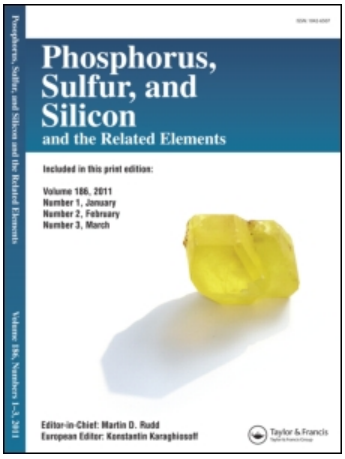

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Sulfoxides and Sulfines: Some Synthetic Applications

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SULFOXIDES AND SULFINES: SOME SYNTHETIC APPLICATIONS

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Abstract Our initial interest in the sulfoxide group arose from some photochemical investigations in this area. We subsequently turned our attention to the resolution of two important methodological problems in organic sulfur chemistry — the reduction (deoxygenation) of sulfoxides to sulfides and, albeit somewhat less successfully, the reduction of sulfones to sulfides or sulfoxides. Currently, we have been exploring the application of a novel intramolecular sila–Pummerer reaction to the construction of ring D in the eudistomin series of alkaloids, several of which possess interesting antiviral and antitumor properties.

Our interest in sulfines was originally an offshoot of our work on the reduction of sulfoxides and from our attempts to identify unambiguously the thiosulfine (>C=S(S)) functional group. Recently, we have explored the cycloaddition reactions of a number of *α*–oxosulfines. The quite distinct reaction pathways available to this interesting sub–class of sulfines are presented and discussed.

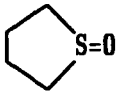
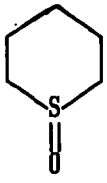
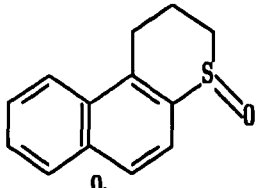
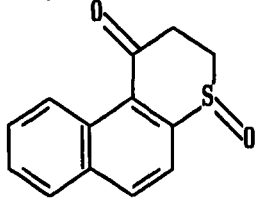
DEOXYGENATION OF SULFOXIDES

We first began our studies in organosulfur chemistry, with an investigation of the photochemical behavior of sulfoxides and sulfones.[1] Reliable procedures for the reduction of sulfoxides to sulfides were not at the time readily available and we set out to correct this deficiency.

The first successful reagent to be discovered was phosphorus pentasulfide (P_4S_{10}), an inexpensive reagent already well known for its use in the conversion of >C=O into >C=S. Some of our results using P_4S_{10} are summarized in Table I.[2]

$$RS\overset{\overset{O}{\|}}{R}R' \xrightarrow[CH_2Cl_2,\ 25^\circ C]{P_4S_{10}} RSR' \qquad (1)$$

TABLE I Reduction of sulfoxides to sulfides with P_4S_{10} at 25°C in CH_2Cl_2.

Sulfoxide	Yield[a,b] of Sulfide (%)
$(CH_3)_2SO$	67
$(n\text{-}C_4H_9)_2SO$	51
$(sec\text{-}C_4H_9)_2SO$	42
$(tert\text{-}C_4H_9)_2SO$	69
	50
	31
$(C_6H_5CH_2)_2SO$	61
$(C_6H_5)_2SO$	72
$(p\text{-}CH_3C_6H_4)_2SO$	99
$(p\text{-}ClC_6H_4)_2SO$	61[c]
$(p\text{-}CH_3OC_6H_4)_2SO$	100
	78
	60

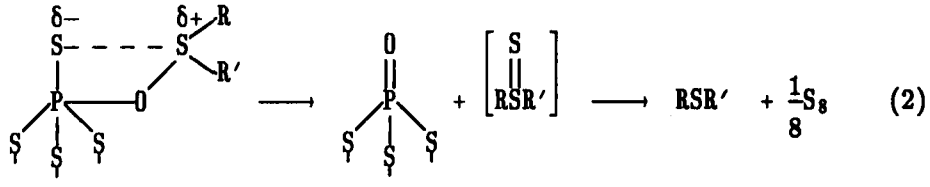
[a]Yield of isolated product, based on starting material actually consumed.

[b]Reaction times of 4–5 h unless otherwise noted.

[c]After 16 h.

A proposed transition state for this process is shown in equation (2) — indirect evidence has been obtained for the concomitant formation of the thiosulfoxide.[3] The reaction rate appears to depend strongly on the

nucleophilicity of the sulfoxide oxygen atom. Interestingly, phosphorus pentaselenide proved to be completely ineffective in the same transformation. Phosphorus pentasulfide, however, readily reduces sulfimides (sulfilimines)[4] and selenoxides[2] to the corresponding sulfides and selenides respectively.



(2)

$$R_2S{=}NX \xrightarrow{P_4S_{10},\ 25^\circ C} R_2S \quad (59\text{-}98\%) \qquad (3)$$

(X=H, $SO_2C_6H_4(p\text{-})$)

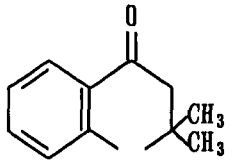
$$R_2Se{=}O \xrightarrow{P_4S_{10},\ 25^\circ C} R_2Se \quad (83\text{-}85\%) \qquad (4)$$

While P_4S_{10} is clearly a versatile reagent for such reductions and deoxygenations it does suffer from at least two potential disadvantages. The reactions are typically slow, given the almost total insolubility of P_4S_{10} in organic solvents, and appear to be somewhat dependent on the origin and commercial preparation and purification of the reagent.[5] We discovered that the reagent $PSBr_3$, thiophosphoryl bromide, which is commercially available and also easily prepared from P_4S_{10},[6] much more rapidly reduces sulfoxides to sulfides. The results obtained with this reagent are summarized in Table II.[7]

$$RS(O)R' \xrightarrow[CH_2Cl_2,\ 25^\circ C]{PSBr_3} RSR' + POBr_3 + \tfrac{1}{8}S_8 \qquad (5)$$

As can be seen from Table II, yields for the deoxygenation are higher, and reaction times much shorter, with the thiophosphoryl bromide reagent which, unlike P_4S_{10}, is a low-melting solid soluble in CH_2Cl_2. (The analogous $PSCl_3$, a much more readily available compound, unfortunately proved to be ineffective.) Again, as with P_4S_{10}, the $PSBr_3$ reagent did not react significantly with the carbonyl group in keto-sulfoxides (Tables I, II).

TABLE II Reduction of sulfoxides RS(=O)R′[a] to sulfides with $PSBr_3$[b] at 25° C in CH_2Cl_2.

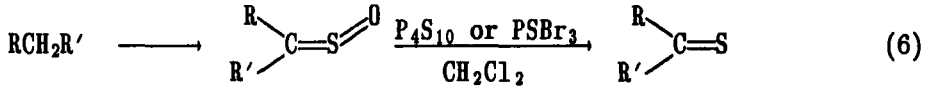
R	R′	Yield[c] [%]	Reaction time
CH_3	CH_3	99	10 min
n-C_4H_9	n-C_4H_9	90	2 h
$C_6H_5CH_2$	$C_6H_5CH_2$	66	2 h
CH_2=$CHCH_2$	C_6H_5	99	2 h
(p-)$CH_3C_6H_4$	(p-)$CH_3C_6H_4$	84	6 h
C_6H_5	C_6H_5	98	4 h
(p-)ClC_6H_4	(p-)ClC_6H_4	78	24 h
		99	2 h
C_6H_5	C_6H_5	88	5 min

[a]With the exception of 2,2-dimethylthiochroman-4-one 1-oxide the sulfoxides used in this investigation were commercially available and were used as supplied.

[b]Thiophosphoryl bromide was obtained from Ventron Corporation and used without purification.

[c]The purity of all products, confirmed by TLC, ^1H NMR, IR, and by mp and mixed mp with an authentic sample where appropriate, was >99%.

When we were able to successfully extend these deoxygenation reactions to the conversion of sulfines to thiones,[8] interestingly, P_4S_{10} was found to be somewhat more effective overall because certain thiones are sensitive to the acidic aqueous work-up conditions involved when using $PSBr_3$ (see equation (5)). The deoxygenation of sulfines completes the synthetic sequence shown in equation (6) for the first transformation of $>CH_2$ into $>C=S$, based on the earlier work of Zwanenburg and coworkers.[9]



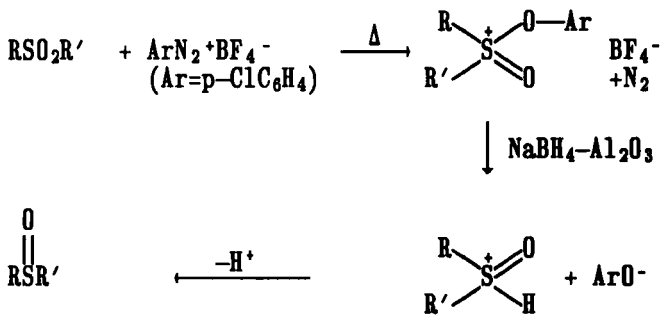
(6)

REDUCTION OF SULFONES TO SULFOXIDES

A much more difficult deoxygenation to accomplish is the reduction of a sulfone to a sulfide. Lithium aluminum hydride can be used for this purpose but its strongly basic nature can cause complications arising from deprotonation *α*– to the sulfone group. In our search for an alternative reducing agent to $LiAlH_4$ or diisobutylaluminum hydride[10] we fortuitously discovered a two–step procedure for the previously unknown general conversion of sulfones to *sulfoxides*.[11] Based upon earlier work of Whiting and coworkers[12] we first formed an O–aryloxosulfonium salt, which was smoothly reduced at 25° C by sodium borohydride adsorbed on alumina to give the sulfoxide in 45–78% overall yield. A plausible mechanism was established by deuterium labelling studies[13] and is outlined in Scheme 1. For simple alkyl and aryl sulfones this represents an effective procedure for the transformation in equation (7). Using p–chlorobenzenediazonium tetrafluoroborate as the preferred reagent no problems were encountered with the first step in the sequence, normally carried out without solvent or in chlorobenzene.

$$RSO_2R' \xrightarrow[2)\ NaBH_4–Al_2O_3,\ 25°C]{1)\ ArN_2{}^+BF_4{}^-,\ 130°C} R\overset{\overset{O}{\|}}{S}R' \qquad (7)$$

SCHEME 1

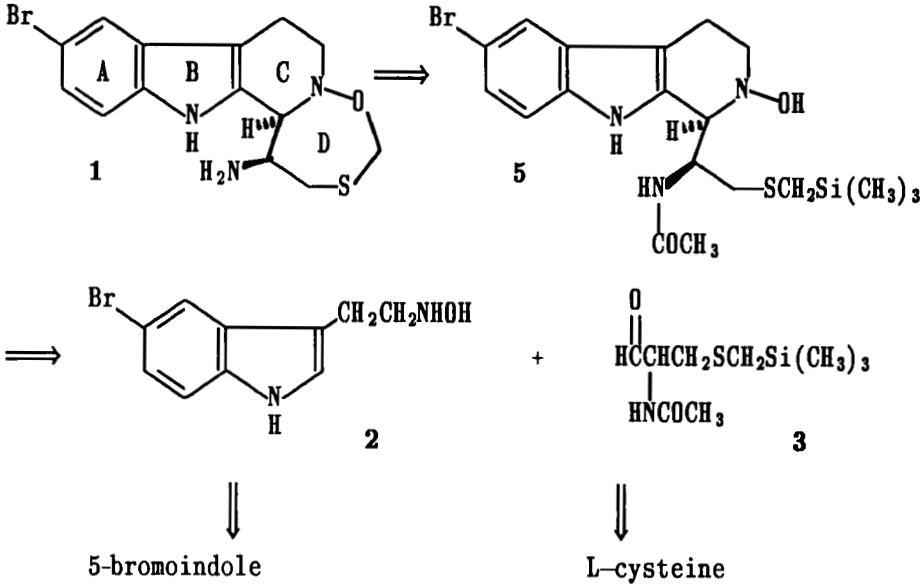


SULFOXIDES IN SYNTHESIS

More recently, our research interests have turned to the synthesis of natural products of biological interest. In one such case, the synthesis of an indole alkaloid, eudistomin L 1, which possesses potent antiviral properties, we were able to draw upon our experience in sulfoxide

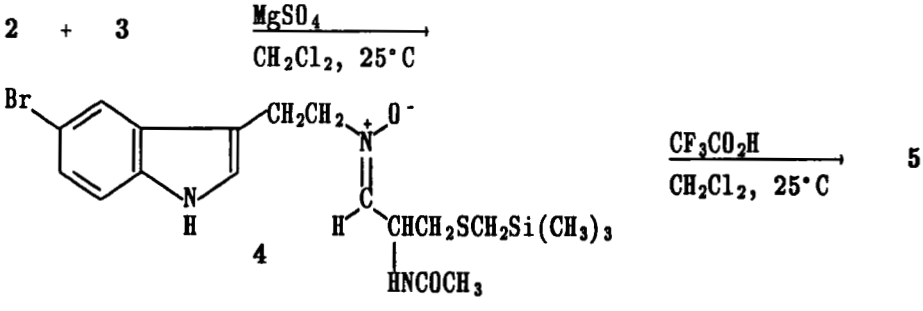
chemistry to achieve the difficult seven-membered ring cyclization required to construct the novel 1,3,7-oxathiazepine ring in **1**. The retrosynthetic approach to the synthesis of eudistomin L is outlined in Scheme 2.[14]

SCHEME 2

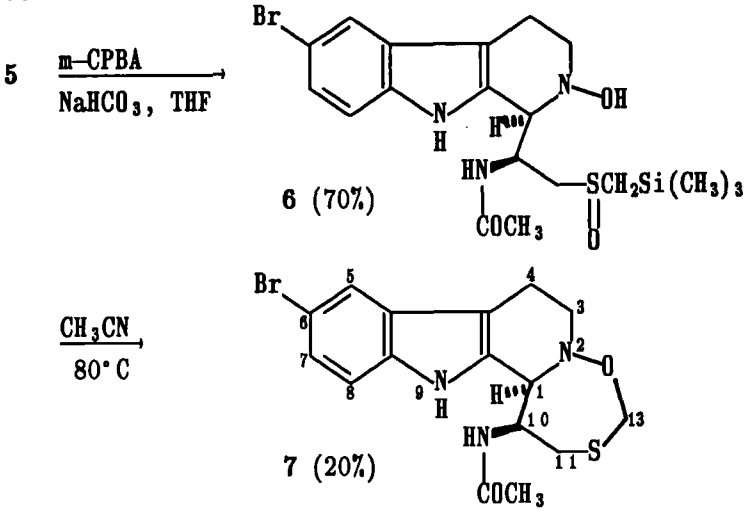


The key intermediates **2** and **3** were prepared by short synthetic sequences involving known procedures, or modifications of known procedures.[15] Ring C in **1** was constructed (Scheme 3) by a modified Pictet-Spengler

SCHEME 3

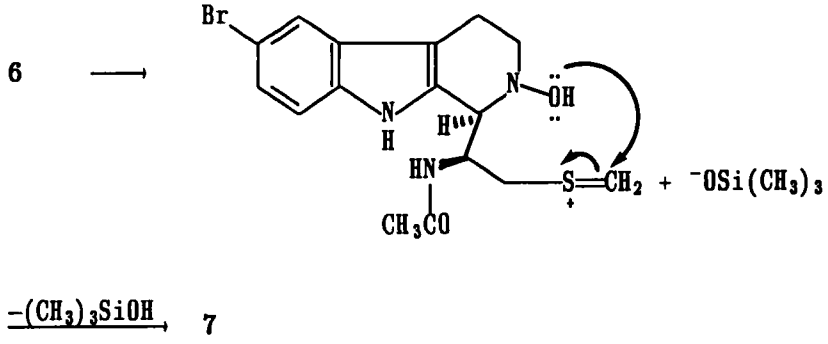


SCHEME 4



cyclization to produce **5** via the intermediate nitrone **4**, which may be isolated and purified if desired. Oxidation of **5** (Scheme 4) with m-chloroperoxybenzoic acid (m-CPBA) gave the sulfoxide **6**, which was cyclized to **7** in an intramolecular sila-Pummerer reaction in 20% yield. An alternative approach to this cyclization step by Nakagawa et al.,[16] using more classical Pummerer conditions, was less effective. A mechanistic suggestion for the cyclization to N(10)-acetyleudistomin L is shown as Scheme 5 and the structure of **7** was confirmed by X-ray analysis (Figure 1), as well as by the usual spectroscopic methods.[14,17]

SCHEME 5



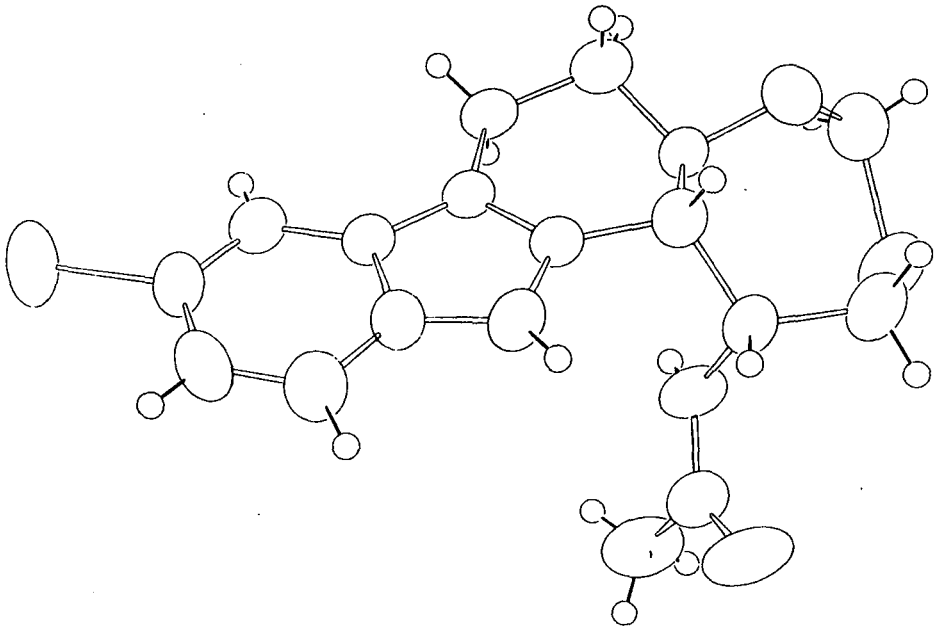
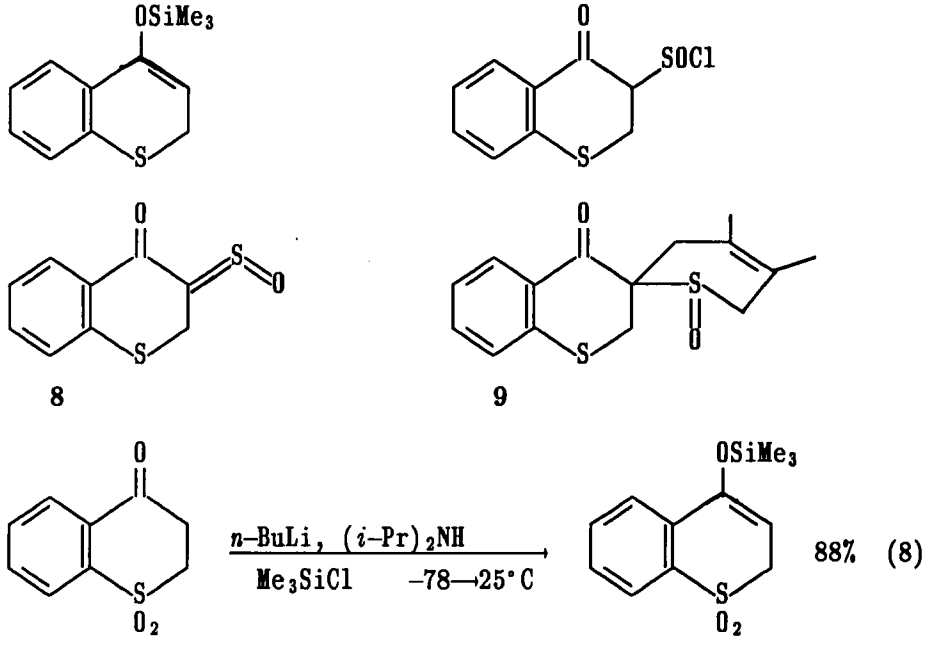


FIGURE 1 ORTEP drawing of structure 7

REACTIVITY OF α–OXOSULFINES

Recently, our research group[18] and that of Zwanenburg[19] independently discovered a new type of sulfine with potentially interesting reactivity. Sulfines were first isolated many years ago but it was not until the 1960's that interest in their structure and chemical reactivity really blossomed. The chemistry of sulfines has been comprehensively reviewed recently by Zwanenburg.[20] The most general method for the preparation and characterization of the new sub–class of α–oxosulfines involves initial conversion of the enol silyl ether of the ketone in question to the β–oxosulfinyl chloride, followed usually by HCl elimination and *in situ* trapping of the α–oxosulfine with 2,3–dimethyl–1,3–butadiene in a Diels–Alder reaction (Scheme 6). In a small number of cases[19] the α–oxosulfines may crystallize from the reaction mixture and can be isolated.

SCHEME 6

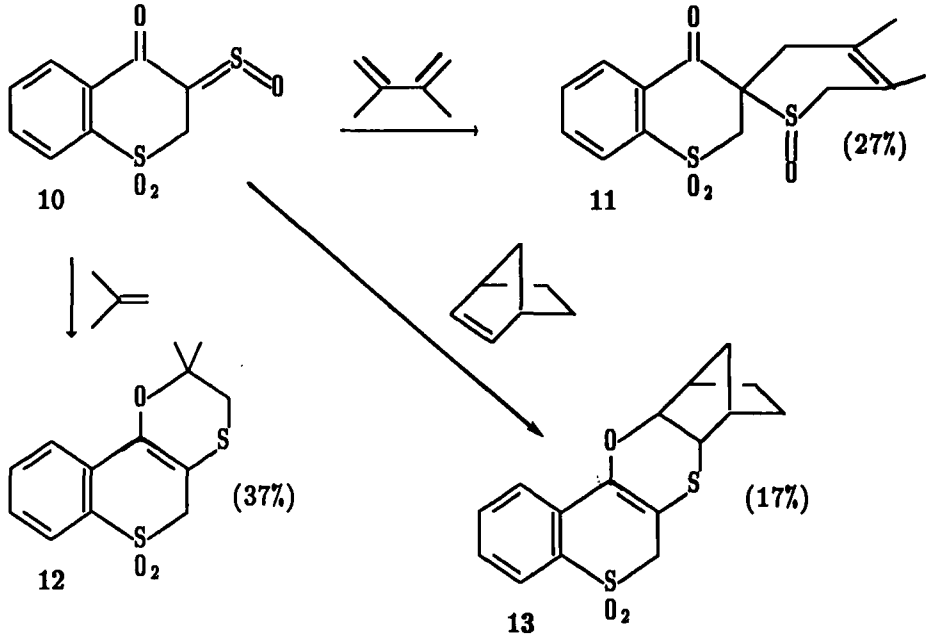


Our initial investigation of the *α*–oxosulfine **10** derived from 4–thiochromanone 1,1–dioxide led to the interesting finding that **10**, in addition to its Diels–Alder reactivity as a *dienophile* (2π) unit towards 2,3–dimethyl–1,3–butadiene to give **11**, also underwent successful Diels-Alder reactions as a *diene* (4π) unit when reacted with electron–rich alkenes such as isobutylene or norbornene, to give the dihydro–1,4-oxathiin derivatives **12** and **13** respectively (Scheme 7). (The sulfine unit is drawn in the *Z* configuration in **8**, **10**, and related compounds. While we have no firm evidence on this point, dipole–dipole repulsion between the C=O and S=O bonds should be much reduced in this configuration.)

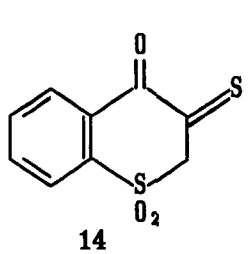
It was initially very surprising to us to discover that **12** and **13**, unlike **11**, had experienced deoxygenation during the formation and trapping sequence. The sulfoxide oxygen atoms in **12** and **13** are undoubtedly quite nucleophilic because of conjugative electron release by the ring oxygen atom, in contrast to **11** which experiences no such effect and is sterically more congested. Under our conditions, deoxygenation may be

effected either by excess $SOCl_2$ present or by the $ClSiMe_3$ liberated during the reaction.

SCHEME 7



Both of these reagents have been reported to effect the deoxygenation of sulfoxides.[21-23] This deoxygenation has been a consistent feature of all Diels–Alder reactions of the type leading to **12** and **13** in our experience. While it is conceivable that deoxygenation might occur on the *α*-oxosulfine itself, leading to the *α*-thioxoketone **14**, no evidence exists for the trapping of such a species by 2,3-dimethyl-1,3-butadiene and we think therefore that this is an unlikely possibility. The isolation of the *α*-dichloro compound **15**,[24] in 10% yield, provides further support for our proposed deoxygenation pathway, since Cl_2 is expected to be formed concurrently (equations (9), (10)).[21-22]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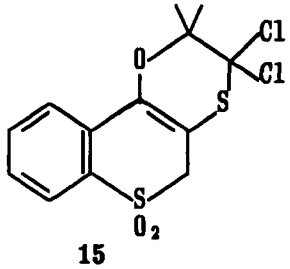
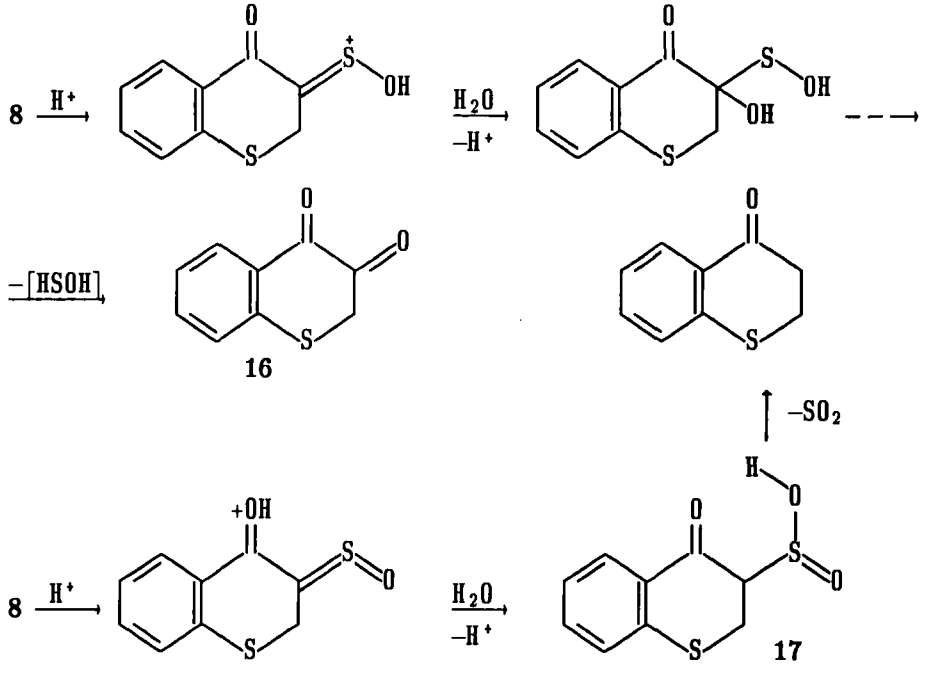

15

$$R_2S{=}O + SOCl_2 \longrightarrow R_2S + SO_2 + Cl_2 \quad (9)$$

$$R_2S{=}O + 2ClSiMe_3 \longrightarrow R_2S + (Me_3Si)_2O + Cl_2 \quad (10)$$

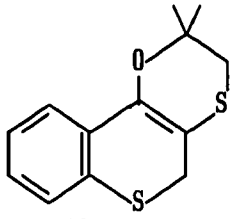
One other general observation is of interest here. The ketone corresponding to the enol silyl ether used in the preparation of our *α*–oxosulfines is usually found among the products isolated from our trapping experiments, but not the corresponding *α*–diketone **16**. Possible hydrolytic pathways are shown in Scheme 8. Under the generally acidic conditions employed in our work–up it is perhaps surprising that no *α*–diketone was ever found. It is possible, however, that alternative protonation at the *carbonyl* oxygen site might lead to nucleophilic attack by water at *sulfur* rather than carbon, thus leading to the *β*–oxosulfinic acid **17** and hence loss of SO_2 to give the (mono) ketone observed.

SCHEME 8

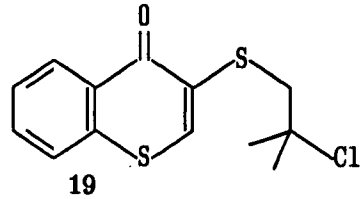


When we attempted to extend this novel Diels–Alder reaction to the *α*–oxosulfines derived from 4–thiochromanone and cyclohexanone a most unusual finding resulted. For example, when **8** was trapped with isobutylene, instead of the expected Diels–Alder adduct **18**, we obtained a chlorinated compound eventually identified as **19**, by a combination of ^1H,

^{13}C NMR, and IR evidence. Similar adducts (**20–22**), were obtained from analogous reactions of **8** with 2-butyne, 1-hexyne and cyclopentene, respectively. Final confirmation of structure was obtained from an X-ray analysis of the cyclopentene adduct **22**.[25]



18



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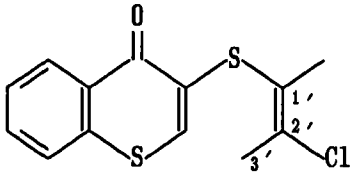

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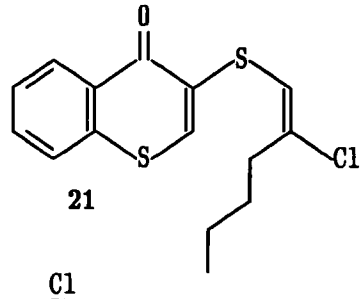

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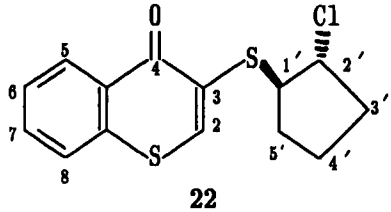
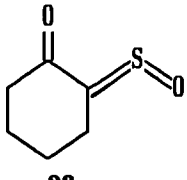
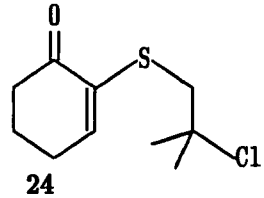


22



23



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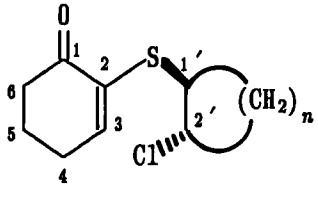
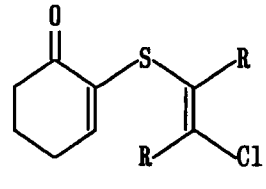


25a–c $n = 3, 4, 6$



26a, R=CH_3
b, R=C_6H_5

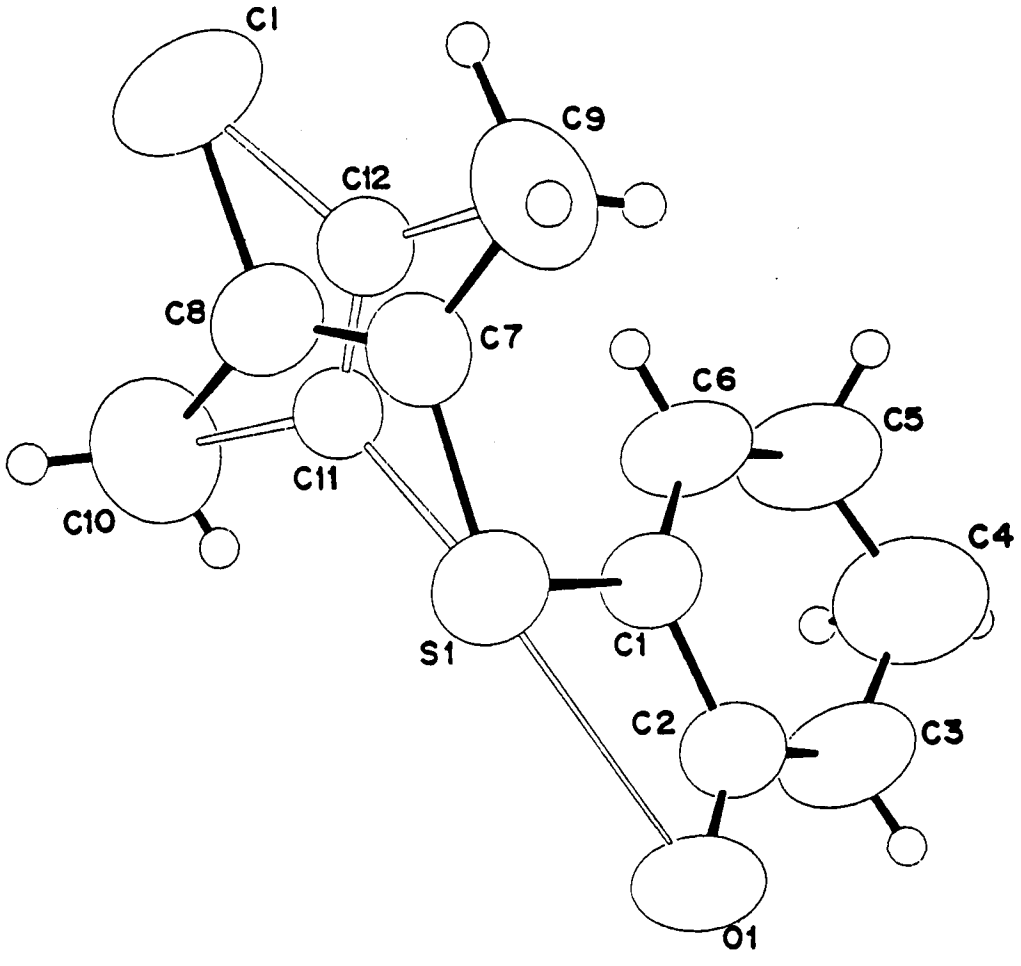


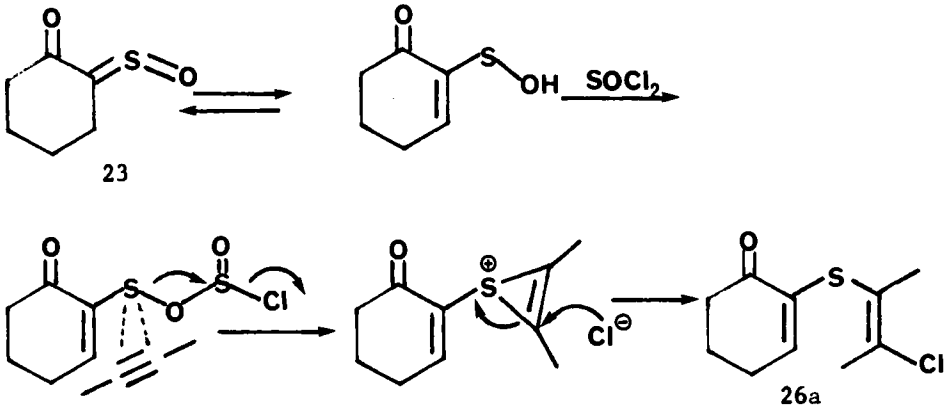
FIGURE 2 ORTEP drawing of structure 26a

Similar results were obtained with the *α*–oxosulfine **23** derived from cyclohexanone.[25] Adducts of the non–Diels–Alder (**24–26**) type were again obtained using isobutylene, cyclopentene, cyclohexene, cyclo–octene, 2-butyne and diphenylacetylene. The X–ray crystal structure of the 2–butyne adduct **26a** is shown in Figure 2 — interestingly, two conformations are found to be present, in a 85:15 ratio, in the solid state.

All the adducts described above result from what appears to be the electrophilic addition of a sulfenium ion species to the appropriate alkene or alkyne.[26] Generally, in these electrophilic addition reactions, Markovnikov–governed regiochemistry is followed and the reactions

proceed exclusively in the *anti* addition mode. A possible mechanism for the generation of a sulfenium ion (or reactive sulfenyl derivative) under our reaction conditions is presented in Scheme 9. Initial tautomerism to a vinyl sulfenic acid, followed by formation of a sulfenyl chloride, or mixed sulfenic–chlorosulfinic anhydride, with $SOCl_2$ would lead, via a thiiranium or thiirenium intermediate,[27] to the products described. Some possible reasons for the fascinating dichotomy of behavior between two systems as similar as 8 and 10 will be touched upon in the next section.

SCHEME 9

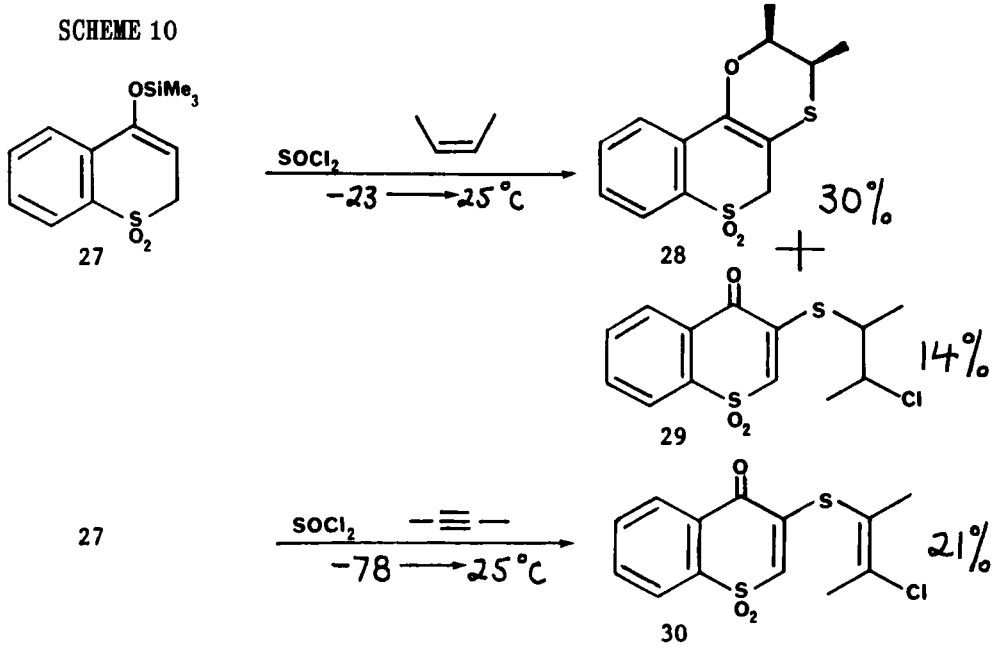


In an attempt to shed some light on the hitherto baffling reactivity pattern of the *α*–oxosulfines we decided very recently to re–examine the original *α*–oxosulfine system 10, which we knew afforded Diels–Alder adducts with electron–rich alkenes,[18 24] and its behavior towards a wider variety of structural types of trapping agent. Schemes 10 to 14 below summarize our most recent results. In Scheme 10, reaction of the enol silyl ether 27 with $SOCl_2$ in the usual way, in the presence of cis–2–butene, afforded *two* products, isolated after careful flash chromatography — the expected dihydro–1,4–oxathiin (Diels–Alder adduct) 28, in 30% yield, and the electrophilic addition product 29, in 14% yield. (We plan to investigate the stereospecificity of the reaction with respect to the dienophile by using trans–2–butene as the trapping agent but these results are not yet available.) In considerable contrast, the trapping reaction with 2–butyne afforded *only* the electrophilic addition product

30, in 21% yield.

As shown in Scheme 11, the trapping reactions on 10 with cyclopentene and cyclohexene gave the two types of adduct 31/33 and 32/34 — again, as for the cis-2-butene experiment, in about a 2:1 ratio in favor of the Diels-Alder adducts. When 1-pentene was used as the trapping agent (Scheme 12), *both* regioisomers were observed, in the case of the electrophilic addition product only, with the Diels-Alder adduct, however, again predominating by about 2:1. Less surprisingly, for the 2-pentene case (Scheme 13), regioisomers were observed for both types of adduct.

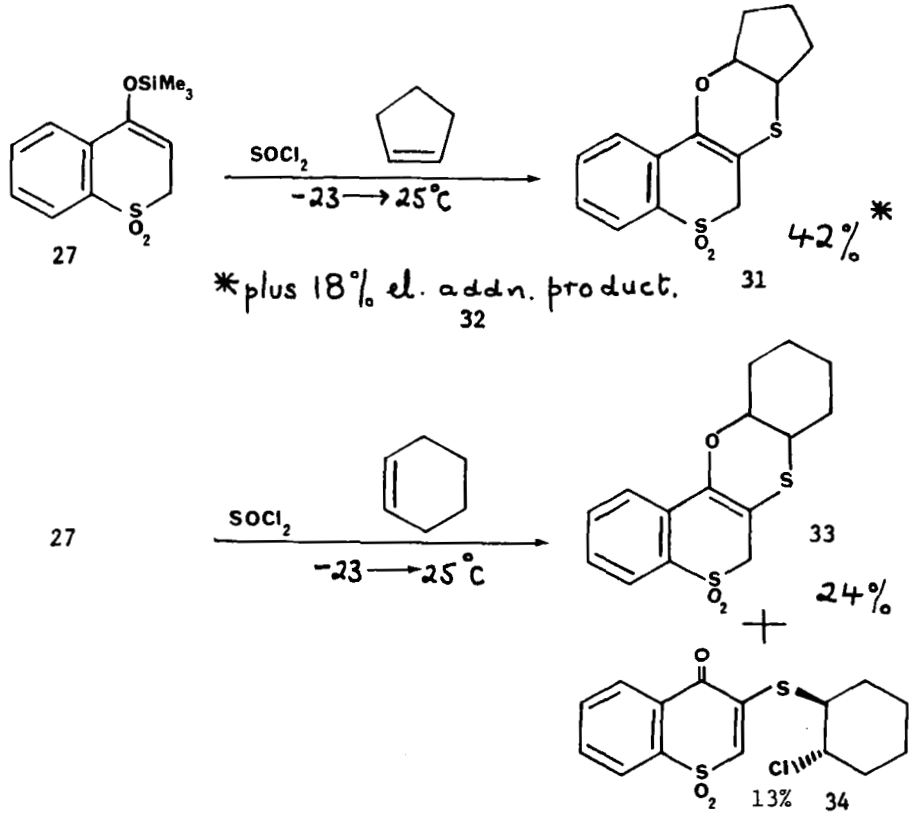
SCHEME 10



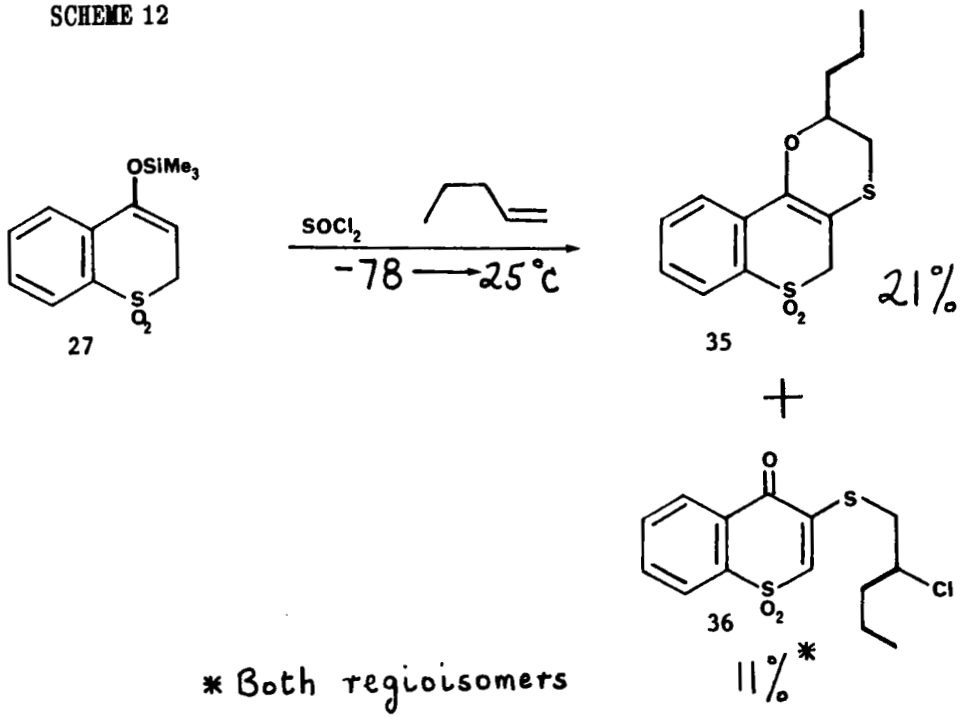
The effect of increasing the substitution in the dienophile unit was next explored using t-butylethylene (3,3-dimethyl-1-butene) and 1,1-diethylethylene (2-ethyl-1-butene) (Scheme 14). The results in the latter case were not especially interesting in that the now familiar ~2:1 preference for 1,4-oxathiin formation (Diels-Alder product, 40) over electrophilic addition is once again observed. On the other hand, with t-butylethylene, no Diels-Alder product was formed at all (reminiscent of the result obtained with 2-butyne but probably for different reasons). The electrophilic addition product 39 was still formed, however, in 28% yield.

The X-ray crystal structure determination on compound **40** is shown in Figure 3. The results of oxidation experiments carried out on adducts **20** and **22** from the earlier 4-thiochromanone series studied (Scheme 15) show clearly that selective oxidation with *m*-CPBA at the exo (sulfur) site in the electrophilic addition products is easily effected. These findings enhance the synthetic potential of this type of adduct. For example, the sulfone **43b** might be expected to undergo base-catalyzed *α*-substitution by electrophilic agents at C-1′, while the sulfoxide **43a** could undergo *nucleophilic α*-substitution under Pummerer reaction conditions. Both compounds bear a chlorine atom at C-2′ which may also therefore be a site for nucleophilic attack.

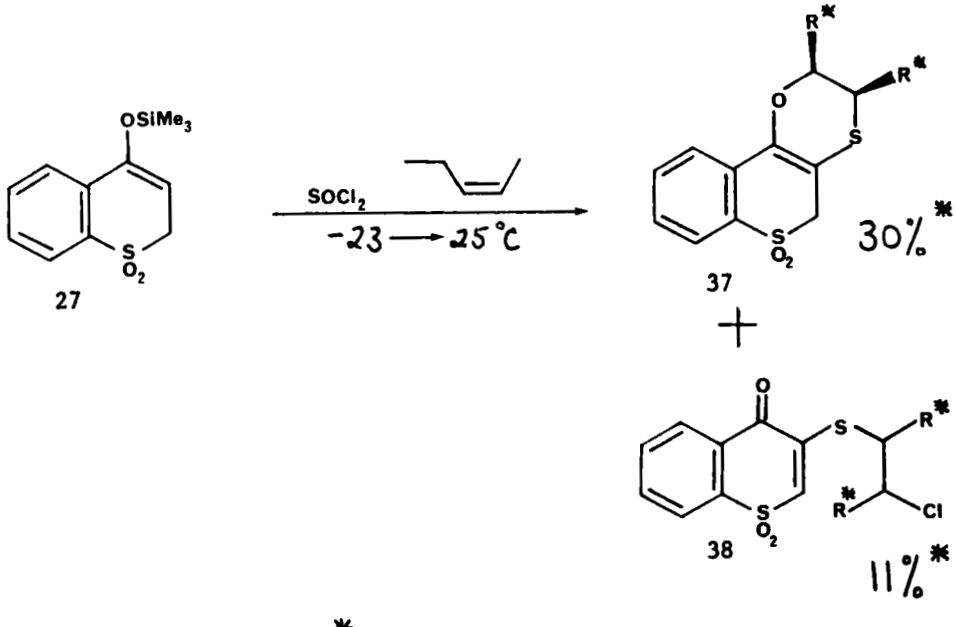
SCHEME 11



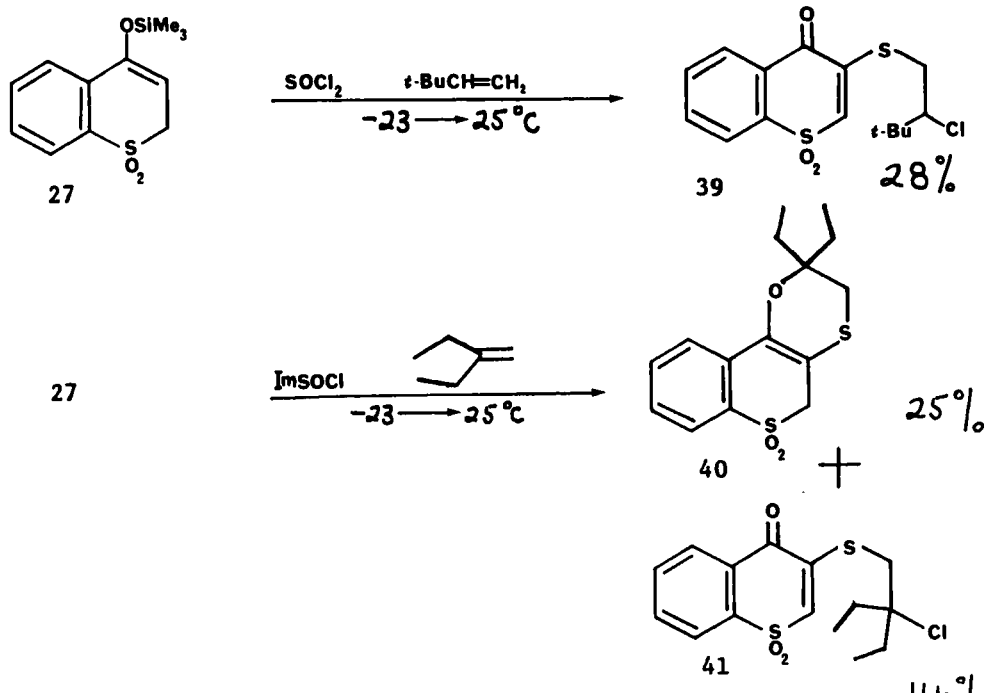
SCHEME 12



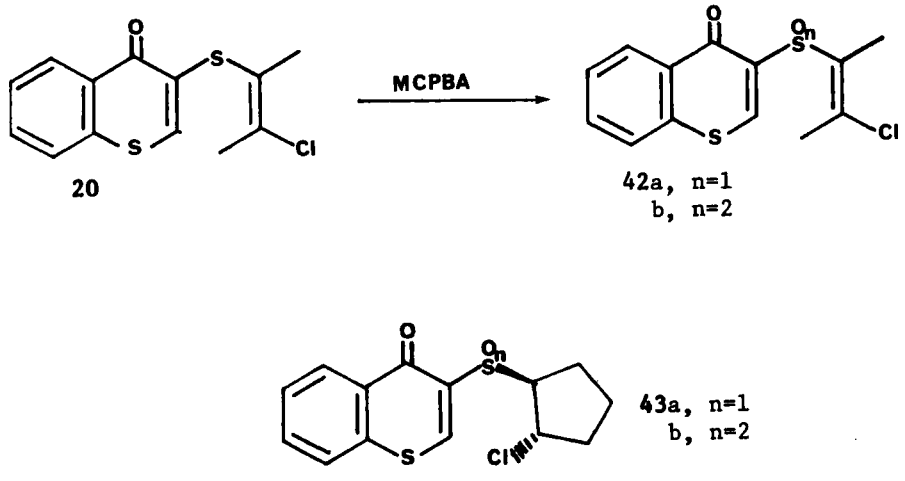
SCHEME 13



SCHEME 14



SCHEME 15



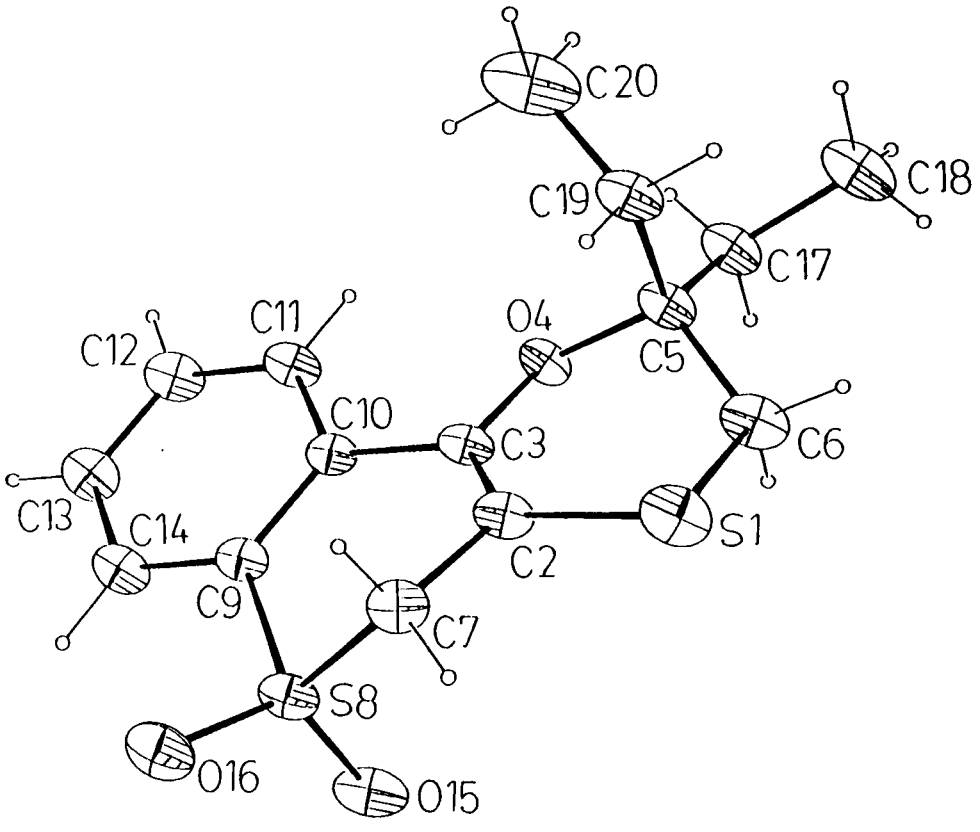


FIGURE 3 ORTEP drawing of structure 40

In summary, we have shown that α-oxosulfines, even those which are too unstable to isolate, may be used successfully as 4π units in Diels-Alder trapping experiments with electron-rich alkenes and alkynes, to produce 1,4-oxathiins. In many cases, however, anti electrophilic addition to the alkene or alkyne is a significant competing pathway, leading to products which represent the formal, "one-pot" conversion of the $-COCH_2CH_2-$ structural unit into —COC(SR)=CH—, i.e. into an α-(alkylthio) substituted α,β-unsaturated ketone. This represents a dienophile (alkyne synthon) whose synthetic potential we are currently exploring. While the existence of the competing pathways above represents a serious potential limitation to the synthetic utility of the α-oxosulfines, we intend to explore further possible cycloadditions involving α-oxosulfines, including those with 2π units (dienophiles) such as C=S, C=N, and C=C

(allenes), as well as with 1,3-dipolar molecules.

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