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Synthesis of New Cyclic Dialkoxy Disulfides

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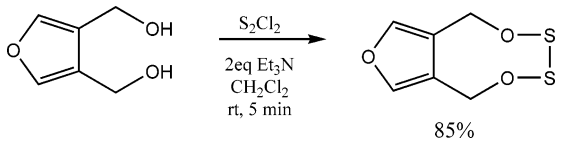

Five new cyclic dialkoxy disulfides have been synthesized and fully characterized. An X-ray structure was obtained for the 2,3-furandimethylene dialkoxy disulfide.

Although known for more than a century, dialkoxy disulfides **1**[1] have not received much attention. It is only recently that interest has grown concerning this class of compounds along with their structural thionosulfite isomers **2** (Figure 1). Much of this attraction has been due to the nature of the two different sulfur−sulfur bonds. Molecules containing the dialkoxy disulfide and/or the thionosulfite moieties have indeed demonstrated intriguing stereochemical properties.[2] Motoki,[3] Lunazzi,[2a,4] Braverman,[5] Nakayama,[2b] and our group[2c,6] are among the few authors who have investigated these chalcogenic structures. In addition, reviews concerning these molecules have been published.[7]

Until recently, only acyclic dialkoxy disulfides have been isolated and characterized. The opposite situation is found for its structural thionosulfite isomer **2** where the molecules are only known in cyclic form. In 1965 Thompson,[8] attempting to prepare cyclic dialkoxy disulfides, discovered the branch-bonded

FIGURE 1. Dialkoxy disulfide **1** and its thionosulfite isomer **2**.

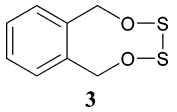

FIGURE 2. The first cyclic dialkoxy disulfide **3** from 1,2 benzenedimethanol **3a**.

thionosulfite isomer. This class was fully confirmed in 1980 with the publication of the first X-ray structure.[9]

Better insight into this chemistry was recently provided with our isolation of the first cyclic dialkoxy disulfide **3** (Figure 2);[10,11] the newly synthesized molecule was confirmed by X-ray analysis and closely related in overall structural characteristics to **3**. To expand the substrate scope of these cyclic dialkoxy disulfides and further study their physical and chemical properties, other molecules were synthesized. Results are presented in Table 1. Some of the precursor diols were accessed according to the literature.[12] The remainder of them, **4a**, **5a**, **6a**, **13a**, and **14a**, were either ordered from commercial sources or previously synthesized in our group.[9] They were reacted with sulfur monochloride employing optimized conditions.[13]

The cyclization reaction did not proceed well with some of the substrates but five new dialkoxy disulfides were prepared. In the cases where such disulfides were not isolated, the reaction afforded what appears to be linear oligomers of the target dialkoxy disulfide.[14] The new cyclic dialkoxy disulfides were fully characterized including an X-ray structure for compound **9b** (Figure 3).

As illustrated by literature precedent[6,10] and by the X-ray structure obtained, the dihedral angle between the four atoms O−S−S−O is expected to be as close as possible to 90° for

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(4) Borghi, R.; Lunazzi, L.; Placucci, G.; Cerioni, G.; Plumitallo, A. *J. Org. Chem.* **1996**, *61*, 3327−3331.

(5) Braverman, S.; Pechenick, T.; Gottlieb, H. E.; Sprecher, M. *J. Am. Chem. Soc*. **2003**, *125*, 14290−14291 and related references therein.

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(7) (a) Zysman-Colman, E.; Harpp, D. N. *J. Sulfur Chem.* **2004**, *25*, 155−182. (b) Zysman-Colman, E.; Harpp, D. N. *J. Sulfur Chem.* **2004**, *25*, 291−316.

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(9) Harpp, D. N.; Steliou, K.; Cheer, C. J. *J. Chem. Soc., Chem. Commun.* **1980**, 825−826.

(10) Zysman-Colman, E.; Nevins, N.; Eghbali, N.; Snyder, J. P.; Harpp, D. N. *J. Am. Chem. Soc*. **2006**, *128*, 291−304.

(11) Zysman-Colman, E. McGill University, Ph.D. Thesis, 2003.

(12) (a) For **7a**, **8a** and **11a**: Bloomfield, J. J.; Lee, L. S. *J. Org. Chem.* **1967**, *32*, 3919−3924. Yoon, N. M.; Gyoung, Y. S. *J. Org. Chem.* **1985**, *50*, 2443−2450. (b) For **9a** and **10a**: Anderson, W. K.; Heider, A. R.; Raju, N. and Yucht, J. A. *J. Med. Chem.* **1988**, *31*, 2097−2102. (c) For the protection of **10a**: Vora, M. M.; Yi, C. S.; Blanton, C. DeW. *J. Heterocycl. Chem.* **1981**, *18*, 507−510. (d) For **12a**: Hoch, P. E.; Clegg, J. M. *J. Am. Chem. Soc*. **1959**, *81*, 5413−5417. (e) For **15a**: Kraft, M. E.; Schmidt, P. *Synth. Commun*. **2002**, *32*, 2723−2732.

(13) The procedure described in this paper permits the isolation of the dialkoxy disulfide **3** in high yield even more rapidly than an earlier report.[11] There is no requirement for keeping the reaction under nitrogen and the procedure can be carried out without dropwise addition of S_2Cl_2. This reagent requires no purification other than being taken from a relatively new bottle of the reagent. Cooling the reaction mixture during the addition of S_2Cl_2 was optional as it proceeds well at room temperature.

(14) An attempt to isolate and characterize these molecules by FTMS was made but results were not conclusive. For instance, the oligomer from **13a** could not be detected but instead elimination and substitution products were observed in the mass spectrum. When α,α,α′,α′-tetramethyl-2,2′-biphenyldimethanol (**16a**) was treated under the reaction conditions, the molecule afforded an unstable dialkoxy disulfide that oligomerized. According to MALDI analysis, the sample studied was mainly constituted of 7-unit oligomers. The latter was then further used as a chemical reference for the interpretation of other systems.

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TABLE 1. Preparation of Cyclic Dialkoxy Disulfides

Entry[a]	Substrate	Product	Yield[b]	Entry[a]	Substrate	Product	Yield[b]
1[c]	**4a**		-	7	**10a**	**10b**	5%
2	**5a**		-	8	**11a**		-
3	**6a**		-	9[e]	**12a**		-
4	**7a**	**7b**	90%	10	**13a**		-
5	**8a**	**8b**	90%	11[f]	**14a**		-
6[e]	**9a**	**9b**	88%	12	**15a**	**15b**	62%

[a] All reactions were performed as follows: The diol (1 mmol) and triethylamine (2 mmol) were dissolved in dichloromethane. The mixture was cooled with an ice bath to minimize possible side reactions. A CH_2Cl_2 solution of S_2Cl_2 (1 mmol) was added slowly usually over 2−3 min. [b] Isolated yield. [c] A significant amount of 1,3-dichloro-1,3-diphenylpropane was isolated along with the oligomer; this byproduct was not detected when the reaction was carried out in diethyl ether. [d] No trace of the corresponding dimer could be detected. [e] The diene was isolated along with the remaining starting material. [f] Traces of what appear to be the corresponding sulfite and thionosulfide could be observed by ^{1}H NMR; the oligomer remained the major product with a characterless spectrum.

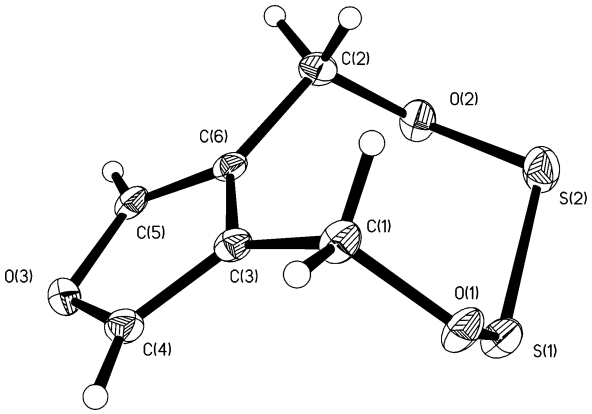

FIGURE 3. X-ray structure for compound **9b**. Key metric parameters include: S(1)−S(2) 1.9704(14), S(1)−O(1) 1.6488(17), S2−O2 1.6769(19) Å, O(1)−S(1)−S(2) 108.66(8), O(2)−S(2)−S(1) 108.05(7) and O(1)−S(1)−S(2)−O(2) 97.46(9)°.

the molecule to adopt the most stable conformation. Significant deviation from this angle would most likely be translated into an increase of the global energy of the molecule as was predicted earlier. Therefore, for small rings, the dihedral angle would present a too important distortion resulting in an absence of cyclization and subsequent polymerization. No cyclic dialkoxy disulfide has been isolated for rings of size five, six, and seven although a limited number of substrates were tested.

Our recent calculations[10] indicate that eight-membered OSSO rings were likely to be the more stable entities. Entries 1−3 and 11 (seven- and nine-membered-ring possibilities) were unsuccessful. We were, however, able to prepare four new eight-membered dialkoxy ring systems. Analysis of entries 4 to 10 (eight-membered-ring substrates) revealed that the presence of an aromatic ring connected to the dialkoxy disulfide ring was effective for their successful preparation[15] as it may provide a suitable orientation for the diols to cyclize with S_2Cl_2. This aspect is illustrated by the synthesis of the products **7b** to **10b**. These compounds were isolated relatively easily in high yield and good purity; they were stable in the refrigerator under an inert atmosphere for months.

Compound **10b** (entry 7) was nevertheless only obtained in 5% yield or less. The reactivity of the hydroxyl groups of 3,4-

(15) The only cyclic dialkoxy disulfide synthesized without a direct adjacent aromatic ring was derived from (*Z*)-2,3-diphenyl-2-butene-1,4-diol (**17a**). Detected only by ^{1}H NMR, this unstable molecule quickly underwent elimination at room temperature to form the corresponding diene. Oligomerization was observed as well during an attempt to isolate the molecule at low temperature. The nature of the effects involved still remains unclear but the synthesis of cyclic dialkoxy disulfides from open chain diols appears difficult to achieve.

dihydroxymethyl-*N*-propylpyrrole **10a** was lower toward S_2Cl_2 compared with faster side reactions.

The system was extended to another[10] 10-membered ring and the synthesis of compound **15b** was surprisingly efficient. Indeed it is known that side reaction polymerizations are more difficult to control with molecules containing 10-membered rings and higher. Nevertheless, a mixture of oligomer and cyclic dialkoxy disulfide was obtained with the major product being our target molecule (~60% isolated). This kind of polymerization reaction could be influenced not only by the concentration of the substrate, but also by the nature of the solvent used during the experiment.[16]

In summary, with a diol and sulfur monochloride as starting materials, we were able to access five new molecules as **7b**−**10b** and **15b**. However, due to the instability of some of the products, the scope of the reaction is limited; only specific substrates could be converted. Among the criteria used to select appropriate starting material, ring size, the presence of an adjacent aromatic ring, or the conformation of the molecule can be found as important variables. In the absence of cyclization, oligomers or elimination products were generated.

Experimental Section

General Procedure for the Synthesis of Cyclic Dialkoxy Disulfides. The diol (1 mmol) and the triethylamine (2 mmol) were successively added in a beaker containing dichloromethane (50 mL/mmol of diol). Sulfur monochloride (1 mmol) was added dropwise by syringe at room temperature (addition at 5−10 °C is appropriate). After 2−5 min of addition according to the volume of reagent used, the reaction mixture was immediately washed 3 times with water. The solvent was dried over $MgSO_4$ and evaporated. The temperature of the water bath was kept near 30 °C during solvent removal. In all cases, a white or yellowish solid was obtained that was usually purified by silica gel column chromatography (1:3 dichloromethane/hexane). Most of the procedures were repeated several times; the yields are shown as a range.

Dialkoxy Disulfide 7b from 4,5-Dichloro-1,2-benzenedimethanol (7a). Obtained as a white solid in 87−93% yield. R_f 0.56 (2:1 petroleum ether/dichloromethane); mp 108−109 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ ABq system 4.86 (d, 2H, J = 12.3 Hz), 5.01 (d, 2H, J = 12.3 Hz), 7.52 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 71.3, 134.1, 134.5, 136.3; IR (KBr) 440, 573, 637, 794, 890, 947, 1140, 1466 cm^{-1}; HRMS calcd for $C_8H_6Cl_2O_2S_2$ 267.9186, found 267.9195.

(16) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95−102 and references cited therein.

Dialkoxy Disulfide 8b from 4-Methyl-1,2-benzenedimethanol (8a). Obtained as a white solid in 88−92% yield. *Rf* 0.42 (2:1 petroleum ether/dichloromethane); mp 70−71 °C; mixture of enantiomers; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.41 (s, 3H), ABq system 4.91 (d, 2H, J = 12 Hz), 5.05 (d, 2H, J = 12 Hz), 7.29 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6, 72.3, 73.0, 131.2, 132.4, 133.1, 140.6, 150.0; IR (KBr) 413, 470, 569, 647, 683, 716, 757, 826, 925, 1041, 1161, 1345, 1472, 1614; HRMS calcd for $C_9H_{10}O_2S_2$ 214.0122, found 214.0116.

Dialkoxy Disulfide 9b from 3,4-Furandimethanol (9a). Obtained as a white solid in 85−90% yield. R_f 0.78 (2:1 petroleum ether/dichloromethane); mp 83−84 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ ABq system 4.75 (d, 2H, J = 12.8 Hz), 4.93 (d, 2H, J = 12.8 Hz), 7.55 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 63.9, 121.1, 144.1; IR (KBr) 438, 604, 652, 668, 759, 825, 875, 943, 1047, 1136, 1354, 1460, 1548; HRMS calcd for $C_6H_6O_3S_2$ 189.9758, found 189.9749.

Dialkoxy Disulfide 10b from 3,4-Dihydroxymethyl-*N*-propylpyrrole (10a). Obtained as a white solid in 5% yield. R_f 0.45 (2:1 hexane/THF); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (t, 3H, J = 7.2 Hz), 1.81 (m, 2H), 3.84 (t, 2H, J = 7.2 Hz), ABq system 4.74 (d, 2H, J = 12.3 Hz), 4.91 (d, 2H, J = 12.3 Hz), 6.73 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.6, 24.9, 52.0, 66.5, 122.8; HRMS calcd for $C_9H_{13}N_1O_2S_2$ 231.0388, found 231.0392.

Dialkoxy Disulfide 15b from Benzenediethanol (15b). Obtained as a white solid in 60−65% yield. R_f 0.14 (3:1 hexane/dichloromethane); mp 48−50 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.22 (m, 4H), 4.11 (m, 2H), 4.50 (m, 2H), 7.20 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.5, 75.7, 127.1, 129.4, 137.5; IR (KBr) 642, 756, 839, 988, 1045, 1109, 1443, 1489, 1622, 2924, 3015; HRMS calcd for $C_{10}H_{12}O_2S_2 + K^+$ 266.9915, found 266.9916.

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Supporting Information Available: Experimental procedures for the synthesis of **10a** and **10d**; copies of ^{1}H and ^{13}C NMR spectra for compounds **7b**, **8b**, **9b**, **10b**, and **15b**. This material is available free of charge via the Internet at http://pubs.acs.org. The crystal structure for **9b** has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 614641.

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