JOC*Note*

Optimization of the Synthesis of Symmetric Aromatic Tri- and Tetrasulfides

Eli Zysman-Colman and David N. Harpp*

Deparment of Chemistry, McGill University, Montreal, Quebec, Canada H3A 2K6

david.harpp@mcgill.ca

Received October 10, 2002

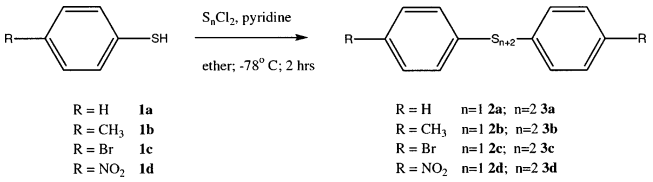
Abstract: The reaction of aromatic thiols with sulfur dichloride and sulfur monochloride to form the corresponding aromatic trisulfides, **2a**−**d**, and tetrasulfides, **3a**−**d**, has been optimized with respect to yield and purity. The use of pyridine as an amine base and the use of freshly distilled sulfur monochloride (S_2Cl_2) serve as important alterations to the synthetic method. Their physical properties have been characterized, revealing some discrepancies with the literature.

The preparation of symmetric, acyclic trisulfides is well-documented.[1] The methods include the use of sulfur dichloride[2,3] with thiols in the absence of base, the coupling of alkyl halides with sodium trisulfide,[4] mixtures of thiols[5,6] or disulfides with sulfur,[7] the reaction of a metal sulfide with alkanesulfenyl chlorides,[8] the reduction of thiosulfonates and disulfonyl sulfides with phosphines,[9] and sulfur insertion reactions into thiosulfinates, thiosulfonates,[10] sulfides, and disulfides.[11,12]

Preparation of the analogous tetrasulfides is not as well researched. To our knowledge, there exists no comprehensive study of the formation of this class. Oxidation of hydrodisulfides in the presence of iodine,[13] coupling of thiols with dialkoxy disulfides (ROSSOR),[14,15] sulfur insertion reactions,[12] and electrophilic aromatic substitution with sulfur monochloride[16] have all been reported as preparative methods.

These methods suffer from either low yields or the formation of undesirable polysulfide byproducts. Some methods require the presynthesis of appropriate precursors, which complicates the procedure.

SCHEME 1



The synthesis of unsymmetric trisulfides is more difficult. Among the known procedures are the coupling of chlorodisulfides with thiols[17,18] or similarly with *N*-arylamidthiosulfites.[19] Other methods require the use of unwieldly and often unstable hydrodisulfides (RSSH)[20] or the desulfurization of highly functionalized dialkanesulfonic thioanhydrides (RSO_2SSO_2R').[9] Stable alkyl or aryl phthalimido disulfides as sulfur transfer reagents, developed in our lab,[21] have been used as a key step in the preparation of calicheamicin γ_1^I.[22] Another procedure involves the sequential coupling of two thiols using sulfur dichloride.[23] To our knowledge, no high-yield, general method exists for the formation of unsymmetric tetrasulfides, although two such tetrasulfides were formed[23] using sulfur monochloride as the coupling reagent.

As part of another research effort dedicated to the rapid sulfurizing of oligonucleotides with these substrates, we required pure samples of a variety of symmetric polysulfides.

We report a modification of two literature procedures[2,23] (Scheme 1) to form aromatic trisulfides **2a**−**d**, wherein yields and purity are significantly improved. We also report for the first time the synthesis of a corresponding set of aromatic tetrasulfides **3a**−**d**. All compounds were characterized by ^{1}H NMR, ^{13}C NMR, MS, and HRMS or elemental analysis; crystal structures of **2b** and **3b** were also obtained.

To a solution of easily accessible aromatic thiols **1a**−**d** and equimolar pyridine in anhydrous diethyl ether was added a freshly distilled solution of sulfur dichloride for **2a**−**d** or sulfur monochloride for **3a**−**d** at −78 °C, Scheme 1. After workup, the sample was usually analytically pure but could be recrystallized in the freezer with *n*-pentane. The procedure was readily scaled up to 10 g.

The use of freshly distilled sulfur monochloride, ether as the solvent, with pyridine as a hydrochloride sink and possible activator were all necessary components of the reaction to ensure the purity of the product and its high

(1) Steudel, R.; Kustos, M. In *Encyclopedia of Inorganic Chemistry*; King, R. B., Ed.; John Wiley & Sons: Athens, GA, 1994; Vol. 7, pp 4009−4038.
(2) Schoberl, A.; Wagner, A. *Methoden der Organishen Chemie*, 4th ed.; Houben-Weyl: Stuttgart, 1955; Vol. 9.
(3) Clayton, J. O.; Etzler, D. H. *J. Chem. Soc.* **1974**, *69*, 974.
(4) Reid, E. E. *Organic Chemistry of Bivalent Sulfur*; Chemical Publishing Company: New York, 1960; Vol. 3.
(5) Vineyard, B. D. *J. Org. Chem.* **1966**, *31*, 601.
(6) Otten, S.; Frohlich, R.; Haufe, G. *Heterocycles* **1999**, *51*, 505−512.
(7) Westlake Jr., H. E.; Laquer, H. L.; Smyth, C. P. *J. Am. Chem. Soc.* **1949**, *72*, 436−438.
(8) Buckman, J. D.; Field, L. *J. Org. Chem.* **1967**, *32*, 2.
(9) Hayashi, S.; Furukawa, M.; Yamamoto, J.; Hamamura, K. *Chem. Pharm. Bull.* **1967**, *15*, 1310−1314.
(10) Capozzi, G.; Capperucci, A.; Degl'Innocenti, A.; Del Duce, R.; Menichetti, S. *Tetrahedron Lett.* **1989**, *30*, 2991−2994.
(11) Harpp, D. N.; Hou, Y.; Abu-Yousef, I. A. *Tetrahedron Lett.* **2000**, *41*, 7809.
(12) Harpp, D. N.; Rys, A. Z. *Tetrahedron Lett.* **2000**, *41*, 7169−7172.
(13) Kawamura, S.; Nakabayashi, T.; Horii, T.; Hamada, M. *Ann. Rep. Radiat. Cent. Osaka Prefect.* **1977**, *18*, 81−82.
(14) Steudel, R.; Schmidt, H. *Chem. Ber.* **1994**, *127*, 1219−1221.
(15) Steudel, R.; Kruger, P.; Florian, I.; Kustos, M. *Z. Anorg. Allg. Chem.* **1995**, *621*, 1021−1024.
(16) Ricci, J. S.; Bernal, I. *J. Chem. Soc. B* **1979**, 1928−1932.
(17) Böhme, H.; Van Ham, G. *Justus Liebigs Ann. Chem.* **1958**, *617*, 62.
(18) Von Szczepanaski, C.; Heindl, J.; Schroeder, E.; Kessler, H. J.; Redmann, U. German Patent, 1972.
(19) Nakabayashi, T.; Tsurugi, J. *J. Org. Chem.* **1961**, *26*, 2482.
(20) Kresze, G.; Patzscheke, J. *Chem. Ber.* **1960**, *93*, 380.
(21) Harpp, D. N.; Ash, D. K. *Int. J. Sulfur Chem. A* **1971**, *1*, 211−214.
(22) Nicolaou, K. C.; Hummel, C. W.; Nakada, M.; Shibayama, K.; Pitsinos, E. N.; Saimoto, H.; Mizuno, Y.; Baldenius, K.-U.; Smith, A. L. *J. Am. Chem. Soc.* **1993**, *115*, 7625.
(23) Harpp, D. N.; Derbesy, G. *Tetrahedron Lett.* **1994**, *35*, 5381−5384. The method in this article can be used to prepare the aliphatic analogues; however, the yields are not generally as high as in this modification.

10.1021/jo0265481 CCC: $25.00
Published on Web 02/14/2003

TABLE 1. Data for Tri- and Tetrasulfides

entry	thiol	S_nCl_2[a]	product	yield[b] (%)	mp (°C)	lit. mp (°C)
1	**1a**	1	**2a**	61	51−52	ca. 5[26]
2		2	**3a**	71	30−31	34−35[27]
3	**1b**	1	**2b**	97	78−79	82−84[24]
4		2	**3b**	99	62−64	oil[28,d], 71−72[29]
5	**1c**	1	**2c**	97	61−64	68−71[25], 70−71[30]
6		2	**3c**	97	53−57	
7	**1d**	1	**2d**	90	131−136[c]	114−116[30]
8		2	**3d**	99	154−158	

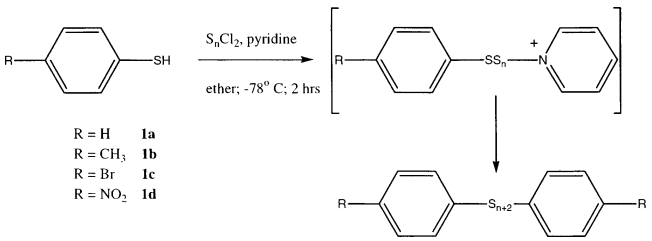
[a] $n = 1$ for sulfur dichloride, $n = 2$ for sulfur monochloride. [b] Yields reported after one recrystallization. [c] Sample turned dark yellow at 122−124 °C. [d] The combustion analysis in the reference is not accurate and the claim of synthesis should be questioned.

TABLE 2. Temperature Study of Thiol Coupling with Sulfur Monochloride

entry	product	temp (°C)	yield[b] (%)	mp (°C)
1	**3b**	−78	99	62−64
2	**3b**	0	91	60−61
3	**3b**	rt[a]	86	63−64

[a] rt = 25 ± 1 °C. [b] Yields reported after one recrystallization.

SCHEME 2



yield (Table 1). Maintaining the temperature at −78 °C may also serve to increase purity as compared with previous syntheses.[24,25] We investigated this criterion by repeating the reaction for the production of **3b** at 0 °C and at room temperature, Table 2. The yields remained high but decreased with increasing temperature, as did the purity of the sample. It therefore seems that the coupling rate of the second equivalent of thiol to the intermediate (Scheme 2) is faster than its decomposition.

The addition of pyridine as the amine base distinguishes this method from previous uses of sulfur dichloride or sulfur monochloride as coupling agents. While this is a simple alteration in the normal procedure, the greatly enhanced yields and purity clearly show the advantage. It is likely that the increased yield and higher purity is because the pyridinium salt is insoluble in the ether solvent. Upon addition of the yellow chlorosulfane to the thiol/pyridine solution, an immediate conversion to a white precipitate was observed. The precipitation of this pyridinium salt byproduct apparently drives the reaction to completion. It may also be that the activated intermediate is that of a sulfenyl pyridinium complex or a thiosulfenyl pyridinium complex (Scheme 2). Activated complexes of sulfur monochloride are not without precedent.[31]

The nitro analogues **2d** and **3d** also precipitated from solution. In all cases, no higher order polysulfides were observed upon completion of the reaction. This proved to be important and beneficial, as separation of polysulfides by chromatography is often problematic as a result of their very similar properties.

Compound **2a** had previously been reported to be an oil;[10,25,32] however, after being placed in the freezer in *n*-pentane for 24 h, pure crystals were determined.

Crystal structures of **2b** and **3b** were determined. The geometry of these aromatic polysulfides is unexceptional[15,33,34] compared to that previously reported for others of this class, with an average S−S bond length of 2.045 Å.

All compounds in Table 1 were bench-stable for months; however, on exposure to light they would decompose in a matter of hours, forming different-order polysulfides of $n = 2-6$. No special precautions need be made with respect to air exposure if the compounds are weighed and used directly. Thermally, tetrasulfides were less stable than their trisulfide counterparts. The nitro group significantly increased the thermal stability of the compounds.

This optimized method provides a convenient preparation of acyclic aromatic tri- and tetrasulfides in high yield and purity from readily accessible materials under very mild conditions.

Experimental Section

General Experimental. All reagents were commercially available and were used without further purification save for the following exceptions. Methylene chloride was distilled over calcium hydride. Diethyl ether was dried over molecular sieves. Sulfur monochloride, S_2Cl_2 (135−137 °C), was distilled according to procedures adapted from Fieser and Fieser (100:4:1 S_2Cl_2/sulfur/charcoal).[35] Sulfur dichloride, SCl_2 (59−60 °C), was fractionally distilled over 0.1% phosphorus pentachloride, PCl_5. Both S_2Cl_2 and SCl_2 were used immediately after distillation. All glassware was oven-dried. All melting points are uncorrected. NMR spectra were recorded in $CDCl_3$ at 300, 400, or 500 MHz for ^1H and 75, 101, or 125 MHz for ^{13}C.

Synthesis of *p*-Aryl Trisulfides. An example of the synthetic procedure is as follows. A solution of thiol (20 mmol, 1 equiv) and pyridine (20 mmol, 1 equiv) in 50 mL of diethyl ether was allowed to stir under nitrogen at −78 °C. A solution of sulfur dichloride (10.0 mmol, 0.5 equiv) in 50 mL of ether was added dropwise over 0.5 h. The reaction mixture was allowed to stir for a further 1.5 h. The reaction mixture was quenched with 25 mL of H_2O. The organic phase was washed 3 × 25 mL of H_2O or until the aqueous phase became clear. The organic phase was dried over $MgSO_4$. This mixture was vacuum filtered, and the solvent was removed first under reduced pressure and then in vacuo.

(24) Harpp, D. N.; Smith, R. A. *J. Org. Chem.* **1979**, *44*, 4140−4144.
(25) Harpp, D. N.; Ash, D. K.; Smith, R. A. *J. Org. Chem.* **1980**, *45*, 5155−5160.
(26) *Beilsteins Handbuchen Der Organischen Chemie*, 1965; Vol. 6, E111.
(27) Lechler, H.; Holzschneider, F. *Chem. Ber.* **1925**, *58*, 417.
(28) Saville, R. W. *J. Chem. Soc.* **1958**, 2880−2888.
(29) Kawamura, S.; Horii, T.; Tsurugi, J. *J. Org. Chem.* **1971**, *36*, 3677−3680.
(30) Feher, F.; Kurz, D. *Z. Naturforsch., B: Chem. Sci.* **1968**, *23*, 1030−1033.
(31) Rees, C. W.; Rakitin, O. A.; Marcos, C. F.; Torroba, T. *J. Org. Chem.* **1999**, *64*, 4376−4380.
(32) Harpp, D. N.; Granata, A. *Tetrahedron Lett.* **1976**, *35*, 3001.
(33) Cox, P. J.; Wardell, J. L. *Acta Crystallogr.* **1997**, *C53*, 122−124.
(34) Howie, R. A.; Wardell, J. L. *Acta Crystallogr.* **1996**, *C52*, 1533−1534.
(35) Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; John Wiley and Sons: New York, 1967; Vol. 1.

Diphenyl Trisulfide (2a). Yield 61%; recrystallization from *n*-pentane at −15 °C afforded light white needles; mp 51−52 °C (lit. mp[26] ∼5 °C); ^{1}H NMR δ 7.14−7.34 (m, 6H), 7.47−7.59 (m, 4H); ^{13}C NMR δ 127.14, 127.47, 129.05, 137.00; MS (EI) *m*/*z* (rel intensity) 250 (4.3), 218 (100.0) −S, 185 (16.2) −S_2, 154 (15.4), 141 (9.7) −SC_6H_5, 109 (76.5) −$S_2C_6H_5$. HRMS for $C_{12}H_{10}S_3$: 249.9945. Found: 249.993(6)

Bis(*p*-tolyl) Trisulfide (2b). Yield 97%; recrystallization from *n*-pentane at −15 °C afforded light yellow needles; mp 78−79 °C (lit. mp[24] 82−84 °C).

Bis(*p*-bromophenyl) Trisulfide (2c). The product was a light, flaky solid. Yield 97%; mp 61−64 °C (lit. mp[30] 70−71 °C).

Bis(*p*-nitrophenyl) Trisulfide (2d). The above procedure was scaled up by a factor of 2. Upon quenching with 100 mL of H_2O, a grayish precipitate formed. This precipitate was vacuum filtered and further washed with 2 × 100 mL of H_2O. The filtrate was further purified as above, and the solute was dried. The products were combined to yield a tan-colored solid. Yield 90%; mp 122−124 °C turning dark yellow then melting at 131−136 °C (lit. mp[30] 114−116 °C).

Synthesis of *p*-Aryl Tetrasulfides. The following is a general example of the synthetic procedure. A solution of thiol (40 mmol, 2 equiv) and pyridine (40 mmol, 2 equiv) in 100 mL of diethyl ether was allowed to stir under nitrogen at −78 °C. A solution of sulfur monochloride (20.0 mmol, 1 equiv) in 100 mL of ether was added dropwise over 0.5 h. The reaction mixture was allowed to stir for a further 1.5 h. The reaction mixture was quenched with 100 mL of H_2O. The organic phase was washed 3 × 50 mL of H_2O or until the aqueous phase became clear; the organic phase was dried over $MgSO_4$. This mixture was vacuum filtered, and the solvent was removed first under reduced pressure and then in vacuo.

Diphenyl Tetrasulfide (3a). Yield 71%; recrystallization from *n*-pentane at −15 °C afforded light yellow needles; mp 30−31 °C (lit. mp[27] 34−35 °C).

Bis(*p*-tolyl) Tetrasulfide (3b). Yellow powder. Yield 99%; recrystallization from *n*-pentane at −15 °C afforded bright yellow needles; mp 62−64 °C (lit. mp oil,[28] 71−72 °C[29]).

Bis(*p*-bromophenyl) Tetrasulfide (3c). Light yellow, flaky solid. Yield 97%; mp 53−57 °C; ^{1}H NMR δ 7.38 (AB, 4H J = 8.40 Hz); ^{13}C NMR δ 131.7, 132.3, 132.4, 132.4; MS (EI) *m*/*z* (rel intensity) 440 (1.6), 408 (6.7) −S, 376 (100) −S_2, 189 (74.5) −$S_2C_6H_4Br$, 108 (76.2) −$S_2C_6H_4Br$. Anal. Calcd for $C_{12}H_8S_4Br_2$: C, 32.74; H, 1.83. Found: C, 32.77; H, 1.43.

Bis(*p*-nitrophenyl) Tetrasulfide (3d). Upon quenching with 100 mL of H_2O, a grayish precipitate formed. This precipitate was vacuum filtered and further washed with 2 × 100 mL of H_2O. The filtrate was further purified as above, and the solute was dried. The products were combined to yield a sandy colored solid. Yield 99%; mp 154−158 °C; ^{1}H NMR δ 7.88 (AB, 4H J = 9.20 Hz); ^{13}C NMR δ 124.4, 126.3, 144.0, 146.9; MS (CI) *m*/*z* (rel intensity) 308 (100) −S. Anal. Calcd for $C_{12}H_8N_2O_4S_4 + NH_4$: 389.9711. Found: 389.971(6).

Acknowledgment. We thank the Natural Sciences and Engineering Research Council (NSERC) for support. E.Z.-C. thanks FCAR for a personal scholarship. We thank Dr. Anne-Marie Lebuis for resolving the structures of **2b** and **3b**.

JO0265481