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Dialkoxy disulfides from cubycarbinols

Ronny Priefer, Patrick G. Farrell and David N. Harpp*

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

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Abstract—Two dialkoxy disulfides **2** and **3** have been synthesized in respectable yields. The behaviour of **2** and **3** under thermal and photolytic conditions has been examined and we report the first examples of S_2 liberation from aliphatic dialkoxy disulfides.

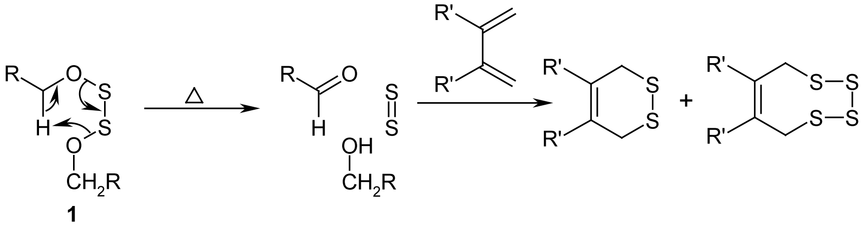
Alkoxy disulfides **1** have been known for over a century[1] but only recently have attracted significant attention[2] in spite of a seminal paper by Thompson in 1965.[3] Of particular interest is the unusually short S–S bond (ca. 1.95 Å) in these compounds that raises the S–S bond rotational barrier to ca. 18 kcal/mol[2c,d] from the usual barrier of ca. 6–10 kcal/mol in the corresponding disulfides.[3,4] In addition, benzylic dialkoxy disulfides **1** ($R=4\text{-X-}C_6H_4$) have been shown to decompose smoothly under moderate heat to deliver a diatomic sulfur fragment that can be trapped by dienes[2f] (Scheme 1).

Recently we described the successful introduction of a sulfur atom onto the cubyl framework;[4a] as part of a study of the sulfur–sulfur bond in dicubyl disulfide and related structures, we have investigated dialkoxy disulfides **2** and **3**.

For nearly 4 decades, Eaton and co-workers have reported numerous syntheses of variably substituted cubane derivatives.[5] Following these, we have readily synthesized the two precursor alcohols (**7** and **8**)[6,7] of the corresponding dialkoxy disulfides in excellent yield. Commercially available dimethyl 1,4-cubane dicarboxylate (**4**) was hydrolyzed to 4-methoxycarbonyl cubane carboxylic acid (**5**)[6] and then converted to the 4-iodocubanecarboxylic acid (**6**) via a Moriarty reaction followed by hydrolysis.[7] Reduction of **6** with borane afforded 1-iodo-4-(hydroxymethyl)cubane (**7**)[5b,7] and with LAH gave cubylcarbinol (**8**)[7] (Scheme 2). Alcohols **7** and **8** were each reacted with 0.5 equiv. of sulfur monochloride in the presence of Et_3N to yield the corresponding dialkoxy disulfides **2** and **3** (85% and 89% yield.)

The barrier of rotation for compound **3** was determined to be 18.7 kcal/mol from the coalescence of the proton AB quartet at 98°C (aldehyde and alcohol were detected starting at 90°C.) An accurate value for the barrier of rotation of **2** could not be obtained due to the overlap of the AB quartet with the cubyl signal in the ^{1}H NMR in high boiling solvents.

The crystal structure of bis-(4-iodocubylmethyl)-dialkoxy disulfide **3** (Fig. 1) revealed no unusual features. The O–S–S–O dihedral bond angle is 87.6° and the S–S bond length is 1.97 Å, which are comparable to values in other dialkoxy disulfides.[8]



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Scheme 1. Intramolecular fragmentation of dialkoxy disulfides.

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* Corresponding author. Tel.: 514-398-6685; fax: 514-398-3797; e-mail: david.harpp@mcgill.ca

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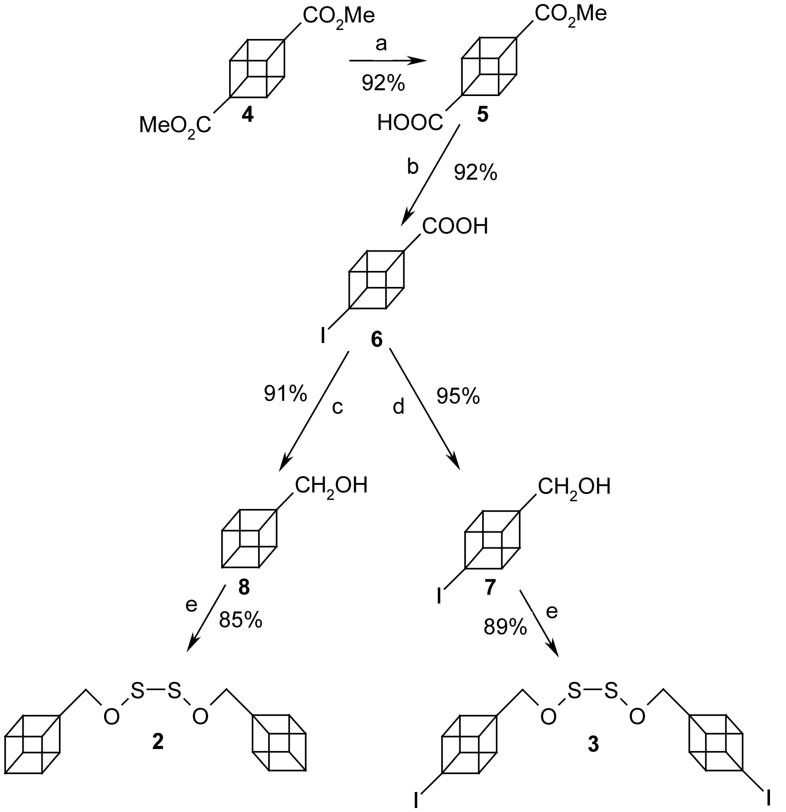


Scheme 2. Synthetic routes to dialkoxy disulfides from cubylcarbinols. (a) i. 1 equiv. NaOH/MeOH/THF, ii. HCl; (b) i. IBDA, I_2/C_6H_6, reflux 6 h, ii. NaOH/MeOH, iii. HCl; (c) i. 50 equiv. LAH, THF, reflux 5 days, ii. HCl; (d) i. $BH_3·SMe_2$/THF, 0°C, ii. HCl; (e) S_2Cl_2, Et_3N/CH_2Cl_2, 0°C.

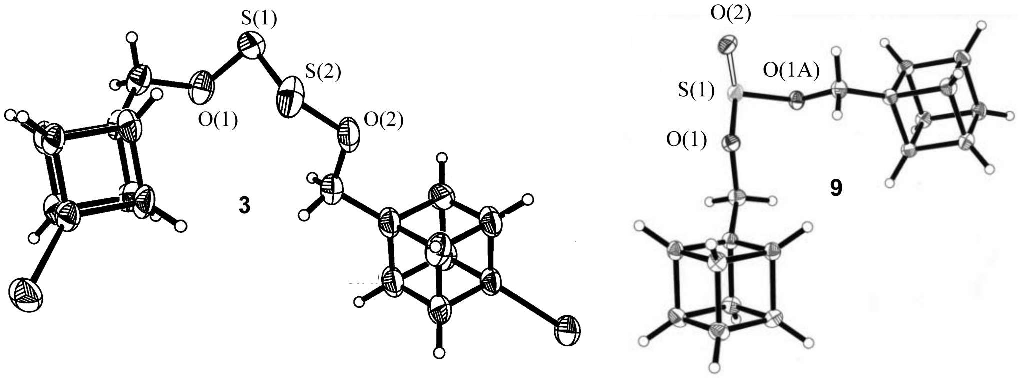


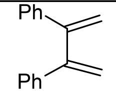
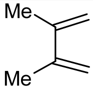
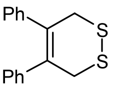
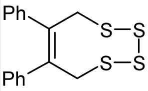
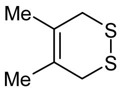
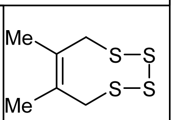
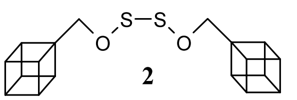
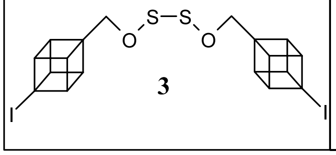
Figure 1. X-ray structures of bis-(4-iodocubylmethyl)dialkoxy disulfide **3** and bis-cubylmethylsulfite **9**.

To date, only benzylic dialkoxy disulfides have been reported to liberate trappable diatomic sulfur fragments upon heating. If this decomposition occurs as proposed in Scheme 1, then it is possible that the relative ease of abstraction of the benzylic proton accounts for this moderate-temperature intramolecular rearrangement. Because of the relatively high s-character of the external bonds of cubanes,[4a,9] we considered it possible that compounds **2** and **3** might similarly liberate S_2 on thermolysis. Since **2** has a much lower melting point than **3** (49–51°C compared with 119–121°C), we expected that it would decompose more rapidly than **3** at a given temperature. This however was not the case as in refluxing toluene compound **2** is stable for at least 4 days, whereas **3** decomposes completely within 24 h.

Table 1 shows the data obtained for S_2 trapping from **2** and **3** with both 2,3-dimethyl and 2,3-diphenyl-1,3-butadienes.

In general agreement with previous reports,[2f,8b] a larger amount of cyclic tetrasulfide than cyclic disulfide was obtained on heating **2** or **3** with excess 2,3-dimethyl-1,3-butadiene. However, proportionally more cyclic disulfide was obtained using excess 2,3-diphenyl-1,3-butadiene with dialkoxy disulfide **2**, in contrast to the results obtained with **3**. In view of the thermal stabilities of the two products obtained from 2,3-diphenyl-

Table 1. S_2 trapping by dienes

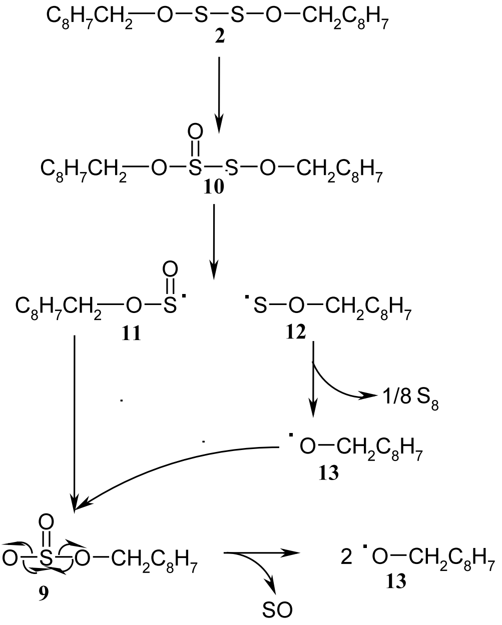
				
				
 **2**	2.3[a](48%)[b]	1.0(23%)	1.0(18%)	2.5(51%)
 **3**	1.0(31%)	1.3(42%)	1.0(31%)[c]	1.8(55%)

Averaged data: experiments performed in refluxing chlorobenzene for 24h with 3eq of diene a: NMR ratio before purification b: percent isolated yield c: reaction was performed in refluxing toluene for 24h.

1,3-butadiene, no interconversion between them is probable[10] and we have no explanation for the differing product ratios obtained.

Upon attempted recrystallization of bis-cubylmethyl-dialkoxy disulfide **2**[11], bis-cubylmethyl-sulfite **9** was formed (Fig. 1). This was confirmed by X-ray crystallography, followed by independent synthesis.[12] It was also observed that on standing, **2** was eventually completely converted to **8**; thus it was suspected that it might be light sensitive. Lunazzi and Placucci[2e] suggested that under photolytic conditions, dialkoxy disulfides undergo homolytic cleavage to give ROS$^\bullet$ that is quickly oxidized to ROS$^\bullet$=O; this species was then trapped with *t*-BuNO. When the photolysis was carried out at −100°C in the absence of a good oxidizing agent (possibly *t*-BuNO), sulfite and sulfoxylate (ROSOR) were detected.[2e]

We therefore performed two photolysis experiments with compound **2**: one under nitrogen and the other open to air. After 24 h of irradiation with a sun lamp (GE-ultraviolet), the sample in the oxygen free environment contained dialkoxy disulfide, **2**, and cubylcarbinol, **8** (~1:1 ratio), whereas the sample that was open to the atmosphere showed no trace of **2** but revealed both the sulfite **9** and the alcohol **8** (~2:3 ratio). The sample that had been under nitrogen was photolyzed for an additional 24 h after which time it was completely converted to alcohol **8**, as was observed with the photolyzed sample that was open to the atmosphere for the full 48 h. What this may suggest is that the dialkoxy disulfide initially becomes oxidized to give **10**, followed by S–S bond cleavage, affording both ROS$^\bullet$=O (**11**) and ROS$^\bullet$ (**12**) (Scheme 3).



Scheme 3. Proposed photolytic fragmentation of dialkoxy disulfide, **2**.

Lunazzi and Placucci have suggested that ROS$^\bullet$ radicals can lose sulfur easily at temperatures above −100°C (our reactions were performed at 50°C). Thus, **12** would likely yield the alkoxy radical (**13**), that can react with the more stable sulfinate radical (**11**) to afford the sulfite **9**; this would eventually be completely converted to alcohol.

When the photolysis was performed in an inert atmosphere, slower homolytic S–S bond cleavage should take place to form **12**, which could lose sulfur to form the alkoxy radical **13**. This might explain why the only product that we observed in this experiment was cubylcarbinol (**8**). Currently, mechanistic studies are under way on this class of compounds to deduce their precise mode of fragmentation.

In summary, we have prepared the two dialkoxy disulfides **2** and **3** in good yield. These compounds represent the first examples of non-benzylic dialkoxy disulfide that liberate S_2 upon heating. In addition, we have shown that in the presence of oxygen, photolysis of dialkoxy disulfide **2** yields the precursor alcohol **8**, via sulfite **9**.

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8. (a) 85.4° and 1.96 Å for $(4\text{-NO}_2\text{-C}_6\text{H}_4\text{-CH}_2\text{-O-S})_2$ in Ref. 2d; (b) 76.8° and 1.93 Å for $(4\text{-Cl-C}_6\text{H}_4\text{-CH}_2\text{-O-S})_2$ in Tardif, S. L. Ph. D. Dissertation, McGill University, 1997.
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11. Recrystallization was performed with hexanes and the dissolved sample was allowed to stand on the bench for 2 days.
12. Cubylcarbinol (**8**), SO_2Cl_2, pyridine, CH_2Cl_2, −10°C, 1 h. mp 94–96°C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.05, 4.16 (ABq, $J=11.0$ Hz, 2H), 4.01 (m, 1H), 3.91 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 62.8, 55.6, 48.5, 47.2, 44.5 ppm. Anal. calcd for $C_{18}H_{18}O_3S$: C, 68.77; H, 5.77; found: C, 68.58; H, 5.79.