Disulfides. 1. Syntheses Using 2,2′-Dithiobis(benzothiazole)

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2,2′-Dithiobis(benzothiazole) produces unsymmetric disulfides containing the 2-benzothiazolyl fragment in both high yield and purity when reacted with 1 equiv of a variety of alkane and arene thiols under mild conditions. In turn, these unsymmetric disulfides react with a variety of thiols to produce either symmetric disulfides or new unsymmetric disulfides in excellent yields. At room temperature, 2 equiv of most thiols are oxidized essentially quantitatively to the corresponding symmetric disulfide by 2,2′-dithiobis(benzothiazole). Thiols employed at various stages include 1-propanethiol, 2-propanethiol, 2-methyl-2-propanethiol, phenylmethanethiol, 2-mercaptoethanol, 2-mercaptoethylamine (MEA) hydrochloride, 2-methoxybenzenethiol, 4-methoxybenzenethiol, 4-aminobenzenethiol, 4-acetamidobenzenethiol, 4-bromobenzenethiol, 4-methylbenzenethiol, *N*-acetyl-L-cysteine, and sodium 2-mercaptoethanesulfonate (MESNA). Various disulfides were inactive in vivo against cyanide poisoning.

Introduction

Perusal of the literature reveals the availability of a variety of techniques for preparing both symmetric and unsymmetric disulfides, many of which are based upon the reaction of a thiol (RSH) with a sulfenylating ("sulfur-transfer") agent (R′SL).[2] Available sulfenylating agents include, but are not limited to, sulfenyl halides,[3] sulfenamides,[4] sulfenimides,[5] sulfenyl hydrazides,[6] and disulfides.[7] No single procedure is universally applicable and some have limitations which may not be obvious. For example, sequences involving sulfenyl hydrazides have yields which can be quite sensitive to reaction temperatures.[8]

$$\mathrm{RSH + R'SL \rightarrow RSSR' + HL}$$

The use of symmetric disulfides to sulfenylate thiols is especially intriguing to us since such disulfides are much more readily available and more stable under a variety of conditions than are other sulfur-transfer agents.[9] The biological/pharmaceutical implications of the thio–disulfide interchange reaction are far reaching since, among other things, this represents a route to the *in vivo* reduction of disulfides, a critical process for maintaining the redox state within and without cells,[10] and a method for latentiating thiols in prodrugs.[11,12]

A recent review[13] includes a discussion of the mechanism of thiol–disulfide interchange, concluding that the process is "a simple S_N2" reaction. In this regard, it is known that the attack of a thiol/thiolate[14] upon an unsymmetric disulfide leads to the departure of the more acidic thiol.[15] With this in mind, perhaps the most obvious drawback to the in vitro use of symmetric

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(2) For an overview see Okuyama, T. In *The Chemistry of Sulphenic Acids and their Derivatives*; Patai, S., Ed.; John Wiley: New York, 1990; Ch. 18.

(3) (a) Field, L.; Hanley, W. S.; McVeigh, I. *J. Org. Chem.* **1971**, *36*, 2735. (b) Castell, J. V.; Tun-Kyi, A. *Helv. Chim. Acta* **1979**, *62*, 2507. (c) Galpin, I. J.; Hoyland, D. A. *Tetrahedron* **1985**, *41*, 895. (d) Galpin, I. J.; Hoyland, D. A. *Tetrahedron* **1985**, *41*, 901. (e) Harris, J. F. *J. Org. Chem.* **1965**, *30*, 2190. (f) Matsueda, R.; Aiba, K. *J. Chem. Soc., Chem. Commun.* **1978**, 951. (g) Barton, D. H. R.; Choi, L. S. L.; Hesse, R. H.; Pechet, M. M.; Wilson, C. *J. Chem. Soc., Perkin Trans. 1*, **1979**, 1166.

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(8) Ternay, A. L., Jr.; Cook, C. M.; Chang, G., unpublished results. In these reactions we have found that temperature variations of ± 20 °C can lead to dramatic loss of product purity.

(9) Symmetric disulfides also can serve as precursors to other reagents which are sulfenylating agents (e.g., thiosulfinates or thiosulfonates). For a review see Oae, S. *Organic Sulfur Chemistry: Structure and Mechanism*, C.R.C. Press: Boca Raton, 1991; pp 216–253. See, also: (a) Singh, P. K.; Field, L. *J. Org. Chem.* **1988**, *53*, 2608, and references cited therein. (b) Field, L.; Parson, T. F.; Pearson, D. E. *J. Org. Chem.* **1966**, *31*, 3550. (c) Field, L.; Giles, P. M. *J. Org. Chem.* **1971**, *36*, 309. (d) Brocklehurst, K.; Brocklehurst, S. M.; Kowlessur, D.; O'Driscoll, M.; Patel, G.; Salih, E.; Templeton, W.; Thomas, E.; Topham, C. M.; Willenbrock, F. *Biochem. J.* **1988**, *256*, 543. (e) Mannervic, B.; Larson, K. *Methods Enzymology* **1981**, *71*, 420.

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(11) For a presentation of in vitro protection of thiol groups as disulfides and the corresponding in vitro deprotection see, for example, Green, T. W.; Wuts, P. G. M. *Protective Groups In Organic Synthesis*, 2nd ed.; John Wiley: New York, 1991; p 302.

(12) For example, it is known that mercaptoethylamine hydrochloride is radioprotective as are related disulfides. We suggest that the disulfide activity is derived from a thiol (or equivalent) liberated in vivo. We also have observed (unpublished results; submitted to the 16th International Symposium on the Organic Chemistry of Sulphur, Merseburg, 1994) that some disulfides may be suitable as preexposure therapies for the prevention of cyanide poisoning. To date, none of the disulfides described in the present report have exhibited significant in vivo anticyanide activity. Biological evaluations have been conducted with the assistance of the U. S. Army Medical Research and Development Command.

(13) See ref 1, pp 753–755.

(14) Since the thiolate is much more nucleophilic than is the corresponding thiol, attack is believed to be via the thiolate: Singh, R.; Whitesides, M. *J. Am. Chem. Soc.* **1990**, *112*, 1190.

(15) Freter, R.; Pohl, E. R.; Wilson, J. M.; Hupe, D. J. *J. Org. Chem.* **1979**, *44*, 1771.

(16) For an overview see, for example, Oae, S. *Organic Sulfur Chemistry: Structure and Mechanism;* C.R.C. Press: Boca Raton, **1991**; pp 296–298.

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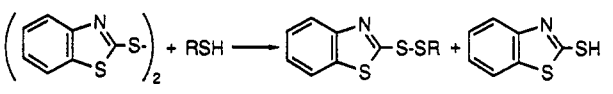
disulfides to convert thiols to unsymmetric disulfides is the potential for reversibility and the establishment of an equilibrium distribution of thiols and disulfides.[16]

Of the symmetric disulfides which have been used to convert thiols to disulfides, those that afford a rather stable, non-nucleophilic thiol byproduct are the most synthetically useful. Since some heterocyclic thiols can exist as thiono–thiolo tautomers,[17] their symmetric disulfides have proven especially useful starting materials. Most of the recently reported syntheses using this approach have concentrated upon the application of 2,2′-dipyridyl disulfide and its derivatives as sulfenylating agents.[18] For example, the reaction of 2,2′-dithiodipyridine *N,N′*-dioxide with various alkane and arene thiols provides a good route to various 2-alkyl- and 2-(aryldithio)pyridine *N*-oxides.[19] In turn, these unsymmetric disulfides can be used to sulfenylate other thiols, thus creating new unsymmetric disulfides. It has been reported[20] that activation of alkyl or aryl pyridyl disulfides with alkylating agents gave very effective sulfenylating agents. Recently, an interesting synthesis of unsymmetric disulfides using bis(1-methyl-1*H*-tetrazol-5-yl) disulfide has been described.[21] Unfortunately, it appears that among those symmetric disulfides which are frequently employed as thiol sulfenylating agents, only 2,2′-dipyridyl disulfide is commercially available.[22]

We now wish to report[23] the reaction of 2,2′-dithiobis(benzothiazole) (BTS-SBT, **1**)[24] with a variety of thiols (RSH, **2**) to prepare a range of the unsymmetric disulfides (RS-SBT, **3**) containing the 2-benzothiazolyl (BT) fragment, in both high yield and purity. Additionally, we report that these unsymmetric disulfides are, themselves, excellent precursors for the synthesis both of other unsymmetric disulfides lacking the BT moiety (i.e., RSSR′, **6**) as well as symmetric disulfides (i.e, RSSR, **7**), again in excellent yield and purity. Finally, we note that a wide variety of thiols may be directly oxidized to their symmetric disulfides, again in excellent yield, using **1**.

Results and Discussion

The reaction of **1** with 1 equivalent of various alkene and arene thiols (**2a–k**) affords the corresponding unsymmetric disulfides **3** and 2-mercaptobenzothiazole (BTSH, **4**) (eq 1). The reaction usually was carried out



BTS-SBT **1** **2** BTS-SR **3** BTSH **4** (1)

2a,3a: R = $CH_3CH_2CH_2$ **2h,3h**: R = 4-CH_3-OC_6H_4
2b,3b: R = $HOCH_2CH_2$ **2i, 3i**: R = 4-H_2N-C_6H_4
2c,3c: R = $(CH_3)_2CH$ **2j, 3j**: R = 4-Br-C_6H_4
2d,3d: R = $(CH_3)_3C$ **2k, 3k**: R = $HO_2C(NHAc)CHCH_2$
2e,3e: R = C_6H_5-CH_2 **2l, 3l**: R = $Cl^-N^+H_3CH_2CH_2$
2f, 3f: R = 4-CH_3-C_6H_4 **2m,3m**: R = 2-pyrimidyl
2g,3g: R = 2-CH_3O-C_6H_4 **2n, 3n**: R = 2-pyridyl

Table 1. Synthesis of Benzothiazolyl-Containing Disulfides BTS-SR (3)[a]

compd	product R	thiol	reaction time (h)	yield (%) (purity)[b]	mp (°C)
3a	$CH_3CH_2CH_2$-	**2a**	1	85.0 (98.3)	–
3b	$HOCH_2CH_2$-	**2b**	1	92.5 (97.4)	69–71
3c	$(CH_3)_2CH$-	**2c**	2	86.9 (98.3)	–
3d	$(CH_3)_3C$-	**2d**	6	94.9 (98.7)	83–84
3e	$C_6H_5CH_2$-	**2e**	1	91.6 (98.9)[c]	67–68
3f	4-CH_3-C_6H_4-	**2f**	2	98.4 (98.5)	50–52
3g	2-CH_3O-C_6H_4-	**2g**	1.5	93.6 (98.5)[d]	62–63
3h	4-CH_3O-C_6H_4-	**2h**	3	97.4 (96.7)[d]	61–62
3i	4-H_2N-C_6H_4-	**2i**	1	95.6 (–)	128–130
3j	4-Br-C_6H_4-	**2j**	1.5	98.7 (96.7)[e]	67–68
3k	$HO_2C(NHAc)CHCH_2$-[f]	**2k**	1.5	79.2 (–)	170–172

[a] Prepared by reacting thiol RSH **2** with **1** in chloroform at rt unless otherwise noted. See eq 1. [b] Yield isolated from 20-mmol-scale reaction. Purity assessed by HPLC using acetonitrile:water (95:5) eluent except as noted. [c] Methanol eluent. [d] Acetonitrile eluent. [e] Acetonitrile:water (9:1) eluent. [f] Reaction conducted at rt in a mixture of chloroform:ethanol:water (5:2:1).

in chloroform at room temperature and, in most cases, was complete within 2 h. For thiols which were not very soluble in chloroform, e.g., **2k**, the reaction was conducted in a mixture of chloroform, ethanol, and water. After the reaction was complete,[25] separation of byproduct **4** from the desired **3** was accomplished with an aqueous alkaline wash.[26] The data in Table 1 indicate that this procedure is successful with a wide variety of thiols and, in most cases, affords desired unsymmetric disulfides **3** in near quantitative yield. For example, HPLC analysis of the crude product from the reaction of 2-mercaptoethanol (**2b**) with **1** indicated it to be 97% of the desired unsymmetric disulfide **3b** and 1.9% of **1**. Once isolated and purified[27] all of the unsymmetric disulfides containing the BT residue were found to be stable in both air and dilute aqueous base (20 °C).

That the reaction of **1** with 1 equiv of either alkane or arene thiols is fairly rapid and affords **3** exclusively is consistent with the ability of the departing **4** to exist in tautomeric forms (thiono–thiolo) and its concomitant stability. Indeed, with many thiols the process behaves as if it were essentially irreversible. Our ability to isolate **3** in excellent yield[28] indicates that the sulfur–sulfur bond in these unsymmetric disulfides containing the BT fragment is much less electrophilic than is the sulfur–sulfur bond in **1**.[29]

BTS-SBT also reacts rapidly with heterocyclic thioamides such as 2-mercaptopyrimidine (**2m**) and 2-mercaptopyridine (**2n**). However, these reactions are not easily halted after the initial conversion to unsymmetric

(17) Of special interest are thioamides.
(18) (a) Carlsson, J.; Kierstan, M. P. J.; Brocklehurst, K. *Biochem. J.* **1974**, *139*, 221. (b) Carlsson, J.; Drevin, H.; Axen, R. *Biochem. J.* **1978**, *173*, 723. (c) Brocklehurst, K.; Malthouse, J. P. G. *Biochem. J.* **1981**, *193*, 819. (d) King, T. P.; Li, Y.; Kochoumian, L. *Biochemistry* **1978**, *17*, 1496. (e) Yee, J. K.; Parry, D. B.; Cadwell, K. D.; Haris, J. M. *Langmuir* **1991**, *7*, 307. (f) Jayasuriya, N.; Regen, S. L. *Tetrahedron Lett.* **1992**, *33*, 451.
(19) (a) Barton, D. H. R.; Chen, Ch.; Wall, G. M. *Tetrahedron* **1991**, *47*, 6127.
(20) Barton, D. H. R.; Hesse, R. H.; O'Sullivan, A. C.; Pechet, M. M. *J. Org. Chem.* **1991**, *56*, 6697.
(21) Ohtani, M., Narisada, M. *J. Org. Chem.* **1991**, *56*, 5475.
(22) For example, Aldrich Chemical Co.
(23) Presented at the 205th American Chemical Society National Meeting, Denver, CO, March, 1993, O-277.
(24) This commercially available material is quite inexpensive compared to other symmetric disulfides which have been used as sulfur-transfer agents. Other heterocyclic symmetric disulfides are being examined in our laboratories as sulfenylating agents. However, **1** appears to be the most promising to date.
(25) The reactions were monitored by TLC on silica gel.
(26) Unsymmetric disulfides containing the BT fragment could be washed with 5% aqueous base with no evidence of decomposition.
(27) Often the isolated "crude" product was sufficiently pure to use without further purification. Some gave satisfactory elemental analyses (C, H, N, and S) without any further purification.
(28) Traces of symmetric RSSR, believed to arise from the reaction of RS-SBT with RSH, were found in only a few examples.
(29) Of course, it does not follow that *all* unsymmetric disulfides containing S-SBT will be as nonreactive.

Table 2. Synthesis of Benzothiazolyl-Free Disulfides RS-SR' (6)[a]

cmpd	product RSSR'	starting RS-SBT	reaction time (h)	yield (%)[b]	mp (°C)
6ho	4-$CH_3OC_6H_4S$-SC_6H_4-(4-NHAc)	**3h**	24[c]	94.9	114–115
6fk	AcNHCH(CO_2H)CH_2S-SC_6H_4-(4-CH_3)	**3k**	4	98.1	182–186
6fk	4-$CH_3C_6H_4S$-$SCH_2CH(CO_2H)NHAc$	**3f**	24	72.7	183–186
6ak	AcNHCH(CO_2H)CH_2S-$SCH_2CH_2CH_3$	**3k**	8	96.0	111–112

[a] Prepared by reacting thiol R'SH **5** with **3** in chloroform:ethanol:water (5:2:1) at rt unless otherwise noted. See eq 2. [b] Yield isolated from 10-mmol-scale reaction. [c] Chloroform solvent.

disulfide **3** due, in part, to the similarity of the S–S bond in the desired unsymmetric disulfides (i.e., **3m** and **3n**) and of that in **1**. (This is associated with an acidity, tautomeric character, and leaving group nucleophilicity which renders **2m** and **2n** too similar to **4**.) Consequently, such reactions tend to produce mixtures of all possible products. For example, HPLC[30] analysis of the crude product of the reaction of equimolar amounts of **2m** and **1** indicated the presence of **1**, the desired unsymmetric disulfide, **3m**, 2,2'-dithiodipyrimidine (**7m**), and **4**. Compounds **3m** and **7m** were present in a ratio of approximately 1:5. Reacting **1** with a large excess of **2m** also affords a mixture. Similarly, the reaction of equimolar amounts of **1** with **2n** produced a mixture containing 2,2'-dithiopyridine (**7n**) and 2-benzothiazolyl 2-pyridyl disulfide (**3n**) in a ratio of approx. 1:2. The reaction of **1** with 2 equiv of **2n** produced similar results. To further define this limitation, the reactions of symmetric disulfides **7m** and **7n** with thiol **4** were examined. Reacting **7m** with 2 equiv of **4** yielded a mixture which included **3m** and **7m** in a ratio of 1:5. The reaction of **7n** with **4** affords a mixture which contains the unsymmetric disulfide **3n** and **7n** in a ratio of 1:2.

The unsymmetric disulfides **3** were able to sulfenylate thiols (R'SH, **5**) producing unsymmetric disulfides (RSSR', **6**) now free of BT (eq 2). High yields of **6** were obtained

BTS-SR + R'SH ⟶ RS-SR' + BTSH (2)

3 **5** **6** **4**

3h: R = 4-CH_3O-C_6H_4 **5o**: R' = AcNH-C_6H_4 **6ho**: R = 4-CH_3O-C_6H_4, R' = AcNH-C_6H_4

3k: R = AcCys **5f**: R' = 4-CH_3-C_6H_4 **6fk**: R = AcCys, R' = 4-CH_3-C_6H_4

3f: R = 4-CH_3-C_6H_4 **5k**: R' = AcCys **6fk**: R = 4-CH_3-C_6H_4, R' = AcCys

3k: R = AcCys **5a**: R' = $CH_3CH_2CH_2$ **6ak**: R = AcCys, R' = $CH_3CH_2CH_2$

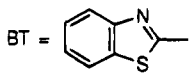
AcCys = $HO_2C(NHAc)CHCH_2$

using both aliphatic and aromatic thiols in this process. Reaction conditions were similar to those used to make series **3** (e.g., chloroform; 20 °C); however, as noted above, disulfides in set **3** are less electrophilic than is **1** and, thus, it was necessary to extend the reaction time to as much as 24 h. As an example, **3k** reacted with *p*-toluenethiol (**5f**) to afford *S*-(*p*-tolylthio)-*N*-acetyl-L-cysteine (**6fk**) in 98% yield. Our methodology permits the approach to unsymmetric disulfides from both possible directions. Thus, **6fk** also was prepared by the reaction of *N*-acetylcysteine (**5k**) with **3f**, in slightly lower yield (73%). Our results, summarized in Table 2, indicate a much higher yield of *S*-(*N*-propylthio)-*N*-acetyl-L-cysteine using the benzothiazole approach compared to a similar one involving pyridine-based unsymmetric disulfides.[31,32]

The reaction of **1** can be used to convert thiols to their symmetric disulfides, **7**. One route involves the preparation and isolation of a series **3** disulfide, RS-SBT, by the reaction of RSH with **1**, followed by its reaction with a second mole of RSH. Thus, dibenzyl disulfide (**7e**) was prepared using this two-step procedure in 95% yield.[33] A more direct path to **7** involves the oxidation of 2 mol of thiol with **1** (eq 3). By prolonging reaction times, but

BTS-SBT + 2 RSH ⟶ RS-SR + BTSH (3)

1 **2** **7** **4**

BT = 

2a,7a: R = $CH_3CH_2CH_2$
2c,7c: R = $(CH_3)_2CH$
2e,7e: R = C_6H_5-CH_2
2f,7f: R = 4-CH_3-C_6H_4
2h,7h: R = 4-CH_3O-C_6H_4
2j,7j: R = 4-Br-C_6H_4
2l,7l: R = $Cl^-N^+H_3CH_2CH_2$
2p,7p: R = $NaO_3SCH_2CH_2$

using the same conditions, this one-step route provides symmetric disulfides in excellent yields. For example, the oxidation of 4-methoxybenzenethiol (**2h**) afforded the corresponding symmetric disulfide, **7h**, in 97% yield. An interesting comparison of this route and that employing hot DMSO[34] is found in the oxidation of sodium mercaptoethanesulfonate (MESNA, **2p**). While MESNA was not cleanly converted to its symmetric disulfide when heated for 7 days at 120 °C in DMSO,[35] it was cleanly converted using **1** after only 2 h at room temperature. Results are summarized in Table 3.[36]

To date we have encountered only one aliphatic system which has not afforded an unsymmetric disulfide, **3**, in good yield when reacted with **1**. When equimolar amounts of cysteamine (MEA) hydrochloride (**2l**) and **1** were reacted, a mixture of the anticipated unsymmetric disulfide, **3l**, the symmetric cystamine dihydrochloride (**7l**), **1** and **4** was obtained. When 2 mol of **2l** was employed, the only products formed were **7l** and **4**. This result was observed whether the reaction was conducted under homogeneous (chloroform/methanol) or heterogeneous (chloroform/water) conditions. Since the procedure works

(30) Acetonitrile:water (90:10) eluent.

(31) These yields compare quite favorably to those reported by other workers, since our values reflect isolated, pure product. See, for example, the elegant work of Barton and co-workers (*Tetrahedron* **1991**, *47*, 6127).

(32) Barton, D. H. R.; Chen, C; Wall, G. M., *op. cit.*, see p 6135.

(33) This method is useful for preparing "symmetric" disulfides which differ only in isotopic distribution.

(34) (a) Yiannios, C. N.; Karabinos, J. Y. *J. Org. Chem.* **1966**, *28*, 3246. (b) Tagaki, W.; Tada, T.; Nomura, T.; Oae, S. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 1696.

(35) Cook, C. M., Ternay, A. L., Jr., unpublished results.

(36) This method fails to work with highly hindered disulfides, e.g., 2-methyl-2-propanethiol.

Table 3. Synthesis of Symmetric Disulfides RSSR (7)[a]

R	product	starting thiol	reaction time (h)	yield (%) (purity)[b]	mp/bp (°C)
$CH_3CH_2CH_2$-	**7a**	**2a**	24	82.4 (–)	88–90/30 torr[c]
$(CH_3)_2CH$-	**7c**	**2c**	168	85.8 (–)	69–70/2 torr[d]
$C_6H_5CH_2$-	**7e**	**2e**	24	98.7 (100)	71–72[e]
4-H_3C-C_6H_4-	**7f**	**2f**	24	95.5 (98.2)	45–46[f]
4-H_3CO-C_6H_4-	**7h**	**2h**	24	96.9 (100)[g]	44–45[h]
4-Br-C_6H_4-	**7j**	**2j**	6	95.7 (98.5)	94–95[i]
$H_2NCH_2CH_2$-[j]	**7l**	**2l**	2	96.9 (–)	217–220[k]
Na^+-$O_3SCH_2CH_2$-	**7p**	**2p**	2	97.1 (–)	302–303[l]

[a] Prepared by oxidation of RSH (**2**) with **1** in chloroform at rt unless otherwise noted. See eq 3. [b] Yield isolated from 20-mmol-scale reaction. When listed, purity assessed by HPLC using acetonitrile:water (90:10) eluent except as noted. [c] Literature 105–107 °C/60 torr: Ho, T. L.; Hall, T. W.; Wong, C. M. *Synthesis* **1974**, 872. [d] Literature 77–80 °C/30 torr: Field, L.; Lawson, J. E. *J. Am. Chem. Soc.* **1958**, *80*, 838. [e] Literature 72 °C: Drabowicz, J.; Mikolajczyk, M. *Synthesis* **1980**, 32. [f] Literature 46 °C: Colichman, E. L.; Love, D. L. *J. Am. Chem. Soc.* **1953**, *75*, 5736. [g] HPLC: 100% acetonitrile eluent. [h] Literature 43 °C: Drabowicz, J.; Mikolajczyk, M. *Synthesis* **1980**, 32. [i] Literature 93–94 °C: Challenger, F.; Collins, A. D. *J. Chem. Soc.* **1924**, *125*, 1377. [j] As hydrochloride. Reaction solvent chloroform:methanol (8:1, v:v) at rt. [k] Literature 203 °C: Coblentz, W.; Gabriel, S. *Chem. Ber.* **1891**, *24*, 1122. [l] Lit 277 °C: Feedoseva, V. N.; Petrun'kin, V. E. *Ukr. Khim. Zh.* **1967**, *33*, 596 (*Chem. Abstr.* **1967**, *67*, 8541).

well with 2-mercaptoethanol, it is assumed that the presence of an amine hydrochloride is responsible. This hypothesis was tested by reacting 4-methoxybenzenethiol (**2h**) with **1** in the presence of triethylamine hydrochloride. As expected, this reduced the yield of unsymmetric disulfide by at least 20% under the conditions employed.[37]

In conclusion, we report that **1** reacts with a wide variety of thiols to form unsymmetric disulfides containing the 2-benzothiazolyl moiety. In turn, these unsymmetric disulfides are, themselves, excellent reagents for the production of additional unsymmetric disulfides as well as symmetric disulfides. Procedures employing **1**, or its derived unsymmetric disulfides, are conducted under mild conditions and afford the desired products in outstanding yields.

Experimental Section

General. Melting points (uncorrected) were determined in open tubes using a capillary melting point apparatus. Infrared spectra generally were recorded in the solid state.[38] ^1H and ^{13}C NMR spectra were recorded at ambient temperature (≈32 °C) and 200 or 50.31 MHz. Chemical shifts are reported in ppm downfield from internal TMS. Combustion analyses were performed by Micro-Analysis, Inc. (Wilmington, DE). Thin layer chromatography (TLC) was conducted using silica gel plates with UV and/or iodine visualization. Reversed-phase HPLC analyses were performed with a tunable UV detector set at 254 nm, using an Econosphere C18 5U Cartridge (Alltech) column (150 × 4.6 mm) and flow rate of 2 mL/min. Mixtures of CH_3CN or MeOH (solvent A) and H_2O (solvent B) were used as the mobile phase. Reactions were conducted under nitrogen and solvents were either reagent- or HPLC-grade. All commercially available thiols and 2,2′-dithiobis(benzothiazole) were used as received.

General Procedure for the Synthesis of Unsymmetric Disulfides Containing the Benzothiazolyl Group (3). Method A (for Thiols Soluble in Chloroform). A solution of 0.02 mol of thiol **2** in 50 mL of chloroform was added, dropwise, to a well-stirred suspension of 6.64 g (0.02 mol) of 2,2′-dithiobis(benzothiazole) (**1**), in 300 mL of chloroform. Addition required about 30 min and during this time the reaction mixture became homogeneous. Stirring was continued at rt for the time listed in Table 1, i.e., until TLC did not reveal any starting material. The chloroform solution then was washed successively with 5% aqueous NaOH (2 × 50 mL) to remove **4**, water (2 × 50 mL) and then dried over anhydrous $MgSO_4$. After the drying agent was removed by filtration evaporation of the solvent in vacuo gave unsymmetric disulfide **3** which was characterized by ^1H NMR, TLC, and HPLC.

2-Benzothiazolyl n-Propyl Disulfide (3a). Reaction of **1** with 1.68 g (0.0220 mol) of 1-propanethiol (**2a**) gave, after workup, an oily residue which was dried in vacuo to yield **3a** (4.10 g, 85%) as a pale yellow oil. ^1H NMR ($CDCl_3$): 7.85 (d, 1H, J = 7.8 Hz), 7.78 (d, 1H, J = 7.3 Hz), 7.41 (dt, 1H, J = 7.8 Hz, J = 1.1 Hz), 7.30 (dt, 1H, J = 7.3 Hz, J = 1.1 Hz), 2.91 (t, 2H, J = 7.2 Hz), 1.78 (sext, 2H, J = 7.2 Hz), 1.01 (t, 3H, J = 7.2 Hz). ^{13}C NMR ($CDCl_3$): 173.2, 154.9, 135.6, 126.1, 124.4, 121.9, 121.0, 41.4, 22.3, 13.0. IR (neat): 3080, 2970, 2940, 2880, 1460, 1430, 1235, 1080, 1020, 1010, 750, and 730 cm^{-1}. Anal. Calcd for $C_{10}H_{11}NS_3$: C, 49.76; H, 4.59; N, 5.80; S, 39.85. Found: C, 49.93; H, 4.59; N, 5.73; S, 39.80.

2-Benzothiazolyl 2-Hydroxyethyl Disulfide (3b). A slurry of **1** was treated with 1.56 g (0.0200 mol) of 2-mercaptoethanol (**2b**). The reaction mixture was worked up as described above to yield 4.50 g (93%) of a pale yellow oil which solidified upon standing at rt. HPLC indicated that this crude product contained 97% of **3b** and 1.9% of **1**. Recrystallization from hexane gave 4.15 g (85%) of **3b** as off-white crystals, mp 69–71 °C. ^1H NMR ($CDCl_3$): 7.92 (d, 1H, J = 8.0 Hz), 7.78 (d, 1H, J = 8.0 Hz), 7.48 (t, 1H, J = 8.0 Hz), 7.36 (t, 1H, J = 8.0 Hz), 4.36 (s, 1H), 3.92 (t, 2H, J = 5.3 Hz), 3.10 (t, 2H, J = 5.3 Hz). ^{13}C NMR ($CDCl_3$): 171.3, 152.2, 135.4, 126.6, 125.2, 121.6, 121.2, 58.9, 42.7; IR (KBr): 3300, 1470, 1425, 1060, 1020, 1010, 760 cm^{-1}. Anal. Calcd for $C_9H_9NOS_3$: C, 44.42; H, 3.73; N, 5.76; S, 39.52. Found: C, 43.74; H, 3.55; N, 5.60; S, 39.23.

2-Benzothiazolyl Isopropyl Disulfide (3c). Starting with 1.68 g, (0.0220 mol) of 2-propanethiol (**2c**), and using the preceding procedure, an oily residue was obtained which was dried in vacuo to yield **3c** (4.2 g, 87%) as a pale yellow oil. ^1H NMR ($CDCl_3$): 7.86 (d, 1H, J = 8.0 Hz), 7.78 (d, 1H, J = 7.5 Hz), 7.42 (td, 1H, J = 8.0 Hz, J = 1.2 Hz), 7.32 (td, 1H, J = 7.5 Hz, J = 1.2 Hz), 3.29 (sep, 1H, J = 6.8 Hz), 1.40 (d, 6H, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$): 174.0, 154.8, 135.8, 126.2, 124.5, 121.9, 121.0, 42.5, 22.4. IR (neat): 3070, 2970, 2930, 2870, 1460, 1420, 1235, 1020, 1005, 755, 730 cm^{-1}. Anal. Calcd for $C_{10}H_{11}NS_3$: C, 49.76; H, 4.59; N, 5.80; S, 39.85. Found: C, 50.05; H, 4.70; N, 5.86; S, 40.09.

2-Benzothiazolyl *tert*-Butyl Disulfide (3d). The reaction of **1** with 1.80 g (0.0200 mol) of 2-methyl-2-propanethiol (**2d**) gave **3d** as a white solid (4.85 g, 95%). Recrystallization from ethanol gave 4.5 g (88%) of white crystals, mp 83–84 °C (lit.[4a] 80.5 °C). ^1H NMR ($CDCl_3$): 7.85 (d, 1H, J = 7.8 Hz), 7.77 (d, 1H, J = 7.4 Hz), 7.42 (td, 1H, J = 7.8 Hz, J = 1.2 Hz), 7.31 (td, 1H, J = 7.4 Hz, J = 1.2 Hz), and 1.42 (s, 9H). ^{13}C NMR ($CDCl_3$): 166.3, 154.9, 135.8, 126.1, 124.5, 122.1, 121.0, 50.2, and 29.9. IR (KBr): 2960, 1460, 1425, 1160, 1000, 755, and 725 cm^{-1}. Anal. Calcd for $C_{11}H_{13}NS_3$: C, 51.73; H, 5.13; N, 5.48; S, 37.66. Found: C, 51.48; H, 4.70; N, 5.32; S, 37.86.

2-Benzothiazolyl Benzyl Disulfide (3e). Using the preceding procedure, **3e** was obtained from 2.50 g (0.020 mol) of benzyl mercaptan (**2e**) as a white solid (5.30 g, 92%). Recrystallization from methanol gave 5.05 g (87%) of **3e** as white plates, mp 67–68 °C (lit.[4f] mp 64.5–65.5 °C). ^1H NMR ($CDCl_3$): 7.88 (d, 1H, J = 7.9 Hz), 7.79 (d, 1H, J = 7.7 Hz), 7.48–7.22 (m, 7H), 4.18 (s, 2H). ^{13}C NMR ($CDCl_3$): 154.6, 135.8, 135.4, 135.2, 129.5, 128.8, 128.1, 126.3, 124.7, 122.1, 121.1, 44.1. IR (KBr): 3060, 3030, 1460, 1430, 1240, 1020, 1010, 750, 700 cm^{-1}. Anal. Calcd for $C_{14}H_{11}NS_3$: C, 58.10; H, 3.83; N, 4.84; S, 33.23. Found: C, 57.78; H, 3.56; N, 4.75; S, 33.14.

2-Benzothiazolyl *p*-Tolyl Disulfide (3f). Starting with 2.56 g (0.0210 mol) of *p*-thiocresol (**2f**) and using the preceding procedure resulted in an oily residue (5.70 g, 98%). HPLC indicated that this crude product contained 99% of unsymmetric disulfide **3f** and 1% of *p*-tolyl disulfide (**7f**). The oil

(37) A detailed investigation of the utility of mercaptoethylamine hydrochloride to reduce disulfides is underway in our laboratories.

(38) Only the strongest and structurally more important peaks (ν_{max}) are listed.

crystallized from a mixture of ethyl acetate–hexane to yield 4.05 g (70%) of the desired **3f**, mp 50–52 °C. ^{1}H NMR ($CDCl_3$): 7.88 (d, 1H, J = 7.6 Hz), 7.78 (d, 1H, J = 7.9 Hz), 7.54 (d, 2H, J_{AB} = 8.1 Hz), 7.43 (td, 1H, J = 7.6 Hz, J = 1.1 Hz), 7.32 (td, 1H, J = 7.9 Hz, J = 1.1 Hz), 7.15 (d, 2H, J = 8.1 Hz), 2.32 (s, 3H). ^{13}C NMR ($CDCl_3$): 172.4, 154.5, 139.2, 135.6, 131.3, 130.1, 129.9, 126.3, 124.7, 122.0, 121.1, and 21.2. IR (KBr): 1600, 1450, 1420, 1020, 1010, 820, 760, 755 cm^{-1}. Anal. Calcd for C_{14} H_{11} N S_3: C, 58.10; H, 3.81; N, 4.84; S; 33.23. Found: C, 57.53; H, 3.74; N, 4.82; S, 32.59.

A second crop of 1.63 g, mp 44–48 °C, was obtained by evaporation of solvents from the filtrate. This was determined (HPLC) to be a mixture of **3f** (85%) and **7f** (12%).

2-Benzothiazolyl 2-Methoxyphenyl Disulfide (3g). Reaction of **1** with 2.80 g (0.0200 mol) of 2-methoxybenzenethiol (**2g**), followed by the usual workup, afforded 5.72 g (94%) of a yellowish oil which solidified while drying overnight at 0.01 torr. HPLC indicated that this crude material contained 99% of **3g** and 1.3% of bis(2-methoxyphenyl) disulfide (**7g**). Recrystallization from methanol produced 5.30 g (87%) of pure **3g** as off-white crystals, mp 62–63 °C. ^{1}H NMR ($CDCl_3$): 7.86 (d, 1H, J = 8.0 Hz), 7.74 (d, 1H, J = 7.8 Hz), 7.65 (dd, 1H, J = 7.9 Hz, J = 1.1 Hz), 7.41 (t, 1H, J = 7.8 Hz), 7.29 (t, 1H, J = 7.8), 7.27 (dt, 1H, J = 7.9 Hz, J = 1.1 Hz), 6.91 (t, 1H, J = 8.2 Hz), 6.89 (d, 1H, J = 8.2 Hz), and 3.89 (s, 3H). ^{13}C NMR ($CDCl_3$): 157.6, 154.8, 136.1, 129.8, 126.5, 126.1, 125.2, 124.5, 122.7, 122.2, 121.3, 121.1, 111.3, and 56.0. IR (KBr): 2900, 1570, 1450, 1430, 1230, 1050, 1020, 1000, 740 cm^{-1}. Anal. Calcd for $C_{14}H_{11}NOS_3$: C, 55.06; H, 3.63; N, 4.59; S, 31.49. Found: C, 54.65; H, 3.59; N, 4.53; S, 31.52.

2-Benzothiazolyl 4-Methoxyphenyl Disulfide (3h). Starting with 2.80 g (0.0200 mol) of 4-methoxybenzenethiol (**2h**), and using the preceding procedure, afforded an oily residue (5.95 g, 97%) which solidified while drying overnight at 0.01 torr. Analysis by HPLC revealed that this crude material contained 97% of desired **3h** and 2.8% of bis(4-methoxyphenyl) disulfide (**7h**). Recrystallization from ethanol produced 4.75 g (78%) of pure **3h** as off-white crystals, mp 61–62 °C. ^{1}H NMR ($CDCl_3$): 7.88 (dd, 1H, J = 7.7 Hz, J = 1.0 Hz), 7.80 (dd, 1H, J = 8.4 Hz, J = 1.0 Hz), 7.64 (d, 2H, J8.6 Hz), 7.43 (td, 1H, J = 8.4, J = 1.0), 7.33 (td, 1H, J = 7.7 Hz, J = 1.0 Hz), 6.85 (d, 2H, J = 8.8 Hz), 3.78 (s, 3H). ^{13}C NMR ($CDCl_3$): 160.9, 154.5, 135.8, 133.4, 132.7, 126.4, 125.8, 124.8, 122.2, 121.2, 115.4, 55.5. IR (KBr): 2840, 1580, 1490, 1485, 1460, 1420, 1300, 1250, 1000, 700 cm^{-1}. Anal. Calcd for C_{14}-$H_{11}NOS_3$: C, 55.06; H, 3.63; N, 4.59; S, 31.49. Found: C, 54.54; H, 3.73; N, 4.68; S, 30.91.

4-Aminophenyl 2-Benzothiazolyl Disulfide (3i). Reaction of **1** with 3.13 g (0.0250 mol) of 4-aminothiophenol (**2i**), followed by the usual workup, produced **3i** (5.55 g, 96%) as a yellow solid. TLC indicated that this crude material contained a traces of bis(4-aminophenyl) disulfide. Recrystallization from methanol yielded pure **3i** as yellow crystals (4.10 g, 71%), mp 128–130 °C. ^{1}H NMR ($CDCl_3$): 7.82 (t, 2H, J = 8.3 Hz), 7.50 (d, 2H, J_{AB} = 8.3 Hz), 7.44–7.25 (m, 2H), 6.58 (d, 2H, J_{AB} = 8.3 Hz), and 3.86 (bs, 2H). ^{13}C NMR: ($CDCl_3$) 172.8, 155.0, 148.3, 136.0, 134.3, 126.2, 124.5, 122.6, 122.2, 121.1, 115.5. IR (KBr): 3350, 3200, 1580, 1490, 1450, 1420, 1280, 1020, 1010, 750, and 720 cm^{-1}. Anal. Calcd for $C_{13}H_{10}N_2S_3$: C, 53.77; H, 3.47; N, 9.65; S, 33.12. Found: C, 53.44; H, 3.46; N, 9.43; S, 32.99.

2-Benzothiazolyl 4-Bromophenyl Disulfide (3j). Reaction of **1** with 3.78 g (0.020 mol) of 4-bromothiophenol (**2j**) afforded, after the usual workup, a light yellow solid (7.0 g, 99%). Recrystallization from ethanol produced 5.90 g (83%) of pure **3j** as white plates, mp 67–68 °C. ^{1}H NMR ($CDCl_3$): 7.89 (d, 1H, J = 7.9 Hz), 7.78 (d, 1H, J = 7.9 Hz), and 7.48–7.30 (m, 6H). ^{13}C NMR ($CDCl_3$): 154.8, 136.3, 134.3, 132.5, 131.5, 130.7, 126.4, 124.9, 124.8, 122.5, and 121.2. IR (KBr): 1460, 1430, 1390, 1070, 1010, 820, 760, and 730 cm^{-1}. Anal. Calcd for $C_{13}H_8NS_3Br$: C, 44.07; H, 2.28; N, 3.95; S, 27.15. Found: C, 43.87; H, 2.17; N, 3.91; S, 27.32.

Method B (for Thiols Insoluble in Chloroform). *S*-(2-Benzothiazolylthio)-*N*-acetyl-L-cysteine (3k). A solution of 3.26 g (0.0200 mol) of *N*-acetyl-l-cysteine (**2k**) in water (50 mL) was added, dropwise and with stirring, to a suspension of **1** (6.64 g, 0.0200 mol) in a mixture of chloroform (250 mL) and ethanol (100 mL). Stirring was continued at rt, the mixture became clear and, after 1.5 h, the reaction was complete (TLC). The organic phase was separated and the aqueous phase was washed with chloroform (50 mL). The combined organic phase was extracted with saturated solution of $NaHCO_3$ (2 × 50 mL) and then with water (50 mL). The combined aqueous extracts were acidified with 15% HCl to pH 3 (Hydrion paper). The resulting white precipitate was removed by filtration and washed with cold water (2 × 5 mL). Drying in vacuo afforded 5.2 g (79%) of a white powder, mp 166–168 °C. Recrystallization from ethanol gave 4.70 g (72%) of **3k**, mp 170–172 °C. A second crop 0.4 g (mp 170–172 °C) was obtained by reducing the volume of the filtrate. The overall yield was 5.10 g (78%). ^{1}H NMR (DMSO-d_6): 8.47 (d, 1H, J = 7.7 Hz), 8.08 (d, 1H, J = 7.7 Hz), 7.87 (d, 1H, J = 8.0 Hz), 7.50 (t, 1H, J = 7.7 Hz), 7.42 (t, 1H, J = 7.7 Hz), 4.59–4.58 (m, 1H), 3.46–3.24 (m, 2H), 1.88 (s, 3H). ^{13}C NMR (DMSO-d_6): 171.5, 171.4, 169.5, 154.6, 135.4, 126.6, 124.9, 122.0, 121.8, 51.4, 40.5, 22.4. IR (KBr): 3340, 1700, 1690, 1620, 1550, 1430, 1270, 1000, 760 cm^{-1}. Anal. Calcd for $C_{12}H_{12}N_2O_3S_3$: C, 43.89; H, 3.68; N, 8.53; S, 29.29. Found: C, 43.64; H, 3.63; N, 8.24; S, 29.57.

General Procedure for Producing Unsymmetric Disulfide RSSR' 6 from BT-SR (3) and Thiol 5. Method A (for Reagents Soluble in Chloroform). A solution of thiol **5** (0.01 mol) in 20 mL of chloroform was added at rt, dropwise and with vigorous stirring, to a solution of unsymmetric alkyl or aryl benzothiazolyl disulfide **3** (0.01 mol) in 150 mL of chloroform. During the addition the reaction mixture became homogeneous. The solution was maintained at rt and the reaction's progress monitored by TLC. As soon as the reaction was completed (approximately 24 h), the chloroform solution was washed first with 5% aqueous NaOH (2 × 20 mL) and then with water (2 × 20 mL). Drying ($MgSO_4$), followed by removal of the drying agent and evaporation of the solvent, yielded the desired unsymmetric disulfide **6**.

4-Acetamidophenyl 4-Methoxyphenyl Disulfide (6ho). The Reaction of 2-Benzothiazolyl 4-Methoxyphenyl Disulfide (3h) with 4-Acetamidothiophenol (5o). Using the preceding procedure, the reaction of 3.05 g (0.0100 mol) of 2-benzothiazolyl 4-methoxyphenyl disulfide (**3h**) with 1.68 g (0.0100 mol) of 4-acetamidothiophenol (**5o**) yielded, after workup, an oily residue (2.45 g, 95%) which solidified while drying overnight at 0.01 torr. HPLC indicated that this crude product contained 94% of unsymmetric disulfide **6ho** and 5% symmetric disulfides. The oil crystallized from a mixture of ethyl ether–hexane to yield 2.45 g (81%) of the desired **6ho**, mp 114–115 °C, which was 99.6% pure by HPLC. ^{1}H NMR ($CDCl_3$): 7.43–7.36 (m, 8H), 6.80 (d, 1H, J = 8.0 Hz), 3.77 (s, 3H), and 2.16 (s, 3H). ^{13}C NMR ($CDCl_3$): 168.3, 159.9, 137.6, 132.6, 132.3, 130.4, 128.1, 120.3, 114.7, 55.4, 24.6. IR (KBr): 1730, 1590, 1490, 1320, 1250, and 830 cm^{-1}. Anal. Calcd for $C_{15}H_{15}NS_2O_2$: C, 58.99; H, 4.95; N, 4.59. Found: C, 59.08; H, 4.78; N, 4.52.

Method B (for Reagents Insoluble in Chloroform). *S*-(*p*-Tolylthio)-*N*-Acetyl-L-Cysteine (6fk). The Reaction of S-(2-Benzothiazolylthio)-*N*-acetyl-L-cysteine (3k) with *p*-Toluenethiol (5f). A solution of *p*-toluenethiol (**5f**) (1.24 g, 0.0100 mol) in chloroform (50 mL) was added, dropwise and with stirring, to a suspension of *S*-(2-benzothiazolyl)-*N*-acetyl-L-cysteine (**3k**) (3.28 g, 0.0100 mol) in a mixture of chloroform (200 mL), ethanol (100 mL), and water (50 mL). The resulting mixture was stirred vigorously at rt and became homogeneous after 30 min. After the reaction was complete (4 h), the organic phase was separated and the aqueous phase extracted with chloroform (2 × 30 mL). The combined organic phase was washed with saturated solution of $NaHCO_3$ (2 × 50 mL) and then with water (50 mL). The combined aqueous extract was treated with 15% HCl to pH 3. The resulting white precipitate, collected by filtration and washed with cold water (2 × 5 mL), yielded 2.80 g (98%) of **6fk**, mp 170–174 °C, after drying. Recrystallization from a mixture of ethanol (50 mL) and ethyl ether (20 mL) yielded 2.60 g (91%) of product, mp 182–186 °C. ^{1}H NMR (DMSO-d_6): 8.37 (d, 1H, J = 7.8 Hz), 7.43 (d, 2H, J = 8.0 Hz) 7.21 (d, 2H, J = 8.0 Hz), 4.55–4.44 (m, 1H),

3.20–2.87 (m, 2H), 2.30 (s, 3H), and 1.85 (s, 3H). ^{13}C NMR (DMSO-d_6): 171.7, 169.2, 137.1, 132.3, 129.1, 128.2, 51.0, 39.3, 22.2, 20.4. IR (KBr): 3340, 1725, 1710, 1600, 1560, 1320, 1260, 1230, and 800 cm^{-1}. Anal. Calcd for $C_{12}H_{15}NO_3S_2$: C, 50.51; H, 5.30; N, 4.91; S, 22.47. Found: C, 50.30; H, 5.00; N, 4.91; S: 22.17.

The Reaction of 2-Benzothiazolyl *p*-Tolyl Disulfide (3f) with *N*-Acetyl-L-cysteine (5k). A solution of *N*-acetyl-L-cysteine (**5k**) (1.63 g, 0.0100 mol) in water (50 mL) was added, dropwise and with stirring, to a solution of 2-benzothiazolyl *p*-tolyl disulfide (**3f**) (2.89 g, 0.0100 mol) in a mixture of chloroform (250 mL) and ethanol (100 mL). The resulting mixture was stirred at rt until completion of the reaction (24 h) and then worked up as described above. The crude product was dried to yield 2.10 g (73%) of slightly impure **6fk**, mp 178–183 °C. Recrystallization from a mixture of ethanol-ethyl ether (3:1 v/v) afforded 1.90 g (67%) of the desired **6fk**, mp 183–186 °C. This was identical (mixed mp, TLC and spectra) to the *S*-(*p*-tolylthio)-*N*-acetyl-L-cysteine, **6fk**, prepared in the previous experiment.

***S*-(n-Propylthio)-*N*-acetyl-L-cysteine (6ak). The Reaction of *S*-(2-Benzothiazolylthio)-*N*-acetyl-L-cysteine (3k) with 1-Propanethiol (5a).** A solution of 0.76 g (0.010 mol) of 1-propanethiol (**5a**) in chloroform (50 mL) was added, dropwise and with stirring, to a suspension of *S*-(2-benzothiazolylthio)-*N*-acetyl-L-cysteine (**3k**) in a mixture of chloroform (200 mL), ethanol (100 mL), and water (50 mL). The resulting mixture was stirred vigorously at rt and became clear after 30 min. After the reaction was completed (8 h), the organic phase was separated and the aqueous phase extracted with saturated $NaHCO_3$ (2 × 50 mL) and then with water (50 mL). The combined aqueous extract was treated with 15% HCl to pH ≈ 3 and then extracted with 3 × 50 mL of chloroform. Evaporation of the solvent afforded 2.28 g (96%) of **6ak** as white crystals, mp 108–111 °C. Recrystallization from a mixture of ethyl ether/hexane yielded 2.15 g (91%) of the desired product, mp 111–112 °C. ^1H NMR ($CDCl_3$): 8.20 (brs, 1H), 6.73 (d, 1H, J = 7.1Hz), 4.95–4.84 (m, 1H), 3.38–3.12 (m, 2H), 2.69 (t, 2H, J = 7.2 Hz), 2.12 (s, 3H), 1.71 (q, 2H, J = 7.2 Hz), 0.99 (t, 3H, J = 7.2 Hz). ^{13}C NMR ($CDCl_3$): 173.2, 171.4, 52.3, 40.9, 39.8, 22.9, 22.3, 12.9; IR (KBr): 3350, 1700, 1620, 1560, 1320, 1260, 1230 cm^{-1}. Anal. Calcd for $C_8H_{15}NO_3S_2$: C, 40.49; H, 6.37; N, 5.90. Found: C, 40.53; H, 6.57; N, 5.76.

General Procedure for Oxidizing Thiols to Symmetric Disulfides 7 Using 2,2′-Dithiobis(benzothiazole). Method A (for chloroform-soluble thiols). A solution of thiol **2** (0.04 mol) in 50 mL of chloroform was added dropwise, at rt and with stirring, to a suspension of **1** (6.64 g, 0.02 mol) in 300 mL of chloroform; the solution became homogeneous during addition. The resulting solution was stirred at rt and the progress of the reaction monitored by TLC. After several hours an off-white solid began to precipitate. As soon as the reaction was completed (≈24 h), the precipitated 2-mercaptobenzothiazole (**4**)[39] was removed by filtration and washed with chloroform (10 mL). The combined filtrates were washed first with 5% aqueous NaOH (2 × 50 mL) and then water (2 × 50 mL) and ultimately dried ($MgSO_4$). Evaporation of the solvent gave virtually pure symmetric disulfide **7**. The purity of the isolated product was confirmed by HPLC while spectra (IR and/or NMR), and bp or mp, were in agreement with literature values (Table 3).

Method B (for chloroform-insoluble thiols). Disodium 2,2-Dithiobis(ethanesulfonate) (DIMESNA) (7p). A solution of 3.28 g (0.0200 mol) of sodium 2-mercaptoethanesulfonate (MESNA) (**2p**) in 100 mL of water was added to a solution of 3.32 g (0.0100 mol) of **1** in 250 mL of chloroform. The mixture was stirred vigorously and, after 2h at rt, gave a negative Ellman's test. The aqueous phase was separated and the water evaporated. The solid residue was dissolved in a mixture of methanol/water (8:2, v:v), and acetone was added to reach the cloud point. The resulting white precipitate was removed by filtration and dried to yield 3.15 g (97%) of the desired symmetric disulfide, **7p**, mp 302–303 °C dec (lit.[40] mp 277 °C).[41,42]

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(39) It was identical (mixed mp, TLC and spectral data) to an authentic sample.

(40) Feedoseva, V. N.; Petrun'kin, V. E. *Ukr. Khim. Zh.* **1967**, *33*, 596 (*Chem. Abstr.*, **1967**, *67*, 8541). We believe the mp provided in *Chem. Abstr.* to be in error since, in our labs, the disulfide of MESNA prepared by two different procedures possesses a mp of ≈303 °C.

(41) Attempted oxidation of MESNA using DMSO at ≈100 °C afforded **7p** in low yield even after several days; unpublished results.

(42) A similar oxidation of cysteamine hydrochloride (**2l**) was conducted as both a homogeneous (chloroform/methanol) and a heterogeneous (chloroform/water) process with comparable yields of cystamine dihydrochloride.