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Efficient Synthesis of 5,8-Disubstituted-1,4-Dihydrobenzoxathiin-3-Oxides and Their Isomeric Structures, 4,7-Disubstituted-1,3-Dihydrobenzo[b] Thiophene-2,2-Dioxides

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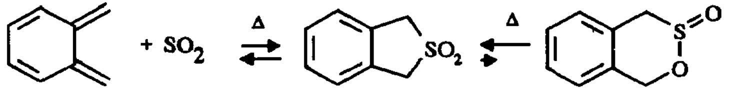
‡Dedicated to the late Dr. B. Belleau.

***Abstract*:** Functionalized dihydrobenzoxathiin oxides and dihydrobenzothiophene-2,2-dioxides **11-18** have been prepared via trapping of sulfur dioxide under photolytic or ground state conditions.

o-Quinodimethane (**1**) has been a useful intermediate in cycloaddition reactions and its synthetic applications have been well documented.[1]

Sulfone **2** can be considered a protected quinodimethane which upon heating rapidly dissocates SO_2 to regenerate **1**. Since the thermal extrusion takes place under neutral conditions, it becomes a method of choice in cycloadditions with dienophiles that are sensitive to other conditions such as the use of metals or nucleophiles.[2]

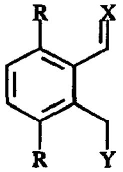
Related to structure **2** is the cyclic sulfinate analog or sultine (**3**). It is thermally less stable and is also a convenient source of masked o-quinodimethane. Preparations of sulfones and sultines (such as **2** and **3**) have been achieved previously via various means.[3,4]



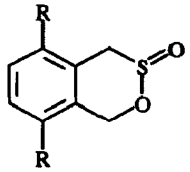
1 2 3

We were interested in 5,8-dialkoxy (or diacetoxy) sultines (**11-13**) and sulfones (**14-18**) for their potential of forming useful quinonic synthon **20** and found that very few examples have been reported.[5] Initially, we investigated the possibility of generating 1-hydroxy sulfone (**17**) via trapping of SO_2 from photo-enolized 2-methyl-3,6-dimethoxybenzaldehyde (a 4+2, n+ππ process). This approach was previously employed to synthesize **19** by Charlton and Durst,[6] but photoenolization of several alkoxy substituted tolualdehydes were unsucessful in the past. The substituent effects[6b] were not clearly defined and needed to be experimentally determined for the 1,4-alkoxy substituted tolualdehydes. However the capability of stabilizing required E-enol geometry[7] through hydrogen bonding, as seen in 4, should favor the photoenolization process.

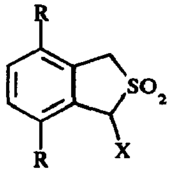
Indeed, irradiation at 350 nm, using a Rayonet reactor, of a solution containing 0.8% of aldehyde 4 and 11% of sulfur dioxide in benzene resulted in the formation of the 1-hydroxysulfone 17 in excellent yield (93%). This process also proved effective for the bulky siloxy analog and sulfone 17a was obtained in 66% isolated yield.



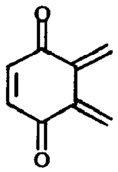
4,R=OMe, X=O, Y=H
4a, R=OSitButMe$_2$, X=O,Y=H
5,R=OMe, X=H, Br, Y=Br
6,R=OAc, X=H, Br, Y=Br
7,R=OH, X=H, Br, Y=Br
8,R=OMe, X=H, I, Y=I
9,R=OMe, X=O, Y=I
10,R=H, X=H, Br,Y=Br



11,R=OMe
12,R=OAc
13,R=H

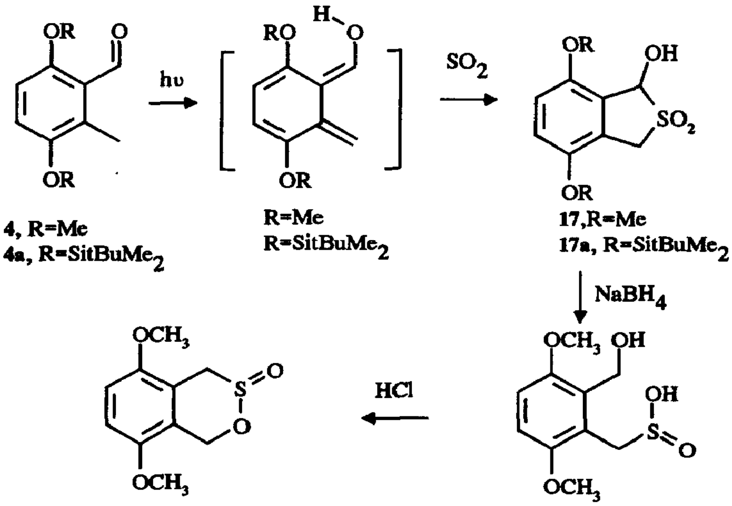


14,R=OMe, X=H
15,R=OAc, X=H
16,R=H, X=H
17,R=OMe, X=OH
17a,R=OSitBuMe$_2$, X=OH
18,R=OMe, X=OAc
19,R=H, X=OH



20

The sulfones could be converted to the corresponding sultines uneventfully. For example, 17 was reduced by sodium borohydride and then cyclized under acidic catalysis to give sultine 11 in good yield. (scheme 1) Thus, we have established the effectiveness of the Charlton-Durst sequence in the para-disubstituted systems and allowed 4,7-disubstituted 1-hydroxyl (or alkoxy) sulfones as well as sultines to be efficiently synthesized.



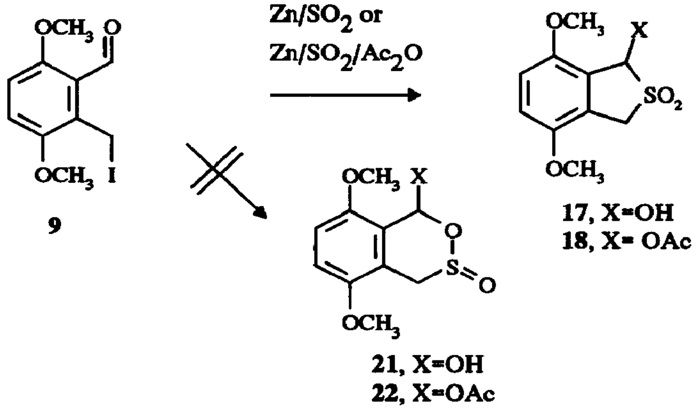
11

Scheme 1

The success of direct trapping of SO$_2$ by photolytically generated quinodimethane prompted us to look for complimentary radiationless approaches. This would be particularly attractive when large scale synthesis of sultines would be required.

Our initial trials to trap sulfur dioxide using dihalides and sodium iodide or zinc were not satisfactory.[8a] After further experimentation, we found that the combination of both zinc and sodium iodide readily effected formation of o-quinodimethane which subsequently trapped SO_2. A typical procedure is as follows: SO_2 (15-20 eq) was condensed (below -10°C) and diluted with DMF (or DMA). NaI (2 eq), zinc[8b](6 eq) and the bromide (1 eq) were added sequentially. The reaction mixture was stirred at room temperature for several hours until the halide was consumed. After aqueous work up, the desired sultine was obtained in good purity. The method worked well regardless of the nature of R (either electron-donating or electron-withdrawing) and starting from various dihalides[9] (5,6,8 and 10) the desired sultines (11-13) could be obtained on multi-gram scale in high yields (80%-90%). Dibromide 7[9] also underwent rapid reactions, but the isolation of the product was not successful. To our knowledge, formation of sultines 11-13 via direct entrapment of SO_2 has not been reported.[10] The current method therefore provides an efficient approach to these molecules.

As an extension of this work, the method was applied to 1'-iodo-o-tolualdehyde (9, from DMSO oxidation of 8). The reaction proceeded to give a single product (85%) but assigned as sulfone 17. Attempt to trap the putative hydroxyl sultine was made by carrying out the reaction in the presence of excess of acetic anhydride but the acetate of sulfone 17 (namely, 18) was obtained exclusively.



9

17, X=OH
18, X= OAc

21, X=OH
22, X=OAc

Scheme 2

The fact that we did not observe any sultine (21 or 22) is probably due to quick ring opening and recyclization[11] leading to the sulfone. The above examples demonstrate for the first time that a ground-state o-quinodimethane approach could be of synthetic value for the preparation of hydroxyl sulfones.

Interestingly, sultines 11 and 12 are stable at room temperature and can be chromatographed. Greater stability of substituted sultines (versus non substituted sultine such as 13) has been also observed by other workers.[12] Conversions of 11 and 12 to sulfones (14 and 15) are undertaken in refluxing benzene or toluene, suggesting an alternative source of o-quinodimethane, which would be otherwise formed at much higher temperature.[5b]

In summary, a number of novel and synthetically useful sultines and sulfones[13] were prepared under either photolytic or ground state conditions. Several syntheses using disubstituted sulfones (such as 14) have been reported recently.[14] Our own synthetic examples using these intermediates will be reported shortly.

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8. a. The dibromide **5** was treated with sodium iodide in presence of sulfur dioxide only to give the corresponding diiodide **8**. Zinc powder effected reaction but less cleanly; b. The zinc powder was treated according to *Reagents for Organic Synthesis*, **1967**, *1*, 1285-1286;
9. These compounds were prepared from commercially available 2,3-dimethylhydroquinone following a methylation (Me_2SO_4)or acetylation (Ac_2O)-NBS bromination sequence. See: G. Eck, M. Julia , B. Pfeiffer and C. Rolando, *Tetrahedron Lett.*, **1985**, *26*, 4725-4726; **7** was prepared from **5** via CAN oxidation and hydrogenation sequence.
10. During the course of this investigation, we became aware of a report by Dittmer et al[3a] where Rongalite, hydroxymethanesulfinic acid mono sodium salt, was used in place of sulfur dioxide. This method was shown by us to be equally effective in the synthesis of substituted sultine (such as **11**).
11. It is known from the literature (ref.6a) as well as from our own experiences that hydroxy sulfone (such as **17** or **19**) is in equilibrium with its open form.
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13. All the analogs have been characterized by ^1H NMR, ^{13}C NMR, MS and HRMS.
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