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α-Thiodisulfides: construction and biological activities

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REVIEW ARTICLE

α-Thiodisulfides: construction and biological activities

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An overview of new synthetic methods for the construction of α-thiodisulfides is presented. α-Sulfone disulfide construction is prominently featured in the synthetic discussion. Biological test results on α-thiodisulfides, aryl disulfides, and thiosulfonates are reviewed and some organic-chemical mechanistic discussion is provided to rationalize them.

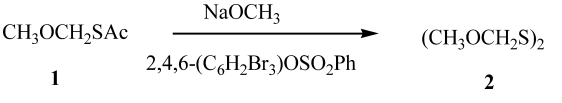
Keywords: disulfides; synthesis; biological activities

AMS Codes: 92E20 and 80A50

1. Introduction

An earlier review (*1*) provides an account of ionic reactions involving sulfonic acid esters. A novel preparative method, disclosed therein, employs 2,4,6-tribromophenyl sulfonates as oxidants, which convert mercaptans into disulfides. Subsequent work (*2*) established that this methodology could be successfully applied to the one-pot conversion of an α-thiolacetate into the corresponding symmetrical disulfide (see Scheme 1).

The tribromophenyl sulfonates join a very long list of oxidants (*3, 4*), which can accomplish the condensation of mercaptans to furnish symmetrical disulfides. Hence, it is generally a simple problem to prepare symmetrical disulfides in this way, provided that the appropriate mercaptan is available. The synthesis of unsymmetrical disulfides presents greater difficulty and may require a good deal of effort.



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Scheme 1.

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2. Synthesis of unsymmetrical disulfides

2.1. *Mesylmethyl phenyl disulfide*

Well before we became interested in the synthesis and biological testing of α-thiodisulfides, work on the exhaustive aqueous chlorinolysis of 3 (see Scheme 2 and reference 5) led us to undertake the synthesis of mesylmethyl phenyl disulfide 5.

$CH_3SO_2CH_2SSPh$

5

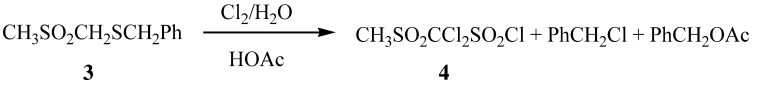
A pathway problem posed by the Scheme 2 reaction is this: does mesylmethanesulfenyl chloride intervene as an intermediate? The disulfide 5 was targeted for synthesis because (i) it was expected to be stable with respect to storage and (ii) disulfides were known to react with molecular chlorine to produce sulfenyl chlorides. Thus, exhaustive aqueous chlorinolysis of 5 should produce mesylmethanesulfenyl chloride initially and, subsequently, product analysis would establish whether the sulfenyl chloride had been converted into 4. Our novel synthesis of 5 is presented in Scheme 3.

To the best of my knowledge, Scheme 3 outlines the first reported demand synthesis of an α-sulfone disulfide.

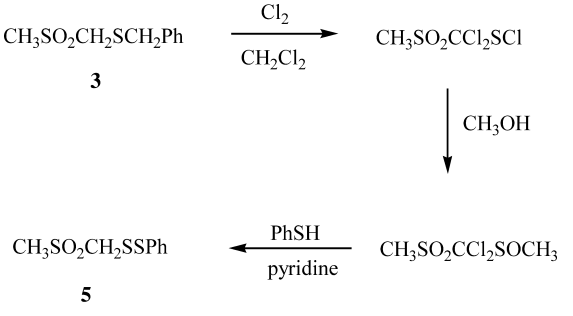
Although our synthesis of the α-sulfone disulfide 5 provided adequate supplies of it, the synthesis had some significant drawbacks. The starting material, 3, required a multistep synthesis and the cleavage of the CS bond in 3 (Scheme 3) was accompanied by unwanted chlorination at carbon resulting in the addition of a step, sulfenate ester preparation, to enable controlled dechlorination at carbon. Furthermore, efforts to initiate a synthesis modeled after Scheme 3, but starting with the phenyl sulfone 6, failed to furnish the target α-sulfone disulfide (*5*). Thus, improved synthetic methodologies for α-sulfone disulfides

$PhSO_2CH_2SCH_2Ph$

6



Scheme 2.



Scheme 3.

would need to be more flexible and more economical. At the time, we had no reason to pursue this problem further.

2.2. *An approach to target molecule selection*

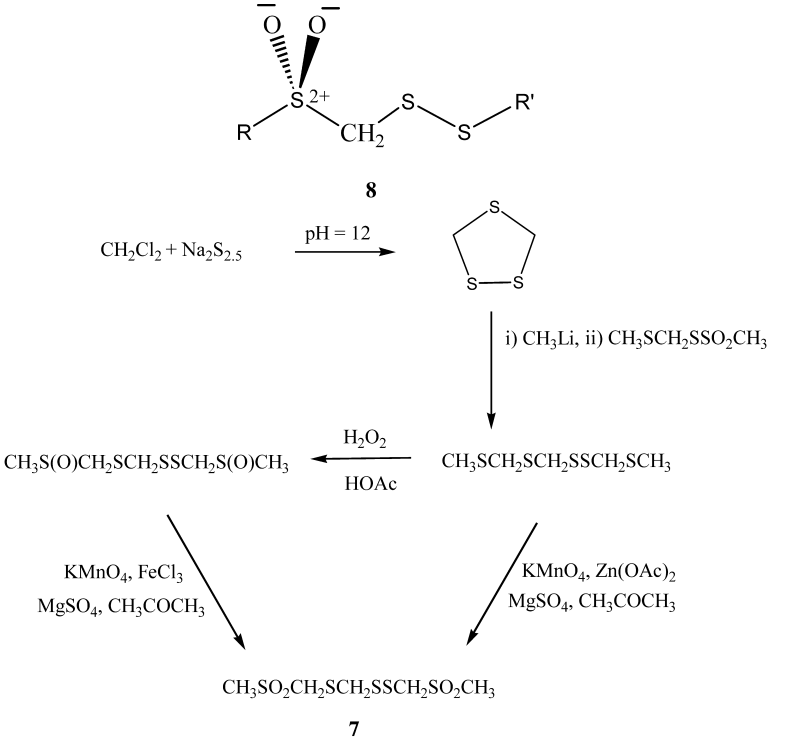
Some time after our work on the synthesis and chlorinolysis of 5 was disclosed (*6*), Andersen, Clardy *et al.* (*7*) reported an examination of extracts from the leaves of Fijian mahogany plants. In Fiji, these leaves are harvested, boiled in water and the resultant tea given to people who are not feeling well. Andersen's group was able to isolate an active principle from the extracts and obtain some preliminary biological test results for it. The active principle was called dysoxy*di*sulfone, later renamed dysoxysulfone 7.

$$CH_3SO_2CH_2SCH_2SSCH_2SO_2CH_3$$

7

The quantity of dysoxysulfone available to Andersen's group was not sufficient to obtain well-defined biological test results. Subsequently, Block *et al.* (*8*) made dysoxysulfone 7 and obtained unambiguous biological test results showing, *inter alia*, promising activity against some fungi and some cancers. Block's economical synthesis of dysoxysulfone is presented in Scheme 4.

Following the disclosure of dysoxysulfone's structure, we established an antifungal testing program with a view to identifying those moieties in 7 that could be linked to antifungal activity. Our first report (*9*) indicated that the functionality in 7, associated with antifungal properties, was that of an α-sulfone disulfide 8. Antifungal testing of 5 played a key part in our first study.



Scheme 4.

Subsequent biological test results on malaria, leukemia, thromboses, and immune cytopaenias are consonant with this view of the active seat responsible for the biological activity of 7. Structure-activity correlations for a variety of disulfides in the aforementioned biological testing will be covered later in this review.

A biological testing program aimed at defining optimum substituents R and R′ in 8 requires an efficient and flexible approach to the synthesis of such molecules. At this point in our work, no such approaches were known to us.

2.3. *Strategic considerations for unsymmetrical disulfide construction*

Three general approaches are possible, in principle, for the creation of an unsymmetrical acyclic disulfide. First, the SS bond may be introduced linking sulfur atoms which bear non-equivalent substituents. A commonly-employed approach condenses a mercaptan with a molecule that features an electrophilic sulfenyl sulfur atom *e.g.* Scheme 5 in which X=Cl, SO_2Q, or SQ.

Second, the SS bond may be present in a symmetrical disulfide. One substituent may then be modified producing an unsymmetrical disulfide (see Scheme 5).

Third, a symmetrical disulfide might be converted into an unsymmetrical intermediate by modifying the SS linkage itself. Such an approach would require another step to transform the intermediate into an unsymmetrical disulfide. Scheme 6 presents an intermediate upon which one might base such an approach.

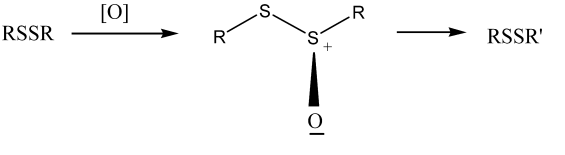
Of the three approaches outlined in Schemes 5 and 6, the latter is the least attractive because it is longer. The left hand side of Scheme 5 requires broad accessibility for two structural types, one of which is a mercaptan. Although mercaptans are generally stable, there was reason to be concerned about the stability of α-mercaptosulfones. We had shown (*10*) that α-mesylmethyl mercaptan 9 is unstable and appears to decompose as shown in Scheme 7.

For those reasons, *inter alia*, our attention shifted, initially, to method development intended to exploit the approach proposed in the right hand side of Scheme 5.

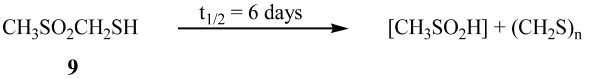
The various proposals in Schemes 5 and 6 have counterparts in the synthetic task of making unsymmetrical sulfides. The problem of converting a symmetrical sulfide into an unsymmetrical sulfide functionalized with a leaving group at the α-carbon has a particularly convenient solution (see Scheme 8).

These reactions have been discussed in detail earlier (*11*). A straightforward mechanism for the Scheme 8 reaction is presented in Scheme 9.

Scheme 5.



Scheme 6.



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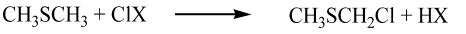
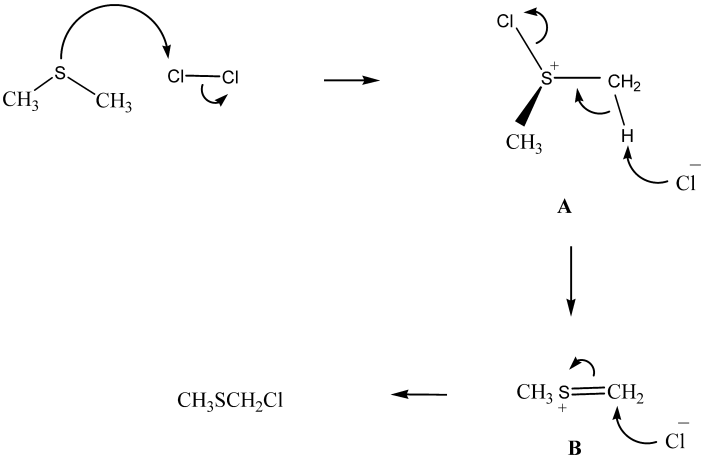
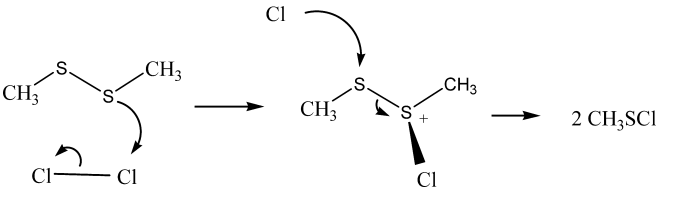
Scheme 7.



Scheme 8.



Scheme 9.



Scheme 10.

Although disulfides will do the nucleophilic attack pictured at the outset of Scheme 9, the disulfide counterpart of the chlorosulfonium cation A in Scheme 9, avoids the Pummerer rearrangement that sulfide chlorinations choose. Scheme 10 shows the corresponding chlorination reaction for dimethyl disulfide.

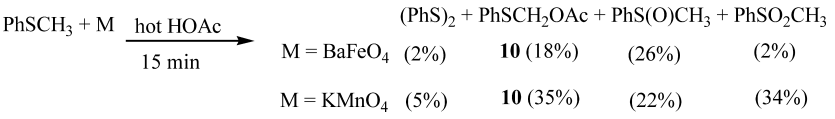
Hence, disulfide chlorinations do not lead directly to unsymmetrical disulfides functionalized at α-carbon. At this point, we were not aware of any one-pot chemistry, which would transform dimethyl disulfide into a disulfide equipped with a leaving group at α-carbon.

Nonetheless, α-chlorodimethyl disulfide had been prepared by Douglass *et al.* (*12*) It was prepared in two steps over several weeks, the latter step giving a complex mixture containing a low yield of the α-chlorodisulfide. We chose to pursue the development of alternative intermediates for the construction of α-thiodisulfides.

2.4. *Novel methods for CO-linked α-ester disulfide construction*

2.4.1. *Transition-metal oxidation of disulfides*

At this point, we have selected α-sulfone disulfides as the first target molecules for synthesis and biological testing as well as a symmetrical disulfide (dimethyl disulfide) for the starting point upon which to develop an approach of the type depicted in the right hand side of Scheme 5.



Scheme 11.

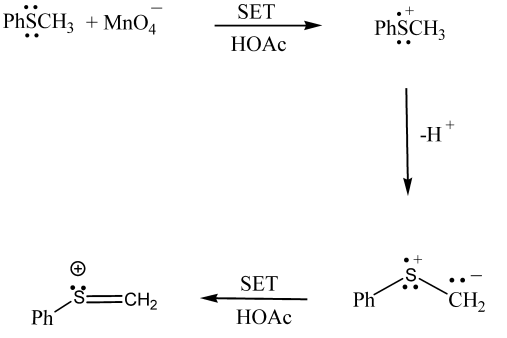
Fortuitously, during the initial stages of this work, we were engaged in an effort to develop reaction conditions that would be suitable for the transformation of sulfides into sulfoxides using barium ferrate as the oxidant (*13*). An early result is shown in Scheme 11.

The acetoxy sulfide 10 was an unexpected and intriguing product. Further exploration established that potassium permanganate gave a better yield of 10 than barium ferrate had (see Scheme 11). Other pertinent observations included (i) the failure of phenyl methyl sulfoxide to form α-acetoxysulfide 10 in hot glacial acetic acid and (ii) the failure of benzyl methyl sulfide to furnish any α-acetoxysulfides upon reaction with permanganate/hot glacial acetic acid (good yields of sulfoxide and sulfone were obtained).

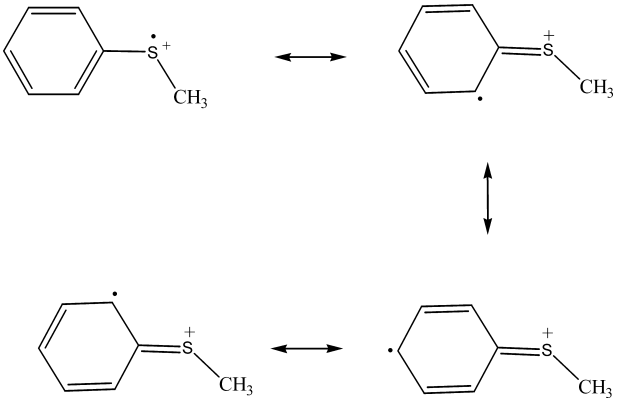
The foregoing results are compatible with solvolysis of the thionium ion 11 that could arise as proposed in Scheme 12.

PM3 molecular orbital calculations were provided to support the Scheme 12 proposal (*13*).

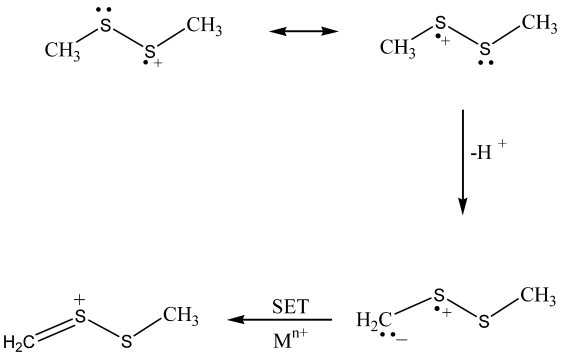
The key to rationalizing relatively facile thionium ion formation from phenyl methyl sulfide as well as the total failure to get a corresponding intermediate from benzyl methyl sulfide lay with the resonance stabilization uniquely available to the radical cation assumed to form, initially, from phenyl methyl sulfide (see Scheme 13). Greater stability for a radical cation allows for



Scheme 12.



Scheme 13.



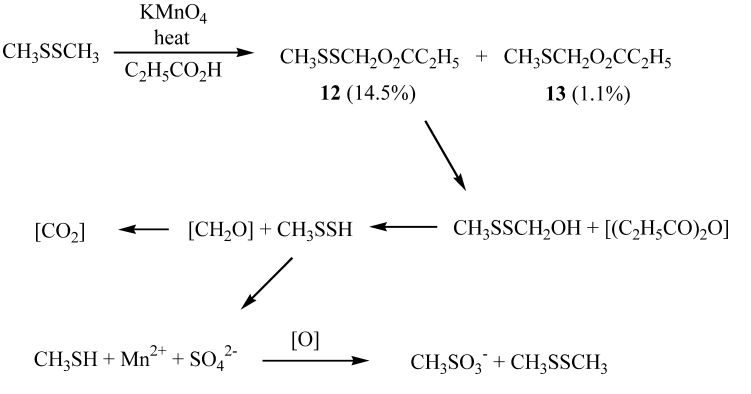
Scheme 14.

alternative chemistry to compete with radical anion/radical cation coupling. Radical coupling without deprotonation should lead to the introduction of oxygen at sulfur.

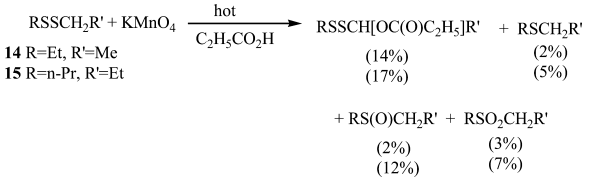
The preceding rationale raises the possibility that other stabilized S-centered radical cations might competitively deprotonate at α-carbon, thereby permitting access to thionium-ion-like species. Application of this notion to dimethyl disulfide would lead to the possibility presented in Scheme 14.

The speculation offered in Scheme 14 assumes that the three-electron bond in the disulfide radical cation would confer stability on it analogous to the conventional resonance stabilization presumed for the phenyl methyl sulfide radical cation (see Scheme 13). Assuming that such chemistry was carried out in a carboxylic acid solvent, it would be expected to furnish a CO-linked α-ester disulfide. These compounds, in turn, might serve as suitable carbon-centered electrophiles for the preparation of, *inter alia*, α-sulfone disulfides 8.

The application of potassium permanganate oxidations to dimethyl disulfide did, indeed, furnish α-ester disulfides. Unhappily, the corresponding α-ester sulfide was also formed. Optimum results for disulfide ester formation [13] are shown in the first line of Scheme 15. In an effort to provide a more compelling mechanistic framework for the novel chemistry depicted in Scheme 15, other products were isolated and identified (*13, 14*). The colorless precipitate, which formed during the permanganate oxidation of dimethyl disulfide in hot propionic acid contained sulfate (31%) and methansulfonate anions (34%). Furthermore, permanganate oxidation of the disulfide propionate 12 furnished dimethyl disulfide (3.3%). Scheme 15 also provides a rationale for these results which presumes that 12 is the key intermediate.



Scheme 15.



Scheme 16.

Scheme 14 provides a clear mechanistic basis for anticipating the formation of the α-ester disulfide 12, but does not deal with the observation of sulfide formation (see Scheme 15). To gain further insight into the chemistry, diethyl disulfide and di-*n*-propyl disulfide were each reacted with permanganate in hot propionic acid. The results are given in Scheme 16.

These results make it very likely that dimethyl disulfide was also transformed into the corresponding sulfide, sulfoxide, and sulfone, which were lost during the reaction itself (volatility) or during the extractive workup as a result of water solubility. Hence, both the starting dialkyl disulfides and the product α-ester disulfides undergo novel sulfur extrusion under these reaction conditions. Scheme 17 provides a complete mechanistic proposal for the formation of the α-ester disulfides and the simple sulfides. Presumably, sulfoxide and sulfone formations consume sulfide formed by sulfur extrusion. Note that the Wagner–Meerwein-like radical-cation rearrangement postulated in Scheme 17 is expected to produce more sulfur extrusion with propyl, which should be the best migrator in the disulfide desulfurizations we examined.

The reaction presented in the first line of Scheme 15 proved to be a reliable way to obtain useful quantities of the disulfide ester 12 for the development of new methodologies for the preparation of unsymmetrical α-substituted disulfides.

2.4.2. *Dibenzoyl peroxidations of disulfides*

Subsequent exploratory work confirmed that the α-ester disulfide 12 was, indeed, a very useful intermediate for the economical construction of a goodly number of unsymmetrical acyclic disulfides. The modest optimized yield of 12 along with unwanted sulfur extrusion (first line of Scheme 15) led to a search for a superior approach to α-ester disulfide preparation. Substantial earlier experience with sulfide chlorinations (Scheme 9) led to speculation about a possible related ionic pathway for the reaction of dimethyl disulfide and dibenzoyl peroxide. The anticipated pathway is depicted in Scheme 18.

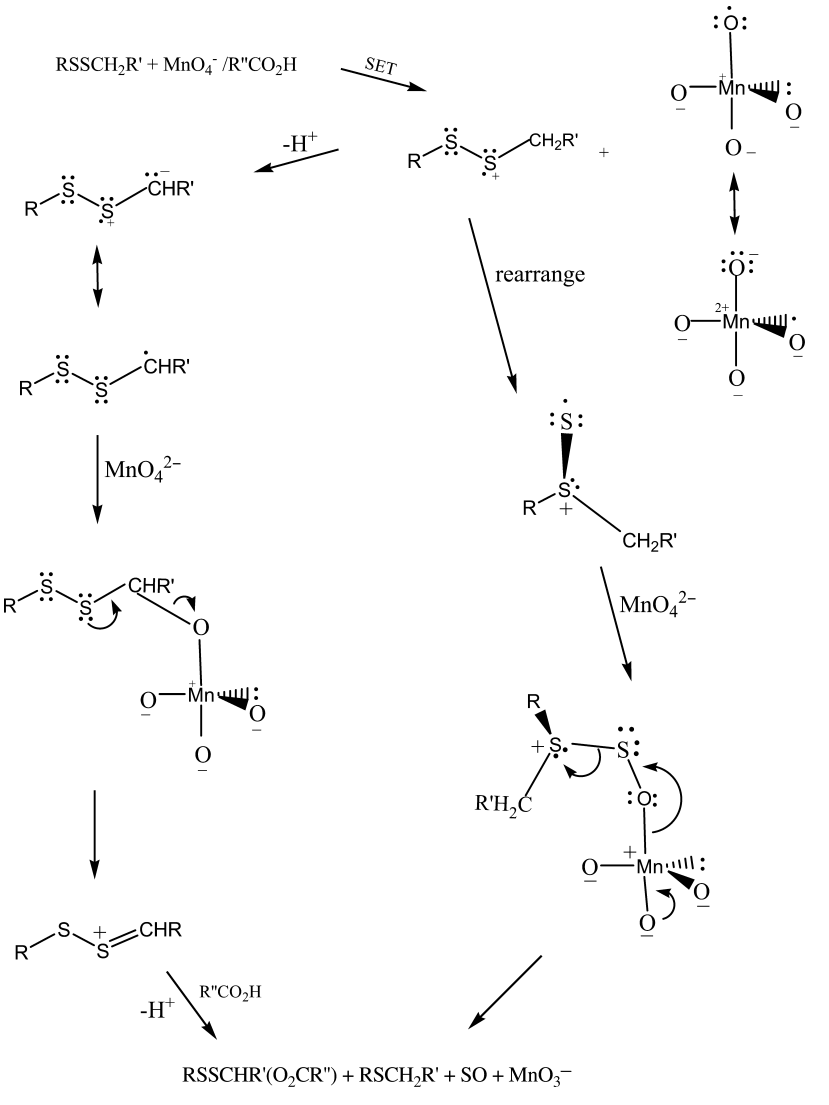
An earlier report (*15*) examined disulfide oxidations with a diacyl peroxide. Because the authors assumed a free-radical pathway, they selected a non-polar solvent (CCl_4) and obtained a very low yield (<1%) of α-ester disulfide. Since we expected an ionic pathway, we chose a more polar solvent ($CHCl_3$). Scheme 19 gives our published results (*16*).

Evidence that α-ester disulfides may be available from ionic pathways of the sort presented in Scheme 18 is provided by the earlier report (*17*) of a successful Pummerer reaction on a thiosulfinate (see Scheme 20).

Although the yield of the α-ester disulfide in Scheme 19 is better than the yield of the corresponding compound in Scheme 15, it is still low and there remains a need for a significantly more effective new method to prepare α-ester disulfides.

2.5. *Conversion of CO-linked α-ester disulfides into α-sulfone disulfides*

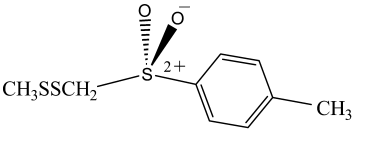
With assured access to α-ester disulfides in hand, work turned to the question of their transformation into α-sulfone disulfides. Sulfinate anions were selected as appropriate nucleophiles and



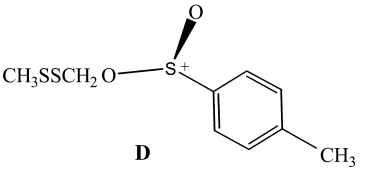
Scheme 17.

either warm aqueous acetone or warm aqueous acteonitrile as appropriate solvent systems. From the beginning (*18*), these substitution reactions went well (see Scheme 21).

Since sulfinate anions are ambident nucleophiles, the substitution product 17 might have been an α-sulfone (*i.e.* C, below) or an α-sulfinate ester (*i.e.* D, below).

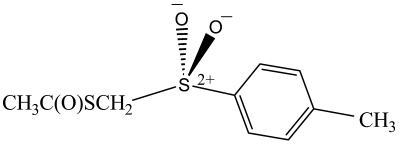


C

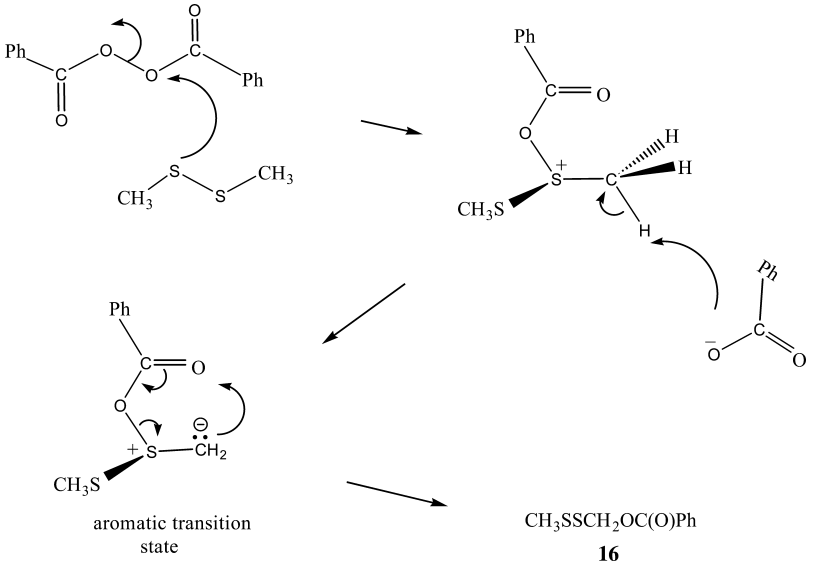


D

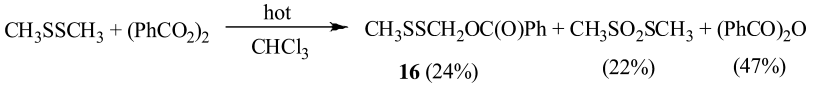
Initial efforts, aimed at settling this question (*18*), involved the unambiguous synthesis of the sulfone α-thiolacetate 18 from *p*-tolyl methyl sulfide.



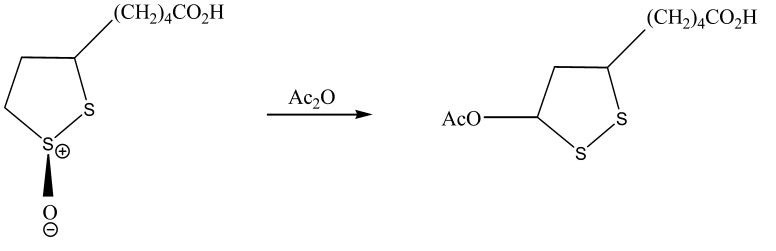
18



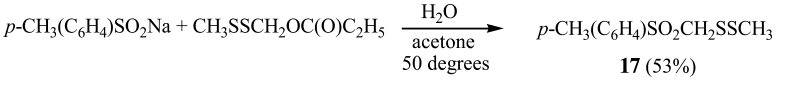
Scheme 18.



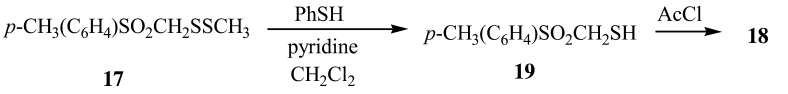
Scheme 19.



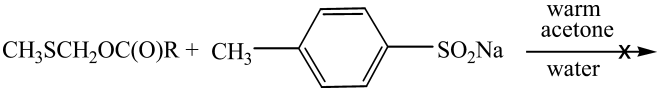
Scheme 20.



Scheme 21.



Scheme 22.



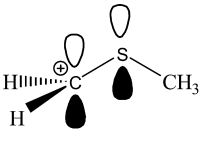
Scheme 23.

Thereafter, 17 was successfully converted into 18 (see Scheme 22) establishing that C is the correct structure for 17.

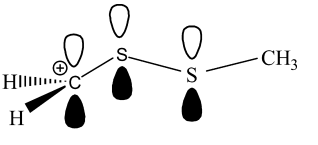
More recently, an X-ray crystal structure determination of 19 has been reported (*19*) offering independent confirmation that 17–19 are all sulfones. Note that, in sharp contrast to the instability of the oily α-mercaptosulfone 9 (Scheme 7), the crystalline α-mercaptosulfone 19 is quite stable with respect to storage.

Some effort was expended to gain insight into the probable mechanism for the novel substitution presented in Scheme 21. Our practice of admixing a protic with an aprotic solvent does not simplify the choice between S_N1 and S_N2 as the likely pathway. Since ester groups are not widely deployed as leaving groups, it seemed likely that the disulfide moiety was assisting in the process. Attempted displacement of the α-ester groups in α-ester sulfides, under our reaction conditions, failed to produce substitution products (*18*) (see Scheme 23).

Thus, the disulfide linkage is promoting the substitution in a manner which the sulfide functionality finds to be difficult or impossible. At the outset, unimolecular substitution seemed the more reasonable mechanism since intermediate cations 20A, 21A would have significantly different π-systems, with 21A offering higher π-electron density and greater charge dispersal.

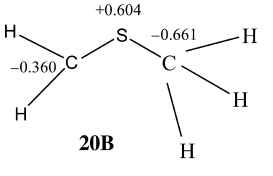


20A

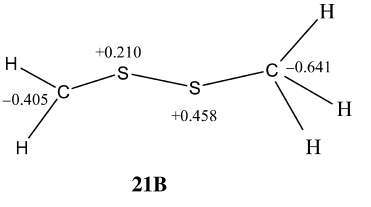


21A

To explore this premise further, a molecular orbital study (*20*) was undertaken on the parent systems 20 and 21. That study included computations at the PM3, DFT, MP2, and G2(MP2) levels of theory. All computations led, unambiguously, to the conclusion that both cations have planar optimized skeleta and that the *sulfide-derived cation* 20 is the more stable cation. The computational results were satisfactorily rationalized on Coulombic grounds. The sulfide-derived cation skeleton is predicted to have alternating partial charge types whereas the disulfide-derived cation has substantial destabilization attending the buildup of positive charge on each sulfur atom (see 20B, 21B for DFT Mulliken charges).



20B



21B

These computational results are in complete accord with Block's findings (*21*) that chloromethyl methyl sulfide undergoes unimolecular hydrolysis 6800 times faster than does chloromethyl methyl disulfide. The computational results do not support Block's rationale, which presumes a non-planar conformation for the skeleton of the disulfide-derived cation. The reasonable conclusion is that Scheme 22 is most likely to proceed by an S_N2 pathway.

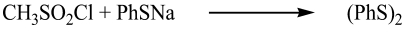
We have prepared many α-sulfone disulfides from CO-linked α-ester disulfides and established that yields near 50% are typical (*e.g.* Scheme 21). Available methodology for the construction of α-sulfone disulfides has moved from the relatively inflexible six-step approach (actually starts from DMSO), the latter part of which is portrayed in Scheme 3, to a much more economical two-step approach (see Schemes 15, 21). The two-step approach is more flexible with regard to the sulfonyl substituent, but can only produce methyl disulfides. Of course, flexibility in the selection of a sulfonyl substituent requires access to a wide selection of sulfinic acid salts. Since only a few such salts are commercially available, the next goal was to improve/modify methodology for the preparation of sulfinic acid salts.

2.6. *Preparation of sulfinic acid salts*

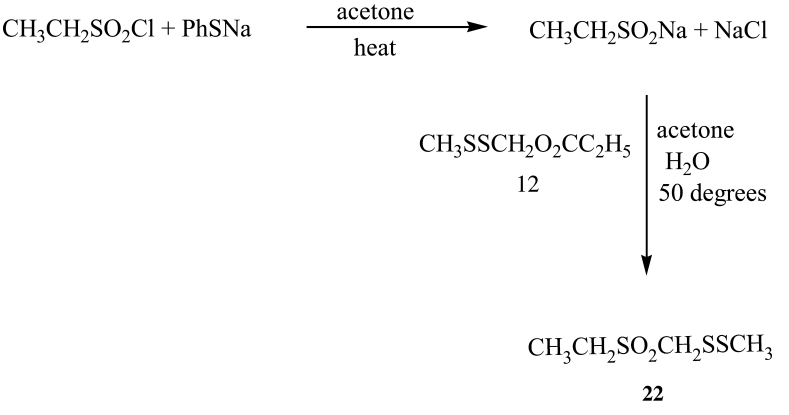
An early, unpublished result, observed in my laboratory, is shown below (see Scheme 24).

No sulfonyl-containing organic-soluble product was obtained. Upon reflection, it seemed likely that Scheme 24 provides a nice example of X-philic attack (*22, 23*) and that the missing product in Scheme 24 is sodium methanesulfinate. Hence, treatment of a sulfonyl chloride with sodium thiophenate in acetone, followed by extractive workup, culminating in discarding the organic layer and concentrating the aqueous layer should and does provide a mixture of sodium chloride and the corresponding sulfinic acid salt. Commonly, a small amount of the corresponding sulfonic acid salt is also present. Scheme 25 portrays the application of this chemistry to the preparation of ethylsulfonylmethyl methyl disulfide 22 as previously reported (*24, 25*).

Although only a modest array of sulfonyl chlorides are commercially available, many can be prepared by exhaustive aqueous chlorinolyses of, *inter alia*, sulfides or disulfides or mercaptans (*11*)



Scheme 24.



Scheme 25.

Ergo, a broad array of sulfinic acid salts are conveniently available for the construction of α-sulfone disulfides from CO-linked α-ester disulfides. With the advent of reasonable flexibility in the selection of the sulfonyl substituent, R, in 8, we began to work on an approach that would provide corresponding flexibility in the choice of the terminal SS substituent, R′, in 8.

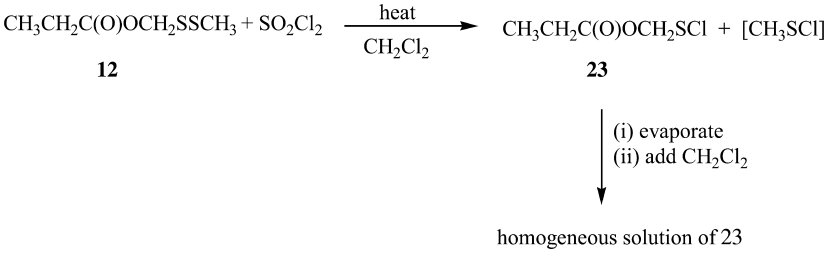
2.7. *Preparation of homogeneous sulfenyl chlorides from unsymmetrical disulfides*

A complete, flexible approach to the construction of α-sulfone disulfides 8 would require access to a synthetic equivalent for $^{+}CH_2S^{+}$. Sulfinate anions could be added to electrophilic carbon and mercaptide anions to electrophilic sulfur. Given the developmental work, just described, we elected to use CO-linked α-ester substituents to establish electrophilicity at carbon. Chlorine was selected as the nucleofugal group to establish electrophilicity at sulfur. The initially-targeted synthetic equivalent for the thioformaldehyde dication was the α-ester sulfenyl chloride 23, which was prepared by mild cleavage of 12 with sulfuryl chloride in warm methylene chloride (*16*) (see Scheme 26).

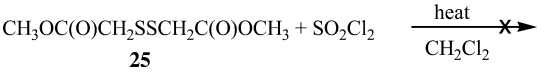
Homogeneous solutions of 23 were easily prepared. Crude reaction product (first line, Scheme 26) was rotary evaporated, which removed the volatiles, methylene chloride and methanesulfenyl chloride. Fresh, dry methylene chloride was added to the residue producing the desired homogeneous sulfenyl chloride solution (Scheme 26).

Later research (*26*) required access to the CC-linked α-ester sulfenyl chloride, $CH_3OC(O)CH_2SCl$ 24. Application of the traditional approach (use a symmetrical disulfide) gave no reaction with sulfuryl chloride (see Scheme 27).

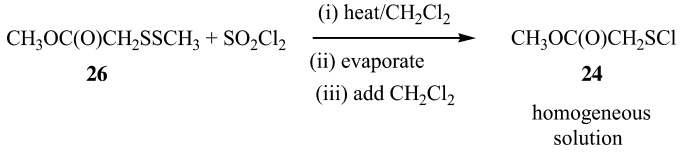
Presumably, the failure of the Scheme 27 reaction is attributable to excessive electron withdrawal by the flanking ester groups. Happily, use of the Schemes 25 and 26 approach worked smoothly (see Scheme 28).



Scheme 26.



Scheme 27.



Scheme 28.

Provided that the target sulfenyl chloride is significantly less volatile than methylene chloride, unsymmetrical methyl disulfides can serve as precursors for the preparation of homogeneous sulfenyl chloride solutions.

The α-ester disulfide 16 was smoothly transformed into the benzoate sulfenyl chloride, $PhC(O)OCH_2SCl$ 27 (*27*), using this same methodology. Thus, two new $^{+}CH_2S^{+}$ synthetic equivalents were available (23 and 27).

2.8. *A flexible synthesis of α-sulfone disulfides* 8

As a part of one of our biological testing programs, a study of the impact of varying hydrocarbon substituent chain lengths on fungitoxicity was undertaken (*25*). One of the α-sulfone disulfides targeted for synthesis was $CH_3(CH_2)_6SO_2CH_2SS(CH_2)_6CH_3$ 28. Although 1-mercaptoheptane was commercially available, the corresponding sodium sulfinic acid salt was not. The requisite sulfinic acid salt was smoothly prepared in two steps (*25*) (see the first line, Scheme 29).

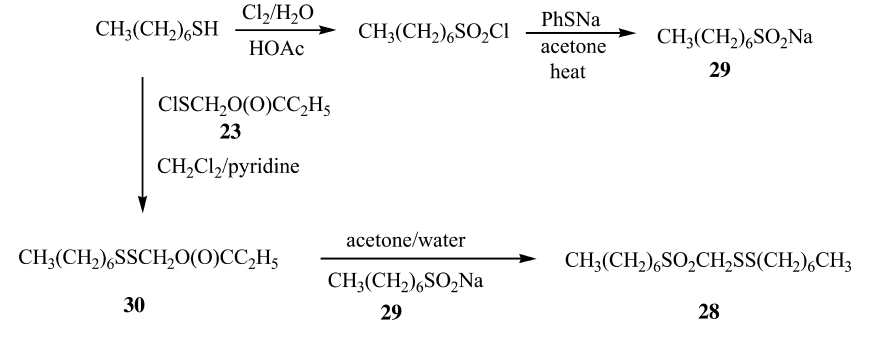
The synthetic equivalent, 23, for the thioformaldehyde dication was condensed with 1-mercaptoheptane to give the α-propionate disulfide 30 (see Scheme 29). Thereafter, the convergent synthesis of 28 was completed (see second line, Scheme 29) and the biological testing carried out. The synthesis of 28 serves to illustrate the methodology that we have relied upon to access an array of α-sulfone disulfides 8 for our biological testing programs.

2.9. *Synthesis of dideoxydysoxysulfone*

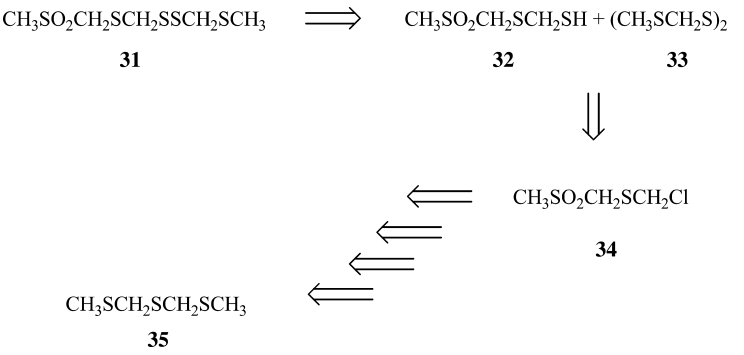
In the beginning, we established (*9*) that appropriate, simple molecules *e.g.* dimethyl sulfone, mesylmethyl methyl sulfide, and methylthiomethyl methyl disulfide lacked the pronounced antifungal activity associated with dysoxysulfone 7. Subsequently, we showed (*2, 9, 16, 18*) that a variety of simple α-sulfone disulfides *e.g.* 28 (*25*) exhibited pronounced antifungal activity. As a result, we felt that the biological activity, especially fungitoxicity, established earlier (*7, 8*) for dysoxysulfone 7, was due to the presence of an α-sulfone disulfide moiety in that compound. It seemed very likely that , absent that functionality, the residual skeleton of 7 would lose its antifungal activity. Dideoxydysoxysulfone 31 was targeted for construction (see retrosynthetic analysis, Scheme 30) and antifungal testing.

Because there was some reason to be concerned about the stability of α-thiomercaptans (see Section 2.3 and Scheme 7), 32 was replaced, in our synthetic plan, with $CH_3SO_2CH_2SCH_2SSCH_3$ 36 which was expected to be quite stable.

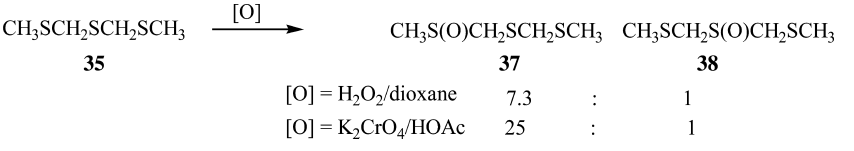
Another consideration played a role in fashioning the Scheme 30 plan. We had a longstanding interest in the outcome of a chlorinolysis reaction on 34 (*28*). For that reason, 34 was selected as the pivotal intermediate in our approach to the synthesis of 31.



Scheme 29.



Scheme 30.



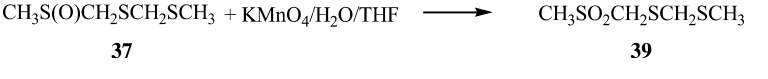
Scheme 31.

Although the trissulfide 35 was previously known (*29*), the earlier preparation was awkward, requiring that sodium sulfide be dried over anhydrous phosporus pentoxide. A modified procedure (*30*) facilitated the preparation of 35. The tris-sulfide was selected because it offers a statistical advantage to oxidation at a penultimate sulfur atom, which is required for the successful synthesis of 36. Exploratory work established that hydrogen peroxide gave good regioselectivity (*30*), but our newly-developed reagent, potassium chromate in refluxing glacial acetic acid (*13*), gave better regioselectivity (see Scheme 31).

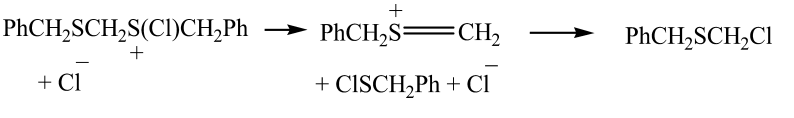
Although the yields of 37 were the same (50%), with each oxidant, the improved purity of crude 37 obtained with chromate, permitted the preparation of the sulfone bissulfide 39 (Scheme 32) without the need to chromatograph 37.

The permanganate oxidation pictured in Scheme 32 employs conditions developed by Henbest and Kahn (*31*). Typically site-selectivity in these sulfur atom oxidations is excellent.

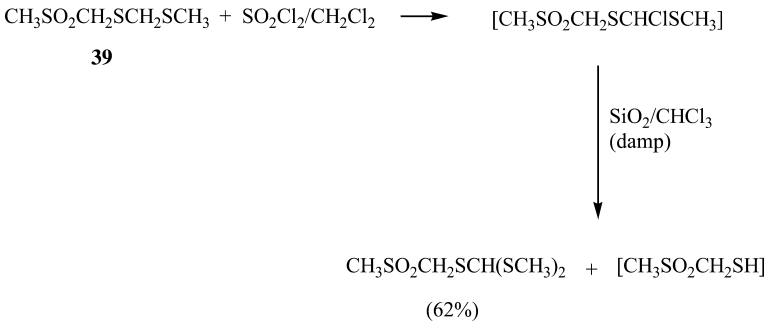
The original plan for chlorosulfone sulfide 34 preparation envisioned chlorination-induced cleavage of the dithioacetal functionality in 39. That expectation rested on our earlier success (*32*) in carrying out such a cleavage during an exhaustive aqueous chlorinolysis (see Scheme 33 for a depiction of the key step).



Scheme 32.



Scheme 33.



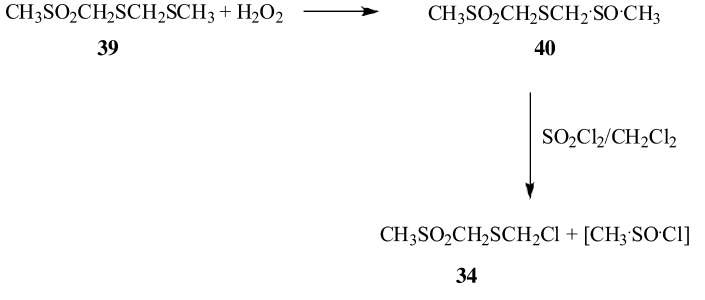
Scheme 34.

Unfortunately, chlorination of 39 in an aprotic medium gave chlorination at carbon (see Scheme 9) to produce a metastable chlorodithioacetal, which decomposed during column chromatography (*30*) (see Scheme 34).

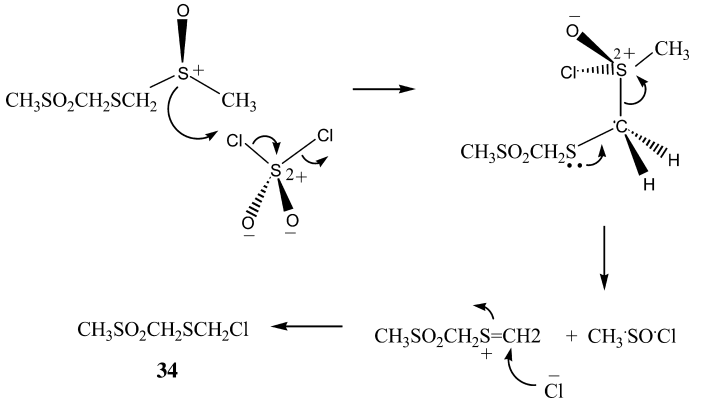
Reasoning that an oxochlorosulfonium cation should be more prone to cleavage, we prepared and chlorinated the sulfone sulfide sulfoxide 40 (*30*) as shown in Scheme 35.

A proposed mechanism for the final step in Scheme 35 is presented in Scheme 36.

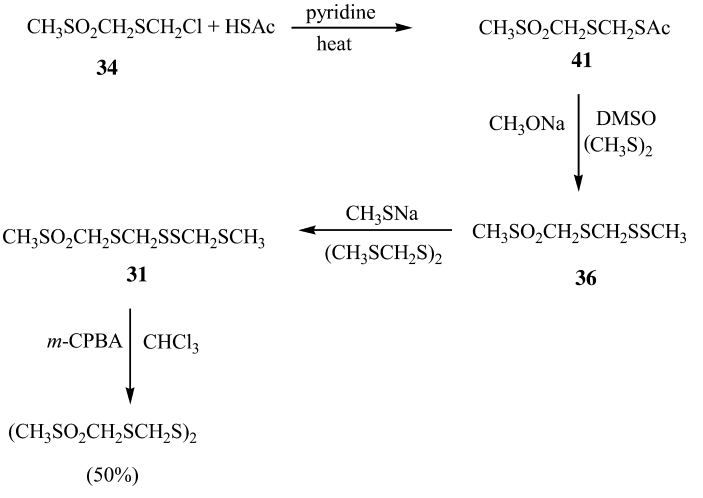
The ideal site selectivities realized in each of the Scheme 35 reactions are noteworthy.



Scheme 35.



Scheme 36.



Scheme 37.

As an aside, exhaustive chlorination of 34 in an aprotic medium gave the longsought answer – incoming chlorine is directed to the central carbon (*30*).

Elaboration of 34 to access the sulfone sulfide disulfide 36 began with the introduction of a thiolacetate group (*33*) (see first line, Scheme 37).

To minimize the risk of decomposition of the expected intermediate anion $[CH_3SO_2CH_2S\ CH_2S]^-$, conditions were developed to facilitate its immediate conversion to the target disulfide 36 (*33*) (see 41 → 36 Scheme 37). Disproportionation employing 36 and 2,4,5,7-tetrathiaoctane (*34*) furnished dideoxydysoxysulfone 31 (see second line, Scheme 37).

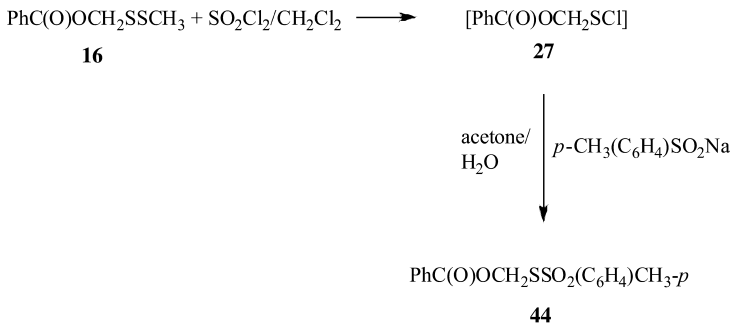
Given Block's synthesis of dysoxysulfone 7 (see Scheme 4), it appeared that the successful synthesis of 31 completed a formal synthesis of dysoxysulfone. Unfortunately, oxidation of 31 uncovered the unexpected result shown as the last line of Scheme 37 and blocked our attempt to obtain dysoxysulfone 7 from 31 (*33*).

2.10. *Synthesis of some α-sulfide disulfides*

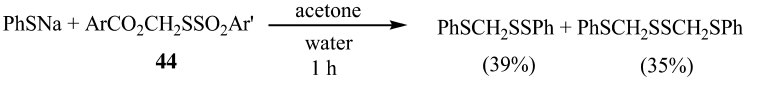
The development of the $^+CH_2S^+$ synthetic equivalent, 23 (Section 2.7), permitted access to a wide variety of α-sulfone disulfides for biological testing. Nonetheless, 23 is difficult to purify well, has a foul odour and requires freezer storage. Moreover, early biological test results suggested that the α-sulfide disulfide functionality, a moiety present in dysoxysulfone 7, might have some anticancer activity. These considerations led us to target the development of a new, crystalline, stable $^+CH_2S^+$ synthetic equivalent which would be applied to the one-pot construction of the quasi-symmetrical α-sulfide disulfides $RSCH_2SSR$ 42.

A new reagent was envisioned which would exploit an α-ester as the leaving group from carbon but would replace the sulfur leaving group, Cl in 23, with a sulfonyl group. The hope was that a thiosulfonate ester could be found that was nicely crystalline. A pair of thiosulfonate propionates, $RSO_2SCH_2OC(O)C_2H_5$ 43, were prepared but proved to be persistent oils (*27*).

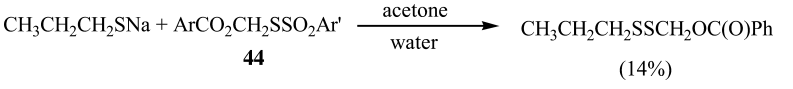
In the next phase, the ester group was changed to a benzoate, which led to the preparation of a very nicely crystalline, stable $^+CH_2S^+$ synthetic equivalent that had no perceptible odour (see Scheme 38).



Scheme 38.



Scheme 39.



Scheme 40.

The new reagent, 44, converted aryl mercaptans into the corresponding quasi-symmetrical α-sulfide disulfides, 42, along with the symmetrical bissulfide disulfides. Scheme 39 presents a typical result (*27*).

Unexpectedly, mercaptide anions from alkyl mercaptans failed to give the target α-sulfide disulfides. Instead, typical reactions (see Scheme 40) stopped at the benzoate disulfide stage (*27*).

The greater difficulty of reactions involving alkyl mercaptide anions and 44 may signal that aryl mercaptide anions reduce thiosulfonates by means of a single-electron transfer mechanism, which should not be as readily available to the alkyl systems. Later biological testing discouraged further interest in α-sulfide disulfides.

3. The practical side: improved techniques

3.1. *Improved vacuum distillations*

Throughout the course of the experimental work described herein, it has been necessary to subject some samples to vacuum distillation. Sample sizes ranged from 0.1 to 100 g. Routine vacuum distillation with commercial glassware has led to substantial losses of material, which did not end up in the receiving flask. On the other hand, the standard short-path apparatus with a Kugelrohr oven, typically does not permit one to obtain the mass of the distillate or its boiling point and is not readily adapted to the distillation of larger quantities.

We have developed, and routinely deploy, a set of short-path distillation apparati along with the attendant technique, which readily accommodate any size sample, providing yield, boiling point information, and excellent recoveries. The apparatus design and the technique have been described in detail (*35*). The distillation technique in question has been particularly helpful in the purification of the pivotal compounds 12, 16, 23, and 35.

3.2. *Bundled column chromatography*

Conventional column chromatography has proved to be very useful for the routine purification of organic compounds. When successful synthetic work leads to a need for larger amounts of precursor, column chromatography becomes more and more cumbersome, largely due to increased times for sample elution and product isolation. Moreover, when compounds prove to be metastable with respect to column chromatography, larger columns can provide less product (both % recovered and number of grams recovered).

Although we have previously noted both the tedium of routine large-scale column chromatography and the problem of metastable compound decomposition during column chromatography, it was not until our research required routine preparation of the benzoate disulfide 16 that we allocated the time and effort needed to modify the technique. We have developed an apparatus (*36*), which employs a dozen parallel chromatography columns that are run simultaneously. The technique, bundled chromatography, significantly diminishes eluting time and maximizes recoveries of metastable compounds. Compound 16 is now routinely purified by bundled chromatography (*36*).

4. Biological activities

4.1. *Disulfides as antifungal agents*

4.1.1. α-*Sulfone disulfides as fungitoxins*

Given Block's report (*8*) of antifungal activity for dysoxysulfone 7, we have undertaken a research program intended to reveal the pharmacore in dysoxysulfone 7 and, thereafter, to develop more effective antifungals based on any rationale for structure–activity relationships that our work might bring to light. A*spergillus niger* and *Aspergillus flavus* were selected as representative fungi to use in testing sulfur antifungals.

Initially, small molecules, which featured a variety of the sulfur functional groups found in 7, were shown to be harmless to our representative fungi (see Table 1).

The sole remaining bifunctional moiety in dysoxysulfone 7, the α-sulfone disulfide group, proved to be associated with pronounced fungitoxicity (see Table 2).

To explore the question of pharmacore topology, a pair of homologues of 45 (Table 2), $CH_3SO_2(CH_2)_2SSCH_3$ and $CH_3SO_2(CH_2)_3SSCH_3$, were tested and shown to be inactive against *A. niger* and *A. flavus*. Hence, the conclusion that dysoxysulfone 7 is a fungitoxin because it is an α-sulfone disulfide.

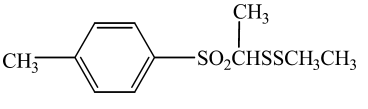
Table 1. Antifungal testing of selected sulfur compounds (*9*). Each compound was introduced onto a small paper disk which was placed in a culture medium. The diameter of the clear zone (the area where fungus – *Aspergillus niger* or *Aspergillus flavus* – did not grow) around each disk quantified antifungal activity.

		Diameter (mm) of clear zone	
Compound tested	Dose (μg/disk)	*A. niger*	*A. flavus*
$CH_3SO_2CH_3$	100	0	0
CH_3SSCH_3	100	0	0
$CH_3SCH_2SCH_2SCH_3$	100	0	0
$CH_3SO_2CH_2SCH_3$	100	0	0
$CH_3SO_2CH_2SCH_2SO_2CH_3$	100	0	0
$CH_3SCH_2SSCH_3$	100	0	0

Table 2. Antifungal testing of simple α-sulfone disulfides (*9, 18*). The diameter of the clear zone is a direct measure of antifungal activity for the specified dose level (see Table 1).

Compound tested	Dose (μg/disk)	Diameter (mm) of clear zone	
		A. niger	*A. flavus*
$CH_3SO_2CH_2SSPh$ 5	25	0.8	1.8
p-$CH_3(C_6H_4)SO_2CH_2SSCH_3$ 17	25	10.9	8.0
$CH_3SO_2CH_2SSCH_2CH_3$	25	4.8	3.3
$CH_3SO_2CH_2SSCH_3$ 45	25	2.7	3.8

In attempting to modify small α-sulfone disulfides (*e.g.* 45, Table 2), it is inevitable that more carbon atoms would be introduced. Optimizing pharmacological activity requires one to balance hydrophilicity (required for mobility in cytoplasm) and lipophilicity (required for transport across membranes) (*37*). Thus, increasing carbon content, in the form of alkyl groups, enhances lipophilicity at the expense of hydrophilicity. Branching is believed to depress cytoplasm transport by a modest amount (*37*). In accord with the latter point, the introduction of a methyl group on the central carbon of the α-sulfone disulfide moiety appears to be responsible for the sharply diminished fungitoxicity of 46 (*25*) (less than half the clear zone diameters presented for 17 in Table 2).



46

Test results for 46 discouraged us from preparing/testing other systems bearing central substituents and led to a focus on α-sulfone disulfides as defined in 8.

An examination of unbranched hydrocarbon chain-length variation uncovered the most potent of the simple α-sulfone disulfides we have examined (*25*) (see Table 3).

As an aside, we had one opportunity to compare sufonyl and sulfinyl groups as disulfide activators in the antifungal test arena (*2*). The results suggest that α-sulfinyl disulfides may well be worth further examination vis a vis biological activity (Table 4).

With clear evidence that α-sulfone disulfides are effective fungitoxins and that efficacy is sensitive to substituent chain lengths, we turned to the question of dysoxysulfone 7 as a fungitoxin. First we constructed a reference α-sulfone disulfide $CH_3SO_2CH_2SS(CH_2)_4CH_3$ 48 which, like 7 itself, had an unbranched backbone of 10 heavy atoms. Secondly, dideoxydysoxysulfone 31 was constructed in the manner outlined in Section 2.9. In accord with our contention, 31 is a much weaker antifungal agent than 48. Thirdly, we prepared and tested 49, which was inactive against our representative fungi (see Table 5).

Table 3. Optimized simple α-sulfone disulfide fungitoxins (*25*). The diameter of the clear zone is a direct measure of antifungal activity for the specified dose level (see Table 1).

Compound tested	Dose (μg/disk)	Diameter (mm) of clear zone	
		A. niger	*A. flavus*
$CH_3SO_2CH_2SS(CH_2)_6CH_3$	2.5	2.9	3.8
$CH_3(CH_2)_6SO_2CH_2SSCH_3$ 47	2.5	3.2	2.9

Table 4. An α-sulfoxide disulfide as a fungitoxin (*2*). The diameter of the clear zone is a direct measure of antifungal activity for the specified dose level (see Table 1).

Compound tested	Dose (μg/disk)	Diameter (mm) of clear zone	
		A. niger	*A. flavus*
$CH_3SO_2CH_2SSCH_2SCH_3$	50	1.5	1.3
$CH_3S(O)CH_2SSCH_2SCH_3$	50	4.3	3.0

Table 5. Antifungal activities for some dysoxysulfone relatives (*25, 33*). The diameter of the clear zone is a direct measure of antifungal activity for the specified dose level (see Table 1).

Compound tested	Dose (μg/disk)	Diameter (mm) of clear zone	
		A. niger	*A. flavus*
$CH_3SO_2CH_2SS(CH_2)_4CH_3$ 48	25	13.8	11.7
$CH_3SO_2CH_2SCH_2SSCH_2SCH_3$ 31	25	1.9	2.7
$CH_3SO_2(CH_2)_3SSCH_2SCH_3$ 49	100	0.0	0.0

The test results are presented in Tables 1–5 provide a basis for mechanistic speculation. There are two straightforward possibilities, which would account for the fact that α-sulfone disulfides show biological activities, while compounds cited in Table 1, do not. First, the sulfonyl group acidifies α-protons, which might facilitate an elimination reaction as shown in Scheme 41.

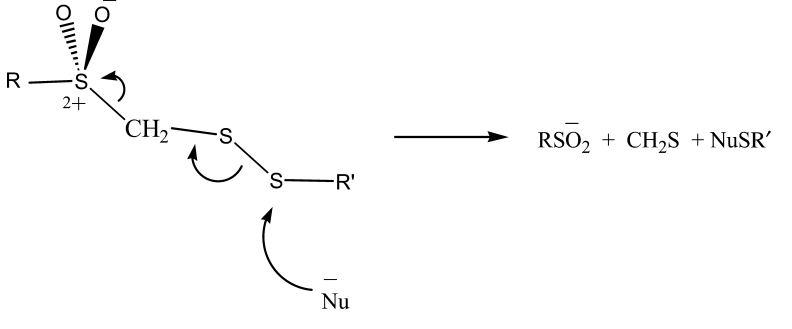
The thiocarbonyl group in 50 (Scheme 41) could then serve as a reactive electrophile (at either carbon or sulfur) which could add to biochemically significant nucleophilic sites.

Alternatively, the sulfonyl group might serve as an activator, which facilitates soft base attack at the remote disulfide sulfur as envisioned in Scheme 42. In Scheme 42, the biochemically significant nucleophilic site would be sequestered by thioalkylation.

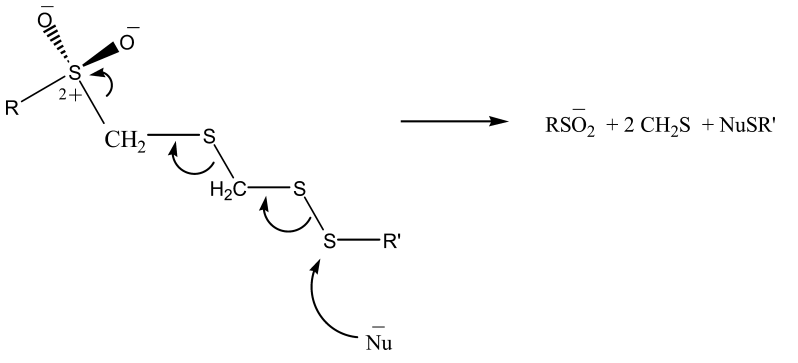
The results in Table 5 conform to the mechanism in Scheme 42. Both 31 and 49 have been deprived of significantly enhanced acidic protons on carbon α to the disulfide linkage. However, only 31 provides a link between the sulfonyl sulfur and the disulfide moiety, which permits

$$RSO_2CH_2SSR' + \text{Base} \longrightarrow \underset{\mathbf{50}}{RSO_2HC{=}S} + \overset{+}{B}H + \overset{-}{S}R'$$

Scheme 41.



Scheme 42.



Scheme 43.

Table 6. Linkage isomeric α-ester disulfides as fungitoxins (*9*). The diameter of the clear zone is a direct measure of antifungal activity for the specified dose level (see Table 1).

Compound tested	Dose (μg/disk)	Diameter (mm) of clear zone	
		A. niger	*A. flavus*
$CH_3SSCH_2C(O)OCH_3$ 51	100	0.0	0.0
$CH_3SSCH_2OC(O)CH_3$ 52	100	2.3	2.3
$CH_3SSCH_2CH_2OC(O)CH_3$ 53	100	0.0	0.0

dampened reactivity of the sort proposed in Scheme 42 (see Scheme 43). Hence, the differences in fungitoxicity between 31 and 49 are rationalized.

To shed more light on the mechanistic dichotomy presented in Schemes 41 and 42, a pair of linkage isomeric α-ester disulfides were prepared and tested (see Table 6).

Unlike α-sulfone disulfides, linkage isomeric α-ester disulfides provide individual structures, which are unable to do both Schemes 41 and 42 reactions. The CC-linked isomer 51 could only pursue the mechanism in Scheme 41 but shows no antifungal activity. In contrast, the CO-linked isomer 52 could only follow the mechanism in Scheme 42 and does show antifungal activity. Thus, the Table 6 results provide additional support for the Scheme 42 view.

Assuming that *in vivo* antifungal activity is more realistically depicted in Scheme 42, α-sulfone disulfides can be regarded as activated electrophiles, which should show significant selectivity for soft base sites. Given their high thiophilicity, biochemically significant mercaptide anions should be attractive target sites for α-sulfone disulfides.

The decision to employ α-ester disulfides as mechanistic probes for fungitoxicity revealed that the CO-linked α-esters may have useful activity and, as a result, testing of selected ester disulfides was initiated.

4.1.2. *CO-linked* α*-ester disulfides as fungitoxins*

The ester test results in Table 6 establish that biological activity requires both CO linkage and α-attachment for efficacious antifungal ester disulfides.

Consistent with the Table 3 results, moderately increased carbon content, on one side of the ester disulfide moiety, led to significantly enhanced fungitoxicity. Branching at the central carbon had an even more deleterious effect on the fungitoxicity of α-ester disulfides (see Table 7) than was observed for branching in an α-sulfone disulfide (see discussion of 46).

Table 7. Antifungal activities for some CO-linked α-ester disulfides (*16, 18, 25*). The diameter of the clear zone is a direct measure of antifungal activity for the specified dose level (see Table 1).

Compound tested	Dose (μg/disk)	Diameter (mm) of clear zone	
		A. niger	*A. flavus*
$CH_3SSCH_2OC(O)Ph$ 16	2.5	3.1	3.9
$PhSSCH_2OC(O)C_2H_5$ 53a	2.5	3.5	2.3
$CH_3SSCH_2OC(O)C_2H_5$	25.0	14.8	7.6
$CH_3CH_2SSCH(CH_3)OC(O)C_2H_5$	100.0	0.0	0.0
$C_3H_7SSCH(C_2H_5)OC(O)C_2H_5$	100.0	0.0	0.0

Table 8. Antifungal activities for α, α′ disubstituted disulfides (*2*). The diameter of the clear zonc is a direct measure of antifungal activity for the specified dose level (see Table 1).

Compound tested	Dose (μg/disk)	Diameter (mm) of clear zone	
		A. niger	*A. flavus*
$CH_3OC(O)CH_2SSCH_2C(O)OCH_3$ 55	100.0	0.0	0.0
$CH_3OC(O)CH_2SSCH_2OC(O)C_2H_5$ 56	0.25	3.0	2.3
$C_2H_5C(O)OCH_2SSCH_2OC(O)C_2H_5$ 57	0.25	3.6	6.7
$C_2H_5C(O)OCH_2SSCH_2SO_2(C_6H_4)CH_3$-*p* 58	0.25	8.5	5.2

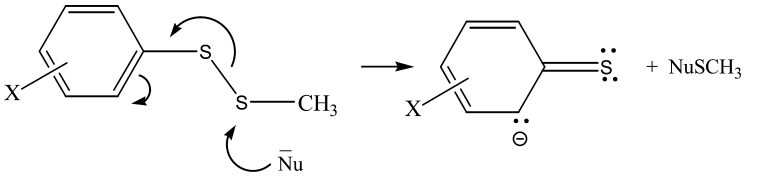
Note that, although some simple α-ester disulfides exhibit significant fungitoxicity, as plates aged, disks were overgrown more completely and much sooner than was observed for disks impregnated with α-sulfone disulfides. Presumably, esters hydrolyze after longer periods in aqueous media leading to loss of their antifungal activity.

In the final stage of α-ester disulfide synthesis and testing, we elected to construct α, α′ functionalized disulfides $C_2H_5C(O)OCH_2SSCH_2X$ 54. First, we prepared a CC-linked α, α′-diester disulfide 55 to confirm that an additional CC-linked ester would not induce antifungal activity. The structures, 54 (55→ 58) in which X was varied through a CC-linked ester group, a CO-linked ester group and a sulfonyl group, led to the most potent fungitoxins we have prepared and examined (see Table 8).

Test results on 56→ 58 were sufficiently good that we tested the commercial antifungal agents Griseofulvin, Nystatin, and Amphotericin B against *A. niger* and *A. flavus* for comparison with our antifungals. Both 57 and 58 were superior to the best of the commercial antifungals, Amphotericin B, against our test fungi (*2*).

4.1.3. *Aryl disulfides as fungitoxins*

Given the proposed mechanistic basis (Schemes 42 and 43) for the antifungal activities of α-sulfone disulfides, which applies equally well to fungitoxic CO-linked α-ester disulfides (Tables 7 and 8), we undertook the development of a new type of fungitoxic disulfide. For those agents, disulfide activation was introduced by means of an attached π-system that might have its activating effect enhanced when good electron-withdrawers were appended to it. Scheme 44 depicts anticipated behavior of antifungal aryl disulfides.

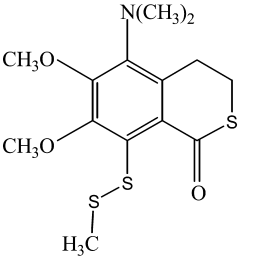


Scheme 44.

Neither phenyl methyl disulfide nor diphenyl disulfide showed detectable antifungal activity (100 μg/disk) against either *A. niger* or *A. flavus.* Hence, good electron-withdrawers must be attached to the phenyl ring if any fungitoxic behavior is to be observed. Table 9 presents test results for aryl disulfides in which the phenyl ring bears a nitro group, or an ester group, or a sulfonyl group.

Each system tested in Table 9 showed good fungitoxicity. The best antifungal aryl disulfide employed the most powerful electron withdrawer (nitro) in the para position as would be expected on the basis of Scheme 44 and rudimentary resonance arguments. Note that the replacement of methyl by heptyl (last two cases, Table 9) apparently makes the last structure too hydrophobic, thereby significantly depressing its fungitoxic behavior.

A modest set of naturally-occurring disulfides have been isolated from *Polycarpa auzata* (*39*). Of these disulfides, 60 → 62, only 60 showed *in vitro* inhibition of the fungi *Saccharomyces cerevisiae* and *Candida albicans* (*39*).



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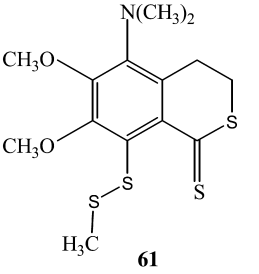

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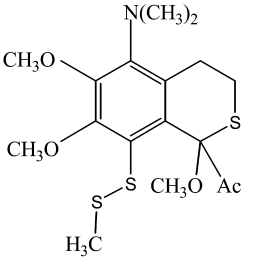


62

Given the Scheme 44 rationale, it is not surprising that the only antifungal polycarpamine is the one with a credible electronwithdrawing group, a carbonyl, located in a suitable position to activate the disulfide linkage *i.e.* 60.

Table 9. Antifungal activities for aryl disulfides (*25, 38*). The diameter of the clear zone is a direct measure of antifungal activity for the specified dose level (see Table 1).

Compound tested	Dose (μg/disk)	Diameter (mm) of clear zone	
		A. niger	*A. flavus*
o-$CH_3OC(O)(C_6H_4)SSCH_3$	25	2.8	4.3
[*p*-$CH_3SO_2(C_6H_4)S]_2$	25	4.0	6.9
m-$O_2N(C_6H_4)SSCH_3$	10	1.7	1.8
o-$O_2N(C_6H_4)SSCH_3$	10	2.8	1.9
p-$O_2N(C_6H_4)SSCH_3$ 59	10	3.9	4.0
p-$O_2N(C_6H_4)SS(CH_2)_6CH_3$	25	2.9	2.4

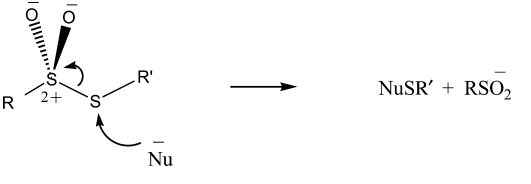
4.1.4. *Broad antifungal screening*

Two α-sulfone disulfides (17, Table 2; 47, Table 3) and our best aryl disulfide (59, Table 9) were tested against 10 species of three phyla classified as true fungi (Zygomycota, Acomycota, Basidomycota) and two species of Oomycota (Stramenopila) (*40*). At 100 μg/disk none of our disulfides inhibited growth of either Oomycete. Although the true fungi showed differences in their sensitivity to the test disulfides, five species were most inhibited by 17 and three species were most inhibited by 59 (*40*).

4.2. *Thiosulfonates as fungitoxins*

Although the thiosulfonate moiety is not a disulfide, it is closely related. Thiosulfonates are included here, because our decision to explore their antifungal potential derived from the mechanistic proposals, already advanced herein, for disulfide antifungal behavior. We reasoned that enhanced electrophilicity at sufenyl sulfur might be induced by direct modification of the disulfide linkage itself (see Scheme 45 and compare with Schemes 42–44).

Table 10 presents selected results from our examination of ten thiosulfonates.



Scheme 45.

Table 10. Antifungal activities for thiosulfonates (*24*). The diameter of the clear zone is a direct measure of antifungal activity for the specified dose level (see Table 1).

Compound tested	Dose (μg/disk)	Diameter (mm) of clear zone	
		A. niger	*A. flavus*
$C_6H_5SO_2SC_6H_5$ 63	25	3.9	3.8
p-$CH_3(C_6H_4)SO_2SC_6H_5$ 64	25	4.3	3.3
$CH_3SO_2SCH_3$ 65	100	3.3	0.0
$CH_3SO_2SC_6H_5$ 66	25	0.0	3.7

Table 11. Sulfur compounds as *in vitro* antithrombotic agents (*41, 42*). Aggregation experiments were performed with 350 μL of washed platelets at 25°C with constant stirring in an optical aggregometer (Chrono-log Corp.). Platelets were incubated for 3 min with 100 μM of test compound prior to initiation of aggregation with 0.01 U of thrombin. IC_{50} is the concentration required to inhibit platelet aggregation by 50%.

Compound tested	Antithrombotic (100 μM dose)	IC_{50} (μM)
$CH_3SO_2CH_2SSPh$ 5	YES	5
$CH_3SO_2CH_2SPh$	NO	–
$CH_3SO_2CH_2SSCH_2CH_3$	NO	–
p-$O_2N(C_6H_4)SSCH_3$ 59	YES	20
p-$O_2N(C_6H_4)CH_2SSCH_3$	NO	–
p-$O_2N(C_6H_4)SS(CH_2)_6CH_3$	YES	10
[*p*-$CH_3SO_2(C_6H_4)S]_2$	YES	5

In Table 10, results for 63 and 64 are the best we obtained for antifungal thiosulfonates. Clearly, the thiosulfonates examined are much weaker fungitoxins than our best disulfides are. The most interesting feature of our thiosulfonate test results is the finding of very high selectivity for 65 and 66. This opens the possibility, not observed for disulfides, that one could kill one kind of fungus in the presence of others using thiosulfonate antifungals.

4.3. *Disulfides as antithrombotic agents*

In accord with our findings for fungitoxicity, the best antithrombotic disulfides tested were either α-sulfone disulfides or aryl disulfides in which the aromatic ring bears a good electron-withdrawing group. In contradistinction to the antifungal test results, antithrombotic efficacy requires that one carbon attached to the disulfide linkage be trigonal. Key results are given in Table 11.

Note that one of the very best antithrombotic agents, in the published study, was *p*-nitrophenyl methanethiosulfonate (*42*) (not shown in Table 11).

4.4. *Disulfides as antimalarial agents*

A brief study of disulfides as antimalarial agents has been reported (*43*). Tests were conducted on two malaria cell lines (*Plasmodium falciparum*), *Malaria ItG* and *Malaria 3D7* as well as a representative mammalian cell line (Chinese hamster ovary or CHO cells). Three of our compounds (an α-sulfone disulfide, a β-sulfone disulfide and a CC-linked α-ester disulfide) showed pronounced selectivity – *i.e.* low dose levels for antimalarial activity and high dose levels for inhibition of normal (CHO) cells. These results are portrayed in Table 12.

Table 12. Disulfides as *in vitro* antimalarial agents (*43*). IC_{50} is the amount of each compound that resulted in 50% inhibition of malaria cells and representative mammalian (CHO) cells.

	IC_{50} ($\mu g/mL^{-1}$)		
Compound tested	Malaria ItG	Malaria 3D7	CHO cells
p-$CH_3(C_6H_4)SO_2CH_2SSCH_3$ 17	20 ± 8	1.6 ± 0.4	~200
$CH_3SO_2CH_2CH_2SSCH_3$ 67	35 ± 11	2.0 ± 0.4	>200
$CH_3SSCH_2C(O)OCH_3$ 51	40 ± 17	15 ± 5	>200

4.5. *Disulfides as antileukemic agents*

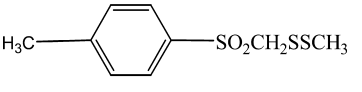
Our initial report (*44*), which examines a set of sulfur compounds as antileukemic agents, described testing against an acute myelogenous leukemia cell line (AML-3) and an acute lymphotic leukemia cell line (KK). Non-transformed (*i.e.* normal) cells were represented by a human diploid fibroblast cell line (WI38). Although the simple α-sulfone disulfides 5 and 17 showed good inhibition of both leukemic cell lines (AML-3 and KK), they induced pronounced decreases in normal cell (WI38) viability. Similar findings were revealed for the CO-linked α-ester disulfide, 2,3-dithiabutyl acetate. On the other hand, both the β-sulfone disulfide 67 and the CC linked α-ester disulfide 51 (see Table 12 for structures) showed reasonable inhibition of the leukemic cell lines and failed to decrease the viability of the WI38 cell line. The superior selectivity of 51 and 67 led to an examination of selected structural relatives which has not yet been published. Note that similar results were observed for 51 and 67 when they were tested against a human skin cancer cell line (*43*).

In a second study (*45*), improved selectivity was observed for one α-sulfone disulfide, 48 (see Table 5 for structure) and one CO-linked α-ester disulfide, 53a (see Table 7 for structure). The only thiosulfonate examined, CH_3SO_2SPh 68, also showed interesting and potentially useful selectivity.

4.6. *Disulfides as inhibitors of the phagocytosis of anti-Rh(D)-coated red blood cells*

Immune cytopenias are the pathological conditions in which red blood cells become coated with antibodies and are subsequently recognized by Fc-γ receptors on the mononuclear phagocyte membrane that can lead to human morbidity. We targeted membrane thiol groups on phagocytes hoping to derivatize them and inhibit this destructive behavior. Based on the mechanistic proposals presented in Schemes 42–44, we chose activated disulfides as trans-sulfenylating agents.

Although the representative α-sulfone disulfide 17 inhibited phagocytosis effectively at 10^{-4} M, *p*-nitrophenyl methyl disulfide 59 was more than twice as effective as 17 at low dose (10^{-9} M) levels (*46*).



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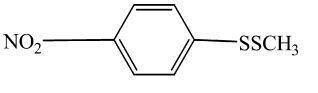
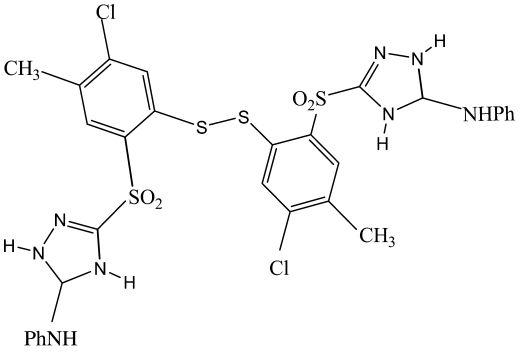


59

To support the assumption that direct attachment of a π-system to the disulfide, establishes biological activity, we tested phenyl methyl disulfide, which proved to be about half as effective as 59 in inhibiting the phagocytosis of anti-Rh(D)-coated red blood cells (*47*). Furthermore, *p*-nitrobenzyl methyl sulfide was nearly inactive. Hence, the promising biological activity of 59 results from the cumulative electron-withdrawing effect of both the phenyl and nitro groups in 59.

4.7. *Disulfides and other biological activities*

Note that some suitably substituted aryl disulfides (see Section 4.1.3 for a structure-activity rationale) have been successfully applied to other health problems. Compound 69 has established antiviral activity against HIV-1 in proliferating T-cell cultures (*48*).



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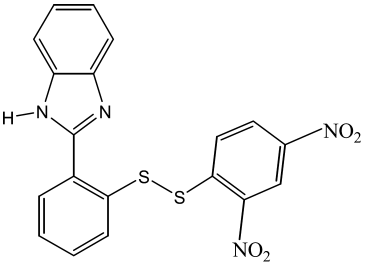
Compound 70 has been patented for use in inhibiting the production of Interleukin-1-β and Tumour Necrosis Factor-α (*49*).



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