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Direct Synthesis of Functionalized Unsymmetrical β-Sulfonamido Disulfides by Tetrathiomolybdate Mediated Aziridine Ring-Opening Reactions

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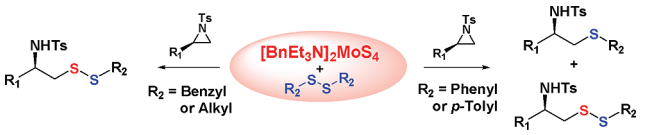

Direct synthesis of unsymmetrical β-sulfonamido disulfides by ring-opening of aziridines by using benzyltriethylammonium tetrathiomolybdate **1** as a sulfur transfer reagent in the presence of symmetrical disulfides as thiol equivalents has been reported. Reaction of benzyl and alkyl disulfides gave unsymmetrical β-sulfonamido disulfides as the only product in very good yields. From the study, it has been observed that aryl disulfides containing *p*-NO_2, *p*-Cl, and *p*-CN led to the formation of the corresponding β-aminosulfides as the exclusive products. However, unsubstituted aryl disulfides and the one containing electron-donating substituents (*p*-Me) provide a mixture of β-sulfonamido mono- and disulfides as the products.

The disulfide bond plays an important role in natural product chemistry, drug targets and in controlling and stabilizing the protein folding phenomena. These disulfides are generally unsymmetrical in nature.[1a,b] Development of new synthetic routes to unsymmetrical disulfides is challenging and has attracted considerable interest among the synthetic organic chemists for the past few decades because of their practical applications.[1] Generally, symmetrical disulfides are obtained by direct oxidation of the corresponding thiols but, in the case of unsymmetrical disulfides, oxidation of two different thiols would lead to a mixture of disulfides. In the literature, although different approaches have been reported to obtain mixed disulfides,[2,4−14] most of the methods suffer from disadvantages like harsh conditions and the disulfide−thiol exchange reaction.[3] The most prominent and widely explored methods to achieve the synthesis of mixed disulfides are via sulfenyl derivatives of a thiol, viz., sulfenyl chloride,[4] dithioperoxy ester,[5] thiosulfonates,[6] thiosulfates (Bunte salts),[7] thioimides,[8] alkylthiodialkylsulfonium salts,[9] thiocarbonates,[10] thiocyanates,[11] *N*-trifluoroacetylsulfenamides,[12] and benzotriazoles[13] of the corresponding thiols, using a variety of reagents that are capable of forming an activated intermediate. These intermediates would readily undergo nucleophilic substitution with another thiol partner to give the desired mixed disulfide. These methods involve the formation and isolation of the activated sulfenyl derivative followed by the treatment with thiols. In addition to the number of steps, the usage of free thiols is not preferred because of the handling issues.

Earlier, we reported our work on the ring-opening of aziridines in the presence of tetrathiomolybdate **1** using disulfides containing electron-withdrawing groups (*p*-NO_2, *p*-Cl) which yielded the corresponding β-sulfonamido sulfides exclusively (Scheme 1).[14e] We now report a direct synthesis of unsymmetrical β-sulfonamido disulfides mediated by benzyltriethylammonium tetrathiomolybdate $[BnNEt_3]_2MoS_4$ (**1**)[14] involving the ring-opening of aziridines by using symmetrical disulfides as thiol equivalents.

The versatility of reagent **1** in organic synthesis as a sulfur transfer agent has been explored extensively in recent years.[14] Moreover, it effects the reductive cleavage of the disulfide bond to give thiolate anion in situ which can act as a nucleophile as well.[14a] Reagents commonly reported in the literature for reducing the disulfide bond are, viz., SmI_2,[15]

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(5) Leriverend, C.; Metzner, P. *Synthesis* **1994**, 761.

(6) (a) Capozzi, G.; Capperucci, A.; Degl'Innocenti, A.; Del Duce, R.; Menichetti, S. *Tetrahedron Lett.* **1989**, *30*, 2995. (b) Rajca, A.; Wiessler, M. *Tetrahedron Lett.* **1990**, *31*, 6075.

(7) Hiver, P.; Dicko, A.; Paquer, D. *Tetrahedron Lett.* **1994**, *35*, 9569.

(8) (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. (b) Boustang, K. S.; Sullivan, A. B. *Tetrahedron Lett.* **1970**, *11*, 3547. (c) Klose, J.; Reese, C. B.; Song, Q. *Tetrahedron* **1997**, *53*, 14411.

(9) Dubs, P.; Stüssi, R. *HeIv. Chim. Acta* **1976**, *59* (4), 1307.

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

(11) (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. (b) Hiskey, R. G.; Ward, B. F. Jr. *J. Org. Chem.* **1970**, *35*, 1118.

(12) Bao, M.; Shimizu, M. *Tetrahedron* **2003**, *59*, 9655.

(13) Hunter, R.; Caira, M.; Stellenboom, N. *J. Org. Chem.* **2006**, *71*, 8268.

(14) (a) Prabhu, K. R.; Sivanand, P. S.; Chandrasekaran, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 4316. (b) Devan, N.; Ramu Sridhar, P.; Prabhu, K. R.; Chandrasekaran, S. *J. Org. Chem.* **2002**, *67*, 9417. (c) Prabhu, K. R.; Devan, N.; Chandrasekaran, S. *Synlett* **2002**, *11*, 1762. (d) Sureshkumar, D.; Koutha, S. M.; Chandrasekaran, S. *J. Am. Chem. Soc.* **2005**, *127*, 12760. (e) Sureshkumar, D.; Gunasundari, T.; Ganesh, V.; Chandrasekaran, S. *J. Org. Chem.* **2007**, *72*, 2106.

(15) Jia, X.; Zhang, Y.; Zhou, X. *Synth. Commun.* **1994**, *24*, 387.

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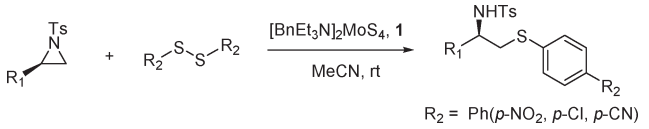
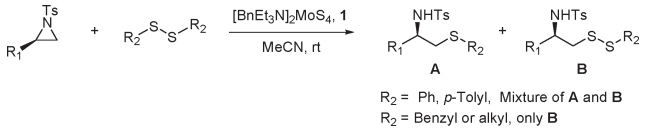
SCHEME 1. Reaction of Aryl Disulfides Bearing Electron-Withdrawing Groups with Aziridines in the Presence of 1



SCHEME 2. Reaction of Aziridines with Organic Disulfides in the Presence of 1

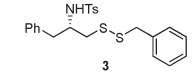
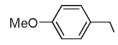
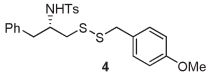
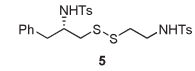
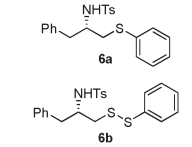
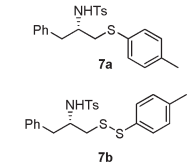
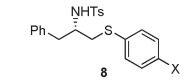


LiCl/$NaBH_4$, $ZrCl_2$/$NaBH_4$,[16] Zn/$AlCl_3$,[17] InI,[18] rongalite,[19] tranistion metal complexes,[2,20] sodium hydrogen telluride (NaHTe),[21] etc. However, these reagents suffer from disadvantages of incompatibility with other functional groups capable of undergoing reduction. The present study focuses on the reaction of alkyl disulfides with aziridines mediated by **1**. Interestingly, the reaction of alkyl disulfides with aziridines in the presence of **1** formed the β-sulfonamido disulfides **B** as the only product (Scheme 2). A detailed study of the electronic effect of substituents on the organic disulfide has been carried out to determine the product selectivity. Further, the study resulted in a versatile methodology for the synthesis of a variety of functionalized unsymmetrical disulfides.

Ring-Opening of Phenylalanine-Derived Aziridine 2 with Various Organic Disulfides Mediated by 1. Our investigation began with a study of the ring-opening of optically pure phenylalanine-derived aziridine **2** with benzyl disulfide mediated by tetrathiomolybdate **1**. Aziridine **2** (1 equiv) was treated with a well-stirred solution of benzyl disulfide (1 equiv) and tetrathiomolybdate **1** (2 equiv) in acetonitrile (28 °C, 3 h) to afford the unsymmetrical disulfide **3** as the exclusive product in 83% yield. The studies were then extended to the reaction of various alkyl and aryl disulfides with aziridine **2** in the presence of **1**. The results of this investigation are presented in Table 1.

To study the effect of substituents in the disulfide precursors on the course of the reaction, phenylalanine-derived aziridine **2** was taken as reference starting material. Reaction of aziridine **2** with *p*-methoxybenzyl disulfide and **1** (entry 2) resulted in the formation of disulfide **4** exclusively in 78% yield. Further, reaction of 2-aminoethanethiol derived disulfide (entry 3) with **1** in the presence of aziridine **2** successfully gave the corresponding mixed disulfide **5** as the only product in 80% yield. Following the results obtained, when the reaction was carried out with diphenyl disulfide (entry 4), to our surprise it resulted in an inseparable mixture of monosulfide **6a** and disulfide **6b** (72%). Similarly, with *p*-tolyl disulfide (entry 5) the reaction led to an inseparable mixture of

TABLE 1. Ring-Opening Reaction of Phenylalanine-Derived Aziridine with Various Disulfides

entry	reactant	R-S-S-R	product	time (h)	yield (%)
1				3	83
2	**2**			3	78
3	**2**			4	80
4	**2**			3	72 (6 : 1)
5	**2**			3	69 (<6 : 1)
6	**2**	 X = NO_2, Cl, CN		3	ref. 14b

monosulfide **7a** and disulfide **7b** (69%). Summing up the results from the earlier report[14b] and the present study, it clearly shows the product dependence on the electronic environment on disulfide substrates. Thus, in the case of aryl disulfides carrying electron-withdrawing substituents (entry 6)[14e] it resulted in the formation of the corresponding β-sulfonamido sulfides, whereas, other aryl disulfides led to the formation of an inseparable mixture of the corresponding mono- and disulfides (entries 4 and 5). In the case of aliphatic disulfides (entries 1−3), the reaction led to the formation of the corresponding β-sulfonamido disulfides exclusively.

Ring-Opening of Various *N*-Tosylaziridines with Benzyl Disulfides Mediated by 1. To explore this methodology further, we studied tetrathiomolybdate **1** mediated ring-opening of various monosubstituted aziridines in the presence of benzyl disulfide. Optically pure *S*-(+)-2-aminobutanol derived aziridine **9a** when treated with a mixture of benzyl disulfide and tetrathiomolybdate **1** in acetonitrile under the same reaction conditions resulted in the ring-opening of aziridine from the less hindered side following an S_N2 pathway to give the corresponding mixed disulfide **9b** in 81% yield. Similarly, various monosubstituted aziridines (**10a**−**13a**) were subjected to ring-opening with benzyl disulfide under the same conditions and in all the cases ring-opening took place at the less hindered site as expected to offer the corresponding mixed disulfides **10b**−**13b** in good yields (Table 2, entries 3−7).

3-Buten-1-ol derived aziridine **12a** on treatment with a mixture of benzyl disulfide and tetrathiomolybdate **1** furnished the corresponding mixed disulfide **12b** as a crystalline white solid in 69% yield. Similarly, when carbohydrate derived aziridine **13a**[14e] was treated with a mixture of benzyl disulfide and tetrathiomolybdate **1**, the reaction led to the formation of the carbohydrate-derived β-sulfonamido disulfide **13b** in 83% yield.

Proposed Mechanism for the Formation of β-Amino Sulfides and β-Amino Disulfides Mediated by 1. From the reactivity pattern of various aziridines toward benzyl disulfide

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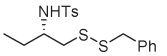
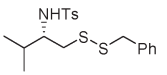
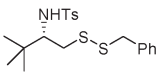
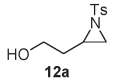
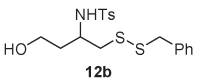
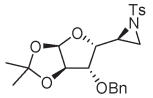
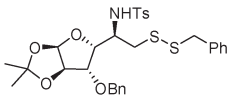
(17) Movassagh, B.; Sobhani, S.; Kheirdoush, F.; Fadaei, Z. *Synth. Commun.* **2003**, *33*, 3103.
(18) Ranu, B. C.; Mandal, T. *J. Org. Chem.* **2004**, *69*, 5793.
(19) Tang, R.; Zhong, P.; Lin, Q. *Synthesis* **2007**, *1*, 85.
(20) (a) Alexakis, A.; Normant, J. F. *Synthesis* **1985**, 72. (b) Chowdhury, S.; Roy, S. *Tetrahedron Lett.* **1997**, *38*, 2149.
(21) Kong, F.; Zhou, X. *Synth. Commun.* **1989**, *19*, 3143.

TABLE 2. Ring-Opening of Monosubstituted Aziridines with Benzyl Disulfide Mediated by Tetrathiomolybdate 1

entry	aziridines	disulfides	time (h)	yield (%)
1	 **9a**	 **9b**	3	71
2	 **10a**	 **10b**	3	72
3	 **11a**	 **11b**	3	70
4	 **12a**	 **12b**	3	69
5	 **13a**	 **13b**	3	83

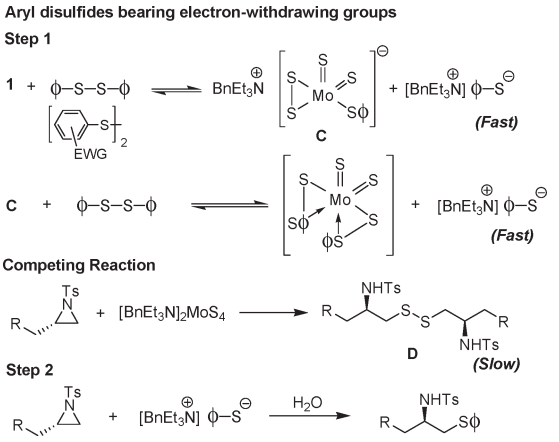
mediated by tetrathiomolybdate **1**, the formation of unsymmetrical disulfide was observed consistently. Though a detailed study of the mechanism of this interesting observation has not been carried out, a tentative mechanism has been proposed on the basis of the pioneering work of Stiefel et al.,[22] on the cleavage of aromatic disulfides mediated by tetrathiomolybdate as well as our own studies of reactivity of **1** and its utility in organic synthesis.[14] To place the present work in the right perspective the mechanism that we proposed earlier for the formation of β-sulfonamidosulfides from aziridines and aryl disulfides in the presence of **1** is discussed first.

On the basis of the investigation by Stiefel et al.[22b] on the kinetics of tetrathiomolybdate-mediated disulfide cleavage reactions, aromatic disulfides bearing electron-withdrawing groups (EWG) undergo disulfide cleavage faster than diphenyl disulfide and the equilibrium is largely shifted toward the formation of thiolate (step 1, Scheme 3). In the case of aziridine ring-opening with disulfides mediated by tetrathiomolybdate **1**, one of the competing reactions is the direct ring-opening by tetrathiomolybdate leading to the formation of a symmetrical disulfide (D).[14e] In the case of aromatic disulfides bearing EWG, since the cleavage of the disulfide with **1** is much faster than the competing aziridine ring-opening reaction, the thiolate formed in situ acts as a nucleophile to open the aziridine ring to form the β-sulfonamido sulfide as depicted in step 2, Scheme 3.

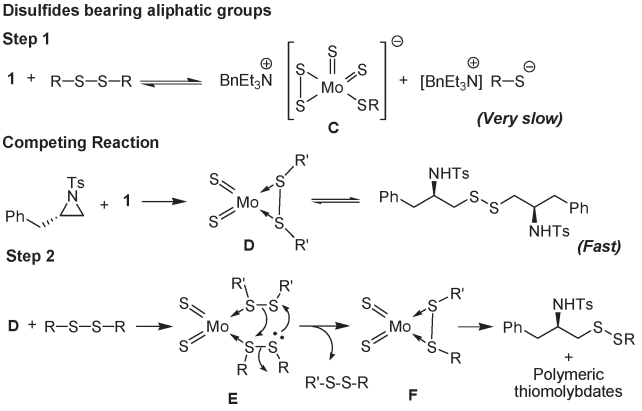
When the reaction of **1** with an aziridine in the presence of an aliphatic disulfide is carried out, the cleavage of the S−S bond is very slow (step 1, Scheme 4). Therefore, the competing direct attack of tetrathiomolybdate **1** on the aziridines takes over leading to the ready formation of symmetrical disulfide. The intermediate (D) and the aliphatic disulfide in the presence of tetrathiomolybdate **1** undergo a disulfide exchange reaction to form the unsymmetrical disulfide as the product.

(22) (a) Pan, W. H.; Harmer, M. A.; Halbert, T. R.; Stiefel, E. I. *J. Am. Chem. Soc.* **1984**, *106*, 459. (b) Coyle, C. L.; Harmer, M. A.; George, G. N.; Daage, M.; Stiefel, E. I. *Inorg. Chem.* **1990**, *29*, 14.

SCHEME 3. Proposed Mechanistic Pathway for the Formation of β-Sulfonamido Sulfides



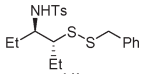
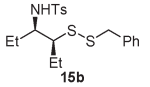
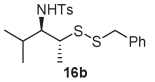
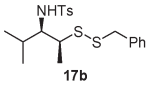
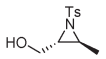
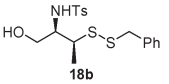
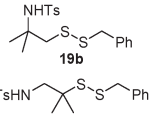
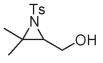
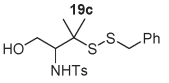
SCHEME 4. Proposed Mechanistic Pathway for the Formation of Unsymmetrical Disulfides Mediated by 1



The aromatic disulfides bearing no electron-withdrawing group (diphenyl disulfide and *p*-tolyl disulfide) fall in-between the two cases. The disulfide cleavage and the direct ring-opening of aziridine with tetrathiomolybdate **1** become equally facile, which leads to the formation of a mixture of the corresponding β-sulfonamido sulfide and β-sulfonamido disulfide.

Reactivity of Substituted Aziridines with Benzyl Disulfide in the Presence of 1. It was then decided to study the reactivity of a number of substituted aziridine derivatives. In the case of symmetrically disubstituted aziridines, the reaction was generally slower than that of the monosubstituted aziridines (Table 3, entry 1 and 2). In the case of unsymmetrically disubstituted aziridines like *cis*-isopropylmethyl-*N*-tosylaziridines **16a** and *trans*-isopropylmethyl-*N*-tosylaziridines **17a**, the ring-opening occurred generally at the less hindered side due to steric hindrance offered by the bulky isopropyl group, to yield unsymmetrical disulfide **16b** and **17b** respectively in good yields with full regio- and stereocontrol. In the same fashion, *gem*-disubstituted aziridine **19a** was expected to open from the less hindered side. But, the reaction led to a mixture of (1:1 regioisomer) unsymmetrical disulfides **19b** (78% overall conversion), due to equally facile ring-opening at the more substituted site. Then, the reaction was carried out with trisubstituted aziridine **20a**, which led

TABLE 3. Ring-Opening of Di- and Trisubstituted Aziridines with Benzyl Disulfide Mediated by 1

entry	aziridines	disulfides	time (h)	yield (%)
1	 **14a**	 **14b**	3	62
2	 **15a**	 **15b**	3	66
3	 **16a**	 **16b**	3	60
4	 **17a**	 **17b**	3	72
5	 **18a**	 **18b**	3	63
6	 **19a**	 **19b** **19c**	3	78 (1 : 1)
7	 **20a**	 **20b**	3	68

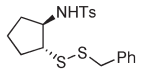
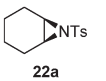
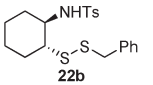
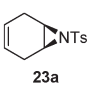
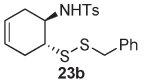
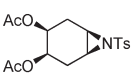
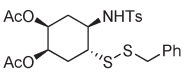
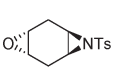
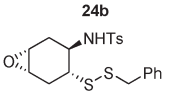
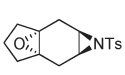
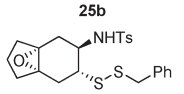
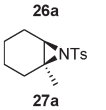
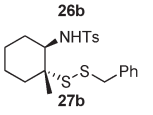
to ring-opening at the more substituted site giving **20b** as the only product in 68% yield. This kind of selectivity in the ring-opening at the more hindered site can be rationalized by considering a larger polarization of the carbon−nitrogen bond along the disubstituted side, due to the stabilization of the positive charge at the tertiary center. This facilitates the nucleophile to attack at the more substituted site with equal facility.[23]

The methodology was further explored by studying the ring-opening of aziridines attached to cyclic structures. The aziridines **21a**−**24a** and **27a** were prepared from the corresponding alkenes. When cyclopentene and cyclohexene derived aziridines **21a**−**27a** were treated with tetrathiomolybdate **1** in the presence of benzyl disulfide, as expected, the corresponding unsymmetrical disulfides **21b**−**27b** respectively were formed in good yields (Table 4). It is pertinent to mention the chemoselective ring-opening of aziridines in the presence of epoxide (entries 5 and 6) to obtain the corresponding mixed disulfides leaving the epoxide untouched. In the methylcyclohexene derived aziridine **27a**, the ring-opening took place at the more hindered side as in the case of trisubstituted aziridines to afford the mixed disulfide **27b** as the only product in 72% yield.

In the case of *gem*-disubstituted aziridines, the nucleophile ring-opening at the more hindered side has been observed. The versatility of the reaction has been demonstrated in the presence of two different functionalities. In summary, we have developed optimized conditions to the number of functionalized unsymmetrical disulfides through ring-opening of

(23) Forbeck, E. M.; Evans, C. D.; Gilleran, J. A.; Li, P.; Joullié, M. M. *J. Am. Chem. Soc.* **2007**, *129*, 14463.

TABLE 4. Ring-Opening of Cyclic Aziridines with Benzyl Disulfide Mediated by 1

entry	aziridines	disulfides	time (h)	yield (%)
1	 **21a**	 **21b**	3	76
2	 **22a**	 **22b**	3	76
3	 **23a**	 **23b**	4	78
4	 **24a**	 **24b**	3	72
5	 **25a**	 **25b**	3	75
6	 **26a**	 **26b**	3	72
7	 **27a**	 **27b**	5	72

aziridines using tetrathiomolybdate **1** in the presence of symmetrical disulfides.

Experimental Section

Typical Procedure for the Synthesis of 3. To a stirred solution of benzyl disulfide (43 mg, 0.17 mmol, 1 equiv) in CH_3CN (2 mL) was added $[BnEt_3N]_2MoS_4$ (**1**) (213 mg, 0.35 mmol, 2 equiv). The mixture was allowed to stir for 1 h, followed by the addition of a solution of **2** in acetonitrile (1 mL) in one portion. The reaction was allowed to stir for 3 h at room temperature (28 °C). When the starting material disappeared (TLC), the solvent was removed in vacuo and the residue was extracted repeatedly (3 × 5 mL) with a DCM/ether mixture (4:1). The extract was filtered through a thin pad of Celite and the filtrate was concentrated in vacuo. The reaction mixture was further purified by column chromatography to yield the mixed disulfide **3** (64 mg, yield 83%): pale yellow gummy liquid; IR (neat) ν_{max} 3280, 1497, 1326, 1157, 813, 700, 665 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, J = 8.1 Hz, 2H), 7.32−7.18 (m, 10H), 6.98−6.95 (m, 2H), 4.61 (d, J = 6.9 Hz, 1H), 3.84 (s, 2H), 3.64−3.57 (m, 1H), 2.90 (dd, J = 13.8, 6.3 Hz, 1H), 2.70 (dd, J = 13.8, 6.3 Hz, 1H), 2.54 (dd, J = 14.0, 6.0 Hz, 1H), 2.40 (dd, J = 14.0, 6.6 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.3, 136.9, 136.7, 136.3, 129.6, 129.4, 129.3, 128.6, 127.6, 127.1, 126.7, 54.1, 42.9, 42.0, 39.6, 21.5; HRMS calcd for $C_{23}H_{25}NO_2S_3$ ($M + Na^+$) 466.0945, found 466.0940.

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Supporting Information Available: ^1H, ^{13}C spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.