of CS_2 and base in an appropriate solvent such as THF or MeCN. Treatment with thiazolium salt **2** at 0 °C (addition of **2** to a solution of **1**) activated the dithiocarbamate salt. The structure of the activated species was not fully characterized. The formation of thiazolinethione **4** indicates that the active species is **5**, which was generated from the initial adduct **3**. Subsequent one-pot reaction with a variety of nucleophiles followed by workup, i.e., usually silica gel chromatography to separate **4**, afforded the desired product **6**. The results are summarized in Scheme II and Table I. To activate **1**, **2c** was less effective than **2a** and **2b**. A one-pot reaction of the active species with primary or secondary amines afforded tri- or tetrasubstituted thioureas, respectively (eq 2). A method for preparing trisubstituted thioureas using hexamethylphosphoric triamide has been reported.[3]

When the active species is the initial adduct **3**, it is less reactive than thiocarbamoyl halide **5**.

With Et_2NH as nucleophile, **1a** was not sufficiently activated by **2c**, while **2b** gave **7d** in 50% yield. Furthermore, activation of dithiocarbamates **1b,c,e,f** with **2b** followed by nucleophilic reaction with Et_2NH was unsuccessful. In such cases, conversion of **1e,f** to silyl ester (**1g,h**)[4] followed by activation with **2** changed the nature of the activated species, and the subsequent nucleophilic reaction with Et_2NH gave **7e** and **7f** in 32% and 28% yield, respectively.

Scheme II



1	R^1	R^2	Z
1a	$PhCH_2$	Me	$HNEt_3$
1b	Ph	Me	$HNEt_3$
1c	morpholino		$HNEt_3$
1d	$PhCH_2$	Me	Na
1e	Ph	Me	Na
1f	morpholino		Na
1g	Ph	Me	$SiMe_3$
1h	morpholino		$SiMe_3$

2	R	X	Y
2a	Me	Br	FSO_3
2b	Me	Cl	FSO_3
2c	Et	Br	BF_4
2d	Et	Cl	BF_4

(1) (a) Mukaiyama, T. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 707. (b) Mukaiyama, T. *Pure Appl. Chem.* **1979**, *51*, 1337. (c) Corey, E. J.; Brunelle, D. J. *Tetrahedron Lett.* **1976**, 3409. (d) Souto-Bachiller, F.; Bates, G. S.; Masamune, S. *J. Chem. Soc., Chem. Commun.* **1976**, 719.

(2) Ralhan, N. K.; Sandu, G. S.; Sachdev, H. S.; Harang, K. S. *J. Indian Chem. Soc.* **1960**, *37*, 773; *Chem. Abstr.* **1961**, *55*, 12388*f*.

(3) Yamazaki, N.; Tomioka, T.; Higashi, F. *Synthesis* **1975**, 384.

(4) Preparation of the dithiocarbamate silyl ester by the reaction of Me_3SiCl and dithiocarbamate is described by: Breederveld, H. *Recl.: J. R. Neth. Chem. Soc.* **1962**, *82*, 276.

0022-3263/88/1953-2263$01.50/0

Table I. Reaction of 1 and 2 Followed by Nucleophile

product	R^1R^2NH	nucleophile	yield, %	
7a	$PhCH_2MeNH$[a]	$MeNH_2$	77[b]	
7b	PhMeNH	$MeNH_2$	65	
7c	morpholine	$MeNH_2$	17	47[e]
7d	$PhCH_2MeNH$	Et_2NH	50	
7e	PhMeNH	Et_2NH	0	32[f]
7f	morpholine	Et_2NH	0	28[f] 78[e]
8a	$PhCH_2MeNH$	PhSH	37	
8b	$PhCH_2MeNH$	2-MBT[c]	83	
9a	$PhCH_2MeNH$	corresponding **1**[d]	75	
9b	PhMeNH	corresponding **1**[d]	74	
9c	morpholine	corresponding **1**[d]	27	87[e]

[a] Dithiocarbamate was prepared in situ. [b] Normal addition procedure. [c] 2-MBT = 2-mercaptobenzimidazole. [d] Reaction of molar ratio of 1:2 = 2:1. [e] Inverse addition procedure. [f] Silyl ester of 1 was prepared in situ.

A third modification in the reaction conditions was examined. Activation of morpholinodithiocarbamate (**1c**) by the normal procedure gave the products in poor yield (**7c** in 17% yield and **7f** in 0% yield). When a solution of dithiocarbamate **1c** or **1f** was inversely added to the suspension of **2** in CH_2Cl_2, the active species **5** was clearly produced as the formation of **4** was monitored on TLC. Subsequent one-pot nucleophilic reaction afforded the products in much improved yields of 47% for **7c** and 78% for **7f**. Reaction of the active species with ammonia or hydrazine hydrate gave little corresponding thiourea or thiosemicarbazide. Further reaction of the product with **5** might take place in a polar solvent.[5]

Mercaptide anion reacted with active species to afford dithiocarbamate ester **8** (eq 3).

When the mixture of a molar ratio of 1:2 = 2:1 was allowed to react, the nucleophilic rection of dithiocarbamate **1** toward the active species yielded thiuram sulfide **9** (eq 4). Aliphatic amines yielded **9**, which were stable in refluxing MeCN. Base is necessary to convert **9** into **7**. For example, **7g** was obtained in 85% yield by refluxing **9a** with 2 equivalent moles of benzylmethylamine in MeCN. On the contrary, reaction with benzimidazole or imidazole carried out at low temperature gave only the elimination product (thiocarbonyl)diazole (discussed in a later section).

Of the several methods that can be used to synthesize thiuram sulfide,[6] this method seems to be a very simple one for obtaining symmetric **9**.

A similar difference in the reactivity between azole and non-azole amines for the reaction with (chlorocarbonyl)-sulfenyl chloride has recently been described, where desulfurization from the azole adduct took place with ease to give (carbonyl)diazole.[7]

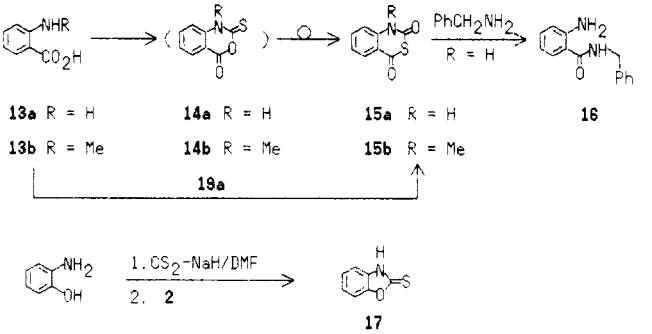
Carboxylate reacted with the active species as a nucleophile; however, the mixed anhydride **10** was not isolated. The product was found to be an amide (eq 5). Dithiocarbamate **1d** gave (benzyloxycarbonyl)glycinamide **11a** in 66% yield on activation with **2a** followed by nucleophilic reaction with Z-Gly-OCs. Activation of amine via dithiocarbamate followed by reaction of the acid salt to produce amide can be a useful synthetic tool if activation of the acid component is not accessible. Thus, we examined the activation of dithiocarbamate prepared from primary amine and its reaction with carboxylate salt.

Table II. Amide Formation through Activation of 1

amide	amine	acid salt	yield, %
11a	$PhCH_2MeNH_2$	Z-Gly-OCs	66
11b	Val-OMe	Z-Gly-OCs	50
11c	Gly-OEt	Z-Gly-OCs	45
11d	Gly-OEt	Bz-Leu-OCs	75[a]

[a] Racemization took place.

Scheme III



Treatment of the dithiocarbamate derived from Gly-OEt·HCl with **2c** in the presence of NEt_3 and CS_2 in MeCN and then with Z-Gly-OH/NEt_3 at room temperature or refluxing gave ethyl α-isothiocyanatoacetate (**12**) as the major product. However, the same reaction at refluxing temperature using the Cs salt of Z-Gly-OH gave dipeptide **11c** in 45% yield. Use of the Cs salt of the acid enhanced the nucleophilic reactivity of the carboxylate anion.[8] When a mixture of isothiocyanate **12** and Z-Gly-OH or Z-Gly-OCs was subjected to the reaction conditions of amide formation (refluxing in MeCN), no dipeptide **11c** was detected on TLC but **12** was recovered almost quantitatively. We concluded that the initial step for the formation of amide is not addition of acid to isothiocyanate, but nucleophilic attack by the carboxylate anion on the active species, e.g., thiocarbamoyl halide **5**, to yield **10** followed by elimination of COS. Addition of carboxylic acid to isothiocyanate is known to require more severe experimental conditions.[9] The Young test[10] of amide **11d** proved that complete racemization had occurred.

Intramolecular Reactions. A molecule having both an amino group and an additional nucleophilic moiety can undergo intramolecular reaction.

Activation of the amino group through dithiocarbamate and subsequent intramolecular nucleophilic attack might result in enhancement of the stability of the initial adduct of the type **10** compound. Unsubstituted anthranilic acid (**13a**) was converted into its dithiocarbamate in the presence of NEt_3 and CS_2 in MeCN, which was then treated with **2** (Scheme III). Product **15a** (mp 232–235 °C) was a result of a formal thiocarbonyl transfer; that is, its analytical data indicated that no elimination of COS had occurred. Kricheldorf[11] has described the preparation of **14a** by the reaction of *N*-(trimethylsilyl)anthranilic acid trimethylsilyl ester with thiophosgene in 80% yield, and Beam and co-workers[12] have reported the formation of **14a** (mp 239–241 °C) by the condensation of *o*-isocyanato-

(5) A marked solvent effect on the reaction of thiocarbonyl chloride with hydrazine hydrate has been reported: Klayman, D. I.; Scovill, J. J.; Bartpsevich, J. F.; Mason, C. J. *J. Med. Chem.* **1979**, *22*, 1367.

(6) (a) Braun, J. V.; Stechele, F. *Chem. Ber.* **1903**, *36*, 2275. (b) Henry, P. A.; Dehn, W. M. *J. Am. Chem. Soc.* **1950**, *72*, 2806.

(7) Walter, W.; Radke, M., *Liebigs Ann. Chem.* **1979**, 1756.

(8) (a) Wang, S. S.; Gishi, B. F.; Winter, D. P.; Markofske, R.; Kulesha, I. E.; Tzougraki, C.; Meienhofer, J. *J. Org. Chem.* **1977**, *42*, 1286. (b) Kruizinga, W. H.; Kellog, R. M. *J. Chem. Soc., Chem. Commun.* **1979**, 286.

(9) Losse, G.; Vieddige, H. *Liebigs Ann. Chem.* **1960**, *636*, 144.

(10) Williams, M. W.; Young, G. T. *J. Chem. Soc.* **1963**, 881.

(11) Kricheldorf, H. R. *Chem. Ber.* **1971**, *104*, 3156.

(12) Beam, C. F.; Heindel, N. D.; Chun, M.; Stefanski, A. *J. Heterocycl. Chem.* **1976**, *13*, 421.

Table III. Reaction of in Situ Generated 19a

product	R^1R^2NH	R^3R^4NH or R^5OH	yield, %
20a	$PhCH_2MeNH$		64
20b	PhMeNH		47
21a	$PhCH_2MeNH$	NH_3	58[a]
21b	PhMeNH	NH_3	75[a]
21c	morpholine	NH_3	48[b]
22a	$PhCH_2MeNH$	$H_2NNH_2·H_2O$	41[b]
22b	PhMeNH	$H_2NNH_2·H_2O$	74[a]
22c	morpholine	$H_2NNH_2·H_2O$	52[b]
23a	$PhCH_2MeNH$	MeOH	31[a,c]
23b	$PhCH_2MeNH$	$PhCH_2OH$	73[b]
23c	PhMeNH	MeOH	18[a,c]
23d	PhMeNH	$PhCH_2OH$	90[a]
7h	PhMeNH	piperidine	88[a]
24a		$PhCH_2OH$	46
24b		*m*-cresol	24[d]

[a] yield was based on **20**. [b] Yield was based on R^1R^2NH. [c] Byproduct for the reaction of **20** with NH_3–MeOH. [d] Spectroscopic yield.

benzoyl chloride with thioacetamide. The IR spectrum of product **15a** was identical with that of the rearranged 3,1-benzothiazine derivative **15a**.[11]

N-Methylanthranilic acid (**13b**) gave rearranged **15b** in poor yield (only trace) under the same conditions as for **13a**. The structure of **15b** was confirmed by comparing the spectroscopic data of it with those of the product obtained from methylation of **15a** with NaH–MeI in DMF (93% yield). The difference in the reactivity between **13a** and **13b** is likely to be due to the difference in the formation step of dithiocarbamate under the same conditions.

o-Aminophenol also afforded a thiocarbonyl-transferred product **17** in 47% yield upon treatment with CS_2 and 2 equivalent moles of NaH followed by the reaction with **2**. These thiocarbonyl-transfer reactions to the substrate, which contains both amino and nucleophilic groups or two nucleophilic substituents, can be accomplished more effectively by using (thiocarbonyl)diimidazole prepared in situ, and this is discussed in the next section.

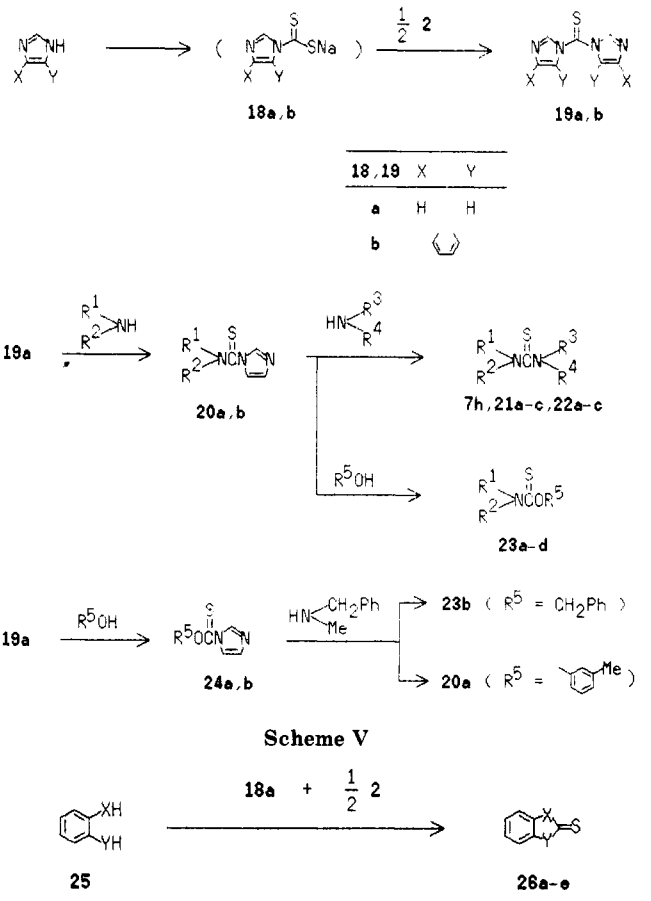
Aminolysis of **15a** with benzylamine took place at the carbonyl carbon followed by loss of COS, producing amide **16** in 36% yield. The same behavior was noted for isatoic anhydride.[13]

In Situ Generation of (Thiocarbonyl)diimidazole and Its Reaction with Nucleophiles. Imidazole or benzimidazole on activation through its dithiocarbamate **18** produced a highly versatile reagent, (thiocarbonyl)-diazole **19**, in situ. Although **19a** could not be identified by isolation on silica gel chromatography due to its decomposition, its behavior on TLC was identical with that of the authentic sample. Synthetic application of **19a** is discussed below. Treatment of imidazole with NaH and CS_2 in THF at 0 °C for 20 min followed by reaction with 0.5 equiv of **2** at ambient temperature for 1 h gave an orange reaction mixture. The structure of the orange product as (thiocarbonyl)diimidazole (**19a**) was indicated by TLC. The R_f of **19a** was identical with that of (thiocarbonyl)diimidazole. We could not separate **19a** from **4** by silica gel chromatography due to its instability on the SiO_2 column and performed the subsequent nucleophilic reaction of **19a** without isolating **4**. With benzimidazole as the starting amine, (thiocarbonyl)dibenzimidazole (**19b**) was isolated in 75% yield without any stability problem on silica gel chromatography.

Carbonyl- or (thiocarbonyl)diimidazole has been thus far prepared by the reaction of phosgene or thiophosgene with imidazole or silylated imidazole.[14] The 2-halo-

(13) Coppola, G. M. *Synthesis* **1980**, 505.

Scheme IV



Scheme V

thiazolium salt method has the advantage that hazardous thiophosgene need not be used, and reaction of **19a** prepared in situ can be carried out without difficulty. We tried a number of nucleophilic reactions with **19a** generated by our procedure. The results are summarized in Scheme IV and Table III.

Secondary amines are known to react with (thiocarbonyl)diimidazole to give imidazolide **20**.[15] Benzylmethylamine or phenylmethylamine afforded **20a** and **20b** in 64% and 47% yield, respectively, upon reaction with **19a** prepared in situ. Particularly useful reactions are those of **20** with ammonia and hydrazine hydrate. Thus one-pot reaction of imidazole, which was converted into dithiocarbamate, was treated with 0.5 equiv of **2** followed by successive nucleophilic reaction with ammonia or hydrazine hydrate, resulting in the formation of N,N-disubstituted thiourea **21** or thiosemicarbazide **22**, respectively. As known preparative methods for the type **21** thiourea are very limited,[16] this procedure is very useful for preparing **21**, which is an important starting material for a variety of heterocyclic compounds.[17] Imidazolide **20** reacts also with alcohols to yield thiocarbamate derivatives **23**. Here, **23a** and **23c** are byproducts of the reaction of **20a**

(14) (a) Staab, H. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 351. (b) Rebek, J.; McCredy, R.; Wolf, S.; Mossmann, A. *J. Org. Chem.* **1979**, *44*, 1485. (c) Ogata, M.; Matsumoto, H.; Kida, S.; Shimizu, S. *Tetrahedron Lett.* **1979**, 5011. (d) Ogata, M.; Matsumoto, H.; Kida, S.; Shimizu, S. *Heterocycles* **1980**, *14*, 955.

(15) Larsen, J.; Stelieu, K.; Harpp, N. N. *J. Org. Chem.* **1978**, *43*, 337.

(16) (a) Hartmann, H.; Reuther, I. *J. Prakt. Chem.* **1973**, *315*, 144. (b) Esmail, R.; Kurzer, F. *Synthesis* **1975**, 301. (c) Tamura, Y.; Kawasaki, T.; Adachi, M.; Kita, Y. *Chem. Pharm. Bull.* **1979**, *27*, 1636. (d) Takiyama, Y.; Inoue, N.; Sato, R.; Takizawa, S. *Chem. Lett.* **1982**, 641.

(17) Griffin, T. S.; Woods, T. S.; Klayman, D. L. *Adv. Heterocycl. Chem.* **1975**, *18*, 99.

Table IV. Thiocarbonyl-Transfer Reaction of 19a

product	X	Y	yield, %
26a	O	O	82
26b	NH	O	62
26c	NH	S	92
26d	NMe	CO_2	77[a]
26e	NH	CH_2O	74

[a] Product 26d is rearranged 15b.

and 20b with NH_3 in MeOH.

When alcohols were allowed to react with 19a prepared in situ, imidazolides 24 were obtained, although they were less stable than 20. Subsequent nucleophilic reaction of 24 with amines was dependent on the nature of the OR^5 moiety. Reaction of benzylmethylamine with 24a gave 23b, while with 24b elimination of *m*-cresol took place to yield 20a. That is, the substituent with the lower pK_a was eliminated.[18]

(Thiocarbonyl)diimidazole generated in situ can readily be used in the thiocarbonyl-transfer reaction to form a compound having two nucleophilic substituents.[14,19] The results are summarized in Scheme V and Table IV. This reaction proceeded very rapidly with 25. Reaction of 19a with 25 in THF for about 10–30 min at room temperature followed by chromatography to separate 4 afforded 26. For the thiocarbonyl-transfer reaction, the (thiocarbonyl)diimidazole method proved to be better than the intramolecular nucleophilic reaction discussed in the previous section with respect to yield, reaction time, and easiness of the procedure.

Experimental Section

Melting points are uncorrected. UV spectra were measured with a Hitachi EPS-2 spectrophotometer, IR spectra (Nujol) with a JASCO DS-403G spectrometer, NMR spectra with a Varian T-60 instrument (Me_4Si internal standard), and mass spectra with a Hitachi RMU-8GN spectrometer. Sodium hydride (50% oil dispersion) was used without removal of oil unless otherwise noted. Column chromatography was performed with Merck silica gel (70–230 mesh). Solvents used for recrystallization are given in parentheses next to the melting point.

The preparation of 7a (larger scale preparation) and 7e and the physicochemical properties of the products in this study are summarized in the Supplementary Material (see paragraph at end of paper about Supplementary Material).

2-Bromo-3-methyl-4-phenylthiazolium Fluorosulfonate (2a). To a solution of 50.0 g (208 mmol) of 2-bromo-4-phenylthiazole[2] in 200 mL of CH_2Cl_2 was added 25.0 g (219 mmol) of methyl fluorosulfonate at room temperature. The mixture was refluxed for 5 h and then cooled, and the precipitated solid was separated by filtration. Washing of the residue with hot EtOH gave 59.0 g (80.0%) of analytically pure 2a: mp 174–176 °C: NMR (DMSO-d_6) δ 3.72 (s, 3 H, Me), 7.58 (s, 5 H, Ph), 8.25 (s, 1 H, CH). Anal. Calcd for $C_{10}H_9BrFNO_3S_2$: C, 33.91; H, 2.56; N, 3.95; S, 18.10. Found: C, 34.08; H, 2.67; N, 3.89; S, 18.79.

Compounds 2a–d were prepared by an analogous procedure: 2b, mp 138–139 °C, yield 81.0%; 2c, mp 109–110 °C (EtOH), yield 74.6%; 2d, mp 120–121 °C, yield (69.6%).

***N*-Benzyl-*N*,*N*'-dimethylthiourea (7a).** A mixture of 282 mg (2.33 mmol) of benzylmethylamine, 0.330 mL of NEt_3, and 0.4 mL of CS_2 in 5 mL of MeCN was stirred for 50 min at −5 °C. The mixture was cooled to −25 °C, and 850 mg (2.40 mmol) of 2a was added portionwise. The suspended mixture was stirred for 30 min at −25 to +20 °C, and excess $MeNH_2$ (30% MeOH solution, about 1 mL) was added. The colorless mixture was stirred overnight at room temperature. The solvent was removed in vacuo, and the residue was dissolved in AcOEt and H_2O. The organic layer was separated, dried, and concentrated in vacuo followed by chromatography with ether as the eluant. 3-Methyl-4-phenyl-4-thiazoline-2-thione (4a) was eluted with a yield of 439 mg (91.0%): mp 126–127 °C (EtOH). After the forerun of 4a, elution gave 7a (350 mg, 77.0%); mp 84.8 °C (EtOH; lit.[20] mp 87 °C).

***S*-Phenyl *N*-Benzyl-*N*-methyldithiocarbamate (8a).** A mixture of 282 mg (2.33 mmol) of benzylmethylamine, 0.330 mL of NEt_3, and 0.4 mL of CS_2 in 5 mL of MeCN was stirred for 50 min at 0 °C, and the solvent was removed in vacuo. The residue was again suspended in 5 mL of MeCN, and the mixture was cooled to −20 °C followed by addition of 850 mg (2.40 mmol) of 2a. The cooling bath was removed, and the mixture was stirred for 50 min at room temperature. This solution was added to a suspension of NaSPh in THF, which was prepared from 115 mg of NaH and 0.250 mL (2.40 mmol) of thiophenol in 5 mL of THF. The mixture was stirred overnight at room temperature. The solvent was removed in vacuo, and the residue was extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried, and concentrated. The crude product was separated on chromatography with CH_2Cl_2–CCl_4 (1:1 (v/v)) as the eluant and yielded 234 mg (36.7%) of 8a as an oil.

***N*,*N*'-Dibenzyl-*N*',*N*'-dimethylthiuram Sulfide (9a).** A mixture of 282 mg (2.33 mmol) of benzylamine, 0.330 mL of NEt_3, and 0.4 mL of CS_2 in 5 mL of MeCN was stirred for 50 min at 0 °C, and the solvent was removed in vacuo. The residue was taken up in 5 mL of MeCN, and the mixture was cooled to −20 °C followed by addition of 425 mg (1.20 mmol) of 2a. The cooling bath was removed, and the mixture was allowed to warm to room temperature with stirring for 1 h. The solvent was removed in vacuo, and the residue was extracted with AcOEt. The organic layer was washed with H_2O, separated, dried, and concentrated. The crude product was separated on column chromatography with ether–*n*-hexane (1:3 (v/v)) as eluant and afforded 314 mg (75.1%) of 9a: mp 98–100 °C (EtOH).

***N*,*N*'-Dibenzyl-*N*,*N*'-dimethylthiourea (7g) from 9a.** A mixture of 100 mg (0.28 mmol) of 9a and 68 mg (0.56 mmol) of benzylamine in 0.3 mL of MeCN was refluxed for 2 h, cooled, and concentrated. The residual oil was extracted with $CHCl_3$, washed with H_2O, and concentrated. The residue was separated on column chromatography with CH_2Cl_2 as eluant, giving 60 mg (75%) of 7g as an oil.

DL-(Benzoylleucyl)glycine Ethyl Ester (11d). To a cooled solution of 284 mg (2.03 mmol) of Gly-OEt·HCl in 4 mL of MeCN were added 0.56 mL of NEt_3 and 0.5 mL of CS_2 at −10 °C. The mixture was stirred for 1 h at −10 °C, and 770 mg (2.17 mmol) of 2c was added. After the mixture was stirred for 10 min at −10 °C, 750 mg (2.04 mmol) of Bz-Leu-OCs, prepared as described by Wang et al.,[8] was added. The resulting mixture was stirred overnight at room temperature. The solvent was removed in vacuo, and the residue was extracted with AcOEt. The organic layer was washed with H_2O, separated, dried, and concentrated. The remaining crude product was separated on chromatography with ether as eluant, giving 490 mg (75.3%) of 11d: mp 145–146 °C (AcOEt–*n*-hexane; lit.[10] mp 146 °C).

3,1-Benzothiazine-2,4-dione (15a). A mixture of 227 mg (1.66 mmol) of anthranilic acid, 0.46 mL of NEt_3, and 0.5 mL of CS_2 in 5 mL of MeCN was stirred for 50 min at room temperature. After the mixture was cooled to −20 °C, 600 mg (1.69 mmol) of 2c was added. The mixture was allowed to warm to room temperature and then stirred for 5 h. The solvent was removed in vacuo and chromatography of the residue, first with CH_2Cl_2 to remove 4b and then with AcOEt, gave 224 mg (81%) of 15a; mp 232–233 °C (AcOEt). The IR spectrum was identical with that of a sample prepared as previously described.[11]

***o*-Amino-*N*-benzylbenzamide (16).** A mixture of 220 mg (1.23 mmol) of 15a and 0.14 mL of benzylamine in 6 mL of CH_2Cl_2 was stirred for 3 days at room temperature. Excess ether was added and the mixture was filtered off. The filtrate was concentrated and recrystallization of the residue from EtOH gave 100 mg (36%) of 16: mp 124–125 °C (EtOH).

2(3*H*)-Benzoxazolethione (17). Sodium hydride (250 mg) was washed with *n*-hexane and suspended in 6 mL of DMF, and

(18) Displacement reaction of trithiocarbonate with amines is described by: Howves, P. D.; Pinka, M. *J. Chem. Soc., Perkin Trans. 1* **1980**, 762.

(19) Shanzer, A. *Angew. Chem.* **1980**, *92*, 325.

(20) Walter, W.; Rohloff, C. *Liebigs Ann. Chem.* **1975**, 295.

the mixture was cooled to 0 °C. *o*-Aminophenol (273 mg, 2.50 mmol) was added portionwise at 0 °C, the red mixture was stirred for 5 min, and 0.5 mL of CS_2 was added at −10 °C. After the mixture was stirred for 15 min, 890 mg (2.50 mmol) of **2c** was added and the cooling bath was removed. After the resulting mixture was stirred for 2 h at room temperature, it was diluted with excess AcOEt and H_2O. The organic layer was separated, dried, and concentrated. Chromatography of the residue was $CHCl_3$ as eluant gave 176 mg (47%) of **17**: mp 189–190 °C (CCl_4–$CHCl_3$).

(Thiocarbonyl)dibenzimidazole (19b). NaH (105 mg) was washed twice with *n*-hexane and then suspended in 5 mL of THF. To this was added 251 mg (2.12 mmol) of benzimidazole, and the mixture was stirred for 5 min at room temperature. After the mixture was cooled to 0 °C, 0.1 mL of CS_2 was added and the orange mixture was stirred for another 15 min. Next 383 mg (1.08 mmol) of **2a** was added and the orange-red reaction mixture was stirred for 5 h at room temperature followed by separation by filtration. The filtrate was concentrated and the residue was chromatographed. After a forerun of **4a** with CH_2Cl_2, **19b** was eluted with CH_2Cl_2–ether (1:1 (v/v)), yielding 220 mg (74.6%), which was analytically pure: mp 143–145 °C (lit.[15,21] mp 137–138, 149–150 °C).

1-(*N*-Benzyl-*N*-methylthiocarbamoyl)imidazole (20a). Sodium hydride (110 mg) was washed with *n*-hexane and then suspended in 5 mL of THF, and the mixture was cooled to 0 °C. To this were added 156 mg (2.29 mmol) of imidazole and 0.2 mL of CS_2 followed by stirring for 25 min at 0 °C. Next 355 mg (1.15 mmol) of **2b** was added and the orange mixture was stirred for 1 h at room temperature. Benzylmethylamine (0.30 mL) was added and the mixture was stirred for 1 h. The solvent was removed in vacuo, and separation of the residue on column chromatography with AcOEt as eluant gave 170 mg (64%) of **20a** as an oil. This oil product was used for subsequent reaction without further purification.

Reaction of 20a with NH_3–MeOH. A mixture of 120 mg (0.52 mmol) of **20a** in 5 mL of 11% NH_3 in MeOH was stirred overnight at room temperature. The solvent was removed in vacuo and chromatography of the residue with AcOEt as eluant gave 31 mg (31%) of **23a** as an oil and then 54 mg (58%) of **21a**; mp 144–145 °C (EtOH).

4-Benzyl-4-methylthiosemicarbazide (22a). Compound **20a** in 3.2-mmol scale of imidazole was prepared as described above. The oily **20a** was dissolved in 5 mL of MeCN, and 0.2 mL of hydrazine hydrate was added. The mixture was refluxed for 1 h, cooled, and evaporated. The residue was separated on column chromatography with AcOEt as eluant, giving 123 mg (41%) of **22a** as an oil.

***O*-Benzyl *N*-Benzyl-*N*-methylthiocarbamate (23b).** To a solution of oily **20a**, which was prepared in 3.1-mmol scale of imidazole, and 0.15 mL of benzyl alcohol in 5 mL of MeCN was added 110 mg of NaH (50% oil dispersion). The mixture was stirred for 20 min at room temperature and acidified with AcOH, dissolved in aqueous $NaHCO_3$ and AcOEt. The organic layer was separated, dried, and concentrated and then subjected to column chromatography with CCl_4–CH_2Cl_2 (5:1 (v/v)) as eluant, giving 270 mg (73%) of **23b** as an oil.

***N*-Methyl-*N*-phenylpiperidinothiourea (7h).** A solution of 153 mg (0.705 mmol) of **20b** and 0.20 mL of piperidine in 5 mL of MeCN was refluxed for 4.5 h. The solvent was removed in vacuo, and the residue was chromatographed with AcOEt as eluant, yielding 144 mg (88%) of **7h** as an oil.

1-((Benzyloxy)thiocarbonyl)imidazole (24a). To a solution of **19a**, prepared in 2.5-mmol scale of imidazole in situ, was added a suspension of $PhCH_2ONa$, which was prepared from 60 mg of NaH and 134 mg of $PhCH_2OH$ in 5 mL of THF, and the mixture was stirred for 4 h at room temperature. The solvent was removed in vacuo, and the residue was washed with CH_2Cl_2. The filtrate was concentrated and separated on chromatography with ether–CH_2Cl_2 (1:1 (v/v)) as eluant, giving 100 mg (46%) of **24a** as an unstable oil.

Treatment of **24a** with benzylmethylamine in MeCN at room temperature for 24 h gave **23b** after column separation (SiO_2, CH_2Cl_2). NMR and TLC were identical with those of **23b** given above.

Reaction of 19a with *m*-Cresol and Subsequent Aminolysis. To a solution of **19a**, prepared in 4.2-mmol scale of imidazole, was added a suspension of 200 mg of NaH and 450 mg (4.17 mmol) of *m*-cresol in 10 mL of THF at 0 °C. The heterogeneous mixture was stirred for 2 days at room temperature. The solvent was evaporated in vacuo, and the residue was extracted with $CHCl_3$. The organic layer was washed with H_2O, separated, dried, and concentrated. The NMR of the residue (750 mg) in $CDCl_3$ showed it to be a 2:1.5:1 mixture of **4a**, 1-((*m*-methylphenoxy)thiocarbonyl)imidazole (**24b**), and *m*-cresol. The yield of **24b** estimated from NMR was 24%.

A mixture of 370 mg of the above crude product (**24b**) and 118 mg of benzylmethylamine in 5 mL of MeCN was allowed to stand overnight at room temperature. Removal of the solvent followed by silica gel column chromatography with AcOEt as eluant gave 75 mg of **20a**. The NMR was identical with that of **20a** described above.

2-Thioxobenzodioxole (26a). Compound **19a** was prepared in 2.1-mmol scale with respect to imidazole. To this suspension was added 111 mg (1.00 mmol) of catechol **26a**, and the mixture was stirred for 20 min at room temperature. Evaporation of the solvent and column chromatography (CH_2Cl_2) yielded 126 mg (82%) of **26a**; mp 152–153 °C (EtOH, lit.[22] mp 154 °C).

Supplementary Material Available: Experimental method for large-scale preparation of **7a** or **7e** and physicochemical properties for the products in this study (3 pages). Ordering information is given on any current masthead page.

(21) Orth, R. E.; Localigdo, S. *J. Pharm. Sci.* **1965**, *54*, 1702.

(22) Autenrieth, A.; Hafner, H. *Chem. Ber.* **1925**, *58*, 2151.

(23) General procedure: (a) Heyningen, E. V.; Brown, C. N. *J. Med. Chem.* **1965**, *8*, 174. (b) Garin, J.; Martinez, V.; Mayoral, J.; Melendez, E.; Merchan, F. *Synthesis* **1981**, 961. (c) The sodium salt can also be prepared under anhydrous conditions by CS_2 treatment of the Na salt of the amine: Reuchschwalbe, G.; Ahlbrecht, H. *Synthesis* **1974**, 663.

(24) Poliza, A.; Zahariadi, C.; Bontea, V.; Marches, C.; Bucur, E. *Stud. Cercet. Biol., Ser. Botan.* **1965**, *17*, 93; *Chem. Abstr.* **1966**, *64*, 8061*f*.

(25) Katsoyannis, P. G. *J. Am. Chem. Soc.* **1961**, *83*, 4053.