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Inexpensive, One-Pot Synthesis of Unsymmetrical Disulfides Using 1-Chlorobenzotriazole

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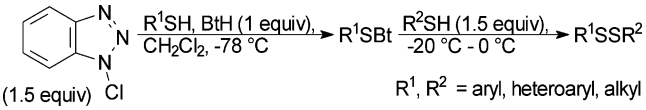

A new synthesis of unsymmetrical disulfides is described. The reaction of a thiol R^1SH with 1-chlorobenzotriazole (BtCl) at −78 °C in DCM affords a high-yielding conversion to R^1SBt without appreciable formation of the symmetrical disulfide R^1SSR^1. R^1SBt is then reacted with R^2SH to form the unsymmetrical disulfide in a one-pot sequence with green character that avoids the use of toxic and harsh oxidizing agents. The methodology has been developed for synthesis of various types of disulfides.

The synthesis of unsymmetrical disulfides is a pivotal transformation in modern medicinal chemistry research.[1] Although many different approaches exist for the transformation, the majority of them suffer from involving highly toxic reagents, such as Br_2, $SOCl_2$, and SO_2Cl_2, and/or harsh conditions of pH that promote thiol exchange reactions. Furthermore, few procedures are one-pot transformations. These drawbacks arise because the most prevalent approach involves substitution of a sulfenyl derivative with a thiol or its derivative, necessitating the preparation of the sulfenyl derivative in a separate step. Sulfenyl derivatives utilized to date include *N*-alkyltetrazolyl disulfides,[2] alkylthiodialkylsulfonium salts,[3] *S*-alkylthioisothioureas,[4] *S*-alkylthiosulfates and *S*-arylthiosulfates (Bunte salts),[5] 2-benzothiazolyl disulfides,[6] dithioperoxyesters,[7] 2-pyridyl disulfides and derivatives,[8] sulfenamides,[9] sulfenyl chlorides,[10] sulfenyldimesylamines,[11] 4-nitroarenesulfenanilides,[12] sulfenylsulfinamidines,[13] sulfenyl thiocarbonates,[14] sulfenyl thiocyanates,[15] thionitrites,[16] thioimides,[17] thiolsulfinates and thiolsulfonates,[18] and thiophosphonium salts.[19] Two popular examples that illustrate these points are the thioimide[17] and thiocarbonate[14] methodologies. Both methods involve two-step procedures, and both involve harsh reagents for the sulfenyl intermediate preparation, Br_2 or SO_2Cl_2 for the former and ClCOSCl for the latter. Other procedures of practical use involve reaction of a thiol with a sulfinylbenzimidazole,[20] sequential oxidation of thiols with barbituric acid derivatives,[21] rhodium-catalyzed exchange of a disulfide,[22] an electrochemical approach via a sulfenium cation,[23] and use of DEAD[24] in a sequential coupling of two different thiols. In conjunction with a medicinal chemistry project on garlic mimics as potentially new antimicrobial agents, it became our objective to develop a one-pot procedure involving an environmentally friendly oxidant that could be recycled in order to furnish a procedure with "green" character. We were inspired by the work of Abe[25] from the 1970s which demonstrated that *N*-chlorosuccinimide reacts with a thiol to form a sulfenyl chloride, which on addition of triethylamine subsequently reacts with the byproduct succinimide to form an *N*-sulfenylsuccinimide (Scheme 1).

From the point of view of unsymmetrical disulfide synthesis, this sequence suffers from reaction of the reactive sulfenyl

(1) (a) *Solid-Phase Synthesis*; Andreu, D., Nicolas, E., Kates, S. A., Albericio, F., Eds.; Marcel Dekker: New York, 2000; pp 365−375. (b) Vrudhula, V. M.; MacMaster, J. F.; Zhengong, L.; Kerr, D. E.; Senter, P. D. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3591−3594. (c) Mu, Y.; Nodwell, M.; Pace, J. L.; Shaw, J.-P.; Judice, J. K. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 735−738.

(2) Ohtani, M.; Narisada, N. *J. Org. Chem.* **1991**, *56*, 5475−5478.

(3) Dubs, P.; Stuessi, R. *Helv. Chim. Acta* **1976**, *59*, 1307−1311.

(4) Sirakawa, K.; Aki, O.; Tsujikawa, T.; Tsuda, T. *Chem. Pharm. Bull.* **1970**, *18*, 235−242.

(5) (a) Swan, J. M. *Nature* **1957**, *180*, 643−645. (b) Hiver, P.; Dicko, A.; Paquer, D. *Tetrahedron Lett.* **1994**, *35*, 9569−9572.

(6) (a) Ternay, A. L.; Cook, C.; Brzezinska, E. *Phosphorus, Sulfur Silicon Relat. Elem.* **1994**, *95*, 351−352. (b) Ternay, A. L.; Brzezinska, E. *J. Org. Chem.* **1994**, *59*, 8239−8244.

(7) Leriverend, C.; Metzner, P. *Synthesis* **1994**, 761−762.

(8) (a) Barton, D. H. R.; Chen, C.; Wall, M. G. *Tetrahedron* **1991**, *47*, 6127−6138. (b) Barton, D. H. R.; Hesse, R. H.; O'Sullivan, A. C.; Pechet, M. M. *J. Org. Chem.* **1991**, *56*, 6697−6702.

(9) Bao, M.; Shimizu, M. *Tetrahedron* **2003**, *59*, 9655−9659.

(10) (a) Schoberl, A.; Tausent, H.; Grafje, H. *Angew. Chem.* **1956**, *68*, 213−214. (b) Wardell, J. L.; Clarke, P. L. *J. Organomet. Chem.* **1971**, *26*, 345−352. (c) Kuliev, A. M.; Kyazim-Zade, A. K.; Guseinov, K. Z. *Azer. Khim. Zh.* **1972**, *1*, 50−52. (d) Endo, T.; Tasai, H.; Ishigami, T. *Chem. Lett.* **1975**, *8*, 813−814. (e) Harpp, D. N.; Friedlander, B. T.; Larsen, C.; Steliou, K.; Stockton, A. *J. Org. Chem.* **1978**, *43*, 3481−3485. (f) Brown, C.; Evans, G. R. *Tetrahedron Lett.* **1996**, *37*, 9101−9104.

(11) Blaschette, A.; Naveke, M. *Chem. Zeit.* **1991**, *115*, 61−64.

(12) Benati, L.; Montevecchi, P. C.; Spagnolo, P. *Tetrahedron Lett.* **1986**, *27*, 1739−1742.

(13) Koval, I. V. *Russ. J. Org. Chem.* **2002**, *38*, 232−234.

(14) Brois, S. J.; Pilot, J. F.; Barnum, H. W. *J. Am. Chem. Soc.* **1970**, *92*, 7629−7631.

(15) (a) Hiskey, R. G.; Carroll, F. I.; Babb, R. M.; Bledsoe, J. O.; Puckett, R. T.; Roberts, B. W. *J. Org. Chem.* **1961**, *26*, 1152−1155. (b) Hiskey, R. G.; Ward, B. F., Jr. *J. Org. Chem.* **1970**, *35*, 1118−1121.

(16) Oae, S.; Kim, Y. H.; Fukushima, D.; Shinhama, K. *J. Chem. Soc., Perkin Trans. 1* **1978**, 913−917.

(17) (a) Harpp, D. H.; Ash, D. K.; Back, T. G.; Gleason, J. G.; Orwig, B. A.; VanHorn, W. F.; Snyder, J. P. *Tetrahedron Lett.* **1970**, *11*, 3551−3554. (b) Boustang, K. S.; Sullivan, A. B. *Tetrahedron Lett.* **1970**, *11*, 3547−3549. (c) Klose, J.; Reese, C. B.; Song, Q. *Tetrahedron* **1997**, *53*, 14411−14416.

(18) (a) Parsons, T. F.; Buckman, J. D.; Pearson, D. E.; Field, L. *J. Org. Chem.* **1965**, *30*, 1923−1926. (b) Cragg, R.; Husband, J. P. N.; Weston, A. F. *J. Chem. Soc., Chem. Commun.* **1970**, 1701. (c) Armitage, D. A.; Clark, M. J.; Tsao, C. C. *J. Chem. Soc., Perkin Trans. 1* **1972**, 680−683. (d) Capozzi, G.; Capperucci, A.; Degl'Innocenti, A.; DelDuce, R.; Menichetti, S. *Tetrahedron Lett.* **1989**, *30*, 2995−2998. (e) Rajca, A.; Wiessler, M. *Tetrahedron Lett.* **1990**, *31*, 6075−6076.

(19) Masui, M.; Mizuki, Y.; Sakai, K.; Ueda, C.; Ohmori, H. *J. Chem. Soc., Chem. Commun.* **1984**, *13*, 843−844.

(20) Graber, D. R.; Morge, R. A.; Sih, J. C. *J. Org. Chem.* **1987**, *52*, 4620−4622.

(21) Tanaka, K.; Chen, X.; Yoneda, F. *Tetrahedron* **1988**, *44*, 3241−3249.

(22) Tanaka, K.; Ajiki, K. *Tetrahedron Lett.* **2004**, *45*, 5677−5679.

(23) Do, Q. T.; Elothmani, D.; Le Guillanton, G.; Simonet, J. *Tetrahedron Lett.* **1997**, *38*, 3383−3384.

(24) Mukaiyama, T.; Takahashi, K. *Tetrahedron Lett.* **1968**, *9*, 5907−5908.

(25) Abe, Y.; Nakabayashi, T.; Tsurugi, J. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 1898−1899.

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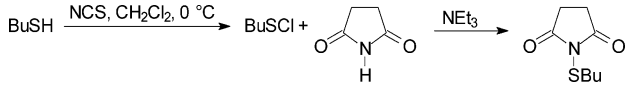
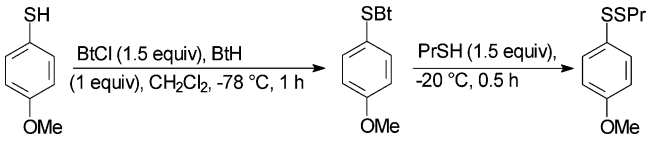
SCHEME 1. Abe's Sulfenylation of NCS[25]



SCHEME 2. Conditions for Unsymmetrical Disulfide Formation



chloride with incoming thiol (BuSH in this case) to generate homodimer disulfide. However, it suggested to us that a concise one-pot unsymmetrical disulfide synthesis might be achieved if (i) a chlorinating agent could be found to convert a thiol into an *N*-sulfenyl derivative without the intermediacy of base; (ii) experimental conditions could be identified for chemoselective formation of the *N*-sulfenyl intermediate without subsequent interception by thiol to form the symmetrical disulfide; and (iii) the *N*-sulfenyl intermediate were to efficiently react with a second thiol to form the desired unsymmetrical disulfide. In this paper, we describe such a process based on using the chemistry of 1-chlorobenzotriazole (BtCl) as the oxidizing source. The overall process achieves unsymmetrical disulfide synthesis in a one-pot reaction in a green sense since BtCl is readily prepared by oxidation of 1,2,3-benzotriazole (BtH) using sodium hypochlorite, and the BtH formed as a byproduct in the reaction can be recycled using an acid/base extraction. 1-Chlorobenzotriazole was introduced by Rees and Storr[26] in 1968 as an air-stable oxidant of alcohols, and although used in a variety of functional group transformations over the years it has found little application to thiols other than in their analytical determination.[27]

Reaction Development. In view of our interest in garlic (allicin) mimics, we began by targeting aralkyl disulfides in which one of the allyl groups in allicin is replaced by an aromatic ring and the other by an alkyl group.[28] Thus, *p*-anisylthiol and 1-propanethiol were selected for the model study. After a number of experiments, it was determined that slow addition of a solution of *p*-anisylthiol in DCM to a cold solution of BtCl (1.5 equiv) in DCM at −78 °C containing BtH (1 equiv) resulted in immediate formation of a red color that faded over time. After about 30 min, the reaction was allowed to warm to −20 °C and 1-propanethiol was added (1.5 equiv). After a further 30 min, the reaction was quenched with aqueous sodium thiosulfate with sodium bicarbonate to produce the unsymmetrical disulfide product following conventional workup and column chromatography. The overall scheme of events is summarized in Scheme 2.

TLC monitoring of the reaction revealed the complete conversion of *p*-anisylthiol in the first step to form two closely running more polar products assigned as isomeric 1-BtSR and 2-BtSR intermediates (R = *p*-MeOPh) (Figure 1).

Significantly, no significant amounts of the homodimer disulfide, di-*p*-anisyl disulfide, could be detected. The yield of

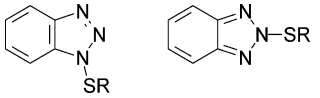


FIGURE 1. Structures of the BtSR intermediates.

TABLE 1. Additives for Unsymmetrical Disulfide Synthesis

entry	additive (equiv)[a]	yield (%)[b]
1		67
2	thiourea (1)	41
3	NEt_3 (1.5)	18
4	BtH (1)	89

[a] Relative to R^1SH. [b] Yield of disulfide as depicted in Scheme 2.

SCHEME 3. Mechanistic Course of the Reaction

the product disulfide was optimized by adding BtH (1equiv to R^1SH) into the reaction vessel containing BtCl, to assist trapping of the sulfenyl chloride intermediate. BtH turned out to be superior to other additives tested, as shown in Table 1.

These results are consistent with the simplified overall mechanistic course depicted in Scheme 3 based on Abe's reaction described previously.[25]

The mechanistic rationale in Scheme 3 draws attention to several important features of this novel one-pot disulfide synthesis. First, triethylamine is not required to promote the *N*-sulfenylation step as in the Abe reaction on account of the greater nucleophilicity of BtH compared to succinimide. Furthermore, and most importantly, the resultant *N*-sulfenyl derivative **1** is not as reactive at −78 °C as BtCl toward incoming ArSH. The in situ trapping of the sulfenyl chloride intermediate by BtH is a highlight and unique aspect of this new method as it prevents homodimer formation of the first thiol. Substitution with the second thiol is facile at around −20 °C. BtH as its hydrochloride together with the excess BtH can be recycled using an acid/base extraction (see Experimental Section), thus ensuring a cost-effective procedure with green character. It is conceivable that compound **1** exchanges its HCl with BtH, thus the nature of the exact intermediate in the disulfide formation step with the second thiol is open to speculation. Subsequent reactions to investigate the scope of the reaction were divided into the various types of disulfide.

Aralkyl Disulfide Synthesis. Aromatic thiols for this study were selected to address the influence of both steric and electronic factors on the efficacy of the process. Thus *p*-tolSH and *p*-anisylSH provided an opportunity for evaluating electron-releasing substituents, while methyl thiosalicylate was chosen as an electron-deficient system with an *ortho* steric effect. 2-Pyridylthiol was also reacted as a π-deficient heteroaromatic thiol. Reactions were run under the optimized set of conditions described previously[28] with added BtH to scavenge the initial sulfenyl chloride formed. The results are shown in Table 2.

The results reveal a number of interesting trends. First, the question of order of thiol addition arose. Adding the aliphatic thiol first resulted in formation of significant amounts of aliphatic homodimer, indicating the greater nucleophilicity of the aliphatic thiol (compared with the aromatic ones) toward

(26) Rees, C. W.; Storr, R. C. *J. Chem. Soc., Chem. Commun.* **1968**, 1305−1306.

(27) (a) Channegowda, C.; Mayanna, S. M. *Mikr. Acta* **1990**, *3*, 271−276. (b) Gowda, C. C.; Mayanna, S. M. *Talanta* **1991**, *38*, 1427−430.

(28) Hunter, R.; Caira, M.; Stellenboom, N. *Ann. N.Y. Acad. Sci.* **2005**, *1056*, 234−241.

TABLE 2. Yields of Aralkyl Disulfides

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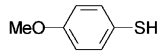
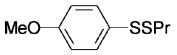
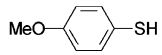
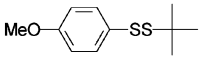
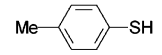
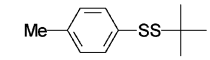
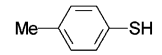
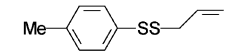
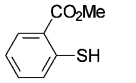
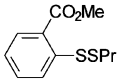
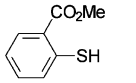
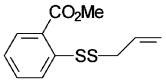
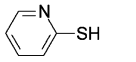
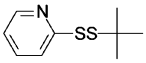
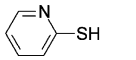
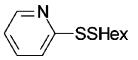
1		PrSH		89
2		*t*-BuSH		79
3		*t*-BuSH		81
4		allylSH		60[a]
5		PrSH		97
6		allylSH		55
7		*t*-BuSH		92
8		*n*-HexSH		91

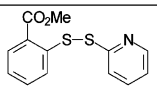
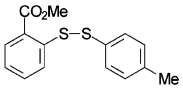
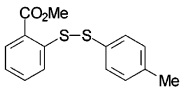
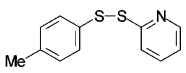
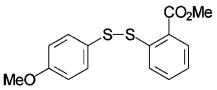
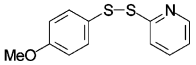
[a] Isolated as an 80:20 inseparable mixture with di-*p*-tolyl disulfide using BtCl (2 equiv).

the intermediate sulfenyl chloride. Conversely, adding the aromatic thiol first did indeed result in the formation of the unsymmetrical disulfide and in excellent yield right across the spectrum of both types of thiol except for the case of allyl, for which yields were consistently around 55−60%. Importantly, no homodimer of the aromatic thiol was observed, except for entry 4 in which di-*p*-tolyl disulfide was observed coeluting with the product as an 80:20 mixture, and even using 2 equiv of BtCl. In all cases, excess BtCl inevitably converted the excess second aliphatic thiol to its homodimer, which could be easily separated by chromatography in the nonpolar fractions. Therefore, provided that the thiols are added in the correct order, this method appears to have good scope for a number of potential coupling partners.

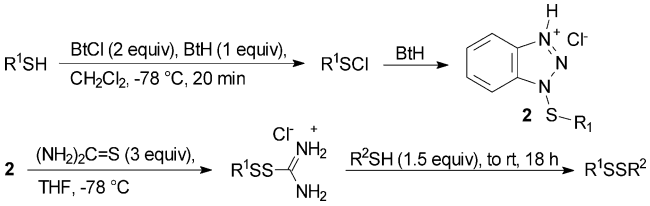
Unsymmetrical Aromatic−Aromatic Disulfide Synthesis. In this category, once again, the issue of order of thiol addition arose with some interesting results that gave valuable insight into kinetic aspects of reactions in the sequence. The ratio of the various reactants was maintained as before as BtCl:BtH: R^1SH:R^2SH = 3:2:2:3, to optimize the formation of $BtSR^1$ and minimize the formation of homodimer R^1SSR^1. Inevitably, though, the excess BtCl and R^2SH reacted to form homodimer R^2SSR^2, yields of which are not given. However, in all cases, the disulfide mixture could be separated by column chromatography. Results are given in Table 3.

Except for entry 10, yields of the unsymmetrical disulfide were excellent. In entry 10, formation of large amounts of *p*-TolSSTol (70% based on *p*-TolSH) indicated that the rate of interception of *o*-MeO_2CPhSBt by *p*-TolSH was much lower than interception of *p*-TolSBt by *p*-TolSH; hence, the second thiol was mainly channelled through to its homodimer. This presumably indicates a steric effect from the thiosalicyl intermediate coming into play with the less nucleophilic *p*-TolSH since the yield went up with the more nucleophilic 2-pyridylthiol

TABLE 3. Yields for Aromatic−Aromatic Disulfides

entry	R^1SH	R^2SH	R^1SSR^2	yield (%)
9	*o*-$MeO_2CC_6H_4SH$	2-pyridylSH		89
10	*o*-$MeO_2CC_6H_4SH$	*p*-MeC_6H_4SH		41
11	*p*-MeC_6H_4SH	*o*-$MeO_2CC_6H_4SH$		90
12	*p*-MeC_6H_4SH	2-pyridylSH		85
13	*p*-$MeOC_6H_4SH$	*o*-$MeO_2CC_6H_4SH$		88
14	*p*-$MeOC_6H_4SH$	2-pyridylSH		80

SCHEME 4. Mechanistic Course for Unsymmetrical Disulfide Synthesis Using Thiourea



(entry 9). The low yield in entry 10 could be easily rectified by simply reversing the order of addition (see entry 11) and introducing the sterically bulkier and more acidic thiol second. A small amount of homodimer (R^1SSR^1) formed from the first thiol was isolated from entry 10 (∼8%), but generally this was not a competing side reaction in other cases. Studies to evaluate the importance of exchange reactions occurring in this type of system will be reported on in a subsequent full paper.

Aliphatic−Aliphatic Disulfide Synthesis. Development of an effective protocol for reliable synthesis of this category of disulfide proved to be the most challenging of the three, as unsymmetrical disulfide and homodimers cannot be readily separated on column chromatography in nonpolar cases. As mentioned previously, reaction of an aliphatic thiol with BtCl resulted in competing interception of the intermediate sulfenyl chloride by aliphatic thiol. Eventually, a set of conditions was worked out as follows. Addition of aliphatic R^1SH to a 2-fold excess of BtCl ensured complete conversion to the desired $BtSR^1$ intermediate as inferred from TLC without any R^1SSR^1 being formed. Destruction of excess BtCl by thiourea (3 equiv) in order to avoid formation of the homodimer of the second thiol also resulted in reaction of $BtSR^1$, presumably to form an isothiouronium salt.[4] Addition of R^2SH and allowing the reaction to stir at room temperature overnight ensured complete conversion to the desired unsymmetrical disulfide without significant interference from homodimer formation as determined by NMR analysis of the product. Scheme 4 and Table 4 summarize the results. Of note is the formation of the disulfide alcohol product from entry 17, which was achieved without hydroxyl group protection.

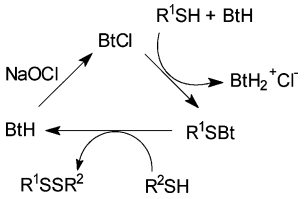
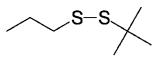
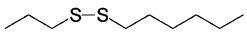
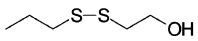


FIGURE 2. Unsymmetrical disulfide process cycle using BtCl.

TABLE 4. Yields for Dialkyl Disulfides

entry	R^1SH	R^2SH	R^1SSR^2	yield (%)
15	PrSH	*t*-BuSH		72
16	*n*-HexSH	PrSH		82
17	PrSH	$HS(CH_2)_2OH$		98

In summary, the methodology offers attractive environmentally friendly and cost-saving aspects in that effectively bleach is used as the oxidant with a carrier (BtH) that can be recycled. The latter could be achieved by chromatography (96% recovery) or using an acid/base extraction, which necessitated acidifying and stirring the aqueous solution in the presence of CH_2Cl_2 for 1 h to ensure complete extraction of the benzotriazole (99%) into the aqueous layer as its hydrochloride salt, in which case the yield of disulfide product (entry 1, Table 2) dropped to 70% (see Experimental Section). Lower stirring times diminished the benzotriazole recovery yield owing to incomplete extraction into the acidified layer. The key features of this new one-pot synthesis are summarized in Figure 2.

A subsequent paper will present studies on aspects of the scope and mechanism of the methodology as well as its application to the preparation of bioconjugates.

Experimental Section

Procedure for Aromatic−Aromatic and Aromatic−Aliphatic Disulfides as Illustrated for Entry 1 in Table 2. To a stirred solution of 1-chlorobenzotriazole (0.61 g, 4 mmol) and benzotriazole (0.32 g, 2 0.7 mmol) in CH_2Cl_2 (30 mL) under N_2 at −78 °C was added dropwise a solution of *p*-methoxybenzenethiol as R^1SH (0.37 g, 2.7 mmol) in CH_2Cl_2 (2 mL). The solution was allowed to stir for 2 h with slow warming to −20 °C. 1-Propanethiol as R^2SH (0.30 g, 4 mmol) in CH_2Cl_2 (2 mL) was then added slowly at −20 °C and the solution stirred at 0 °C for 30 min. The reaction was then quenched with a solution of $Na_2S_2O_3$ (0.50 g in 10 mL water) together with saturated aqueous $NaHCO_3$ (20 mL), with rapid stirring at 0 °C for 20 min before being extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The crude material was purified by silica gel column chromatography using light petroleum/EtOAc mixtures to afford *p*-methoxyphenyl 1-propyl disulfide (entry 1, 0.515 g, 2.4 mmol, 89%) as a pale-yellow oil. IR ($CHCl_3$): ν_{max} 495 cm^{-1} (S−S). ^1H NMR (400 MHz, $CDCl_3$): δ 0.96 (t, J = 7.3 Hz, 3H), 1.70 (sextet, J = 7.3 Hz, 2H), 2.71 (t, J = 7.3 Hz, 2H), 3.80 (s, 3H), 6.86 (d, J = 8.9 Hz, 2H), 7.48 (d, J = 8.9 Hz, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 13.1, 22.1, 40.9, 55.4, 114.6, 128.6, 131.6, 159.5. HRMS: calcd for $C_{10}H_{14}OS_2$ $(M)^+$, 214.0486; found, 214.0487. Further elution produced recovered benzotriazole (0.77 g, 6.4 mmol, 96%), mp 96−97 °C (lit[26] 98−99 °C) with ^1H and ^{13}C NMR spectra identical to those of an authentic sample. The benzotriazole could also be recovered by an acid/base extraction procedure. Thus, following reaction with 1-propanethiol, the reaction was quenched with a solution of $Na_2S_2O_3$ (0.50 g in 10 mL water) and then acidified with excess concentrated HCl to pH 1, stirred for 1 h in a two-phase system with CH_2Cl_2 (100 mL) and then extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$, dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The crude material was purified by chromatography using light petroleum/EtOAc mixtures to afford *p*-methoxyphenyl 1-propyl disulfide (0.40 g, 1.87 mmol, 70%). The aqueous layer was basified with solid Na_2CO_3 to pH 8 and extracted with CH_2Cl_2 (5 × 70 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure to give benzotriazole (0.79 g, 6.64 mmol, 99%), mp 96−97 °C (lit[26] 98−99 °C) with ^1H and ^{13}C NMR spectra identical to those of an authentic sample.

Procedure for Aliphatic−Aliphatic Disulfide Synthesis as Illustrated for Entry 15 in Table 4. To a stirred solution of 1-chlorobenzotriazole (0.61 g, 4 mmol) and benzotriazole (0.24 g, 2 mmol) in CH_2Cl_2 (20 mL) under N_2 at −78 °C was added dropwise a solution of 1-propanethiol as R^1SH (0.15 g, 2 mmol) in CH_2Cl_2 (2 mL). After 10 min, a solution of thiourea (0.46 g, 6 mmol) in dry THF (5 mL) was added and the solution stirred for a further 10 min. *t*-Butanethiol as R^2SH (0.27 g, 3 mmol) in CH_2Cl_2 (2 mL) was added slowly at −78 °C and the solution stirred for 18 h with slow warming to room temperature. The solvent was evaporated under reduced pressure and the crude material purified directly by silica gel column chromatography using light petroleum/EtOAc mixtures to afford *tert*-butyl 1-propyl disulfide (entry 15, 0.24 g, 1.46 mmol, 73%) as a pale-yellow oil. IR ($CHCl_3$): ν_{max} 478 cm^{-1} (S−S). ^1H NMR (300 MHz, $CDCl_3$): δ 0.98 (t, J = 7.4 Hz, 3H), 1.33 (s, 9H), 1.68 (sextuplet, J = 7.3 Hz, 2H), 2.69 (t, J = 7.3 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 13.1, 22.6, 30.0, 43.0, 47.6. HRMS: calcd for $C_7H_{16}S_2$ $(M)^+$, 164.0693; found 164.0693.

Acknowledgment. We thank the South African National Research Foundation and the University of Cape Town for funding.

Supporting Information Available: Synthetic procedures, analytical and spectral characterization data (entries 2−8 in Table 2; entries 9−14 in Table 3; and entries 16 and 17 in Table 4), as well as ^1H and ^{13}C NMR spectra of all disulfides synthesized. This material is available free of charge via the Internet at http://pubs.acs.org.

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