SYNTHESES OF SULPHONES, SULPHOXIDES AND CYCLIC SULPHIDES

G. Capozzi, J. Drabowicz, P. Kiełbasinski,
S. Menichetti, M. Mikołajczyk, C. Nativi,
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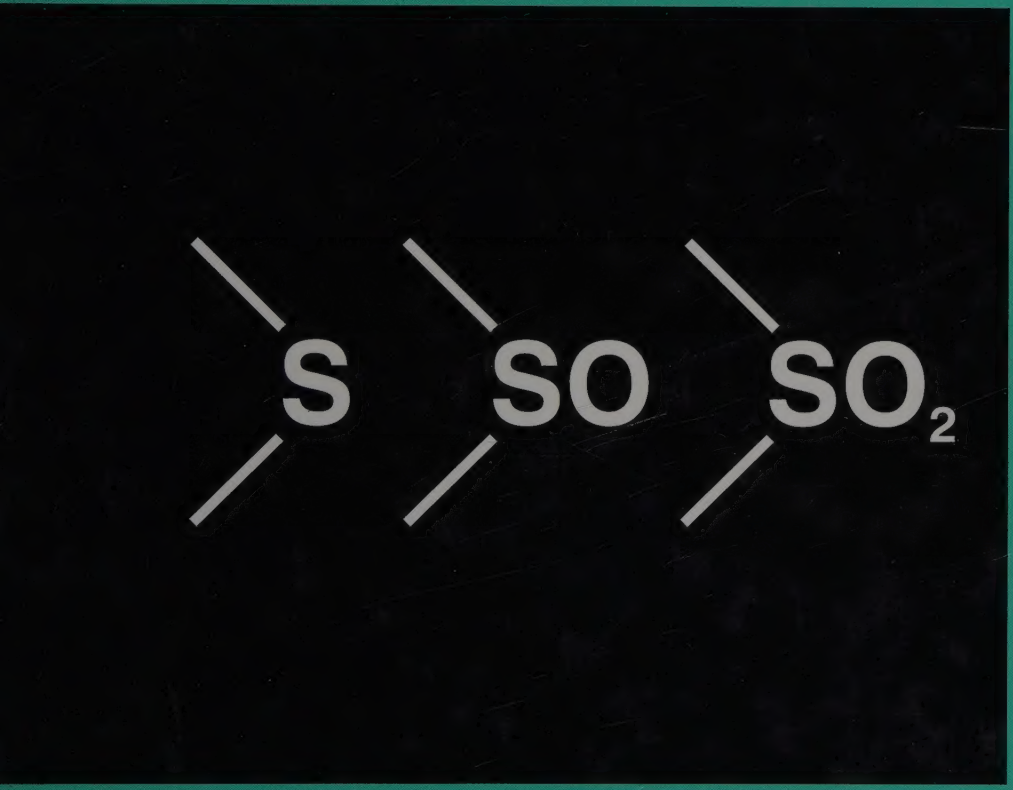

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Edited by Saul Patai and Zvi Rappoport

The syntheses of **sulphones, sulphoxides and cyclic sulphides**

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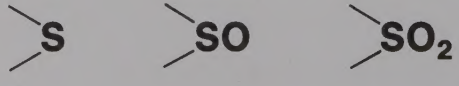

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Updates from the Chemistry of Functional Groups

1994

JOHN WILEY & SONS
CHICHESTER · NEW YORK · BRISBANE · TORONTO · SINGAPORE

An Interscience® Publication

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Baffins Lane, Chichester,
West Sussex, PO19 1UD, England
Telephone: National Chichester (0243) 779 777
International +44 243 779 777

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John Wiley & Sons (SEA) Pte Ltd, 37 Jalan Pemimpin #05-04,
Block B, Union Industrial Building, Singapore 2057

British Library Cataloguing in Publication Data

A Catalogue record for this book is available from the British Library

ISBN 0 471 93970 6

Typeset in Times 9/10 pt by Thomson Press (I) Ltd, New Delhi
Printed and bound in Great Britain by Biddles, Guilford, Surrey

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Foreword and Envoi

This is the last volume of the series 'Updates from the Chemistry of Functional Groups'. When this series was launched the Publishers and the Editors hoped that it would enable us to present selected chapters on a single topic or on closely related topics from various volumes in main series. The two main aims were to update these topics by appendix chapters dealing with studies as near as possible to the publication date and to make these available for individual chemists in the form of modestly sized and priced volumes.

These aims were nearly achieved in the first few volumes, but in later ones both the size, and hence the price, increased drastically. So it was decided, with sorrow, by the Publishers and the Editors to discontinue the 'Updates' and to concentrate on the main series. The present volume deals with the syntheses of sulphoxides, sulphones and cyclic sulphides and complements several volumes on sulphur chemistry in the main series.

Jerusalem
January 1994

SAUL PATAI
ZVI RAPPOPORT

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CHAPTER 1

Synthesis of open-chain sulfones

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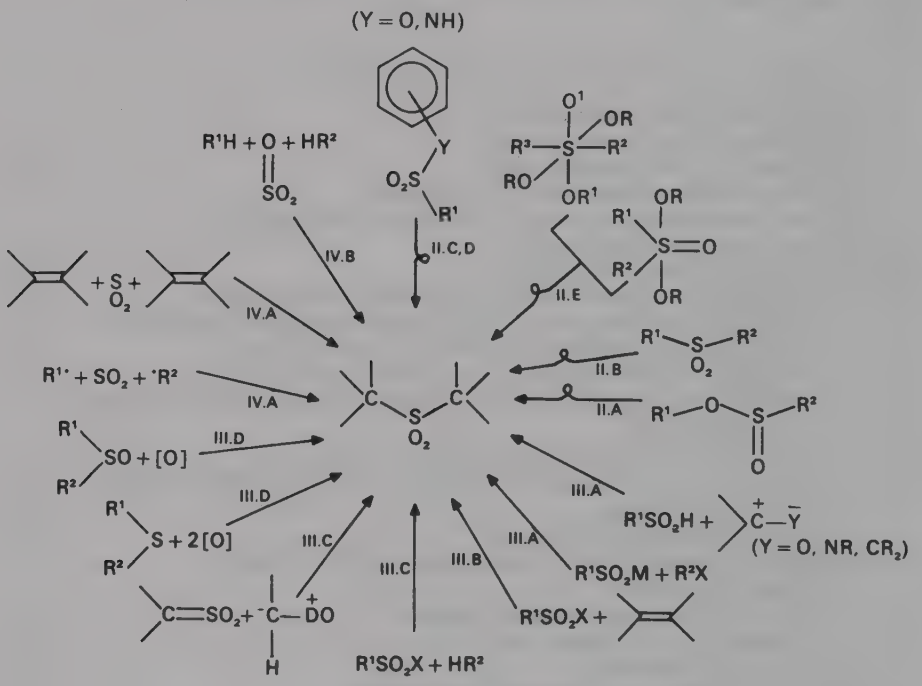
I. INTRODUCTION

Sulfones have been prepared by three principally different strategies: *One-component methods* include various isomerizations, rearrangements under degradation, and hydrolysis of oxygen-substituted dialkyl (diaryl) sulfuranes(VI).

Two-component methods represent the most widely applied principles in sulfone syntheses, including C—S bond formation between carbon and RSO_2 species of nucleophilic, radical or electrophilic character as well as oxidations of thioethers or sulfoxides, and cheletropic reactions of sulfur dioxide. *Three-component methods* use sulfur dioxide as a binding link in order to connect two carbons by a radical or polar route, or use sulfur trioxide as an electrophilic condensation agent to combine two hydrocarbon moieties by a sulfonyl bridge with elimination of water.

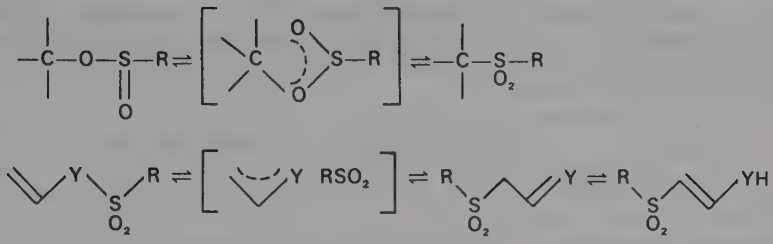
Scheme 1 presents a general survey on methods discussed in this chapter. References 1–5 are a selection of some recently published comprehensive reviews.



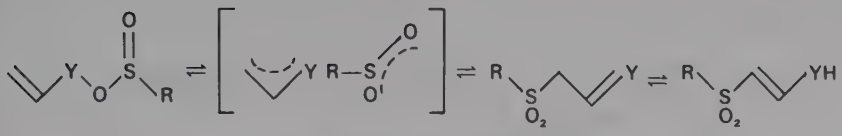
SCHEME 1. Syntheses of sulfones.

II. ONE-COMPONENT METHODS

The most important types of these methods are the isomerizing rearrangements. According to whether the reaction occurs at the sulfone site or at the carbon site on the one hand, or at both sites on the other, one should distinguish between *unifold* and *twofold* transformations (Schemes 2 and 3).



SCHEME 2. Unified types.

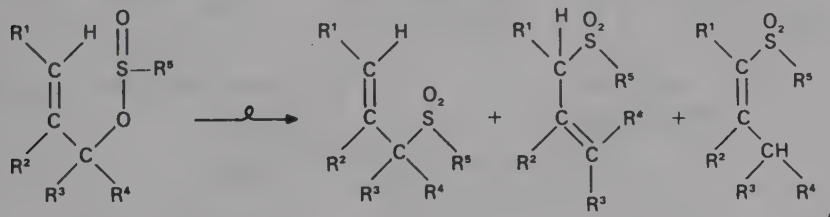


SCHEME 3. Twofold types.

The nature of the initial bond cleavage (homolytic, heterolytic, or by a concerted pathway) cannot be generalized because it depends on substituent effects and/or reaction conditions.

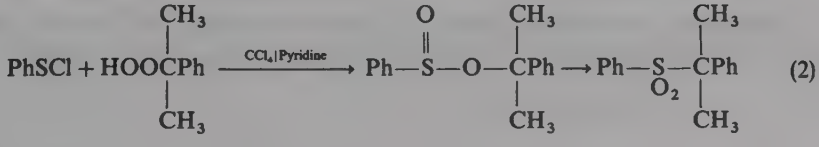
A. Sulfinate–Sulfone Rearrangements

This reaction type has been intensely studied[6–10]. The application of highly polar solvents, catalysis with tertiary amines[11] or with acids[6,12,13], mesomeric stabilization of intermediate carbenium ions[6,11,14–16] (allylic and benzylic systems; propargylic systems[17–21]) as well as derivatives of sulfinic acids with increasing acidity[15,22] usually indicate an ionic pathway (intra- and/or inter-molecular):



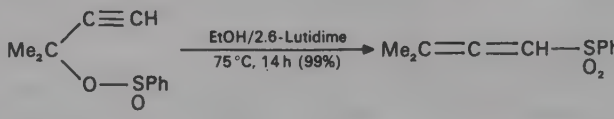
(1)

Principally, both unifold and twofold transformation types ensue in these cases. A unifold transformation occurs in the case of the rearrangement of cumyl benzenesulfinate, which arises from the conversion of cumyl hydroperoxide with benzenesulfenyl chloride[23] (equation 2). Closely related sulfoxylate–sulfone rearrangements, which pass intermediate sulfinate steps similarly, are equally known[24,25].



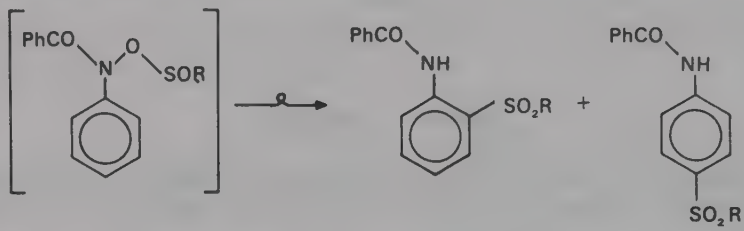
(2)

A neat twofold transformation, obviously a consequence of a sigmatropic [2.3]rearrangement rather than by an ionic pathway, occurs in the case of a propargyl sulfinate[20] (equation 3).



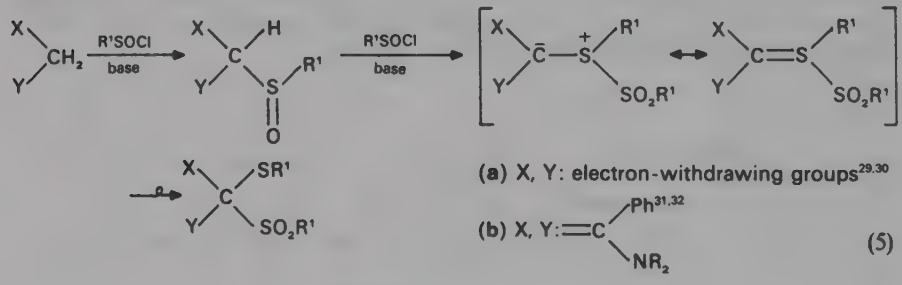
(3)

Allyl sulfones formed from allyl sulfinates (cf. equation 1) can easily tautomerize to give α,β-unsaturated sulfones[26]; in cases for which R^1, R^2 are part of an (hetero) aromatic system, this tautomerization occurs spontaneously. Similarly, sulfinic acid esters from *N*-phenylhydroxamic acids as reactive intermediates rearrange to give *o*-(major part) and *p*-sulfonylanilines (minor part)[27]:



(4)

Another type of sulfinate–sulfone rearrangement similar to the Pummerer rearrangement takes place in the course of treating α-morpholinostyrenes or reactive methylene compounds with sulfinyl chlorides in the presence of bases. The intermediate sulfoxides are rearranged by further sulfinyl chloride through a sulfinyloxysulfonium ylide stage[28] (equation 5).



(5)

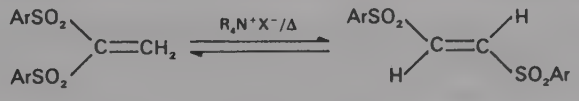
B. Sulfone–Sulfone Rearrangements*

Rearrangements of this type are unifold transformations, which show [1.*n*]shifts of the sulfonyl group within the carbon moiety.

1. [1.2]Rearrangements

The simplest rearrangement of this type represents the vinylidene disulfone–vinylene disulfone rearrangement[33–35], which has been reported to proceed equally in both

directions[36] (equation 6). Possibly the anti-Michael addition, which has been found to proceed beside the normal Michael addition in the course of the addition of nucleophiles to α,β-unsaturated sulfones[37], plays here a deciding role. *o*-Sulfonyl substituents in pyrroles suffer similar acid catalyzed 1,2-migrations[38] (equation 7). In contrast to these reactions, in the subsequent rearrangements additional changes in the molecular structure accompany 1,2-sulfonyl migrations. Acid catalysis yields β-oxo sulfones from sulfonyl-substituted oxiranes[39–46a] (equation 8). Whether α-oxo carbenium ions[46b] are participating in this reaction is unknown. However, in a case in which oxirane ring opening dominated a primary sulfonyl elimination, the β-oxo sulfonyl system has been formed without sulfonyl migration[47] (equation 9). In another type of β-oxo sulfone derivative, mineral acid catalysis yields only a normal hydrolysis reaction whereas dilute acetic acid catalyzes an unexpected concerted [1.2]sulfonyl[1.4]acyl shift[48] (equation 10).



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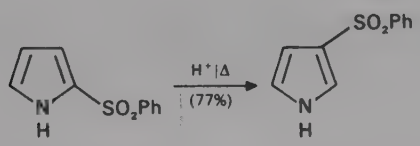

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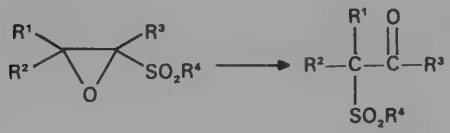

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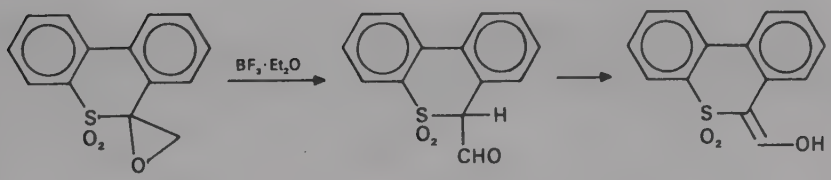

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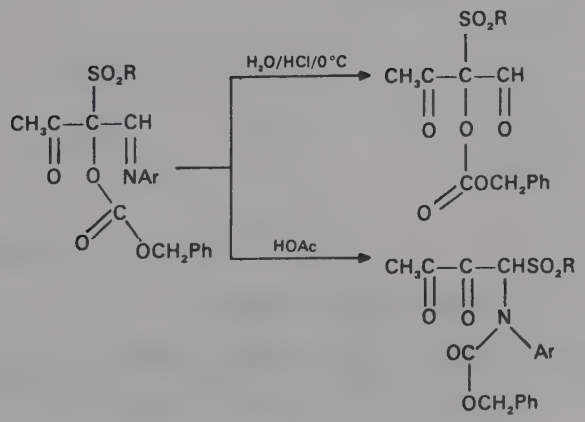
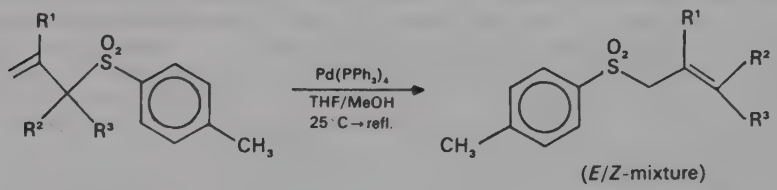


(10)

2. [1.3]Rearrangements

In allyl sulfones 1, 3-migrations of the sulfonyl group take place thermally[49–51] or Pd(0)-catalyzed[52] (equation 11).

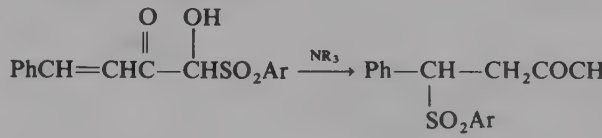


(11)

(*E*/*Z*-mixture)

3. [1.4]Rearrangements

Reactions of this type have been observed without (equation 12)[53] and with (equation 13)[54] additional condensation.



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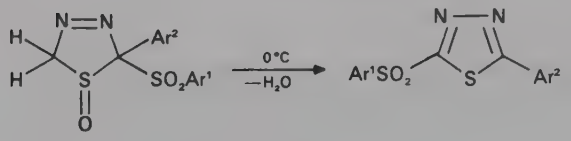
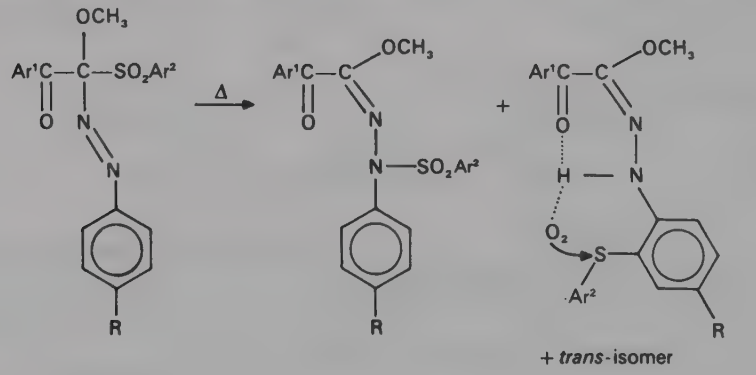


(13)

4. [1.5]Rearrangements

Reaction products of concomitant anionotropic 1, 3-shifts to nitrogen and 1, 5-shifts to carbon of sulfonyl groups in azo coupling products of α-methoxy β-oxo sulfones have been found under thermal conditions[55,56] (equation 14).

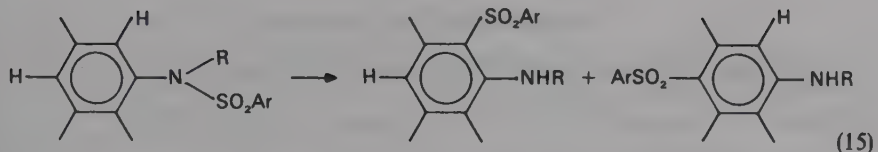


(14)

+ *trans*-isomer

C. Sulfonanilide–Anilinosulfone Rearrangement[57]

Sulfonanilides suffer 1, 3- and 1, 5-shifts of the sulfonyl group under various conditions. The reactions may be spontaneous[58–60], thermal[61,62], photochemical[62,63], base-catalyzed[61,64,65], acid-catalyzed[66–69] or oxidative[70] (equation 15).



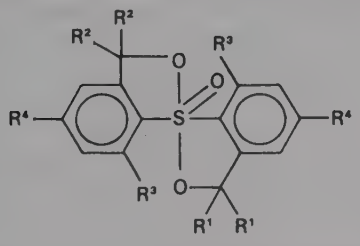
(15)

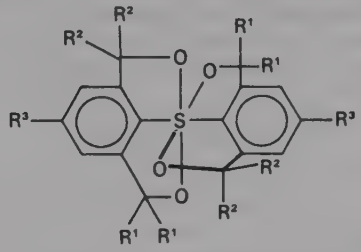
D. Arene Sulfonate–Aryl Sulfone (Sulfone-Fries) Rearrangement[71]

This rearrangement ensues principally according to the same scheme as shown in equation 15 yielding *o*- and/or *p*-sulfonyl-substituted phenols. Yields under Friedel–Crafts conditions are poor[72]; only under photochemical conditions[73] or in exceptional cases[74] are the yields over 10–25%.

E. Isomerization of Oxysulfuranes

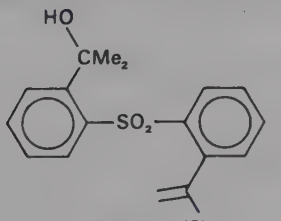
The interesting work of Martin and coworkers[75–77] on oxygen-substituted sulfuranes(VI) 10-S-4 and 12-S-6 species made available for the first time quasi 'mono- and bis-acetals' of sulfones (**1** and **2**). Proton-catalyzed fragmentation of **1b** led to the sulfone isomer **3**[76]; the corresponding fragmentation of **2a** gave, depending on reaction conditions, the isomeric sulfone **4** or a mixture of the sulfone isomers **4** and **5**[77].



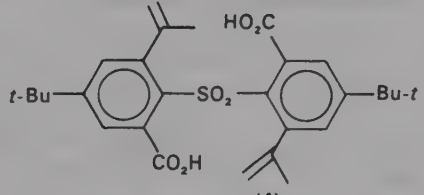


(**1**) (**a**) $R^1 = R^2 = CF_3$; $R^3 = H$; $R^4 = t\text{-Bu}$[75]
(**b**) $R^1 = R^2 = Me$; $R^3 = R^4 = H$[76]
(**c**) $R^1 = R^2 = Me$; $R^4 = t\text{-Bu}$; $R^3 = CO_2Et$, CH_2OH, $C(CH_3)_2OH$[77]

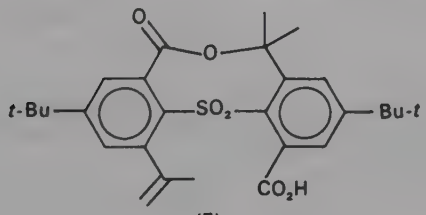
(**2**) (**a**) $R^1 = Me$; R^2, $R^2 = O$; $R^3 = t\text{-Bu}$[77]
(**b**) $R^1 = R^2 = Me$; $R^3 = t\text{-Bu}$[77]



(**3**)



(**4**)



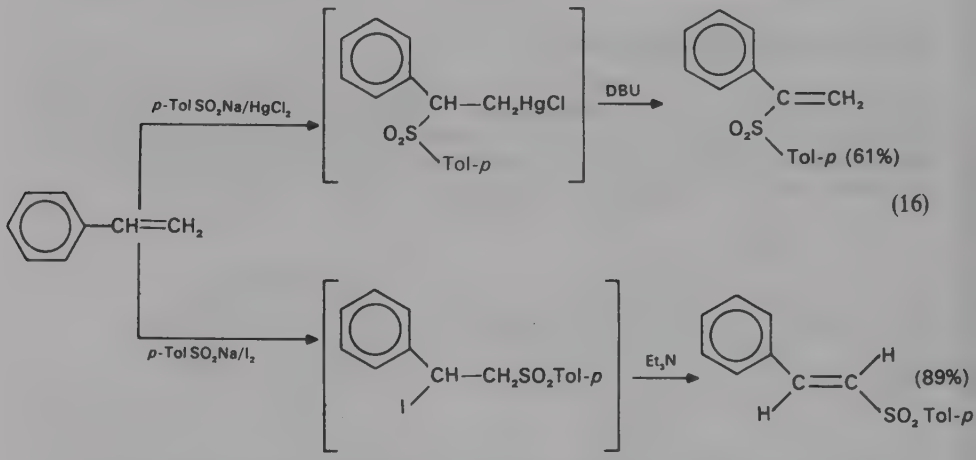
(**5**)

III. TWO-COMPONENT METHODS

A. S-Substitution of Sulfinate Nucleophiles with C-Electrophiles

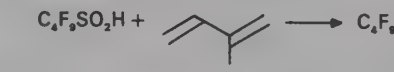
1. Addition of sulfinic acids (or salts) to unactivated C=C double bonds

Usually, isolated C=C double bonds do not react with sulfinic acids or their salts to form sulfones. Exceptions represent the 'chloropalladiosulfonylation' of dicyclopentadiene[78] and the 'sulfonylmercuration' of 1-alkenes[79] (equation 16). Interestingly, the corresponding 'iodosulfonylation' yields the regioisomeric sulfone[79]. Further investigations concerning the mechanism of this second reaction which could involve the addition of intermediately formed tosyl iodide (cf. Section III.B.1) are announced.

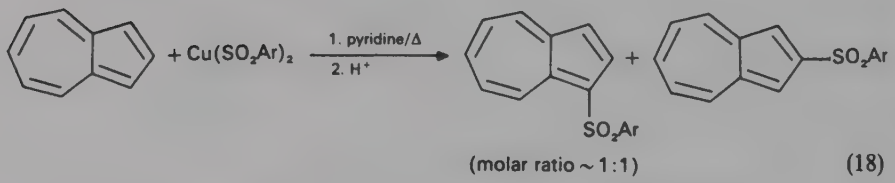


(16)

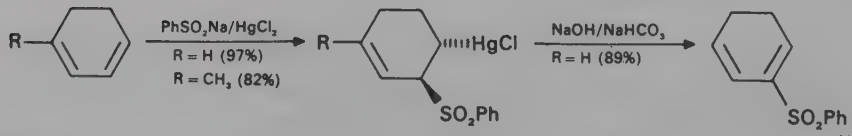
Additions of sulfinic acids to polyenes ('hydrosulfonylation'), however, proceed with very strong acids[80] or under catalysis of Pd complexes[81] (equation 17). With copper(II) arenesulfinates, azulene has been oxidatively sulfonylated in the 1- and 2-positions of the five-membered ring[82] (equation 18). The 'sulfonylmercuration' has also been applied with success to conjugated dienes[83] (equation 19).



(17)



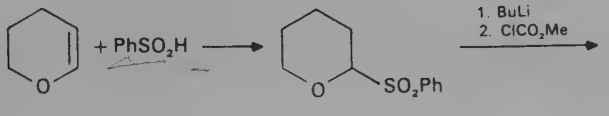
(18)



(19)

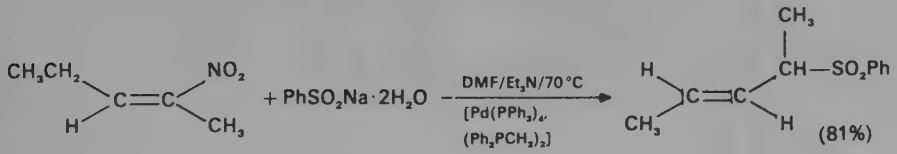
2. Addition of sulfinic acids to polar C=C double bonds

Polarization of C=C double bonds can be effected by adjacent electron donor[84] (equation 20) or electron acceptor systems. In the second case, a large number of Michael-acceptor olefins have been added successfully to sulfinic acids[85] (equation 20a). Table 1 gives a survey on this addition[86–93].



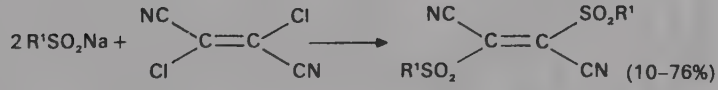
(81%) (20)

Some particular features should be mentioned. Instead of Michael additions, α-nitroolefins are reported to yield allyl sulfones under Pd catalysis[94] (equation 21). Halogenated acceptor-olefins can substitute halogen β to the acceptor by *ipso*-substitution with sulfinate (equation 22[95], equation 23[96]) or can lose halogen α to the acceptor in the course of a secondary elimination occurring β to the introduced sulfonyl groups[97] (equation 24). On the other hand, the use of hydrated sodium sulfinates can lead to cleavage at the C=C double bond[98] (equation 25).



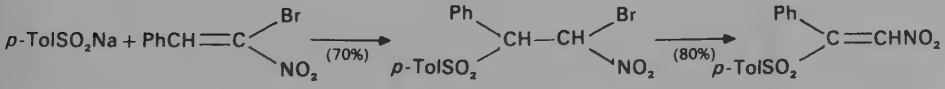
(81%) (21)

$$PhSO_2H + ClCH{=}CHNO_2 \longrightarrow PhSO_2CH{=}CHNO_2\ (72\%) \qquad (22)$$

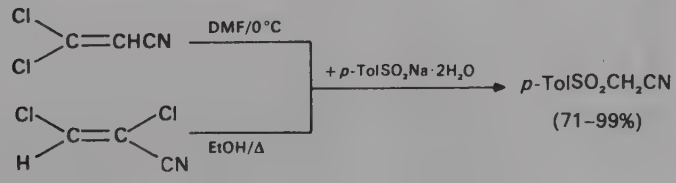


(23)

(R^1 = alkyl, allyl, benzyl, aryl)

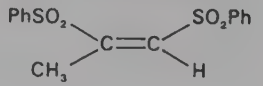
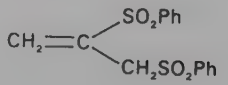


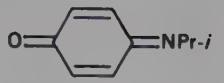
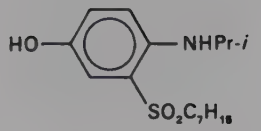
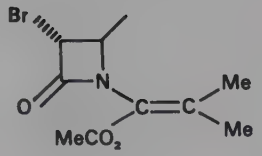
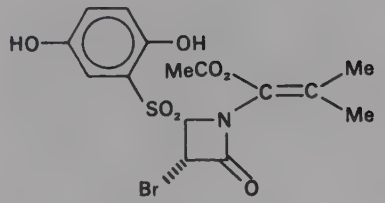
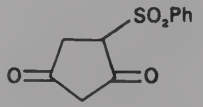
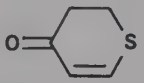
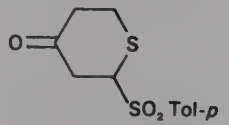
(24)



(25)

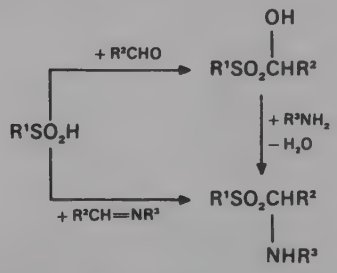
TABLE 1. Sulfones from sulfinic acids RSO_2H and acceptor-substituted olefins, acetylenes or quinones

R	Michael acceptor	Sulfone	Yield (%)	Ref.
p-Tol	$CH_3CH{=}CHCHO$	*p*-TolSO_2CHCH_2CHO (CH$_3$)	84	86
p-Tol	$CH_2{=}CHCOCH_3$	*p*-Tol$SO_2CH_2CH_2COCH_3$	92	87
p-ZC_6H_4 (Z = H, Me, NHAc, Br, Cl)	$PhCH{=}CHCOCH_2NO_2$	*p*-$ZC_6H_4SO_2CH(Ph)CH_2COCH_2NO_2$	40–55	88
Ph	1. $CH_2{=}CHCONEt_2$ 2. P_4S_{10}	$PhSO_2CH_2CH_2CSNEt_2$	90	89
p-$O_2NC_6H_4$	$PhCH{=}CHNO_2$	*p*-$O_2NC_6H_4SO_2CHCH_2NO_2$ (Ph)	83	90
p-Tol	$CH_2{=}C(SO_2Ph)_2$	*p*-Tol$SO_2CH_2CH(SO_2Ph)_2$	95	91
Ph	$CH_3C{\equiv}CSO_2Ph$		84	92
Ph	$CH_2{=}C{=}CHSO_2Ph$		73	92

C_7H_{15}			92	93a
			78	93b
Ph			98	93c
p-Tol			94	93d

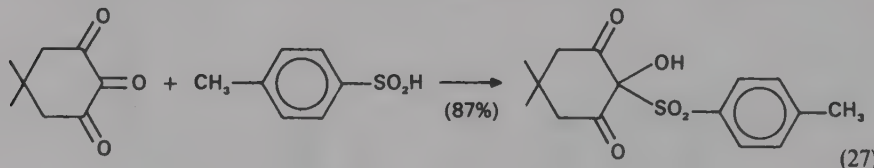
3. Addition of sulfinic acids to polar C=Y double bonds

Polar C=Y double bonds (Y = NR, O, S) with electrophilic carbon have been added to sulfinic acids under formation of sulfones. As in the preceding section one must distinguish between carbonyl groups and their derivatives on the one hand, and carboxylic acids (possessing leaving groups at the electrophilic carbon) on the other. Aldehydes[99–101] of sufficient reactivity—especially mono-substituted glyoxals[102,103]—and their aryl or arylsulfonyl imines[104] have been added to sulfinic acids (in a reversible equilibrium) to yield α-hydroxy or α-amino sulfones; the latter could also be obtained from the former in the presence of primary amines[99,100] (equation 26).



(26)

In the case of the carbonyl group of cyclohexanone, two flanking carbonyl groups were necessary to afford the corresponding adduct[104] (equation 27). In the course of tertiary amine- or silica gel-catalyzed rearrangements of benzyl (and related) thiosulfonates to α-monosulfonylated dibenzyl (and related disulfides[105], an intermediate carbophilic S-addition of sulfinate to a thioaldehyde as reactive intermediate according to equation 27a must have taken place. The intermediacy of the thioaldehydes could be proved by trapping with cyclopentadiene after base-catalyzed fragmentation of **7** at room temperature.



(27)

$$R^2CH_2SSO_2R^1 \xrightarrow[SiO_2(c,d)]{Et_3N(a,b)\ or} \left[R^2\underset{R^2}{\overset{S}{\overset{\|}{C}}}H + R^1SO_2H \longrightarrow R^2\underset{R^2}{\overset{SH}{\overset{|}{C}}}HSO_2R^1 \right]$$

$$\xrightarrow[-R^1SO_2H]{+6} R^2CH_2SSCHSO_2R^1 \qquad (27a)$$

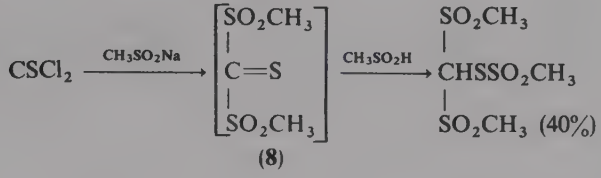
(6) **(7)**

R^1 = *p*-Tol; R^2 = (**a**) *p*-$O_2NC_6H_4$ (95%) (**b**) Ph (78%)
(**c**) COC_6H_4Br-*p* (~ 100%) (**d**) CO_2Et (~ 100%)

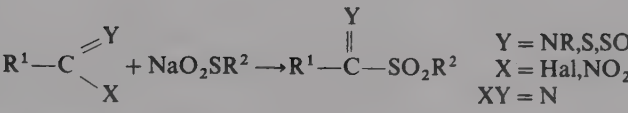
An inverse addition of sulfinic acid to a thiocarbonyl group could have taken place with the reactive intermediate **8**, which should arise from thiophosgene and methanesulfinic acid (sodium salt)[106] (equation 28). The first step of this reaction represents an S-acylation

of the ambident sulfinate anion, which occurs only with thiono or imino derivatives of acyl halides and related species; acyl halides themselves[107,108] react with sulfinate anions under O-substitution followed by disproportionation of the initially formed mixed anhydride[109].

Table 2 surveys different types of addition–elimination sequences (equation 29).

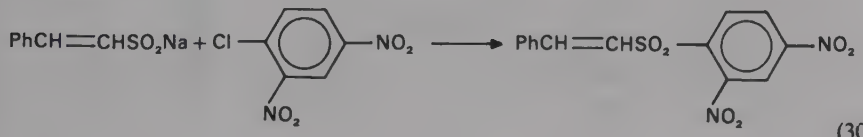


(28)

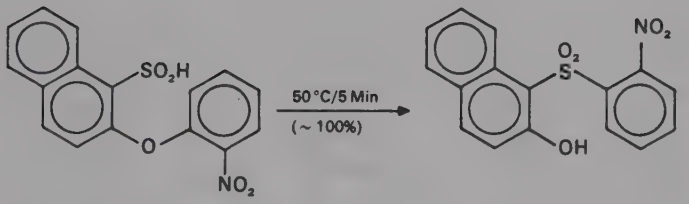


(29)

Nucleophilic substitutions of halogen by the addition–elimination pathway in electron-deficient six-membered hetarenes by sulfinate anions under formation of sulfones have been described earlier[120]. The corresponding electron-poor arenes behave similarly[121] (equation 30). A special type of this reaction represents the inverse Smiles rearrangement in equation 31[122].



(30)

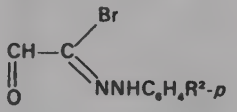
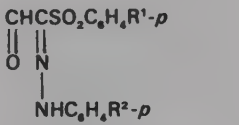
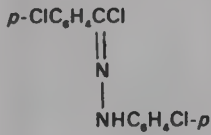
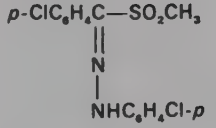
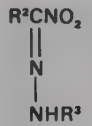
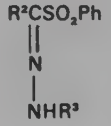
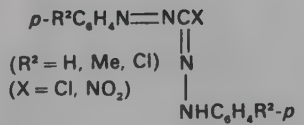
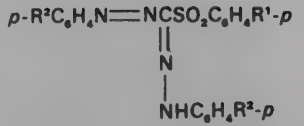


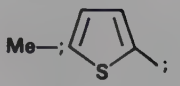
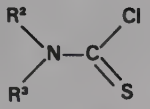
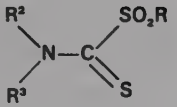
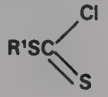
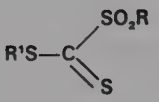
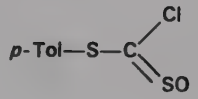
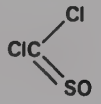
(31)

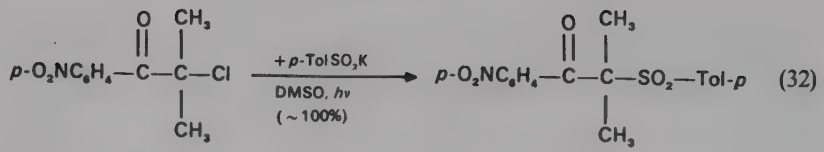
4. Nucleophilic displacement of sp^3-carbon bonded halide and related leaving groups

The usual sulfone synthesis by displacement of halide by sulfinate is assumed to have a nucleophilic S_N2 mechanism[123]. However, in special cases of alkyl halides with additional, electron-withdrawing substituents a radical substitution pathway has been observed[124–127] (equation 32). Correspondingly, substitutions under formation of sulfones take place with α-nitroalkyl iodides[125] or bromide[126] as well as with α-nitroalkyl thiocyanates[127]. Related reactions are the co-oxidations of sulfinates and anions of nitroalkanes yielding sulfones under the influence of iodine[128], hexacyanoferrate(III)[129–131], caroate[131], and peroxidisulfate[129,130] as oxidants. Further radical sulfone formations from sulfinic acids are shown in the examples[132–136] for arylation and alkenylation in equations 33–35.

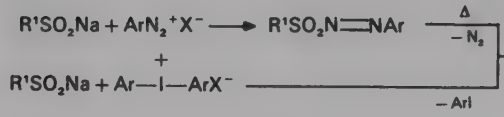
TABLE 2. Sulfones from S-acylations of sulfinate anions RSO_2^-

R	Acylation reagent	Sulfone	Yield (%)	Ref.
p-$R^1C_6H_4$ (R^1 = H, Me, Cl)			50–70	110
Me			33	111 (110)
Ph			/	112
p-$R^1C_6H_4$ (R^1 = H, Me)			/	113

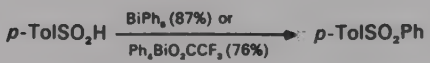
Ph	$Br_2C{=}N{-}N{=}CBr_2$	$(PhSO_2)_2C{=}N{-}N{=}C(SO_2Ph)_2$	93	114
p-$R^1C_6H_4$ (R^1 = H, OMe, Hal, NHAc)	Cl—C≡N	*p*-$R^1C_6H_4SO_2CN$	92–97	115
 *p*-$R^1C_6H_4$ (R^1 = H, Hal, NO_2)	 R^2, R^3 = Alkyl, Aryl		10–71	116
Me–; Ph–; 1-Adamantyl-			7–70	117, 118
p-Tol		*p*-TolSCH$_2$SO$_2$Tol-*p*	81	119
p-Tol		(*p*-TolSO$_2$)$_2$CH$_2$	80	119



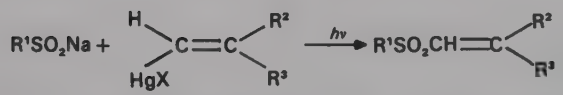
(32)



(33)[132,133]

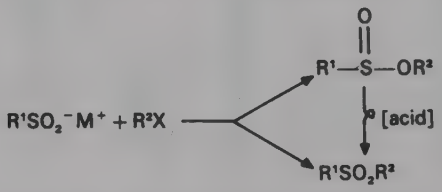


(34)[134]



(35)[135,136]

Alkylation of the ambident sulfinate ions by variation of alkylating agent, countercation, solvent, and reaction conditions has been the subject of extensive investigations previously as well as today, since sulfone synthesis by S-alkylation is probably the most important method[137]. Usually, alkyl halides have been used in order to synthesize sulfones, in combination with sodium, potassium or silver salts of sulfinic acids in protonic solvents (ethanol, dipropylene glycol[138], polyglycol[139], or water) at elevated temperature; however, by using α-halogeno ethers instead of alkyl halides, protonic solvents as well as solvents of a too enhanced polarity must be avoided, since they lead to undesired side-reactions[140–142]. On the other hand, sulfinates from weaker sulfinic acids are more favorable on account of their higher S-nucleophilicity[143] than those of very strong sulfinic acids. Sulfinate esters are obtained primarily in the latter cases as products of kinetic control and can be easily rearranged to their sulfone isomers under acid catalysis[22,143] (equation 36). Table 3 gives a survey of sulfones generated by this method.



(36)

The conversions of α-halogeno carbonyl compounds seem to be of particular interest. α-Halogeno monocarbonyl compounds are able to yield sulfones by either a radical[124–127] or a nucleophilic (Table 3[148–150,153,156,157]) pathway. This proves to be correct also for α-halogeno β,β-dicarbonyl compounds[158] with certain limitations. In the case of α-halogeno β,β,β-tricarbonyl compounds, however, the halogen is so strongly positive that it is reductively eliminated by means of a sulfinate to form a sulfonyl halide. In a subsequent reaction, this sulfonyl halide reacts as an electrophilic derivative of a sulfonic acid and attacks the simultaneously formed enolate anion on oxygen according to the scheme of a Schotten–Baumann reaction (equation 37). On the other hand, enolates are

TABLE 3. Sulfones from sulfinates R^1SO_2M and alkyl halides

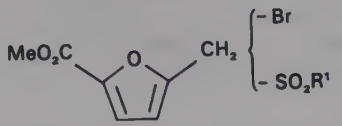
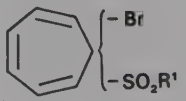
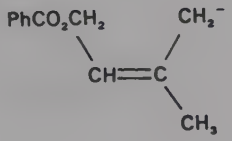
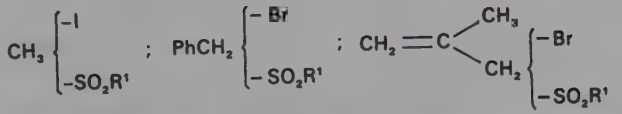
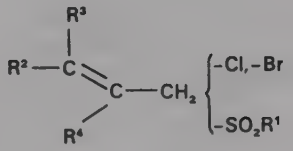
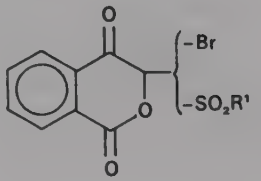
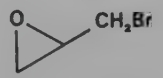
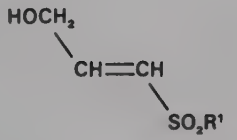
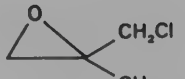
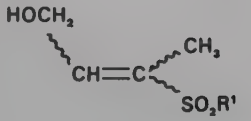
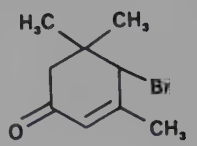
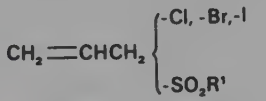
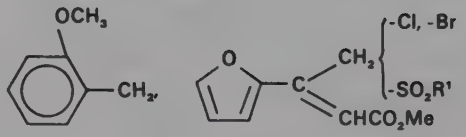
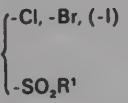
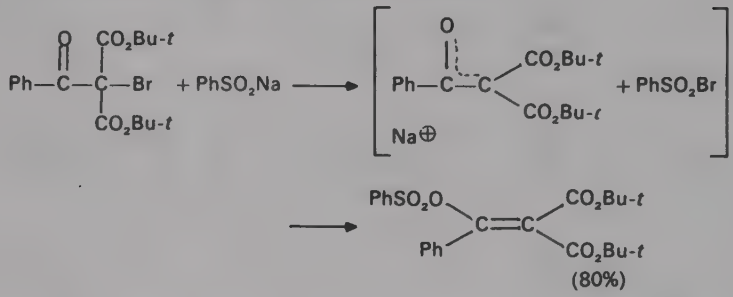
R^1	M	R^2X and $R^2SO_2R^1$	or rearranged sulfones	Yield (%)	Ref.
CCl_3	Na			45	144
C_4H_9	$\frac{1}{2}Mg$			/	145
p-$NO_2C_6H_4$	Na			/	145
	MgBr			75–80	146
p-RC_6H_4— (R = H, Br)	Na			63–89 ($E+Z$)	147
p-RC_6H_4 (R = H, Cl, OMe, NO_2)	Na			40–54	148

TABLE 3. (Contd.)

R^1	M	R^2X and $R^2SO_2R^1$	or rearranged sulfones	Yield (%)	Ref.
Ph	Amberlyst A-26	CH_3(-I; $-SO_2R^1$); C_6H_{17}(-I; $-SO_2R^1$); $PhCOCH_2$(-I; $-SO_2R^1$); EtO_2CCH_2(-Br; $-SO_2R^1$)		83–100	149
p-Tol	Bu_4N (PTC)	C_6H_{13}, $PhCH_2$, C_7H_{15}, Et, 2-C_7H_{15}, $CH_2{=}C(CH_3)CH_2$, $CH_2{=}CHCH_2$, CH_3COCH_2, $CH_3CH(CO_2Et)$, ICH_2, $Cl(CH_2)_3$(-Cl, -Br, -I; $-SO_2R^1$)		≦94	150
				81	150
				95 (E/Z = 65:35)	150

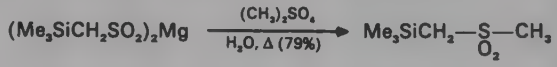
p-Tol	Na		65	151
p-Tol	Bu_4N (PTC)	Me, $MeOCH_2$, *p*-ClC_6H_4, $NCCH_2$, $BrCH_2$; $PhCOCH_2$, $(CH_3)_2CH$, 	59–96	152, 153
p-Tol	Na		94,74	154, 155
p-RC_6H_4 (R = H, Me, OMe, Cl, NO_2)	Li, K, Na	$R^2COCH(OMe)$  (R^2: Me, *t*-Bu, Aryl)	20–60	156
o-$O_2NC_6H_4$	Na	NaO_2CCH_2	91	157

able to yield sulfones with sulfonyl halides (cf. Section III.C.2)[159].

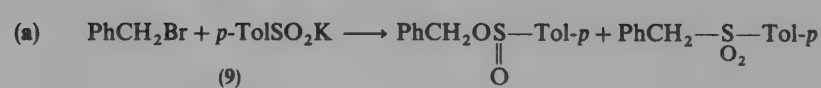


(37)

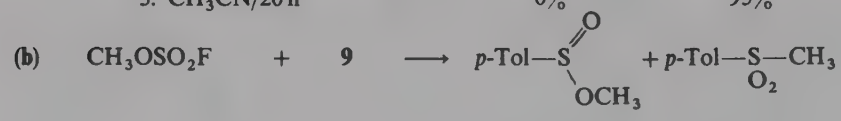
In connection with alkylations of ambident sulfinates by alkyl halides, manifold efforts have been made to find rules for either O- or S-alkylations. In the course of these investigations various leaving groups instead of halides as well as different reaction conditions have been applied: Sodium arenesulfinate and trimethyloxonium tetrafluoroborate yield O-substitution[160], whereas phase-transfer catalysis (PTC) conversion of potassium benzene sulfinate with trialkylsulfonium salts leads to S-substitution[161,162]. A comparative investigation of the reaction of 4-toluenesulfinate (as free acid, as sodium salt or as silver salt) describes exclusive S-substitution with methyl iodide and exclusive or at least predominant O-substitution with diazomethane, dimethyl sulfate and methyl tosylate[163,164]. On the other hand, 4-toluenesulfinic acid has been found to be O- and S-alkylated with diazoalkanes[165–167], and magnesium trimethylsilylmethanesulfinate has been described to furnish the corresponding sulfone with dimethyl sulfate[168] (equation 38). Recently, investigations on the effects of cryptands with regard to the O- and S-selectivity in the alkylation of sulfinic acids have been reported[169]:



(38)



conditions:		(9)	
1.	CH_2Cl_2/20 h	0%	0%
2.	C_6H_6/18-crown-6/2.5 h	0%	96%
3.	CH_3CN/20 h	0%	95%



conditions:		(10)	(11)
1.	CH_2Cl_2/2 h	40%	60%
2.	CH_2Cl_2/18-crown-6/2 h	70%	30%
3.	CH_2Cl_2/cryptofix(222), 2 h	83%	17%
4.	HMPA/2 h	100%	0%

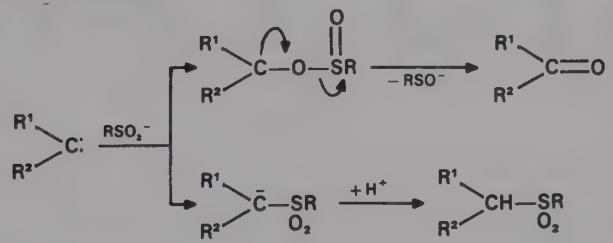
(c)	$CH_3\overset{+}{S}Ph_2\ ClO_4^-$	+ 9	⟶	10	+	11
	conditions:	1. CH_2Cl_2/24 h		44%		56%
		2. CH_2Cl_2/18-crown-6/2 h		40%		60%
(d)	$CH_3\overset{+}{S}Ph_2\ ClO_4^-$ (=O)	+ 9	⟶	10	+	11
	conditions:	1. CH_2Cl_2/24 h		56%		44%
		2. CH_2Cl_2/18-crown-6/2 h		25%		75%
		3. DMF/26 h		24%		76%

Dimethyl methanephosphonate has been successfully applied in synthesis of aryl methyl sulfones[170]. In the above-mentioned cases, the alkylating agents contained as efficient leaving groups either anions of very strong acids (halide, sulfate, sulfonate, phosphonate) or onium cations (diazonium, oxonium, sulfonium, oxosulfonium ions). However, weaker leaving groups can also be used[137b,137e] on condition that the adjacent alkyl group assists in expelling such groups. Thus in connection with benzyl and allyl groups, sulfinyloxy[171,172] and acetoxy groups without[173] and with metal catalysis [Ni(0)[174], Pd(0)[175–179]] have been applied. Generally, syntheses of allyl sulfones afford isomers, however, the relative rates can be directed[175,177]. Table 4 summarizes some nucleophilic displacements of varying weak leaving groups by sulfinate.

Sulfone exchanges by more nucleophilic sulfinates have also been reported[196].

5. *Addition of sulfinic acids (or salts) to carbenes*

Normal carbenes with two carbon substituents are highly reactive electrophiles ("hard acids") and add to sulfinates on oxygen[197,198]; decomposition of such sulfinyloxy carbanions yields carbonyl compounds and sulfenates[199]. On the other hand, carbenes which are deactivated by one or two π-donor substituents add to sulfinates on sulfur yielding sulfonyl stabilized carbanions; the latter are usually protonated in the course of work-up (equation 39). As to the reaction of haloforms with sulfinates in the presence of bases, it is noteworthy that only *one* halogen is able to be substituted by sulfinate under formation of α-halogen sulfones, as is the case with methylene halide[150,152,205–207] (cf. Table 3). After introduction of the sulfonyl group instead of one halogen, the remaining halogens are strongly positivated and cannot be substituted by a second sulfonyl group; on the other hand, excess of sulfinate can dehalogenate α-halogeno sulfones[207]. However, if the positivating effect of the sulfonyl group is internally compensated by an appropriate electron-releasing substituent[203], α-elimination of halide becomes possible again and a β-disulfone may be formed.



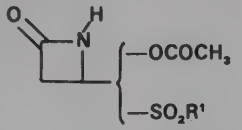
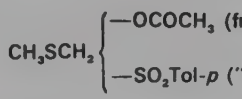
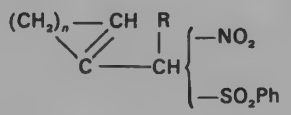
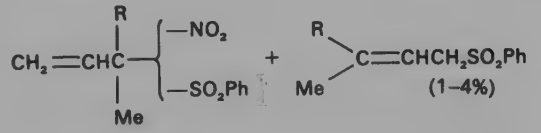
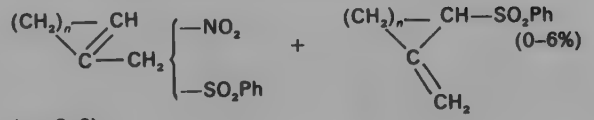
(39)

(a) R^1,R^2 = Cl, Br; R = *t*-Bu, CH_2Ph, Ph, *p*-ZC_6H_4(Z = Me, Cl), 2-Naphthoyl[200,201]

(b) R^1 = OMe; R^2 = CO_2Me; R = *p*-Tol[202]

(c) R^1 = OMe; OEt, OPh, SMe, SPh; R = *p*-ZC_6H_4(Z = Me, Cl)[203,204]

TABLE 4. Sulfones from nucleophilic displacement of different weak leaving groups by sulfinates R^1SO_2M

R^1	MX	R^2X and $R^2SO_2R^1$ or rearranged sulfone	Yield (%)	Ref.
Et, CH_2Ph, 4-Tol, 3-$NO_2C_6H_4$, 4-Cl-3-MeC_6H_3	HOAc		61–95	180
p-Tol	HOAc		71	181
Ph	$NaNO_2$		70–75	182
Ph	$NaNO_2$		76–96	182 (cf. 94)
Ph	$NaNO_2$		65–92	183

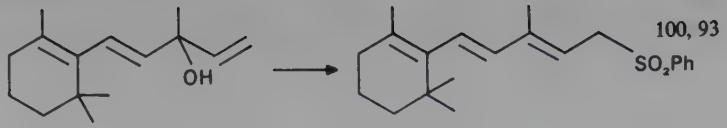
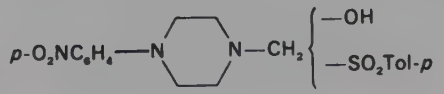
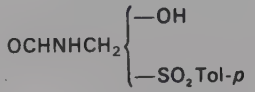
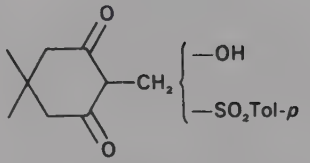
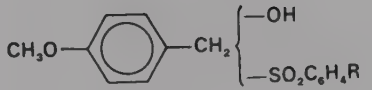
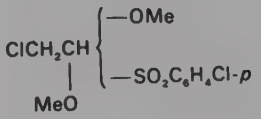
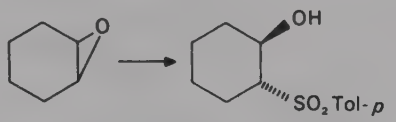
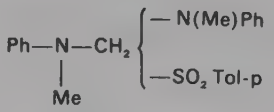
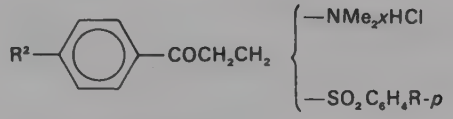
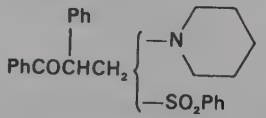
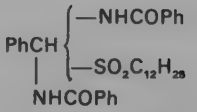
Ph	H_2O		100, 93	184 185
p-Tol	H_2O		77	186
p-Tol	H_2O		55	187
p-Tol	H_2O		95	188
RC_6H_4	H_2O		74–92	189
p-RC_6H_4 (R = H, Me, Cl)	MeOH		57	190
p-ClC_6H_4	ROH		83	191

TABLE 4. (Contd.)

R^1	MX	R^2X and $R^2SO_2R^1$ or rearranged sulfone	Yield (%)	Ref.
p-Tol	ROH		89	150
p-Tol	PhNHMe		51	192
p-RC_6H_4 (R = H, Me, OMe, NO_2, Cl, NH_2, NHAc)	Me_2NH (*x*HCl)	 (R^2 = H, Me, OMe, Cl)	*a*	193
Ph			83	194 (cf. 186)
$C_{12}H_{25}$	$PhCONH_2$		27	195 (cf. 192)

[a]Yields partially in g.

In this connection it should be mentioned that dihalogenomethyl methyl ethers did not furnish the expected β-disulfone nor the α-halogeno sulfones as preliminary steps in appreciable amounts; surprisingly, sulfonyl halides have been isolated as main products of these conversions[208]:

$$CH_3OCHX_2 + p\text{-}TolSO_2Na \longrightarrow p\text{-}TolSO_2X \quad [X = Cl(34\%),\ Br\ (59\%)]$$

B. Radical Addition of Sulfonic Acid Derivatives to Unsaturated Systems

1. Halosulfonylation

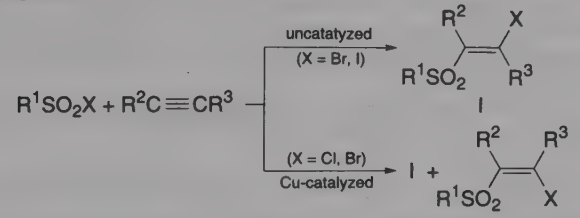
As a consequence of facile homolytic cleavages, sulfonyl halides (I > Br > Cl; F unsuitable) are able to add to unsaturated C—C systems. To prevent (or reduce) competing polymerizations, the additions of sulfonyl chlorides have been recommended to be carried out in the presence of copper(I/II) salts (Asscher–Vofsi reaction[209,210]). Comprehensive surveys have been published[211] on the resulting β-halogeno sulfones (or their vinylogous compounds) as well as on their dehalogenation products (vinyl sulfones, 1-sulfonyl-1,3-dienes, etc.). Table 5 reviews a series of sulfonyl halide additions and facile hydrogen halide eliminations.

Some details on the course of these reactions should be emphasized:

(1) Sulfonyl chlorides are added in the presence of copper(I)- or copper(II)-chloride exclusively[212], however, mostly in the further presence of triethylamine hydrochloride[213–220], especially in additions to conjugated systems[214–218].

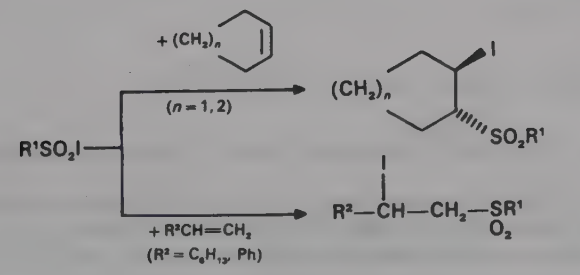
(2) Copper salts may be replaced also by other catalysts[221–224].

(3) Sulfonyl bromides and iodides react similarly[217,218,225]; copper-salt catalysis in these cases facilitates the additions but is not absolutely necessary; however, it influences the stereochemistry of the additions. Addition of sulfonyl iodides[226] as well as the uncatalyzed thermal addition of sulfonyl bromides[227] to *alkynes* leads to an exclusive *trans*-addition, whereas $CuBr_2$ catalysis in the latter case causes the formation of *cis*-addition products to some extent (11–16%); correspondingly, copper-salt catalysis in sulfonyl chloride additions to alkynes leads to the formation of a mixture of *Z*,*E*-isomers[228,229] (equation 40).



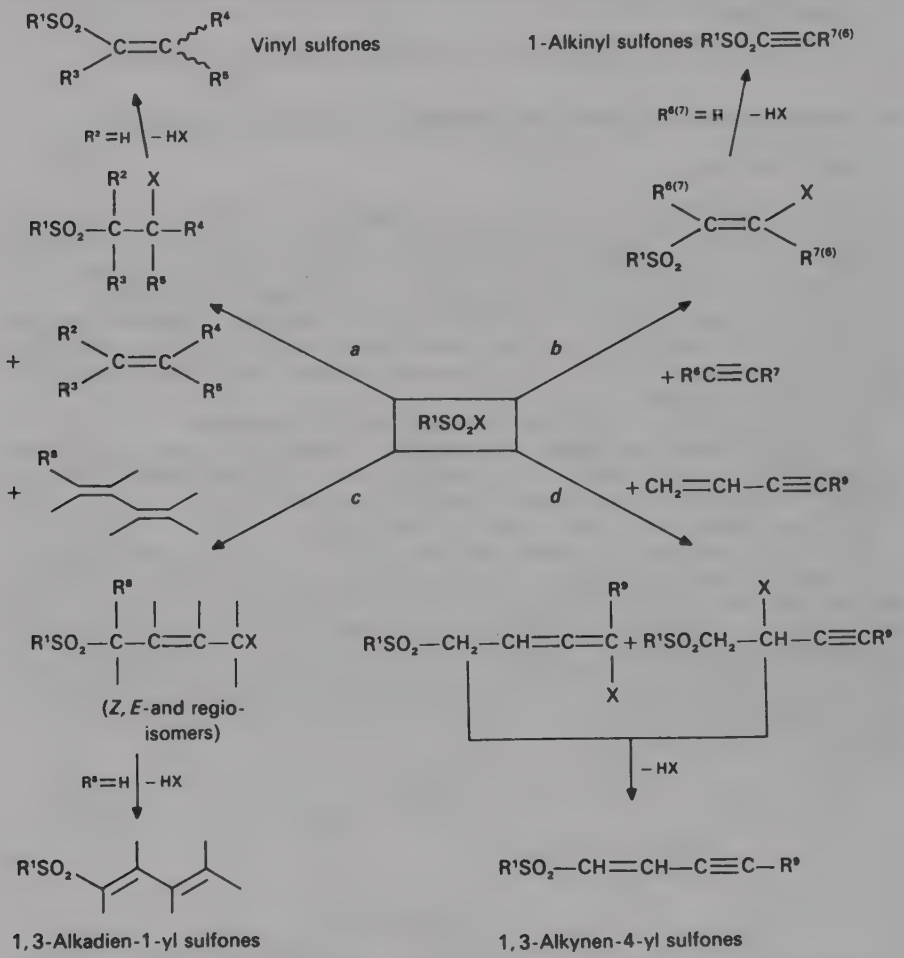
(40)

(4) Addition of sulfonyl iodides to alkenes ensues stereo- and regiospecifically[231] (equation 41).



(41)

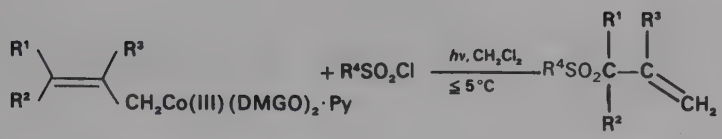
TABLE 5. Survey of sulfonyl halide additions to unsaturated systems and hydrogen halide eliminations to unsaturated sulfones



[a] References 209, 210, 212, 214, 215, 217, 218, 220, 230, 231; cf. 79.
[b] References 213, 226–229.
[c] References 210, 214, 215, 220.
[d] Reference 216.

Table 6 gives a selection of reactions of sulfonyl halides with different unsaturated systems.

Recently, Co(III)–allyl complexes have been described to be sulfonylated regiospecifically by sulfonyl halides under irradiation[232] (equation 42). Similarly, allyl methyl sulfone has been obtained from allyltrimethylsilane under copper(I) catalysis[213].



(42)

DMGO = Dimethylglyoximate

R^1, R^2 = H; R^3 = Me

R^1 = Me; R^2, R^3 = H

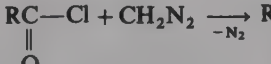
R^1, R^2 = Me; R^3 = H

R^4 = *p*-FC_6H_4; 2,4,5-$Cl_3C_6H_2$

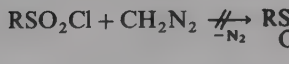
2. Thio- and seleno-sulfonylation

In the same manner as described before, arenesulfonyl thiocyanates are able to show self-addition to conjugated systems yielding sulfones[243,244]. More important, however, is that reactions of selenosulfonates with unsaturated systems as well as with nucleophilic carbon have been proved.

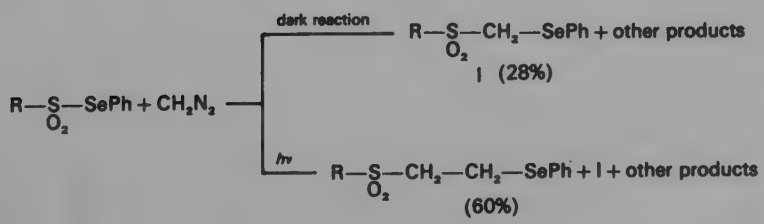
In the first step of the Arndt–Eistert homologation of carboxylic acids, the nucleophilic carbon of diazomethane replaces chloride from the corresponding carboxylic acid chloride. If the evolved hydrogen chloride is not removed, the initially formed diazomethyl ketone is immediately transformed to the corresponding chloromethyl ketone under evolution of molecular nitrogen. Principally, this reaction represents an insertion of a methylene group into the carbon–chlorine bond of the acid chloride (equation 43). This reaction sequence proceeds with sulfenic and sulfinic acid chlorides too, but it does not occur with sulfonyl chlorides[245] (although this is controversial[246] (equation 44)). However, if the sulfonyl chloride is replaced by the corresponding selenosulfonate, an insertion takes place both in a dark reaction and under irradiation[247] (equation 45). The addition of selenosulfonates to unsaturated C—C bonds appears to be of particular interest, because the introduced seleno function can be easily removed by oxidation yielding vinyl or alkynyl sulfones. Additions have been performed with alkenes[248–250], alkynes[251–255], and allenes[256,257]. Table 7 gives a survey on these reactions.



(43)

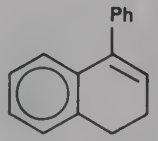
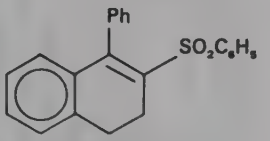
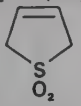


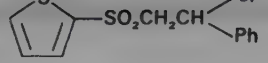
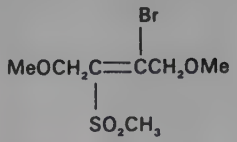
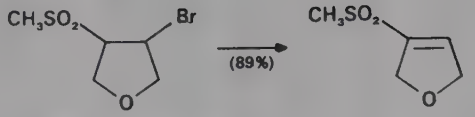
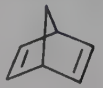
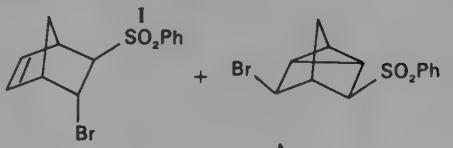
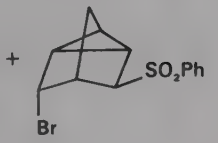
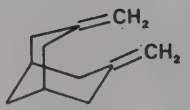
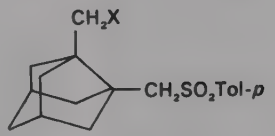
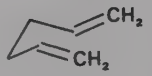
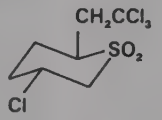
(44)



(45)

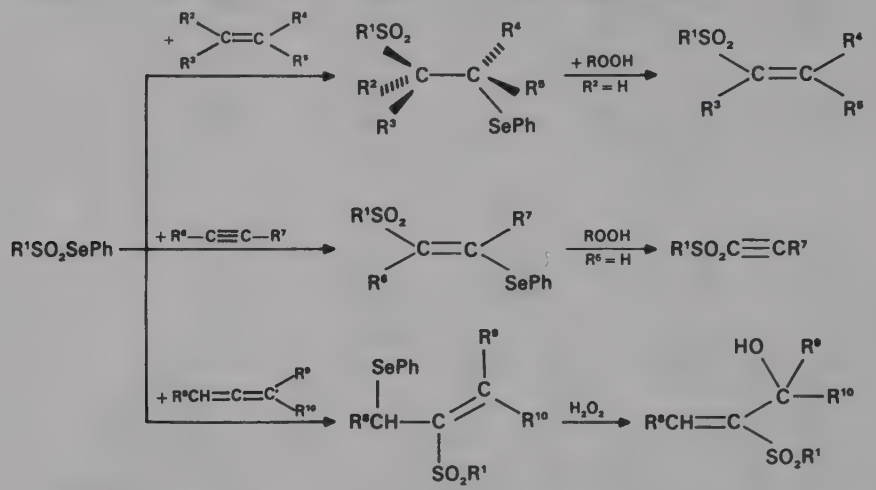
TABLE 6. Sulfones from unsaturated systems and sulfonyl halides R^1SO_2X by radical routes

R^1	X	Unsaturated C—C compound	Catalyst	Sulfone	Yield (%)	Ref
CH_3	Cl	$Me_3SiCH{=}CH_2$	*a*	$Me_3SiCHClCH_2SO_2CH_3$ → $Me_3SiCH{=}CHSO_2CH_3$	70	213
C_6H_5	Cl	*p*-$ZC_6H_4OCH{=}CH_2$ (Z = Me, OMe, Hal)	*b*	*p*-$ZC_6H_4OCHClCH_2SO_2C_6H_5$	40–95	222, 223
		$CH_3CH{=}CHCH_3$ (*Z* + *E*)	*c*	$CH_3CHClCH(CH_3)SO_2C_6H_5$ (diastereomers)	51	209, 233
						
p-Tol	Cl	$CH_2{=}CH_2$	*c*	*p*-$TolSO_2CH_2CH_2Cl$ + *p*-$TolSO_2CH{=}CH_2$	95	220
		$CH_2{=}CH{-}CH{=}CH_2$	*c*	*p*-$TolSO_2CH_2CH{=}CHCH_2Cl$	95	220
		$CH_2{=}C(Me){-}CH{=}CH_2$	*a*	mixture of 3 sulfones	82	214
			*c*	*p*-$TolSO_2CH_2CH{=}CHCH_2Cl$	67	210
		$PhCH{=}CH_2$	*d*	*p*-$TolSO_2CH{=}CHPh$	86 36	221a, 234 234
		$Ph_2C{=}CH_2$	*d*	*p*-$TolSO_2CH{=}CPh_2$	59	213
		$PhC{\equiv}CH$	*c* *c*	*p*-$TolSO_2CH{=}C(Cl)Ph$ *E*/*Z*: 92/8 *E*/*Z*: 35/65	88 85	235 235
p-$ClCH_2C_6H_4$	Cl	$CH_2{=}CH_2$	*c*	*p*-$ClCH_2C_6H_4SO_2CH_2CH_2Cl$ + *p*-$ClCH_2C_6H_4SO_2CH{=}CH_2$	90	220
p-$O_2NC_6H_4$	Cl	$PhC{\equiv}CH$	*c*	*p*-$O_2NC_6H_4SO_2CH{=}C(Cl)Ph$ *E*/*Z*: 93/7 *E*/*Z*: 42/58	94 92	235 235

	Cl	$PhCH{=}CH_2$	*c*		93	219, 236
CH_3	Br	$MeOCH_2C{\equiv}CCH_2OMe$	*f*		59	237
			g		95	237
p-Tol	I	$PhCH{=}C{=}CH_2$	/	*p*-$TolSO_2CH_2C{=}CHPh$	80	238
Ph	Br		/			
					8, 32, 24	239
p-Tol	Cl Br		/		70 96	240 241
CCl_3	Cl		/		14	242

Catalysts: [a] $CuCl/Et_3NHCl$; [b] AIBN/*hv*; [c] $CuCl_2/Et_3NHCl$; [d] $Ru[PPh_3]Cl_2/Bu_3N$; [e] $CuCl/CH_3CN$; [f] *t*-BuOOH/$ZnCl_2$; [g] H_2O_2/*t*-BuOOH/$ZnCl_2/Et_3N$.

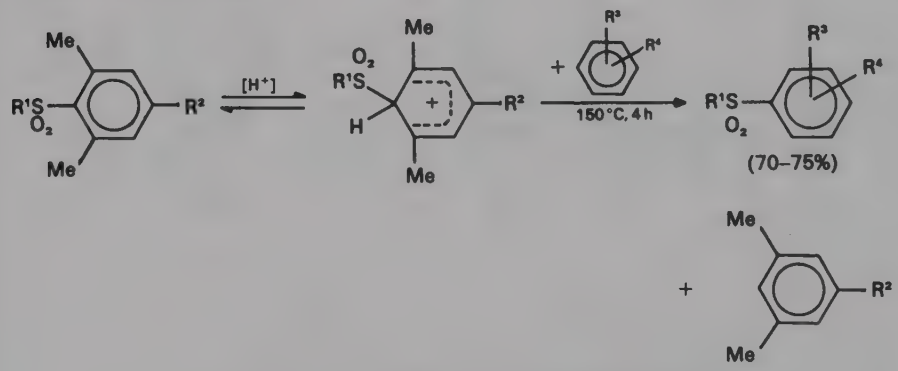
TABLE 7. Sulfones from unsaturated C—C systems and selenosulfonates



It is noteworthy that in these selenosulfonylations, the direction of the addition is opposite to the corresponding additions of sulfonyl iodides to allenes (cf. Table 7 in Reference 238).

C. S-Substitution of Sulfonyl Electrophiles with C-Nucleophiles

In principle, sulfonyl compounds bearing highly-electron-accepting substituents are able to transfer the sulfonyl group as an electrophile. Thus, the exchange of aryl substituents in methyl aryl sulfones under catalysis of trifluoromethanesulfonic acid takes place[258] (equation 46). This reaction represents a further example for the reversibility of Friedel–Crafts reactions.



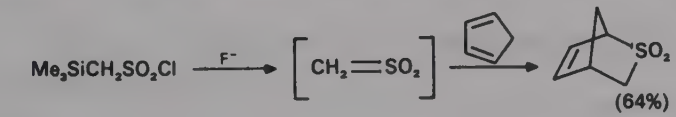
$R^1 = Me$ $R^3 = H, Me, OMe, OEt, OPh$

$R^2 = H, Me, Ph$ $R^4 = H, Me$ (46)

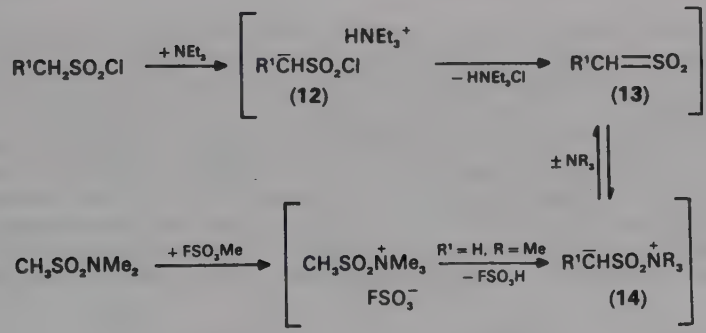
Normally, reactive derivatives of sulfonic acids serve to transfer electrophilic sulfonyl groups[259]. The most frequently applied compounds of this type are sulfonyl halides, though they show an ambiguous reaction behavior (cf. Section III.B). This ambiguity is additionally enhanced by the structure of sulfonyl halides and by the reaction conditions in the course of electrophilic sulfonyl transfers. On the one hand, sulfonyl halides can displace halides by an addition–elimination mechanism; on the other hand, as a consequence of the possibility of the formation of a carbanion α to the sulfonyl halide function, sulfenes can arise after halide elimination and show electrophilic as well as dipolarophilic properties.

1. *Sulfene reactions*

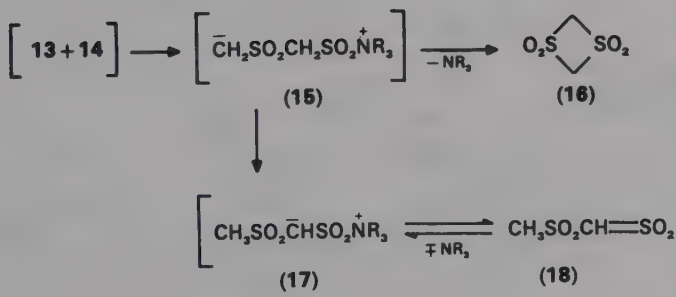
Recent investigations show that *free* sulfenes arise from fluoride-induced fragmentation of trimethylsilylmethanesulfonyl chloride, as could be proved by trapping in the course of a Diels–Alder reaction[260] (equation 47). Usually, generation of sulfenes[261] starts from sulfonyl halides with at least one α hydrogen and tertiary bases, where the ammonium ylide **14** dominates over **13**. Mixtures of **13** and **14** may also be obtained by N-alkylation of methanesulfonic acid dimethylamide[262] (equation 48). In the absence of efficient trapping reagents[263], the intermediates **12**, **13** and **14** are able to react with each other in different ways. With $R^1 = H$, **13** and **14** may yield **15**, which undergoes either ring closure to the cyclic disulfone **16**[264] or proton migration to yield **17** (equation 49). On the other hand, **17**



(47)

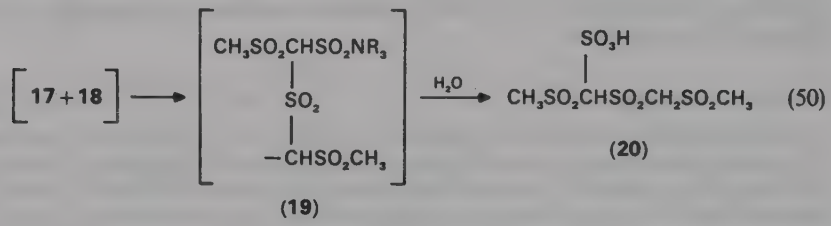


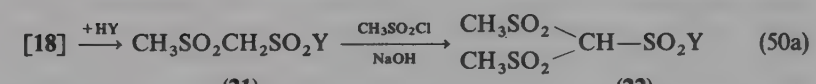
(48)

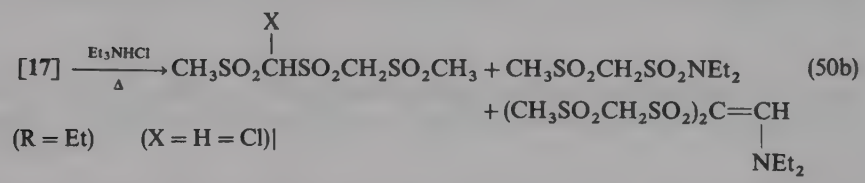


(49)

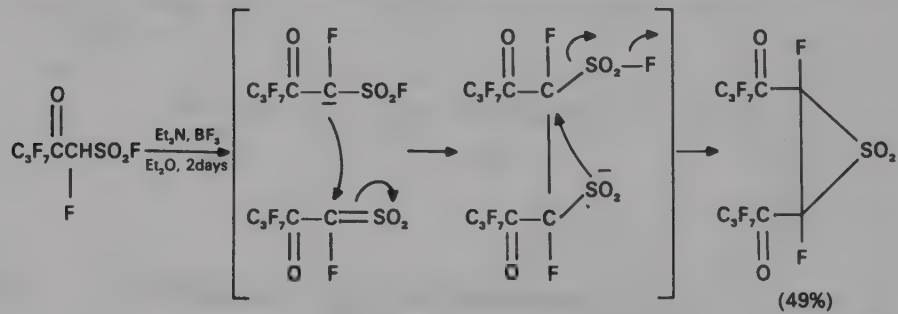
and **18** exhibit the same equilibrium as **13** and **14** as well as addition to yield **19**[265] which in turn is hydrolyzed to give **20** (equation 50). The sulfonyl sulfene **18** can be trapped by appropriate (proton activated) nucleophiles[262,263,265] to furnish **21**, which is further mesylated to **22**[263,265] (equation 50a). At −40 °C the sulfene oligomerizations become slower from step to step; the ylide **17** proves to be storable in acetonitrile at this temperature for several days without significant decomposition[266]. On thermolysis, the products in equation 50b have been identified.





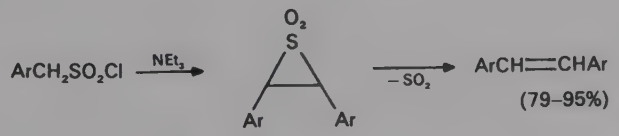


The sulfene reactions discussed above use C—S bonds for dimerizations and oligomerizations. However, starting with appropriate substituents R^1 (equation 48: R^1 = aryl, acyl), more stabilized anions **12** are obtained, which react with their corresponding sulfenes **13** under C—C bond formation followed by ring closure to a three-membered ring sulfone (Wedekind–Staudinger reaction)[267] (equation 51). In most cases these thiirane *S,S*-dioxides extrude sulfur dioxide[268] under formation of olefins[269] (equation 52). In the case of the conversion of cinnamylsulfonyl chloride, a mixture of *Z* and *E* 1,2-bis(*trans*-β-styryl)thiirane *S,S*-dioxides is formed. The *E* isomer undergoes ring enlargement to give a seven-membered ring sulfone[269] (equation 53). On the other hand, reductive ring opening of *Z*-2,3-diphenylthiirane *S,S*-dioxide yields the open-chain

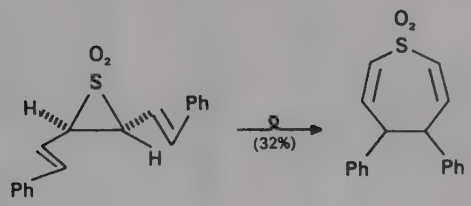


(51)

dibenzyl sulfone[270a] (equation 54). Lewis-acid-catalyzed insertion of thiirane 1, 1-dioxide into α-halo ethers also furnishes open-chain sulfones[270b] (equation 55). In most cases sulfenes are trapped *in situ* with appropriate reagents containing reactive C=C double bonds (equation 56). The four-membered ring sulfones thus obtained by [2 + 2]cycloaddition will be treated in another chapter of this volume. It should be mentioned, however, that in special cases facile hydrolytic cleavages of the initially formed thietane *S*, *S*-dioxides occur with formation of open-chain sulfones[273,274] (equations 57 and 58).



(52)



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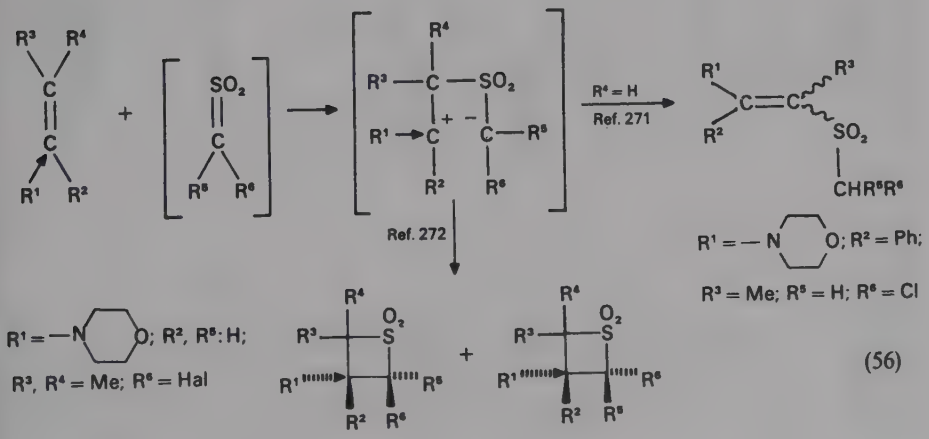
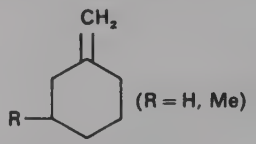
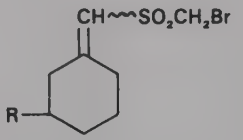
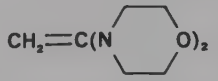
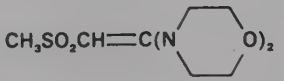
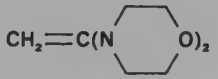
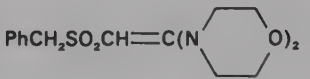
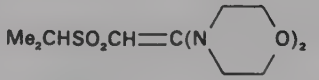
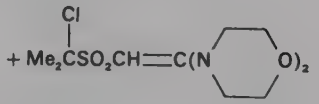
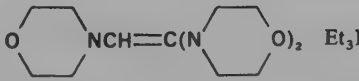
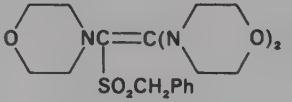
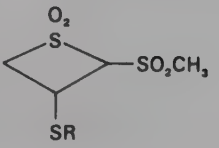
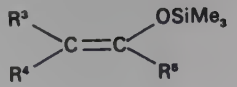
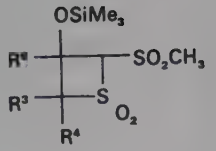
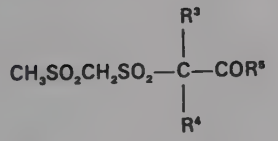
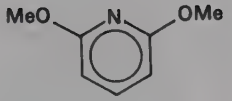
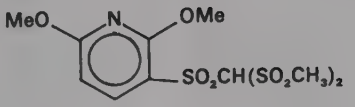
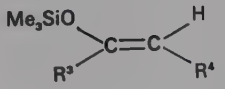
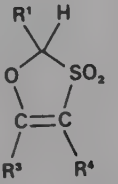
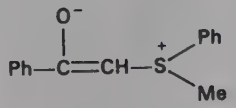
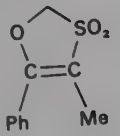
(55)



(56)

TABLE 8. (Partly) open-chain sulfones from sulfenes and their dimers

$R^1R^2CHSO_2X$ R^1	R^2	X	Unsaturated compound	Base (solvent)	Sulfone	Yield (%)	Ref.
Br	H	Br	 (R = H, Me)	Et_3N		*a*	275
H	H	Cl		(DMF)		58	276
Ph	H	Cl		(DMF)		60	276
Me	Me	Cl		Et_2NH(DMF)			
						8,12	276
Ph	H	Cl		Et_3N		26	277
H	H	Cl	CH_2=CHSR (R = Me, Et, Bu, *t*-Bu, *c*-C_6H_{11})	Et_3N		32–75	278

H	H	Cl		Et_3N (EtOH/MeCN)		7–53	279
						7–68	
H	H	Cl		Et_3N		80	280
H, Me	Cl, Br, I	Br		DBN		≤ 70	281
Me	H	Cl		Et_3N		36	282

[a]Obtained only as intermediate.

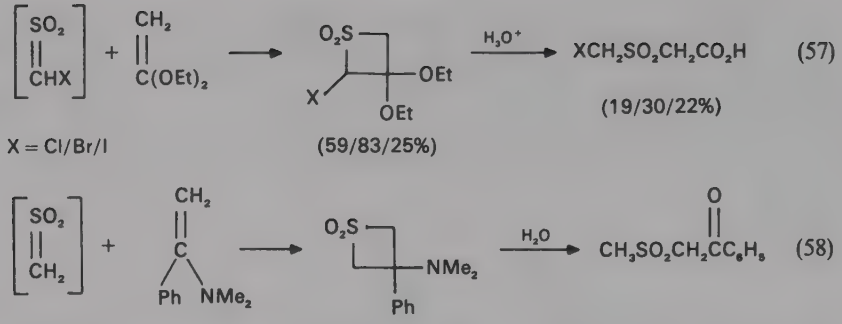


Table 8 gives a survey on some selected syntheses of (partly) open chain sulfones from sulfenes.

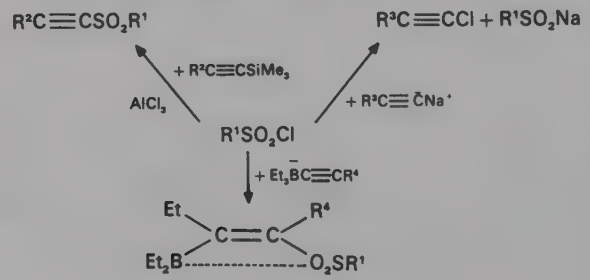
2. Halide substitution in sulfonyl halides

Besides radical additions to unsaturated C—C bonds (Section III.B.1) and sulfene reactions (see above), sulfonyl halides are able to furnish sulfones by nucleophilic substitution of halide by appropriate C-nucleophiles. Undesired radical reactions are suppressed by avoiding heat, irradiation, radical initiators, transition-element ion catalysis, and unsuitable halogens. However, a second type of undesired reaction can occur by transfer of halogen instead of sulfonyl groups[283–286] (which becomes the main reaction, e.g. with sulfuryl chloride). Normally, both types of undesired side-reaction can be avoided by utilizing sulfonyl fluorides.

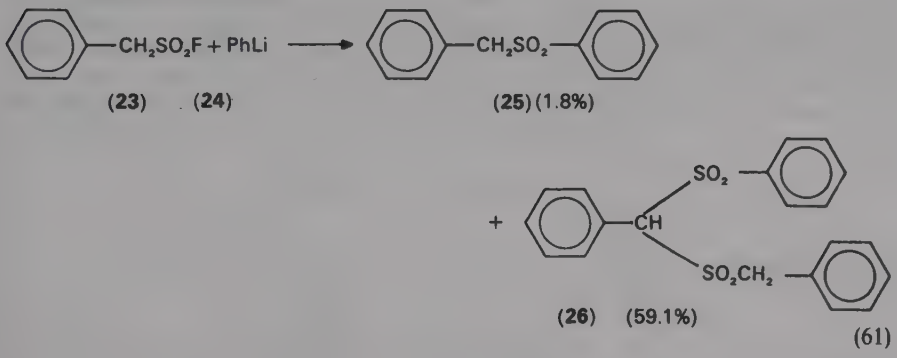
a. Friedel–Crafts related sulfonylations. Sulfonylations of arenes by sulfonyl halides under Friedel–Crafts conditions have been reviewed frequently[288]. Appropriate catalysts are Lewis acids (e.g. $AlCl_3$[289], SbX_5[290], $FeCl_3$[291]) or heteropolyacids[292] (equation 59). In some special cases, cyclopropane[293] and olefins[294] as well as silyl and stannyl compounds[295] are also sulfonylated under Lewis acid catalysis.

$$ArH + RSO_2X \xrightarrow[-HX]{\text{catalyst}} ArSO_2R \qquad (59)$$

b. Sulfonylation of reactive carbon nucleophiles. Whereas bis(trimethylsilyl)acetylene exhibits sulfone formation under Friedel–Crafts catalysis[295b], sodium acetylides are halogenated by arenesulfonyl chlorides, bromides and iodides[296] under simultaneous formation of sodium arenesulfinates. On the other hand, complexation of the nucleophilic carbon by triethylborane and subsequent conversion with sulfonyl chlorides leads to a regiospecific sulfonylation of the vicinal carbon atom[297] (equation 60).

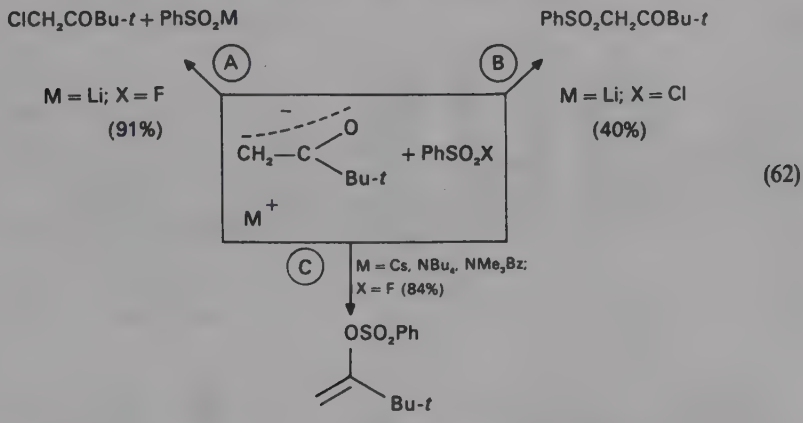


Whereas aryl Grignard compounds afford good yields of sulfones with sulfonyl fluorides[298,299], phenyllithium is mainly chlorinated by α-toluenesulfonyl chloride; on the other hand, the corresponding fluoride yields only a trace of the expected monosulfonylation product, while the main product is **26** obtained by twofold sulfonylation[300] (equation 61).



(61)

Corresponding 1,1-disulfones have been obtained from alkyl Grignard and alkyllithium compounds with tosyl fluoride[301]. From diarylcadmium compounds and aromatic[302] as well as aliphatic[303] sulfonyl chlorides, the formation of sulfones in moderate yields has been reported. Obviously, these reactions follow a radical pathway shown by the additional formation of chloroarenes as well as diaryls. A similar sulfone synthesis from diarylmercury compounds and tosyl iodide[304] has been investigated earlier. Conversions of a twofold ambiguity occur with enolates and arenesulfonyl halides depending on the counter-cation on the one hand, as well on the halogen on the other. Whereas enolates with partly shielded oxygen undergo C-chlorination with sulfonyl chloride (route A; see equation 62) and C-sulfonylation with sulfonyl fluoride[284] (route B), free enolate ions act as O-nucleophiles and yield enol sulfonates with sulfonyl fluoride[305] (route C).

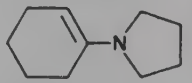
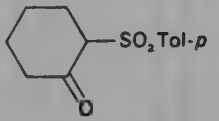


(62)

In connection with route A, the formation of sulfones from sulfinates and α-haloketones on the one hand, and of isomeric enol sulfonates on the other (cf. Section III.A.4), should be pointed out.

Table 9 gives a summary of sulfonylations of several types of C-nucleophiles with

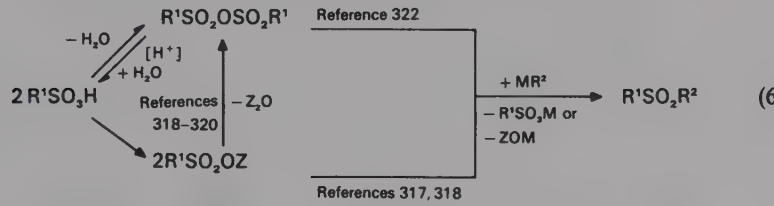
TABLE 9. Sulfones R^1SO_2X from different C-nucleophiles and sulfonyl halides

R^1	X	C-nucleophile	Sulfone	Yield	Ref.
p-BrC_6H_4	F	PhMgBr	*p*-$BrC_6H_4SO_2Ph$	91	299
$PhCH_2$	F	PhMgBr	$PhCH_2SO_2Ph$	88	298 (299)
CH_3	Cl	$(MeO_2C)_2CHNa$	$(MeO_2C)_2CHSO_2CH_3$	58	306
CF_3	F	$(EtO_2C)_2CHNa$	$(EtO_2C)_2CHSO_2CF_3$	86	307a
CF_3	F	$CH_3SO_2CH_2MgBr$	$CF_3SO_2CH_2SO_2CH_3$	70	307b
C_4H_9	F	$(EtO_2C)_2CHNa$	$(EtO_2C)_2CHSO_2C_4H_9$	80	307a
CH_3	Cl	$CH_3COCHCO_2Me$ Na^+	CH_3CO, MeO_2C > $CHSO_2CH_3$	15	306 (308)
		C_6H_5Co $C_6H_5COCHCO_2Et$ Na^+	C_6H_5CO, EtO_2C > $CHSO_2CH_3$	26	308
		$(C_6H_5CO)_2CHNa$	$(C_6H_5CO)_2CHSO_2CH_3$	26	308
p-Tol	F	CH_3CH_2MgBr	$CH_3CH(SO_2Tol\text{-}p)_2$	83	301
		$CH_2{=}PPh_3$	*p*-$TolSO_2CH{=}PPh_3$	74	309
		$PhCH{=}PPh_3$	*p*-$TolSO_2C(Ph){=}PPh_3$	12	309
$MeCH_2$	F	$PhCH{=}PPh_3$	$PhCH_2SO_2C(Me){=}PPh_3$ (rearrangement product!)	94	310
t-$BuCH_2$	F	$PhCH{=}PPh_3$	*t*-$BuCH_2SO_2C(Ph){=}PPh_3$	77	310
p-An	F	CH_2SOMe_2	*p*-$AnSO_2\bar{C}HS^+OMe_2$	91	311
p-Tol	Cl			54	312
		$PhC(OSiMe_3){=}CH_2$	$PhCOCH_2SO_2Tol\text{-}p$	66	313

sulfonyl halides. In this connection, it should be mentioned that organocobalt complexes yield sulfones with sulfonyl chlorides, however, under photochemical conditions[314,315].

3. *Sulfonic acid anhydrides and esters*

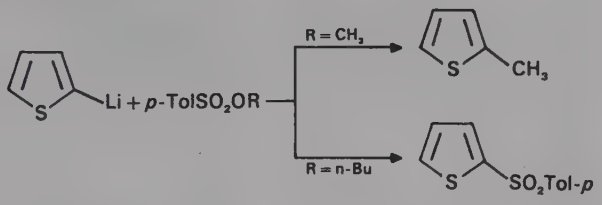
Sulfonic acids themselves are unfit for electrophilic transfer of sulfonyl groups because of the poor nucleofugality of the hydroxide anion. However, the high acidity obviously leads to an equilibrium between the acids and their anhydrides and water, from which water can be removed either by special reaction conditions (i.e., azeotropic distillation with appropriate solvents) or chemically with anhydride forming agents[316] (equation 63). sulfonic acid anhydride sulfonylations are compiled in Table 10.



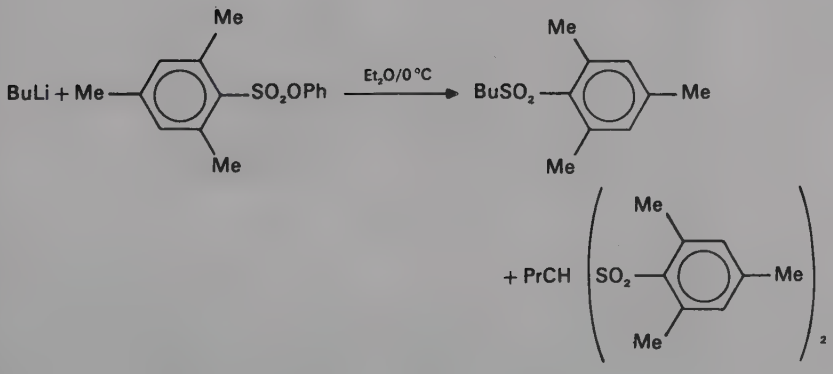
(63)

$Z = ClO_3$[317] SO_3H[318] COR[3 319] $SOCl$[320] etc.; M = H, Na, MgX (X = Br, OEt) etc.; R^2 = nucleofugal groups

The formation of halogenation products from Grignard reagents and sulfonic acid anhydrides is the result of an oxidative reaction pathway[323,327]. This side-reaction can be reduced by using sulfonic acid esters, however, in these cases alkylations[328] as well as twofold sulfonylations[329] (cf. corresponding results with sulfonyl fluorides[301]) are competing (equations 64 and 65).

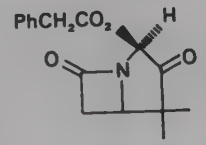
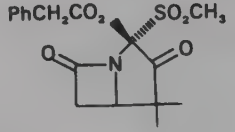


(64)



(65)

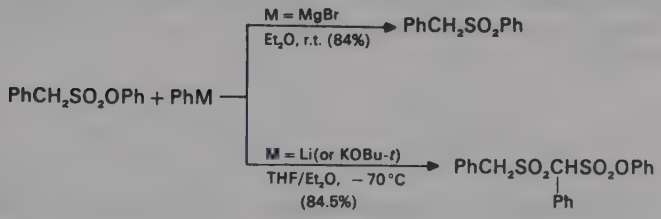
TABLE 10. Sulfones from different C-nucleophiles and sulfonic acid anhydrides $(R^1SO_2)_2O$

R^1	C-Nucleophile	Sulfone	Yield (%)	Ref.
CH_3	*p*-$AnCH{=}PPh_3$	*p*-$AnCH_2SO_2CH{=}PPh_3$ (rearranged product!)	61	310
			/	321
	C_6H_4Z-*p* (Z = Me, OMe)	$CH_3SO_2C_6H_4Z$-*p*	53,70	322
CF_3	$PhCH_2MgCl$	$PhCH_2SO_2CF_3$[+ $PhCH_2Cl$ (13%)]	87	323
	$PhC{\equiv}CMgBr$	$PhC{\equiv}CSO_2CF_3$[+ $PhC{\equiv}CBr$ (63%)]	5	323
	$PhC{\equiv}CLi$	$PhC{\equiv}CSO_2CF_3$	72	324
	TolH	*p*-$TolSO_2CF_3$ + *o*-$TolSO_2CF_3$	46 + 23	325
C_4F_9	$PhC{\equiv}CLi$	$PhC{\equiv}CSO_2C_4F_9$	28	326
Ph	C_6H_4Z-*p* (Z = H, Br)	$PhSO_2C_6H_4Z$-*p*	99,74	327

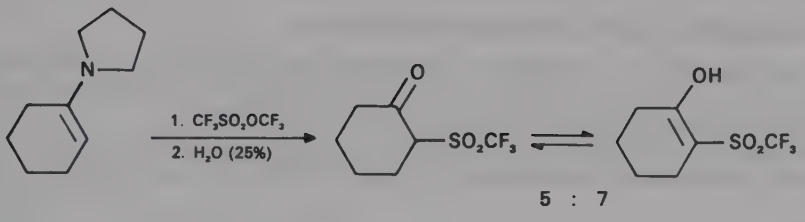
Interestingly, in the latter case no sulfone formation was observed in THF at $-70\,°C$[330]. By ^{18}O-labelling of menthyl phenylmethanesulfonate, sulfone formation through a possible sulfene mechanism could be excluded[331]. Reasonable to good yields of sulfones can be obtained by conversion of organolithium compounds with aryl arenesulfonates[332] (equation 66). Whereas phenyl phenylmethanesulfonate and phenylmagnesium bromide furnish the expected sulfone[333], phenyllithium functions as a base[334] causing a Claisen-like sulfonic acid ester condensation which ensues equally under the influence of potassium *t*-butoxide[334] (equation 67). Activated alkyl sulfonates like trifluoromethyl trifluoromethanesulfonate[335] and β-sultones[336] have been utilized to transfer sulfonyl groups to C-nucleophiles (equations 68 and 69).

$$R^1Li + p\text{-}R^2C_6H_4SO_2OPh \xrightarrow[-25\rightarrow+25\,°C]{Et_2O} R^1SO_2C_6H_4R^2\text{-}p \qquad (66)$$

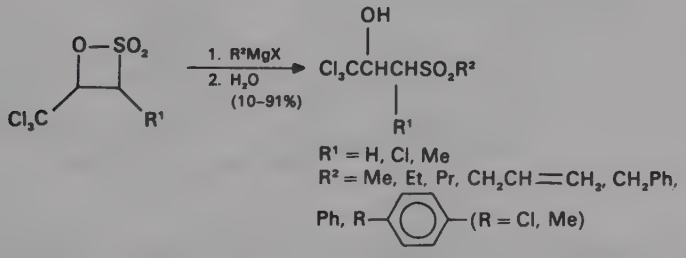
(36–98%, 21 examples)



(67)



(68)

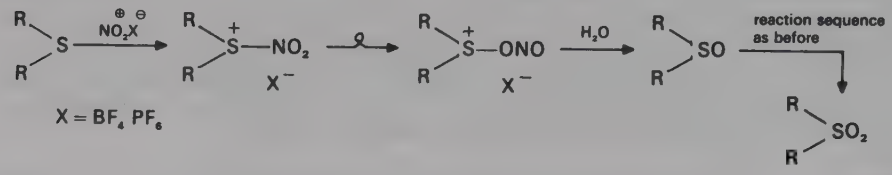


(69)

D. Sulfones by S-Oxidation[336]

The most widely applied method to prepare sulfones is the oxidation of thioethers. In the course of these oxidations sulfoxides must occur as intermediates. However, since oxidation mechanisms for thioethers and sulfoxides are partly different, these oxidations will be discussed separately. A recently published method[337,338] allows oxidation of a

thioether to its sulfoxide without formation of the corresponding sulfone (equation 70). The nitrito sulfonium intermediate is unable to react a second time with the nitrosyl salt. However, after hydrolysis the so-obtained sulfoxide yields the corresponding sulfone in a similar way.



(70)

The usual oxidizing agents transfer oxygen (or halogens and related species with subsequent hydrolysis) stepwise to the sulfur of thioethers: Rates of step A compared with those of step B are faster with electrophilic oxidation agents (peroxy acids); inversely, rates of step B compared with those of step A are faster with nucleophilic oxidation agents (peroxy anions)[339–341].

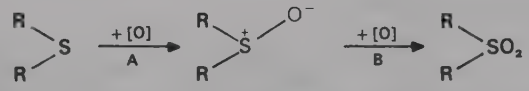
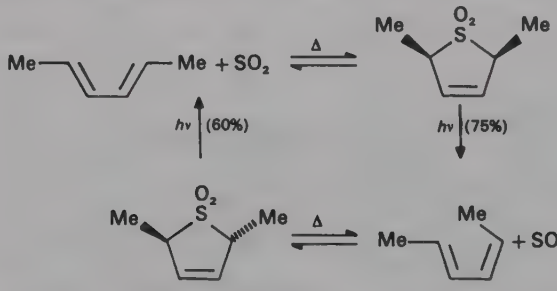


Table 11 affords a survey on oxidation methods of thioethers and sulfoxides.

E. Sulfolene Reaction[426] and Related Cycloadditions

These methods use sulfur dioxide as a building block, generally for cyclic sulfones. However, since several variations allow the preparation of open-chain sulfones too (Section III.D), several selected examples will be presented here.

By a sequence of thermal and photochemical steps in the course of a simple sulfolene reaction, stereospecific isomerizations are possible[429–431] (equation 71). On the other



(71)

hand, in the presence of an appropriate catalyst [consisting of 1 $Pd(acac)_2 + 3PPh_3 + 2AlEt_3$] reaction of sulfur dioxide and butadiene leads to sulfolanes with unsaturated groups in α-, α′-position[432,433]:

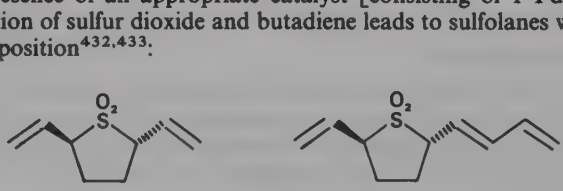


TABLE 11. Oxidation of thioethers and sulfoxides by various methods

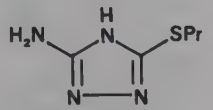
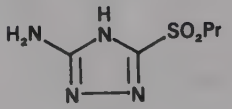
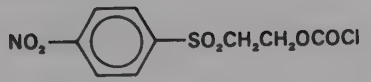
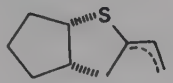
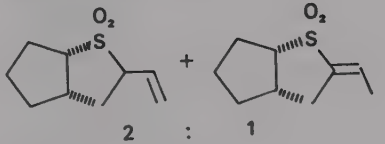
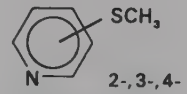
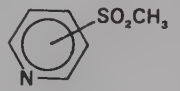
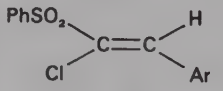
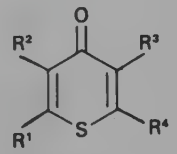
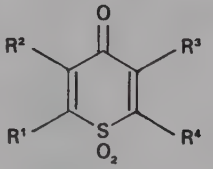
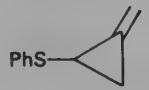
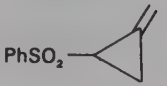
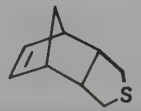
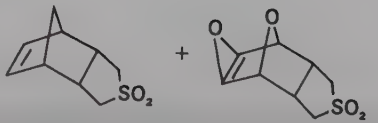
Thioether or sulfoxide	Oxidation conditions (and remarks)	Sulfone	Yield (%)	Ref.*
R^1SR^2 (R^1, R^2 = Et, CH_2Ph; $R^1—R^2$ = —$(CH_2)_n$— n = 5, 6)	$O_2/h\nu$ [TPP] (yields of sulfoxides 36–88%)	$R^1SO_2R^2$	7–33	342
MeSOMe	$O_2/h\nu$[TPP]	$MeSO_2Me$	99	343 (344)
MeSOMe	$^1O_2$	$MeSO_2Me$	/	345, 346
MeSPh	O_3 (1.85 mol only)	$MeSO_2Ph$	97	347
PhSOPh	KO_2/18-crown-6/$(EtO)_2POCl$	$PhSO_2Ph$	73	348 (349)
	H_2O_2/100 °C		47	350
p-$O_2NC_6H_4SCH_2CH_2OH$	1. H_2O_2; 2. $COCl_2$		100	351
$RS(CH_2)_nOH$ (R = Alkyl)	H_2O_2/HCl or HBr	$RSO_2(CH_2)_nCl$ (or Br)	60–85	352
	H_2O_2/THF, 0 °C	 2 : 1	92	353 (354–357)
MeSMe	H_2O_2/EtOH/NaOH	$MeSO_2Me$	98	358 (359)
R^1SR^2	H_2O_2/V_2O_5	$R^1SO_2R^2$	52–79	360

TABLE 11. (Contd.)

Thioether or sulfoxide	Oxidation conditions (and remarks)	Sulfone	Yield (%)	Ref.*
 2-, 3-, 4-	H_2O_2/Na_2WO_4		76,99,36	361 (362,363)
R^1SR^2	H_2O_2/SeO_2	$R^1SO_2R^2$	73–100	364
R^1SR^2	H_2O_2/ArSeOH	$R^1SO_2R^2$	98–100	365 (353)
MeSMe	$H_2O_2/PhCH_2CN$	$MeSO_2Me$	100	366
PhSPh	$H_2O_2/FeCl_3$/dry MeCN (with molar amount: 100% sulfoxide)	$PhSO_2Ph$	100	367
$PhSCH{=}CH_2$	H_2O_2/HOAc/70 °C	$PhSO_2CH{=}CH_2$	78	368
$PhSCHPO(OEt)_2$ Cl	1. H_2O_2/HOAc (or MCPBA); 2. NaH/THF; ArCHO		77–90	369
	H_2O_2/HOAc/100 °C		63–69	370
	H_2O_2/HOAc		80	371 (372)
R^1SR^2	sodium perborate	$R^1SO_2R^2$	91–99	373
	$KHSO_5/KHSO_4/K_2SO_4$ (oxone)		80 + 20	374 (372)

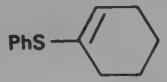
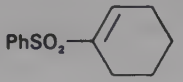
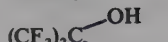
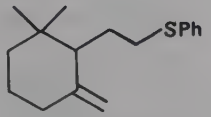
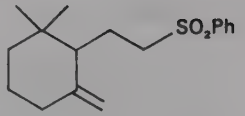
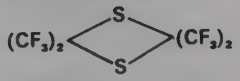
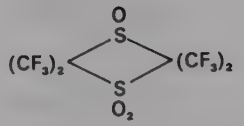
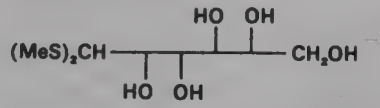
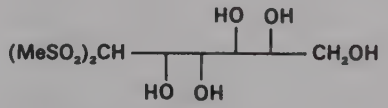
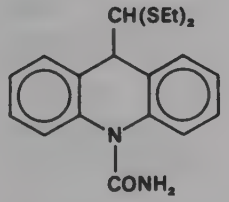
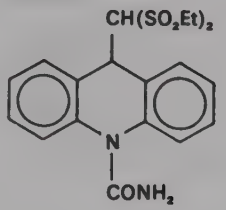
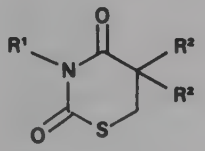
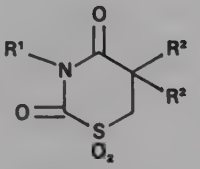
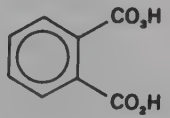
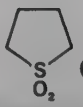
$R^1R^2R^3CSOCH_2CH{=}CH_2$	$KHSO_5/KHSO_4/K_2SO_4$	$R^1R^2R^3CSO_2CH_2CH{=}CH_2$	31–54	375
	$KHSO_5$		98	376a
$(EtO)_2P(=O)CH_2SPh$	$KHSO_5$	$(EtO)_2P(=O)CH_2SO_2Ph$	94	376b
PhSPh		$PhSO_2Ph$	98	377
PhSPh	Me_3COO^-	$PhSO_2Ph$	90	378 (372)
	$Me_3COOH/MnO_2(acac)_2$		72	372
	$Me_3SiOOSiMe_3/80\,°C$		83	379 (372)
$MeSCMe_2CN$	CH_3CO_3H	$MeSO_2CMe_2CN$	95	380 (381)
R^1SR^2	CF_3CO_3H	$R^1SO_2R^2$	58–99	382 (383,384)
	$CF_3SO_3H/20\,°C$		47	384
	$CF_3SO_3H/30\,°C$		56	384

TABLE 11. (Contd.)

Thioether or sulfoxide	Oxidation conditions (and remarks)	Sulfone	Yield (%)	Ref.*
	$C_2H_5CO_3H$		94	385
$(p\text{-}O_2NC_6H_4)_2SO$	$PhCO_3H$ (kinetic measurements)	$(p\text{-}NO_2C_6H_4)_2SO_2$		386
PhSPh	$C_6F_5CO_3H$	$PhSO_2Ph$	92	387
	$3\text{-}ClC_6H_4CO_3H/CHCl_3/-40\,°C$ (MCPBA)		64	388
	$3\text{-}ClC_6H_4CO_3H/CHCl_3/-40\,°C$ (MCPBA)		31–100	389 (372, 390)
$(MeS)_2CHCO_2Me$		$(MeSO_2)_2CHCO_2Me$	78	391 (372,392)
	Resin-CO_3H	 (+ sulfoxide)	/	393

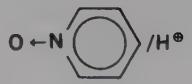
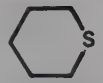
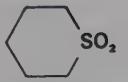
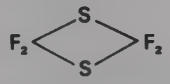
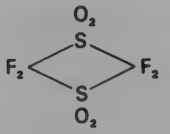
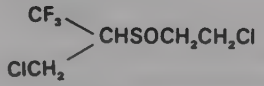
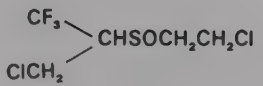
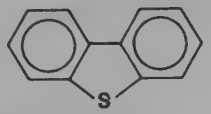
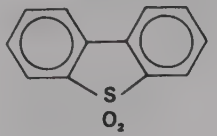
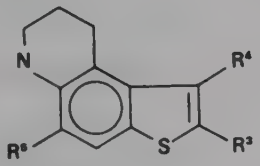
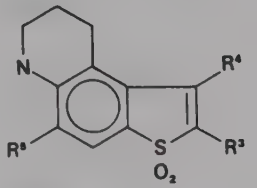
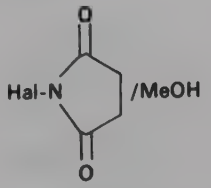
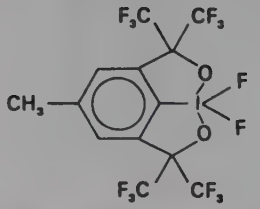
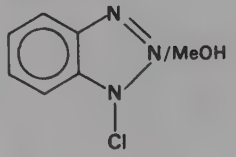
MeSPh		$MeSO_2Ph$ (+ sulfoxide, 20%)	80	394 (395)
MeSOMe		$MeSO_2Me$	94	396
PhSPh	RuO_4	$PhSO_2Ph$	70	397
PhSOPh	RuO_4	$PhSO_2Ph$	93	397
	OsO_4 (oxidizes sulfoxides faster)		58	398
CH_3SOCH_2OMe	MnO_4^-	$CH_3SO_2CH_2OMe$	68	399 (372, 400, 401)
R^1SR^2	1. $NaIO_4$; 2. $KMnO_4/MgSO_4$	$R^1SO_2R^2$	75–93	402
MeSPh	$Zn(MnO_4)_2/SiO_2$	$MeSO_2Ph$	92	403
$ClCH_2CH_2STol\text{-}p$	$KMnO_4/H^+$	$ClCH_2CH_2SO_2Tol\text{-}p$	83	404 (405,406)
	CrO_3/HNO_2		15	407 (372)
	CrO_3/H_2SO_4 (60%)		75	408
ArSAr	1. F_2/Neon; 2. H_2O	$ArSO_2Ar$	/	409

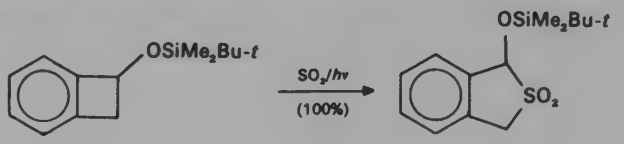
TABLE 11. (Contd.)

Thioether or sulfoxide	Oxidation conditions (and remarks)	Sulfone	Yield (%)	Ref.*
	1. Cl_2; 2. H_2O		93	410 (372)
CH_3SOCH_3	Br_2/OH^-	$CBr_3SO_2CBr_3$	88	411 (412)
$PhCH_2SOCHPh_2$	SO_2Cl_2/CaO	$PhCH_2SO_2CHPh_2$	80	413 (414,415)
	NaOCl		47–53	416 (372)
$(ClCH_2CH_2)_2S$	$Ca(OCl)_2$	$(ClCH_2CH_2)_2SO_2$	22	417
ArSAr		$ArSO_2Ar$	/	418
PhSPh	$PhICl_2/H_2O$/pyridine	$PhSO_2Ph$	100	419
PhSPh	$PhI(OCOCF_3)_2$	$PhSO_2Ph$	91	420

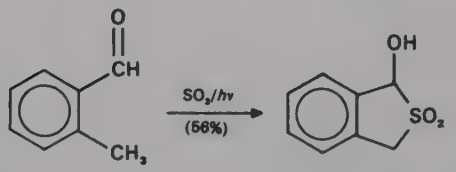
		$(4\text{-}ClC_6H_4)_2SO_2$		
$(4\text{-}ClC_6H_4)_2S$		(+ sulfoxide 53%)	21	421
PhSOPh	$PhIO_2/VO(acac)_2$	$PhSO_2Ph$	73	422
MeSOMe	Chloroamine T	$MeSO_2Me$	100	423a (424,425)
MeSOMe	Disproportionation	$MeSO_2Me$	/	423b
MeSOPh		$MeSO_2Ph$	97	426
	$NaIO_4$	(+ sulfoxide 32%)	47	427 (410,372)

*References in brackets contain material for further reading.

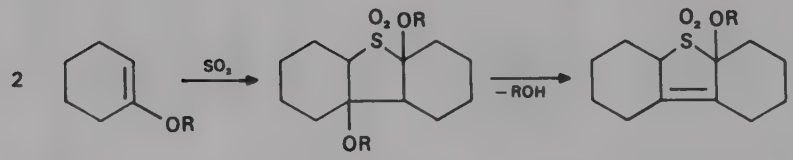
A direct insertion of sulfur dioxide into a C—C bond has been observed under photochemical conditions[434] (equation 72); a related CH insertion followed by an intramolecular sulfinate to carbonyl addition yields the same system[434] (equation 73). A further sulfolene synthesis utilizes a three-component reaction; see equation 74 (cf. Section IV below)[435].



(72)

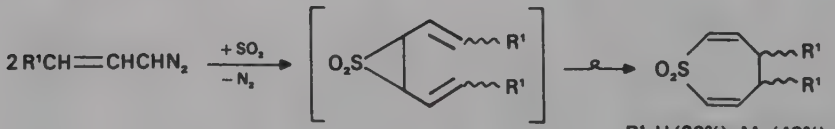


(73)



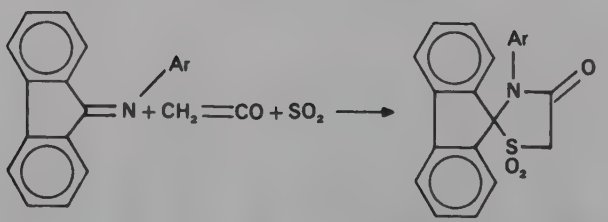
(74)

Other interesting three-component cycloadditions are the following: Sulfur dioxide and diazo compounds lead to episulfones (equation 75)[436]—in a special case to 4,5-dihydrothiepine *S,S*-dioxides[437]; sulfur dioxide, ketene, and arylimine lead to thiazole derivatives[438] (equation 76); sulfur dioxide, quinone, and alkenes lead to benzoxathiane derivatives[439] (equation 77).

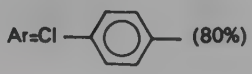


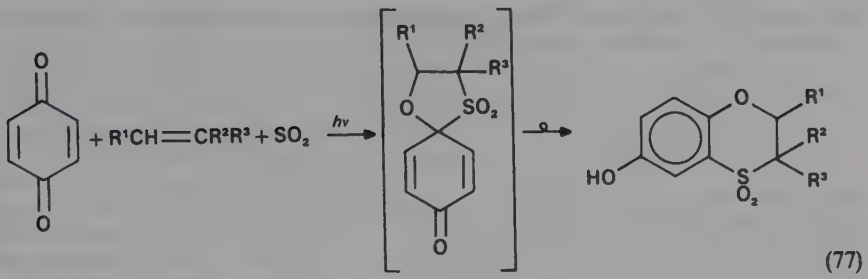
R¹=H (29%); Me(43%)

(75)



(76)



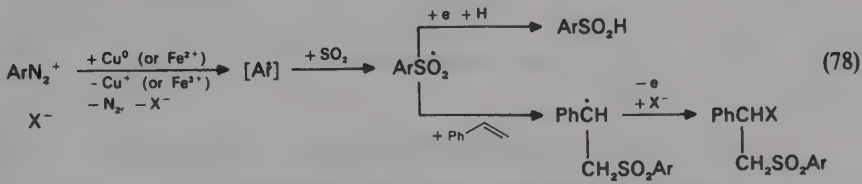


(77)

IV. THREE-COMPONENT METHODS

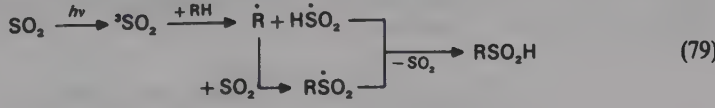
A. Additions to Sulfur Dioxide

Sulfur dioxide (see above) as well as $^3SO_2$, $SO_2^{\cdot\ominus}$, and $\{SO_2^{2\ominus}\}$ have been used as building blocks in three-component sulfone syntheses. It has long been known that aromatic sulfinic acids are easily available from diazonium salts and sulfur dioxide under copper catalysis[440]. Mechanistically, aryl radicals as reactive intermediates add to sulfur dioxide generating arenesulfonyl radicals, which either take up an electron (or hydrogen) yielding a sulfinic acid or add to an olefinic double bond yielding final β-halogenated alkyl aryl sulfones[441] (equation 78).

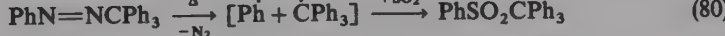


(78)

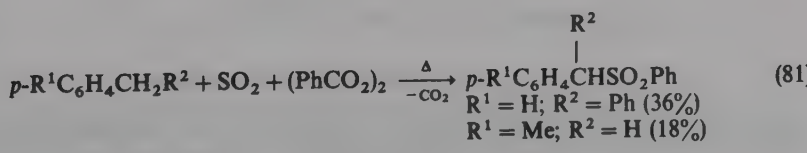
The free-radical reaction may be equally initiated by photoactivated sulfur dioxide ($^3SO_2$)[442] (equation 79). On the other hand, polysulfones are obtained by radical copolymerization of appropriate olefins with sulfur dioxide[443–449], and similarly, uptake of sulfur dioxide by a radical-pair formed by nitrogen extrusion from an azo compound yields the corresponding sulfone[450] (equation 80). Correspondingly, alkylbenzenes, dibenzoyl peroxide, and sulfur dioxide yield sulfones under thermal conditions[451]



(79)

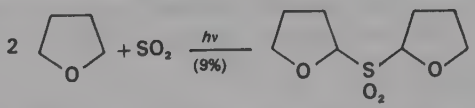


(80)



(81)

(equation 81). A combination between equation 79 and equations 80 and 81 affords the formation of an α-sulfonyl bisether[452]:



Beside these free radical reactions of sulfur dioxide, its electrophilic reactions generating sulfinates with organometallic compounds[453,454] or sulfinic acids with arenes under Friedel–Crafts conditions[455] are well known. To complete these three-component syntheses, the sulfinates prepared first are transformed to sulfones by reactions with appropriate electrophiles, discussed earlier in this chapter, i.e. equation 82.

$$R^1M + SO_2 \longrightarrow R^1SO_2M \xrightarrow[-MX]{+R^2X} R^1SO_2R^2 \tag{82}$$

The electrophilic character of sulfur dioxide does not only enable addition to reactive nucleophiles, but also to electrons forming sulfur dioxide radical anions which possess the requirements of a captodative[456] stabilization (equation 83). This electron transfer occurs electrochemically[457] or chemically under Leuckart–Wallach conditions (formic acid/tertiary amine[458,459], by reduction of sulfur dioxide with 1-benzyl-1,4-dihydronicotinamide[460] or with Rongalite[461]. The radical anion behaves as an efficient nucleophile and affords the generation of sulfones with alkyl halides[462–464] and Michael-acceptor olefins[458–460] (equations 84 and 85).

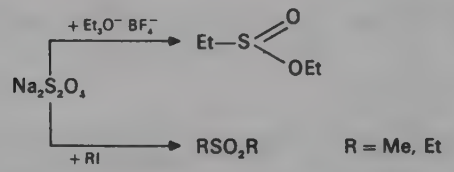
$$SO_2 + e \longrightarrow \bar{O}{-}\dot{S}{=}O \longleftrightarrow \dot{O}{-}\bar{S}{=}O \tag{83}$$

$$R^1X + \dot{S}O_2^- \xrightarrow[-X^-]{} \left[R^1\dot{S}O_2 \xrightarrow[-SO_2]{+SO_2^-} \right] R^1SO_2^- \xrightarrow{+R^2X} R^1SO_2R^2 \tag{84}$$

$$2\,\begin{matrix} R^1 \\ R^2 \end{matrix}\!\!>\!C{=}CH_2 \quad 2\dot{S}O_2^- + 2H^+ \xrightarrow[-SO_2]{} \begin{matrix} R^1 \\ R^2 \end{matrix}\!\!>\!CHCH_2SO_2CH_2CH\!<\!\begin{matrix} R^1 \\ R^2 \end{matrix} \tag{85}$$

Between sulfur dioxide radical anions, dithionite, and sulfoxylate/sulfite there exists a pH-dependent equilibrium[465] (equation 86). Therefore, dithionite has been used as a source of sulfoxylate in order to prepare sulfinate and hence sulfones. Alkylation with triethyl oxonium fluoroborate leads to ethyl ethanesulfinate, alkyl iodides lead to symmetrical sulfones[466] (equation 87).

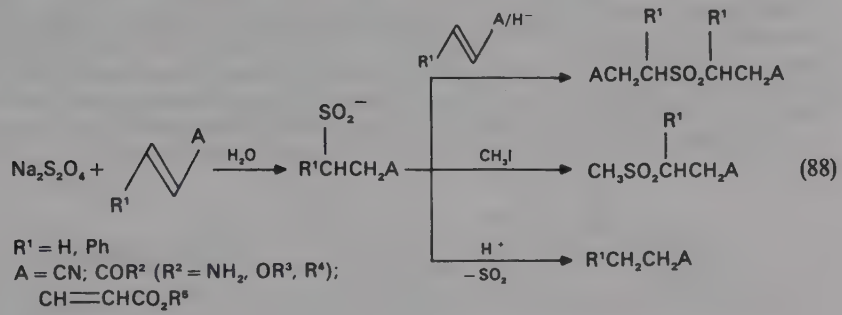
$$2\,\dot{S}O_2^- \rightleftharpoons S_2O_4^{2-} \overset{\pm H_2O}{\rightleftharpoons} HSO_2^- + HSO_3^- \tag{86}$$



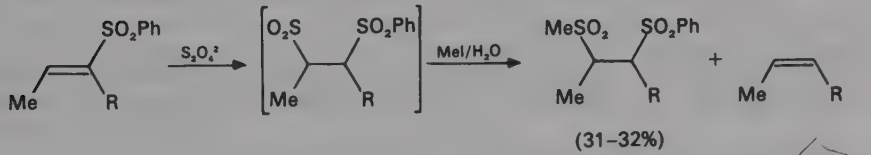
(87)

On the other hand, Michael-acceptor olefins add to the sulfoxylate stage from dithionite, yielding a sulfinate intermediate which yields, according to the reaction

conditions, symmetrical[467] or unsymmetrical sulfones[468,469], or which is decomposed under loss of sulfur dioxide (excess dithionite and PTC conditions) furnishing a hydrogenation product[465] (equation 88). Interestingly, α,β-unsaturated sulfones as acceptor olefins show formation of γ-disulfones in the same way, however, instead of a hydrogenation of the double bond as side-reaction, the formation of olefins has been observed[470] (equation 89). Principally, the same reactions as discussed above have been realized utilizing formamidino sulfinic acid[467] or Rongalite[461,467,471].



(88)

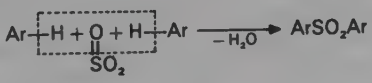


(31–32%)

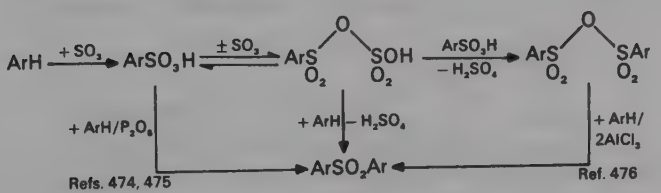
(89)

B. Condensations of Hydrocarbons with Sulfur Trioxide and its Derivatives

It has been known[472] that sulfones are side-products in the course of sulfonation of arenes with sulfur trioxide or its derivatives. Generally, this reaction may be expressed by equation 90. Mechanistic investigations have indicated[473] that this reaction follows the pathway shown in equation 91.



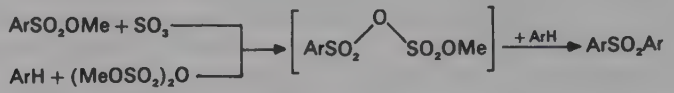
(90)



(91)

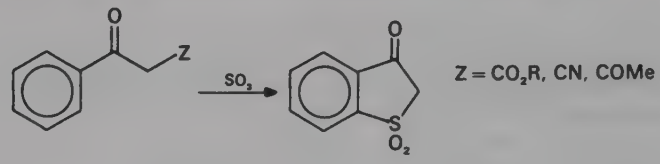
An important role must be attributed to intermediate mixed anhydrides of sulfonic acids and mineral acids; sulfonic acid anhydrides are reported to need Friedel–Crafts conditions to generate sulfones[327,476]. Instead of arenesulfonic acids, their methyl esters may undergo insertion of sulfur trioxide[477,478] yielding mixed anhydrides, which in turn furnish

sulfones in good yields (equation 92). On the other hand, the same reactive intermediate is also accessible from the sulfur trioxide insertion product of dimethyl sulfate and an arene[477].

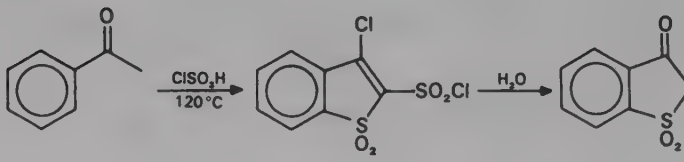


(92)

Using sulfur trioxide a nucleophilic aliphatic carbon and an aromatic nucleus may be connected by a sulfonyl bridge[479] (equation 93). Instead of sulfur trioxide, sulfuric acid or chlorosulfonic acid is utilized mostly. The procedures differ mainly by the manner in which the water is eliminated[480]; e.g., a mixture of sulfuric acid and trifluoroacetic anhydride was used recently[481]. Similarly to equation 93, 3-oxo-2, 3-dihydrobenzothiophene 1, 1-dioxide is available from acetophenone and chlorosulfonic acid[482] (equation 94).



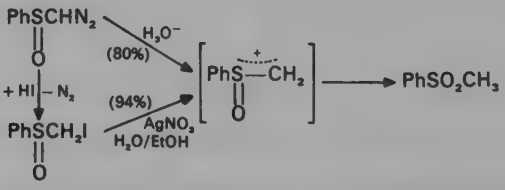
(93)



(94)

V. MISCELLANEOUS METHODS

In the course of the hydrolysis of an α-diazomethyl sulfoxide, a redox-disproportionation through an intermediate sulfinyl carbenium ion occurs[483] (equation 95). Sulfone formation has been observed in the course of several extrusion reactions. As shown in Section IV.A, a radical pair generated by extrusion of nitrogen may be trapped by sulfur dioxide under formation of a sulfone bridge[450]. Heating diazosulfinates (frequently and incorrectly designed as "azosulfones") yields directly sulfones after thermal extrusion of nitrogen, because the sulfone moiety is already incorporated into the starting molecule[484,485] (equation 96). In a related reaction, arenesulfonyl radicals are simultaneously generated by thermolysis of sulfonyl bromides or iodides in the presence of a radical pair obtained by extrusion of nitrogen from an azo compound[487] (equation 97).



(95)

$$ArSO_2N{=}NCF_3 \xrightarrow[-N_2]{\Delta} ArSO_2CF_3 \quad (40\%) \qquad (96)$$

$$p\text{-TolSO}_2\text{X} + \text{PhN=NCPh}_3 \xrightarrow[\substack{-N_2\\-PhX}]{\Delta} p\text{-TolSO}_2\text{CPh}_3 \quad \text{X = Br (56\%), I (78\%)}$$

A corresponding extrusion of sulfur dioxide from disulfones has been reported[486] (equation 98). Extrusions of sulfur have also been observed from thiolsulfinates yielding sulfones[488,489].

Oxidative cleavage of oxosulfonium ylides[490] as well as of sulfoximines[491] leads to sulfone formation. In the course of oxidations of dialkoxy sulfuranes(IV) by hydrogen peroxide[492] or *t*-butyl hydroperoxide[493], sulfone formation takes place (equation 99).

$$\underset{O_2\ O_2}{\text{PhCH}_2\text{S—SCH}_2\text{Ph}} \xrightarrow[-SO_2]{\Delta} \underset{(12\%)}{\text{PhCH}_2\text{SO}_2\text{CH}_2\text{Ph}} + \underset{\text{(main product)}}{\text{PhCH}_2\text{CH}_2\text{Ph}} \qquad (98)$$

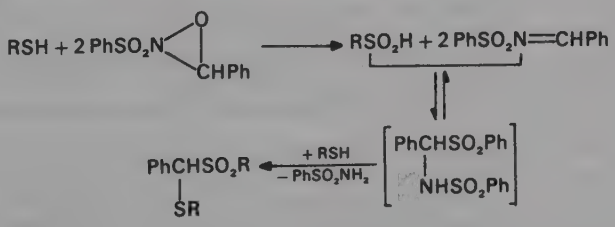
$$\begin{matrix}\text{Ph}\\\text{Ph}\end{matrix}\!\!>\!\text{S(OR)}_2 \xrightarrow[-75\,^\circ\text{C}]{t\text{-BuOOH}} \underset{(88\%)}{\text{PhSO}_2\text{Ph}} \quad \text{R} = \text{C(CF}_3)_2\text{Ph} \qquad (99)$$

Electrochemical oxidation of disulfides and trapping of intermediately formed sulfinates by alkylation yields sulfones in good yields[494].

A very surprising sulfone formation has been investigated by Oae and coworkers[495]. On heating *p*-toluenesulfinic acid with dimethylaniline in ethanol for 15 h, the reaction mixture shown in equation 100 has been obtained. Obviously, the observed products arise from an equilibrium between the sulfinic acid and its pseudo-anhydride (disulfide trioxide), which is able to attack the amine nitrogen and degrade the tertiary amine corresponding to a Polonovsky reaction[496].

$$\begin{aligned} p\text{-TolSO}_2\text{H} + \text{PhNMe}_2 \longrightarrow\ & \underset{O_2\ \ (34\%)}{p\text{-TolSCH}_2\text{C}_6\text{H}_4\text{NMe}_2} + \underset{O_2\ \ (2\%)}{p\text{-TolSCH}_2\text{C}_6\text{H}_4\text{NHMe-}p} \\ & + p\text{-TolSC}_6\text{H}_4\text{NMe}_2 + \underset{O_x\ (x=0,2)}{p\text{-TolS—STol-}p} \qquad (100) \\ & \quad \| \\ & \quad O \\ & + p\text{-TolSO}_3\text{H} \end{aligned}$$

An interesting sulfone formation occurs when thiols are oxidized with a two-molar amount of 2-(benzenesulfonyl)-3-phenyloxaziridine[497]:



R = *t*-Bu

According to reaction conditions, formation of either the sulfinic acid or the α-thiolated sulfone could be observed (up to 80%); the intermediate α-sulfonylamino sulfone proved to be unstable.

VI. REFERENCES

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CHAPTER 2

Appendix to 'Synthesis of open-chain sulfones'†

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*I. INTRODUCTION

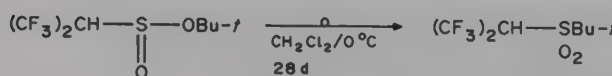
Since our last contribution in 1988 on sulfone syntheses (open-chain compounds), there have appeared worldwide numerous new examples which fit neatly within the previous classification (See Scheme 1 in the original chapter.).

*II. ONE-COMPONENT METHODS

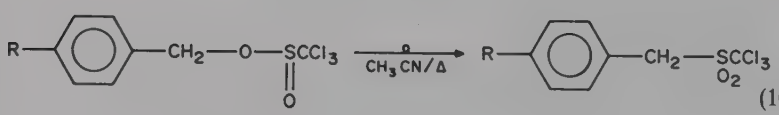
These methods include isomerizing rearrangements at both the sulfur and the carbon site.

*A. Sulfinate–Sulfone Rearrangements

These reactions proceed through polar transition states prefering tertiary[498,499], benzylic[500], allylic[501–508] and propargylic[509–511] carbon centers. In connection with these rearrangements, chirality and regioselectivity have been investigated in allylic systems[505–508] (equations 101–107).



(101)[498]



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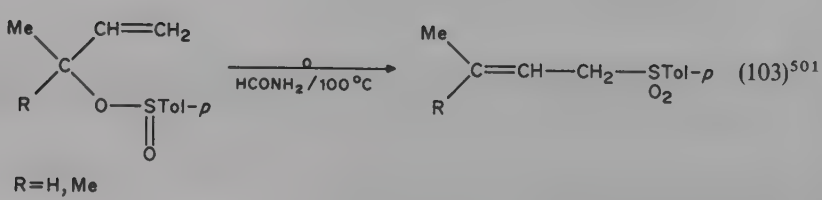

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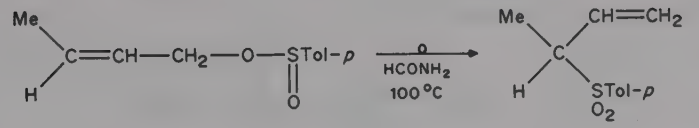

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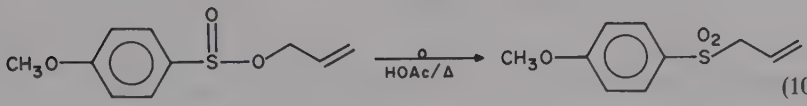
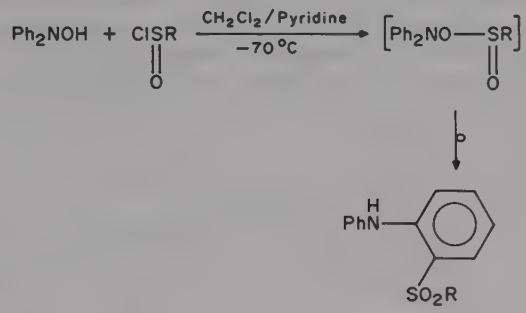
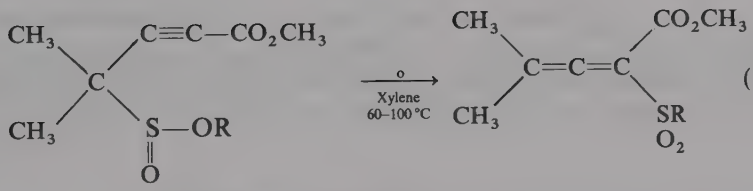


(105)[502]



(106)[503]



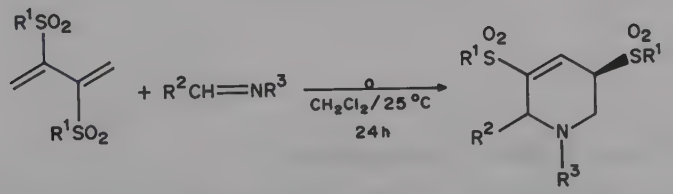
(107)[509]

R = Me(88%), Ph(48%), 4-ClC$_6$H$_4$(47%)

***B. Sulfone–Sulfone Rearrangements**

This type of reaction involves [1.*n*] shifts of the sulfonyl group within the carbon skeleton via extended π-systems.

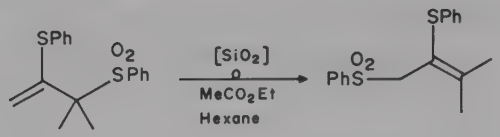
**1. [1,2]Rearrangements[512,513] (equation 108)*



(108)[512]

R^1 = 4-$NO_2C_6H_4$; R^2 = Ph; R^3 = Me, CH_2Ph (62–73%)

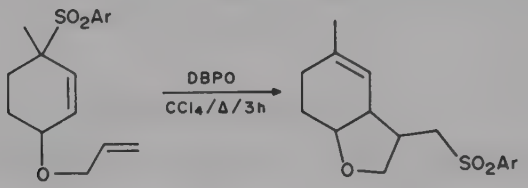
*2. [1,3]Rearrangements[514-519] (equation 109)



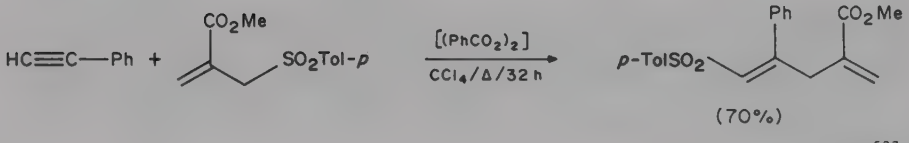
(109)[514]

*3. [1.n]Rearrangements[520–524]

Interesting [1.*n*]rearrangements ($n = 5–8$ according to the considered sequence) have been investigated. Allyloxycyclohexenyl sulfones[522] have been reported to rearrange under radical conditions (equation 110). Though the following example does not belong to the one-component methods, its intermediate rearrangement step obviously follows a related pathway and therefore should be mentioned here[523] (equation 111):



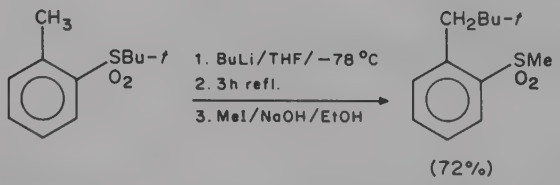
(110)[522]



(111)[523]

*4. Special rearrangements

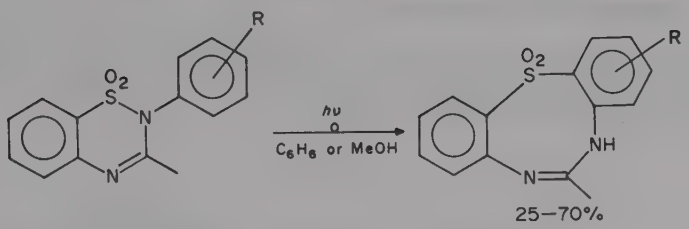
There have been reports in the literature of special isomerizations of sulfones via sulfonyl group migrations[525] as well as Smiles-type reactions[526] with alkyl migrations yielding intermediate sulfinates which are then methylated[527] (equation 112):



(112)[527]

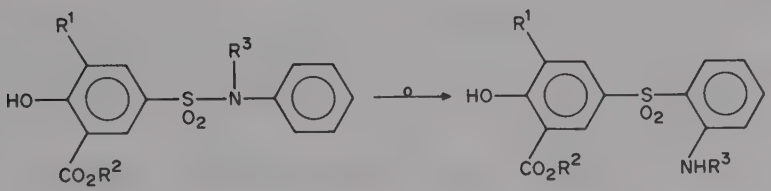
***C. Sulfonanilide–Anilinosulfone Rearrangement**

This type of 1, 3-rearrangement has been carried out under various conditions (photochemical[528], thermal and/or acid catalyzed[529], base catalyzed[530]) (equations 113, 114).



(113)[528]

R=H, 2-Me, 4-MeO, 4-CO_2Me, 3,4-CH=CH—CH=CH

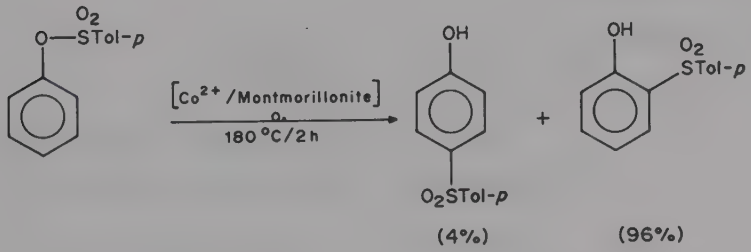


(114)[529]

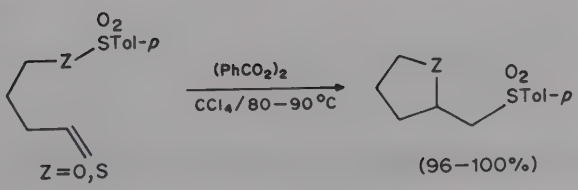
R^1=H, NO_2; R^2=H, Me, Et; R^3=Me, Et

*D. Arene Sulfonate–Aryl Sulfone (Sulfone-Fries) Rearrangement

An improvement of this rearrangement under special catalytic conditions has been described[531] (equation 115). A related sulfonyl migration under radical conditions has been observed with 4-pentene-1-yl esters of sulfonic and thiosulfonic acids[532] (equation 116).



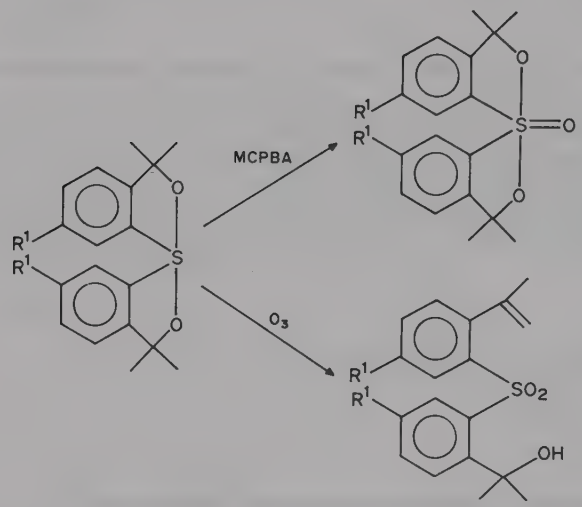
(115)[531]



(116)[532]

*E. Isomerization of Oxosulfuranes

In the course of attempts to generate oxosulfuranes from the corresponding 10-S-4 sulfuranes, only MCPBA proved to be a suitable oxidizing agent whereas ozone led to the corresponding unsaturated sulfone[533] (equation 117).



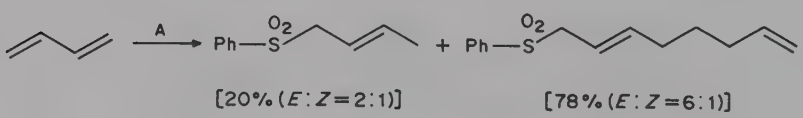
(117)[533]

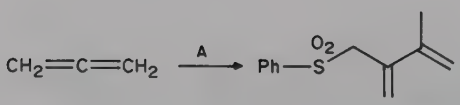
*III. TWO-COMPONENT METHODS

*A. S-Substitution of Sulfinate Nucleophiles with C-Electrophiles

*1. *Addition of sulfinic acids (or salts) to unactivated C,C multiple bonds*

a. Pd(0)-catalyzed sulfonylation[534] (equation 118)

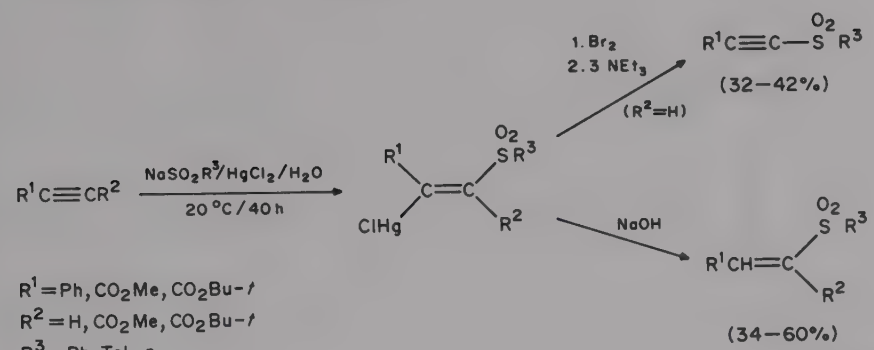




(118)[534]

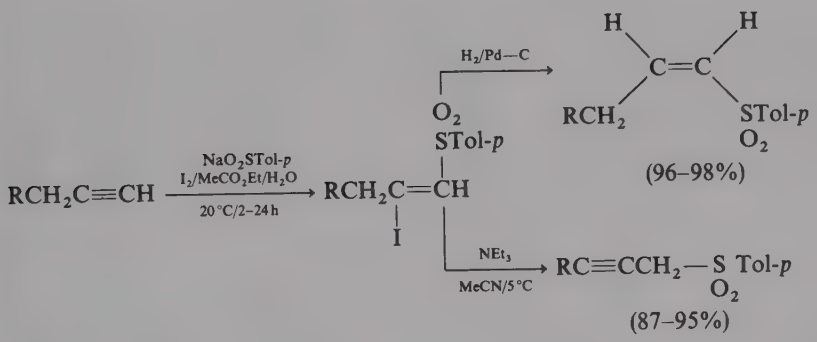
A: $PhSO_2Na \cdot 2H_2O/Pd(PPh_3)_3/CO_2/DMF/80–110\,°C/15\,atm/autoclave$

b. Sulfonylmercuration[535–537] (equation 119)



(119)[536]

c. Iodosulfonylation[538–543] (equation 120)



(120)[539,542]

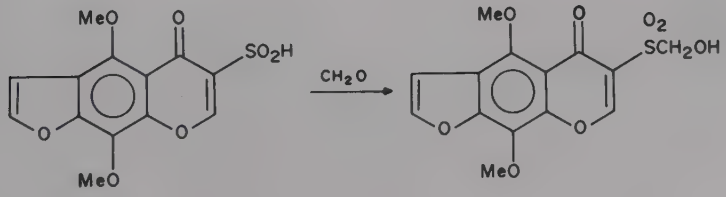
$R = CH_3(CH_2)_n$, $n = 2,3,5,8$; $PhCH_2CH_2$

**2. Addition of sulfinic acids to polar C,C multiple bonds*

A survey on this type[544–556] of addition is given in Table 12.

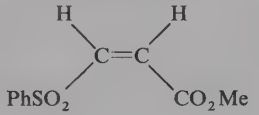
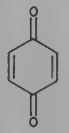
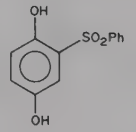
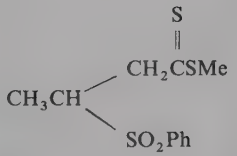
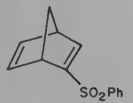
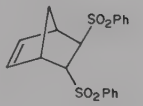
**3. Addition of sulfinic acids to polar C=Y double bonds*

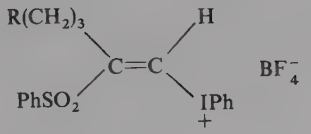
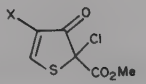
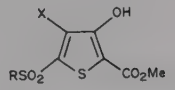
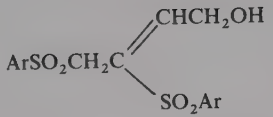
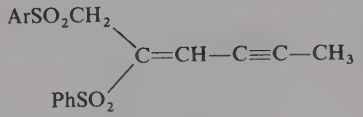
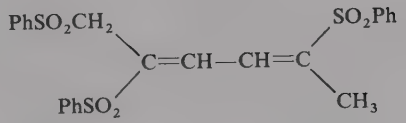
a. Hydroxymethyl sulfones[557] (equation 121)

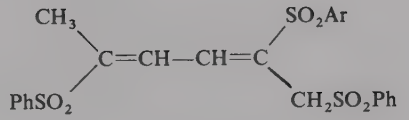
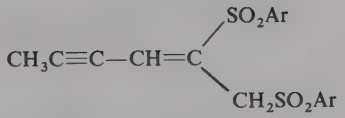
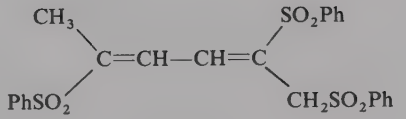
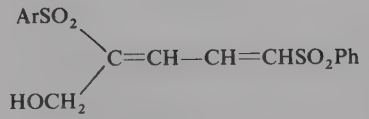


(121)[557]

TABLE 12. Sulfones from sulfinic acids (or salts) and acceptor-substituted olefins, acetylenes or quinones

R in RSO_2H (Na^+ salt)	Michael acceptor	Sulfone	Yield(%)	Ref.
Ph	$HC{\equiv}CCO_2Me$		81–88	544, 550
Ar	$HC{\equiv}CCONH_2$	$ArSO_2{-}CH{=}CHCONH_2$	55–88	545
Ph			—	546
Ph	1. $CH_3CH{=}C(NPh){-}CSMe$ 2. H_2S		75	547
Ph			—	548
Ph	$CH_2{=}CHCN$	$PhSO_2CH_2CH_2CN$	97	549

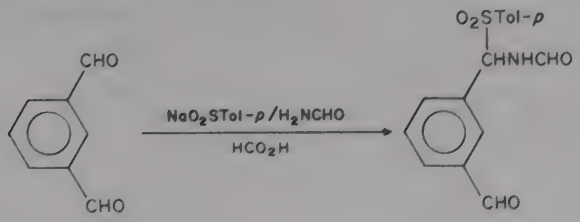
Ph	$R(CH_2)_3—C\equiv C—\ IPh\ ^+\ BF_4^-$		93–100	551
Me,Ar	 X = H,Cl,Br		50–73	552
Ar	$ClCH_2C\equiv CCH_2OH \rightarrow [ArSO_2CH{=}C{=}CHCH_2OH]^a$		32–50	553
Ph			—	554

			60	
Ph		+		555
			20	
Ar	$HOCH_2C{\equiv}C{-}CH{=}CHSO_2Ph$		37–55	556

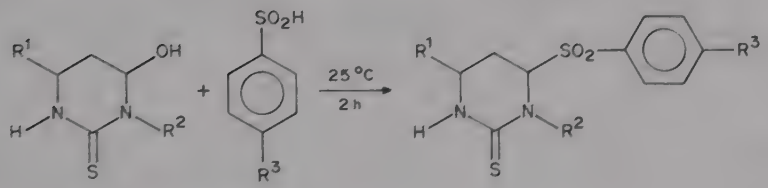
[a] Probable *in situ* formation.

$HOCH_2C{\equiv}C{-}CH{=}CHSO_2Ph$

b. α-N-Substituted sulfones. Compounds of this type are obtained via Mannich-like reactions[558,559] (equations 112 and 123).



(122)[558]



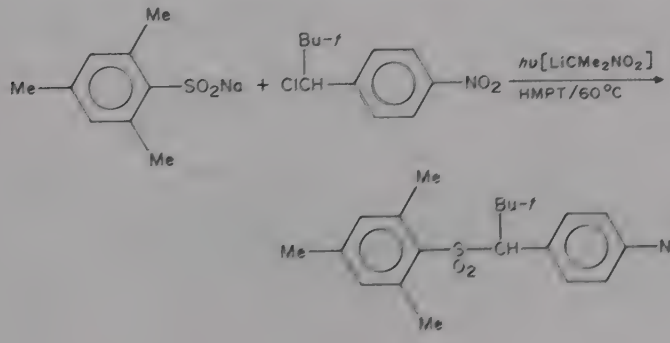
(123)[559]

(a) $R^1=R^2=H$; $R^3=Me$ (97%)
(b) $R^1=Me$, $R^2=R^3=H$ (86%)
(c) $R^1=R^2=R^3=Me$ (100%)

c. Addition of sulfinic acids to X—C=Y or X—C≡N. Frequently, addition–elimination sequences of sulfinate to sp^2- or sp-carbon containing unsaturated functions bearing a leaving group are used for sulfone syntheses[560–567] (Table 13).

*4. Nucleophilic displacement of sp^3-carbon bonded halide and related leaving groups

Sulfone formation from sulfinate and electrophilic carbon according to the classical scheme (equations 124–127) is summarized in Tables 14 and 15: (a) halogen nucleofuges[568–600] (Table 14), (b) oxygen nucleofuges[601–606] (Table 15) and (c) nitrogen nucleofuges[607–614] (Table 15). In some cases modern laboratory techniques have been applied (ultrasound[590,594], special catalysts[591,593,598–603] etc.). Sometimes, *in situ* formation of sulfinate [596,599] is used. Photochemical activation has also been applied[595].



(124)[595]

TABLE 13. Sulfones from formal S-acylations of sulfinate anions RSO_2^-

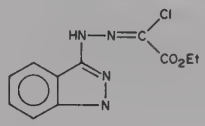
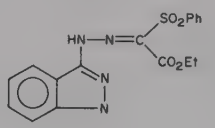
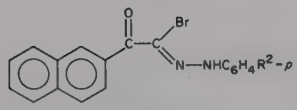
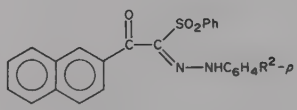
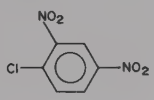
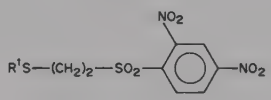
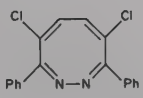
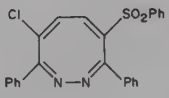
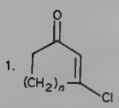
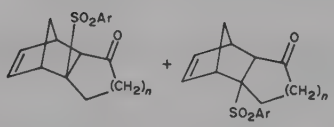
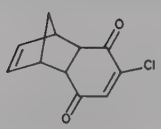
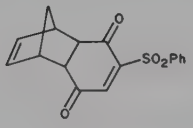
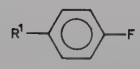
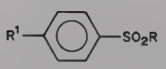
R	Acylation reagent	Sulfone	Yield(%)	Ref.
Ph			90	561
Ph	 (R^2 = H, Cl, CH_3)		70–80	562
R^1S—$(CH_2)_2$—			59	563
(R^1 = *p*-Tol)				
Ph			83	564
Ar	 (n = 1,2)		60–80	565
	2.	3 : 1		
Ph			66	566
Me; Ph	 (R^1 = CHO, COPh, CN, NO_2)		61–95	567

TABLE 14. Sulfones from sulfinates R^1SO_2M and alkyl halides

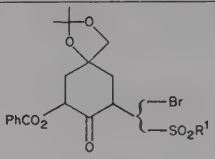
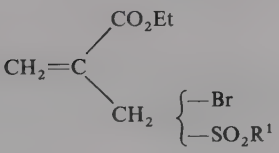
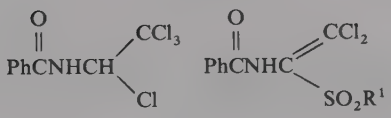
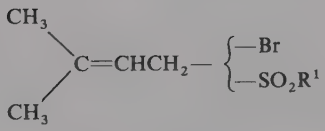
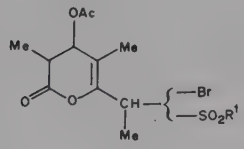
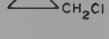
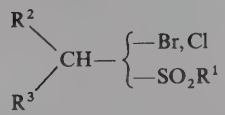
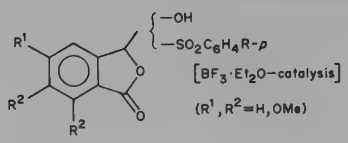
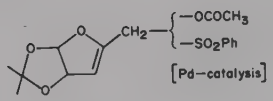
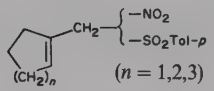
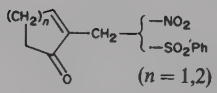
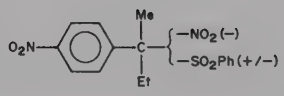
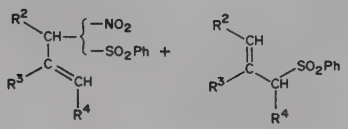
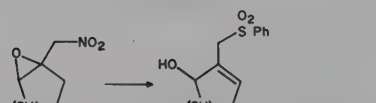
R^1	M	R^2X and $R^2SO_2R^1$ or rearranged sulfones	Yield (%)	Ref.
Ph	Na		88	571
Ph	Na		75	572
p-RC_6H_4 (R = H, Me)			50–63	575
$CF_3(CF_2)_3$	Na		70	576
p-Tol	Na	HO_2CCH_2—{—Br, $—SO_2R^1$	59	578
p-Tol	Na		93	585
p-Tol		 $HOCH_2CH{=}CHSO_2R^1$	72	590
p-RC_6H_4 (R = H, Me)	Na	 (R^2 = CN, CO_2Me, $CONH_2$, Cl, Ph, *p*-$NO_2C_6H_4$) (R^3 = H, CH_3)	35–95	591
p-Tol	Na	R^2—{—Cl, Br, I, $—SO_2R^1$ (R^2 = Et, CH_2I, Bu, Vinyl, *o*-NO_2-benzyl, *p*-Br-phenacyl, benzyl)	42–85	593

TABLE 15. Sulfones from nucleophilic displacement of different weak leaving groups by sulfinates R^1SO_2M

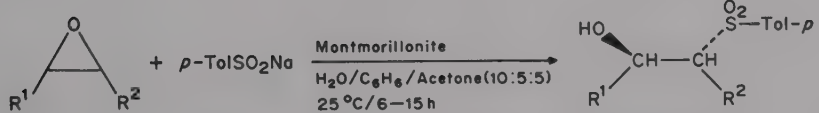
R^1	$-MX$	R^2X and $R^2SO_2R^1$ or rearranged sulfones	Yield (%)	Ref.
p-RC_6H_4 (R = H, Me)	H_2O		40–82	602
Ph	NaOAc		47	606
p-Tol	$NaNO_2$		79–92	607
Ph	$NaNO_2$		72–75	610
Ph	$NaNO_2$		95	611
Ph	$NaNO_2$		51–81	613
Ph	$NaNO_2$		47–83	614

$$R^1SO_2—S—Py \xrightarrow[2.\ R^2X]{1.\ NaOH/MeOH} R^1SO_2R^2 \quad (125)^{596}$$

(67–89%)

$R^1 = C_{15}H_{31}$; Cyclohexyl, Adamantyl
R^2X = MeI, $PhCH_2Br$

$$p\text{-}TolSO_2Cl + MeI \xrightarrow[20–50\,°C]{Bu_3Sb} p\text{-}TolSO_2\text{-}Me \quad (126)^{599}$$



R^1, R^2 = H, Ph, Bu, —$(CH_2)_4$—

(52–78%) (127)[603]

**5. Addition of sulfinic acids (or salts) to carbenes (equation 128)*

$$ArSO_2Na \xrightarrow[12–20\,h/\Delta]{CHCl_3/KOH/H_2O} Ar—\overset{O_2}{S}—CHCl_2 \quad (128)^{615}$$

*B. Radical Addition of Sulfonic Acid Derivatives to Unsaturated Systems

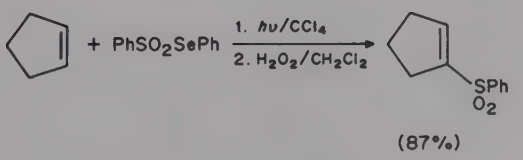
*1. Halosulfonylation

A survey on usual reactions under this topic was presented in Table 5 of our 1988 contribution. Here, recent reactions of alkenes[550,616–633], alkynes and conjugated alkadienes with sulfonyl halides are summarized (Table 16).

*2. Cyano- and seleno-sulfonylation

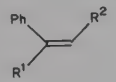
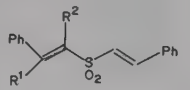
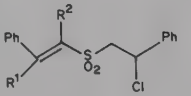
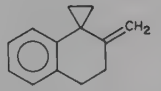
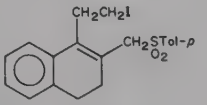
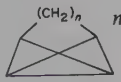
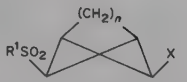
Sulfonyl cyanides are not mentioned very often in the chemical literature[634]. A recent communication[635] deals with an addition to cyclohexene under radical conditions (equation 129). Selenosulfonylation has been reviewed recently[636]. A selection of representative examples is given here[637–646] (equations 130–133):

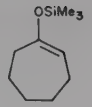
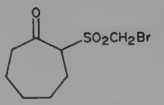
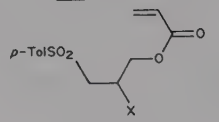
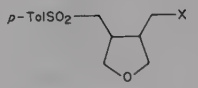
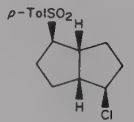
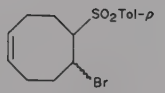
(129)[635]



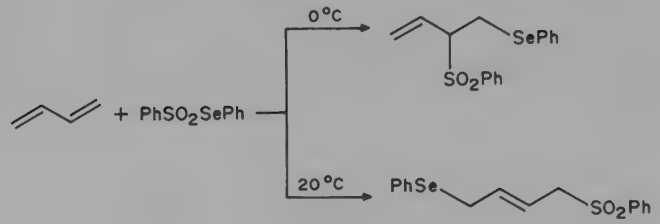
(87%) (130)[637]

TABLE 16. Sulfones from unsaturated systems and sulfonyl halides R^1SO_2X via radical routes

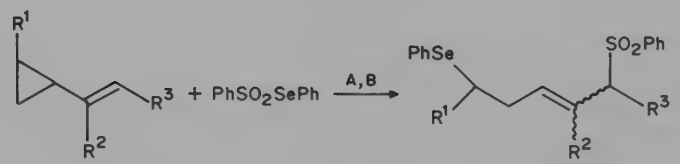
R^1	X	Unsaturated C,C compound	Reaction conditions (and catalysts)	Sulfone	Yield (%)	Ref.
	Cl	CH_2=CHPh	150 °C [a]		21–91	622
(R^1, R^2 = H, Me)			80–100 °C [a]		84–89	
p-Tol	I		CH_2Cl_2/RT		78	625
p-Tol, Ph, Me	Cl Br I	 $n = 1, 3$	*hv*		15–94	626, 627

$BrCH_2$	Br		*hv*		69	628
					51–70	
p-Tol	Br I		*hv*		51–90	629
	Cl				44	
p-Tol	Br		*hv*		55	634

[a] Catalyst $[RuCl_2(PPh_3)_3]$.



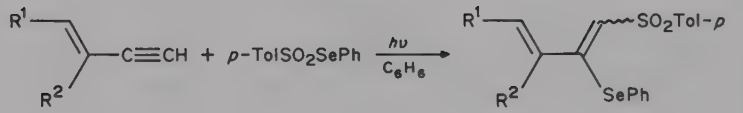
(131)[639]



(132)[641]

R^1 = H, CO_2Et
R^2 = H, Me
R^3 = H, Me, Et, Cl

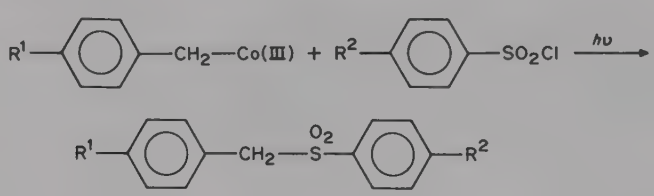
A : $h\nu/CHCl_3$
B : AIBN/$CHCl_3$/Δ



(133)[646]

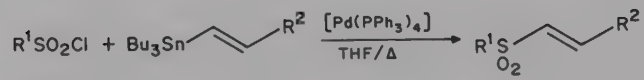
3. *Ipso-Substitution of metal organics by sulfonyl halides*

Different types of organometallics are sulfonylated by sulfonyl chlorides under various conditions, presumably via radical pathways[647–650] (equations 134–136).



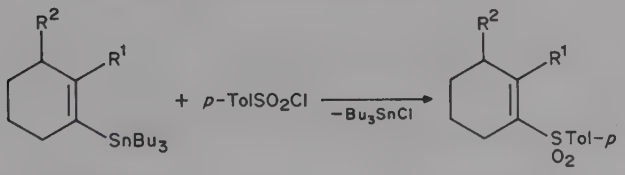
(134)[647]

Co(III) = Co(dmg H)$_2$Py
dmgH = Dimethylglyoxime monoanion
R^1 = H, Me, CN, NO_2, Br; R^2 = H, Me, OMe, Br



(135)[648]

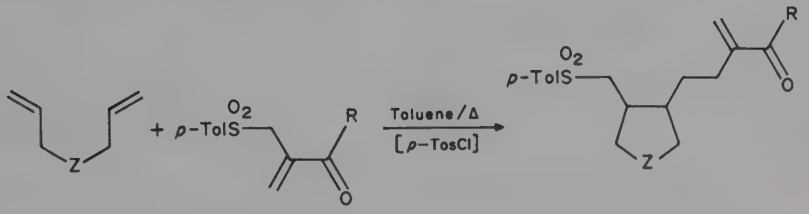
R^1 = Me, Ar
R^2 = Ar, CO_2Et



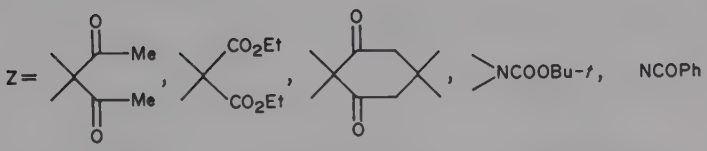
(136)[650]

R^1 = Me, CO_2Me
R^2 = H, CO_2Me

Some interesting examples of free radical cyclization of 1,6-dienes use allylic sulfones as reagents[651,652] (equation 137):



(137)[651]

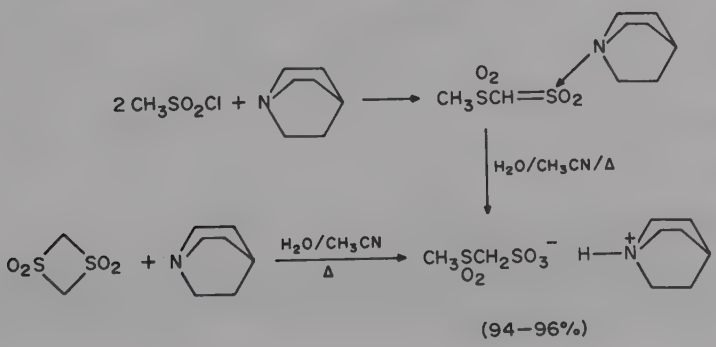


R = OEt, $NHCH_2Ph$

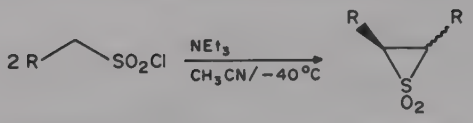
*C. S-Substitution of Sulfonyl Electrophiles with C-Nucleophiles

*1. *Sulfene reactions*

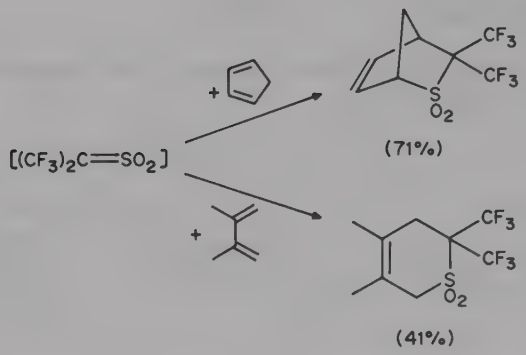
Sulfenes, generated via the usual pathways, have been trapped either by their precursors or by special reagents to give cyclic and/or open-chain sulfones[653–662] (equations 138–140).



(138)[653]

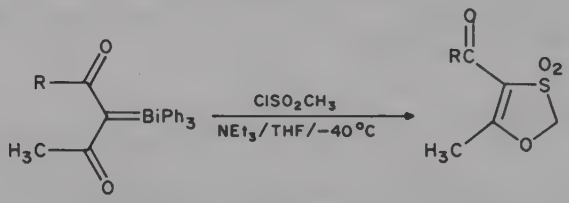


(139)[655]



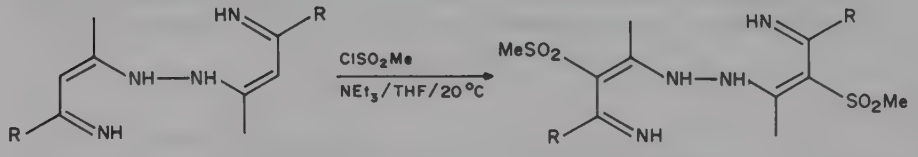
(140)[658]

Equation 141 corresponds in principle to a [2 + 3] cycloaddition of a sulfene to a ketocarbene[659].



(141)[659]

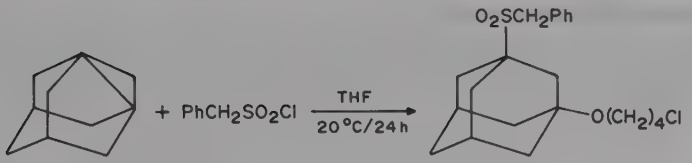
A twofold addition to an ene-hydrazine leads to an open-chain disulfone (equation 142).



(142)[660]

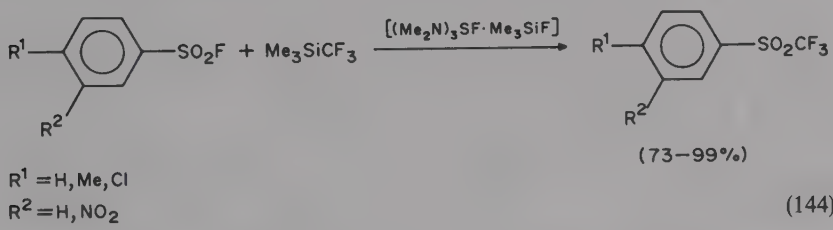
*2. Halide substitution in sulfonyl halides

An interesting halide substitution via combined insertion of a ring-opened strained cyclopropane and a ring-opened tetrahydrofuran component under careful conditions has been reported[663] (equation 143).



(143)[663]

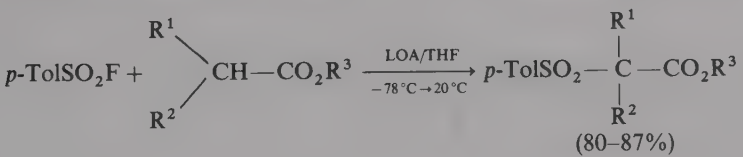
A further unusual trifluoromethyl vs fluorine exchange under catalysis of $(Me_2N)_3SF \cdot Me_3SiF$ has been described[663] (equation 144):



$R^1 = H, Me, Cl$
$R^2 = H, NO_2$

(144)[664]

a. Sulfonylations using metalorganic species[665–668] (equations 145 and 146).

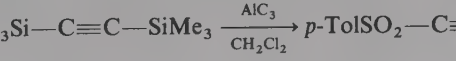


(145)[666]

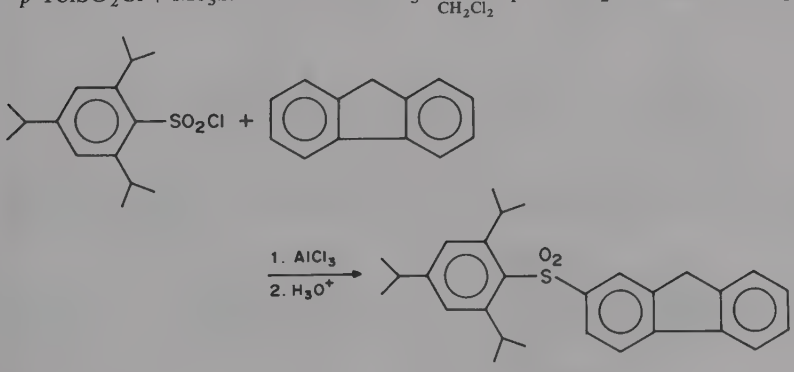
(146)[667]

(a) $R = CF_3$ (44%)
(b) $R = C_4H_9$ (35%)

b. Sulfonylations under Friedel–Crafts conditions[669–671]



(147)[669]



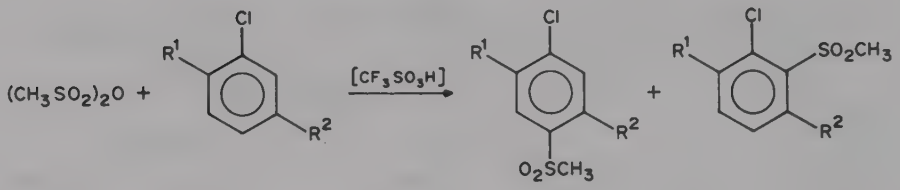
(148)[671]

*3. *Sulfonic acid anhydrides and esters*

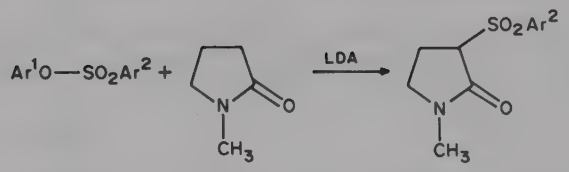
Sulfonic acid anhydrides have been used for sulfonylations under acid or basic conditions, whereas sulfonic acid aryl esters usually react under the latter[672–675] (equations 149–151).

$$(CF_3SO_2)_2O + RC{\equiv}C\,Na \xrightarrow[-78\,^{\circ}C \rightarrow RT]{Et_2O} RC{\equiv}CSO_2CF_3 \qquad (149)^{672}$$

$$R = Ar, n\text{-}Bu, n\text{-}C_5H_{11}, n\text{-}C_6H_{13} \qquad (14\text{–}74\%)$$



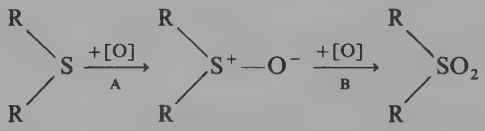
(150)[673]



(151)[674]

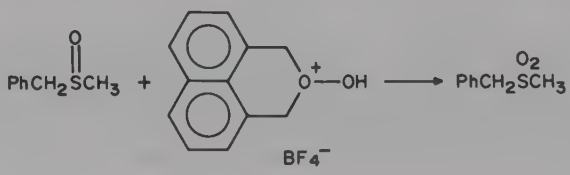
***D. Sulfones by S-oxidation**

Oxygen transfer occurs under radical, electrophilic and nucleophilic conditions to sulfides and sulfoxides. Radical oxidations are mostly carried out by use of oxygen oligomers; molecular oxygen needs activation energy (thermally or by irradiation), whereas more energetic oxygen oligomers $^1O_2$ ($^1\Delta_g$) or ozone are reactive enough for direct conversions:



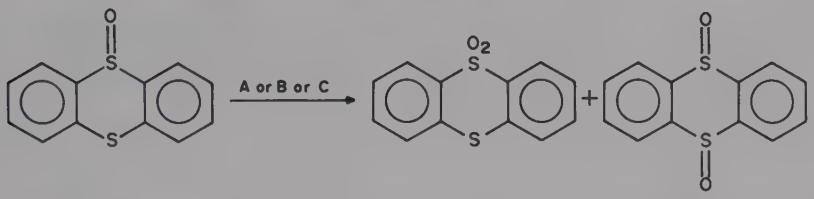
Reactions A are faster with electrophilic O-transfer agents;
Reactions B are faster with nucleophilic O-transfer agents.

Nevertheless, agents with high electrophilic O-transfer ability are capable of oxidizing sulfoxides to sulfones[676] (equation 152). Thianthrene-*S*-monoxide has been shown to be

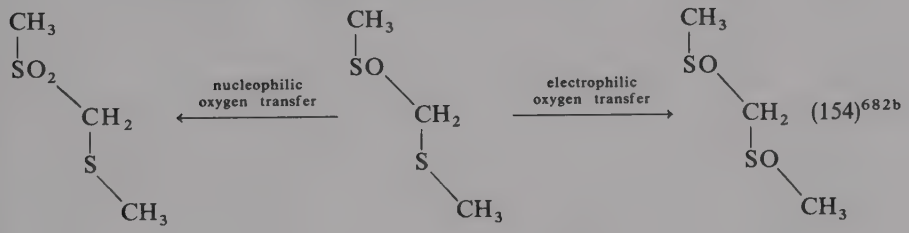


(152)[676]

a mechanistic probe to distinguish unambiguously between electrophilic and nucleophilic oxygen transfer[682a] (equation 153), although this probe is unsuitable in ozonolyis reactions. The value of this probe is reduced by mesomeric interaction between the two sulfur centers and does not offer advantages over the Ogura–Suzuki–Tsuchihashi probe[682b] (equation 154). Recent examples of sulfide/sulfoxide to sulfone oxidation[676–835] by means of various oxidation procedures are collected in Table 17.



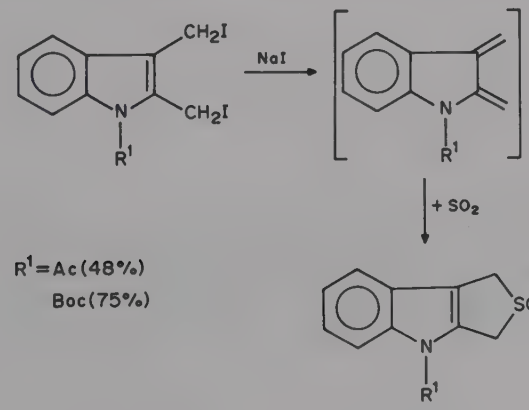
A: $H_2O_2/NaOH/C_6H_6$	100%	< 1%	
B: $H_2O/HCl/Et_2O$	9.3%	89%	(153)[682a]
C: *t*-BuOOH/$HClO_4/CH_2Cl_2$	0.7%	99%	



(154)[682b]

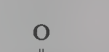
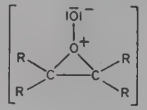
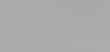
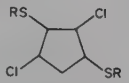
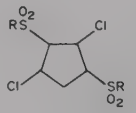
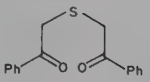
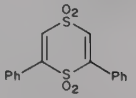
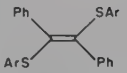
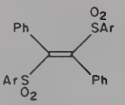
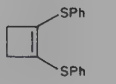
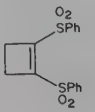
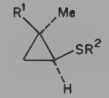
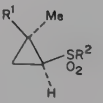
***E. Sulfolene Reaction**

This method uses sulfur dioxide as a building block and leads to cyclic sulfones which are discussed in another chapter. Nevertheless, for methodical completeness some selected examples of this method are given here[836–843] (equations 155–159).



(155)[836]

TABLE 17. Oxidation of thioethers and sulfoxides by various methods

Thioether or sulfoxide	Oxidation conditions (and remarks)	Sulfone	Yield (%)	Ref.
			97	677
 (R = Tol-*p*)	H_2O_2/HOAc		82	697
	1. H_2S/HCl/MeOH/−20 °C 2. H_2O_2/HOAc		78	699
	H_2O_2/HOAc/100 °C		81	702
	H_2O_2/HOAc/100 °C		53	706
 (R^1 = CN, Ph, CO_2H, $CONH_2$) (R^2 = Ph, Pr)	H_2O_2/HOAc		59–79	714

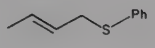
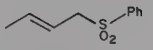
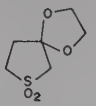
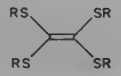
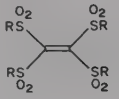
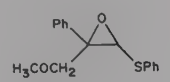
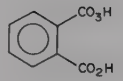
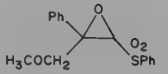
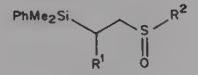
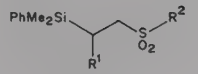
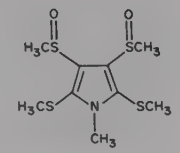
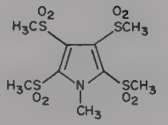
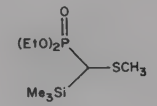
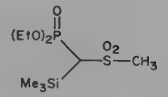
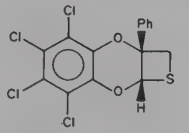
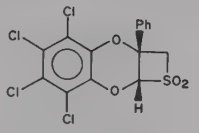
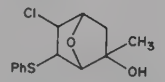
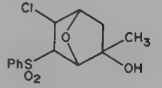
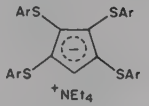
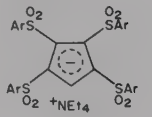
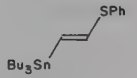
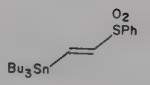
	H_2O_2/SeO_2		70	719
	H_2O_2/V_2O_5		81	721
RSR (R = Et, CH_2Ph, Ph)	$Na_2CO_3 \cdot \frac{3}{2}H_2O_2$	RSO_2R	100	723
Me_3SiCH_2SPh	CH_3CO_3H	$Me_3SiCH_2SO_2Ph$	96	727
 (R = Me, Et, Pr)	CF_3CO_3H		90–97	730
			86	731
	3-$ClC_6H_4CO_3H/CH_2Cl_2$		~100	733
	3-$ClC_6H_4CO_3H$		—	734
	3-$ClC_6H_4CO_3H$		85	738

TABLE 17. (*Contd.*)

Thioether or sulfoxide	Oxidation conditions (and remarks)	Sulfone	Yield (%)	Ref.
	$3\text{-}ClC_6H_4CO_3H$		70	747
	$3\text{-}ClC_6H_4CO_3H$		28	750
	$3\text{-}ClC_6H_4CO_3H$		69–88	751
	$3\text{-}ClC_6H_4CO_3H$		79	764
$R^1—S—R^2$	$KHSO_5/KHSO_4/K_2SO_4$ (Oxone)	$R^1SO_2R^1$	97–100	773
(R^1 = Ar, CH_2=CH—CH_2—) (R^2 = Me, CH_2=CH—CH_2—) (R^1, R^2 = —$(CH_2)_4$—	wet montmorillonite/CH_2Cl_2 or wet kaolin/CH_2Cl_2 or $CHCl_3$			
PhSR (R = Me, —CH_2CH_2X X = CN, CO_2Me, OH)	Oxone/Al_2O_3/$CHCl_3$	$PhSO_2R$	89–100	775
PhSR (R = Me,	Tetra-*n*-butylammonium Oxonate	$PhSO_2R$	78–79	776

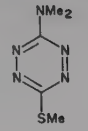
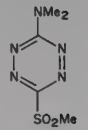
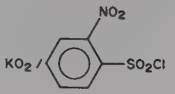
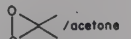
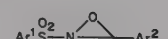
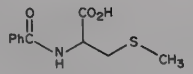
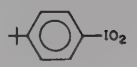
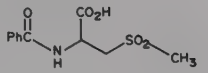
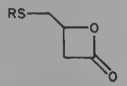
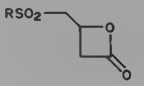
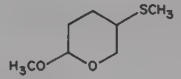
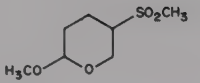
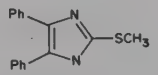
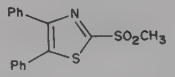
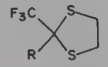
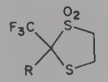
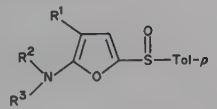
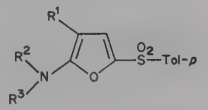
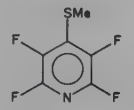
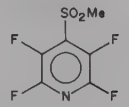
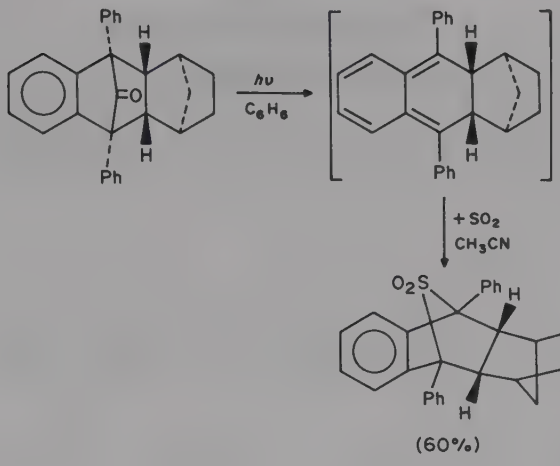
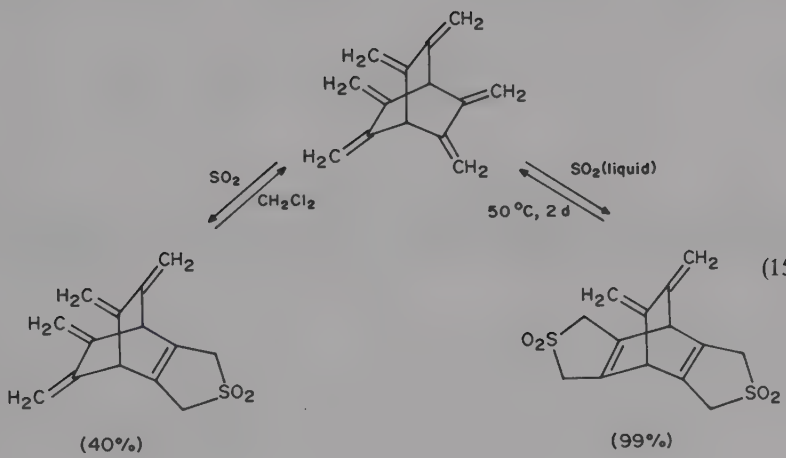
	$KHSO_5$		75	790
R^1SR^2 (R^1, R^2 = Bu, *t*-Bu, Ar, Me)	Sodium perborate	$R^1SO_2R^2$	91–99	794
		$R^1SO_2R^2$	84–98	797
$ArSC{\equiv}CSAr$		$ArSO_2C{\equiv}CSO_2Ar$	—	798
CH_3SOCH_3		$CH_3SO_2CH_3$	—	800
			48	801
 ($R = Et$; $CH_3(CH_2)_n$, $n = 5, 7$; ph)	$NaIO_4/RuCl_3$		9–60	805
	$NaIO_4$		88	806
$(i\text{-PrO})_2PCH_2SR$	$KMnO_4/H_2SO_4$	$(i\text{-PrO})_2PCH_2SO_2R$	63–64	812
CF_3SCH_3	$KMnO_4$/AcOH	$CF_3SO_2CH_3$	63	813

TABLE 17. (*Contd.*)

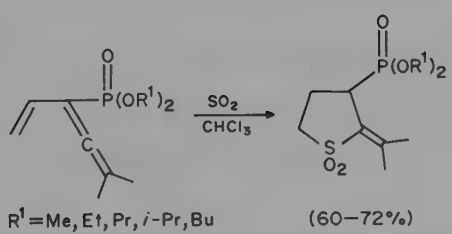
Thioether or sulfoxide	Oxidation conditions (and remarks)	Sulfone	Yield (%)	Ref.
	$KMnO_4/Bu_4NBr/AcOH$		94	815
 (R = Ph, Me)	$KMnO_4/AcOH$		51–73	821
	$KMnO_4$		38–53	825
	CrO_3/conc. H_2SO_4		80	832



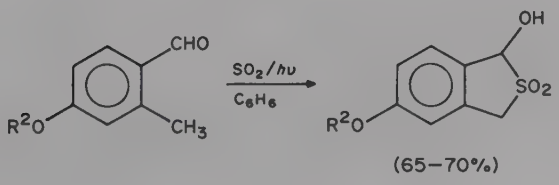
(156)[837]



(157)[838]



(158)[839]

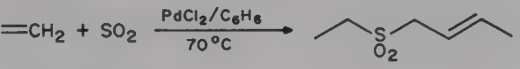


(159)[843]

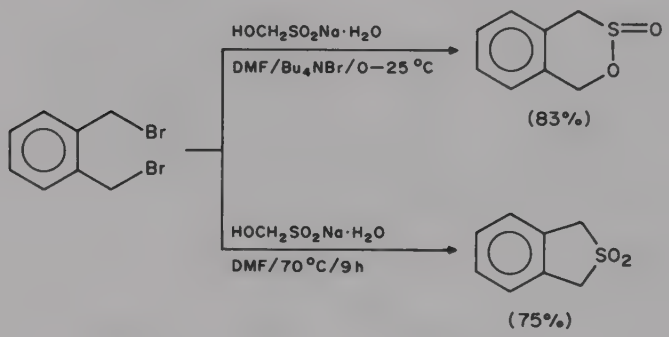
*IV. THREE-COMPONENT METHODS

*A. Reactions with Sulfur Dioxide and its Derivatives

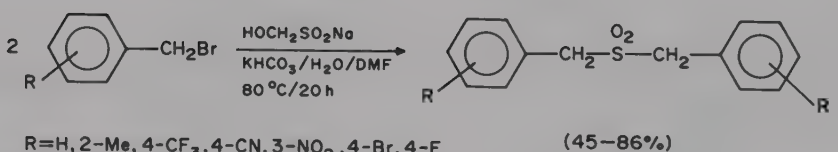
Connection of the SO_2 function with two carbon units can be carried out via different procedures, such as radical connections, metal-catalyzed and metalorganic connections, and ionic connections using sulfur dioxide itself or its masked derivatives (Rongalite, dithionite, sulfinate)[844–853] (equations 160–167).



(160)[844]

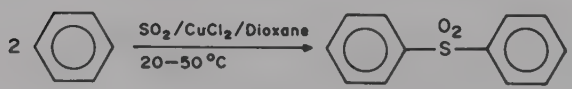


(161)[845]



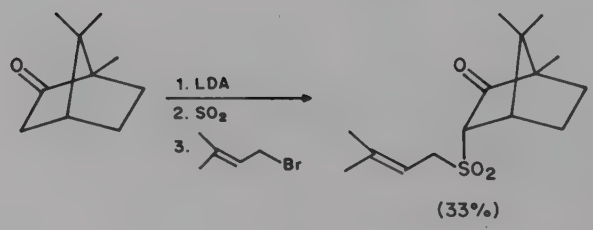
(162)[846]

$$2PhCH_2Br + Na_2S_2O_4 \xrightarrow[120\,^\circ C/20\,h]{[Aliquat\ 336]} PhCH_2SO_2CH_2Ph \quad (61\%) \qquad (163)^{847}$$

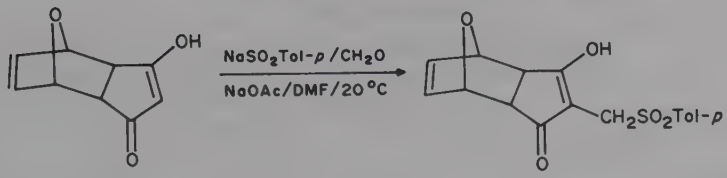


(164)[848]

$$Ph_5Bi \xrightarrow{SO_2} PhSO_2Ph \quad (95\%) \qquad (165)^{851}$$



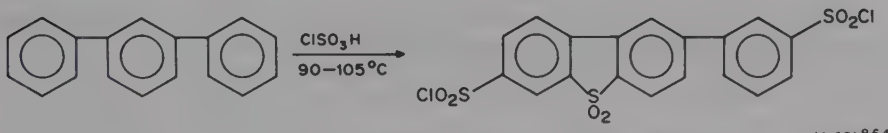
(166)[852]



(167)[853]

***B. Condensations of Hydrocarbons with Sulfur Trioxide and its Derivatives**

When reacting with chlorosulfonic acid, aromatic hydrocarbons suffer sulfonylation together with the usually observed sulfochloride formation[854] (equation 168).

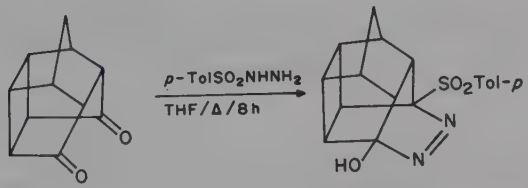


(80%)

(168)[854]

***V. MISCELLANEOUS METHODS**

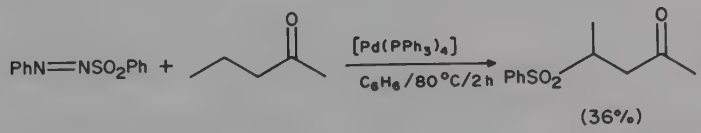
An α-azosulfone is generated starting from a sterically fixed γ-diketone on treatment with tosylhydrazine[855] (equation 169).



(66%)

(169)[855]

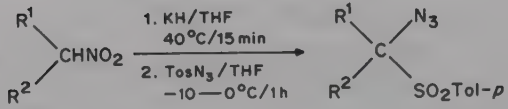
Pd(0)-catalyzed decomposition of diazosulfinates (mostly named azosulfones in the literature) in the presence of pentan-2-one leads to sulfonylation in the β-position to the keto function[856,857] (equation 170).



(36%)

(170)[856]

Secondary nitroalkanes are converted to α-azido sulfones on successive treatment with potassium hydride and tosyl azide[858] (equation 171).



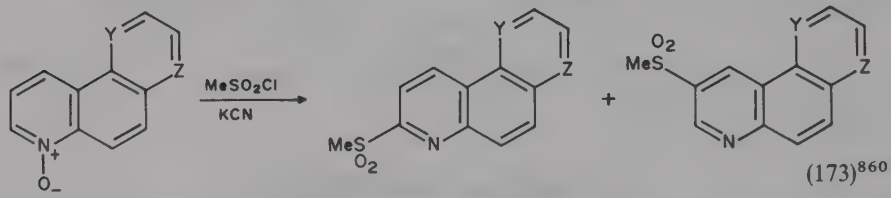
R^1, R^2=Me, —$(CH_2)_5$— (49–56%) (171)[858]

Allyl sulfides are converted to allyl sulfones via $RuCl_2$-catalyzed exchange of the thioether function with a sulfone function by means of a sulfonyl chloride[859] (equation 172).

(172)[859]

A: $[RuCl_2(PPh_3)_3]/C_6H_6/140°C/24\,h$

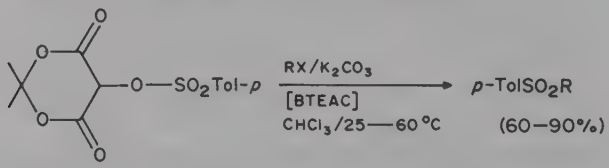
Reaction of mesyl chloride with a polynuclear pyridine N-oxide leads to unusual sulfone formation according to a Reissert–Heinze reaction[860] (equation 173).



(173)[860]

(a) Y = N; Z = CH (36%)
(b) Y = CH; Z = N (< 1%)
(c) Y = N→O; Z = CH (—)

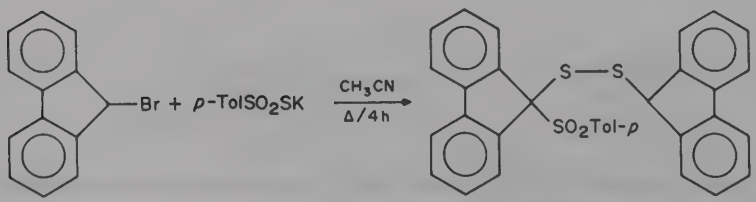
Redox disproportionation of CH acidic *p*-toluenesulfonates[861] (equation 174) and *p*-toluenethiosulfonates[862] (equation 175) leads to intermediate formation of *p*-toluenesulfinate, which is subsequently trapped by sulfone formation.



174)[861]

R=Me, Pr, Ar, CH_2COPh

X=I, Br, Cl; BTEAC=Benzytriethylammonium



(175)[862]

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CHAPTER 3

Synthesis of sulphoxides

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Edited by S. Patai and Z. Rappoport © 1988, 1994 John Wiley & Sons Ltd

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I. INTRODUCTION

Earlier methods for the synthesis of sulphoxides have been reviewed up to 1955 by Schöberl and Wagner in 'Houben–Weyl'[1]. A new edition of the sulphur volume of this series contains a comprehensive review of the chemistry of sulphoxides by Kresze in which preparative procedures have also been collected up to 1982[2]. As a rule, small chapters presenting very briefly the standard procedures used for the preparation of sulphoxides are parts of organic chemistry textbooks[3,4]. More detailed, but still far from exhaustive, are surveys of the sulphoxide syntheses in the books devoted to the chemistry of organic sulphur compounds. For example, such compilations of the sulphoxide syntheses may be found in *Organic Chemistry of Sulphur* edited by Oae[5] and in the book by Block, *Reactions of Organosulfur Compounds*[6]. The synthesis of sulphoxides is also discussed by Johnson and Sharp in their review on the chemistry of sulphoxides[7] and more recently by Drabowicz and Mikołajczyk in a review article on the synthesis of sulphoxides[8]. Moreover, the synthetic procedures used for the preparation of the particular groups of sulphoxides are included in many other reviews which have been published in the last two decades[2].

The purpose of the present chapter is to provide an up-to-date review of methods which may be applied for the synthesis of both achiral and chiral (racemic and optically active) sulphoxides as well as their derivatives. Since the synthesis of optically active sulphoxides is based on many special procedures, it was found necessary to separate the syntheses of achiral and racemic sulphoxides from those of optically active ones.

Some limitations of the subject surveyed have been necessary in order to keep the size of the chapter within the reasonable bounds. Accordingly, to make it not too long and readable, the discussion of the methods of the sulphoxide synthesis will be divided into three parts. In the first part, all the general methods of the synthesis of sulphoxides will be briefly presented. In the second one, methods for the preparation of optically active sulphoxides will be discussed. The last part will include the synthetic procedures leading to functionalized sulphoxides starting from simple dialkyl or arylalkyl sulphoxides. In this part, however, the synthesis of achiral, racemic and optically active sulphoxides will be treated together. Each section and subsection includes, where possible, some considerations of mechanistic aspects as well as short comments on the scope and limitations of the particular reaction under discussion.

II. SYNTHESIS OF ACHIRAL AND RACEMIC SULPHOXIDES

A. Oxidation of Sulphides

The oldest and generally applied sulphoxide synthesis consists of the oxidation of sulphides to sulphoxides. This reaction was reported for the first time by Märcker[9] as early as 1865. He found that treatment of dibenzyl sulphide with nitric acid afforded the corresponding dibenzyl sulphoxide in a high yield. Since that time the oxidation of

sulphides to sulphoxides has been the subject of extensive studies and a number of useful synthetic procedures are now available. They will be discussed below.

1. Oxidation by hydrogen peroxide

The simplest procedure for oxidation of sulphides to sulphoxides used till now involves the oxidation of sulphides with hydrogen peroxide alone or in the presence of various catalysts (equation 1).

$$R{-}S{-}R^1 + H_2O_2 \longrightarrow R{-}\underset{\underset{O}{\|}}{S}{-}R^1 + H_2O \qquad (1)$$

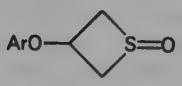
The major difficulty encountered in the preparation of sulphoxides by this method is a facile over-oxidation to the corresponding sulphones.

a. Hydrogen peroxide. Since 1908, when Gazdar and Smiles[10] reported that sulphides may be almost quantitatively oxidized to sulphoxides by hydrogen peroxide in acetone, this solvent has been commonly used as a reaction medium[11–13]. The only drawback is the relatively long reaction time needed for completion of the oxidation. This limitation may be simply overcome by the use of methanol as solvent[14]. It was found that various sulphoxides can be obtained selectively by keeping the corresponding sulphides with 2–4 equivalents of hydrogen peroxide in methanol solution at room temperature for 1 to 75 h depending on the structure of the starting sulphide. The use of methanol as solvent makes this oxidation procedure preparatively simple because the work-up is limited only to the addition of water to the reaction mixture and extraction of the resultant solution with chloroform. Since oxidation with hydrogen peroxide is very mild, it can be successfully applied to the preparation of acid-sensitive sulphoxides, such as allyl sulphoxide (Table 1) or silyl-substituted vinyl sulphoxides of structure **1**[15].

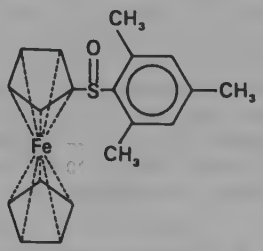
$$R_3Si(CH_2)_nS\underset{\underset{O}{\|}}{C}H{=}CH_2$$

(1)

Thietane sulphoxide **2** was isolated in 65% yield after treatment of the parent sulphide with hydrogen peroxide[16]. Mesityl ferrocenyl sulphoxide **3** and the corresponding



(2)



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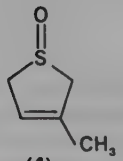

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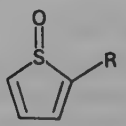


(5)

TABLE 1. Oxidation of sulphides to sulphoxides, R^1R^2SO, with hydrogen peroxide

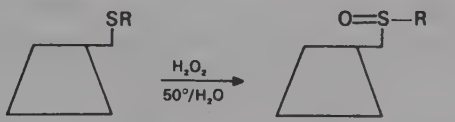
R^1	R^2	Solvent[b]	Reaction time (h)	Yield (%)	Ref.
Me	*n*-Bu	M	1	99	14
n-Bu	*n*-Bu	M	2	83	14
t-Bu	*t*-Bu	A	24	c	13
i-Am[a]	*i*-Am[a]	A	24	45	10
$PhCH_2$	$PhCH_2$	A	48	75	10
$PhCH_2$	Me	A	12	77	11
Ph	Me	A	24	c	12
Ph	Me	M	18	99	14
Ph	Ph	A	24	c	12
Ph	Ph	M	170	50	14
p-Tol	CH_2NO_2	A	120	25	11
Me	CH_2CO_2Et	A	72	87	11
Me	$CH(Me)CH{=}CH_2$	A	24	c	13
Me	$CH(Et)CH{=}CH_2$	A	24	c	13

[a] Am = C_5H_{11}.
[b] M = methanol, A = acetone.
[c] Not given.

sulphone were obtained in almost equivalent amounts after oxidation of the starting sulphide with hydrogen peroxide in methanol – water/potassium hydroxide solution at pH 7–9[17].

3-Methyl-2, 5-dihydrothiophene was converted into the corresponding *S*-oxide **4** in 57% yield after treatment with 30% excess of hydrogen peroxide for 60 h. By the same procedure the sulphoxides **5** derived from thiophene and its α-substituted analogues were also prepared[18].

Recently, 6-alkylsulphinyl β-cyclodextrins **6** were obtained from the corresponding sulphides by oxidation with dilute aqueous hydrogen peroxide[19] (equation 2).

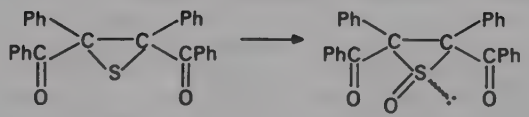


(2)

(6) (a) R = Me
(b) R = *n*-Pr

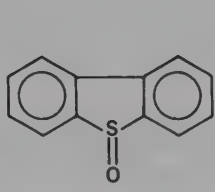
b. Oxidation by hydrogen peroxide in the presence of catalysts. Oxidation of sulphides by hydrogen peroxide has been found to be subject to catalysis. In 1908 Hinsberg[20] used acetic acid as a catalyst. He found that sulphides may be oxidized to sulphoxides in very high yields by hydrogen peroxide in acetone/acetic acid mixture or in acetic acid alone. Later on, it was found that sulphuric and perchloric acids[21] function also as efficient catalysts. The main drawback of the acid-catalyzed oxidation is a relatively long reaction time and a facile over-oxidation to the corresponding sulphones. However, by means of this procedure some sulphoxides of more than routine interest were prepared. For instance, Dittmer and Levy[22] reported that oxidation of dibenzoylstilbene episulphide **7** with hydrogen peroxide in acetic acid gave two diastereoisomeric sulphoxides **8**

(equation 3).



(7) (8) (3)

Dibenzothiophen *S*-oxide **9**[23] and 2,5-diphenyl-1,4-dithiacyclohexadiene-1-oxide **10**[24] were prepared from the corresponding sulphides by treatment with hydrogen peroxide in the presence of acetic acid. Selective oxidation of the penicillin derivative **11** to *S*-oxide **12** was achieved using hydrogen peroxide in methylene chloride solution containing 5 equivalents of acetic acid[25] (equation 4). Another interesting example is the synthesis of disulphoxides **13**, **14** and **15** which were obtained by oxidation of the parent sulphides with two equivalents of hydrogen peroxide in acetic acid at room temperature[26]. It was demonstrated that substantial through-bond interactions of the sulphur lone electron pairs occur in these structures. Treatment of α-pyridyl sulphides with hydrogen peroxide in acetic acid gave exclusively sulphoxides **16** in very good yields[27]. Similarly, oxidation of dithioacetals[28,29] resulted in the formation of the corresponding *S*-monooxides **17**. Apart from acids, few other compounds were found to be effective catalysts for the hydrogen peroxide oxidation of sulphides to sulphoxides. Thus, sulphides are oxidized to sulphoxides with hydrogen peroxide in absolute *t*-butyl alcohol containing a catalytic amount of vanadium pentoxide at 15°. The conversion of sulphides and sulphoxides to sulphones takes place only at 45 °C in the presence of this catalyst[30]. Yields of sulphoxides (Table 2) are good even in the oxidation of labile sulphides such as α-chlorosulphides and α-acetoxysulphides. Also thiirane-1-oxides **18** may be prepared by this procedure in 55–60% yields.



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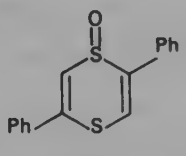

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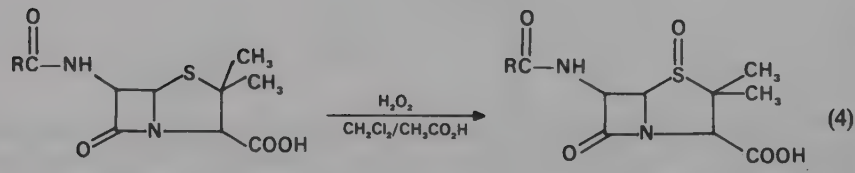
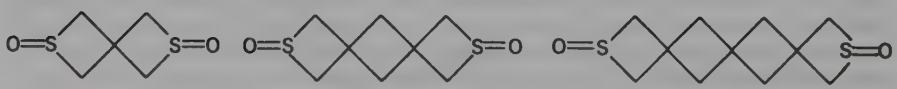
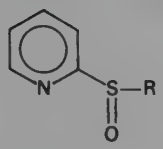


(11) (12) (4)



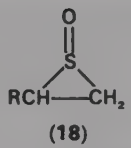
(13) (14) (15)



(16)

(17)

R = Me, Et, Bu



(18)

(a) R = H

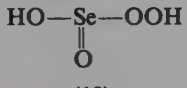
(b) R = CH_2OH

Vanadium pentoxide and mercuric oxide were used as catalysts for the hydrogen peroxide oxidation of bis(phenylthio)methane to its monooxide **17a**[31] (equation 5). From the synthetic point of view, it is interesting to note that vanadium pentoxide, in addition to its catalytic action, functions also as an indicator in this reaction. In the presence of hydrogen peroxide, the reaction mixture is orange while in the absence of hydrogen peroxide a pale yellow colour is observed. Thus, it is possible to perform the oxidation process as a titration ensuring that an excess of oxidant is never present.

$$PhSCH_2SPh \xrightarrow[V_2O_5]{H_2O_2} Ph{-}S(=O){-}CH_2SPh \qquad (5)$$

(17a)

A highly selective and rapid oxidation of sulphides to sulphoxides occurs when hydrogen peroxide/selenium dioxide system is used[32]. The reaction takes place immediately upon addition of a solution of hydrogen peroxide and selenium dioxide to a solution of a sulphide in methanol at room temperature. Yields of sulphoxides (Table 2) are in the range between 80 and 95%. It is most probable that perseleninic acid **19** is the true oxidizing agent.



(19)

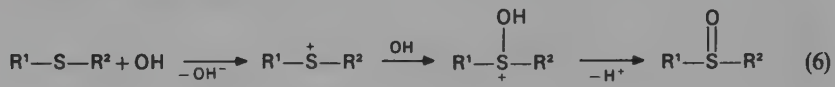
It is interesting to note that Reich and coworkers[33] reported the conversion of methyl

TABLE 2. Catalyzed oxidation of sulphides to sulphoxides, R^1R^2SO, with hydrogen peroxide

R^1	R^2	Catalyst	Yield (%)	Ref.
n-Bu	*n*-Bu	SeO_2	90	32
t-Bu	*t*-Bu	$TiCl_3$	98	35
$PhCH_2$	$PhCH_2$	V_2O_5	62	30
$PhCH_2$	$PhCH_2$	SeO_2	88	32
$PhCH_2$	$PhCH_2$	$TiCl_3$	98	35
Ph	Me	SeO_2	95	32
Ph	Me	$TiCl_3$	100	35
Ph	Ph	V_2O_5	60	30
Ph	Ph	SeO_2	92	32
Ph	Ph	$TiCl_3$	100	35
$C_{12}H_{25}$	CH_2Cl	V_2O_5	69	30
Ph	CH_2Cl	V_2O_5	73	30
CH_2CO_2Me	CH_2CO_2Me	V_2O_5	49	30
Dibenzothiophene		$TiCl_3$	99	35

phenyl sulphide to the corresponding sulphoxide by means of phenylperseleninic acid and Melnikov[34] found that sulphides may be oxidized to sulphoxides by refluxing with selenium dioxide for a few hours in chloroform.

A rapid and clean oxidation of sulphides to sulphoxides can also be carried out using the titanium(III) trichloride/hydrogen peroxide reagent[35]. On a milimole scale, the oxidation takes place in a time shorter than 20 min upon addition of a solution of hydrogen peroxide to a solution of the sulphide and titanium(III) trichloride in methanol at room temperature. It was suggested that the formation of a sulphoxide in this reaction resulted from a direct coupling of the hydroxy radical with cation radical **20** formed at the sulphur atom of the sulphide (equation 6).



(6)

(20)

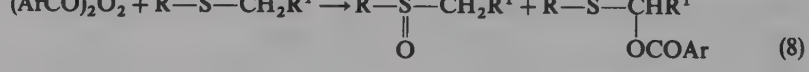
2. Oxidation with organic peroxides

Benzoyl hydroperoxide was used for the conversion of divinyl sulphide into divinyl sulphoxide by Levin[36] as early as 1930. In 1954 Bateman and Hargrave[37] reported that saturated sulphides may be oxidized to sulphoxides by means of cyclohexyl or *t*-butyl hydroperoxide. These authors found that in both polar and non-polar solvents oxygen transfer occurred to give quantitative yields of sulphoxides over a wide range of experimental conditions according to equation 7. It was also reported[38] that a quantitative yield of sulphoxides was obtained from the reaction of unsaturated sulphides with *t*-butyl and cyclohexyl hydroperoxides in methanol. With *t*-butyl hydroperoxide in benzene the sulphoxide yield was in no case stoichiometric, varying from 90 to 5% under the condition chosen.

(7)

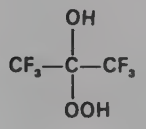
$R^3 = t$-Bu or cyclohexyl

Horner and Jürgens[39] reported that benzoyl peroxides **21** in the presence of sulphides decompose to give sulphoxides and α-acyloxysulphides **22** (equation 8). The latter compounds are undoubtedly formed as a result of the Pummerer reaction. The oxidation reaction leading to sulphoxides has been shown to be an ionic process[40]. However, till now it has not found wider synthetic applications. Ganem and coworkers[41] showed that 2-hydroperoxyhexafluoro-2-propanol **23** formed *in situ* from hexafluoroacetone and



(8)

(21) **(22)**



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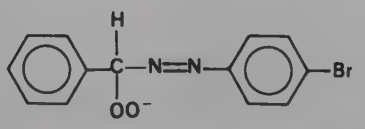


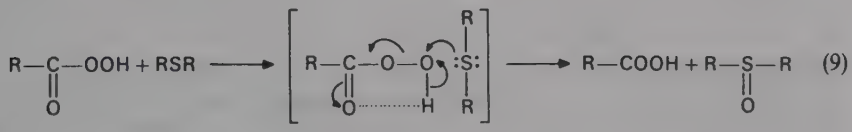
(24)

hydrogen peroxide is a convenient reagent for the conversion of sulphides into the corresponding sulphoxides under mild conditions. The reaction takes place quickly below room temperature affording sulphoxides almost quantitatively. The first oxidation of sulphides to sulphoxides under basic conditions was achieved using diazohydroperoxide anion **24**[42].

3. *Oxidation with peracids*

It is well established that organic peroxides are much stronger oxidizing agents than hydrogen peroxide. Among them organic peracids are strong oxidants even in the cold[43]. Levin[44] as early as 1928 commented on the ease with which organic sulphides may be oxidized to sulphoxides by perbenzoic acid at room temperature. Since that time, a variety of other peracids have been used for this conversion[2].

Based on the kinetic studies, a mechanism for this oxidation was proposed[45] which involves a nucleophilic attack by the sulphide on a cyclic hydrogen-bonded form of the peracid (equation 9). Since oxidation using peracids occurs under very mild conditions, it can be successfully applied to the preparation of base sensitive sulphoxides. Thus, di(α-bromobenzyl) sulphoxide **25**, which is very labile in the presence of a base, was obtained by careful oxidation of α-di(α-bromobenzyl) sulphide by means of *m*-chloroperbenzoic acid (MCPBA)[46] (equation 10).



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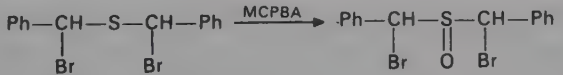
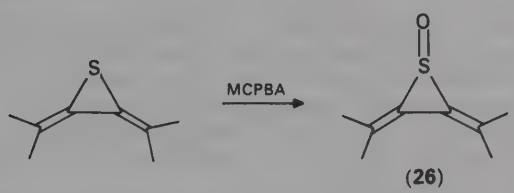


(10)

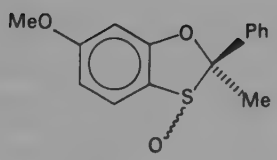
(25)

Oxidation of a thiiraneradialene with equimolar amounts of MCPBA in CH_2Cl_2 at about 0 °C gave the corresponding thiiraneradialene *S*-oxide **26** in a quantitative yield[47] (equation 11). 5-Membered heterocyclic sulphoxides such as 1,3-benzoxathiolane sulphoxide **27**, 1,3-benzdithiolane sulphoxide **28** and 1,3-dithiolane sulphoxide **29** were readily obtained from their sulphide precursors by oxidation with MCPBA in dichloromethane solution[48].



(11)

(26)



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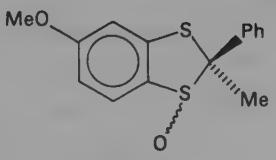

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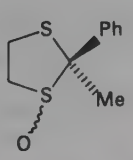


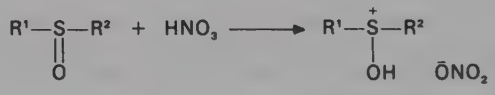
(29)

The use of optically active peracids for asymmetric oxidation of sulphides will be discussed in Section III dealing with the synthesis of optically active sulphoxides.

4. Oxidation with nitrogen-containing compounds

a. Nitric acid. Märcker[9] in 1865 first showed that dibenzyl sulphide may be oxidized to the corresponding sulphoxide by nitric acid of a proper strength. Soon after, this oxidant was used for the preparation of dialkyl sulphoxides[49]. More recently alkyl aryl[50] and long-chain dialkyl sulphoxides[51] were prepared by oxidation of parent sulphides with nitric acid in acetic anhydride. The first preparation of polyfluoroalkyl sulphoxides involved the oxidation of trifluoromethyl methyl sulphide with concentrated nitric acid to give trifluoromethyl methyl sulphoxide in 30% yield[52]. Later on, it was found that by the use of fuming nitric acid and longer reaction time the yields of perfluoroalkyl sulphoxides may be increased[53].

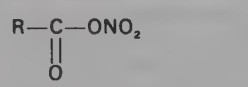
A detailed study revealed that sulphides may react with nitric acid to give sulphoxides, sulphones and their nitro derivatives[54]. However, under suitable conditions the nitric acid oxidation of sulphides leads to a selective formation of sulphoxides. This is probably due to the formation of a sulphonium salt **30** which is resistant to further oxidation[50] (equation 12).



(12)

(30)

b. Organic nitrates and nitronium salts. In 1976 Low and coworkers[55] reported that organic nitrates, which were known as nitrating agents, have also oxidative properties. They found that acyl nitrates **31** react rapidly with dialkyl and arylalkyl sulphides at $-78°$ to give sulphoxides in very high yields (Table 3).

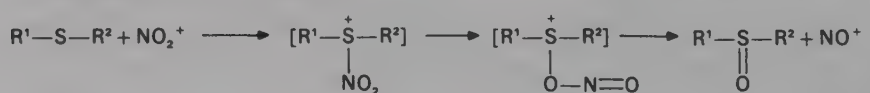


(31) (a) R = Me (b) R = Ph

(32) (a) $X = PF_6$ (b) $X = BF_4$

Olah and coworkers[56] found that treatment of dialkyl, arylalkyl and diaryl sulphides with nitronium hexafluorophosphate (or tetrafluoroborate) **32** at $-78°$ in methylene chloride resulted in the formation of sulphoxides in moderate to high yields (Table 3). In the oxidation of diphenyl sulphide which affords diphenyl sulphoxide in 95% yield, small amounts of the ring nitration products (*o*- and *p*-nitrophenyl phenyl sulphides) were formed. However, diphenyl sulphone and nitrophenyl phenyl sulphoxide were not detected among the reaction products.

It was proposed that an initially formed *S*-nitrosulphonium ion **33** rearranges into the *S*-nitritosulphonium ion **34**, which is then stabilized by loss of NO^+ ion to give the corresponding sulphoxide (equation 13).

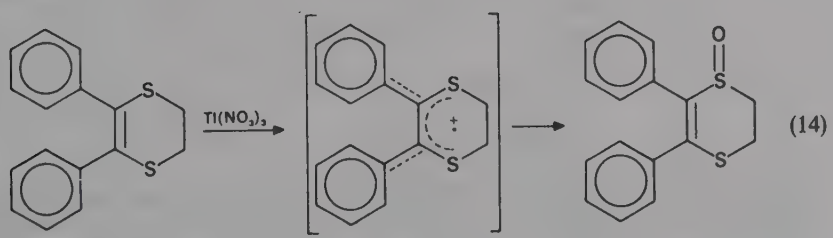


(33) **(34)** (13)

TABLE 3. Oxidation of sulphides to sulphoxides, R^1R^2SO, with nitrogen-containing oxidants

R^1	R^2	Oxidant	Yield (%)	Ref.
Me	Me	$MeCONO_3$	100	55
Me	Me	$PhCONO_3$	95	55
Me	Me	NO_2PF_6	46	56
Et	Et	$MeCONO_3$	83	55
Et	Et	$PhCONO_3$	100	55
Et	Et	NO_2PF_6	90	56
Et	Et	$Tl(NO_3)_3$	86	57
Et	Et	N_2O_4	95	64
n-Pr	*n*-Pr	NO_2PF_6	95	56
n-Pr	*n*-Pr	$Tl(NO_3)_3$	92	57
n-Pr	*n*-Pr	N_2O_4	100	64
Me	Ph	$MeCONO_3$	85	55
Me	Ph	$PhCONO_3$	100	55
Me	Ph	NO_2PF_6	89	56
Ph	Ph	NO_2PF_6	61	56
Ph	Ph	$Tl(NO_3)_3$	82	57
p-ClC_6H_4	*p*-ClC_6H_4	NO_2PF_6	90	57

c. Inorganic nitrates. It was reported[57] that reaction of dialkyl and arylalkyl sulphides with an excess of thallium(III) nitrate at room temperature in a chloroform–acetic acid (3:1) solution afforded the corresponding sulphoxides in high yields (Table 3). However, in a chloroform–acetic anhydride (3:1) solution the exclusive formation of sulphones was observed. 2, 3-Diphenyl-5, 6-dihydro-1, 4-dithiin **35** on treatment with 1.2 equivalent of thallium(III) nitrate in chloroform–methanol (1:1) solution at room temperature gave the corresponding sulphoxide **36** in 72% yield within 15 min (equation 14). The ESR spectrum of the reacting solution indicated the presence of the cation radical **37**. Therefore, the formation of **36** in this reaction was suggested to proceed by a one-electron oxidation mechanism.



(35) (37) (36) (14)

Ceric ammonium nitrate was also used as an efficient reagent for the conversion of diaryl sulphides into the corresponding sulphoxides under very mild conditions[58]. Over-oxidation, even in the presence of an excess of the reagent, was not observed. However, this reagent is not suitable for the oxidation of sulphides possessing α-hydrogens. This is most probably due to the Pummerer reaction which occurs in the presence of cerium(III) nitrate. An improved procedure utilizing catalytic amounts of cerium(IV) salt together with a cooxidant (BrO_3^-), which recycles the spent cerium(III)ions, avoided this limitation and can be applied also to the oxidation of dialkyl sulphides[59].

d. Nitrogen tetroxide. The first report on oxidation of organic sulphur compounds by 'nitrous fumes' was published by Pummerer[60] in 1910. In 1927 Bell and Bennett[61] reported that oxidation of 1,4-dithiane by this reagent gave predominantly the *trans*-isomer of 1,4-dithiane β-disulphoxide and a little of the *cis*-isomer of 1,4-dithiane α-disulphoxide. This observation was later confirmed by Whitaker and Sisler[62]. Horner and Hübenett[63] reported also on the use of dinitrogen tetroxide in carbon tetrachloride for oxidation of methyl phenyl sulphide to the corresponding sulphoxide. Soon after, liquid dinitrogen tetroxide was used for the selective oxidation of dialkyl sulphides to sulphoxides[64]. It was also found that dinitrogen tetroxide forms molecular addition compounds with dialkyl sulphoxides. Most probably, the formation of such addition compounds may prevent further oxidation at sulphur. Dinitrogen tetroxide may be used for oxidation of α-chlorosulphides, provided that the formation of N_2O_3 is prevented by scavenging the reaction mixture with oxygen[65].

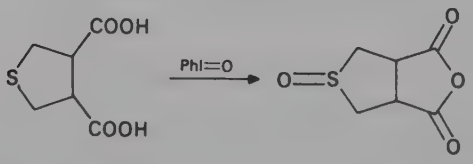
5. Oxidation with trivalent iodo compounds

a. Iodosobenzene. Ford-Moore[66] reported that iodosobenzene is a very convenient reagent for the conversion of β-hydroxy and β-chlorosulphides **38** to the corresponding sulphoxides **39** (equation 15). An interesting example of the oxidation of cyclic dicarboxylic acids *cis*-**40** and *trans*-**40** by iodosobenzene has been described by Takaya and coworkers[67]. They found that treatment of *trans*-acid **40** with iodosobenzene gave the expected sulphoxide. However, oxidation of *cis*-**40** was accompanied by dehydration and afforded sulphoxide **41** (equation 16).

$$XCH_2CH_2{-}S{-}CH_2CH_2X + PhI{=}O \longrightarrow XCH_2CH_2{-}\underset{\underset{O}{\|}}{S}{-}CH_2CH_2X + PhI \qquad (15)$$

(38) **(39)**

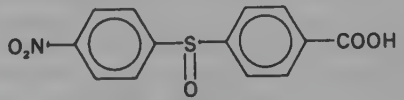
(a) X = OH
(b) X = Cl



(16)

cis-(**40**) (**41**)

b. Iodobenzene diacetate. Iodobenzene diacetate was used by Szmant and Suld[68] for the preparation of *p*-(nitrophenylsulphinyl)benzoic acid **42**. The oxidation of the starting sulphide in boiling acetic acid for 24 h with an equivalent amount of iodobenzene diacetate gave sulphoxide **42** in 90% yield. Later on, oxidation of benzyl phenyl and dibenzyl sulphide by this reagent was found to be much less efficient and afforded the corresponding sulphoxides in 51 and 21% yields, respectively[69].



(42)

c. Iodobenzene dichloride. Montanari and coworkers[70] found that sulphides are selectively oxidized to sulphoxides by iodobenzene dichloride in aqueous pyridine according to equation (17). The reaction is almost instantaneous at a temperature below 0° and affords a wide range of aliphatic, aromatic and heterocyclic sulphoxides in yields over 80%. Iodobenzene dichloride is only a controlled source of chlorine. The reaction proceeds via an electrophilic attack of the chlorine at the divalent sulphur to afford a chlorosulphonium salt **43**. This salt is then decomposed by nucleophilic attack of water giving the sulphoxide (equation 18). This procedure is suitable for the synthesis of sulphoxides containing ^{18}O in the sulphinyl group.

$$R^1—S—R^2 + PhICl_2 + 2C_5H_5N + H_2O \longrightarrow R^1—\underset{\underset{O}{\|}}{S}—R^2 + PhI + 2C_5H_5H{\cdot}HCl \qquad (17)$$

$$R^1—S—R^2 + PhICl_2 \longrightarrow R^1—\overset{+}{\underset{\underset{Cl}{|}}{S}}—R^2 \xrightarrow{H_2O} R^1—\underset{\underset{O}{\|}}{S}—R^2 \qquad (18)$$

(43)

6. *Oxidation with metaperiodates*

In 1962, Leonard and Johnson[71] described the selective oxidation of sulphides to sulphoxides by sodium metaperiodate (equation 19). This reaction is general in scope and may be applied to the preparation of acyclic, cyclic, aliphatic, aromatic and heterocyclic sulphoxides. Typically, the reaction is carried out at 0° in methanol–water solution and is complete in 3–24h affording yields of about 90% or higher (Table 4). However, in some cases this reagent does not work efficiently. Thus, the attempted oxidation of methyl heptafluoropropyl sulphide with aqueous sodium periodate at temperatures in the range 5–20° gave unchanged reactants[53]. Moreover, when the reaction was carried out at 100° for 7 days

TABLE 4. Oxidation of sulphides to sulphoxides, R^1R^2SO, by metaperiodates, MIO_4

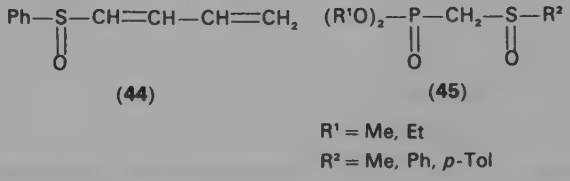
R^1	R^2	M	Solvent (%)	Yield (%)	Ref.
Et	Et	Na	M/W[a]	65	71
Me	Ph	Na	M/W[a]	99	71
Me	Ph	Na/Al_2O_3	EtOH	88	79
Me	Ph	Bu_4N	$CHCl_3$	86	78
$PhCH_2$	$PhCH_2$	Na	M/W[a]	96	71
$PhCH_2$	$PhCH_2$	Na/SiO_2	CH_2Cl_2	66	80
t-Bu	*t*-Bu	Na/Al_2O_3	EtOH	85	79
$CH_2=CH—CH_2$	$CH_2=CH—CH_2$	Na/Al_2O_3	EtOH	87	79
Bz	*i*-Pr	Na/Al_2O_3	EtOH	85	79
Ph	Ph	Na	M/W[a]	98	71
Ph	Ph	Na/Al_2O_3	EtOH	90	79
Ph	Ph	Bu_4N	$CHCl_3$	72	78
Thiane		Na	M/W[a]	99	71
Thiane		Bu_4N	$CHCl_3$	90	78
p-Tol	*p*-Tol	Bu_4N	$CHCl_3$	70	78

[a]M/W = methanol–water solution.

the unchanged sulphide (80%) and heptafluoropropyl sulphone were isolated. No trace of sulphoxide was detected under these conditions [53].

$$R^1—S—R^2 + NaIO_4 \longrightarrow R^1—\underset{\underset{O}{\|}}{S}—R^2 + NaIO_3 \qquad (19)$$

Oxidation of phenyl hexyl sulphide with sodium metaperiodate gave also only a trace amount of the corresponding sulphoxide[72]. On the other hand, Hall and coworkers[73] prepared benzylpenicillin and phenoxymethyl penicillin sulphoxides from the corresponding benzyl esters by oxidation with sodium metaperiodate in dioxane solution with a phosphate buffer. A general procedure for the synthesis of penicillin sulphoxides was reported later by Essery and coworkers[74] which consists in the direct oxidation of penicillins or their salts with sodium metaperiodate in aqueous solution at pH 6.5–7.0. 1-Butadienyl phenyl sulphoxide **44**[75] and α-phosphoryl sulphoxides **45**[76] were also prepared by the same procedure.

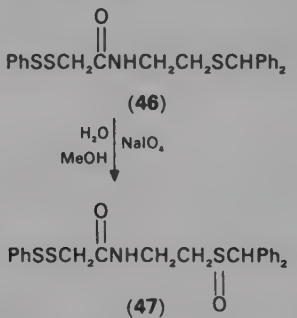


(44) **(45)**

R^1 = Me, Et

R^2 = Me, Ph, *p*-Tol

The selective oxidation of the sulphide grouping in the presence of the disulphide bond was observed when a methanolic solution of amide **46** was treated with an aqueous solution of sodium metaperiodate[77] (equation 20).



(46) **(47)** (20)

Water insoluble tetrabutylammonium metaperiodate, which can be prepared from sodium metaperiodate and tetrabutylammonium hydrogen sulphate in aqueous solution, was found to be a useful reagent for the selective oxidation of sulphides in organic solvents[78]. The reaction was generally carried out in boiling chloroform and gave dialkyl, alkyl aryl and diaryl sulphoxides in yields which are comparable with those reported for sodium metaperiodate in aqueous methanol solution (Table 4). In the case of diaryl sulphoxides, the yields decrease with prolonged reaction time.

Alumina supported sodium metaperiodate, which can be prepared by soaking the inorganic support with a hot solution of sodium metaperiodate, was also found to be a very convenient reagent for the selective and clean oxidation of sulphides to sulphoxides[79]. The oxidation reaction may be simply carried out by vigorous stirring of this solid oxidant with the sulphide solution at room temperature. As may be expected for such a procedure, solvent plays an important role in this oxidation and ethanol (95%) was found to be

superior to benzene, THF and chloroform. It should be noted that dibenzothiophen was not oxidized by this reagent even after 48 h.

Silica gel supported sodium metaperiodate was used for the selective oxidation of dibenzyl sulphide[80]. Metaperiodate anion soaked on strongly basic-ion-exchange resins Amberlite IRA-904 or Amberlyst A-26 was found to be able to oxidize sulphides into the corresponding sulphoxides in 82–99% yield[81].

7. *Oxidation with halogens and compounds containing 'electropositive' halogens*

a. Halogens. Molecular halogens have long been known to form addition compounds with organic sulphides which may be chlorosulphonium salts or sulphuranes **48**. These can be subsequently hydrolyzed to sulphoxides as shown in equation 21. However, it was recognized very early that undesirable side-reactions very often predominate over the sulphoxide formation[23,82]. Thus, oxidation of dimethyl sulphide with chlorine in water gave α-chloromethyl sulphoxides[83]. Treatment of mono-, di- and trichloromethyl sulphides **49** with chlorine in acetic acid–water mixture afforded the corresponding sulphoxides **50** in good yields[84]. On the other hand, the reaction of dichloro- and trichlorosulphoxides **50** with chlorine in methylene chloride gave exclusively the corresponding sulphinyl chlorides **51**, resulting from cleavage of the carbon–sulphur bond[85] in **50** (equation 22). In the case of aryl sulphides, halogenation of the aromatic ring was also observed[86].

$$R^1\text{—}S\text{—}R^2 + X_2 \rightleftharpoons \left[R^1\overset{+}{S}R^2XX^-\right] \rightleftharpoons R^1R^2SX_2 \xrightarrow{H_2O} R^1\text{—}\underset{\underset{O}{\|}}{S}\text{—}R^2 + 2HX \quad (21)$$

(48)

$$R\text{—}S\text{—}R^1 \xrightarrow[H_2O/AcOH]{Cl_2} R\text{—}\underset{\underset{O}{\|}}{S}\text{—}R^1 \xrightarrow[CH_2Cl_2]{Cl_2} R\text{—}\underset{\underset{O}{\|}}{S}\text{—}Cl \quad (22)$$

(49) **(50)** **(51)**

for **b** and **c**

(a) $R^1 = CH_2Cl$

(b) $R^1 = CHCl_2$

(c) $R^1 = CCl_3$

With bromine as an oxidant the formation of by-products may be easily prevented by carrying out the oxidation under appropriate conditions. For example, Oae and coworkers[87] reported oxidation of a number of sulphides with the complexes of bromine and tertiary amines in 70% aqueous acetic acid as solvent. They found that pyridine-bromine and 1,4-diazabicyclo[2,2,2]octane-bromine complexes gave satisfactory results in terms of yields and purity of sulphoxides (Table 5). It was demonstrated[88,89] that sulphoxides (dialkyl, aryl alkyl, diaryl, α-phosphoryl, *S*-oxides of penicillin) can be obtained in high yields and free of the above-discussed side-products if the reaction of sulphides with bromine or chlorine as well as the subsequent hydrolysis of the addition compounds is carried out under two-phase conditions (CH_2Cl_2/H_2O) using potassium hydrogen carbonate as a base. This procedure was applied also for the preparation of sulphoxides containing ^{18}O in the sulphinyl group. However, the ^{18}O content in the sulphoxide formed was much lower than that of ^{18}O in the water used for the reaction. More recently, a modified two-phase oxidation procedure was developed which allows one to synthesize ^{18}O labelled sulphoxides with no loss of ^{18}O enrichment. It involves the use of pyridine instead of potassium hydrogen carbonate as hydrogen bromide acceptor[90].

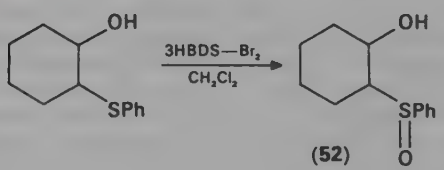
TABLE 5. Oxidation of sulphides to sulphoxides, R^1R^2SO, with bromine

R^1	R^2	Reaction conditions	Yield (%)	Ref.
Me	*n*-Pr	$Br_2/H_2O/CH_2Cl_2/KHCO_3$	85	89
Me	*n*-Bu	$Br_2/H_2O/CH_2Cl_2/KHCO_3$	90	89
Ph	Me	$Br_2/H_2O/CH_2Cl_2/KHCO_3$	97	89
Ph	Me	Br_2/HBDS[a]/CH_2Cl_2	85	72
p-Tol	Me	$Br_2/Py/H_2O$/AcOH	85	87
$PhCH_2$	$PhCH_2$	$Br_2/H_2O/CH_2Cl_2/KHCO_3$	97	89
$PhCH_2$	$PhCH_2$	Br_2/HBDS[a]/CH_2Cl_2	92	72
$PhCH_2$	Ph	$Br_2/Py/H_2O$/Ac	65	87
$PhCH_2$	$PhCH_2$	$Br_2/Py/H_2{}^{18}O/CH_2Cl_2$	90	90
Ph	Ph	$Br_2/H_2O/CH_2Cl_2/KHCO_3$	95	89
Ph	Ph	Br_2/HBDS[a]/CH_2Cl_2	18	72
Ph	Ph	$Br_2/Py/H_2O$/AcOH	95	87
CH_3	CH_2Cl	Br_2/HBDS/CH_2Cl_2	78	72
Ph	C_6H_{13}	Br_2/HBDS/CH_2Cl_2	85	72
C_6H_{13}	C_6H_{13}	Br_2/HBDS/CH_2Cl_2	90	72

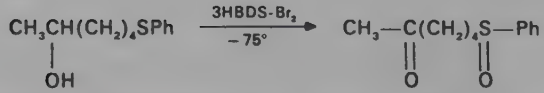
[a]HBDS = hexabutyldistannoxane.

Ueno and coworkers[72] described a procedure in which oxidation of sulphides by bromine can be carried out under anhydrous conditions. They found that treatment of sulphides with bromine and then with hexabutyldistannoxane (HBDS) in organic solvent (room temperature, 1–2 h) afforded sulphoxides in high yields (Table 5) without sulphone contaminations (equation 23). This procedure has a special value for the oxidation of hydrophobic sulphides such as hexyl phenyl sulphide and dihexyl sulphide because, for example, oxidation of the former with sodium metaperiodate gave a trace amount of the corresponding sulphoxide. It is interesting that α-(phenylthio) cyclohexanol after treatment with $HBDS/Br_2$ reagent gave 2-(phenylsulphinyl)cyclohexanol (**52**) in 87% yield (equation 24), whereas acyclic hydroxysulphide **53** was cleanly converted by this reagent to the corresponding ketosulphoxide **54** in almost quantitative yield (equation 25).

$$R^1{-}S{-}R^2 + Br_2 + (Bu_3Sn)_2O \longrightarrow R^1{-}\overset{\overset{O}{\|}}{S}{-}R^2 + 2Bu_3SnBr \qquad (23)$$



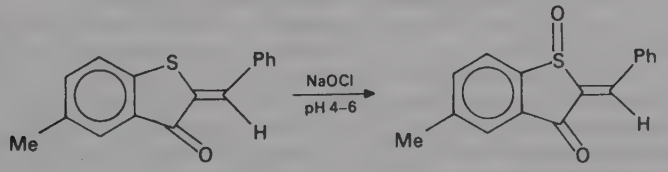
(52) (24)



(53) (54) (25)

The rate of formation of sulphoxides from sulphides and iodine in aqueous solution has been found to be relatively slow. It may be, however, accelerated by certain nucleophiles, such as phthalate ion[91], hydrogen phosphate ion[91] and β-cyclodextrin phosphate ion[92]. The selective oxidation of *N*-acetylmethionine[93] and *N*-acetylmethionine methyl ester[94] to the corresponding *S*-oxides was achieved using iodine in the presence of dicarboxylate ions.

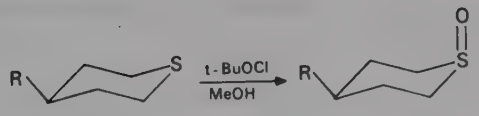
b. Hypochlorites. In the chemical literature there is only a single report on the use of an inorganic hypochlorite (NaOCl) for the selective oxidation of sulphides to sulphoxides. Reamonn and O'Sullivan[95] found that the reaction of 2-benzylidene 2,3-dihydro-5-methylbenzo [*b*] thiophen-3-one gave the corresponding *S*-oxide **55** in a yield over 80% (equation 26). The most stable organic hypochlorite, *t*-butyl hypochlorite, was first used for the oxidation of sulphides in 1964. Skell and Epstein[96] showed that sulphides react with this compound at low temperature to give at first alkoxysulphonium salt **56** which then decomposes to sulphoxides at room temperature (equation 27). Later on, it was found that *t*-butyl hypochlorite in methanol is a very convenient reagent for selective oxidation of cyclic[97], acyclic[98] and β-hydroxy[99] sulphides. Oxidation of cyclic sulphides **57** by this reagent gave in all cases *cis*-sulphoxide **58**[97] (equation 28).



(55) (26)

$$R^1—S—R^2 + BuOCl \longrightarrow [R^1R^2\dot{S}(OBu\text{-}t)Cl^-] \longrightarrow R^1—\underset{\underset{O}{\|}}{S}—R^2 \qquad (27)$$

(56)



(57) (58) (28)

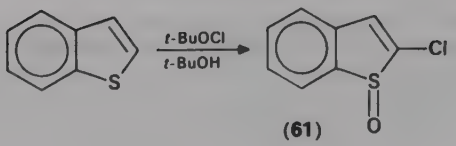
The reaction of sulphides **59** bearing an ethynyl or a carbomethoxy group α to sulphur with *t*-butyl hypochlorite in methanol or ethanol gives high yields of the corresponding α-alkoxy sulphides (**60**) rather than sulphoxides[98] (equation 29). Oxidation of benzo[b]thiophene with *t*-butyl hypochlorite in *t*-butyl alcohol at 30–40° gave the corresponding 2-chloro-1-benzothiophen-1-oxide **61** in 45% yield[100] (equation 30).

$$Ar—S—CH_2X \xrightarrow[MeOH \text{ or } EtOH]{t\text{-}BuOCl} Ar—S—\underset{\underset{OR}{|}}{CH}—X \qquad (29)$$

(59) (60)

(a) X = C≡CH
(b) X = CO_2Me

R = Me or Et



(61) (30)

c. N-Halo compounds. Oae and coworkers[101] reported that aromatic sulphides gave the corresponding sulphoxides in high yields (Table 6) on treatment with one equivalent of *N*-bromosuccinimide (NBS) in a dioxane–water (7:3) solution at room temperature. However, the reaction of NBS with dialkyl and aryl alkyl sulphides under the same experimental conditions resulted in a C—S bond cleavage and gave no sulphoxides. On the other hand, aryl fluoromethyl sulphides when reacted with one equivalent of NBS in methanol or THF containing a few drops of water afforded cleanly the corresponding α-fluoromethyl sulphoxides[102].

It was reported earlier that even dialkyl sulphides are efficiently oxidized to sulphoxides without a concomitant C—S bond cleavage by NBS or *N*-chlorosuccinimide (NCS) when the reaction is performed in anhydrous methanol at low temperature[103]. *N*-Chloro-Nylon-6, 6 in methanol–water or dioxane–water[104] and *N*-bromo-ε-caprolactam in water or alcohols[105] were also used successfully for oxidation of sulphides.

Sulphides are quickly and efficiently converted into sulphoxides by 1-chlorobenzotriazole (NCBT) in methanol at $-78°$[106]. However, this reagent cannot be used for the oxidation of *t*-butyl sulphide and dibenzyl sulphide since C—S bond cleavage takes place.

In the reaction between chloramine B and di-(2-chloroethyl)sulphide in aqueous solvents simultaneous formation of di(2-chloroethyl)sulphoxide and the corresponding sulphimide, $PhSO_2N{=}S(CH_2CH_2Cl)$, was observed[107]. The amount of sulphoxide increased on increasing the concentration of water in the reaction mixture.

d. Sulphuryl chloride. Traynelis and coworkers[108] showed that the low-temperature reaction of sulphuryl chloride with sulphides leads to the formation of the chlorine–sulphide complexes which are then converted to the corresponding sulphoxides by

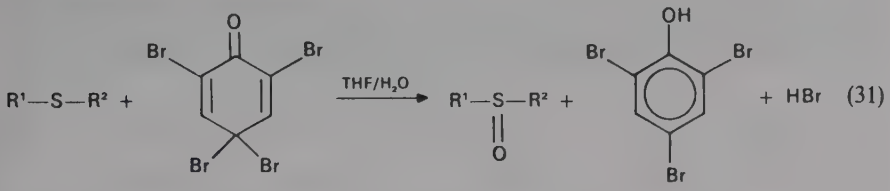
TABLE 6. Oxidation of sulphides to sulphoxides, R^1R^2SO, using *N*-halo compounds

R^1	R^2	*N*-halo compound[a]	Solvent	Yield (%)	Ref.
Me	Me	NCS	MeOH	62	103
Et	Et	NBS	MeOH	65	103
n-Pr	*n*-Pr	NBS	MeOH	76	103
$PhCH_2$	$PhCH_2$	NCS	MeOH	86	103
$PhCH_2$	Ph	NCS	MeOH	82	103
Ph	Ph	NCS	MeOH	93	103
Ph	Ph	NBS	H_2O	75	101
$PhCH_2$	Et	NBS	D/H_2O[b]	85	101
i-Pr	*i*-Pr	NCBT	MeOH	87	106
Ph	Me	NCBT	MeOH	92	106
p-Tol	CH_2F	NBS	MeOH/H_2O	85	102
Ph	CH_2F	NBS	MeOH/H_2O	83	102
p-ClC_6H_4	CH_2F	NBS	MeOH/H_2O	79	102
p-$O_2NC_6H_4$	CH_2F	NBS	MeOH/H_2O	81	102

[a]NCS = *N*-chlorosuccinimide; NBS = *N*-bromosuccinimide; NCTB = 1-chlorobenzotriazole.
[b]D = dioxane.

treatment with ethanol. Yields of sulphoxides are in the range of 60–95%. Hojo and coworkers[109] found that oxidation of aryl alkyl and diaryl sulphides with equivalent amount of sulphuryl chloride in the presence of wet silica gel at room temperature gave sulphoxides in almost quantitative yield without formation of any chlorinated products. With dialkyl and benzyl sulphides, this reaction should be carried out at ice-bath temperature in order to avoid α-chlorination. Allylic sulphoxides were also prepared by this procedure without chlorination at the allylic position.

e. 2,4,4,6-Tetrabromocyclohexadienone. Sulphides could be oxidized efficiently to the corresponding sulphoxides uncontaminated by sulphones by means of 2,4,4,6-tetrabromocyclohexadienone **62** in dioxane–water or tetrahydrofuran–water solution at room temperature[110] (equation 31).

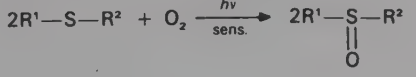


(31)

(**62**)

8. Photochemical oxidation

Photochemical synthesis of sulphoxides was reported for the first time by Foote and Peters[111] in 1971. They found that dialkyl sulphides undergo smoothly dye-photosensitized oxidation to give sulphoxides (equation 32). This oxidation reaction has been postulated to proceed through an intermediate adduct **63**, which could be a zwitterionic peroxide, a diradical or cyclic peroxide, which then reacts with a second molecule of sulphide to give the sulphoxide (equation 33).



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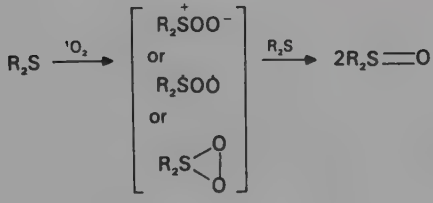
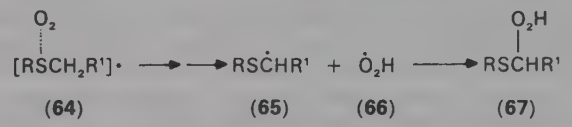


(33)

(**63**)

Direct photooxidation of aliphatic sulphides in hexane solution and as solids gave sulphoxides in a quantitative yield. Only di-*t*-butyl sulphide was not oxidized under these conditions[112]. The appearance of an intense absorption band ($\lambda_{max} = 300$ nm) on saturating liquid sulphides with oxygen provides evidence for the formation of a charge-transfer (C.T.) complex **64** between oxygen as an electron acceptor and sulphur as an electron donor, as a primary step in this reaction. It was suggested that the excited C.T. complex **64** leads to an α-alkylthioalkyl radical **65** capable of combining with a

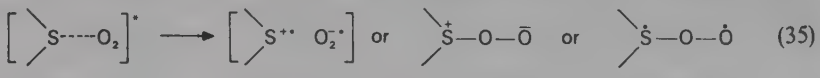
hydroperoxide radical **66** and forming sulphide peroxides **67** (equation 34).



(34)

(64) **(65)** **(66)** **(67)**

Although this mechanism could explain the inertness of di-*t*-butyl sulphide towards oxidation due to the absence of α-hydrogen atoms, it was later ruled out by Tezuka and coworkers[113]. They found that diphenyl sulphoxide was also formed when diphenyl sulphide was photolyzed in the presence of oxygen in methylene chloride or in benzene as a solvent. This implies that α-hydrogen is not necessary for the formation of the sulphoxide. It was proposed that a possible reactive intermediate arising from the excited complex **64** would be either a singlet oxygen, a pair of superoxide anion radical and the cation radical of sulphide **68** or zwitterionic and/or biradical species such as **69** or **70** (equation 35).



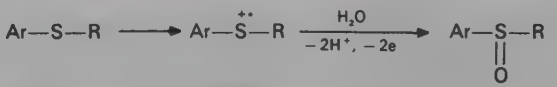
(35)

(64a) **(68)** **(69)** **(70)**

The formation of *cis* and *trans* 3-*t*-butylsulphinylcyclobutanes and *cis* and *trans* 4-*t*-butylsulphinylcyclohexanes in the photochemical oxygen transfer from aza-aromatic *N*-oxides to the corresponding sulphides has been reported by Boyd and coworkers[114]. The results are consistent with a transition state involving oxaziridine intermediate where partial bonding of the oxygen atom to the ring nitrogen atom is maintained during the oxygen transfer process.

9. *Electrochemical oxidation*

An interesting preparation of sulphoxides involves the electrochemical oxidation of sulphides. It was found[115,116] that anodic oxidation of aromatic sulphides leads to the formation of cation radicals **71** which react with water to give the corresponding sulphoxides in yields exceeding in many cases 80% (equation 36). Thus, in acetic acid–water (8:2) solution an electrochemical oxidation of diphenyl sulphide in the presence of perchlorate or chloride anions gave diphenyl sulphoxide almost quantitatively[117,118]. Dibenzothiophene-1-oxide **9** was obtained[119] in 100% yield by oxidation of dibenzo thiophene in the same solvent mixture. Electrooxidation of methyl phenyl sulphide in acetonitrile–water solution in the presence of lithium perchlorate gave methyl phenyl sulphoxide in 74% yield[120]. However, oxidation of phenyl triphenylmethyl sulphide under the same conditions gave products arising from the cleavage of the C—S bond[120]. Oxidation of 1,4-di(methylthio)benzene in methanol–THF (5:1) solution in the presence of tetramethylammonium perchlorate on platinum electrode gave selectively methyl 4-(methylthio)phenyl sulphoxide in 83% yield[121].

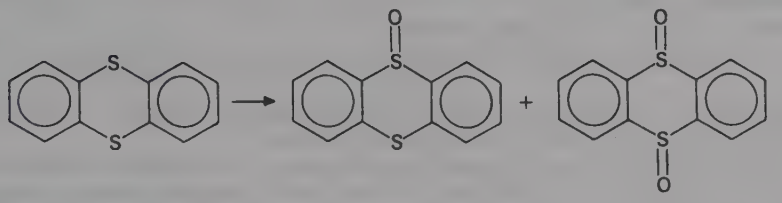


(36)

(71)

Oxidation of thiantrene **72** in acetic acid–water (8:2) mixture in the presence of perchloric acid on silver electrode afforded thiantrene 5-oxide **73** when electrolysis is carried out at 1.5 V or a mixture of *cis* and *trans* thiantrene 5,10-dioxide **74** in 44 and 28%

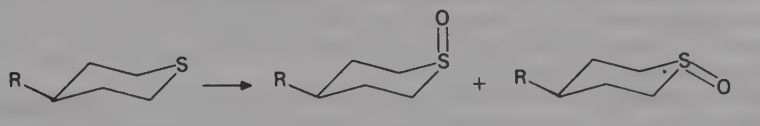
yield, respectively, together with the corresponding sulphone (13%), sulphoxide-sulphone (10%) and disulphone (5%) at 1.6 V[122] (equation 37).



(37)

(72) (73) (74)

Stereoselective conversion of a thiane **57** to the corresponding *trans*-thiane-1-oxide **58** was achieved by bromonium ion mediated electrooxidation while a preferential formation of the *cis*-sulphoxide **58** was observed under acidic electrolysis[123] (equation 38).



(38)

(57) *cis*-(58) *trans*-(58)

R = *p*-ClC$_6$H$_4$

10. Oxidation by miscellaneous reagents

Chromic acid oxidation of sulphides to sulphoxides was reported in 1926[124]. However, this oxidation procedure is not selective and sulphone formation was observed[125]. When pyridine was used as a solvent the sulphone formation was strongly reduced[126].

Oxidation of di-*n*-butyl sulphide with activated manganese dioxide in light petroleum gave di-*n*-butyl sulphoxide exclusively[126]. However, the reaction was very slow at room temperature. This reagent is also suitable for oxidation of diallyl sulphides although, after 76 h, diallyl sulphoxide was isolated in 13% yield only.

Oxidation of dibenzyl and methyl phenyl sulphides by lead tetraacetate in acetic acid was also reported[127].

Selenoxides readily convert dialkyl sulphides into sulphoxides in acetic acid solution being themselves reduced to selenides[128] (equation 39). The yields of sulphoxides are strongly dependent on the steric requirements of the alkyl groups. The reaction does not occur in methanol and benzene. Recently, the photochemical oxygen transfer from selenoxides to sulphides was reported by Tezuka and coworkers[129]. They found that photolysis of a mixture of selenoxide (diphenyl or dibenzoselenophene oxide) with dialkyl and aryl alkyl sulphides in methanol gave the corresponding sulphoxides in good yields (78–97%) along with the deoxygenated aromatic selenide. Sulphones were not formed under any reaction conditions and diphenyl sulphide was unsusceptible to photooxidation with these selenoxides. It was proposed that an excited selenoxide molecule interacts with the sulphide to form a bimolecular intermediate which collapses to a sulphoxide and selenide.

$$R^1—S—R^2 + R—\underset{\underset{O}{\|}}{Se}—R \longrightarrow R^1—\underset{\underset{O}{\|}}{S}—R^2 + R—Se—R \qquad (39)$$

Clean and selective oxidation of dibenzyl and dibutyl sulphides to the corresponding

sulphoxides by aromatic seleninic acid in the presence of a strong acid catalyst in acetonitrile solution was reported by Faehl and Kice[130]. The stoichiometry of the reaction is described by equation 40.

$$R_2S + 2/3\ ArSeO_2H \xrightarrow{H^+} R_2S{=}O + 1/3\ ArSe{-}SeAr + 1/3\,H_2O \qquad (40)$$

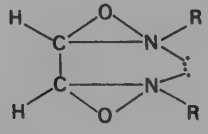
Diphenyl sulphoxide was obtained when a solution of diphenyl sulphide was treated with potassium hydrogen sulphate in ethanol and acetic acid[131].

Dialkyl and alkyl aryl sulphides are converted into the corresponding sulphoxides on oxidation with ozone[132,133]. This method was found to be highly stereoselective. For instance, thianes **57** gave the corresponding *trans*-sulphoxides **58** exclusively[97]. However, the formation of sulphones as by-products is very difficult to avoid. For example, the reaction of di-(2-hydroxyethyl)sulphide with 1.5 equivalent of ozone gave a 1:1 mixture of the corresponding sulphoxide and sulphone[134]. ω-(Chloroalkyl)phenyl sulphoxides were also prepared by ozonolysis of the corresponding sulphides in 55–74% yields[135]. Catalytic oxidation of sulphides by oxygen in the presence of metal catalysts such as metal oxides or metal sulphides was found to occur in the gas phase at higher temperatures and/or higher pressure[2,136]. Generally, the yields of sulphoxides are good, however, the corresponding sulphones are always formed as by-products.

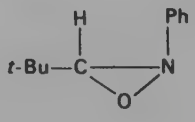
Recently, Davis and coworkers[137] reported the selective oxidation of sulphides under aprotic conditions by 2-arenesulphonyl-3-aryloxaziridines **75**. The reaction (equation 41) is instantaneous at room temperature giving sulphoxides in yields exceeding 80% (equation 41). The structure of oxaziridine is decisive in this reaction. Thus, the stable oxaziridines **76** were found to give the sulphoxides in a very low yield (5–7%) only. Moreover *E*-2-*t*-butyl-3-phenyl oxaziridine **77** failed to undergo any detectable reaction with methyl *p*-tolyl sulphide even on heating for more than 48 h at 60 °C[138]. The rapid oxidation of sulphides by oxaziridine **75** is therefore due to the presence of the 2-arenesulphonyl group which apparently increases the electrophilicity of the oxaziridine oxygen atom. As a result, the first step of the oxidation, namely a nucleophilic attack by the sulphur atom on the oxaziridine oxygen atom, is strongly accelerated[114,138].

$$Ar^2SO_2N{-}CHAr^1 + R^1{-}S{-}R^2 \longrightarrow R^1{-}\overset{\overset{O}{\|}}{S}{-}R^2 + Ar^2SO_2N{=}CHAr^1 \qquad (41)$$

(**75**)



(**76**)



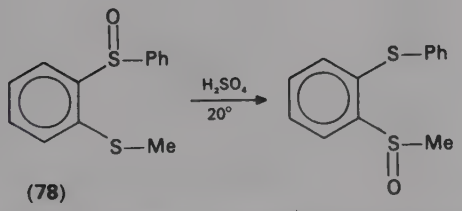
(**77**)

R = *t*-Bu, *c*-Hex

Intermolecular exchange of the sulphinyl oxygen atom between sulphoxide and sulphide (equation 42) may also have preparative value, at least in some special cases. Thermal, non-catalyzed exchange, usually between dimethyl sulphoxide as the oxygen donor and various sulphides, occurs above 160 °C and gives the corresponding sulphoxides in moderate to high yields[139,140]. This reaction is subject to acid catalysis[140]. For example, di-ω-alkanesulphinyl alkanes were prepared in 25–85% yield by the oxidation of the corresponding sulphides with dimethyl sulphoxide in the presence of 2–

6 mol% of hydrogen chloride[141]. Another example is the intramolecular oxygen exchange reaction in sulphoxide **78** which occurs at room temperature in the presence of sulphuric acid[142] (equation 43). Oxidation of sulphides to sulphoxides by 3-iodosylbenzoic acid is highly selective in the presence of dichlorotris(triphenylphosphine)ruthenium[143]. Selective oxidation of sulphides by iodosobenzene catalyzed by manganese/or iron(III) tetraphenylporphynato complexes was also recently described[144].

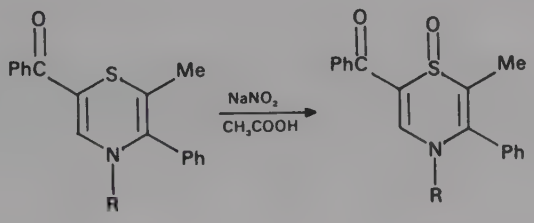
$$R^1—\overset{\overset{O}{\|}}{S}—R^2 + R^3_2S \longrightarrow R^3—\overset{\overset{O}{\|}}{S}—R^3 + R^1—S—R^2 \qquad (42)$$



(43)

(78)

Interesting oxidation of thiazines **79** with sodium nitrite in acetic acid was found to give the corresponding sulphoxides **80** in 67% yield[145] (equation 44).



(44)

(79) **(80)**

B. Cooxidation of Alkenes and Thiols

Kharasch and coworkers[146] were the first to show that thiols and olefins cooxidize in an atmosphere of oxygen at room temperature to yield substituted 2-sulphinylethanols **81** (equation 45). Later on, it was demonstrated that α-mercapto-substituted hydroperoxides are formed as intermediates. Thus, Oswald[147] found that cooxidation of thiophenol with styrene gave the corresponding β-mercaptohydroperoxide **82** which subsequently underwent rearrangement to 2-phenylsulphinyl-α-phenylethanol **83** (equation 46).

$$R—CH=CH_2 + R'SH \xrightarrow{O_2} R'\overset{\overset{O}{\|}}{S}CH_2\underset{\underset{OH}{|}}{CHR} \qquad (45)$$

(81)

$$PhCH=CH_2 \xrightarrow[O_2]{PhSH} PhCH(OOH)CH_2SPh \longrightarrow PhCH(OH)CH_2\overset{\overset{O}{\|}}{S}Ph \qquad (46)$$

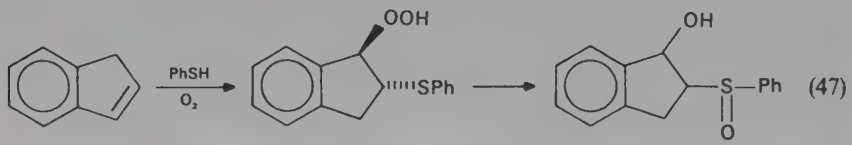
(82) **(83)**

TABLE 7. Formation of β-hydroxysulphoxides, $RCH(OH)CH_2—SOR^1$, via cooxidation of alkenes, $RCH=CH_2$, and thiols, R^1SH

R	R^1	Conditions	Yield (%)	Ref.
$AcOCH_2$	*p*-ClC_6H_4	FL[a]	92	151
$AcOCH_2$	Ph	FL[a]	54	151
$HOCH_2$	*p*-Tol	FL[a]	90	151
$PhOCH_2$	*p*-Tol	FL[a]	80	151
$ClCH_2$	*p*-Tol	FL[a]	79	151
$PhCH_2$	*p*-Tol	FL[a]	83	151
n-Pr	*p*-Tol	V_2O_5[b]	67	151
n-Pr	*p*-Tol	$VO(acac)_2$[b]	66	151
Ph	Ph	$X^c(acac)_2$[b]	23	151
Ph	*p*-Tol	X[c]	73	150
Ph	$PhCH_2$	X[c]	21	150
Ph	*t*-Bu	X[c]	36	150
CN	Ph	X[c]	96	150

[a]Irradiation with a black-light fluorescent lamp.
[b]As catalyst.
[c]Reaction carried out using sodium chloride or potassium bromide as catalysts.

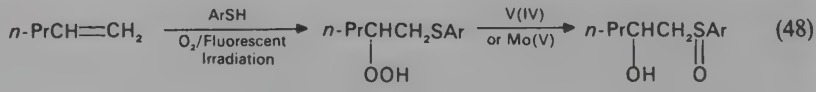
The cooxidation of thiophenol with indene by air in hydrocarbon solvents provides 1-hydroperoxy-2-phenylthioindane **84** in 77% yield. Subsequent rearrangement afforded a mixture of *trans* and *cis* 2-phenylsulphinyl-1-indanols **85**[148,149] (equation 47).



(47)

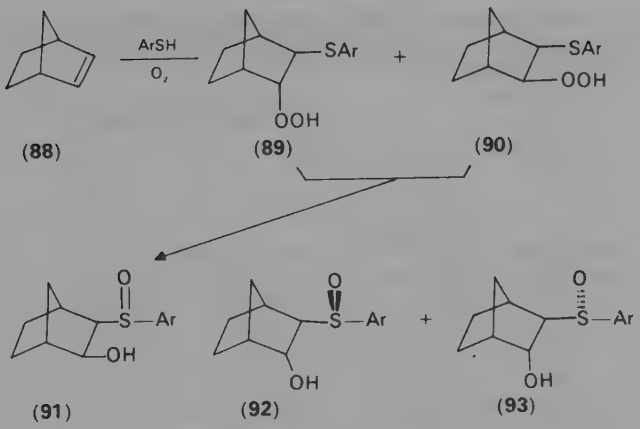
(84) **(85)**

The cooxidation reaction is strongly accelerated by chloride and bromide ions[150]. Tsuchihashi and coworkers[151] reported that irradiation with a black-light fluorescent lamp is effective and most suitable for the direct cooxidation of arenethiols and α, β-unsaturated nitriles and unsaturated allylic esters affording the corresponding β-hydroxysulphoxides (Table 7). On the other hand, the cooxidation of pentene-1 and aromatic thiols with simultaneous fluorescent irradiation afforded the corresponding β-hydroperoxy sulphides **86** in good yields. It was found that these peroxides can be converted into hydroxysulphoxides **87** by stirring the reaction mixture in the presence of catalytic amounts of vanadium(IV) or molybdenum(V) complexes (equation 48). The stereochemistry of this reaction was a subject of detailed investigations of Beckwith and coworkers[152] who established that norbornene **88** and *p*-toluenethiol interact in the presence of oxygen by a free radical chain mechanism to give a mixture of isomeric



(48)

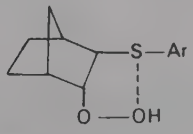
(86) **(87)**



SCHEME 1

hydroperoxy sulphides **89** and **90** which, on rearrangement, gave the corresponding hydroxy sulphoxides as major products. Of the two possible diastereoisomeric exo, exo hydroxy sulphoxides, only one (**91**) was detected. On the other hand, both of the possible diastereoisomeric endo, exo compounds **92** and **93** were detected, but one was formed in very much higher yield than the other (Scheme 1).

These results may easily be rationalized by assuming that the formation of hydroxy sulphoxides **91**, **92** and **93** from hydroperoxysulphides **89** and **90** is an intramolecular oxidation–reduction reaction proceeding through a five-membered transition state **94**. However, an alternative intermolecular mechanism in which the approach of the oxidant is directed by the hydroperoxy or the hydroxy function in the reductant cannot be excluded.



(94)

C. Reaction of Organometallic Compounds with Sulphurous Acid Derivatives

Strecker[153] reported in 1910 that the reaction of thionyl chloride with two equivalents of phenylmagnesium bromide or benzylmagnesium bromide afforded diphenyl or dibenzyl sulphoxides, respectively (equation 49; Table 8). The corresponding sulphides are formed as by-products of this reaction. Recently, other sulphoxides were prepared by this procedure[154,155]. It should be pointed out that this rather simple approach to the synthesis of symmetrical sulphoxides has not yet found wider application.

$$2RMgX + SOCl_2 \longrightarrow R{-}\underset{\underset{O}{\|}}{S}{-}R \qquad (49)$$

Strecker[153] was also the first to show that diethyl sulphite reacts with two equivalents of Grignard reagent in ether solution to yield symmetrical sulphoxides (equation 50). Bert[156]

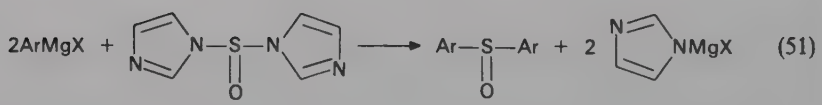
TABLE 8. Formation of sulphoxides, $R_2S{=}O$, from the reaction of Grignard reagents with sulphurous acid derivatives, SOX_2

X	R	Yield (%)	Ref.
Cl	Ph	*a*	153
Cl	$PhCH_2$	*a*	153
Cl	$c\text{-}C_6H_{11}$	85	154
Cl	$p\text{-}MeOC_6H_4$	42	154
OEt	Ph	*a*	153
OEt	$PhCH_2$	*a*	153
OBu-*n*	Ph	40	157
OPh	Ph	74	157
Im[b]	Ph	35	158
Im[b]	$p\text{-}MeC_6H_4$	40	158
Im[b]	$p\text{-}MeOC_6H_4$	60	158
Im[b]	$2,4,6\text{-}Me_3C_6H_2$	84	158
Im[b]	$p\text{-}Me_2NC_6H_4$	50	158

[a]Not given.
[b]*N*-Imidazoyl.

has recommended the use of di-*n*-butyl sulphite as a starting material for the preparation of sulphoxides. However, Gilman and coworkers[157] prepared diphenyl sulphoxide only in 40% yield using this sulphite and found that the reaction of diphenyl sulphite with phenylmagnesium bromide gave diphenyl sulphoxide in 74% yield. Symmetrical diaryl sulphoxides were prepared by Bast and Andersen[158] by the reaction of *N*,*N*-thionyl diimidazole **95** with appropriate Grignard reagents (equation 51).

$$2RMgX + (EtO)_2SO \longrightarrow R{-}\underset{\underset{O}{\|}}{S}{-}R + 2EtOMgX \qquad (50)$$



(**95**)

D. Reaction of Organometallic Compounds with Sulphinic Acid Derivatives

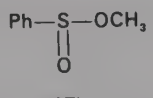
1. Sulphinic acid esters

Gilman and coworkers[157] first reported that the reaction between *p*-toluenesulphinates **96** and Grignard reagents produced sulphoxides in about 60% yield (equation 52).

$$p\text{-Tol}{-}\underset{\underset{O}{\|}}{S}{-}OR + R^1MgX \longrightarrow p\text{-Tol}{-}\underset{\underset{O}{\|}}{S}{-}R^1 + ROMgX \qquad (52)$$

(**96**) R = Et, *n*-Bu; R^1 = Ph, $PhCH_2$

Detailed study of the reaction of methyl benzenesulphinate **97** and two cyclic sulphinates **98** and **99** with a number of Grignard reagents was carried out by Harpp and coworkers[159].



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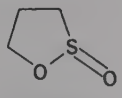

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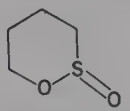
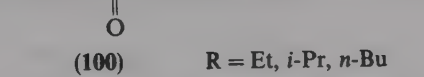


(99)

It was found that all the reactions gave the corresponding sulphoxides in moderate to good yields, but the conditions must be very carefully selected, otherwise considerable quantities of sulphides and other impurities are formed. The presence of the impurities can make purification of the reaction products difficult and thus severely limits the synthetic utility of the reaction. It was also indicated that the use of organocopper reagents in place of the Grignard compounds is advantageous and leads to sulphoxides in higher yields.

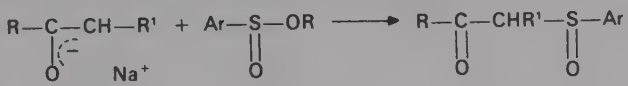
Reaction of alkyl phenylmethanesulphinates **100** with *n*-butyllithium in tetrahydrofuran at $-80\,^{\circ}C$ afforded the corresponding benzyl *n*-butyl sulphoxide[160] (equation 53). Preparation of optically active sulphoxides by this reaction will be discussed later in this chapter.



(53)

(100) R = Et, *i*-Pr, *n*-Bu

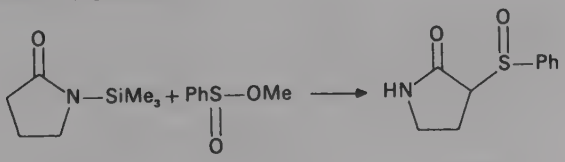
As an extension of the reaction of sulphinates with organometallic compounds, the Claisen-type condensation between ketone enolate anions **101** and arenesulphinates may be considered. It was found[161,162] that this reaction provides an interesting synthetic approach to α-ketosulphoxides **102** (equation 54; Table 9).



(54)

(101) **(102)**

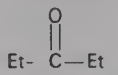
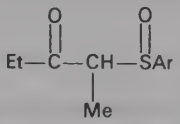
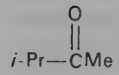
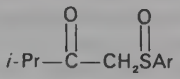
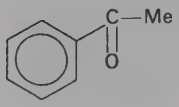
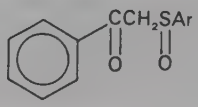
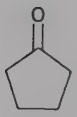
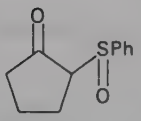
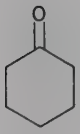
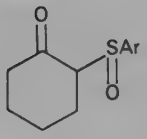
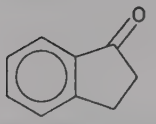
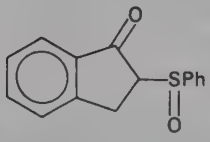
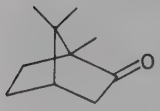
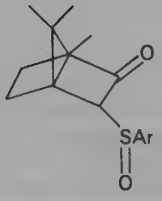
Direct sulphinylation of 1-trimethylsilyl-2-pyrrolidone **103** with methyl benzenesulphinate was found to give the sulphoxide **104** in 67% yield[163] (equation 55). Few sulphinylsulphones **105** were prepared by treatment of arylsulphinates with the carbanions generated from dimethyl[164] or methyl *p*-tolyl sulphones[162] (equation 56). The hydrolytically and thermally unstable α-silylmethyl sulphoxides **106** were prepared[165] in high yield by the reaction of methyl arenesulphinates with the Grignard reagent obtained from halomethyltrialkylsilanes (equation 57). It was found[166] that the sulphoxide **106a** is sufficiently stable for study of its metallation provided care is taken in its preparation and it is stored at temperatures below 0 °C. It is interesting that trimethylgermylmethyl phenyl sulphoxide **107**, prepared in 78% yield in a similar way to its silicon analogue, was found to be thermally stable[165] (equation 58).

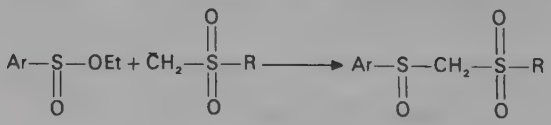


(55)

(103) **(104)**

TABLE 9. α-Ketosulphoxides from the reaction of methyl arenesulphinates, ArSOOMe, with carbonyl compounds

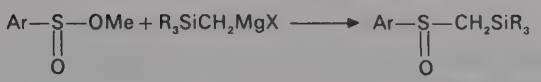
Carbonyl compounds	Ar	α-Ketosulphoxide	Yield (%)	Ref.
	Ph		77	162
	p-Tol		65	161
	*p*-Tol		52	161
	Ph		70	162
	p-Tol		57	161
	Ph		74	161
	*p*-Tol		74	162
	Ph		49	161
	Ph		60	162
	Ph		50	162
	p-Tol		67	161



(56)

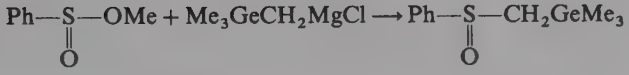
(105)

R = Me or *p*-Tol



(57)

(106) (a) Ar = Ph
(b) Ar = *p*-Tol

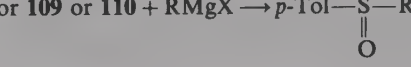


(58)

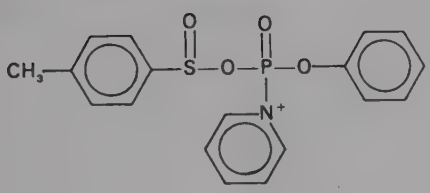
(107)

2. Mixed anhydrides of sulphinic acids

Few racemic alkyl *p*-tolyl sulphoxides were prepared in rather low yields (16–40%) by the reaction of Grignard reagents with mixed anhydrides **108**, **109** and compound **110** formed *in situ* from *p*-toluenesulphinic acid and 3-phthalimidoxy-1,2-benzoisothiazole 1,1-dioxide[167] (equation 59). The mixed anhydrides **109** or **110** when reacted with cyclopentene and cyclohexene enamines **111** gave the corresponding α-ketocycloalkyl sulphoxides **112** in low yields (10–41%) along with small amounts of several by-products such as disulphides and thiosulphonates[167] (equation 60).



(59)



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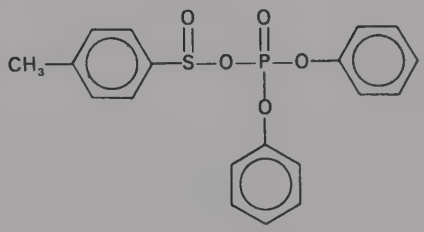

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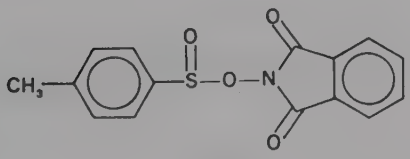

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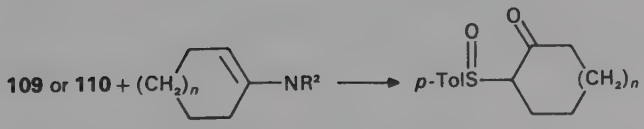


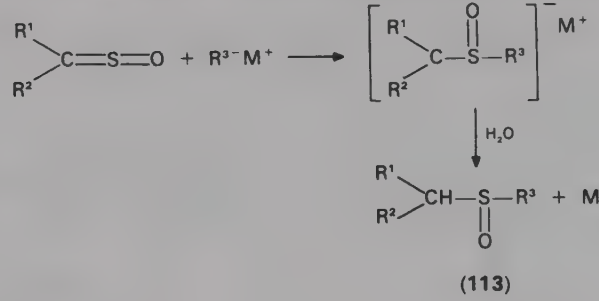
(60)

(111) (a) $n = 0$
(b) $n = 1$

(112)

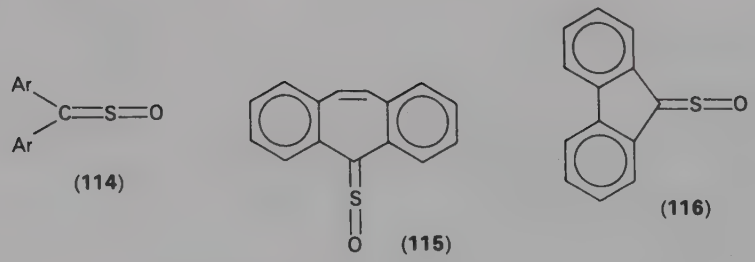
3. Sulphines

Addition of organometallic compounds to sulphines should lead to the formation of sulphoxides **113** (equation 61). Schultz and Schlessinger[168] and Venier and coworkers[169] studied the reaction of diaryl sulphines **114** as well as the sulphines **115** and **116** derived from dibenzotropone and fluorenone, respectively, with alkyl and aryllithium reagents. They found that treatment of **114** and **115** with an equivalent of the lithium reagent in benzene solution at 25° gave the corresponding sulphoxides in 70–80% yields, whereas the reaction of methyllithium with sulphine **116** gave a mixture of various products from which the expected sulphoxides were isolated in a low yield. On the other hand, the reaction of **116** with *n*-butyllithium was more efficient and gave *n*-butyl-(9-fluorenyl)sulphoxide in 65% yield[169]. A series of α-substituted sulphoxides containing functional groups such as CH_2SOMe, CH_2CN and $CH(Et)CONEt_2$ were prepared by the Zwanenburg group from diaromatic sulphines and the appropriate carbanions[170] Zwanenburg and coworkers[171] have also described the synthesis of dithioacetal *S*-oxides **118a** and α-sulphonyl sulphoxides **118b** which result from the reaction between sulphines **117** and alkyllithium reagents (equation 62). The reaction of thioketene *S*-oxides **119** with phenyllithium is, however, less effective and leads to the formation of α,β-unsaturated sulphoxides **120** in low (20–35%) yields[172] (equation 63). Treatment of sulphine **121** with the Grignard reagents or organolithium compounds derived from sulphones, ketones or nitriles afforded α,β-unsaturated-α-thiomethyl sulphoxides **122**[173] (equation 64).

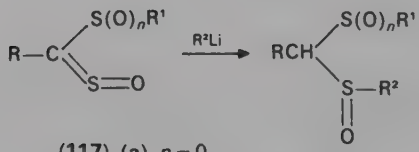


(61)

(113)

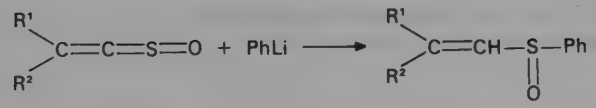


(114) (115) (116)

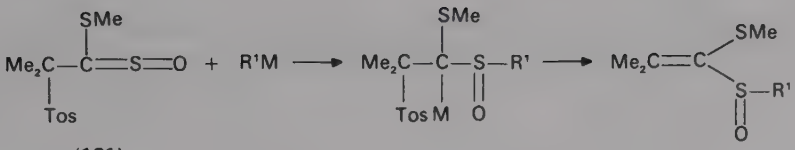


(62)

(117) (a) $n = 0$ (b) $n = 2$ (118) (a) $n = 0$ (b) $n = 2$



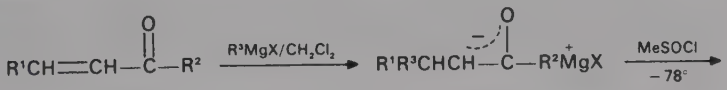
(119) (120) (63)



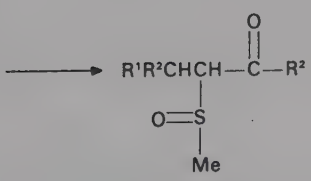
(121) (122) (64)

4. Sulphinyl chloride

Few α-ketosulphoxides **123** were prepared by trapping the enolate anions **124**, which are generated by the Michael addition of Grignard reagents to easily available α, β-unsaturated carbonyl compounds **125**, with methanesulphinyl chloride[174] (equation 65).



(125) (124)

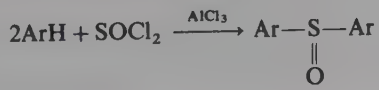


(123) (65)

E. Reaction of Aromatic Derivatives and Compounds Containing Active Hydrogen with Sulphinyl Chlorides

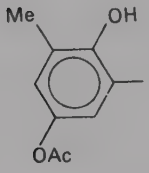
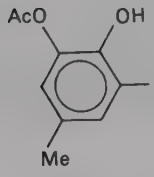
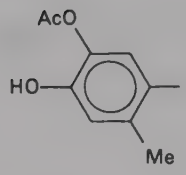
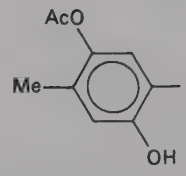
1. Thionyl chloride

In 1887 Colby and McLaughlin[175] found that treatment of benzene with thionyl chloride in the presence of aluminium trichloride produces diphenyl sulphoxide probably via benzenesulphinyl chloride. Later on, some other diaryl sulphoxides were prepared by this procedure[176–180] (equation 66; Table 10). Highly reactive aromatic compounds such as naphthyl ethers react with thionyl chloride in the absence of a catalyst[181].



(66)

TABLE 10. Diaryl sulphoxides, Ar_2SO, from aromatic compounds and thionyl chloride in the presence of $AlCl_3$

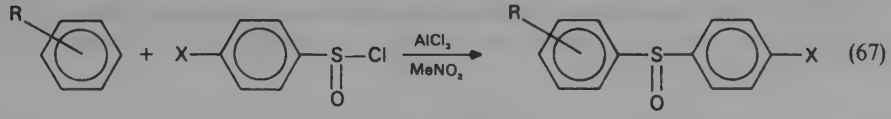
Ar	Yield (%)	Ref.
Ph	50	176
p-ClC_6H_4	*a*	177
p-MeC_6H_4	*a*	178
p-FC_6H_4	75	180
	*a*	179
	*a*	179
	*a*	179
	*a*	179

[a]Not given.

2. *Sulphinyl chlorides*

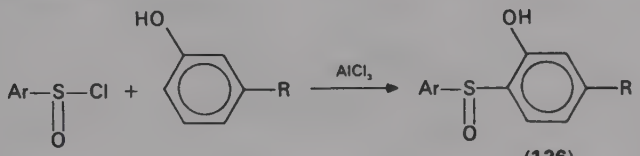
In spite of the fact that phenyl *p*-tolyl sulphoxide had been prepared[182] from benzene and *p*-toluenesulphinyl chloride as long ago as 1926, the preparation of sulphoxides by the reaction of aromatic compounds with sulphinyl chlorides is relatively unexplored. Douglas and Farah[183] reported a 26% yield of methyl phenyl sulphoxide from benzene and methanesulphinyl chloride in the presence of aluminium trichloride. Olah and Nishimura[184] carried out detailed investigation of the aluminium chloride catalyzed arenesulphinylation of benzene and polymethylbenzenes in nitromethane (equation 67). It was found that the reaction is of high selectivity, indicating that the sulphinylating agent is

obviously a very weak electrophile. These observations are in contrast with the previously reported data on sulphonylation and indicate the different nature of both reactions.



(67)

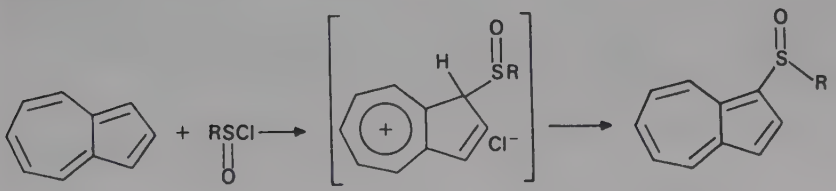
Hydroxy substituted diaryl sulphoxides **126** were prepared by the condensation of *m*-substituted phenols with arenesulphinyl chlorides in the presence of aluminium trichloride[185] (equation 68).



(68)

(126)

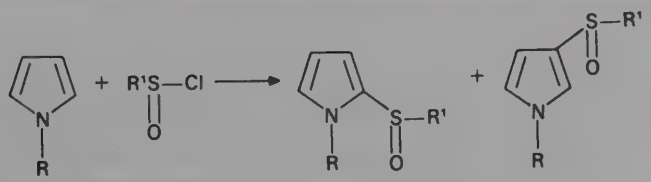
1-Azulyl sulphoxides **127** have also been prepared by a reaction involving a direct electrophilic substitution on the azulene ring by alkane- or arenesulphinyl chlorides[186] (equation 69). Preparation of the methyl and phenyl sulphoxides of 4, 6, 8-trimethylazulene and 4, 6, 8-tri-isopropylazulene by this method resulted in fair yields (57–72%). However, the substitution on azulene itself gave only low yields of the corresponding sulphoxides.



(69)

(127)

Reaction of pyrrole and *N*-methylpyrrole **128** with arene and alkanesulphinyl chlorides gave the corresponding 2-sulphinylpyrroles **129** as major products only when their interaction with the hydrogen chloride formed was eluded[187] (equation 70). When this precaution was not taken the sulphoxides **129** underwent a remarkably facile acid-promoted rearrangement to the isomeric 3-sulphinylpyrroles **130**. Whereas the formation of 3-substituted **130** could not be prevented when sulphinyl chlorides were used, (*N*-phenylsulphinyl)succinimide **131a** reacted with a variety of pyrroles **128** in dichloromethane at room temperature to give the corresponding 2-sulphinylpyrroles **129** in good yields

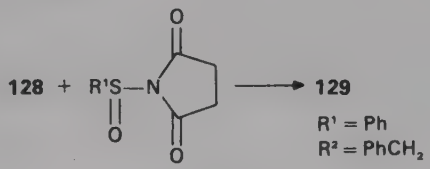


(70)

(128) (a) R = H
(b) R = Me

(129) **(130)**

(equation 71). In contrast to the imide **131a**, (*N*-phenylmethanesulphinyl) succinimide **131b** did not react with pyrroles **128** at room temperature. However, at 72 °C in benzene this reaction occurred and 2-phenylmethanesulphinylpyrroles **129** could be isolated in a low yield. Reaction of compounds **132** containing active hydrogen atoms with sulphinyl chlorides may also be considered as a method for the synthesis of α-substituted sulphoxides **133** (equation 72).



(71)

(131) **(a)** $R^1 = Ph$

(b) $R^1 = PhCH_2$

(72)

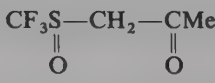
(132) **(133)**

Up to now this possibility was applied for the preparation of α-ketosulphoxides. The first formation of α-ketosulphoxides in the reaction between a ketone and sulphinyl chloride was reported by Oae and Ikura[188] in 1966. They prepared *p*-nitrobenzenesulphinyl chloride and identified it by means of its reaction product with acetone which had the analytical composition of α-sulphinylacetone **134** (equation 73).

(73)

(134)

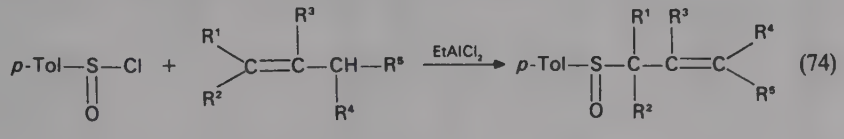
It was reported[189] later that *o*-nitrobenzenesulphinyl chloride reacts with acetone, acetophenone,and dimedone giving the corresponding α-sulphinylketones in about 80% yield. Unstable trifluoromethylsulphinylacetone **135** was generated *in situ* in the reaction between trifluoromethanesulphinyl chloride and acetone which served both as reactant and solvent[190].



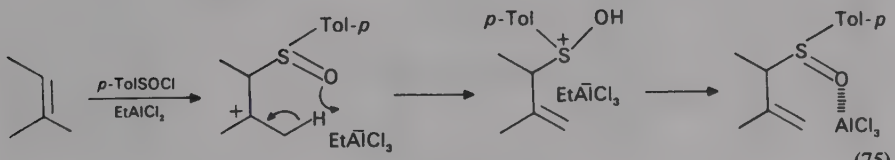
(135)

The ethylaluminium dichloride-catalyzed reaction of *p*-toluenesulphinyl chloride with alkenes **136** successfully applied[191] for the synthesis of allylic sulphoxides **137** (equation 74) may also be regarded formally as a reaction of sulphinyl chlorides with compounds containing active hydrogen atom. Treatment of an alkene **136** with one equivalent each of ethylaluminium dichloride and *p*-toluenesulphinyl chloride at room temperature gave the corresponding **137**. This reaction is very general and proceeds in

good yields with a variety of alkenes. Mechanistically, it may formally be classified as an ene reaction which proceeds through the intermediates shown in equation 75. The proposed mechanism was supported by the fact that α-pinene, which easily undergoes concerted ene reactions, gave a complex mixture of products arising from rearrangement of the intermediate carbocation.



(136) (137) (74)



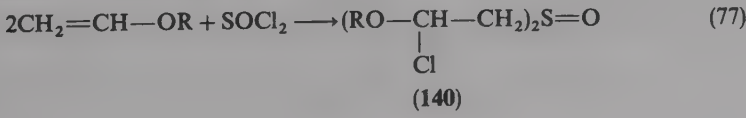
(75)

The addition of sulphinyl chlorides to trimethylsilyl enol ether **138** affording α-ketosulphoxides **139** (equation 76) represents an extension of the reaction of sulphinyl chlorides with ketones. This reaction has attracted attention only recently. Sergeev and coworkers[192] reported that treatment of sulphinyl chlorides with acyclic enol ethers afforded α-ketosulphoxides **139** in good to excellent yields. Meanwell and Johnson[193] observed that in the case of cyclic enol ethers the corresponding sulphoxides were formed only in very low yields. They found, however, that the introduction of an equivalent amount of a Lewis acid into the reaction mixture markedly promotes the desired reaction, whereas the use of catalytic amounts of a Lewis acid led to a substantial reduction in the yield. This is most probably due to the formation of a complex between the α-ketosulphoxide and the Lewis acid.

(138) (139) (76)

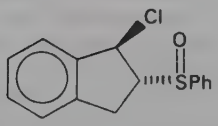
F. Addition of Sulphinyl Chlorides to Unsaturated Compounds

Thionyl chloride and enol ethers react to give high yields (Table 11) of di(β-chloro-β-alkoxyethyl)sulphoxides[194] **140** (equation 77). *p*-Toluenesulphinyl chloride and benzenesulphinyl chloride react with a variety of conjugated aromatic olefins in the presence of zinc chloride to give 1-chloro-1-phenyl-2-arenesulphinylethanes **141** in moderate to good yields[195] (equation 78; Table 11). The addition to indene occurs with anti stereochemistry to give *trans*-1-chloro-2-phenylsulphinylindene[195]. Benzenesulphinyl chloride reacts also with non-conjugated olefins under high pressure (2.5 kbar) to give the corresponding sulphinylethanes in very high yields[196].



(140) (77)

TABLE 11. *β*-Chlorosulphoxides from sulphinyl chlorides, RSOCl, and unsaturated compounds, $R^1CH{=}CH_2$

R	R^1	Sulphoxide	Yield (%)	Ref.
p-Tol	Ph	$PhCHCH_2STol\text{-}p$ (Cl, O)	40	195
Ph	Ph	$PhCHCH_2SPh$ (Cl, O)	80	195
Cl	EtO	$(EtOCHCH_2)_2S{=}O$ (Cl)	97	194
Cl	*n*-BuO	$(n\text{-}BuOCHCH_2)_2S{=}O$ (Cl)	80	194
Cl	*i*-BuO	$(i\text{-}BuOCHCH_2)_2S{=}O$ (Cl)	90	194
Ph	Indene		37	195

$$Ar{-}S{-}Cl + Ar^1CH{=}CH{-}R \xrightarrow{ZnCl_2} Ar^1{-}CH(Cl){-}CH(R){-}S{-}Ar \quad (78)$$

(141)

G. Addition of Sulphenic Acids to Unsaturated Compounds

t-Butanesulphenic acid generated thermally from di-*t*-butyl sulphoxide adds readily at room temperature to ethyl acrylate giving an adduct which was identified as ethyl *β*-(*t*-butanesulphinyl)propionate[197] **142** (equation 79). Addition of *t*-butanesulphenic acid to methyl propiolate gave bis-adduct **143** by a double addition–elimination reaction[197]. Block and O'Connor[198] showed that pyrolysis of alkane thiosulphinates affords alkanesulphenic acids which can be trapped by alkynes leading to *α*,*β*-unsaturated sulphoxides **144** in moderate to high yields (equation 80; Table 12).

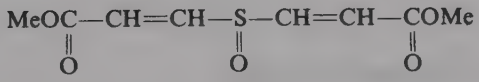
$$[t\text{-}Bu{-}S{-}OH \rightleftharpoons t\text{-}Bu{-}S(O){-}H] + CH_2{=}CHCO_2Et \longrightarrow t\text{-}BuS(O)CH_2CH_2CO_2Et \quad (79)$$

(142)

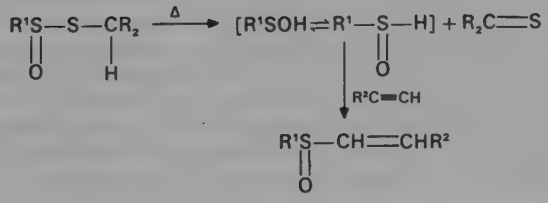
TABLE 12. Synthesis of *E*-α,β-unsaturated sulphoxides, $R^1S(O)CH{=}CHR^2$, by addition of sulphenic acids, R^1SOH, to alkynes, $R^2C{\equiv}CH$

Sulphenic acid precursor	R^1	R^2	Yield (%)	Ref.
MeS(O)SMe	Me	CO_2Me	65	198
EtS(O)SEt	Et	CO_2Me	76	198
i-PrS(O)SMe	*i*-Pr	CO_2Me	49	198
t-BuS(O)SBu-*t*	*t*-Bu	CO_2Me	56	198
EtS(O)SEt	Et	Ph	91	198
EtS(O)SEt	Et	C_5H_{11}-*n*	33	198
PhS(O)N=CHPh	Ph	CO_2Me	70	199
m-$XC_6H_4S(O)N{=}CHC_6H_4X$-*p*[a]	*m*-$NO_2C_6H_4$	CO_2Me	82	199
m-$XC_6H_4S(O)N{=}CHMe$[a]	*m*-$NO_2C_6H_4$	CO_2Me	72	199
$PhS(O)CH_2CH_2CN$	Ph	C_6H_{13}-*n*	94	200
$MeS(O)CH_2CH_2CN$	Me	C_6H_{13}-*n*	86	200
$PhS(O)CH_2CH_2CN$	Ph	CH_2OH	82	200
$PhS(O)CH_2CH_2CN$	Ph	CH_2SMe	52	200
$MeS(O)CH_2CH_2CN$	Me	CH_2SMe	50	200
$PhS(O)CH_2CH_2CN$	Ph	CH_2Br	36	200

[a] $X = NO_2$.



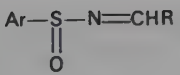
(143)



(80)

(144) $R^2 = CO_2Me$, Ph, n-C_5H_{11}

Davis and coworkers[199] found another convenient way to generate arenesulphenic acids by the thermolysis of *N*-alkylidenearenesulphinamides **145**. On heating **145** for 24 h at 80–115° in methyl propiolate or ethyl acrylate it afforded methyl *trans*-arenesulphinylacrylates **146** and ethyl arenesulphinylpropionate **147**, respectively, in high yields.



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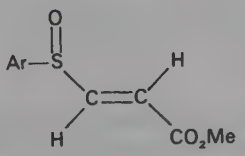
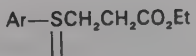


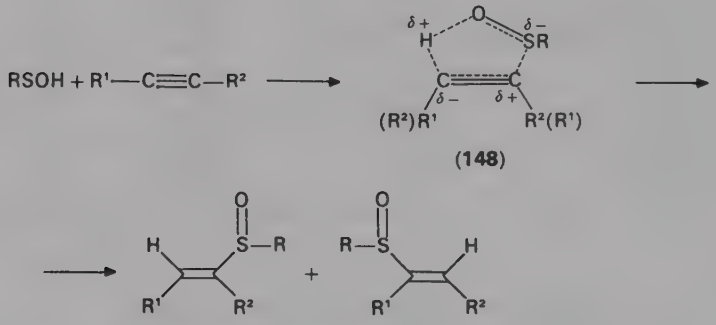
(146)



(147)

Jones and coworkers[200] found that a variety of sulphenic acids may be generated by thermolysis of the readily available β-cyanosulphoxides (equation 81) and observed their highly regiospecific addition also to non-conjugated alkynes (Table 12). As expected for a pericyclic mechanism, the reaction afforded the product of a stereospecific *cis*-addition. However, the regioselectivity of the addition suggests that the partial carbon–sulphur bond in the transition state **148** is polarized in such a way that the carbon atom has some cationic character (equation 82).

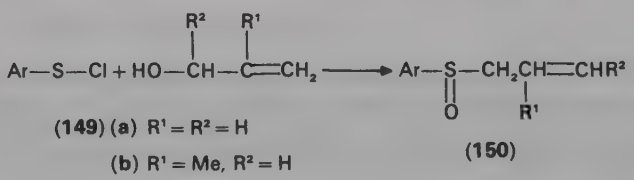
$$R{-}\underset{\underset{O}{\|}}{S}CH_2\underset{\underset{H}{|}}{C}HCN \longrightarrow RSOH + CH_2{=}CHCN \tag{81}$$



(82)

H. Rearrangement of Sulphenic Acid Esters

The spontaneous rearrangement of allyl *p*-toluenesulphenates to allyl sulphoxides was independently recorded by Mislow and coworkers and Braverman and Stabinsky. Mislow and colleagues[201] have demonstrated that simple allyl alcohols such as **149**, on conversion to the corresponding lithium alkoxides followed by treatment with arenesulphenyl chlorides, may be smoothly transformed at room temperature via the sulphenate esters into allylic sulphoxides **150** (equation 83). Braverman and Stabinsky[202] have found that when the more reactive trichloromethanesulphenyl chloride is treated with allyl alcohol and pyridine in ether at $-70°$, it affords trichloromethyl allyl sulphoxide and not allyl trichloromethanesulphenate as reported by Sosnovski[203] (equation 84).

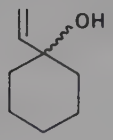
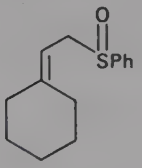
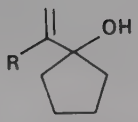
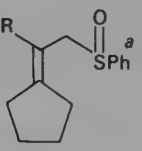
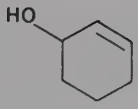
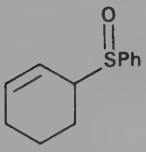
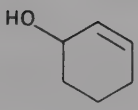
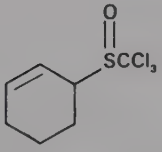


(83)

$$Cl_3C{-}SCl + CH_2{=}CH{-}CH_2OH \xrightarrow[-70°]{C_5H_5N} Cl_3C{-}\underset{\underset{O}{\|}}{S}CH_2{-}CH{=}CH_2 \tag{84}$$

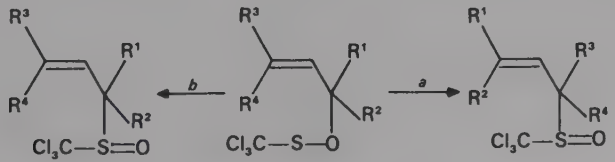
The allyl sulphenate–allyl sulphoxide rearrangement is a general reaction and is applicable to structurally diverse allyl alcohols[204,205] (Table 13). Mechanistically, it represents a typical example of a [2, 3]-sigmatropic rearrangement as shown by the detailed investigations of Mislow and Braverman and their coworkers.

TABLE 13. Synthesis of allyl sulphoxides from sulphenyl chlorides, RSCl, and allyl alcohols

R	Alcohol	Sulphoxide	Yield (%)	Ref.
Ph			80	204
Ph			80	204
Ph			80	204
Cl_3C			*b*	205
Me	$CH_2{=}CHCH_2OH$	$MeSCH_2CH{=}CH_2$ O	*b*	205
Cl_3C	$CH_2{=}CHCH_2OH$	$Cl_3CSCH_2CH{=}CH_2$ O		202

[a]R = H or Me.
[b]Not given.

Braverman and Grendi[206] have shown that, depending on the type of substitution, allylic trichloromethanesulphenates undergo rearrangement to allylic trichloromethyl sulphoxides by one of two different pathways (equation 85). Rearrangement according to route *a* has been observed with allyl, crotyl and α,α-dimethylallyl sulphenates. It occurs



(85)

spontaneously at low temperature and it is reversible and believed to proceed by a concerted intramolecular mechanism. On the other hand, the corresponding cinnamyl and γ,γ-dimethylallyl esters have been found to form the sulphoxides via route *b*. This process takes place only at higher temperatures and could be explained by a dissociation–recombination mechanism. The conversion of benzyl *p*-toluenesulphenate to benzyl *p*-tolyl sulphoxide, which requires temperature above 110 °C, may also be considered to take place by such a mechanism[201].

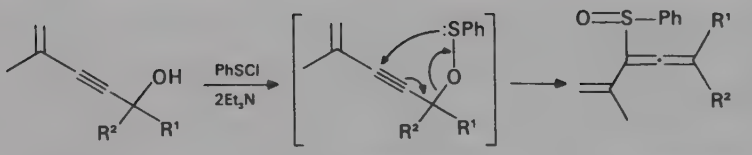
Rearrangement of acetylenic sulphenates to the allenic sulphoxides **151** was discovered when the synthesis of propargylic ester of trichloromethanesulphenic acid **152** was attempted[207] (equation 86). This reaction is of general scope and gives very good yields of allenic sulphoxides (Table 14) from structurally diverse alcohols and various sulphenyl chlorides[208–210]. Reaction of alkynols **153** with benzenesulphenyl chloride in the presence of triethylamine afforded nearly quantitative yields of the corresponding allenic sulphoxides **154** via the initially formed sulphenate esters **155** which undergo a [2, 3]-sigmatropic propargylic rearrangement[211] (equation 87).

$$Cl_3C{-}S{-}Cl + HOCH_2{-}C{\equiv}CH \xrightarrow{C_5H_5N} [Cl_3C{-}SOCH_2C{\equiv}CH] \quad (86)$$

(152)

$$Cl_3C{-}\overset{\overset{O}{\|}}{S}{-}CH{=}C{=}CH_2$$

(151)

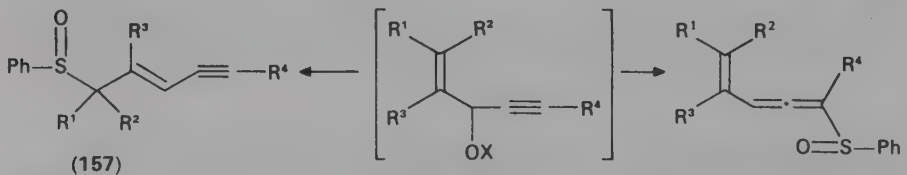


(87)

(153) (155) (154)

(a) $R^1 = R^2 = H$
(b) $R^1 = H$; $R^2 = Me$
(c) $R^1 = R^2 = Me$

Reaction of alkynols **156** with benzenesulphenyl chloride afforded either the vinylacetylene sulphoxides **157** or the allene sulphoxides **158** depending upon the substitution pattern of alkynols **156**. Vinylacetylene sulphoxides **157** result from a [2, 3]-allylic rearrangement of the sulphenate ester **159** (equation 88). In the case of the cyclic



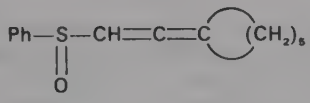
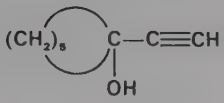
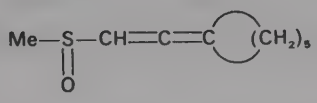
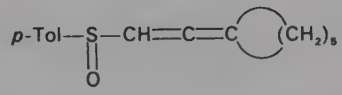
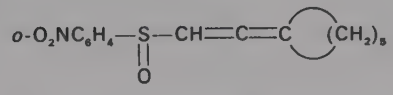
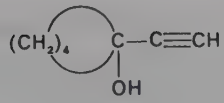
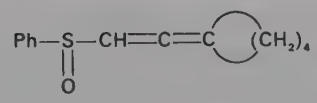
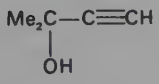
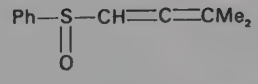
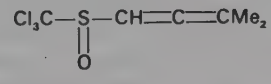
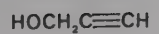
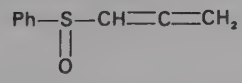
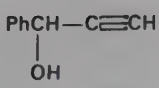
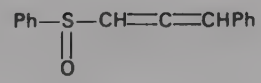
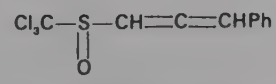
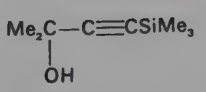
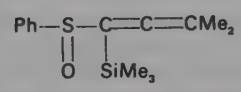
(157)

(156) X = H
(159) X = SPh

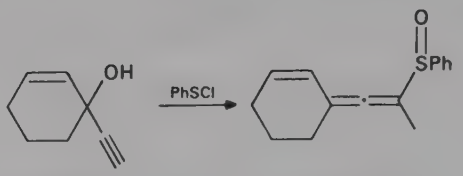
(158)

(88)

TABLE 14. Allenic sulphoxides from propargylic alcohols and sulphenyl chlorides, RSCl

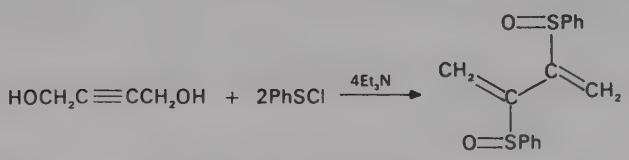
R	Alcohol	Sulphoxide	Yield (%)	Ref.
Ph			75	208
Me			30	208
p-Tol			73	208
o-$O_2NC_6H_4$			48.5	208
Ph			52	208
Ph			48	208
Cl_3C			75	207
Ph			50	208
Ph			50	207
Cl_3C			70	207
Ph			56	211

unsaturated alcohol **160** the vinylallene sulphoxide **161** was formed[210] as the only product (equation 89). The reaction of acetylenic diol **162** with two equivalents of benzenesulphenyl chloride afforded the corresponding unsaturated disulphoxide **163** in 76% yield[212] (equation 90).



(89)

(160) (161)

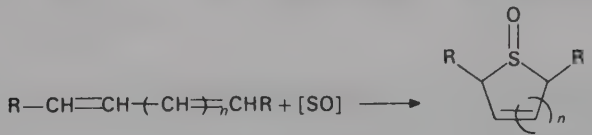


(90)

(162) (163)

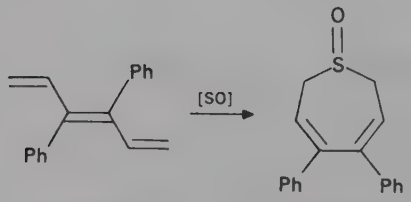
I. Cycloaddition of Sulphur Monoxide and Sulphines to Unsaturated Compounds

Dodson and Sauers[213] were the first to show that sulphur monoxide generated *in situ* by thermolysis of thiirane *S*-oxide could be trapped by dienes or trienes in the form of 2, 5-dihydrothiophene *S*-oxide **164a** or 2, 7-dihydrothiepin *S*-oxide **164b** (equation 91). For the reactions carried out in boiling toluene yields of the cyclic sulphoxides were usually in the range between 20 and 40%; equimolar amounts of isoprene and thiirane *S*-oxide in refluxing toluene gave 3-methyl-3 thiolene *S*-oxide in 83% yield[214]. A low yield (7%) of 4, 5-diphenyl-2, 7-dihydrothiepin-1-oxide **165** was observed when 3, 4-diphenyl-1, 3, 5-hexatriene **166** was reacted with sulphur monoxide[215] (equation 92). The thermal reaction of cyclooctatetraene and thiirane *S*-oxide in boiling xylene resulted in the formation (30% yield) of the cycloaddition product **167** to which the anti configuration was assigned[216].



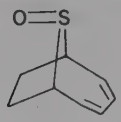
(91)

(164) (a) $n = 1$
(b) $n = 2$



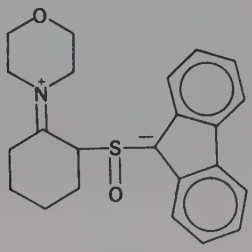
(92)

(166) (165)



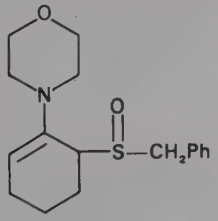
(167)

Due to the presence of a heterocumulene unit, sulphines may be considered as a group of compounds which are able to undergo cycloaddition reactions. Reaction of sulphines with enamines and phosphorus ylides reported by Sheppard[217] and Trippett[218] and their coworkers may be considered formally as an example of [2 + 2] cycloaddition. In fact, Sheppard and Dickman[217] obtained a 1:1 adduct from thiofluorenone *S*-oxide and 1-morpholinocyclohexene to which they assigned the dipolar sulphoxide structure **168**.

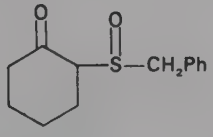


(168)

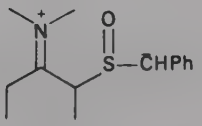
Phenylsulphine prepared *in situ* from phenylmethanesulphinyl chloride and triethylamine reacted with 1-morpholinocyclohexene to form the addition product **169** having the enamine structure[218]. A similar experiment with phenylsulphine and 2-pyrrolidinocyclohexene gave only 2-phenylmethanesulphinyl cyclohexanone **170**. The latter is most probably formed by hydrolysis of the corresponding enamine sulphoxide upon isolation. The reaction of sulphines with enamines is apparently a stepwise process involving the transient formation of the dipolar intermediate **171** which is stabilized by proton transfer, giving the enamine sulphoxide.



(169)



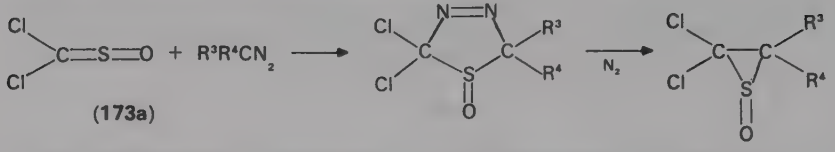
(170)



(171)

The possibility of a [2 + 3] cycloaddition of sulphines was first suggested by Zwanenburg and coworkers[219]. They obtained relatively stable dichloroepisulphoxide **172** from the reaction of dichlorosulphine **173a** with diazo compounds and proposed that it arises from the initially formed cycloaddition product **174** by nitrogen elimination (equation 93). The stability of the thiadiazoline *S*-oxides **174** strongly depends upon the nature of all substituents. Thus, the cycloaddition reaction of aromatic sulphines such as thiobenzophenone *S*-oxide and thiofluorenone *S*-oxide with diazopropane leads to thiadiazoline *S*-oxides in high yield. Diazomethane reacts more sluggishly and in most cases a complex mixture of various products was formed. Only thiofluorenone *S*-oxide

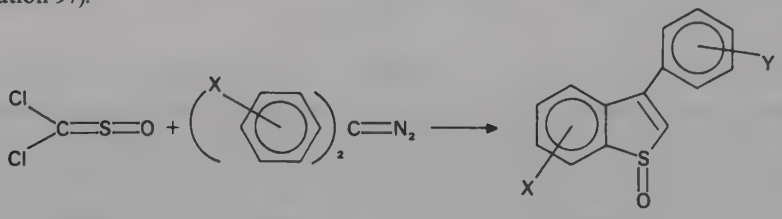
gave the expected cycloadduct in 50% yield[220,221].



(93)

(173a) (174) (172)

Treatment of dichlorosulphine **173a** with diaryldiazomethanes **175** gives derivatives of 2-chlorobenzo[*b*]thiophene *S*-oxide[222] **176** (equation 94). It was proposed that the reaction is initiated by a [2 + 3] dipolar cycloaddition reaction of dichlorosulphine **173a** affording thiadiazoline *S*-oxides **174a** which then lose nitrogen to form episulphoxides **177**. Spontaneous cyclization of the latter leads to the chlorosulphoxides **176** (equation 95). Diarylsulphines **173b**, when dissolved in aprotic solvents such as pentane or ether and treated with aryldiazomethanes **178**, gave smoothly the episulphoxides **179** in good yields[223] (equation 96). It was suggested that the reaction is a two-step process involving the formation of the diazonium intermediate **180** which undergoes cyclization by intramolecular nucleophilic attack, nitrogen being a leaving group. However, the formation of **179** via the thiadiazoline *S*-oxide intermediate cannot be excluded (equation 97).

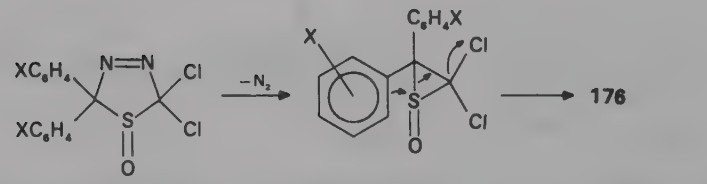


(94)

(173a) (175) (176)

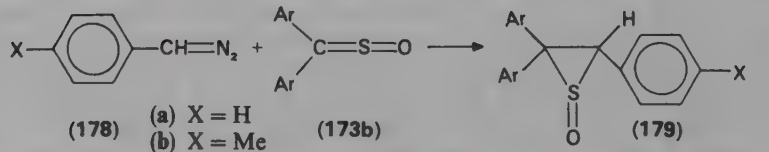
(a) X = H
(b) X = 4-Me
(c) X = 4-Cl
(d) X = 4-OMe
(e) X = 3-OMe

X	Y
(a) H	H
(b) 6-Me	4-Me
(c) 6-Cl	4-Cl
(e) 5-OMe	3-OMe



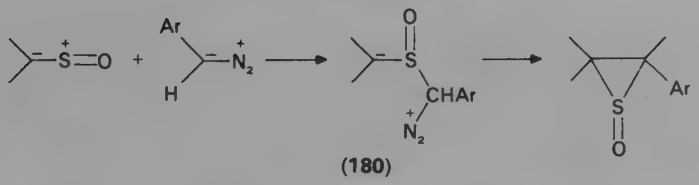
(95)

(174a) (177)



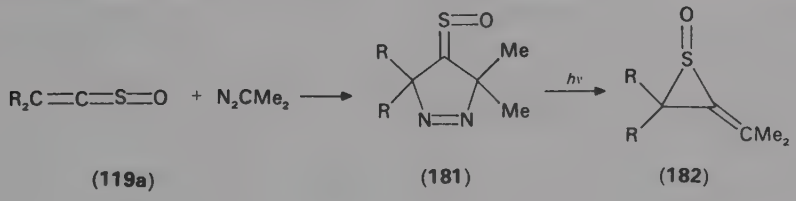
(96)

(178) (a) X = H (b) X = Me (173b) (179)

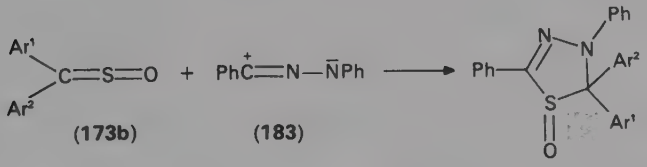


(180) (97)

Thioketene *S*-oxides **119a** react smoothly with diazopropane to give good to excellent yields of a 1:1 adduct **181** resulting from the [2 + 3] cycloaddition across the C=C bond of the heterocumulene[224]. Photolysis of this adduct in benzene or carbon tetrachloride results in rapid elimination of nitrogen and formation of episulphoxide **182** (equation 98). Heterocyclic compounds containing the sulphoxide function have also been prepared by [1 + 3] dipolar cycloaddition of sulphines to nitrilimines. Thus, diaryl sulphines **173b**, upon heating for two hours in boiling benzene with diphenylnitrilimine **183** [generated *in situ* by the action of triethylamine on *N*-(α-chlorobenzylidene)-*N'*-phenyl hydrazine], gave 1,3,4-thiadiazoline *S*-oxides **184** in 58–92% yields[225] (equation 99). The reaction of the pure geometrical isomers of unsymmetrical diarylsulphines **173b** ($Ar^1 \neq Ar^2$) with **183** in refluxing benzene gave either the same single diastereoisomeric adduct or a mixture of both diastereoisomers. However, it was demonstrated that the cycloaddition is completely stereospecific and that the steric integrity is lost by a ring opening–ring closure of the cycloaddition product **184**.



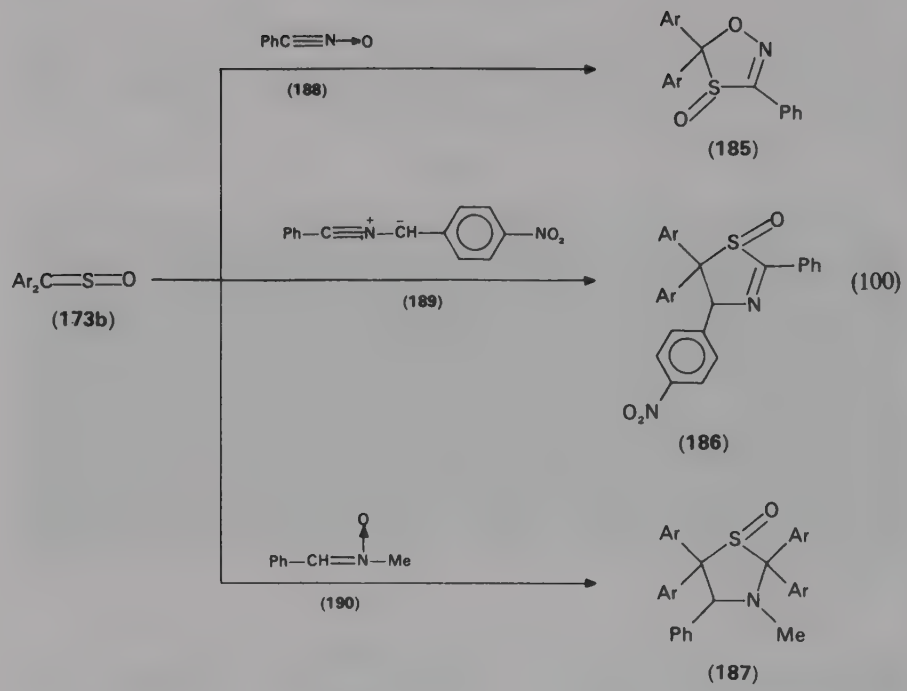
(119a) (181) (182) (98)

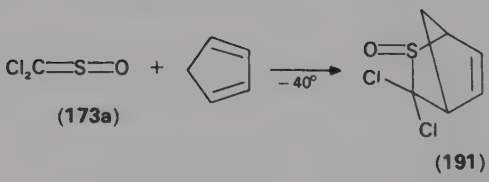


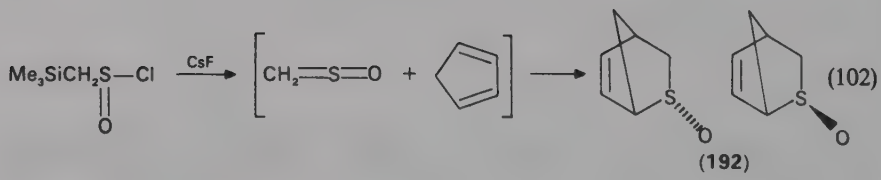
(173b) (183) (184) (99)

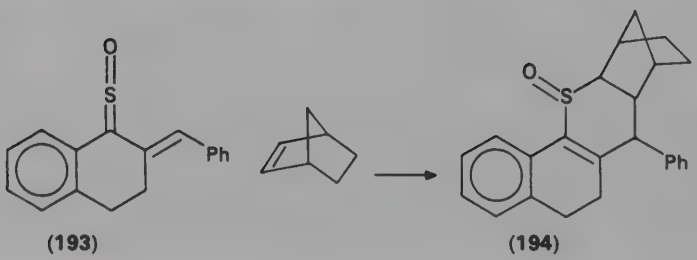
Heterocyclic sulphoxides of general structure **185**, **186** and **187** have been prepared by cycloaddition of diarylsulphines **173b** to nitrile oxides **188**[226], nitrile ylides **189**[227] and nitrones **190**[228], respectively (equation 100).

Sulphines may react as dienophiles with 1,3-dienes with the formation of cyclic sulphoxides. Unstable 2,2-dichloro-5,6-dihydro-2*H*-thiin-1-oxide **191** was formed in an exothermic reaction between **173a** and cyclopentadiene at −40 °C[219] (equation 101). The simplest, parent sulphine, $CH_2=S=O$, prepared *in situ* by treatment of α-trimethylsilylmethanesulphinyl chloride with cesium fluoride, reacts with cyclopentadiene to give bicyclic, unsaturated sulphoxide **192** as a mixture of two diastereoisomers in a 9:1 ratio[229] (equation 102). On the other hand, α,β-unsaturated sulphine **193** (generated by thermolysis of 2-benzylidene-1-thiotetralone dimer *S*-oxide) in boiling toluene behaves as a 1,3-diene and was trapped by norborene forming sulphoxide **194** in 78% yield[230] (equation 103).


PhC≡N→O
(188)
(185)
Ph—C≡N—CH—NO2
(189)
(186)
Ar2C=S=O
(173b)
(100)
(190)
(187)


Cl2C=S=O
(173a)
+
−40°
(191)
(101)


Me3SiCH2S—Cl
CsF
CH2=S=O
+
(192)
(102)


Ph
(193)
(194)
(103)

J. Hydrolysis of Sulphimines

Hydrolysis of sulphimines has rather limited application as a route to racemic sulphoxides. Hydrolysis of *S,S*-diethyl-*p*-toluenesulphonylsulphilimine **195** gave the corresponding sulphonamide and an oily substance believed to be diethyl sulphoxide because of a facile formation of diethyl sulphide upon reduction[231] (equation 104). Hydrolysis of unsubstituted dimethylsulphilimine and diethylsulphilimine is very rapid and gives the corresponding sulphoxides in high yields[232]. According to Oae and coworkers[233] alkaline hydrolysis of alkyl *p*-tolyl *N*-tosylsulphilimines **196** results in the predominant formation of α-alkoxyalkyl sulphides **197** (equation 105).

$$p\text{-TolSO}_2\text{N}{=}\text{SEt}_2 \xrightarrow{\text{H}_2\text{O}} p\text{-TolSO}_2\text{NH}_2 + \text{Et}_2\text{S}{=}\text{O} \qquad (104)$$

(195)

$$p\text{-Tol}{-}\underset{\underset{\text{NTos}}{\|}}{\text{S}}{-}\text{CHR}_2 \xrightarrow[\text{ROH}]{\text{OH}^-} p\text{-Tol}{-}\underset{\underset{\text{OR}'}{|}}{\text{S}}{-}\text{CR}_2 + p\text{-Tol}{-}\underset{\underset{\text{O}}{\|}}{\text{S}}{-}\text{CHR}_2 \qquad (105)$$

(196) **(197)**

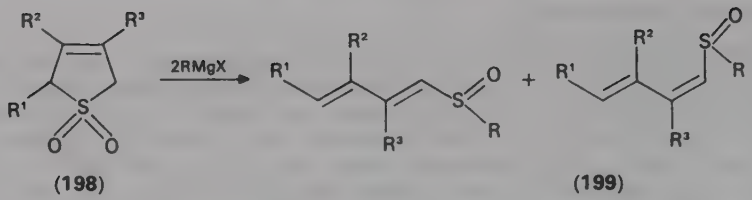
K. From Organic Sulphur Compounds of Higher Oxidation State

An interesting synthesis of sulphoxides involving the reaction of Grignard reagents with sulphonyl chlorides or ethyl chlorosulphonate was reported by Hepwort and Chapham[234] in 1921. They found that treatment of benzenesulphonyl chloride with an excess of phenylmagnesium bromide gave diphenyl sulphoxide as the major reaction product (equation 106). The reaction of ethyl chlorosulphate with PhMgBr, EtMgBr and $PhCH_2MgCl$ afforded the corresponding symmetrical sulphoxides in substantial quantities[234] (equation 107). The reaction of arenesulphonyl chlorides with trialkylaluminium or alkylaluminium chloride was found to give alkyl aryl sulphoxides together with the corresponding sulphides[235] (equation 108). It was reported that sulpholene **198** reacts with two moles of alkyl or arylmagnesium halides to produce isomeric butadienylic sulphoxides **199** in which the *Z*-configuration around the double bond α,β to sulphur predominated[236] (equation 109). Also bicyclic sulphones **200** afforded 1,4-dienylic sulphoxides **201** in 35–58% yield[236] upon treatment with two moles of phenylmagnesium bromide (equation 110). The formation of the dienylic sulphoxides **199** and **201** may be explained by the assumption that the reaction takes place in two steps. The first step is the formation of the sulphinate salt **202** through ring opening of an anion **203**, and the second involving the reaction with another Grignard molecule to form sulphoxides **199** or **201** (equation 111). The latter reaction is similar to that of sulphinic esters with Grignard reagents.

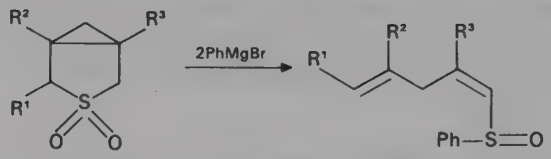
$$\text{PhSO}_2\text{Cl} + \text{PhMgBr} \longrightarrow \text{Ph}{-}\underset{\underset{\text{O}}{\|}}{\text{S}}{-}\text{Ph} \qquad (106)$$

$$\text{EtOSO}_2\text{Cl} + \text{RMgX} \longrightarrow \text{R}{-}\underset{\underset{\text{O}}{\|}}{\text{S}}{-}\text{R} \qquad (107)$$

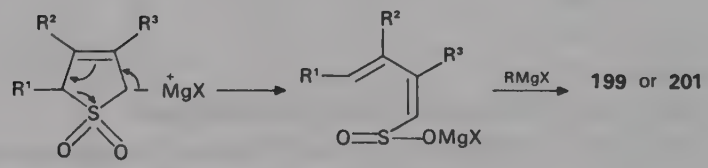
$$\text{ArSO}_2\text{Cl} \xrightarrow[\text{or } \text{R}_n\text{AlCl}_{3-n}]{\text{R}_3\text{Al}} \text{Ar}{-}\underset{\underset{\text{O}}{\|}}{\text{S}}{-}\text{R} + \text{Ar}{-}\text{S}{-}\text{R} \qquad (108)$$



(198) (199) (109)

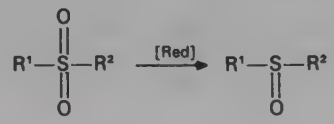


(200) (201) (110)

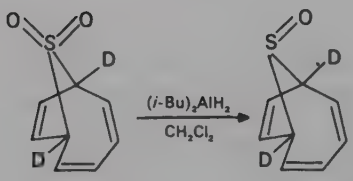


(203) (202) (111)

Since sulphones **204** are easily available compounds one would expect that they could be used as starting materials for the preparation of sulphoxides via the selective removal of one oxygen atom from the sulphonyl group (equation 112). Up to now, there is only one example reported of a direct reduction of a sulphone to a sulphoxide. The bicyclic dideuterio sulphone **205** after 24 h treatment with three-fold excess of diisobutyl aluminium hydride in boiling dichloromethane gave the corresponding sulphoxide **206** in 36% yield[237] (equation 113). A two-step procedure for the selective reduction of sulphones to sulphoxides, which involves an initial reaction of sulphone **204** with aryldiazonium tetrafluoroborate **207** to form aryloxysulphoxonium salt **208** and its subsequent reduction (equation 114), was alluded to by Shimagaki and coworkers[238] and

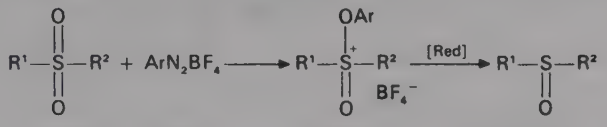


(204) (112)



(205) (206) (113)

studied in detail by Still and his coworkers[239]. Methyl phenyl sulphone was converted into methyl phenyl sulphoxide by this procedure using benzenediazonium tetrafluoroborate **207a** as an arylating reagent and hydrogen sulphide or benzyl mercaptan in the presence of pyridine as the reductant[238]. Few other sulphones were reduced in a similar way via an initial reaction with 4-chlorobenzenediazonium tetrafluoroborate and subsequent reduction of the aryloxysulphonium salts **208b** with sodium borohydride/alumina[239].

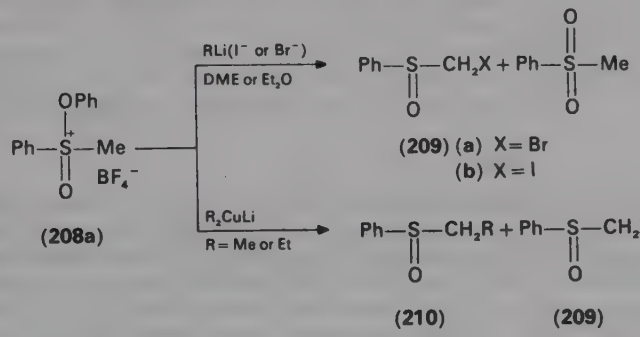


(114)

(204) (207) (208)

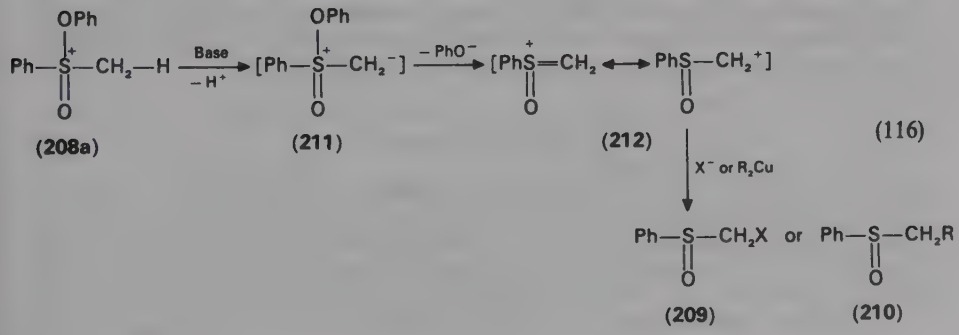
(a) Ar = Ph
(b) Ar = *p*-ClC$_6$H$_4$

The reaction of sulphoxonium salt **208a** with alkyllithium prepared from alkyl iodides or bromides gave the corresponding α-halogenosulphoxides **209** in 45–77% yields along with methyl phenyl sulphone[238] (equation 115). Lithium dimethylcopper prepared from methyl iodide, lithium and cuprous iodide afforded ethyl phenyl sulphoxide **210** (R = Me) in 69% yield. On the other hand, lithium diethylcopper prepared from ethyl iodide gave α-iodosulphoxide **209b** in 71% yield as a single reaction product (equation 115). The formation of α-halogenosulphoxides **209** and α-alkylmethyl derivatives **210** in the reaction of sulphoxonium salt **208a** with organocopper reagents results from the reaction sequence given in equation 116. Deprotonation of **208a** by a base leads to a very unstable ylide **211** which undergoes spontaneous decomposition to the phenoxide anion and a sulphoxonium ion **212**. The latter is trapped by nucleophiles (X^- or R^-) present in the reaction mixture to form the final reaction product **209** and/or **210**.



(208a) (209) (a) X = Br (b) X = I (210) (209)

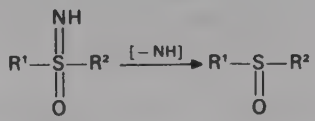
(115)



(208a) (211) (212) (209) (210)

(116)

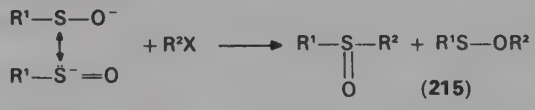
Deimination of sulphoximines **213** as a method of synthesis of racemic sulphoxides (equation 117) has no synthetic value. However, this approach has been applied for the synthesis of optically active sulphoxides and will be discussed in the next part of this chapter.



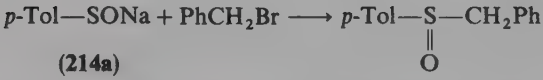
(213) (117)

L. Alkylation of Sulphenate Anion

Anion **214** derived from sulphenic acid may be described by two mesomeric forms in which the negative charge is concentrated on the oxygen or sulphur atom and it shows a typical ambident reactivity. In accord with the HSAB concept[240], its alkylation may be expected to occur either on the sulphur atom to give the corresponding sulphoxides or on the oxygen atom to form sulphenate esters **215** (equation 118). The sulphoxide to sulphenate ratio depends mainly on the 'hardness' of the alkylating reagents. Thus, alkylation of sodium *p*-toluenesulphenate **214a**, formed by alkaline hydrolysis of *p*-toluenesulphenyl chloride, with benzyl bromide gave benzyl *p*-tolyl sulphoxide as the only product[241] (equation 119).

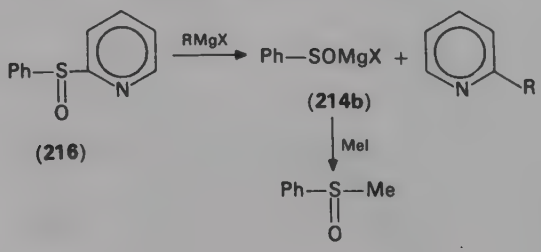


(214) (215) (118)

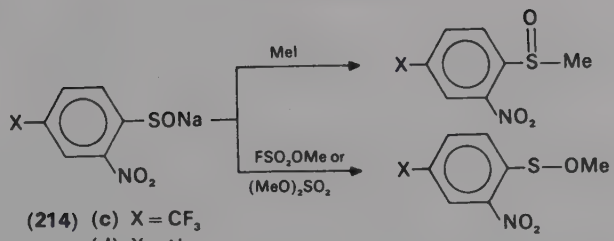


(214a) (119)

The magnesium salt of benzenesulphenic acid **214b**, obtained by the reaction of pyridyl sulphoxide **216** with a Grignard reagent, gave upon alkylation with methyl iodide almost quantitatively methyl phenyl sulphoxide[227] (equation 120). The sulphenate anions **214c** and **214d**, generated by the base-catalysed hydrolysis of the corresponding disulphides or sulphenate esters, undergo *S*-methylation with methyl iodide, but predominant *O*-methylation with 'harder' methylation agents such as methyl fluorosulphonate and dimethyl sulphate[242] (equation 121). Alkylation of the sulphenate anion **214e**, obtained by the addition of lithium-cyclohexanone enolate to sulphine **173c**, gave the corresponding 1-aryl-3-oxo-1-alkenyl sulphoxides in high yields[243] (equation 122).

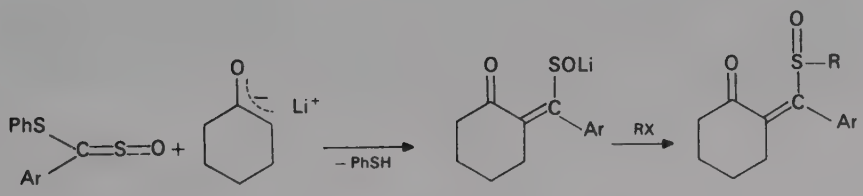


(216) (214b) (120)



(214) (c) X = CF_3
(d) X = H

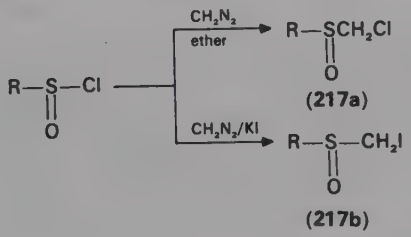
(121)



(173c) (214e) (122)

M. Miscellaneous Methods

Reaction of diazomethane with sulphinyl chlorides has been known since 1957[244]. Effective procedures for the synthesis of α-halogenosulphoxides **217** based on this reaction were reported by Venier and coworkers[245,246]. Treatment of alkane or arenesulphinyl chlorides with diazomethane in ether solution gives α-chlorosulphoxides **217a** in 70–90% yields. When the same reaction was carried out in the presence of iodide anion it yielded the corresponding iodo derivatives **217b** in high yields (equation 123). Bromomethyl trichloromethyl sulphoxide was isolated in 15% yield after treatment of trichloromethanesulphinyl bromide with diazomethane[247] (equation 124).



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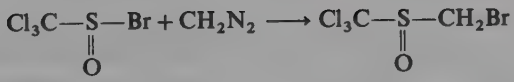
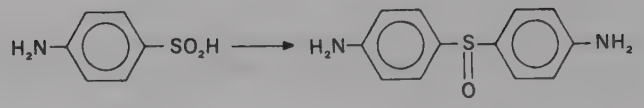


(124)

Heating of *p*-aminobenzenesulphinic acid for a few hours gives the corresponding *p,p'*-diaminophenyl sulphoxide in 57% yield[248] (equation 125). The thermal reaction of 4-acetamidobenzenesulphinic acid with N-alkylanilines affords the corresponding (4-acetamidophenyl)(4'-alkylaminophenyl)sulphoxides[249] (equation 126). Passing a stream of sulphur dioxide through a mixture of benzene and aluminium chloride at reflux temperature afforded diphenyl sulphoxide as a single reaction product[175].



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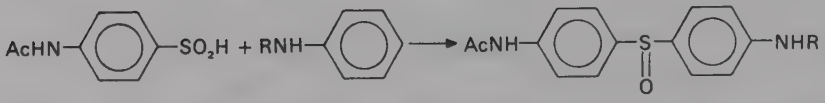
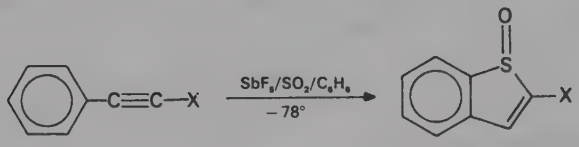


(126)

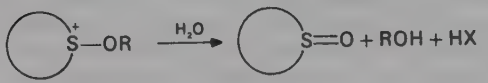
Few 1-benzothiophene-*S*-oxides **218** were obtained in moderate yields by treatment of 1-arylacetylenes **219** with sulfur dioxide and benzene in the presence of antimony pentafluoride[250] (equation 127). A series of cyclic sulphoxides have been prepared by hydrolysis of the corresponding alkoxy sulphonium salts **220**[251–254] (equation 128). Syn-sulphoxide **221** was obtained in a low yield (15–20%) in the reaction of the dianion of cyclooctatetraene **222** with thionyl chloride[255] (equation 129).



(127)

(219) **(218)**

(a) X = Cl
(b) X = Br
(c) X = Ph



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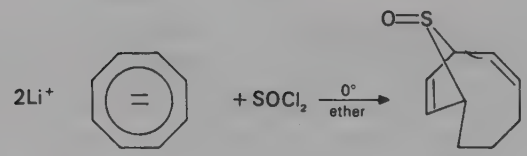


(129)

(222) **(221)**

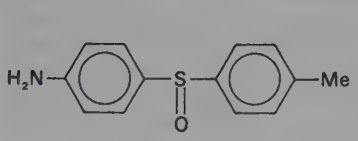
III. SYNTHESIS OF OPTICALLY ACTIVE SULPHOXIDES

Chiral sulphoxides are the most important group of compounds among a vast number of various types of chiral organosulphur compounds. In the first period of the development of sulphur stereochemistry, optically active sulphoxides were mainly used as model compounds in stereochemical studies[256]. At present, chiral sulphoxides play an important role in asymmetric synthesis, especially in an asymmetric C—C bond formation[257]. Therefore, much effort has been devoted to elaboration of convenient methods for their synthesis. Until now, optically active sulphoxides have been obtained in the following ways: optical resolution, asymmetric synthesis, kinetic resolution and stereospecific synthesis. These methods are briefly discussed below.

A. Optical Resolution

1. Classical resolution

Since the pioneering work of Harrison and coworkers[258] on the resolution of 4-aminophenyl 4-tolyl sulphoxide **223** and carboxyphenyl methyl sulphoxide **224** into their enantiomeric forms via formation and crystallization of the diastereoisomeric salts with d-camphorsulphonic acid and brucine, respectively, this technique has been used frequently for the preparation of selected sulphoxides in optically active form[259]. Suszko and his collaborators[260] and later Janczewski and his group published[261] a large number of papers on the synthesis, resolution and optical properties of α-substituted sulphinylacetic acid derivatives of the general structure **225**. 1,6- and 1,8-naphthalenedisulphinylacetic acid **226** and **227** were resolved into their enantiomeric forms using the carboxylic groups for the salt formation with optically active amines[262].



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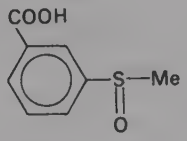

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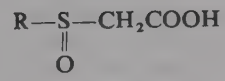

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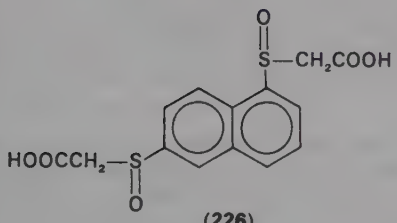

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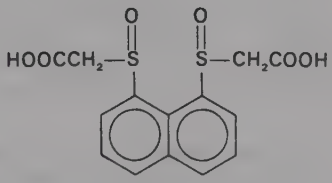
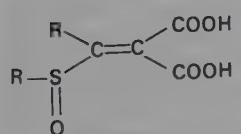


(227)

Bohman and Allenmark[263] resolved a series of sulphoxide derivatives of unsaturated malonic acids of the general structure **228**. The classical method of resolution via formation of diastereoisomeric salts with cinchonine and quinine has also been used by Kapovits and coworkers[264] to resolve sulphoxides **229**, **230**, **231** and **232** which are precursors of chiral sulphuranes. Mikołajczyk and his coworkers[265] achieved optical resolution of sulphoxide **233** by utilizing the phosphonic acid moiety for salt formation with quinine. The racemic sulphinylacetic acid **234**, which has a second centre of chirality on the α-carbon atom, was resolved into pure diastereoisomers by Holmberg[266]. Racemic 2-hydroxy- and 4-hydroxyphenyl alkyl sulphoxides were separated via the diastereoisomeric 2- or 4-(*tetra*-O-acetyl-D-glucopyranosyloxy)phenyl alkyl sulphoxides **235**. The optically active sulphoxides were recovered from the isolated diastereoisomers **235** by deacetylation with base and cleavage of the acetal[267]. Racemic 1,3-dithian-1-oxide **236**



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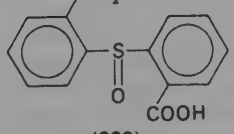

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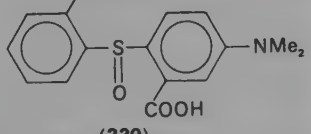
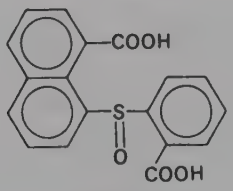


(230)

was resolved by a two-step procedure involving the addition of the 2-lithio derivative of **236** to (+) camphor followed by separation of the diastereoisomeric alcohols and regeneration of the optically active sulphoxide **236** with potassium hydroxide in *t*-butyl alcohol[268].



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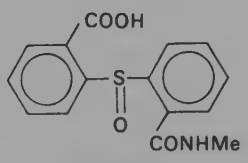

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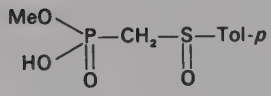

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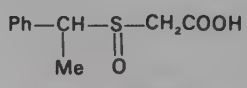

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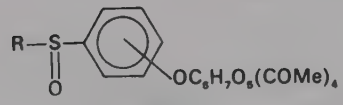

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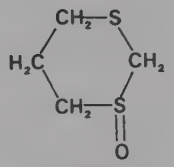


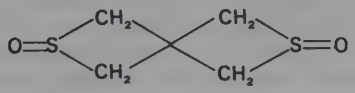
(236)

It is well known that spontaneous resolution of a racemate may occur upon crystallization if a chiral molecule crystallizes as a conglomerate. With regard to sulphoxides, this phenomenon was observed for the first time in the case of methyl *p*-tolyl sulphoxide[269]. The optical rotation of a partially resolved sulphoxide (via β-cyclodextrin inclusion complexes) was found to increase from $[\alpha]_{589} = +11.5°$ (e.e. 8.1%) to $[\alpha]_{589} = +100.8$ (e.e. 71.5%) after four fractional crystallizations from light petroleum ether. Later on, few optically active ketosulphoxides of low optical purity were converted into the pure enantiomers by fractional crystallization from ethyl ether-hexane[270]. This resolution by crystallization was also successful for racemic benzyl *p*-tolyl sulphoxide and *t*-butyl phenyl sulphoxide[271].

2. *Non-classical resolution*

In addition to the classical resolution of racemic sulphoxides via diastereoisomeric salts or derivatives, illustrated above, other so-called non-classical procedures are known to be useful for the resolution of racemic sulphoxides that do not contain acidic or basic functional groups. For the first time this technique was reported in 1934 by Becker and Keuning[272] who resolved 2,5-dithiaspiro[3,3]heptane-2,5-dioxide **237** by means of a cobalt complex with d-camphorsulphonic acid as a ligand. The total resolution of ethyl *p*-tolyl sulphoxide was achieved through the formation and separation of the diastereoisomeric complexes with *trans*-dichloroethylene platinum(II) containing optically active α-phenylethylamine as a ligand[273]. Due to its conceptual simplicity, the direct chromatographic separation of racemic sulphoxides on chiral columns may be considered as a convenient route leading to enantiomeric forms. Montanari and coworkers[274] found

that racemic unsaturated vinyl disulphoxide **238** may be partially resolved by this method on activated α-lactose.



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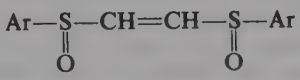
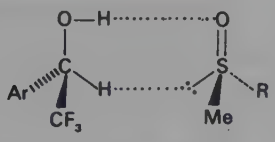
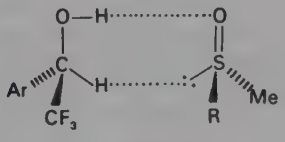


(238)

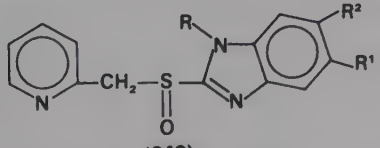
Wudl reported[275] that a polymer prepared from optically active methyl *p*-styryl sulphoxide may also be used as a chiral support in chromatographic resolution of racemic sulphoxides. In an extension of their studies on the NMR determination of enantiomeric purity and absolute configuration of chiral sulphoxides, Pirkle and House introduced recently a silica-gel-bonded chiral fluoroalcoholic stationary phase for the direct separation of racemic sulphoxides[276]. This chromatographic resolution is conceptually based on three types of stereochemically dependent interactions between the chiral fluoroalcoholic moiety of the stationary phase and the racemic sulphoxides to be separated. One assumes that the preferred conformation of the diastereoisomeric solvates **239a** and **239b** is stabilized by hydrogen bonding between the hydroxy and sulphinyl group, by interaction between the weakly acidic methine proton of the fluoroalcohol and the lone electron pair on sulphur (carbinyl hydrogen bonding), and also to some extent by interaction between the aromatic rings (R = Ar). Racemic phenyl vinyl sulphoxide was resolved by high-performance liquid chromatography on (+) poly-(triphenylmethyl)methacrylate column with methanol–water (8:2) mixture as eluent[277]. The stationary phase composed of (*R*)-*N*-(3,5-dinitrobenzoyl) phenyl glycine bound to aminopropyl silica was used for the resolution of a series of alkyl aryl sulphoxides[278]. Pharmacologically active racemic sulphoxides **240** were resolved by the affinity chromatography technique based on enantioselective interactions with immobilized bovine serum albumin[279].



S_C **(239a)** R_S



S_C **(239b)** S_S

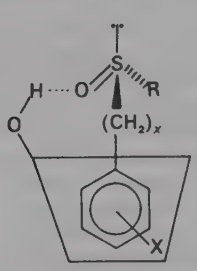


(240)

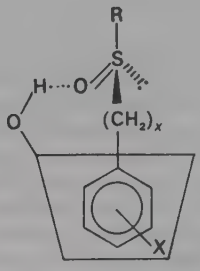
The gas chromatographic separation of some sulphoxide enantiomers was observed on quartz fused silica capillaries coated with the chiral silicon phase chirasil-val[280].

A different non-classical approach to the resolution of sulphoxides was reported by Mikołajczyk and Drabowicz[269,281]. It is based on the fact that sulphinyl compounds very easily form inclusion complexes with β-cyclodextrin. Since β-cyclodextrin as the host molecule is chiral, its inclusion complexes with racemic guest substances used in an excess are mixtures of diastereoisomers that should be formed in unequal amounts. In this way a series of alkyl phenyl, alkyl *p*-tolyl and alkyl benzyl sulphoxides has been resolved. However, the optical purities of the partially resolved sulphoxides do not exceed 22% after

a single inclusion process. Moreover, the optical purities of the included sulphoxides are strongly dependent on the nature of the aromatic ring and the alkyl group connected to the sulphinyl sulphur atom. The stereoselectivity of the inclusion is also dependent on the pH of the solution in which the formation of the inclusion complexes takes place, as well as on the presence of the water-miscible solvents like methanol, acetone or dioxane acting as hydrogen bond acceptors. The stereoselectivity of the inclusion of sulphoxides into β-cyclodextrin was also affected by the addition of inorganic salts to the water solution. The relationship between the stereospecificity of inclusion of sulphoxides into β-cyclodextrin and the structure of the preferentially included sulphoxide was rationalized by assuming that two inclusion complexes **241a** and **241b** are concurrently formed in a ratio that depends on the nature of alkyl and aryl substituents connected with the sulphinyl sulphur atom. In the case of *t*-butyl aryl, isopropyl and *n*-butyl *o*-tolyl sulphoxides, the inclusion complex **241b** is favoured for steric reasons.

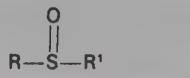


(241a)



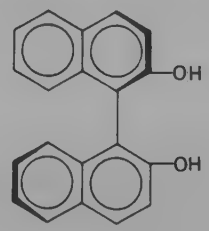
(241b)

A new approach to the resolution of sulphoxides **242** was recently reported by Toda and coworkers[282]. It takes advantage of the fact that some sulphoxides form crystalline complexes with optically active 2,2′-dihydroxy-1,1-binaphthyl **243**. When a two-molar excess of racemic sulphoxide **242** was mixed with one enantiomeric form of binaphthyl **243** in benzene-hexane and kept at room temperature for 12 h, a 1:1 complex enriched strongly in one sulphoxide enantiomer was obtained. Its recrystallization from benzene followed by chromatography on silica gel using benzene-ethyl acetate as eluent gave optically pure sulphoxide. However, methyl phenyl sulphoxide was poorly resolved by this procedure and methyl *o*-tolyl, methyl *p*-tolyl, *s*-butyl methyl and *i*-propyl methyl sulphoxides did not form complexes with **243**.



(242)

(a) R = *m*-MeC_6H_4, R^1 = Me
(b) R = *m*-MeC_6H_4, R^1 = Et
(c) R = *n*-Bu, R^1 = Me
(d) R = *n*-Pr, R^1 = Me



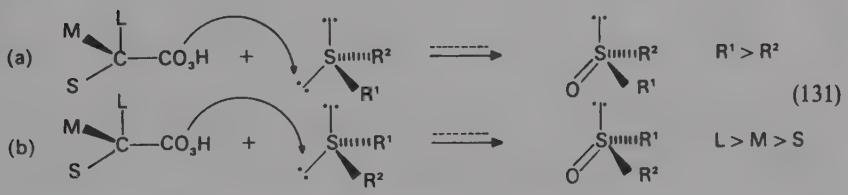
(243)

B. Asymmetric Synthesis

A convenient and simple route to chiral sulphoxides is an asymmetric oxidation of prochiral sulphides by optically active oxidizing reagents.

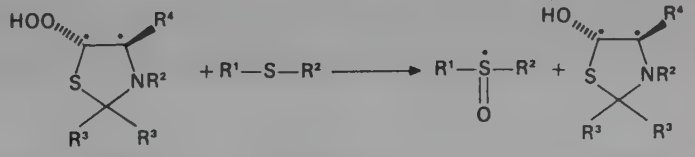
In 1960, Montanari[283] and Balenovic[284] and their coworkers described independently the first asymmetric oxidation of sulfides with optically active peracids. However, the sulphoxides were formed in this asymmetric reaction (equation 130) with low optical purities, generally not higher than 10%. The extensive studies of Montanari and his group on peracid oxidation indicated that the chirality of the predominantly formed sulphoxide enantiomer depends on the absolute configuration of the peracid used. According to Montanari[283], the stereoselectivity of the sulphide oxidation is determined by the balance between one transition state (a) and a more hindered transition state (b) in which the groups R^1 and R^2 at sulphur face the moderately and least hindered regions of the peracid, respectively (equation 131).

$$R^1—S—R^2 + \overset{*}{R}—\overset{O}{\overset{\|}{C}}OOH \longrightarrow R^1—\overset{O}{\overset{\|}{S}}{}^*—R^2 + \overset{*}{R}—COOH \qquad (130)$$



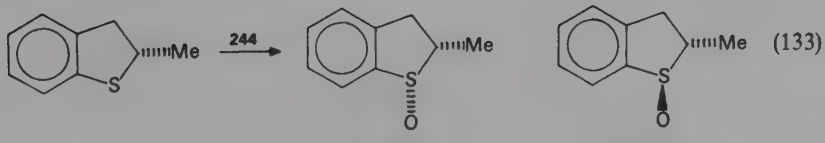
(131)

Optically active hydroperoxides **244** were found[285] to oxidize prochiral sulphides into the corresponding sulphoxides in higher optical yields (up to 27%) in comparison with those observed with peracids (equation 132). Moreover, the optical purity of the sulphoxides formed may be enhanced by addition of $Ti(OPr\text{-}i)_4$. The oxidation of racemic 2-methyl-2, 3-dihydrobenzothiophene **246** with these peroxides gave a mixture of *cis* and *trans*-sulphoxides **247** (equation 133). In all cases of the oxidation with the hydroperoxide alone the formation of the *trans*-isomer was strongly preferred and the e.e. value (up to 42%) of the *cis*-isomer was always higher than that of the *trans*-isomer. Moreover, the addition of $Ti(OPr\text{-}i)_4$ furthermore promoted the selective formation of the *trans*-sulphoxide **247** and remarkably enhanced the e.e. value of both isomers.



(132)

(244) **(245)**



(133)

(246) *cis*-**(247)** *trans*-**(247)**

The standard Sharpless reagent [$Ti(OPr\text{-}i)_4$/(*R*, *R*)-diethyl tartrate (DET)/*t*-BuOOH] oxidizes methyl *p*-tolyl sulphide into a mixture of racemic sulphoxide and sulphone[286].

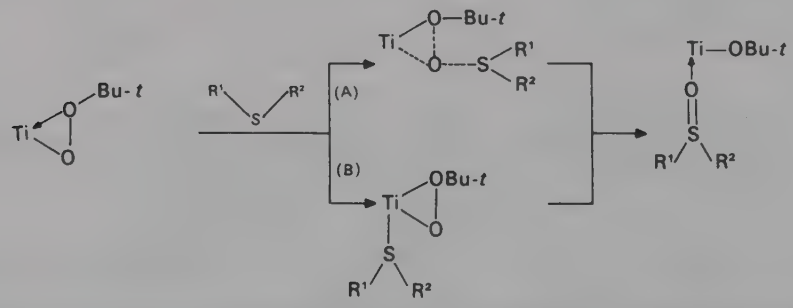
TABLE 15. Asymmetric oxidation of sulphides, R^1SR^2, to optically active sulphoxides, $R^1R^2S{=}O$

R^1	R^2	Oxidant[a]	Yield (%)	$[\alpha]_{589}$	e.e. (%) (conf.)	Ref.
Me	*p*-Tol	A	90	+ 132.0	91.0(*R*)	286
Me	*p*-Tol	B	60	+ 128.5	88.3(*R*)	287
Me	*p*-Tol	C	46	+ 93.5	64.5(*R*)	287
Me	*p*-Tol	D			31.0(*S*)	292
Me	Ph	A	80	+ 130.0	89.0(*R*)	286
Me	*p*-ClC_6H_4	A	95	+ 97.0	78.0(*R*)	286
Me	*p*-BrC_6H_4	A	70	+ 77.0	80.0(*R*)	286
Et	*p*-Tol	A	71	+ 139.0	74.0(*R*)	286
i-Pr	*p*-Tol	A	56	+ 111.0	63.0(*R*)	286
i-Pr	*p*-Tol	*b*			23.0(*S*)	292
n-Bu	*p*-Tol	A	75	+ 38.0	20.0(*R*)	286
Me	*n*-C_8H_{17}	A	77	− 44.0	71.0	286
Me	*t*-Bu	A	72	− 2.1	53.0(*R*)	286
Me	*c*-Hex	A	67	− 44.3	54.0	286

[a]A: Ti(OPr-*i*)$_4$ + (*R*, *R*)-diethyl tartrate + H_2O + *t*-BuOOH (1:2:1:1.1) in methylene chloride; B: Ti(OPr-*i*)$_4$ + (*R*, *R*)-diethyl tartrate + *t*-BuOOH (1:4:2) in 1,2-dichloroethane; C: Ti(OPr-*i*)$_4$ + (*R*, *R*)-diethyl tartrate + *t*-BuOOH (1:4:2) in toluene.
[b]Sulphonyloxaziridine **250a** (Ar = 2-chloro-5-nitrophenyl).

However, this reagent, modified by addition of one molar equivalent of water, was found by Kagan and coworkers[286] to give a new homogeneous reagent [Ti(OPr-*i*)$_4$/DET/*t*-BuOOH/H_2O] which is able to oxidize various types of alkyl aryl sulphides to the corresponding chiral sulphoxides with e.e. in the range of 80–90% in a predictable manner. In the case of dialkyl sulphoxides the e.e. values ranged between 50–71% (Table 15).

Based on detailed kinetic investigations, a tentative mechanism for this asymmetric oxidation was proposed (Scheme 2) according to which optically active sulphoxides may be formed by two pathways: external attack on the sulphur atom by the chiral titanium hydroperoxide (path A) or coordination of sulphur to titanium prior to the oxidation step (path B). Although paths A and B could not be distinguished experimentally, the temperature effect was tentatively ascribed to a change of the mechanism, path A being predominant above − 20 °C and path B becoming competitive at lower temperatures (or vice versa).



SCHEME 2

A closely related asymmetric synthesis of chiral sulphoxides, which involves a direct oxidation of the parent sulphides by *t*-butylhydroperoxide in the presence of metal catalyst and diethyl tartrate, was also reported by Modena and Di Furia and their coworkers[287,288]. The effect of the reaction parameters such as metal catalyst, chiral tartrate and solvent on the optical yield does not follow a simple pattern. Generally, the highest optical purities (up to 88%) were observed when reactions were carried out using $Ti(OPr\text{-}i)_4$ as a metal catalyst in 1,2-dichloroethane.

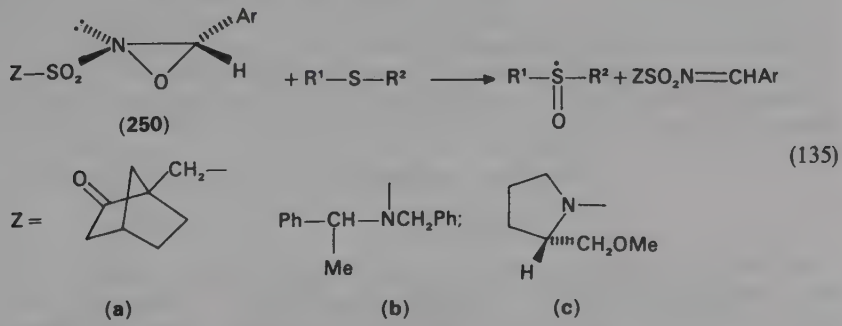
The modified Sharpless reagent was also successfully applied[288] for the asymmetric oxidation of a series of 1,3-dithiolanes **248** to their *S*-monooxides **249** (equation 134). It was observed that the optical induction on sulphur (e.e. from 68 to 83%) is not significantly affected by the substituents R^1 and R^2. Asymmetric oxidation of a few aryl methyl sulphides by organic hydroperoxides in the presence of a catalytic amount of the optically active Schiff base–oxovanadium(IV) complexes gave the corresponding sulphoxides with e.e. lower than 40%[289].

(134)

(248) **(249)**

In contrast to the asymmetric procedures discussed above, the metal-catalyzed oxidation of alkyl aryl sulphides by *t*-butylhydroperoxide carried out in a chiral alcohol gives rise to chiral sulphoxides of low optical purity[290] (e.e. 0.6–9.8%). Similarly, a very low asymmetric induction was noted when prochiral sulphides were oxidized by sodium metaperiodate in chiral alcohols as solvents[291].

Chiral 2-sulphonyloxaziridines **250a** and 2-sulphamyloxaziridines **250b,c** represent another type of efficient asymmetric oxidizing reagent which has recently been used by Davis and coworkers[292] for the synthesis of chiral sulphoxides (equation 135). It was established that the sulphoxide absolute configuration was determined by the configuration of the oxaziridine three-membered ring and that non-bonded steric interactions in the transition state were responsible for the asymmetric induction. The increased enantioselectivity exhibited by 2-sulphonyl and 2-sulphamyloxaziridines, in comparison to peracids or hydroperoxides, is most likely a manifestation of the closer proximity of the oxaziridine substituents to the reactive centre. In oxaziridines the oxygen atom, which undergoes transfer to sulphur, is located in a rigid three-membered ring and is one bond removed from the carbon and nitrogen chiral centres.

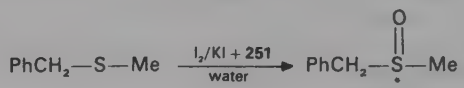


(250) (135)

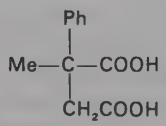
(a) **(b)** **(c)**

Formation of optically active sulphoxides was found to occur during oxidation of sulphides in the presence of chiral catalysts. Thus, the oxidation of benzyl methyl sulphide

with iodine suspended in (*R*)-2-methyl-2-phenylsuccinic acid **251** buffer gives optically active benzyl methyl sulphoxide having 6.35% optical purity[293] (equation 136).



$$PhCH_2—S—Me \xrightarrow[\text{water}]{I_2/KI + \mathbf{251}} PhCH_2—\overset{\overset{O}{\|}}{\underset{\bullet}{S}}—Me \qquad (136)$$



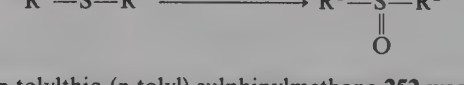
(251)

β-Cyclodextrin mediated oxidation of prochiral sulphides by achiral oxidation reagents leads also to optically active sulphoxides (e.e. up to 30%). When oxidation was carried out in pyridine the highest optical purities were obtained[294] with hydrogen peroxide, whereas in water the best results were observed with *m*-chloroperbenzoic acid[295].

Much higher asymmetric induction was observed in the two-phase oxidation of simple alkyl aryl and diaryl sulphides[296], substituted alkyl aryl sulphides[297] and dithioacetals of formaldehyde[298] by sodium metaperiodate in the presence of proteins such as bovine serum *γ*-globulin and egg albumin. Optical purities of the sulphoxides so formed ranged between 20 and 85%.

Very low asymmetric induction (e.e. 0.3–2.5%) was noted when unsymmetrical sulphides were electrochemically oxidized on an anode modified by treatment with (−)camphoric anhydride or (*S*)-phenylalanine methyl ester[299]. Much better results were obtained with the poly(L-valine) coated platinum electrodes[300]. For example, *t*-butyl phenyl sulphide was converted to the corresponding sulphoxide with e.e. as high as 93%, when electrode coated with polypyrrole and poly(L-valine) was used.

In contrast to asymmetric oxidation of unsymmetrical sulphides with chiral chemical oxidants, microbiological oxidation (equation 137) usually gives much better results. In 1962, optically active benzyl phenyl sulfoxide with 18% optical purity was prepared[301] by oxidation of the parent sulphide via fermentation with Aspergillus niger, NRRL 337. Asymmetric induction during oxidation of 7-α-methylthioandrostane to the corresponding sulphoxide by fermentation with Calonectria decora (CBS) was also observed[302]. Later on, Henbest and coworkers found[303] that the chemical yield and stereoselectivity of the oxidation by Aspergillus niger depend on the structure of the sulphide and on the efficiency with which the enzymatic oxidation system can accommodate the reacting sulphide substrate. The highest optical purity (99%) was observed in the case of *t*-butyl *p*-tolyl sulphoxide and the lowest (32%) for methyl *p*-tolyl sulphoxide. Very recently oxidation of some alkyl aryl sulphides by Mortierella Isabellina RRLL 1757[304,305], and Helminthosporium sp., NRRL 4671[304], was found to give the corresponding sulphoxides with almost 100% optical purity.



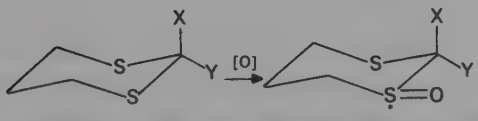
$$R^1—S—R^2 \xrightarrow{\text{microorganism}} R^1—\overset{\overset{O}{\|}}{\overset{*}{S}}—R^2 \qquad (137)$$

However, (−)-(*S*)-*p*-tolylthio-(*p*-tolyl) sulphinylmethane **252** was obtained in 20% e.e. from gem-disulphide **253** using Helmintosporium cultures[306] (equation 138). With this culture much higher asymmetric induction was observed when 1,3-dithianes **254** substituted or unsubstituted at carbon 2 were used as substrates (equation 139). Whereas the optical yield of the (−)-(*S*)-monosulphoxide **255** (X = Y = H) was about 14% only, this

value increased up to 72% for 2-alkyl substituted dithianes **255**[307].

$$p\text{-Tol—S—CH}_2\text{—S—Tol-}p \xrightarrow{[O]} p\text{-Tol—}\overset{\displaystyle O}{\overset{\|}{\dot{S}}}\text{—CH}_2\text{—S—Tol-}p \qquad (138)$$

(253) **(252)**



(139)

(254) **(255)**

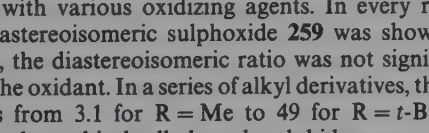
X, Y = H, Me, *t*-Bu

Stereoselective oxygen transfer to the sulphur atom of alkyl aryl sulphides catalyzed by 2-flavoenzyme monooxygenases afforded optically active sulphoxides in high optical yields[308]. For instance, with ethyl *p*-tolyl sulphide as substrate cyclohexanone monooxygenase from Actinetobacter produces predominantly (−)-(*S*)-sulphoxide with 64% e.e. In contrast, FAD-containing dimethylaniline monooxygenase purified from hog liver microsomes affords (+)-(*R*)-enantiomer of this sulphoxide with 90% optical purity[308].

Asymmetric oxidation of this sulphide was also catalyzed by two isocytochromes P 450 purified from phenobarbital induced rat liver[309]. Both P 450 isocytochromes, termed PB-1 and PB-4, when reconstituted with purified rat liver NADPH-cytochrome P 450 reductase and cytochrome b_5 afforded ethyl *p*-tolyl sulphoxide with *S*-configuration at the sulphur atom. In the case of PB-1 optical purity of this sulphoxide was 58% whereas with PB-4 it was 78%.

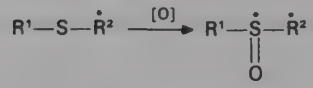
The oxidation of a series of cyclic and acyclic sulphides by cytochrome P 450 from rabbit liver gave sulphoxides with *R*-configuration at sulphur. The maximum of the e.e. value (53.8%) was observed for benzyl *t*-butyl sulphoxide[310].

Dopamine β-hydroxylase (DBH), a copper-containing monooxygenase present in a variety of mammalian tissues, catalyzes the conversion of the protonated 2-aminoethyl phenyl sulphide **256** to the corresponding optically active sulphoxide **257**[311] (equation 140). Formation of diastereoisomeric sulphoxides is also observed when sulphides that are chiral at carbon are reacted with achiral oxidizing agent (equation 141). This internal asymmetric induction was first described by Cram and Pine[312] in 1963. They oxidized (*R*)-2-octyl phenyl sulphide with *t*-butyl hydroperoxide and found that two diastereoisomeric sulphoxides **258** were formed in a 1.6:1 ratio. More recently, Nishihata and Nishio[313] investigated the oxidation of optically active 1-phenylethyl alkyl(phenyl) sulphides with various oxidizing agents. In every reaction studied the predominantly formed diastereoisomeric sulphoxide **259** was shown to have the S_CR_S configuration. Moreover, the diastereoisomeric ratio was not significantly affected by a change in the nature of the oxidant. In a series of alkyl derivatives, the product ratio (S_CR_S)-**259** to (S_CS_S)-**259** varies from 3.1 for R = Me to 49 for R = *t*-Bu. Asymmetric induction was also observed when chiral alkyl aryl sulphides were oxidized either with *N*-chloro-*p*-toluenesulphonamide or with *t*-butyl hypochlorite and TosNHNa[314].

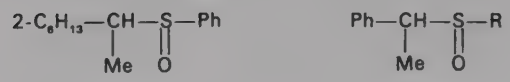


+ dehydroascorbate (140)

(256) **(257)**, $[\alpha]_{589} = -240°$

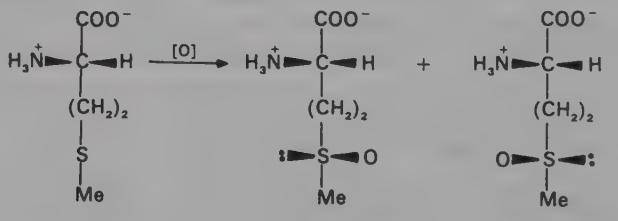


(141)



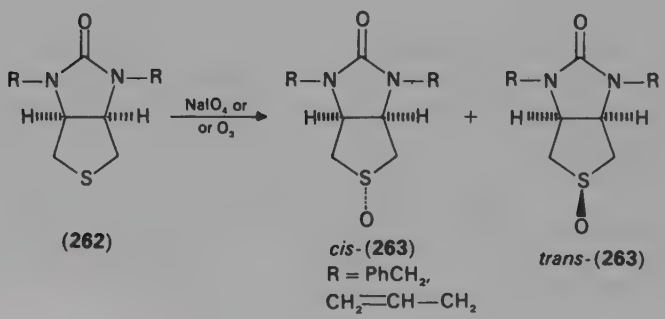
(258) (259)

The oxidation of (*S*)-methionine **260** with hydrogen peroxide was found to give the corresponding diastereoisomeric sulphoxides **261** in nearly equal amounts[315] (equation 142). However, the use of $HAuCl_4$ as oxidant[316] provides a method for the completely stereospecific conversion of (S_C)-**260** into the methionine sulphoxide (S_CS_S)-**261**. A high asymmetric induction at sulphur was observed in the oxidation of the bicyclic sulphide **262**. Marquet and her coworkers[317] reported that treatment of **262**, which is the key intermediate in the total synthesis of biotin, with sodium metaperiodate or ozone gave the two diastereoisomeric sulphoxides *cis*-**263** and *trans*-**263** in a 9:1 ratio (equation 143). The oxidation of esters of *o*-methylthiobenzoic acid **264** containing a chiral alkoxy group by achiral peracids gave **265** which, after hydrolysis, gave optically active *o*-methylsulphinylbenzoic acid **266**[318] (equation 144). The use of 2, 4, 6-trimethylperbenzoic acid and bulky alkyl groups in the ester moiety lead to the highest optical purity of this sulphoxide (40%).



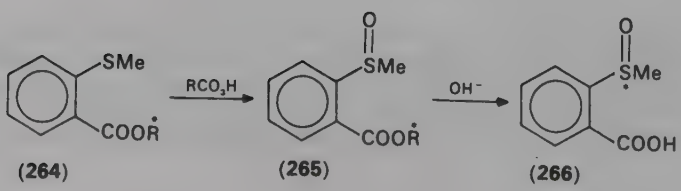
(142)

(*S*)-(**260**) (S_CS_S)-(**261**) (S_CR_S)-(**261**)



(143)

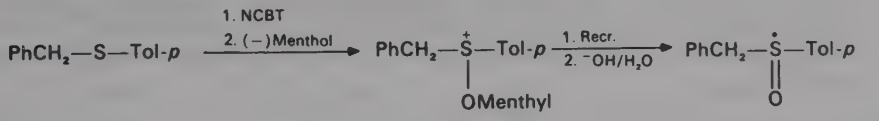
(**262**) *cis*-(**263**) R = $PhCH_2$, $CH_2{=}CH{-}CH_2$ *trans*-(**263**)



(144)

(**264**) (**265**) (**266**)

Chiral alcohols have also been used in an asymmetric synthesis of sulphoxides based on halogenation of sulphides. Johnson and coworkers have found[319] that the reaction of benzyl *p*-tolyl sulphide with *N*-chlorobenzotriazole (NCBT) followed by addition of (−) menthol and silver tetrafluoroborate afforded diastereoisomeric menthoxysulphonium salts **267** which, upon recrystallization and hydrolysis, gave benzyl *p*-tolyl sulphoxide with 87% optical purity (equation 145). More recently, Oae and coworkers reported[320] that optically active diaryl sulphoxides (e.g. up to 20%) were formed either by hydrolysis or thermolysis of the corresponding diaryl menthoxysulphonium salts prepared *in situ* from diaryl sulphides using (−) menthol and *t*-butyl hypochlorite.



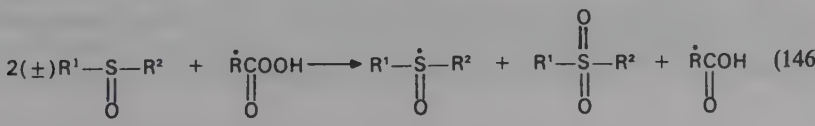
(267) (145)

Optically active sulphoxides were also obtained in low optical and chemical yields by the oxidation of prochiral sulphides with *N*-bromocaprolactam and a chiral alcohol as a solvent[321], or by treatment of sulphides with chiral *N*-chlorocaprolactam and water as oxidant[322].

C. Kinetic Resolution of Sulphoxides

The well-known fact that enantiomers exhibit different reactivity towards chiral reagents has been used to obtain optically active sulphoxides in a process which is called kinetic resolution. Kinetic resolution of sulphoxides usually involves either oxidation to the corresponding sulphones or reduction to sulphides by means of proper chiral oxidizing or reducing agents.

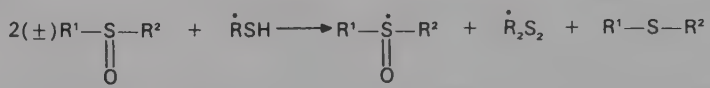
The first oxidative kinetic resolution of racemic sulphoxides was accomplished in the reaction with a deficiency of chiral peracids affording a mixture of optically active sulphoxide and achiral sulphone[323,324] (equation 146). However, the very low optical purity (up to 5%) of the recovered sulphoxides constitutes a serious limitation of this procedure. A more effective kinetic resolution of methyl *p*-tolyl sulphoxide and *t*-butyl phenyl sulphoxide was observed when these sulphoxides were oxidized with a half molar equivalent of the oxaziridine diastereoisomer **250**[325]. The optical purity of the recovered sulphoxides was in the range 0.5 to 23%. The hydrogen peroxide oxidation of racemic sulphoxides carried out in the presence of bovine serum albumin (BSA) is even more efficient[317]. For example, isobutyl phenyl sulphoxide left after partial oxidation of a racemate was optically active and the optical purity increased as the reaction proceeded. After 75% conversion its optical purity was 69%. As expected, relatively high optical purity (up to 30%) of sulphoxides was noted when they were exposed to growing cultures of Aspergillus niger[318]. In connection with asymmetric oxidation of sulphides to sulphoxides, it is interesting to note that the sulphoxide enantiomer formed preferentially in the asymmetric oxidation of a sulphide undergoes slower oxidation to sulphone. Thus, when the oxidation of alkyl phenyl sulphides with sodium metaperiodate in the presence of BSA was carried out for a long time, the optical purity of the *R*-enriched alkyl phenyl sulphoxides increased gradually as the amount of sulphoxides decreased, reaching a constant value of about 90% after 96 h, when the sulphoxides yields were about 45%[326].



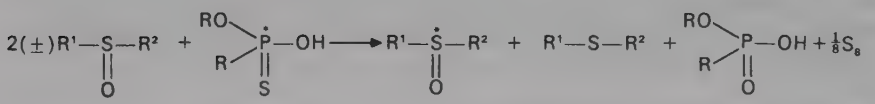
(146)

When racemic 1,3-dithiane *S*-monoxide **236** was exposed to the action of the microorganisms, a kinetic resolution took place and (−)-(*S*)-**236** was obtained with 10% e.e.[327].

The first reductive kinetic resolution of racemic sulphoxides was reported by Balenovic and Bregant[328]. They found that L-cysteine reacted with racemic sulphoxides to produce a mixture of L-cystine, sulphide and non-reduced optically active starting sulphoxide (equation 147). Mikołajczyk and Para[329] reported that the reaction of optically active phosphonothioic acid **268** with racemic sulphoxides used in a 1:2 ratio gave the non-reduced optically active sulphoxides, however, with a low optical purity (equation 148). It is interesting to note that a clear relationship was found between the chirality of the reducing P-thioacid **268** and the recovered sulphoxide. Partial asymmetric reduction of racemic sulphoxides also occurs when a complex of $LiAlH_4$ with chiral alcohols[330], as well as a mixture of formamidine sulphinic acid with chiral amines, are used as chiral reducing systems[331].

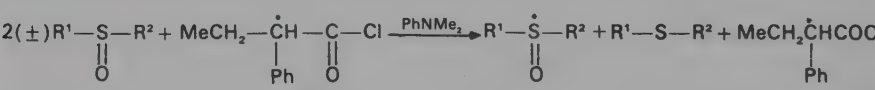


(147)

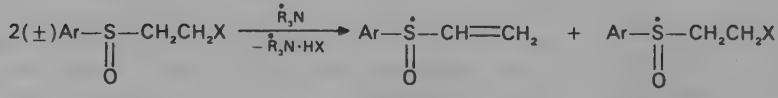


(**268**) (148)

A very interesting approach to optically active sulphoxides, based on a kinetic resolution in a Pummerer-type reaction with optically active α-phenylbutyric acid chloride **269** in the presence of *N*,*N*-dimethylaniline, was reported by Juge and Kagan[332] (equation 149). In contrast to the asymmetric reductions discussed above, this procedure afforded the recovered sulphoxides in optical yields up to 70%. Chiral α,β-unsaturated sulphoxides **270** were prepared via a kinetic resolution elaborated by Marchese and coworkers[333]. They found that elimination of HX from racemic β-halogenosulphoxides **271** in the presence of chiral tertiary amines takes place in an asymmetric way leading to both sulphoxides **270** and **271**, which are optically active (optical yields up to 20%) with opposite configurations at sulphur (equation 150).



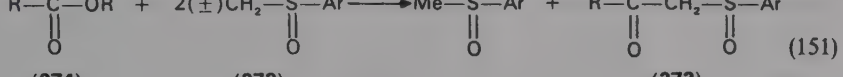
(**269**) (149)



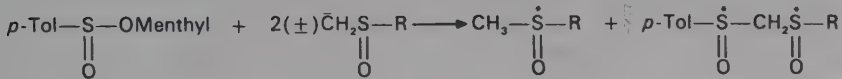
(**271**) (**270**) (**271**) (150)

The preparation of enantiomerically enriched α-ketosulphoxides **272** was also based on a kinetic resolution involving the reaction of the carbanion **273** derived from racemic aryl methyl sulphoxides with a deficiency of optically active carboxylic esters **274**[334] (equation 151). The degree of stereoselectivity in this reaction is strongly dependent on the nature of both the group R and the chiral residue $\overset{*}{R}$ in **274**. Thus, the α-ketosulphoxide formed in the reaction with menthyl esters had an optical yield of 1.3% for R = Et. In the

case of R = Bu-*t*, the optical yield was increased to 71.5%. In a similar way optically active α-disulphoxides **275** were obtained starting from diastereoisomerically pure menthyl *p*-toluenesulphinate **276** and the racemic sulphoxide carbanions **273a**[335] (equation 152).



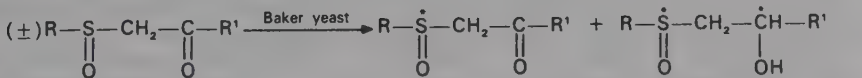
(274) (273) (272) (151)



(276) (273a) (275) (152)

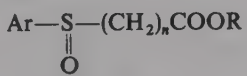
A kinetic resolution of racemic sulphoxides was observed in the reduction by chiral polyiminoalanes. The efficiency of this process depends on the molecular structure of the polyiminoalane. With open pseudo-cubic tetra [*N*-(1-phenylethyl)]imidoalane, unreacted sulphoxides were isolated in enantiomeric enrichment up to 75%. Optical purity was shown to increase with increasing the reaction temperature, a maximum enrichment being observed between 55 and 70 °C[336].

A kinetic resolution was also observed in the reduction of racemic α-ketosulphoxides **277** by fermenting yeast[337] (equation 153). Both the starting ketones **277** and the corresponding β-hydroxysulphoxides **278** formed have been recovered in almost enantiomerically pure form.



(277) (277) (278) (153)

Enzyme mediated hydrolysis of racemic arenesulphinyl alkanoates **279** may also be considered as a method of kinetic resolution. Racemic sulphoxides **279** incubated in the presence of Carynebacterium equi IF 3730 was found to give recovered sulphoxide in optically active form with e.e. higher than 90%[338].



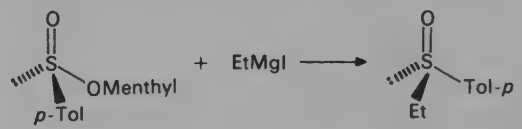
(279)

Partial photochemical decomposition of racemic alkyl aryl sulphoxides in the presence of chiral amines as sensitizers gave non-decomposed sulphoxides in optically active form with optical purity of about 3%[339]. The report[340] on the use of cholesteric liquid crystalline reaction media to change the enantiomeric composition of racemic sulphoxides at high temperatures could not be reproduced[341].

D. Stereospecific Synthesis

A great achievement of the stereochemistry of organosulphur compounds was the stereoselective synthesis of optically active sulphoxides developed by Andersen in 1962[342]. This approach to sulphoxides of high optical purity, still most important and widely used,

is based on the reaction of the diastereoisomerically pure (or strongly enriched in one diastereoisomer) menthyl arene(alkane)sulphinates with Grignard reagents. (+)-(*R*)-Ethyl *p*-tolyl sulphoxide **280** prepared from (−)-(*S*)-menthyl *p*-toluenesulphinate **276** and ethylmagnesium iodide (equation 154) was the first optically active sulphoxide obtained by this method[342].



(154)

(−)-(*S*)-(**276**) (+)-(*R*)-(**280**)

The Andersen sulphoxide synthesis is general in scope and a large number of chiral alkyl aryl and diaryl sulphoxides became available from (−)-(*S*)-**276** and other optically active sulphinates[343–346] (Table 16).

Usually, the reaction of arenesulphinates with Grignard reagents is carried out in ethyl ether solution. However, in this solvent chiral sulphoxides are formed in moderate or low yields depending on the structure of both the sulphinic esters and the Grignard reagents. Harpp and coworkers[159] carried out detailed studies on this reaction and found that the reaction conditions must be carefully selected, otherwise considerable quantities of impurities, which are difficult to separate, are formed. They also found that the use of lithium-copper reagents (R_2CuLi) instead of Grignard reagents gives a cleaner conversion of sulphinates to sulphoxides. However, in this case also the yields of sulphoxides were in the range between 16 and 59%. Chiral sulphoxides of greater chemical and optical purity and in higher yields are obtained when the reactions of menthyl sulphinates with Grignard reagents are carried out in a benzene solution[347]. It is interesting to note that in this solvent the yields of sulphides formed as by-products are much lower.

The synthesis of chiral dialkyl sulphoxides of high optical purity from diastereoisomeric alkanesulphinates has a serious limitation because the sulphinates are not

TABLE 16. Synthesis of optically active sulphoxides, *p*-TolS(O)R, from *O*-menthyl *p*-toluenesulphinate (−)-(*S*)-**276**

$[\alpha]_{589}^{a}$, deg	Conditions	R	Yield (%)	$[\alpha]_{589}^{a}$, deg	Ref.
−198.0	$MeMgI/Et_2O$	Me	*b*	+145.5	343
−195.0	MeMgI/PhH	Me	82	+150.1	347
−210.0	Me_2CuLi/Et_2O	Me	55	+143.2	159
−198.0	$EtMgBr/Et_2O$	Et	*b*	+187.5	343
−195.0	EtMgBr/PhH	Et	92	+198.0	347
−198.0	*i*-$PrMgBr/Et_2O$	*i*-Pr	22	+176.5	343
−195.0	*i*-PrMgBr/PhH	*i*-Pr	40	+173.2	347
−198.0	*n*-$BuMgBr/Et_2O$	*n*-Bu	*b*	+187.0	343
−195.0	*n*-BuMgBr/PhH	*n*-Bu	73	+186.0	347
−195.0	PhMgBr/PhH	Ph	88	+ 20.0	347
−210.0	Ph_2CuLi/Et_2O	Ph	52	+ 20.7	159
−198.0	*o*-$TolMgBr/Et_2O$	*o*-Tol	*b*	− 89.1	343
−198.0	*m*-$TolMgBr/Et_2O$	*m*-Tol	*b*	+ 15.1	343

[a] In acetone solution.
[b] Not given.

epimerically pure at sulphur[343,344,348]. For example, diastereoisomeric menthyl methanesulphinates are oils which cannot be separated into pure diastereoisomers. It was found[349], however, that substitution of cholesterol for menthol leads to crystalline cholesteryl methanesulphinates **281** which, after separation by crystallization into pure diastereoisomers and upon treatment with alkyl Grignard reagents, yielded alkyl methyl sulphoxides **282** of high enantiomeric purity (equation 155). In accord with the original Andersen assumption[342], the reactions of Grignard reagents with arene(alkane)sulphinates proceed with a full inversion of configuration at the sulphinyl sulphur atom. This steric course was firmly established by Mislow[350] and other investigators[351,352]. However, it was recently found that the reactions of alkyl *t*-butanesulphinates with methylmagnesium halides and alkyl methanesulphinates with *t*-butylmagnesium chloride are not fully stereoselective[353].

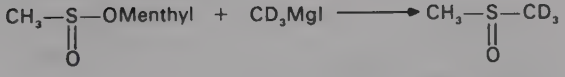
(155)

(281) **(282)**

The stereospecific conversion of menthyl arenesulphinates into chiral aryl methyl sulphoxides may also be achieved by means of methyllithium[354–356]. The reaction of methyllithium with diastereoisomerically[356] or enantiomerically[355] pure arenesulphinamides **283** was found to give optically active aryl methyl sulphoxides **284** (equation 156). The preparation of optically active sulphoxides **285** and **286**, which are chiral by virtue of isotopic substitution (H → D and $^{12}C \rightarrow {}^{13}C$, respectively), involves the reaction of the appropriate non-labelled menthyl sulphinates with fully deuteriated methyl magnesium iodide[357] (equation 157) and with benzylmagnesium chloride prepared from benzyl chloride labelled with carbon ^{13}C[358] (equation 158).

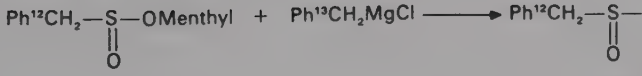
(156)

(283) **(284)**



(157)

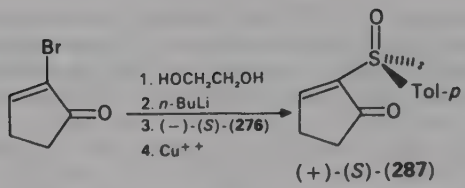
(285)



(158)

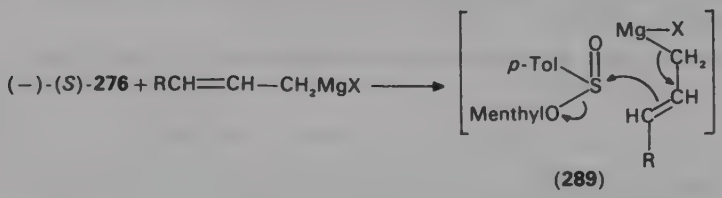
(286)

Further utility of the Andersen sulphoxides synthesis is demonstrated by the preparation of optically active unsaturated sulphoxides which were first prepared by Stirling and coworkers[359] from sulphinate **276** and the appropriate vinylic Grignard reagents. Later on, Posner and Tang[360] prepared in a similar way a series of (*E*)-1-alkenyl *p*-tolyl sulphoxides. Posner's group accomplished also the synthesis of (+)-(*S*)-2-(*p*-tolylsulphinyl)-2-cyclopentenone **287**, which is a key compound in the chiral synthesis of various natural products[361] (equation 159).

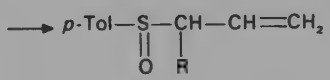


(+)-(*S*)-(**287**) (159)

Treatment of (−)-(*S*)-**276** with allyl Grignard reagents gives optically active allylic sulphoxides **288**. This reaction, however, involves an allylic rearrangement via transition state **289** as evidenced by Mislow and his collaborators[362] (equation 160).

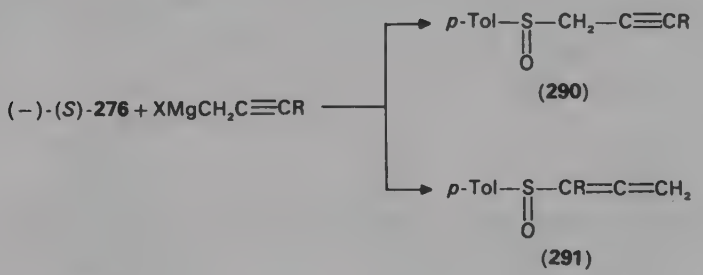


(**289**)

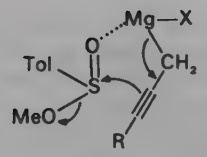


(**288**) (160)

A closely related reaction of (−)-(*S*)-**276** with the Grignard reagents obtained from α-acetylenic halides leads to the formation of mixtures of acetylenic sulphoxides **290** and allenic sulphoxides **291**[363] (equation 161). The latter compounds are most probably formed via transition state **292**, which is analogous to **289**. On the other hand, hex-1-ynyl *p*-tolyl sulphoxide **293** is smoothly prepared from hex-1-ynylmagnesium bromide and (−)-(*S*)-**276**[363] (equation 162).



(**290**) (**291**) (161)



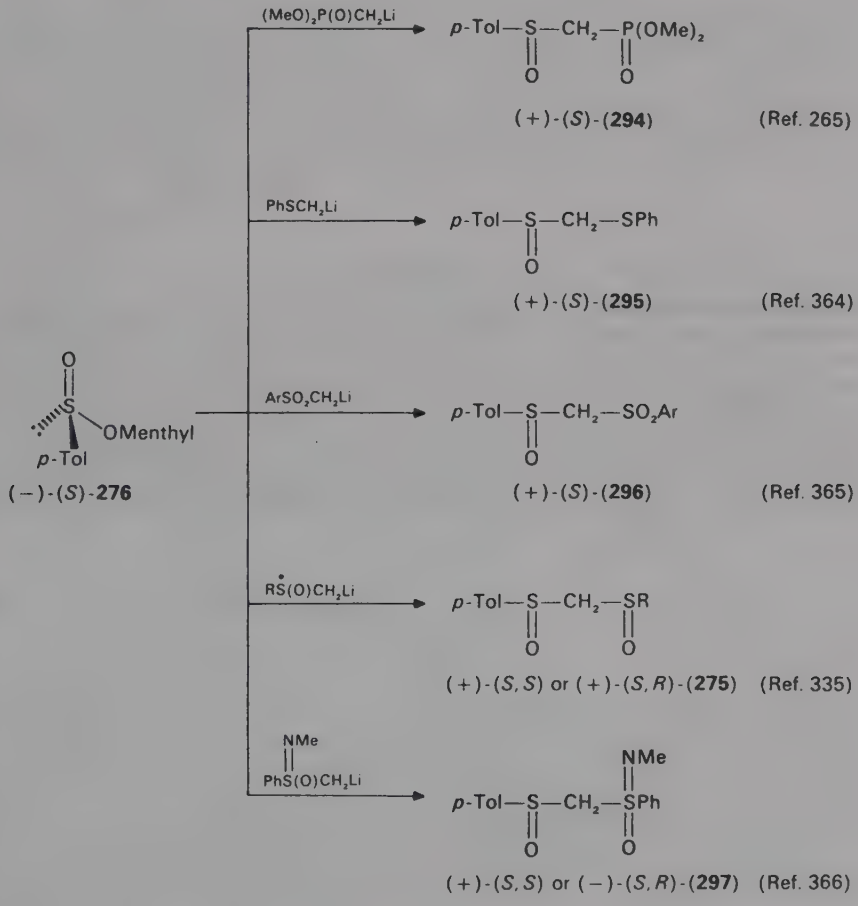
(**292**)

$$(-)\text{-}(S)\text{-}\mathbf{276} + BrMgC{\equiv}C{-}Bu\text{-}n \longrightarrow p\text{-}Tol{-}\underset{\underset{O}{\|}}{S}{-}C{\equiv}C{-}Bu\text{-}n \qquad (162)$$

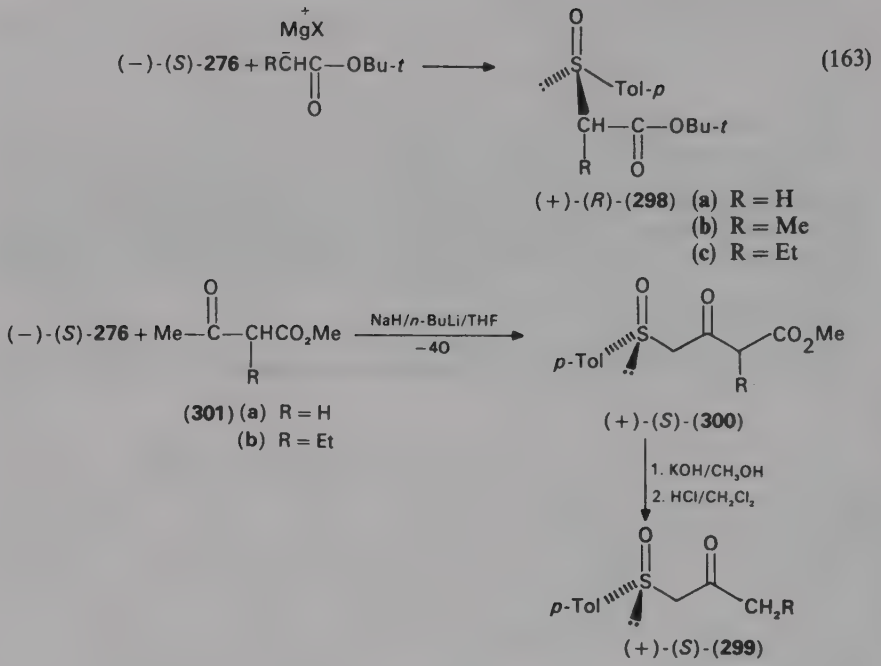
(293)

The Andersen sulphoxide synthesis allows one also to synthesize a variety of α-heteroatom substituted sulphoxides starting from α-heteroatom stabilized carbanions and (−)-(*S*)-**276**. The selected examples shown in Scheme 3 are the best illustration of the generality of this approach. The reaction of enolates or enolate like species with (−)-(*S*)-**276** has been used for the synthesis of optically active α-carbalkoxy sulphoxides. For example, treatment of (−)-(*S*)-**276** with the halogenomagnesium enolates of *t*-butyl acetate, *t*-butyl propionate or *t*-butyl butyrate resulted in the formation of (+)-(*R*)-*t*-butyl *p*-toluenesulphinylcarboxylates **298**[367] (equation 163).

Two chiral *p*-tolylsulphinylmethyl ketones **299** were prepared by decarboxylation of optically active sulphinyl ketoesters **300** which were obtained from (−)-(*S*)-**276** and the

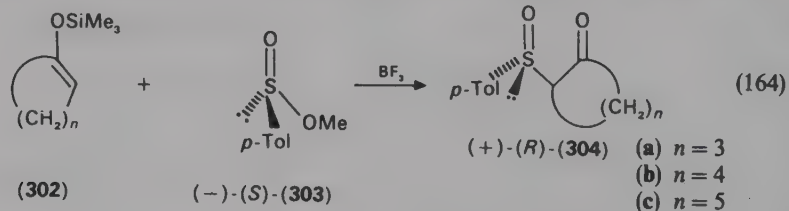


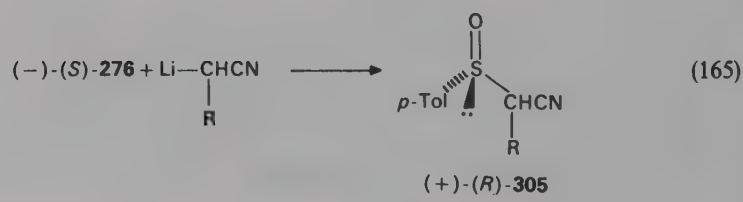
SCHEME 3



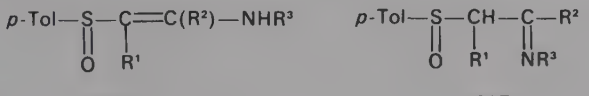
SCHEME 4

dianion derived from methyl acetoacetate **301**[368] (Scheme 4). The acid-catalyzed reaction of enol silyl ethers of cyclic ketones **302** with chiral methyl *p*-toluenesulphinate (−)-(*S*)-**303** was found[369] to be a very convenient and general entry to optically active α-sulphinylketones **304** (equation 164). Boron trifluoride etherate, titanium tetrachloride and tin tetrachloride were applied as acidic catalysts. The highest chemical and optical yields were obtained with boron trifluoride. The reaction of α-cyanocarbanions with (−)-(*S*)-**276** afforded the corresponding α-cyanoalkyl *p*-tolyl sulphoxides (+)-(*R*)-**305** in high chemical yield and optical purity[370] (equation 165). In the reaction of α-lithiated imines

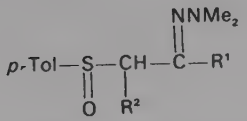




with this sulphinate, optically active β-enamino **306** and/or β-iminosulphoxides **307** were formed[371]. In an analogous way, optically active α-sulphinylhydrazones **308** were prepared from (−)-(*S*)-**276** and α-metallated *N*,*N*-dimethylhydrazones[372].

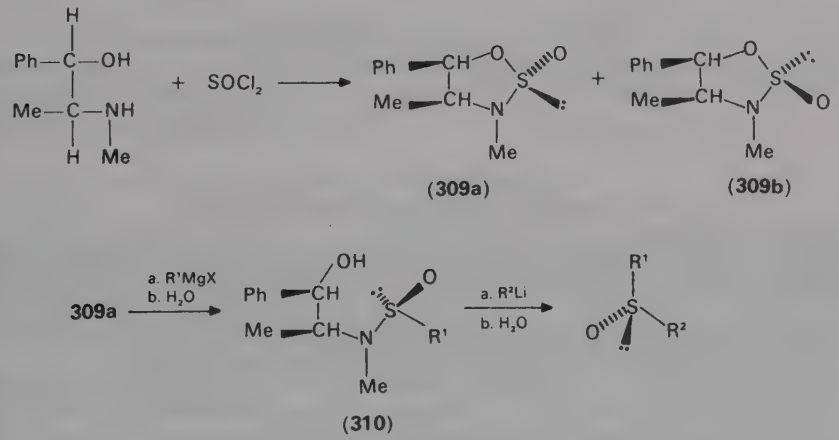


(306) **(307)**



(308) R¹, R² = H, Alkyl, Aryl

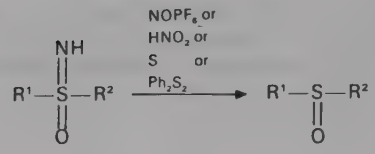
A highly stereoselective cleavage of the S—O bond in cyclic diastereoisomeric amidosulphites **309** by Grignard reagents followed by highly stereoselective cleavage of the S—N bond with alkyllithium reagents in the formed chiral sulphinamides **310**, are the key steps in the stereospecific synthesis of chiral sulphoxides reported by Wudl and Lee[373] (Scheme 5). The precursor amidosulphite **309** was easily prepared from 1-ephedrine and thionyl chloride. It is interesting to note that the order of introduction of the groups R^1 and R^2 determines the configuration of the optically active sulphoxides formed.



(309a) **(309b)**

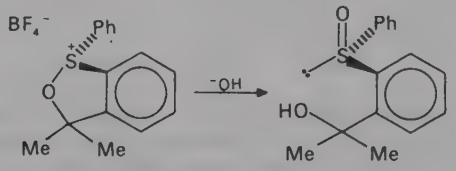
SCHEME 5

A different approach to optically active sulphoxides of high optical purity involves the stereospecific deimination of optically active sulphoximides **213**. These compounds are sufficiently basic and are easily resolved into enantiomers through the formation of the diastereoisomeric salts with optically active sulphonic acids[374]. The stereospecific conversion of sulphoximides **213** into the corresponding sulphoxides was acheived by a low-temperature reaction with nitrosyl hexafluorophosphate or nitrous acid[375]. An alternative deimidation procedure consists in heating at 160 °C with elemental sulphur or diphenyl disulphide (equation 166). All these procedures afford chiral sulphoxides with retention of configuration at the sulphur atom[376].

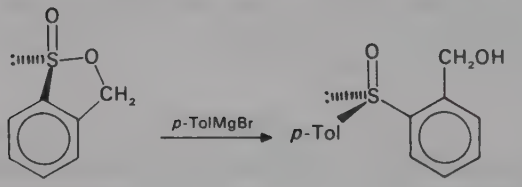


(213) (166)

Optically active sulphoxides **311** and **312** have been prepared stereospecifically either by hydrolysis of the optically active sulphonium salt **313** or by the reaction of *p*-tolyl magnesium bromide with optically active sulphinate **314**, respectively[377] (equations 167 and 168).



(+)-(*S*)-(**313**) (−)-(*S*)-(**311**) (167)



(+)-(*S*)-(**314**) (+)-(*R*)-(**312**) (168)

IV. FUNCTIONALIZATION OF SULPHOXIDES

Functionalization of organic substituents adjacent to the sulphoxide moiety constitutes an important method of the synthesis of a variety of sulphoxides, which are not available by the methods described in the previous sections. Such transformations enable one to synthesize a large number of very sophisticated sulphoxides which are required for special purposes or serve as a source of many sulphur-free organic compounds.

Since a great number of such transformations were described in the chemical literature, only selected examples of general importance will be presented here. This section will consist of the following parts: reactions of the sulphoxide α-carbanions; introduction, substitution, transformation and elimination of heteroatomic groups attached to organic substituents in sulphoxides; additions to unsaturated sulphoxides; other modifications of organic substituents in sulphoxides.

A. Reactions of the Sulphoxide α-Carbanions

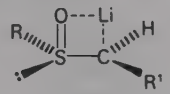
1. Generation of carbanions

Formation of α-sulphinyl carbanions has been widely investigated[378,379]. Several bases have been found to be suitable for the generation of these carbanions, including the use of

methyllithium and LDA which enable formation of carbanions at low temperatures. On the other hand, *n*-butyllithium and *t*-butyllithium must be used with caution since they can cause cleavage of the carbon–sulphur bond, resulting in an exchange of the organic substituent[380,381]. Other basic reagents, such as sodium hydride, sodium or potassium *t*-butoxide, though also effective, particularly for a generation of the methylsulphinyl carbanion in DMSO solution, may cause in some cases side-reactions leading to undesired products arising from condensation reactions of the carbanions formed. Sodium amide in liquid ammonia, when used in an appropriate excess, generates a dianion[382].

Generation of anions α to the sulphinyl group takes place also in 1-alkenyl sulphoxides and can easily be achieved by using such bases as LDA[383–385], *t*-BuLi[386] and *n*-BuLi (for allenyl sulphoxides)[387].

In contrast to the early theoretical work of Rauk and coworkers[388], ^{13}C-NMR investigations had revealed that the metallated carbon atom in the α-sulphinyl carbanion is nearly planar[389,390]. A four-centre chelate structure **315** has been proposed for α-lithiosulphoxides, and it is believed to be responsible for the planar configuration of the anionic carbon atom[389] and for the greater stability of α-sulphinyl carbanions in comparison with α-sulphenyl carbanions[391]. This chelation favours one of the two diastereoisomeric carbanions and for this reason α-sulphinyl carbanions react with electrophiles in a highly stereoselective manner (see below).



(315)

A detailed discussion of the different acidities of the diastereotopic α-methylene protons in sulphoxides, as well as of the stereochemistry of reactions of sulphoxide α-carbanions with electrophilic reagents is beyond the scope of this chapter. A recent review by Wolfe pertinent to these problems is available[392].

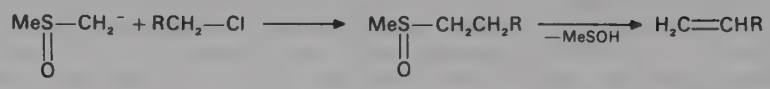
2. *Reactions of α-sulphinyl carbanions with electrophiles*

a. General remarks. Reactions of α-sulphinyl carbanions with electrophilic reagents have been widely applied, usually at one of the stages in multistep syntheses of organic compounds. Very often the sulphinyl moiety which served as a carbanion stabilizing group is finally removed giving sulphur-free products.

In this section alkylation, Michael additions, hydroxyalkylation (reaction with carbonyl compounds), aminoalkylation, acylation and some other reactions of α-sulphinyl carbanions will be discussed.

b. Alkylation of α-sulphinyl carbanions. Simple alkylation of α-sulphinyl carbanions is usually used as a first step in a sequence of reactions leading to sulphur-free organic compounds. Entwistle and Johnstone[393] and later Trost and Bridges[394] obtained in this way a variety of alkenes via the well-known elimination of sulphenic acid (equation 169). Oxiranes react with α-sulphinyl carbanions to give γ-hydroxy sulphoxides[395–397]. The reaction of the anion of optically active methyl *p*-tolyl sulphoxide with cyclohexene oxide was used by Tsuchihashi and coworkers for the synthesis of optically active 2-hydroxy-1-methylcyclohexanes[398] (equation 170). Guittet and Julia alkylated phenyl lithiomethyl sulphoxide with methallyl chloride to obtain the homoallyl sulphoxide **316** which, after subsequent treatment with a base and an oxirane, gave the γ-hydroxysulphoxide **317**. The latter underwent elimination of benzenesulphenic acid to give (*E*)–hotrienol **318**, a

naturally occurring monoterpene[395] (equation 171).



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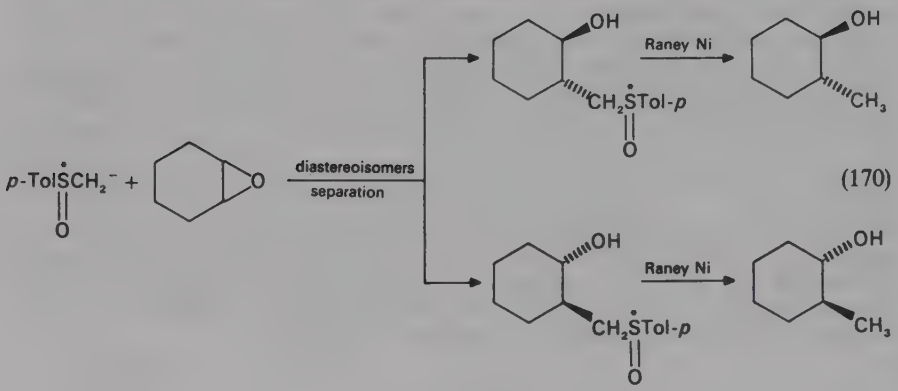

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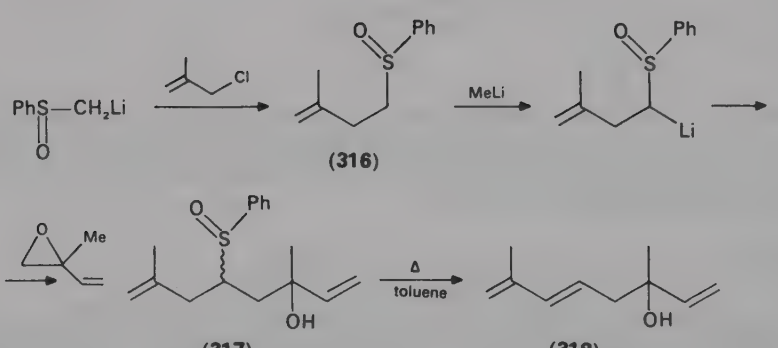
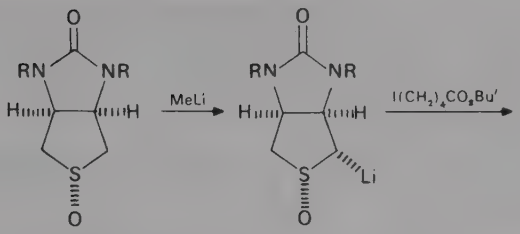


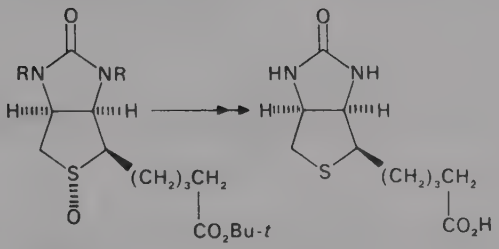
(171)

An interesting application of alkylation of α-sulphinyl carbanions was reported by Marquet and coworkers[317] in their total synthesis of biotine **321** (equation 172). The carbanion **319** generated by MeLi in a HMPT–THF or HMPT–diglyme mixture was alkylated by *t*-butyl ω-iodovalerate. The reaction was highly stereoselective and a single isomer with a side-chain *trans* to the S—O bond was obtained. It must be stressed, however, that the choice of the base and the solvent is crucial for the alkylation yield. More recently, a high diastereoselection (80%) was observed in the alkylation of α-sulphinyl anion with α-bromomethyl acrylate. In this case also the choice of the base appears to be decisive—the highest asymmetric induction is found when metallation of the sulphoxide is carried out by using highly hindered bases, e.g. lithium tetramethylpiperidine[399] (equation 173).

It has been found that aryl groups can also be introduced into the α-position of sulphoxides. Corey and Chaykovsky have demonstrated that chlorobenzene reacts at room temperature with an excess of sodium methylsulphinyl carbanion to give methyl benzyl sulphoxide in 41% yield. The authors believe that a benzyne intermediate may be involved in the reaction[400,401] (equation 174).

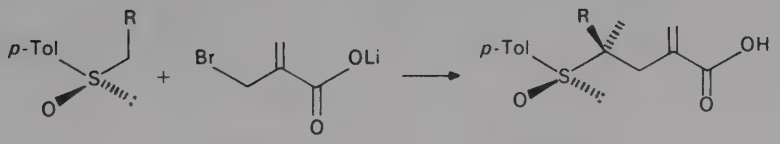


(263) (319)



(320) (321)

(172)



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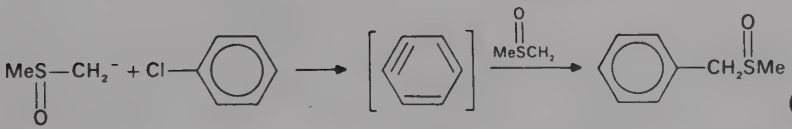
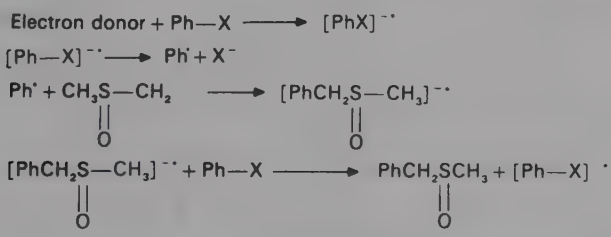


(174)

A similar goal can be achieved using the conditions of the $S_{RN}1$ reaction. The anion of DMSO is generated by $NaNH_2$ in DMSO and the $S_{RN}1$ reaction is initiated by sunlight[402] (Scheme 6).

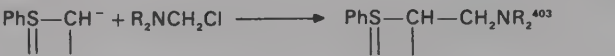
Alkylation of carbanions of α-halogenomethyl sulphoxides enables one to elongate the alkyl chain[403–406] (equations 175 and 176). α-Chlorosulphoxides react with nitroarenes in



SCHEME 6

the presence of bases B (powdered NaOH in DMSO, NaOH in liquid ammonia, Bu_4NOH in *o*-dichlorobenzene or 50% aq NaOH + Bu_4NHSO_4 in benzene) to give the corresponding sulphoxides **322** in yields of 45–68% via the so-called 'vicarious substitution'[407] (equation 177). Nitrobenzyl phenyl sulphoxides serve as a source of a variety of nitroarenes (e.g. equation 178).

Carey and Hernandez have reported that phenyl trimethylsilylmethyllithio sulphoxide reacts with alkyl iodides to give the corresponding phenyl α-trimethylsilylalkyl sulphoxides[166] (equation 179).



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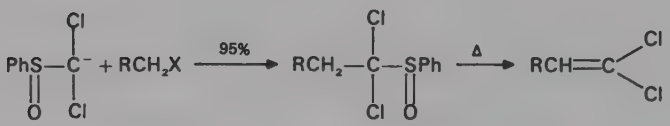

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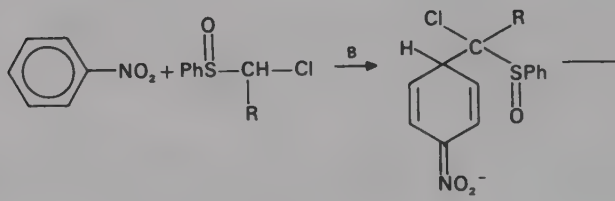

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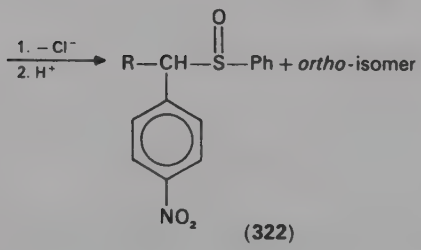

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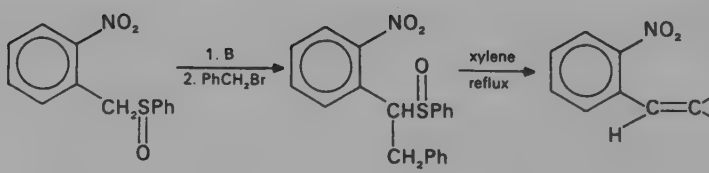

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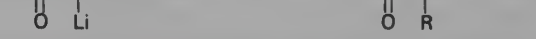
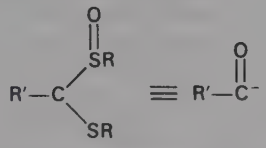


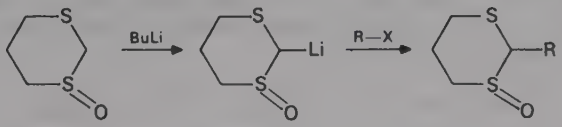
(179)

From the synthetic point of view the most important α-sulphinyl carbanions are the anions derived from dithioacetal *S*-oxides which may be considered as synthons of acyl

anions (for reviews see References 408 and 409).



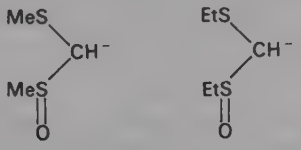
Carlson and Helquist[410] were the first to perform the alkylation of 2-lithio 1,3-dithian-*S*-oxide **323** (equation 180). The yields of this reaction appeared, however, to be low. In spite of the fact that dithian-*S*-oxides have been intensively investigated[268,411], their synthetic applications are rather limited.



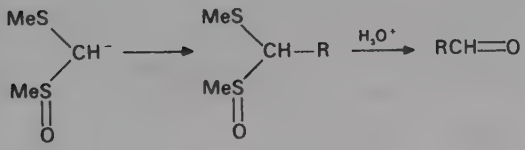
(180)

(236) **(323)**

The anions of alkyl alkylthiomethyl sulphoxides have found a much broader application. Methyl methylthiomethyl sulphoxide **324** was first introduced by Ogura and Tsuchihashi in 1971[412] and ethyl ethylthiomethyl sulphoxide **325** was synthesized by Schlessinger and coworkers in 1973[413]. Ogura and Tsuchihashi performed alkylation of **324** and obtained a series of substituted dithioacetal monoxides **326** which were then hydrolysed to the corresponding aldehydes (equation 181; Table 17)[412].



(324) **(325)**



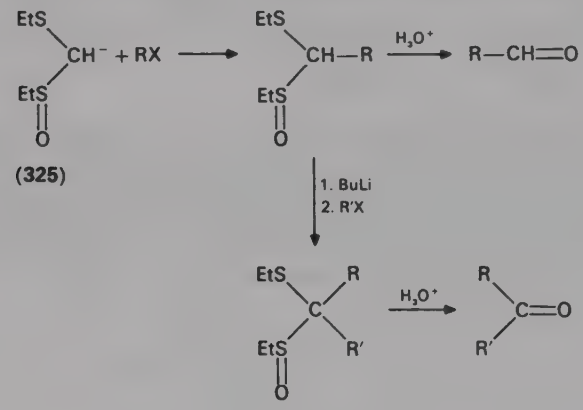
(181)

(324) **(326)**

TABLE 17. Alkylation of the methyl methylthiomethyl sulphoxide anion **324**

Halide	Yield of sulphoxide **326** (%)	Yield of aldehyde (%)
MeI	92	84
n-C_4H_9I	72	91
$PhCH_2Br$	92	88
p-$BrC_6H_4CH_2Br$	37	88

Schlessinger and coworkers[413] claim that the use of ethyl ethylthiomethyl sulphoxide **325** leads to much better yields of the alkylation products. In fact, all the alkylated products were obtained from **325** in yields exceeding 95%. Moreover, the anion **325** may undergo a double alkylation, which enables one to obtain not only aldehydes but also the corresponding ketones (equation 182). Schill and Jones performed a similar cycle of reactions using sodium hydride as a base[29]. Newcome and coworkers reacted methyl methylthiosodiomethyl sulphoxide with bromopyridines and obtained, after hydrolysis, the corresponding pyridine aldehydes **327**[414] (equation 183). Evans and colleagues utilized the alkylation of **324** as a key reaction in their synthesis of the ionophore antibiotic A-23187 (equation 184)[415]. Marshall and Wuts described a method of the synthesis of hexahydronaphthalenol **328** which involves the alkylation of **325**[416] (equation 185). Dithioacetal *S*-oxides undergo easily cycloalkylation reaction when reacted with α,ω-dihalogenoalkanes[417–419] (equations 186, 187). This reaction has been applied to the synthesis of optically active 4-hydroxycyclopentenone **329**[420] (equation 188).



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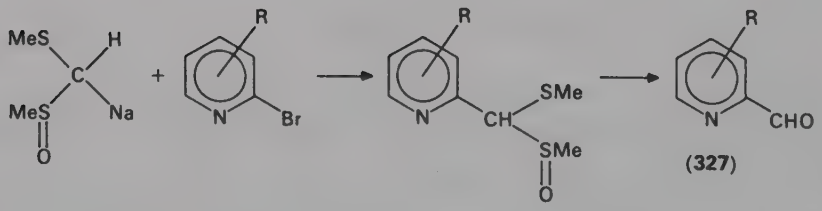

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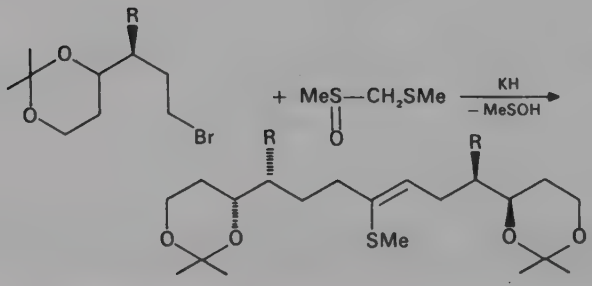

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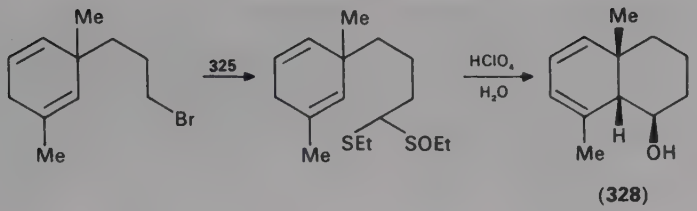

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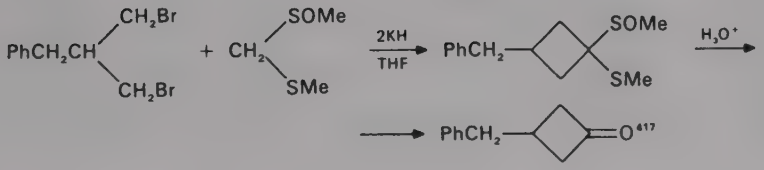

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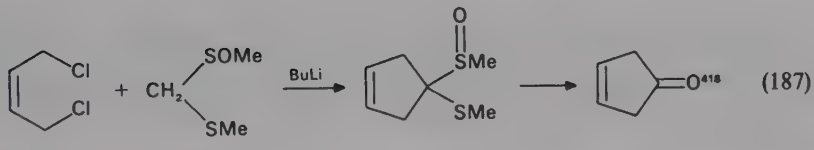

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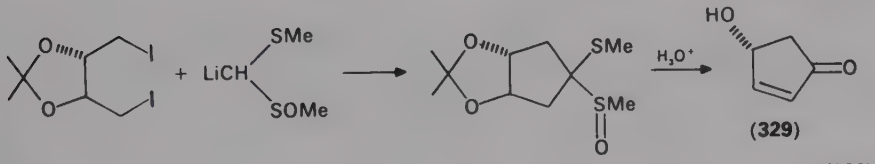
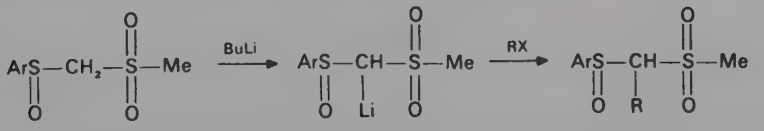


(329)

(188)

Similarly to simple sulphoxides, aryl methylsulphonylmethyl sulphoxides **330** undergo facile alkylation[164] (equation 189). Annunziata and Cinquini have used a chiral analogue of sulphonyl sulphoxides, i.e. phenyl *p*-tolylsulphinylmethyl sulphoximine **297** having two chiral moieties, both capable of inducing optical activity at the α-carbon atom[366] (equation 190). The reaction of the diastereoisomerically pure **297** with alkyl halides was performed under phase-transfer catalytic conditions and resulted in a high asymmetric induction on the α-carbon atom (Table 18). It is interesting to note that the sulphinyl group in **297** exerts the stronger effect on asymmetric induction[366].



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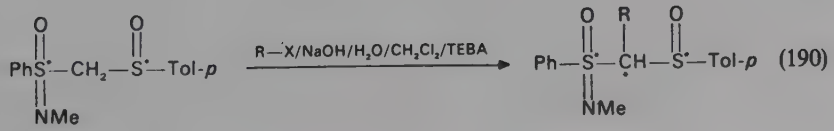


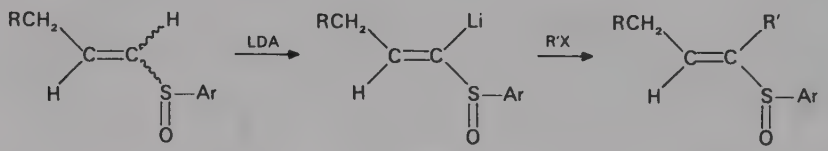
(190)

(297)

TABLE 18. Asymmetric alkylation of **297**

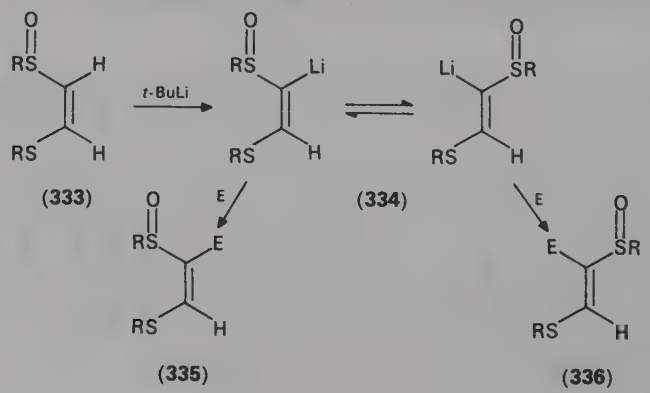
Substrate **297**	Alkyl halide	Yield, alkylated product (%)	Diastereoisomeric ratio
(+)-(*S*,*S*)	$H_2C{=}CH{-}CH_2Br$	93	100:0
(−)-(*S*,*R*)	$H_2C{=}CH{-}CH_2Br$	87	83:17
(+)-(*S*,*S*)	$PhCH_2Br$	77	100:0
(−)-(*S*,*R*)	$PhCH_2Br$	79	80:20
(+)-(*S*,*S*)	$HC{\equiv}C{-}CH_2Br$	91	100:0
(−)-(*S*,*R*)	$HC{\equiv}C{-}CH_2Br$	73	100:0
(+)-(*S*,*S*)	EtBr	80	100:0
(−)-(*S*,*R*)	EtBr	82	80:20
(+)-(*S*,*S*)	EtI	70	100:0
(+)-(*S*,*S*)	*n*-BuBr	30	100:0

As mentioned above, 1-alkenyl aryl sulphoxides can effectively be α-lithiated by treatment with a slight excess of LDA in THF at −78°. The 1-(arylsulphinyl)alkenyllithium reagents **331** so generated react cleanly and rapidly with a variety of electrophiles to give 1-substituted 1-alkenyl sulphoxides **332** in high yields (equation 191).



(331) **(332)** (191)

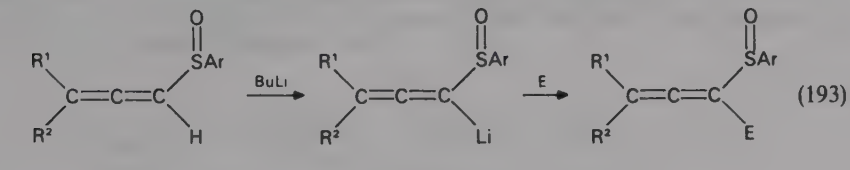
α-Sulphinylalkenyl carbanions appeared to be configurationally unstable. Hence, alkylation of *E*- and *Z*-1-alkenyl sulphoxides leads almost exclusively to the corresponding *E*-2-alkenyl sulphoxides[383–385]. The monosulphoxide **333** obtained from *Z*-dimercaptoethylene gives on treatment with *t*-BuLi α-deprotonated species **334**. The latter are configurationally labile and therefore their reaction with electrophiles affords the two products **335** and **336**[386] (equation 192). Allenyl sulphoxides **337** are also readily metallated at the α-position with BuLi to give the corresponding lithio-derivatives **338**



(333) **(334)** (192)

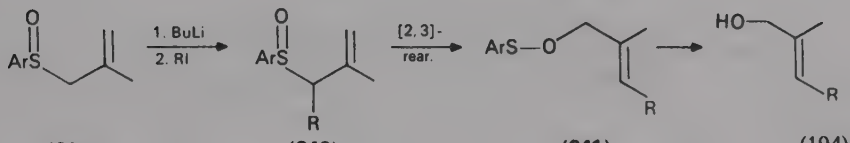
(335) **(336)**

which may react with various electrophiles[387] (equation 193). α-Sulphinyl carbanions, generated easily from 2-alkenyl sulphoxides **339** by BuLi or LDA, can be alkylated. However, the resulting products **340** undergo a [2,3] sigmatropic rearrangement to the corresponding sulphenates **341**. The latter give, after desulphurization, a variety of allylic alcohols[421–426] (equation 194). This method has been applied to the synthesis of 3-hydroxycycloalkenes[423] (equation 195) and terpene alcohols[424] (equation 196).

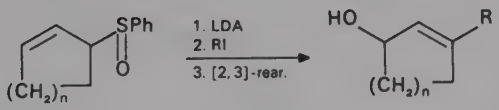


(193)

(337) (338)



(339) (340) (341) (194)



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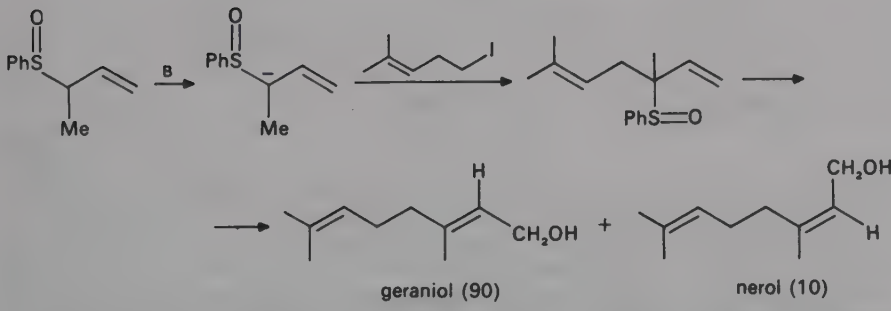
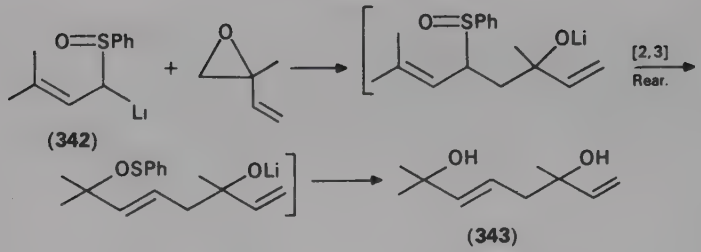


geraniol (90) nerol (10)

(196)

The reaction of the phenylsulphinyl allylic lithium α-carbanion **342** with oxiranes was found by Guittet and Julia to give, after rearrangement and desulphurization, dihydroxydienes **343**[427] (equation 197). Demoute and coworkers have described the alkylation reaction of a very sophisticated 2-alkenyl sulphoxide **344** as a part of the total synthesis of a juvenile hormone **345**[428] (equation 198). Since the allylic sulphoxide carbanion has an ambident character, the alkylation may occur sometimes also at the γ-position. This direction of alkylation is observed in the case of acyclic allylic sulphoxide anions **346**, and results in the formation of the corresponding allylic sulphoxide **347** and vinylic sulphoxide **348**[423] (equation 199).



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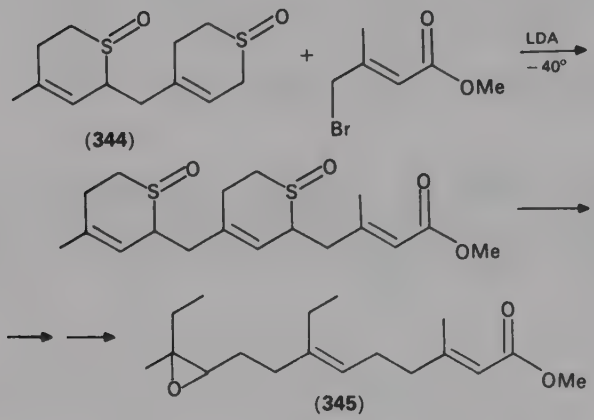

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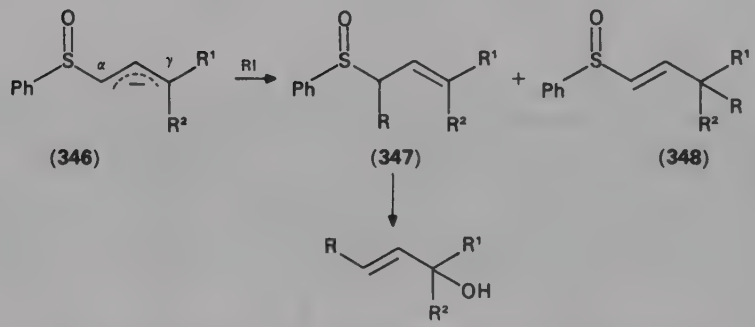
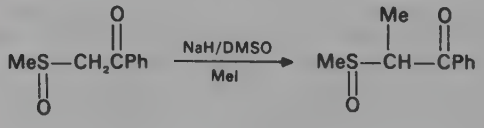


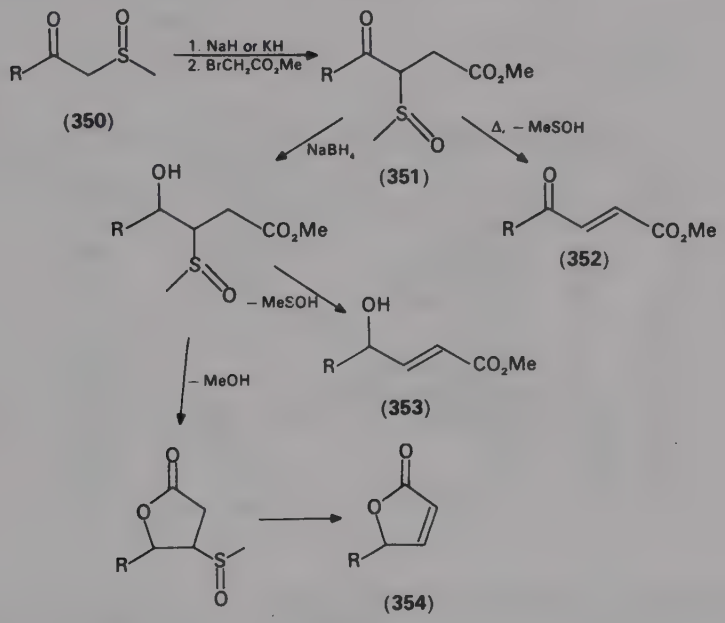
(199)

Alkylation of α-ketosulphoxides **349** creates many interesting synthetic possibilities, since it proceeds easily and allows one to introduce a large number of substituents. The α-ketosulphoxide anion is usually generated by means of sodium or potassium hydride[429] (equation 200). It is also possible to carry out the alkylation of α-ketosulphoxides under phase transfer catalysis conditions, using the $CH_2Cl_2/Bu_4NHSO_4/NaOH$ aq system[430].



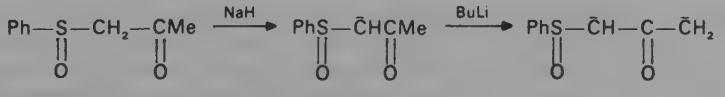
(200)

Bartlett has reported on the alkylation of α-ketosulphoxides **350** with methyl bromoacetate. The product obtained **351** was further transformed into β-keto or γ-hydroxy-α,β-unsaturated esters **352** and **353** and butenolides **354** and other organic compounds[431] (Scheme 7). It is also possible to generate a dianion **355** from α-ketosulphoxides by a subsequent addition of NaH and BuLi[432–434] (equation 201). It undergoes exclusive alkylation at the γ-carbon atom and the α-phenylsulphinyl ketones formed undergo, in turn, a ready elimination of benzenesulphenic acid affording alkyl vinyl ketones[433,434]. The generality of this approach is illustrated by the examples collected in Table 19 (see equation 202 in the table).



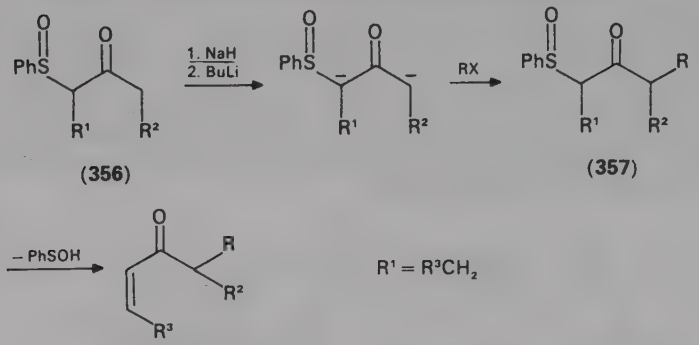
SCHEME 7

The anions derived from α-sulphinyl carboxylic esters **358** can also be easily generated by NaH or LDA[435–437]. Their reaction with alkyl halides gives monoalkylated products **359** which can be transformed into α,β-unsaturated esters **360** (equation 203; Table 20). When a second equivalent of NaH and alkyl halide is added either in one step or in a two-step procedure, the α,α-dialkylated esters can be prepared[436]. The reaction of the anions of α-sulphinyl carboxylic esters with π-allylpalladium complexes **361** (directly available from the corresponding olefins) leads to substitution at the allylic position of an olefin[437–439] (equation 204). In sharp contrast to the highly stereospecific behaviour of the methylene protons of benzyl methyl sulphoxide, the reactivity of the two diastereotopic methylene protons in arylsulphinylacetates is comparable. Solladie and coworkers[367] have investigated the alkylation of optically active *t*-butyl *p*-tolylsulphinylacetate and α-substituted



(201)

TABLE 19. Alkylation of the dianions of α-ketosulphoxides **356**



(202)

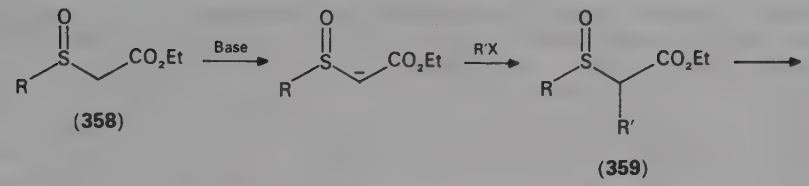
R^1	R^2	R—X	Yield of **357** (%)	Refs.
H	H	n-$C_6H_{13}Br$	79	432
H	H	$C_6H_5CH_2Br$	73	432
H	H	$CH_2{=}CHCH_2Br$	64	432
CH_3	H	$C_6H_5CH_2Br$	72	433
CH_3	H	MeI	65	433
CH_3	H	n-BuI	84	433
CH_3	H	Geranyl chloride	71	433
CH_3	H	$CH_3C(Cl){=}CHCH_2Cl$	70	433
$CH_2{-}CH_2$		$C_6H_5CH_2Br$	50	434
$CH_2{-}CH_2$		n-BuI	65	434
$CH_2{-}CH_2$		EtI	60	434
$CH_2{-}CH_2$		$CH_3C(Cl){=}CHCH_2{-}$ Cl	34	434

TABLE 20. Alkylation of α-sulphinyl carboxylic esters **358**

R	R′	Base	Yield of **359**	or **360**	Refs.
CH_3	n-Pr	NaH/DMSO	60		436
CH_3	n-Bu	NaH/DMSO	54		436
CH_3	CH_2Ph	NaH/DMSO	73		436
CH_3	Et	NaH/DMSO	82		436
CH_3	CH_2CO_2Et	NaH/DMSO	65		
Ph	CH_2Ph	NaH or LDA in HMPT		30	437
Ph	$MeO_2CCH_2(CH_2)_4$	NaH or LDA in HMPT		82	437
Ph	$\lceil{=}(CH_2)_9$	NaH or LDA in HMPT		80	442

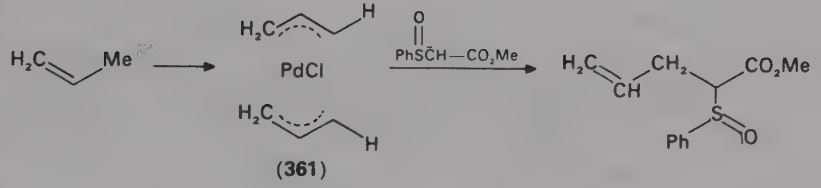
analogues (+)-(*R*)-**298** and found that the stereoselectivity of the alkylation is very poor, being lower than 42:58. Moreover, the alkylation has been found to proceed only when BuLi was used as a base and methyl iodide as an alkylating agent[367].

The dianion of 2-carboxyethyl phenyl sulphoxide **362** undergoes alkylation at the α-position to the sulphinyl group[440,441] (equation 205).

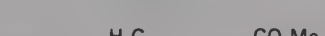


(358) (359)

(360) (203)



(361)



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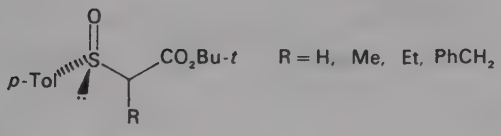
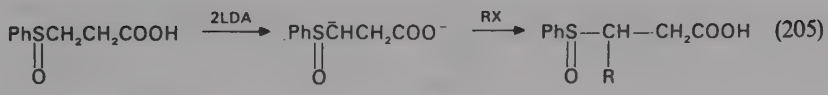


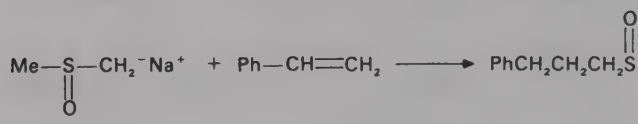
(+)-(*R*)-(**298**)



(362) (205)

c. Michael addition of α-sulphinyl carbanions. The addition of a variety of α-sulphinyl carbanions to activated alkenes can be easily achieved. Thus, methylsulphinylmethyl carbanion obtained from dimethyl sulphoxide adds even to such unusual Michael acceptors as styrenes (equation 206), although in some cases undesired side-reactions may prevail[442–444]. Treatment of *E*-homoallylic eight- to ten-membered ring sulphoxides with BuLi in THF results in a transannular addition of the α-sulphinyl carbanion generated to the *E*-double bond, leading to bicyclic products[445] (equation 207). Alkynes react with α-sulphinyl carbanions to yield 2-alkenyl sulphoxides **363**[446] (equation 208). α-Sulphinyl carbanions add to unsaturated ketones in a 1,4-manner, leading to γ-sulphinyl ketones **364**[447–449] (equation 209). Boger and Mullican have exploited this reaction, followed by a subsequent aldol condensation, for the synthesis of annelated phenols[447] **365** (equation 210). Hauser and Rhee used the reaction for the synthesis of regioselectively constructed naphthalenes[448] and anthracenes **366**[449] (equation 211). The reaction of α-sulphinyl carbanions with α,β-unsaturated esters proceeds in a similar way[450,451]. Ghera and Ben-David have found that the conjugated addition of α-sulphinyl carbanions to ethyl

4-bromocrotonate is followed by displacement of bromide anion which affords cyclopropanecarboxylates **367**[452] (equation 212). The anions derived from (*R*) and (*S*) deacetoxycephalosporanate 1-oxides **368** afford, under very mild conditions, the Michael adducts with acrylonitrile[452] (equation 213). α-Ketosulphoxide carbanions **369** undergo facile Michael reaction with α,β-unsaturated esters, ketones and nitriles[453,454] (equation 214). When an excess of a base and the Michael acceptor is used, the products of a double addition are obtained[453]. The dianion of β-ketosulphoxides **370** reacts with α,β-



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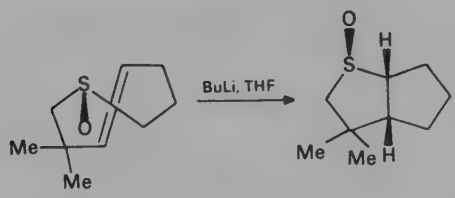

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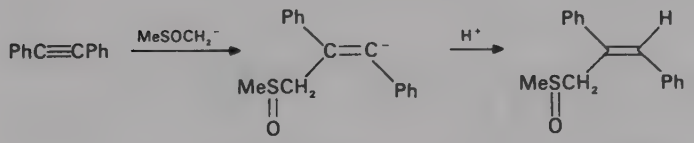
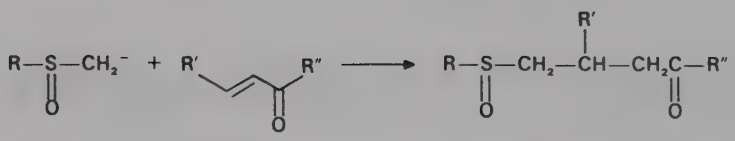


(208)

(**363**)



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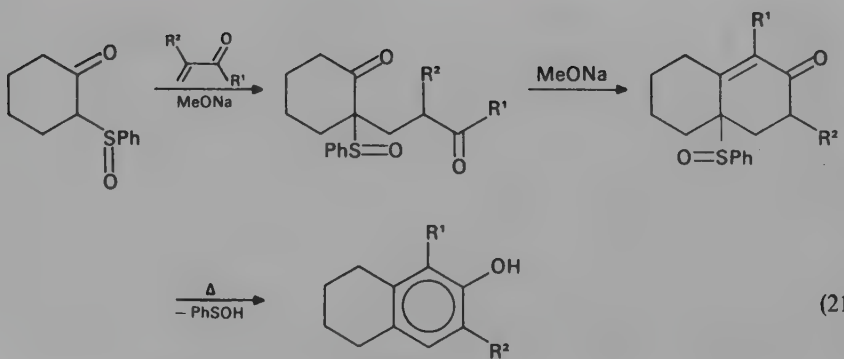
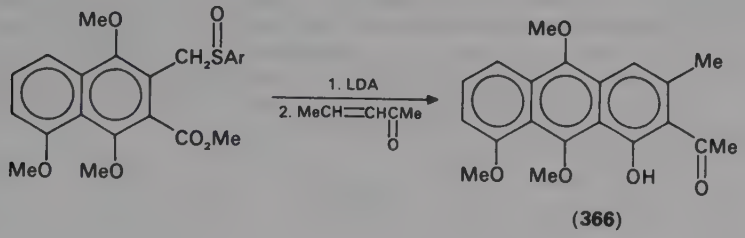
(**364**)



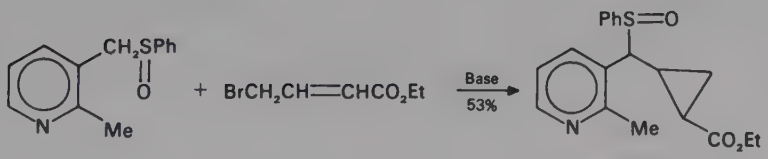
(210)

(**365**)

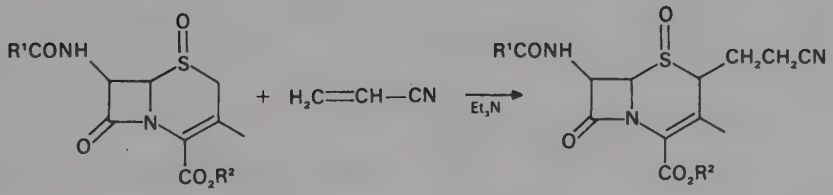
unsaturated carbonyl compounds to give the products of both 1,4- and 1,2-additions **371** and **372**, respectively[432] (equation 215). The carbanion derived from α-sulphinyl acetate



(366) (211)



(367) (212)



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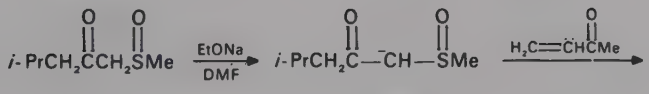

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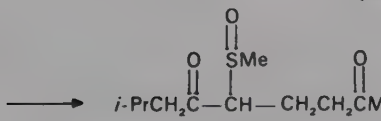

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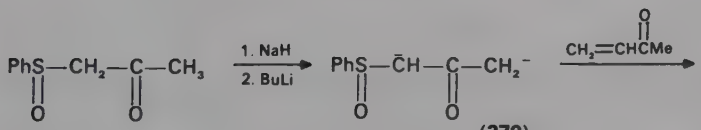

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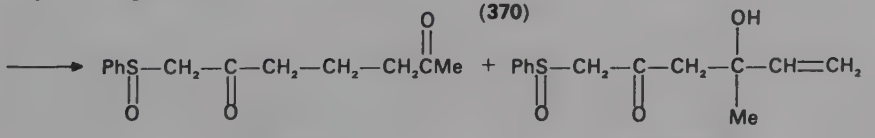
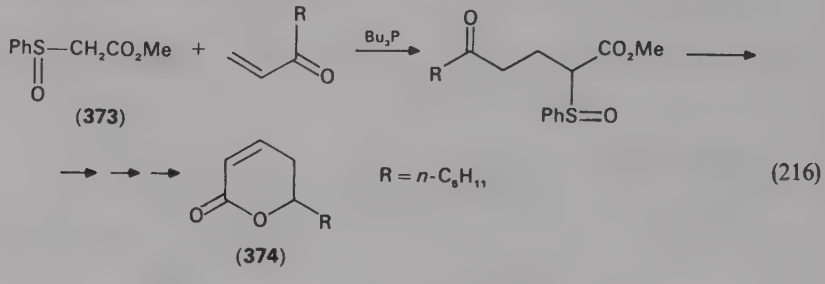


(371) (35%) (372) (65%) (215)

373 adds easily to α,β-unsaturated carbonyl compounds[436,455,456]. The reaction has been applied, among others, to the synthesis of α,β-unsaturated δ-lactones[456] **374** (equation 216). Michael addition of the enolate anion generated from (+)-(*R*) *t*-butyl α-*p*-toluenesulphinylacetate **298a** to α,β-unsaturated esters occurs with asymmetric induction and the optical purity of a newly created asymmetric carbon centre in **375** varies from 12 to 24%[457] (equation 217). In the reaction of the lithium salts of dithioacetal monoxides **376** with α,β-unsaturated carbonyl compounds the products of both 1,2-(**377**) and 1,4-(**378**) additions are formed (equation 218; Table 21)[458].



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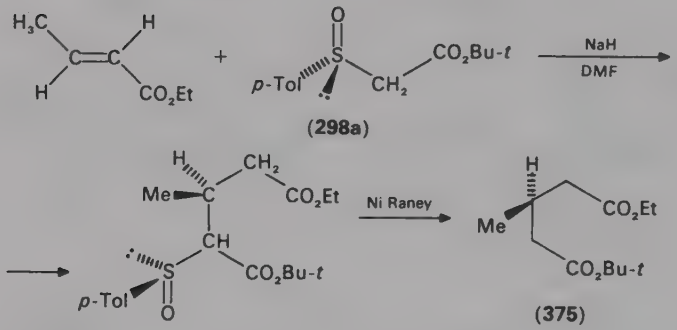

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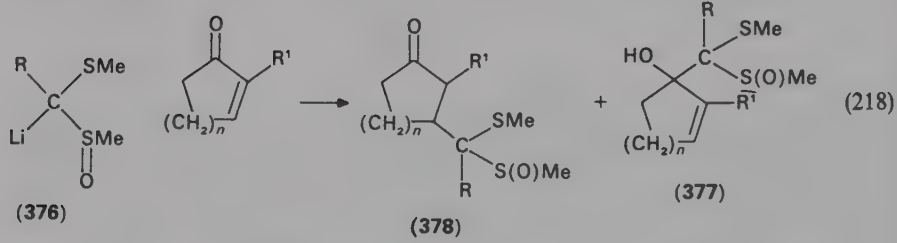


(218)

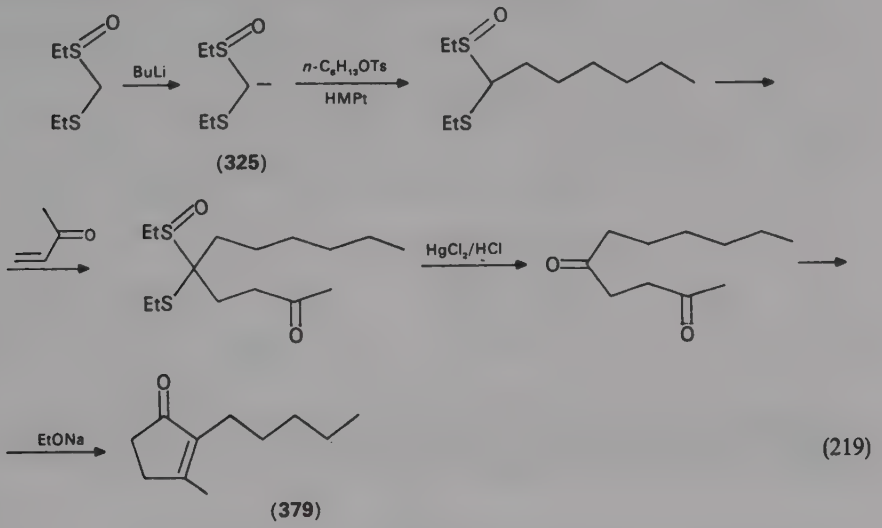
TABLE 21. Addition of dithioacetal monoxide lithium salts **376** to cyclic α,β-unsaturated ketones

R	R^1	*n*	Temp (°C)	Total yield (%)	**378**:**377** Ratio
H	H	1	−78	79	72:28
Me	H	1	−78	89	68:32
Me	H	1	0	68	28:72
H	CH_2Ph	1	−78	68	29:71
H	$(CH_2)_6CO_2Me$	1	−78	73	30:70
H	H	2	−78	75	9:91

The ratio of the 1,2- to 1,4-adducts depends on several factors and the following general conclusions may be formulated[458]:

1. In the case of cyclohexenone the product of 1,2-addition always prevails.
2. In the case of cyclopentenone derivatives introduction of a substituent at the 2-position reduces the yield of 1,4-adduct.
3. Higher temperatures promote 1,2-addition.
4. The presence of HMPT promotes 1,4-addition[459].

Ethyl ethylthiomethyl sulphoxide anion **325** has been found to give better yield of 1,4-adducts compared with its methyl analogue[460]. This anion has been used by Schlessinger and coworkers as a key reagent in the synthesis of 1,4-dicarbonyl precursors of naturally occurring cyclopentenones, e.g. dihydrojasmone[461] **379** (equation 219). Michael addition of the anion of optically active (+)-(*S*)-*p*-tolyl *p*-tolylthiomethyl sulphoxide **380** to the properly substituted cyclopentenone constitutes an important step in the asymmetric synthesis of optically active cyclopentenone **381**, which is a precursor of 11-deoxy-ent-prostanoids[462] (equation 220). The reaction proceeds with a high β- and γ-asymmetric induction (92%), but with a poor α-stereoselection (52:48).



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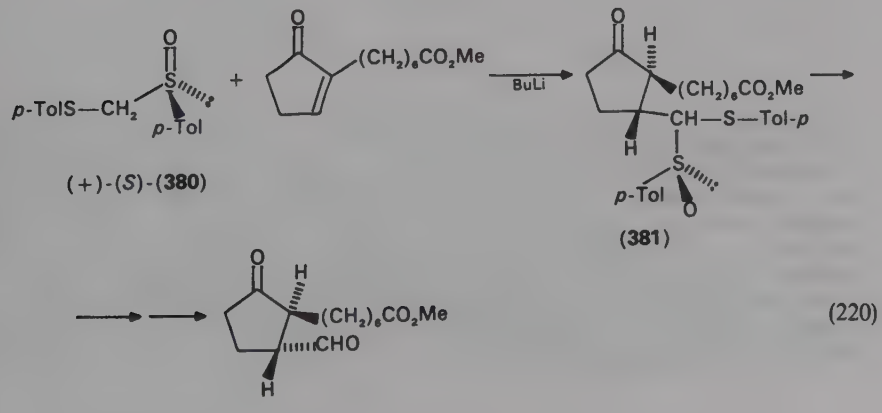
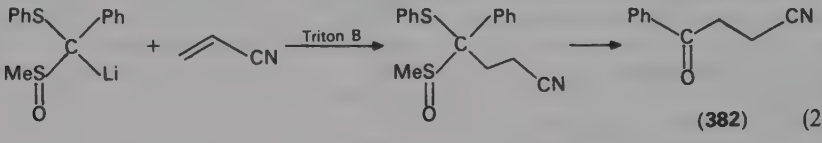
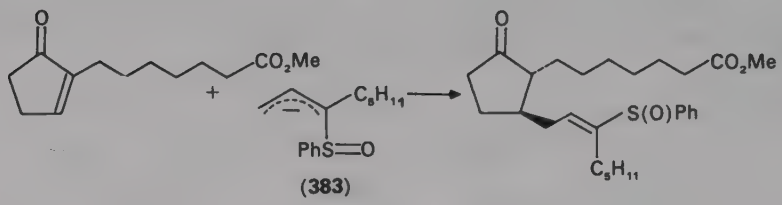


(220)

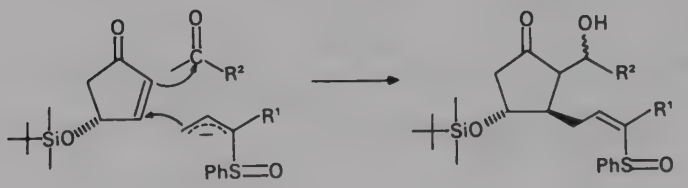
Dithioacetal monoxides undergo Michael addition to acrylonitrile. The addition products are easily converted into γ-ketonitriles[171] **382** (equation 221). Benzenesulphinyl allylic carbanions **383** derived from the corresponding allylic sulphoxides react selectively at the γ-position with a variety of cycloalkenones to give the 1,4-adducts[463–466] (equation 222). Recently, Nokami and coworkers have synthesized some prostaglandin analogues via a three-component coupling process involving 1,4-addition of phenylsulphinyl allylic carbanion (equation 223)[467].



(382) (221)

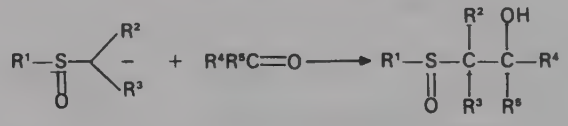


(383) (222)



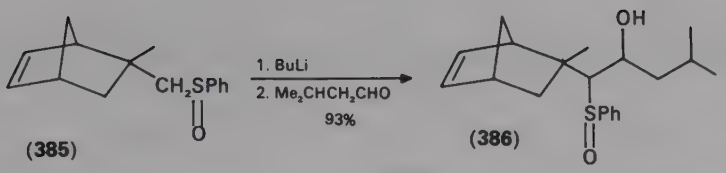
(223)

d. Hydroxyalkylation of α-sulphinyl carbanions and synthesis of vinyl sulphoxides. α-Sulphinyl carbanions undergo an aldol-type condensation with carbonyl compounds affording β-hydroxyalkyl sulphoxides **384** (equation 224).



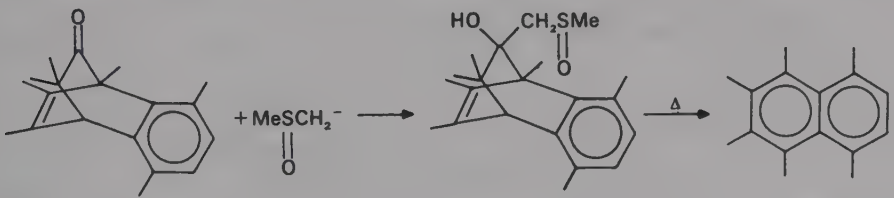
(384) (224)

Corey and Chaykovsky were the first to investigate the reaction of dimethyl sulphoxide anion (dimsyl anion) with aldehydes and ketones[400,401]. They found that the reaction with non-enolizable carbonyl compounds results in the formation of β-hydroxyalkyl sulphoxides in good yields (e.g. Ph_2CO—86%, PhCHO—50%). However, with enolizable carbonyl compounds, particularly with cycloalkanones, poor yields of hydroxyalkyl products are observed (e.g. camphor—28%, cyclohexanone—17%, but cycloheptanone—unusually—64%)[401]. The reaction with cyclopentanone does not afford the desired β-hydroxy compound at all[468], while the reaction of the carbanion of sulphoxide **385** with isobutyraldehyde gives the corresponding β-hydroxy sulphoxide **386**[469] in high yield (equation 225).

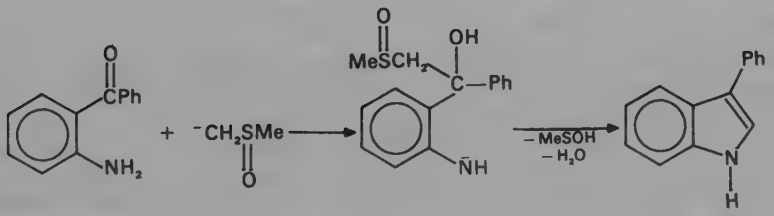


(385) (386) (225)

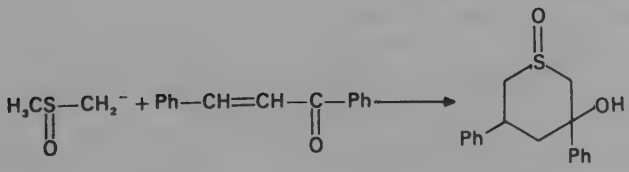
The reaction has been applied for the synthesis of a variety of β-hydroxyalkyl sulphoxides, which then served as the source of other organic compounds. Hart and Oku synthesized in this way polymethylnaphthalenes **387**[470] (equation 226). 2-Aminobenzophenone reacts with dimsyl anion to give, after subsequent condensation and elimination of methanesulphenic acid, 3-phenylindole **388**[471] (equation 227). 3-Hydroxy-3,5-diphenylthiane-1-oxide **389** can be obtained from dimsyl anion and benzalacetophenone via a Michael addition and subsequent intramolecular aldol-type condensation[472] (equation 228). Smith and coworkers reacted the carbanion of *tert*-butyl isopropyl sulphoxide **390** with diaryl ketones and obtained the corresponding β-hydroxy sulphoxides **391** which were then transformed via β-sultines **392** into substituted olefins[473] (equation 229). 4*H*-1,4-Benzothiazine 1-oxides **394** are readily prepared via lithiation of 2-acylaminophenyl sulphoxides **393** followed by subsequent annelation[474] (equation 230). A very efficient conversion of aldehydes and ketones to the one-carbon homologous allyl alcohols (equation 231) involves an initial reaction of sulphoxide anions with carbonyl compounds[475] (compare References 520 and 521). It is interesting to note that γ-lactones, e.g. **395**, react with dimsyl anion without opening of the lactone ring and give the corresponding β-hydroxy sulphoxides **396**[476] (equation 232).



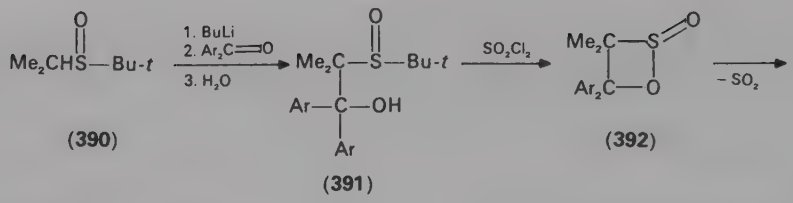
(387) (226)



(388) (227)



(389) (228)



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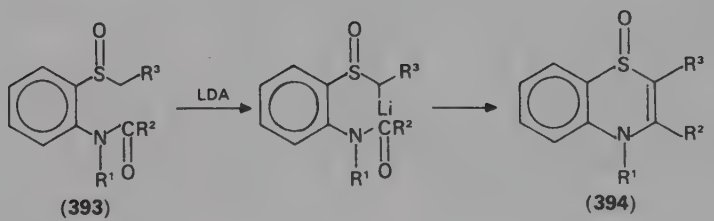

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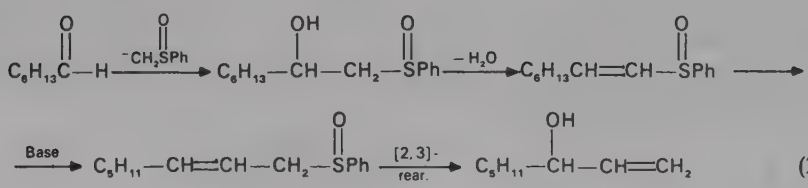

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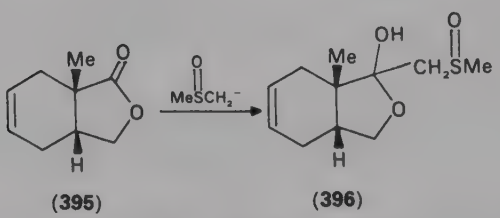
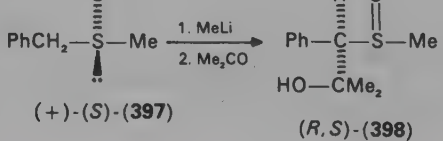


(232)

Durst and coworkers were the first to report the condensation of chiral α-sulphinyl carbanions with carbonyl compounds[477]. They found that metallation of (+)-(*S*)-benzyl methyl sulphoxide **397** followed by quenching with acetone gives a mixture of diastereoisomeric β-hydroxy sulphoxides **398** in a 15:1 ratio (equation 233). The synthesis of optically active oxiranes was based on this reaction (equation 234). In this context, it is interesting to point out that condensation of benzyl phenyl sulphoxide with benzaldehyde gave a mixture of four β-sulphinyl alcohols (40% overall yield), the ratio of which after immediate work-up was 41:19:8:32[478].



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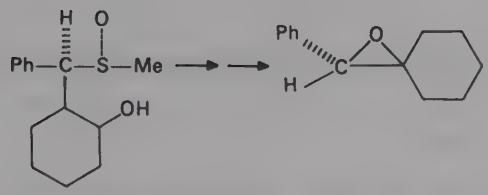
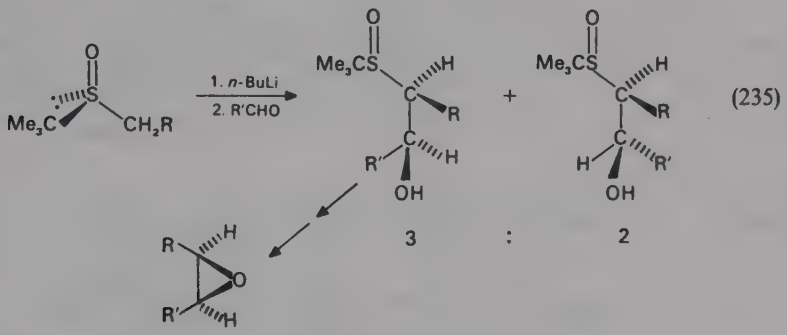


(234)

Condensation of optically active alkyl *t*-butyl sulphoxides with aldehydes gives the corresponding product in a diastereoisomeric ratio 3:2. This reaction has been used for the stereospecific synthesis of optically active oxiranes, among them, a sex-attractant (+)-disparlure[479] (equation 235). The reaction of aldehydes with γ-hydroxyalkyl sulphoxide **399** having three chiral centres provides useful methodology for generating 1,2- and 1,3-asymmetry[480]. The diastereoisomeric ratio observed upon rapid deprotonation of **399** with LDA at −78 °C, quenching with benzaldehyde and work-up at −78 °C, was 91:9 (equation 236). However, the diastereoisomer of **399** with the opposite configuration at sulphur leads to a mixture of four possible stereoisomers in a 67:17:13:3 ratio. This indicates that the carbanion configuration is dependent on the asymmetry at the β-position as well as on the chirality of sulphur[480].



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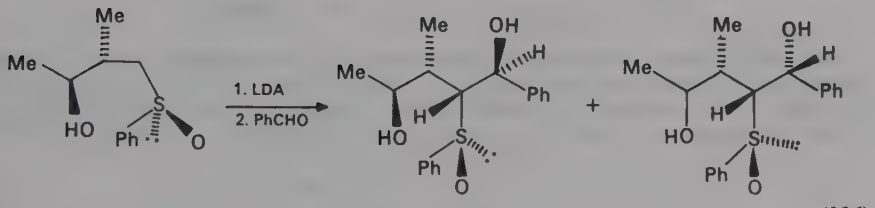
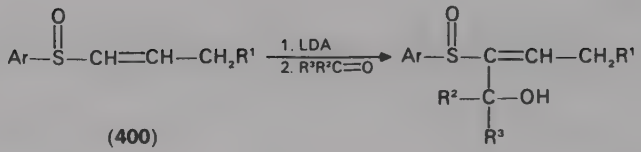


(399) 91 : 9 (236)

The carbanions of 1-alkenyl sulphoxides **400** also react with carbonyl compounds to give the corresponding condensation products[384] (equation 237). Solladie and Moine have used this type of reaction in their enantiospecific synthesis of the chroman ring of α-tocopherol **401**. Addition of the lithio reagent **402** to the aldehyde **403** affords the allylic alcohol **404** in 75% yield as a sole diastereoisomer[481] (equation 238).

α-Lithio derivatives of optically active *E*-β-silyloxy-α,β-unsaturated sulphoxides **405** were reacted with gaseous carbon dioxide, followed by the introduction of *p*-toluenesulphonic acid to allow desilylation and cyclization, affording 2-*p*-toluenesulphinylbutenolides **406** in 50–65% yield[482] (equation 239).



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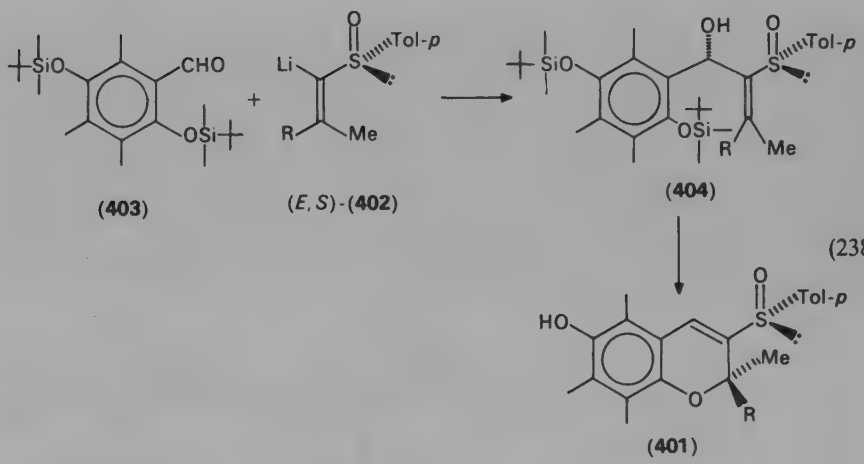

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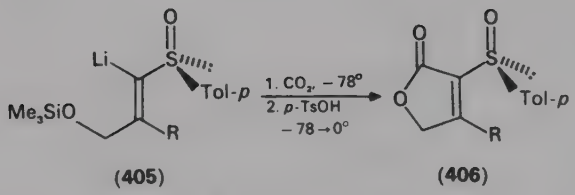
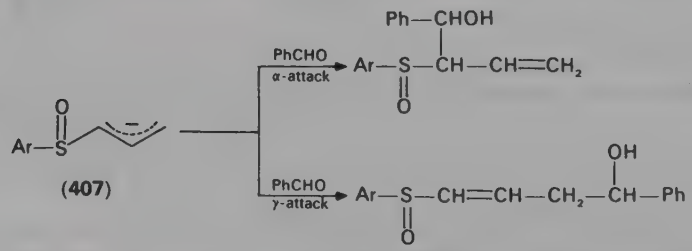


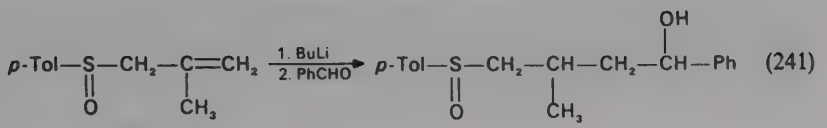
(239)

Addition of the anions of allyl aryl sulphoxides **407** to benzaldehyde proceeds readily and affords a mixture of products resulting from both α- and γ-attack of the allyl anion[483] (equation 240). In the case of the α-attack a mixture of all four possible diastereoisomers is observed, while in the case of the γ-attack, the diastereoisomer ratio exceeds 2:1.



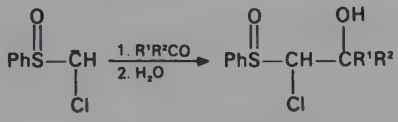
(240)

In contrast, the anion of *p*-tolyl (2-methyl)-2-propenyl sulphoxide **408** reacts with benzaldehyde exclusively at the γ-position[426] (equation 241).

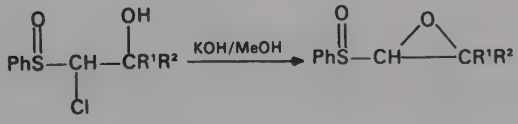


(408) (241)

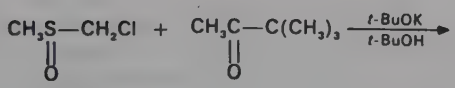
Reaction of the carbanion of chloromethyl phenyl sulphoxide **409** with carbonyl compounds yields the corresponding β-hydroxy adducts **410** in 68–79% yield. Each of these compounds appears to be a single isomer[484] (equation 242). Treatment of adducts **410** with dilute potassium hydroxide in methanol at room temperature gives the epoxy sulphoxides **411** (equation 243). The ease of this intramolecular displacement of chloride ion contrasts with a great difficulty in displacing chloride ion from chloromethyl phenyl sulphoxide by external nucleophiles[484]. When chloromethyl methyl sulphoxide **412** is reacted with unsymmetrical ketones in the presence of potassium *tert*-butoxide in *tert*-butanol oxiranes are directly formed as a mixture of diastereoisomers[485] (equation 244). α-Sulphinyl epoxides **413** rearrange to α-sulphinyl aldehydes **414** or ketones, which can be transformed by elimination of sulphenic acid into α,β-unsaturated aldehydes or ketones[486–489] (equation 245). The lithium salts (**410a**) of α-chloro-β-hydroxyalkyl



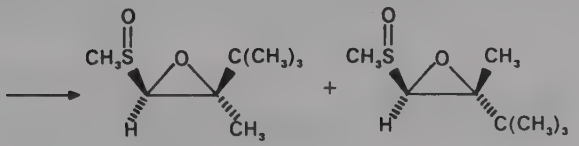
(409) (410) (242)



(410) (411) (243)



(412)



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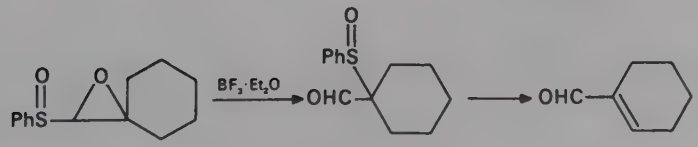
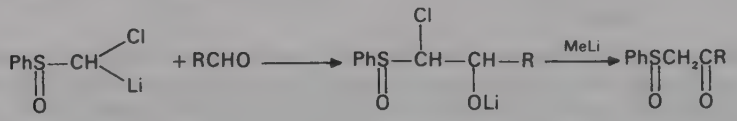


(413) (414) (245)

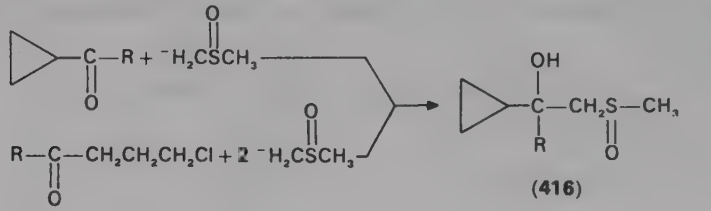
sulphoxides **410** obtained from the condensation of α-lithio-α-chloroalkyl sulphoxides **409** with carbonyl compounds can be transformed into various organic compounds[490,491]. Of interest is that elimination of chloride anion by base used in excess leads to α-sulphinylketones **415**[492] (equation 246).



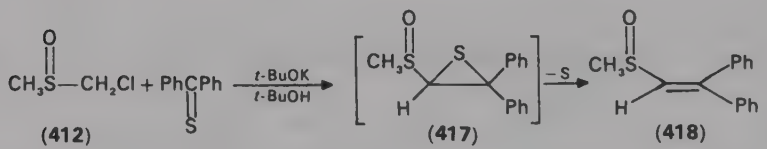
(409) (410a) (415) (246)

2-Cyclopropyl-2-hydroxyalkyl sulphoxides **416** can be obtained either by addition of an α-sulphinyl carbanion to a cyclopropyl ketone, or from alkyl 3-chloropropyl ketones and two moles of an α-sulphinyl carbanion[493] (equation 247).

Reaction of thiobenzophenone with chloromethyl methyl sulphoxide **412** does not give the expected 2,2-diphenyl-3-methylsulphinylthiirane **417**, but the α,β-unsaturated sulphoxide **418** in a 38% yield[485] (equation 248).

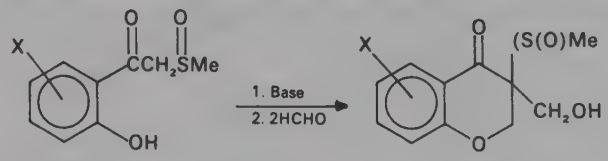


(416) (247)

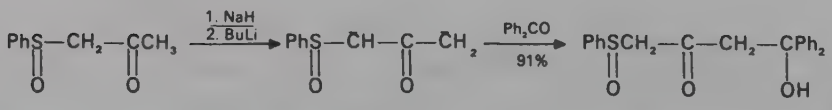


(412) (417) (418)

α-Ketosulphoxides react with aldehydes in the presence of base to give the expected α-condensation products. For example, when *o*-hydroxy-ω-(methanesulphinyl) acetophenones **419** were allowed to react with two moles of formaldehyde in the presence of base, 3-(hydroxymethyl)-3-(methanesulphinyl)-4-chromanones **420** were obtained as a result of the α-condensation[494] (equation 249). A dianion of phenylsulphinylacetone **355** reacts with carbonyl compounds at the more reactive γ-position[432,495] (equation 250).

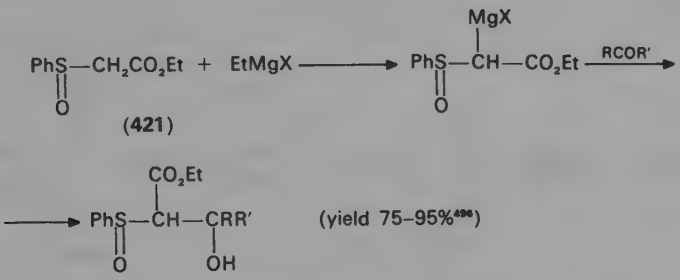


(419) (420) (249)



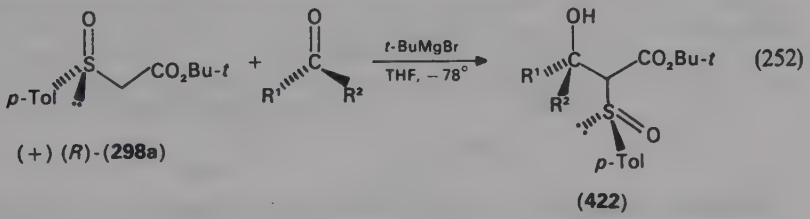
(355) (250)

Reaction of α-sulphinyl carboxylic esters **421** with carbonyl compounds has usually been performed using a Grignard reagent as a base. No condensation products are obtained using *t*-butyllithium or sodium hydride[367,496,497] (equation 251). The condensation products formed are convenient starting materials for the synthesis of α,β-unsaturated esters and β-ketones[497].



(251)

Reaction of optically active α-sulphinyl acetate **298a** with prochiral carbonyl compounds proceeds with a high asymmetric induction[367,498,499], the degree of which depends on the nature of substituents at the carbonyl group (equation 252; Table 22)[498]. The β-hydroxy sulphoxides **422** formed may be transformed to optically active β-hydroxycarboxylic esters **423**[367] (equation 253) and optically active long-chain lactones **424**[499] (equation 254). Corey and coworkers have used this method to introduce a chiral centre at C-3 in their synthesis of maytansin[500], and Papageorgiou and Benezra for the synthesis of chiral α-hydroxyalkyl acrylates **425**[501] (equation 255).



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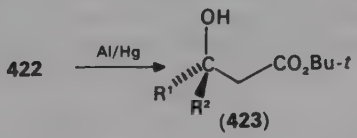
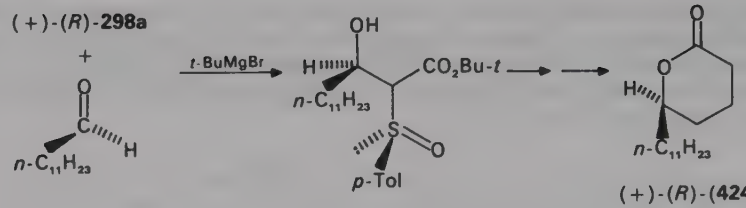


(253)

TABLE 22. Reaction of *t*-butyl *p*-toluenesulphinylacetate **298a** with carbonyl compounds

R^1	R^2	Yield of **422** (%)	Asymmetric induction (%)
H	Ph	85	91
Me	Ph	75	68
Ph	CF_3	75	20
H	*n*-C_7H_{15}	80	86
Me	*c*-Hex	88	95



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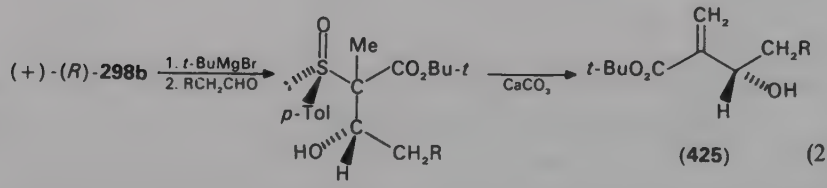
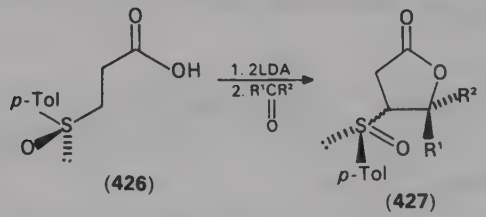


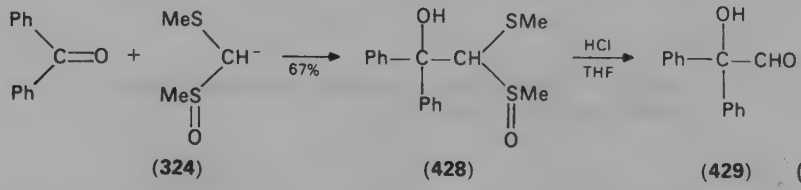
(255)

Addition of the dianion of β-sulphinylcarboxylic acids to carbonyl compounds leads to the formation of the corresponding hydroxy derivatives which undergo spontaneous cyclization to give γ-lactones[440]. Bravo and coworkers have found that when optically active (+)-(*R*)-3-(*p*-toluenesulphinyl)propionic acid **426** is used for this reaction, the corresponding diastereoisomeric β-sulphinyl-γ-lactones **427** are formed in a ratio which is dependent on the substituents in the carbonyl component[441,502,503] (equation 256).



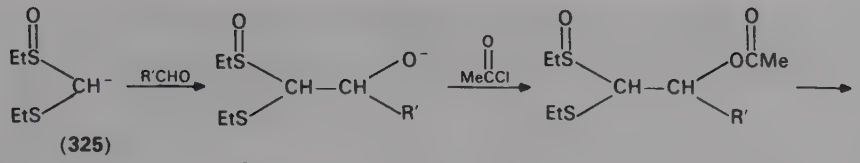
(256)

Dithioacetal monoxide anions react with carbonyl compounds in a similar way affording the corresponding α-hydroxy aldehyde dithioacetal oxides **428**. Ogura and Tsuchihashi, who performed this reaction for the first time using the anion of methyl methylthiomethyl sulphoxide **324**, obtained in this way a series of α-hydroxyaldehydes **429**[504] (equation 257).



(257)

The use of ethyl ethylthiomethyl sulphoxide in this reaction leads to the desired addition products in much better yields (95–97%). These products were then converted into ketene dithioacetal monoxide derivatives **430** by a sequence of reactions (equation 258)[505]. Reaction of 2-lithio-1,3-dithiane-1-oxide with benzophenone affords a mixture of the diastereoisomeric tertiary alcohols **431** in a ratio which is temperature dependent (*cis*:*trans* changes from 3:1 at −78 °C to 1:1 at room temperature)[268].



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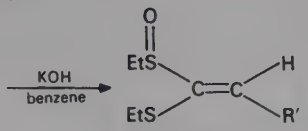
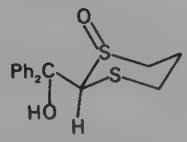


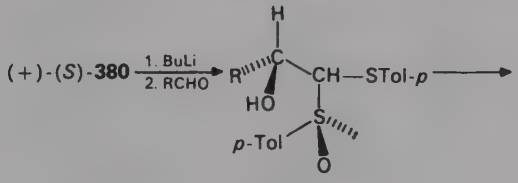
(430) (258)



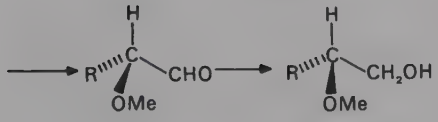
(431)

Condensation of the carbanion of optically active *p*-tolyl *p*-tolylthiomethyl sulphoxide **380** with benzaldehyde and phenylacetaldehyde produces the corresponding sulphoxides **432** which are converted into optically active α-methoxy aldehydes **433** and alcohols **434** with enantiomeric excess of 70% and 46%, respectively[506,507] (equation 259).

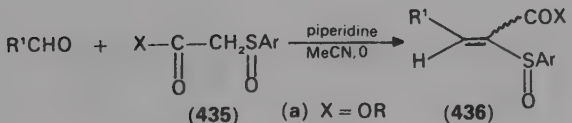
α-Sulphinyl carbanions have been used for the synthesis of vinyl sulphoxides. It was found that α-sulphinylacetates **435a** and α-ketosulphoxides **435b** easily undergo Knoevenagel condensation with aldehydes in the presence of piperidine to give the corresponding α,β-unsaturated sulphoxides **436** (equation 260; Table 23)[508,509]. The Knoevenagel condensation of α-sulphinylacetates with carbonyl compounds is also efficient when sodium hydride and zinc chloride are used[510].



(432)



(433) (434) (259)



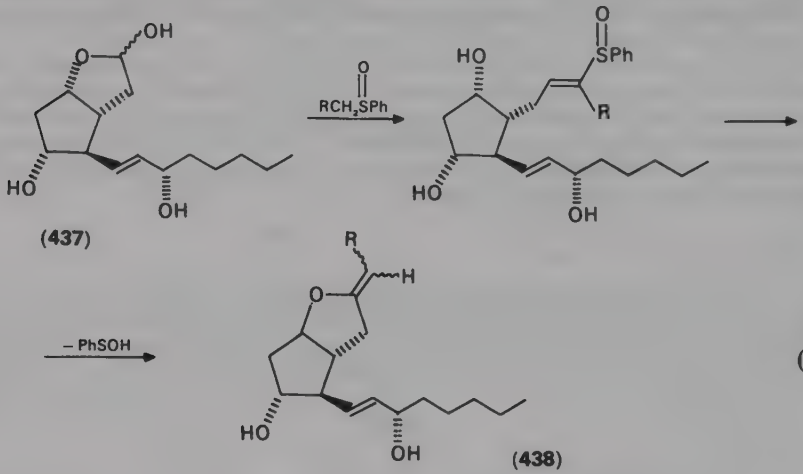
(435) (a) X = OR (b) X = R (436) (260)

TABLE 23. Knoevenagel condensation of α-sulphinylacetates **435a** and α-ketosulphoxides **435b** with aldehydes

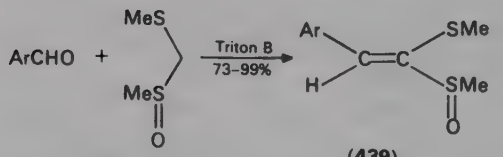
R^1	X	Ar	Yield (%)	Configuration of the product
n-Bu	OMe	*p*-ClC_6H_4	70	*E*
n-Bu	*t*-OBu	Ph	67	*E*
i-Pr	OMe	*p*-ClC_6H_4	90	*E*
Ph	OMe	Ph	85	*E*
n-Bu	Ph	Ph	61	*E*
n-Bu	Me	Ph	68	*Z*

The Knoevenagel condensation of α-lithiosulphoxides with hemiacetal **437** has been used to synthesize PGI_2 analogues **438**[511] (equation 261). The Knoevenagel-type condensation of dithioacetal monoxides with substituted benzaldehydes has been performed using Triton **B** as a base and gave the corresponding ketene dithioacetal monoxides **439**[512,513] (equation 262).

α-Lithio-α-trimethylsilyl sulphoxides **440** undergo the Peterson reaction with saturated or α, β-unsaturated carbonyl compounds to afford α, β-unsaturated sulphoxides **441** in 66–78% yield[166] (equation 263). The limitation of this approach to the synthesis of vinyl sulphoxide is the low or moderate chemical stability of the starting material **440**.



(261)



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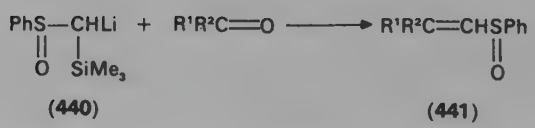
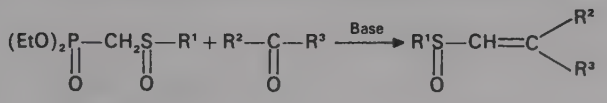


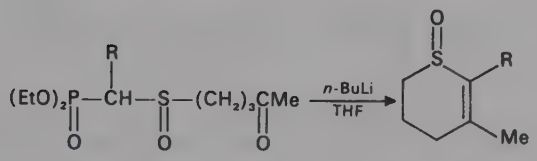
(263)

The Horner–Wittig reaction of α-phosphoryl sulphoxides **442**, which are chemically stable, results in the formation of α,β-unsaturated sulphoxides **443** in high yields[514,515] (equation 264). The reaction has been found to be non-stereoselective, mixtures of *E* and *Z* isomers being formed from aldehydes and unsymmetrical ketones[515–518]. In the case of aromatic aldehydes this reaction can also be advantageously performed in a two-phase catalytic system[516,517], even without the usual PTC catalysts[518] (Table 24). Intramolecular Horner–Wittig reaction of α-phosphoryl-δ-oxosulphoxides **444** leads to α,β-unsaturated cyclic sulphoxides **445**[519] (equation 265). Starting from optically active *O,O*-



(264)

(442) **(443)**



(265)

(444) **(445)**

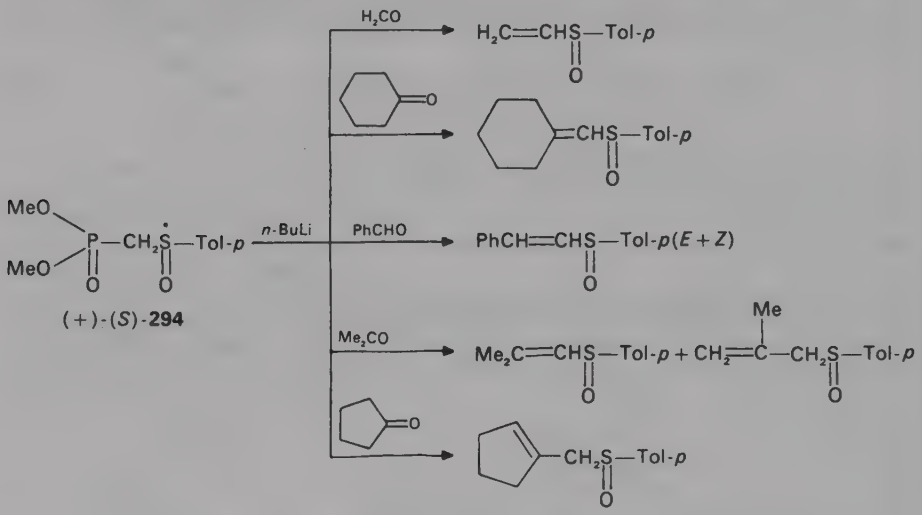
R = H, yield 60%
R = Me, yield 74%

TABLE 24. Synthesis of vinyl sulphoxides **443** from α-phosphoryl sulphoxides **442**

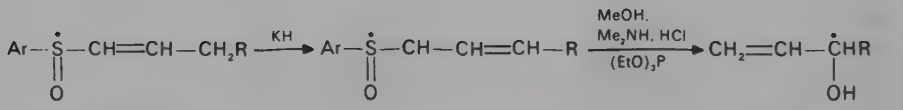
R^1	R^2	R^3	Base	Yield (%)	*E*:*Z* ratio	Refs.
Me	Ph	Ph	BuLi	84	—	515
Me	—$(CH_2)_4$—		BuLi	50	—	515
Me	—$(CH_2)_4$—		BuLi	81	—	515
Me	—$(CH_2)_6$—		BuLi	81	—	515
Me	H	Ph	BuLi	70	58:42	515
Me	H	2,4-$Cl_2C_6H_3$	BuLi	80	45:55	515
Me	H	*p*-MeC_6H_4	BuLi	72	54:46	515
Me	H	*p*-$Me_2NC_6H_4$	BuLi	75	82:18	515
Me	Me	Ph	BuLi	70	45:55	515
Me	Me	2,4-$Cl_2C_6H_3$	BuLi	51	27:73	515
Me	H	Ph	A[b]	51	70:30	516
Ph	H	Ph	A[b]	54	83:17	516
Ph	H	*p*-ClC_6H_4	A[b]	57		516
Ph	H	*p*-$MeOC_6H_4$	A[b]	48		516
Ph	H	Ph	B[b]	53	82:18	518
Me	H	Ph	B[b]	51	77:23	518
CH=CR^2R^3	H	Ph	A[b]	60	95:5[a]	517
CH=CR^2R^3	H	*p*-ClC_6H_4	A[b]	62	92:8[a]	517
CH=CR^2R^3	H	*p*-ClC_6H_4	A[b]	58	87:13[a]	519
CH=CR^2R^3	H	*p*$MeOC_6H_4$	A[b]	68	97:3[a]	517

[a] *E,E*:*E,Z* ratio.
[b] A: 50% NaOH/TEBA (PTC); B: 50% NaOH without catalyst.

dimethylphosphorylmethyl *p*-tolyl sulphoxide **294**, optically active vinyl sulphoxides have been obtained (Scheme 8)[265,520]. In the case of carbonyl compounds having a hydrogen atom in the α-position, allylic sulphoxides are also formed, however, with a great extent of racemization. Vinyl sulphoxides can be totally converted into allylic sulphoxides by means of a base, which has been applied to the synthesis of optically active allyl alcohols[520,521] (compare Reference 475; see equation 266).



SCHEME 8

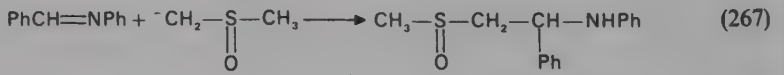


e.e. 0–60%

(266)

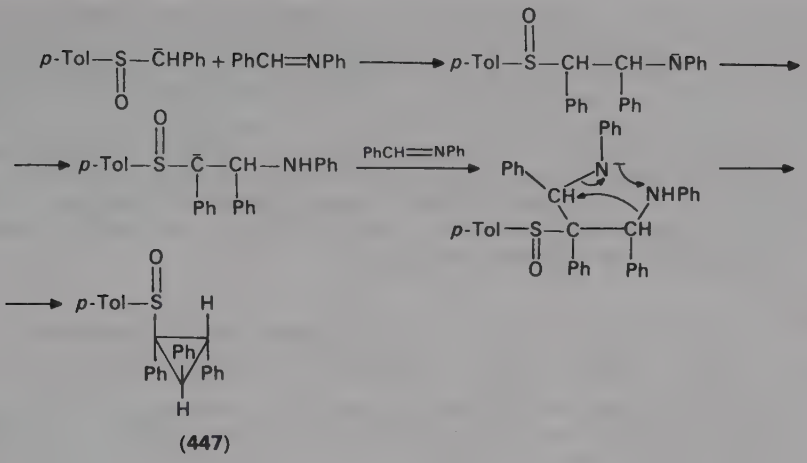
e. Aminoalkylation of α-sulphinyl carbanions. Aminoalkylation of α-sulphinyl carbanions takes place when they are treated with compounds having a double or triple carbon–nitrogen bond.

In this way benzalaniline reacts with dimsyl anion to give β-anilinosulphoxide **446** in 92% yield[401] (equation 267). Nudelman and Cram have found that the analogous reaction with the carbanion of benzyl *p*-tolyl sulphoxide is more complex and leads to the formation of substituted cyclopropyl sulphoxides **447** (equation 268)[522]. The carbanion derived from cyclohexanone dimethyldithioacetal *S*-oxide **448** gives β-mercaptoanilines derivatives on treatment with iminoketones and further elaboration[523] (equation 269).



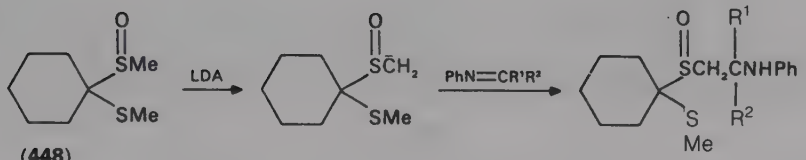
(267)

(446)



(268)

(447)



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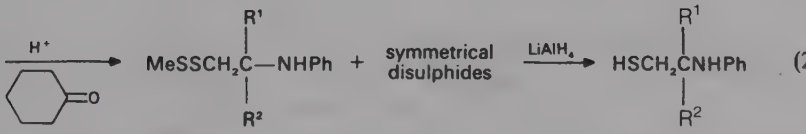
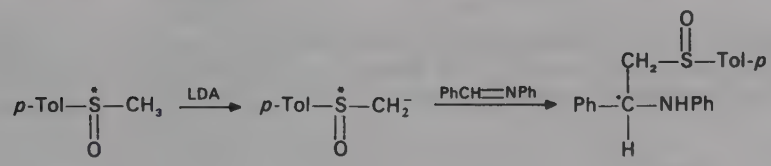
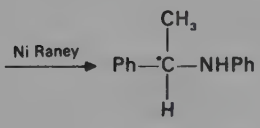


(269)

Reaction of benzylideneaniline with optically active methyl *p*-tolyl sulphoxide **449** in the presence of lithium diethylamide produces the corresponding *β*-anilinosulphoxide **450** with 100% asymmetric induction. Its reductive desulphurization with Raney nickel leads to the enantiomerically pure amine **451**[524] (equation 270). When the same optically active



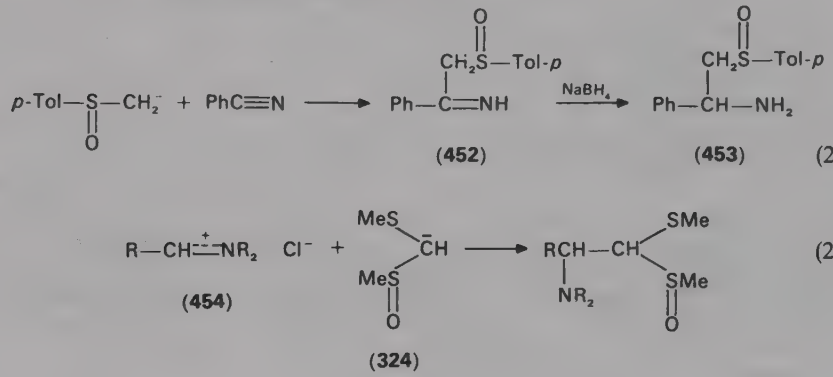
(449) (450)

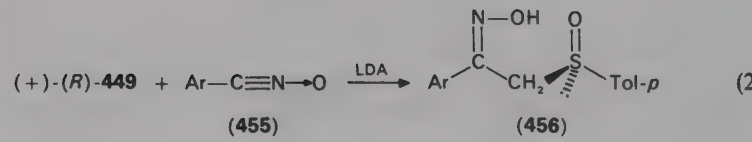


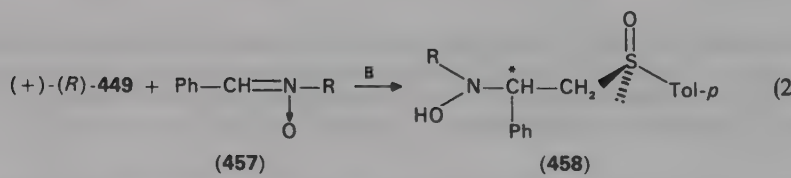
(270)

(451)

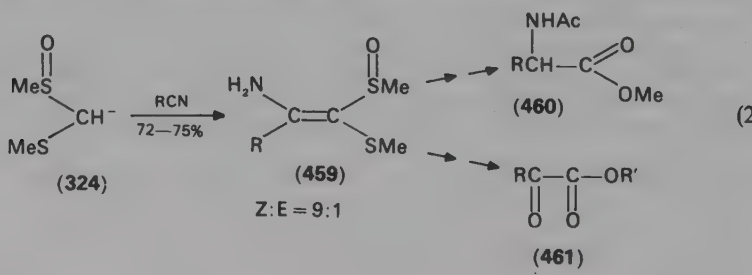
sulphoxide anion is treated with benzonitrile and the addition product **452** is then reduced with $NaBH_4$, 2-amino-2-phenylethyl *p*-tolyl sulphoxide **453** is formed as a 1:1 mixture of both diastereoisomers[524] (equation 271). Iminium salts **454** react with α-sulphinyl carbanions in a similar way as the free imines[525] (equation 272). Reaction of enantiomerically pure (+)-(*R*)-methyl *p*-tolyl sulphoxide **449** with LDA and then with nitrile oxides **455** affords optically active β-oximinosulphoxides **456** in a good yield (equation 273). The adducts have a *Z*-configuration around the C=N double bond[526]. The same anion reacts with nitrones **457** to afford optically active hydroxylamines **458** with very high β-stereoselectivity (equation 274). The diastereoisomeric ratio of the products varies from 75:25 to 100:0, being the highest for R = *t*-Bu[526].



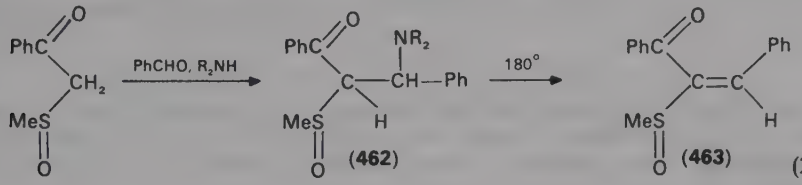




Enaminosulphoxides **459** have been obtained in the reaction of the carbanion of methyl methylthiomethyl sulphoxide **324** with nitriles. This procedure has been applied for converting nitriles into α-aminoacids **460**[527] and α-ketoacids **461**[528] (equation 275).



Sulphoxides also undergo Mannich-type condensation when reacted with aldehydes and secondary amines or their salts. In some cases, stable Mannich bases **462** can be isolated. They undergo amine elimination upon heating to give the corresponding α,β-unsaturated sulphoxides **463**[164,529] (equation 276).



(276)

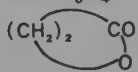
Cephalosporin (S_S)-sulphoxides give 2-exomethylene derivatives under Mannich reaction conditions but the corresponding (R_S)-sulphoxides fail to react[530,531].

f. Acylation of α-sulphinyl carbanions. Synthesis of β-oxosulphoxides. α-Ketosulphoxides have found very broad application in organic synthesis (see, for example, Reference 532). For this reason, a great deal of examples of their syntheses appear in the chemical literature. The main approach to this class of functionalized sulphoxides involves the reaction of α-sulphinyl carbanions with carboxylic esters or acyl halides.

The first reports on this reaction were published almost simultaneously by Russell and coworkers[533] and Corey and Chaykovsky[534], who reacted dimsyl anion with a variety of carboxylic esters and obtained the corresponding α-ketosulphoxides **464** in high yields (equation 277; Table 25).

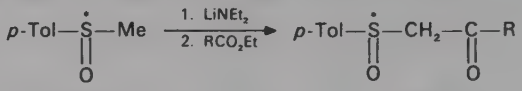
(464) (277)

TABLE 25. Reaction of dimsyl anion with carboxylic esters

Ester	Yield of **464** (%)	Refs.
PhCOOEt	72	533
PhCOOEt	79	534
p-$MeOC_6H_4COOEt$	98	534
α-Naphthyl-COOEt	98	534
α-Furyl-COOEt	71	534
Cyclohexyl-COOEt	98	534
n-$C_5H_{11}COOEt$	70	534
n-$C_{17}H_{35}COOEt$	98	534
$MeOOC(CH_2)_nCOOMe$	55	535
X-*o*-OH-C_6H_3COOEt[a]	28–88	494
p-$MeOC_6H_4COOMe$	71	533
p-MeC_6H_4COOMe	72	533
o-HOC_6H_4COOMe	18	533
	95	536

[a]X: additional substituent in the ring.

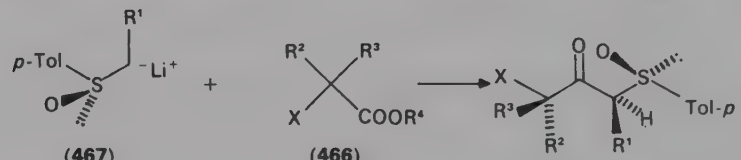
Optically active α-ketosulphoxides **465** have also been obtained in this way starting from the carbanion derived from optically active sulphoxide **449**[537,538] (equation 278).



(278)

(**449**) (**465**)

Even with α-halocarboxylic acid esters **466** the attack of α-sulphinyl carbanion **467** takes place at the carbonyl carbon atom and not at the α-carbon atom and the corresponding α-halo-α-sulphinyl ketones **468** are obtained in high yields[539,540] (equation 279).

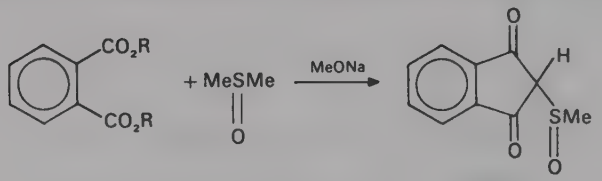


(279)

(**467**) (**466**) (**468**)

X = Cl, Br, F

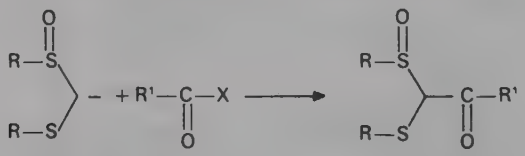
When phthalates are added to a solution of sodium methoxide in DMSO 2-(methanesulphinyl)-1,3-indanone **469** is readily formed[541] (equation 280).



(280)

(**469**)

Acylation of the anions of dithioacetal monoxides proceeds in a similar way leading to the desired products **470** in 83–92% yield[505,542] (equation 281).

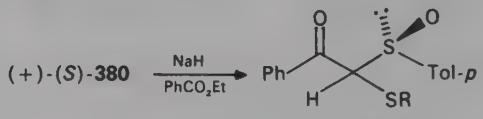


(281)

R = Ph, Me, Pr
X = Cl, OEt

(**470**)

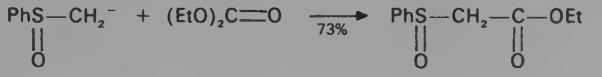
Treatment of the optically active dithioacetal monoxide **380** with ethyl benzoate in the presence of sodium hydride gives the benzoylated product **471** as a diastereoisomeric mixture, in the thermodynamically controlled (65:35) ratio[543] (equation 282).



(282)

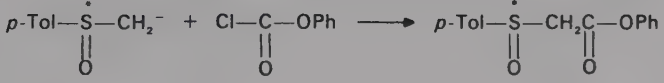
(**471**)

α-Sulphinyl acetates **472** or **473** can be obtained in the reaction of α-sulphinyl carbanions either with diethyl carbonate[496] (equation 283) or with phenyl chloroformate[500] (equation 284). The carbanions of 1-alkenyl sulphoxides **474** react with carbon dioxide and LDA and after subsequent alkylation afford the corresponding α,β-unsaturated α-sulphinylcarboxylic esters **475**[544] (equation 285); see also equation 239 and Reference 482.



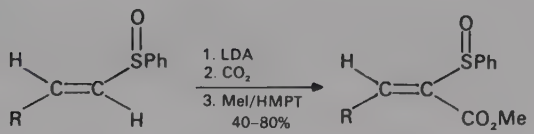
(283)

(472)



(284)

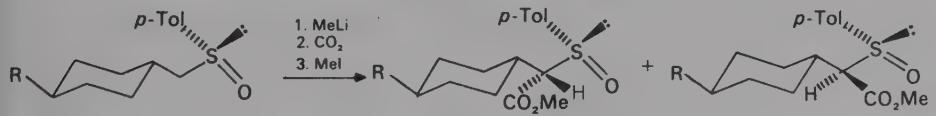
(473)



(285)

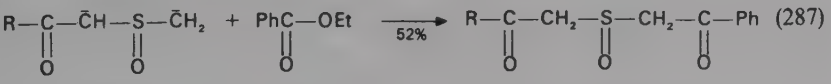
(474) **(475)**

Solladie and coworkers[545] confirmed the earlier result of Nishihata and Nishio[546] that the carbonation of the α-sulphinyl carbanion proceeds under kinetic control with retention of configuration at the metallated carbon atom. However, they also found that the stereochemical outcome of this reaction depends on other factors. They observed that 90% of asymmetric induction may be achieved under kinetic control (reaction time < 0.5 min) by using a base with low content of lithium salts, a result consistent with an electrophilic assistance by the lithium cation (equation 286)[545].



(*S*,*R*) 95 : (*R*,*R*) 5 (286)

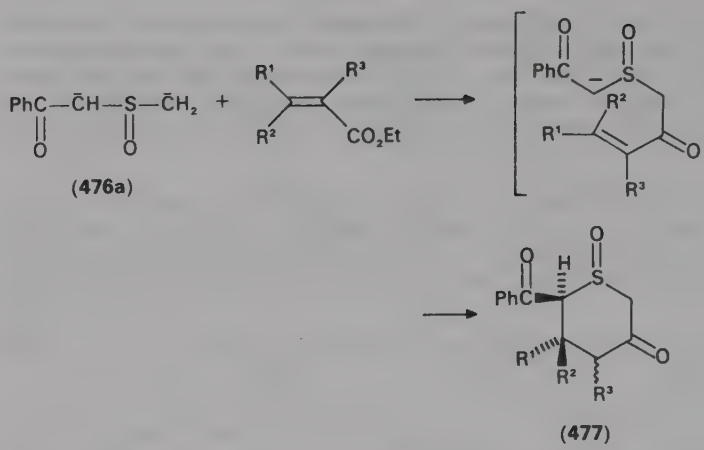
The α,α′-dianions of α-ketomethyl sulphoxides **476** react with esters exclusively at the α′-position[547] (equation 287). With α,β-unsaturated esters these anions afford substituted 3-oxothian-1-oxides **477** the products of annelation[548] (equation 288).



(287)

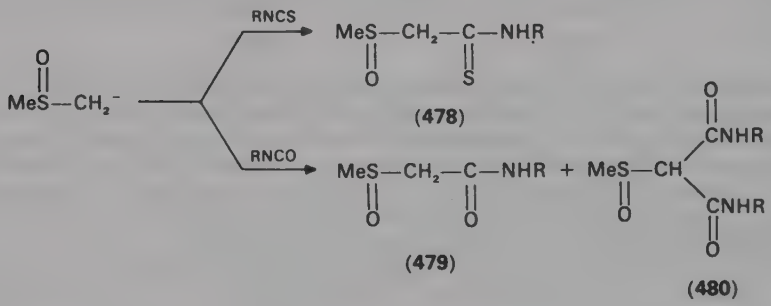
(476)

Reaction of dimsyl anion with isothiocyanates gives α-thioamidosulphoxides **478** in 12–59% yield, whereas with isocyanates it affords a mixture of α-amidosulphoxides **479** and methylsulphinylmalonoamides **480**, the products of a double addition[549] (equation 289).

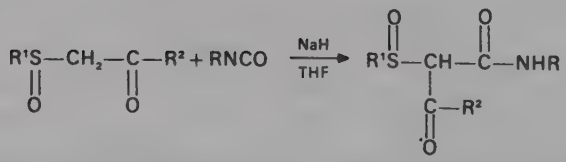


(476a) (477) (288)

In contrast, α-ketosulphoxides react with isocyanates to give the products of a mono-addition only[550] (equation 290). Reaction of dimsyl anion with trithiocarbonates **481** followed by alkylation results in the formation of (methylsulphinyl)ketene dithioacetals **482**[551] (equation 291).



(478) (479) (480) (289)



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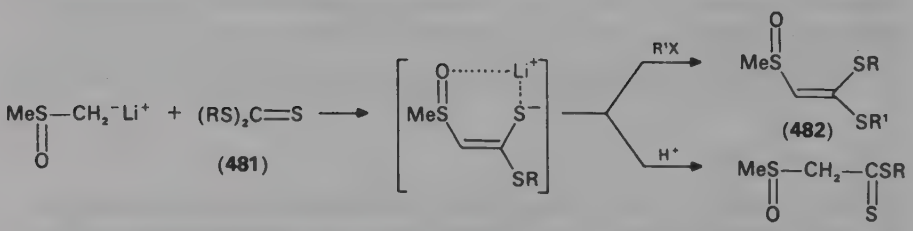
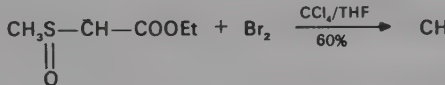


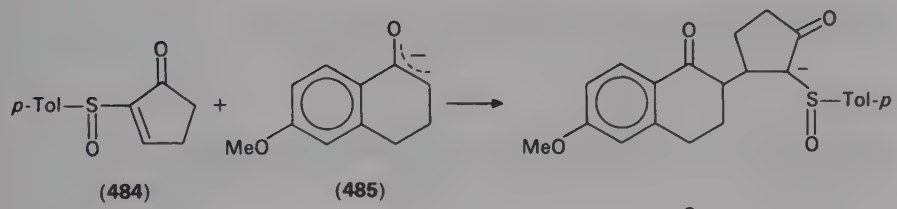
(481) (482) (291)

g. Other reactions of α-sulphinyl carbanions. α-Sulphinyl carbanions can also react with heteroatomic electrophiles. When a solution of bromine in CCl_4 is added to the α-sulphinylacetate anion in THF the corresponding α-bromo-α-sulphinyl acetate **483** is formed[436] (equation 292). Reaction of 1-cyclopentenone sulphoxide **484** with the enolate ion derived from 6-methoxytetralone **485**, followed by fluorination with perchloryl fluoride, gives the α-fluorinated α-ketosulphoxide **486**[552] (equation 293). Treatment of alkyl phenyl sulphoxides in THF with LDA and a dropwise addition of the anion formed to an excess of chlorotrimethylsilane results in the formation of α-trimethylsilylalkyl phenyl sulphoxides **487** in 85–95% yield[553] (equation 294). It must be stressed, however, that the use of NaH in DMSO as a base does not lead to the desired product[554].

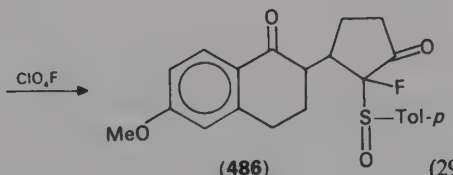


(292)

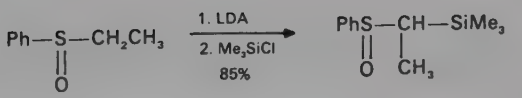
(483)



(484) (485)



(486) (293)

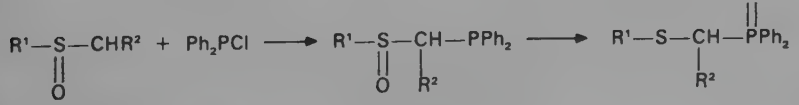


(294)

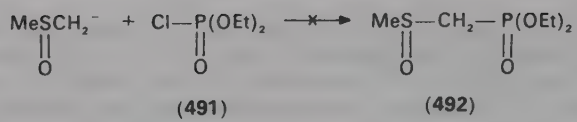
(487)

diast. ratio 10:1

Chlorodiphenylphosphine **488** reacts with α-sulphinyl carbanions to give α-sulphinylphosphines **489** which undergo ready isomerization to α-sulphenylphosphine oxides **490**[555] (equation 295). The report of Almog and Weissman that α-sulphinyl carbanions react with phosphorochloridates **491** to give α-phosphoryl sulphoxides[514] **492** calls for correction (equation 296). Actually, the phosphorylation occurs at the oxygen atom of the ambident dimsyl anion, and is followed by the Pummerer-type reaction affording diethylphosphoric acid and tetraethyl pyrophosphate among other products[76].

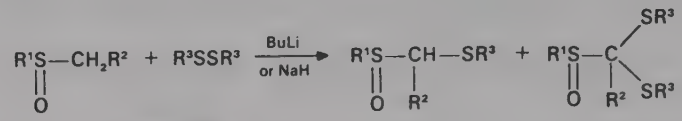


(488) (489) (490) (295)



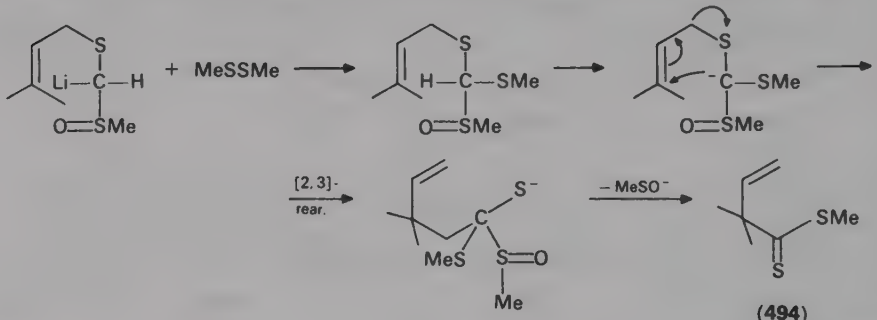
(491) (492) (296)

Reaction of sulphoxides with disulphides **493** in the presence of BuLi or NaH yields mono-, and disulphenylated products (equation 297). The formation of monosulphenylated sulphoxide as the main reaction product (55%) takes place only when Et_2S_2, sulphoxide and BuLi are used in a 1:3:3 ratio[556].



(493) (297)

Julia and coworkers have utilized the sulphenylation reaction in the synthesis of β,γ-unsaturated dithiocarboxylates **494**, via the reaction sequence shown in equation 298[557].



(494) (298)

Racemic or optically active β-disulphoxides can be obtained via a facile one-step procedure from arenesulphinic esters and α-sulphinyl carbanions[558] or by oxidation of α-sulphinyl carbanions[559].

B. Introduction, Substitution, Transformation and Elimination of Heteroatomic Groups at Organic Substituents in Sulphoxides

1. α-Halogenation of sulphoxides

Sulphoxides having at least one hydrogen at the α-carbon atom can be converted into the corresponding α-halogenosulphoxides upon treatment with a variety of electrophilic halogenating reagents. In many cases the reaction is carried out in the presence of bases which act as hydrogen halides trapping agents (equation 299). The presence of bases protects both the substrates and products from undesired side-reactions, such as the Pummerer rearrangement. For the synthesis of α-chlorosulphoxides the following halogenating reagents have been used: chlorine in the presence of bases (mainly pyridine)[560–564], nitrosyl chloride (NOCl) in the presence of pyridine[565–567], *N*-chlorosuccinimide[566,568–572], sulphuryl chloride[562,563,573–575], dichloroiodobenzene ($PhICl_2$)[564,576–579], *t*-butyl hypochlorite[562,563,567,576], *N*-chlorobenzotri-

azole[570,571,576,578,580,581] and *N*-chlorosulphoximine[565,582].

$$R^1—\underset{\underset{O}{\|}}{S}—CHR^2R^3 + [X] \longrightarrow R^1—\underset{\underset{O}{\|}}{S}—\underset{\underset{X}{|}}{CR^2R^3} + H—X \qquad (299)$$

α-Bromosulphoxides have been synthesized by bromination of sulphoxides with bromine[566,570,571,576–579,583,584] or with a mixture of bromine with *N*-bromosuccinimide[585] in the presence of pyridine. In the latter case, NBS is considered to regenerate bromine (being the true brominating agent) by reaction with the hydrogen bromide formed. Another procedure for the synthesis of α-bromosulphoxides involves the reaction of α-sulphinyl carbanion with bromine[436] (see Section IV.A.2.g). An interesting preparative modification is a solid-phase silica-gel catalyzed α-halogenation of alkyl aryl sulphoxides with *N*-halosuccinimides[572].

α-Iodomethyl sulphoxides **495** can be obtained via exchange of chloride anion by iodide in α-chloromethyl sulphoxides[586] (equation 300).

$$Ar—\underset{\underset{O}{\|}}{S}—CH_2Cl + KI \longrightarrow Ar—\underset{\underset{O}{\|}}{S}—CH_2I \qquad (300)$$

(495)

The stereochemistry, kinetics and mechanism of α-halogenation of sulphoxides have been widely investigated[587,588] and exhaustively reviewed[257,589]. Therefore, they will not be discussed here.

2. *Substitution of heteroatomic groups by hydrogen atoms*

The title reaction may be accomplished by using various reducing agents. Thus benzyl α,α-dichlorobenzyl sulphoxide **496** was reduced to a mixture of diastereoisomeric benzyl α-chlorobenzyl sulphoxides **497** by means of $(Me_2N)_3P/Et_3N$ in aqueous solvent, Bu_3SnH, Ph_3P/Et_3N in methanol and $CrCl_2$[590] (equation 301). Similarly, dichlorobis(phenylsulphinyl)methane is reduced to the corresponding monochloro derivative[591].

Aryl α-bromomethyl sulphoxides **498** are reduced by $Co_2(CO)_8/Al_2O_3$ to aryl methyl sulphoxides (equation 302). This procedure appeared to be unsuitable for reducing α-chlorosulphoxides[592].

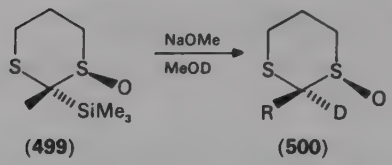
$$PhCH_2—\underset{\underset{O}{\|}}{S}—CCl_2Ph \longrightarrow PhCH_2—\underset{\underset{O}{\|}}{S}—\underset{\underset{Cl}{|}}{CH}—Ph \qquad (301)$$

(496) **(497)**

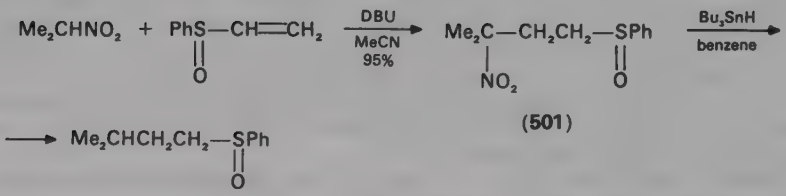
$$ArS(=O)—CH_2—Br \xrightarrow[80\text{–}100\%]{Co_2(CO)_8/Al_2O_3} ArS(=O)—CH_3 \qquad (302)$$

(498)

The stereospecific base-cleavage of the trimethylsilyl group in 1,3-dithiane 1-oxides **499** enables to obtain the specifically deuteriated products **500**[593] (equation 303). A nitro group in γ-nitroalkyl sulphoxides **501** (obtained by the Michael addition of nitroalkanes to α,β-unsaturated sulphoxides) is replaced by hydrogen by means of tributyltin hydride (equation 304). This reagent does not affect the sulphinyl function. The overall procedure provides an efficient method for the conjugate addition of alkyl groups to α,β-unsaturated sulphoxides[594].



(499) (500) (303)

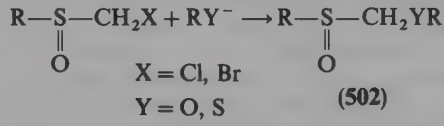


(501) (304)

3. *Nucleophilic substitution of α-halogen atoms in α-halosulphoxides*

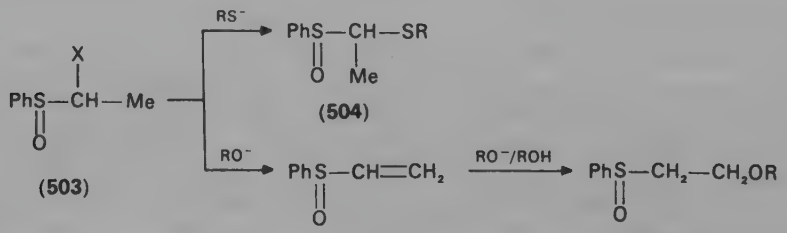
α-Chloroalkyl sulphoxides have been found to be extremely inert in nucleophilic substitution reactions. They are less reactive than *n*-BuCl by a factor of 10^{2} [595]. Nevertheless, substitution of the α-halogen has been successfully carried out by several nucleophiles.

The mechanism of the nucleophilic substitution of α-halogenosulphoxides depends on structural factors and the nature of a nucleophile[596] and may occur according to two competitive mechanisms: a direct S_N2 substitution[597] and an elimination–addition process[577]. Thus, chloromethyl[570,598] and bromomethyl[599] sulphoxides react with alkoxide and mercaptide anions via an S_N2 mechanism to give the corresponding α-alkoxy and α-alkylthiomethyl sulphoxides **502**, respectively (equation 305). Optically active α-alkoxymethyl and α-alkylthiomethyl sulphoxides can also be obtained in this way[570,599].

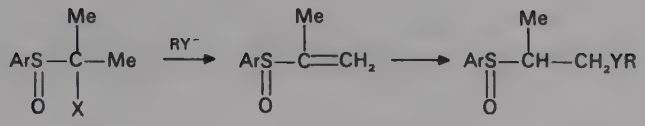


(502) (305)

On the other hand, in the case of α-halogenoethyl sulphoxides **503** an S_N2-type displacement occurs with mercaptide anions and leads to α-alkylthioethyl sulphoxides **504**, while the elimination–addition mechanism is operative with alkoxide anions, affording β-alkoxyethyl sulphoxides[577,596] **505** (equation 306). Finally, the reaction of 1-halogeno-1-methylethyl derivatives with both nucleophiles mentioned above occurs via the elimination–addition mechanism[596] (equation 307). The substitution reaction can also take place intramolecularly (equation 308) and it proceeds very easily (cf. Section IV.A.2.c)[484,600].



(503) (504) (505) (306)



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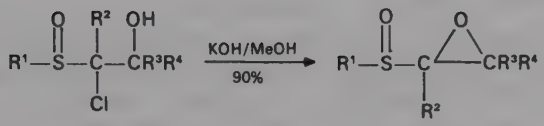
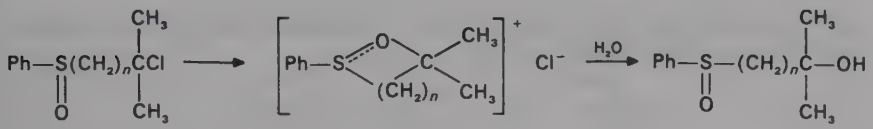


(308)

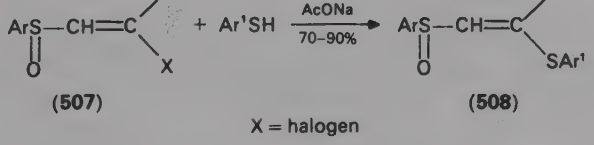
4. Nucleophilic substitution in halogenosulphoxides having a halogen atom in another position

Based on kinetic investigations the solvolysis of ω-chloroalkyl sulphoxides **506** in 80% ethanol was found to proceed via a cyclic intermediate formed via anchimeric assistance of the sulphinyl oxygen atom[601,602]. For a solvolysis of 4-halogenothian-1-oxides see Reference 603 (equation 309).



(309)

β-Halogenovinyl sulphoxides **507** react with arylthiols in basic solution to give the corresponding β-arylthiovinyl aryl sulphoxides **508**, i.e. the products of a formal nucleophilic substitution at the olefinic carbon atom[604] (equation 310). Similarly, 2-bromovinyl phenyl sulphoxide **509** reacts with the anions of 1, 3-dicarbonyl compounds to give the corresponding β-substitution products **510**[605] (equation 311). Addition of β-bromoethynyl sulphoxide **511** to a mixture of diethyl ethylmalonate and BuLi in THF gives the corresponding substituted ethynyl sulphoxides **512** in 72% yield[605] (equation 312). These reactions probably proceed via a nucleophilic addition–elimination process (cf. Section IV.C.2.b).



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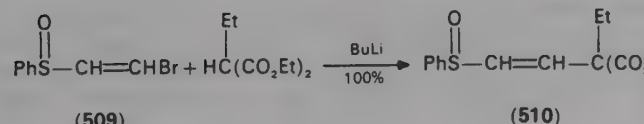

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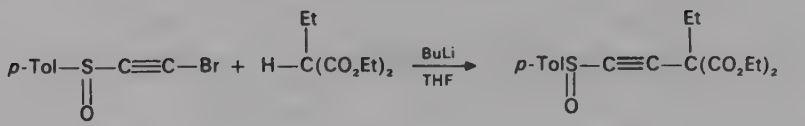
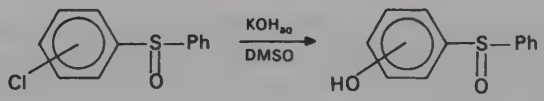


(511) (512) (312)

5. Substitution at the aromatic ring in aryl sulphoxides

Halogenation of diphenyl or methyl phenyl sulphoxides by Cl_2 or Br_2 affords mainly *para*-halogeno derivatives, whereas the *meta*-isomers are formed in low percentages or not at all[606,607]. In contrast, nitration in concentrated sulphuric acid leads to *meta*-substitution whose extent increases with acidity of the medium (up to 100%)[608].

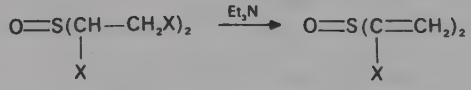
A phenylsulphinyl group has been found to promote the nucleophilic substitutions of chlorine at positions *ortho* and *para* to the aromatic ring (equation 313)[609].



(313)

6. Elimination of heteroatomic substituents in alkyl residue

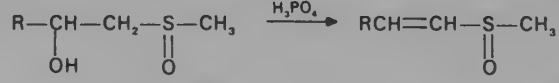
α,β-Dihalogeno sulphoxides **513** undergo dehydrohalogenation to afford α-halogenovinyl sulphoxides **514**[610] (equation 314).



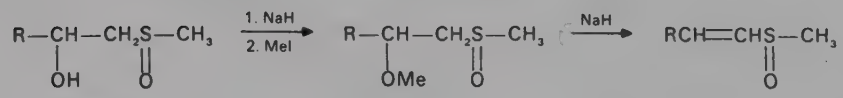
(513) (514) (314)

X = Cl, Br

β-Hydroxyalkyl sulphoxides **515** can be dehydrated either by treatment with phosphoric acid (equation 315) or by the alkylation with MeI in the presence of an excess of sodium hydride[611] (equation 316). For other dehydration reactions see References 475 and 505 (Section IV.A.2.d). For elimination of amines see References 164 and 529 (Section IV.A.2.e).

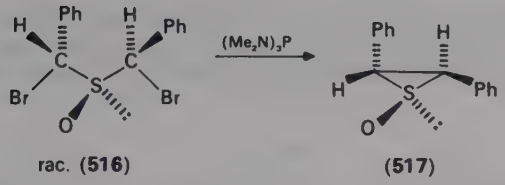


(515) (315)

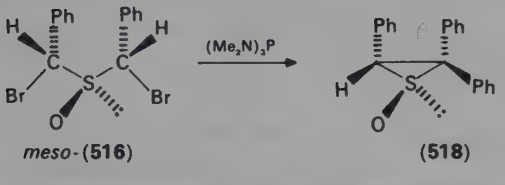


(515) (316)

α,α′-Dibromosulphoxides **516** when treated with $(Me_2N)_3P$ afford thiirane 1-oxides in 65% yield. The reaction is highly stereospecific and has been proven to occur with a double inversion (W elimination). Thus, the racemic sulphoxide yields the *trans*-thiirane 1-oxide **517** while the *meso* compound produces the *cis*, *anti*-thiirane 1-oxide **518**[612] (equation 317).

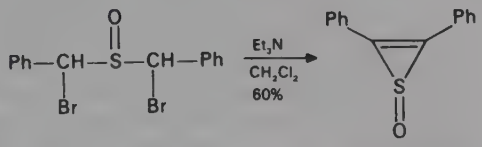


rac. (**516**) (**517**)



meso-(**516**) (**518**) (317)

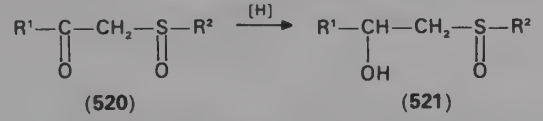
The synthesis of 2, 3-diphenylthiirene 1-oxide **519** has been accomplished by treatment of (±)-α, α'-dibromobenzyl sulphoxide **516** with a slight excess of triethylamine in boiling CH_2Cl_2[46] (equation 318).



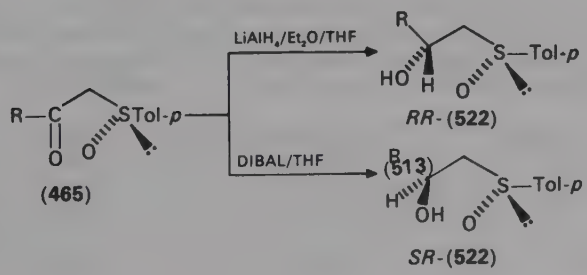
(**516**) (**519**) (318)

7. Reduction of β-oxosulphoxides

β-Oxosulphoxides **520** are reduced to β-hydroxysulphoxides **521** by several reagents, including $NaBH_4$[431,543,611], $LiAlH_4$[538,613–616] and DIBAL[615,616] (equation 319). Reduction of β-oxosulphoxides was found to be a highly stereoselective process. In the case of aryl β-oxosulphoxides $LiAlH_4$ has been found to give higher asymmetric induction than $NaBH_4$[538]. Moreover, Solladie and coworkers have found that reduction of β-oxosulphoxides of identical chirality at sulphur leads to the opposite stereochemistry at the β-carbon atom, depending on the reducing agent used. For instance, the diastereoisomeric ratio *RR*:*RS* changes from 90:10 to 0:100 when DIBAL/THF is used in place of $LiAlH_4/Et_2O/THF$[615] (equation 320). Very recently, the same authors reported



(**520**) (**521**) (319)

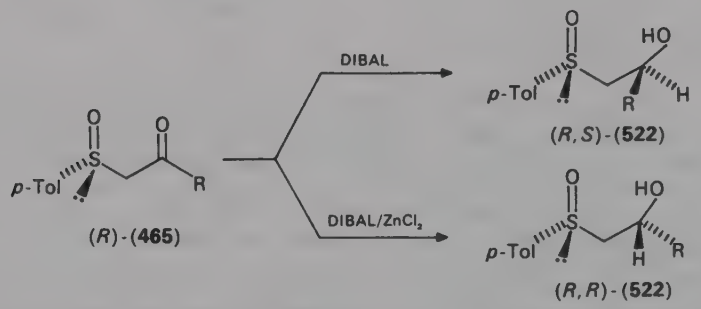


(**465**) *RR*-(**522**) (320)

(**513**)

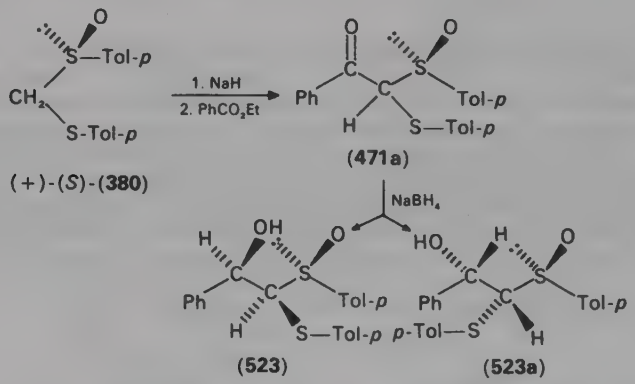
SR-(**522**)

that, starting from one enantiomer of the β-oxosulphoxide **465**, β-hydroxysulphoxides **522** of opposite stereochemistry at the β-carbon atom can be prepared in a very high (up to 95%) diastereoisomeric purity using DIBAL or DIBAL/$ZnCl_2$ as reducing agents[616] (equation 321).



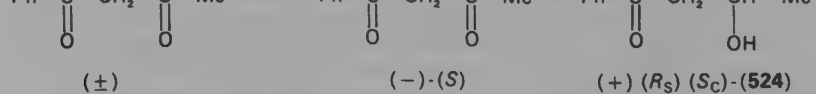
(321)

This procedure has been recently applied to the synthesis of L-lyxitol and the polyhydroxylated chain of amphotericin B[257]. Interesting results have also been obtained in the reduction of β-oxo derivatives of dithioacetal monoxides. In the reaction sequence of equation 322 two successive asymmetric inductions are involved. After the first reaction, involving acylation of the carbanion, a diastereoisomeric mixture in a 65:35 ratio is produced. When this mixture is reduced with $NaBH_4$ in MeOH–conc. aqueous solution of ammonia, among four possible diastereoisomeric alcohols, the stereoisomer **523** is obtained with a stereoselectivity of 98%[543]. Guanti and coworkers have found that the $LiAlH_4$ reduction of the same substrates at −78° in THF/ether leads to **523** with a stereoselectivity 99:1[613,614].



(322)

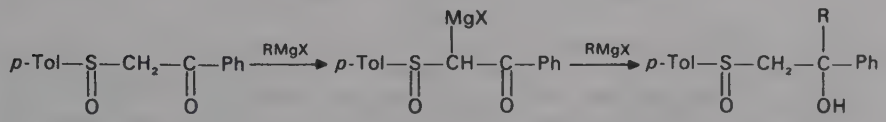
In the reduction of racemic β-ketosulphoxides (e.g. **464a**) with actively fermenting yeast (Saccharomyces cerevisiae) the enantiomers are reduced at sufficiently different rates to allow isolation of optically active β-hydroxy sulphoxide **524** and unreacted optically active β-ketosulphoxide with at least 95% optical purity[617,618] (equation 323).



(323)

A reverse reaction, i.e. oxidation of β-hydroxysulphoxides to β-ketosulphoxides, can be performed using active manganese dioxide[619].

Addition of an excess of a Grignard reagent to β-ketosulphoxide yields a mixture of the diastereoisomeric alcohols **525**[496] (equation 324).

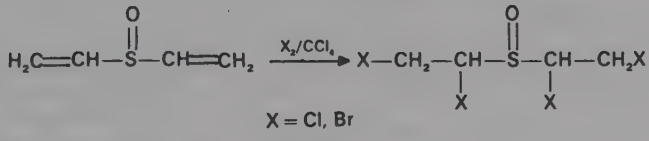


(525) (324)

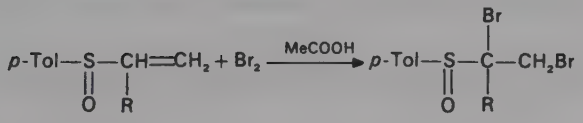
C. Additions to Unsaturated Sulphoxides

1. Electrophilic additions

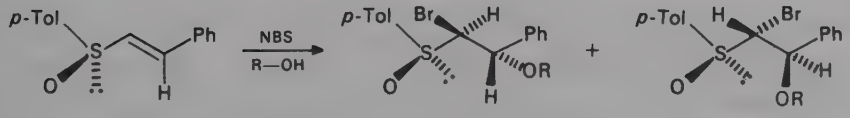
Halogens add easily to α,β-unsaturated sulphoxides to afford α,β-dihalogenosulphoxides (e.g. equation 325)[620,621]. Addition of bromine to (+)-*p*-tolyl vinyl sulphoxides **526** (R = H or Me) gives the corresponding α,β-dibromo sulphoxides **527** with optical yields (α-induction) of 32% (R = H) and 43% (R = Me)[359] (equation 326). Reaction of *N*-bromosuccinimide with (+)-(*R*)-*E*-*p*-tolyl-2-styryl sulphoxide **528** in water or methanol gives diastereoisomeric mixtures of α-bromo-β-hydroxy (or methoxy) sulphoxides **529a** and **529b** in a very high diastereoisomeric ratio (90:10 for R = H and 95:5 for R = Me) (equation 327). This conversion may be considered as a formal electrophilic addition of hypobromous acid or methyl hypobromite, respectively[622]. For iodolactonisation of β-carboxy-β,γ-unsaturated sulphoxides by $I_2/NaHCO_3/H_2O$ see Reference 623. Addition of a variety of electrophiles E—X (Br_2, ArSCl, H_2O/HgO) to allenyl sulphoxides **530** takes place across the β,γ-double bond via a sulphoxonium salt **531** which, after subsequent hydrolysis, produces γ-hydroxy α,β-unsaturated sulphoxides **532**[208] (equation 328). Regioselectivity of hydrogenation of unsaturated sulphoxides depends on the reagents used (e.g. equation 329)[238].



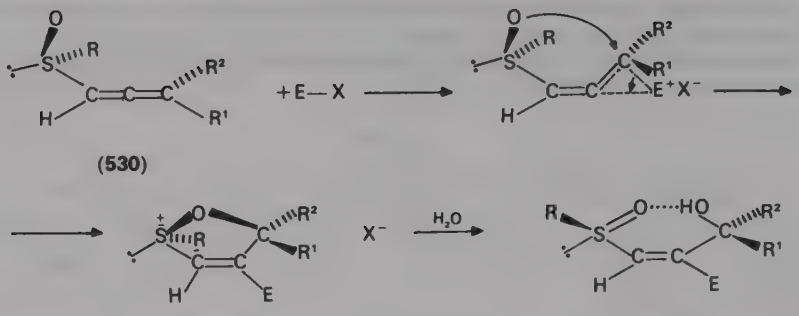
(325)



(526) **(527)** (326)



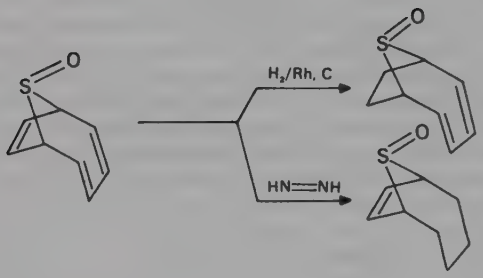
E, (+)-(*R*)-(**528**) **(529a)** **(529b)** (327)



(530)

(531) (532)

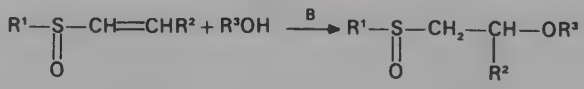
E—X = RSCl, Br_2, H—OH (328)



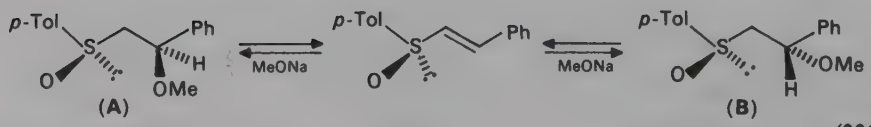
(329)

2. Nucleophilic additions

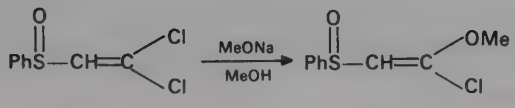
a. Addition of heteroatomic nucleophiles. Alcohols add to α,β-unsaturated sulphoxides in the presence of bases[624–626] (in some cases used in catalytic amounts)[627] to give β-alkoxy(aryloxy)ethyl sulphoxides in good to high yields (equation 330). (See also the discussion in Section IV.B.3. and References 577 and 596). It has been proven that the addition of alkoxides to α,β-unsaturated sulphoxides is a reversible, thermodynamically controlled process (equation 331)[624]. β,β-Dichlorovinyl phenyl sulphoxide **533** reacts with sodium methoxide to give β-chloro-β-methoxyvinyl phenyl sulphoxide **534** via addition of methoxide anion and subsequent elimination of chloride anion[628] (equation 332).



(330)

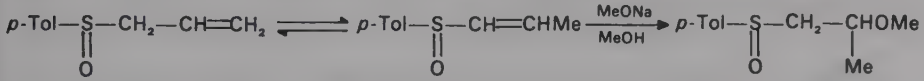


A:B = 39:61 (331)

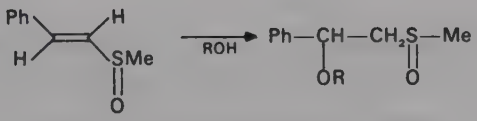


(533) (534) (332)

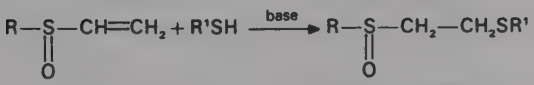
Allyl *p*-tolyl sulphoxide **535** reacts with sodium methoxide in methanol by initial prototropic isomerization and subsequent addition of methanol to give **536**[629] (equation 333). Protic solvents are photochemically incorporated by the open chain olefinic bond of *trans* methyl β-styryl sulphoxide **537** in a Markovnikov regiospecificity[630] (equation 334). Mercaptanes and thiophenols add to vinyl sulphoxides in a similar manner[625,627] (compare also Reference 604 and Section IV.B.3) to give β-alkylthio(arylthio)ethyl sulphoxides **538** (equation 335). Addition of deuteriated thiophenol (PhSD) to optically active *p*-tolyl vinyl sulphoxide is accompanied by a low asymmetric α-induction not exceeding 10% (equation 336)[359]. Addition of amines to vinyl sulphoxides proceeds in the same way giving β-aminoethyl sulphoxides in good to quantitative yields depending on the substituents at the vinyl moiety[359,627]. When optically active *p*-tolyl vinyl sulphoxides are used in this reaction, diastereoisomeric mixtures are always formed and asymmetric induction at the β- and α-carbon atoms is 80:20 ($R^1 = H$, $R^2 = Me$) and 1.8:1 ($R^1 = Me$, $R^2 = H$), respectively (equation 337)[359].



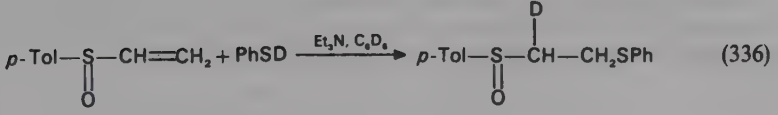
(535) (536) (333)



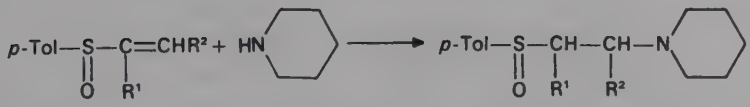
(537) R = Me, MeC=O (334)



(538) (335)



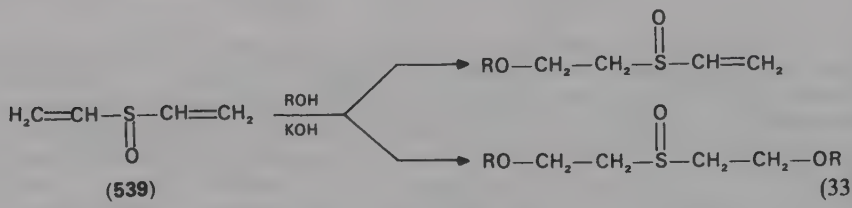
(336)



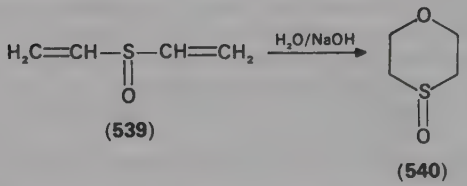
(337)

Addition of heteroatomic nucleophiles to divinyl sulphoxides gives mono and bifunctionalized products as well as compounds resulting from their cyclization. For

example, the reaction of divinyl sulphoxide **539** with alcohols in the presence of a base gives both mono- and diaddition products (equation 338)[631]. On the other hand, reaction of divinyl sulphoxide with dilute solution of NaOH leads to the cyclic 1,4-oxathian-4-oxide **540**[620] (equation 339).

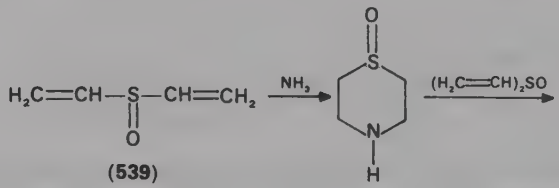


(**539**) (338)

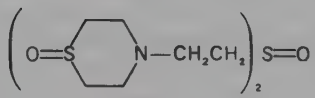


(**539**) (**540**) (339)

Similarly, the reaction of ammonia with an excess of **539** produces bis-[2-(1-oxotetrahydro-1,4-thiazin)-ethyl] sulphoxide **541**[632] (equation 340).

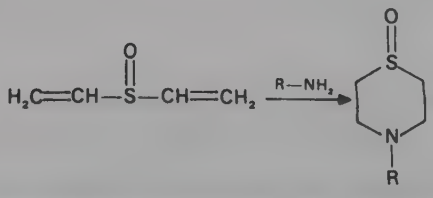


(**539**)

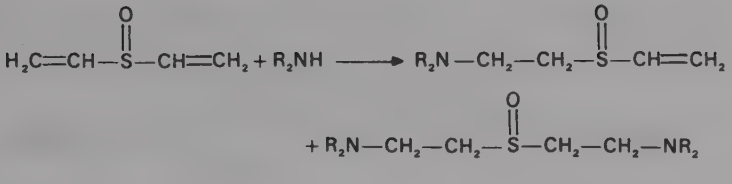


(**541**) (340)

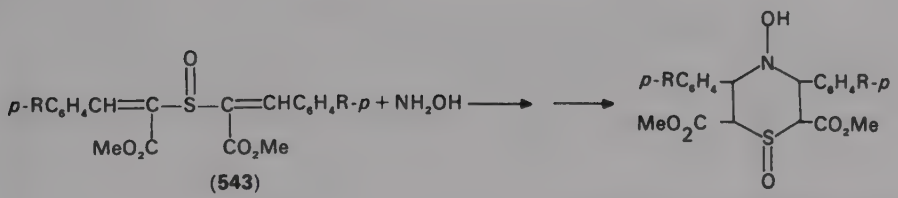
Monoalkylamines give only the cyclic products, i.e. *N*-alkyltetrahydro-1,4-thiazin-1-oxides **542** (equation 341), while dialkylamines afford the mono- and diaddition products (equation 342)[633]. Hydroxylamine undergoes double addition to substituted divinyl sulphoxides **543** to give thiazine 1-oxides **544**[634] (equation 343).



(**542**) (341)

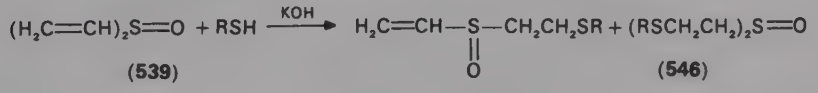


(342)



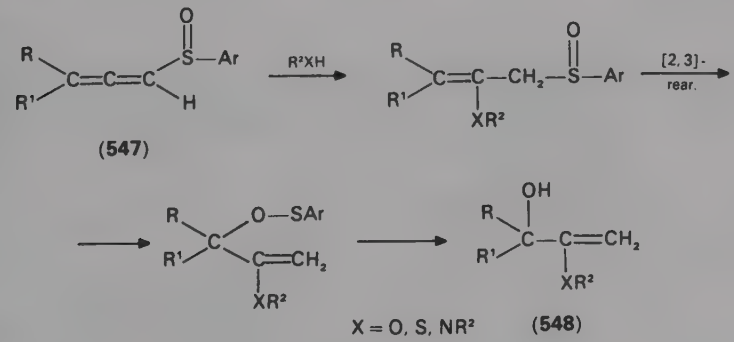
(543) (544) (343)

Mercaptanes add easily to divinyl sulphoxide in the presence of catalytic amounts of bases, giving β-alkylthioethyl vinyl sulphoxides **545** and β,β'-di(alkylthioethyl)sulphoxides **546** (equation 344). When an excess of divinyl sulphoxide is applied the reaction can be stopped at the stage of monoaddition[635,636].



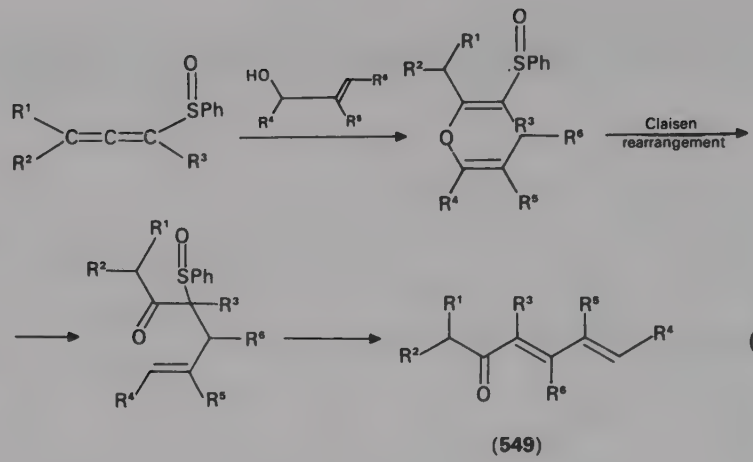
(539) (545) (546) (344)

Nucleophilic addition to allenyl sulphoxides **547** proceeds across the α,β-double bond to produce the corresponding β-substituted allylic sulphoxides which undergo readily a [2,3]-sigmatropic rearrangement affording substituted allyl alcohols[208,637] (equation 345). Under proper basic conditions, the initially formed allylic sulphoxides can rearrange to the corresponding vinyl sulphoxides which can be elaborated to 2,4-dienones **549** (equation 346)[638] and α-ketosulphoxides (equation 347)[639].



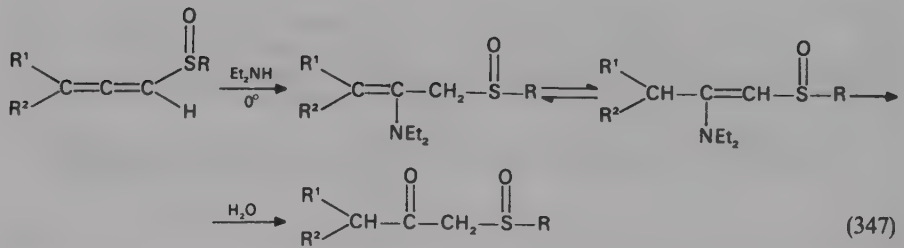
(547) X = O, S, NR² (548) (345)

b. Michael addition to α,β-unsaturated sulphoxides. Michael addition to vinyl sulphoxides (equation 348) allows one to introduce a variety of organic units possessing acidic



(346)

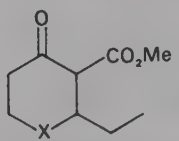
(549)



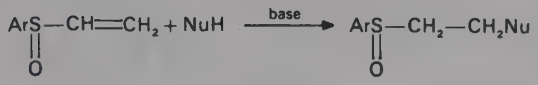
(347)

hydrogen. Selected examples are collected in Table 26. The reaction of (+)-*R-trans*-β-styryl *p*-tolyl sulphoxide with diethyl malonate gives a mixture of diastereoisomers **550**,

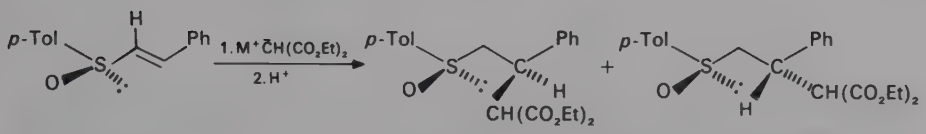
TABLE 26. Michael additions to aryl vinyl sulphoxides

Ar	Nu—H	Yield of adduct (%)	Refs.
p-Tol	$CH_2(CO_2Et)_2$	61	640, 641
p-Tol	$MeCOCH_2CO_2Et$	71	640, 641
Ph	Me_2CHNO_2	87	627
Ph	Me_2CHNO_2	95	594
Ph	$PhCH_2CH(Me)NO_2$	98	594
Ph	$EtCH(CO_2Et)_2$	95	627
p-ClC_6H_4	$Me_2CHCH(CO_2Et)CN$	80	627
Ar	 $X = (CH_2)_n$ $n = 4, 7, 10$	Yields and ratio of regioisomers depend on Ar and *n*	642

the ratio of which is strongly dependent on the nature of the counterion and solvent used[641] (equation 349).



(348)

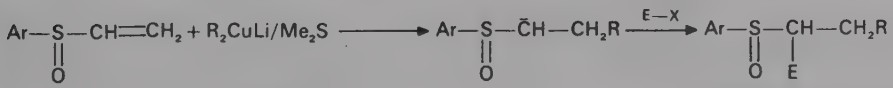


(550a) (550b)

(349)

Solvent	M^+	550a:550b ratio
EtOH	Na^+	81:19
EtOH	K^+	79:21
THF	K^+	55:45
THF	Na^+	36:64
THF	Li^+	22:78
THF/hexane	Li^+	21:79

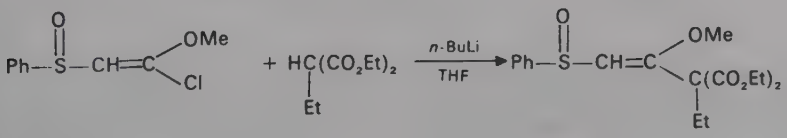
Dialkyl cuprates may also be added to aryl vinyl sulphoxides and the resulting α-sulphinyl carbanions can be treated with various electrophiles such as aldehydes, ketones and alkyl halides (equation 350)[643].



overall yields 13–75%

(350)

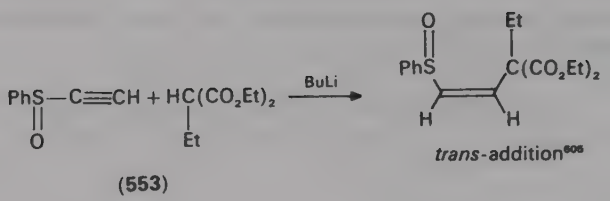
β-Halogenovinyl sulphoxides **551** react with nucleophiles to give β-substituted vinyl sulphoxides **552**. The first step in the reaction is a Michael addition, followed by an elimination of a halide anion[605,627] (equation 351).



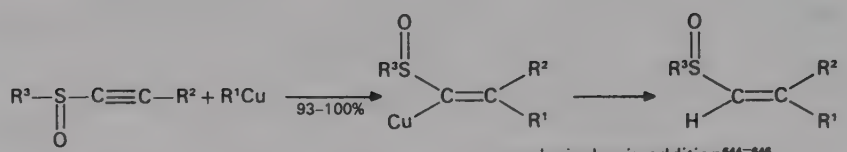
(551) (552)

(351)

Alkynyl sulphoxides **553**, **554** also behave as Michael acceptors and afford the corresponding β-substituted vinyl sulphoxides upon treatment with nucleophiles[605,644–646] (equations 352 and 353).

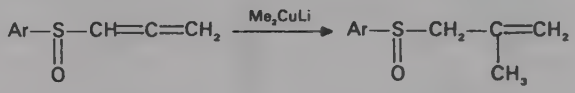


(553) (352)



(554) (353)

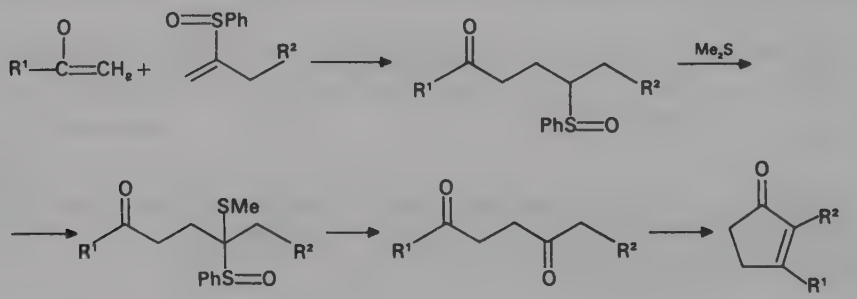
Alkylcopper reagents add to allenyl sulphoxides **555** to give the corresponding allylic sulphoxides **556** in moderate yields[647] (equation 354).



(354)

(555) (556)

Conjugate addition of enolate anions to α,β-unsaturated sulphoxides followed by a sulphoxide→ketone transformation were used for the preparation of 1,4-dicarbonyl compounds and cyclopentenone derivatives (equation 355)[648].

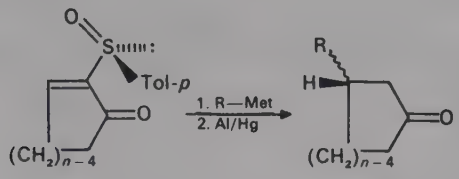


(355)

Posner and coworkers have published a series of papers in which they described a successful application of the Michael reaction between a variety of carbanionic reagents and chiral cycloalkenone sulphoxides **557** to the synthesis of chiral organic compounds (for reviews see References 257, 649, 650). In several cases products of very high optical purity can be obtained. Subsequent removal of the sulphinyl group, serving as a chiral adjuvant, leads to optically active 3-substituted cycloalkenones **558** (equation 356; Table 27).

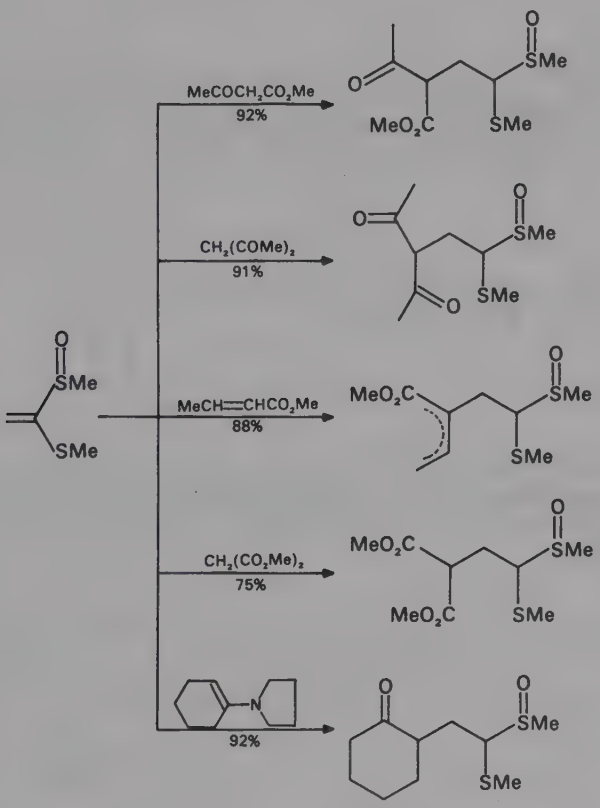
This approach has been found to be general and applicable also to the generation of a

chiral quaternary carbon centre[654] and for the synthesis of chiral 3-substituted 4-butanolides[653,655].



(557) (558) (356)

Schlessinger and coworkers described a conjugate addition of enolate species to ketene dithioacetal monoxides[656] (equation 357). Some of the products obtained were elaborated to dihydrojasmone[657], prostaglandins[658] and rethrolones[659].



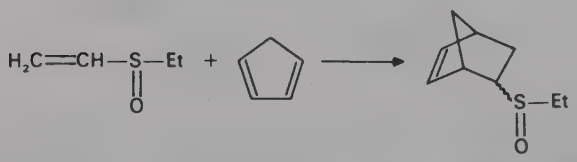
(357)

3. Cycloadditions

a. Diels–Alder reactions. Vinyl sulphoxides have been widely used as dienophiles in [2 + 4]-cycloaddition reactions. For example, in the reaction of vinyl sulphoxides with cyclopentadiene the corresponding diastereoisomeric mixture of bicyclo[2.2.1]-hepten-5-yl sulphoxides **559** is formed[660] (equation 358).

TABLE 27. Michael additions to chiral cycloalkenone sulphoxides **557**

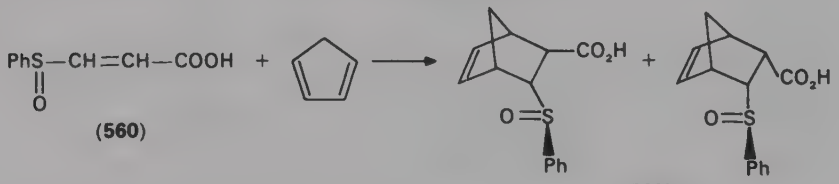
n	*R*-Met	Yield (%)	e.e. (%)	Abs. conf. of **588**	Refs
5	$ZnBr_2/MeMgI$	89	87	*R*	361, 650
5	$MeTi(OPr\text{-}i)_3$	90	90	*R*	361, 650
6	$ZnBr_2/MeMgBr$	95	62	*R*	361, 650
6	$MeTi(OPr\text{-}i)_3$	85	86	*R*	361, 650
5	$ZnBr_2/EtMgCl$	90	90	*R*	650, 651
5	$ZnBr_2/CH_2{=}CHMgBr$	75	98	*R*	650, 651
5	$ZnBr_2/PhMgCl$	70	92	*R*	650, 651
5	Me_2Mg	69	97	*S*	652
5	Et_2Mg	88	81	*S*	652
5	$(CH_2{=}CH)_2Mg$	74	57	*S*	652
5	Ph_2Mg	72	98	*S*	652
6	Me_2Mg	67	79	*S*	652
6	$(s\text{-}Bu)_2Mg$	67	62	*S*	652
5	$MeOC(=O)CH(SiMe_3)Li$	62	70	*S*	653
6		95	95	*S*	653



(358)

(559) endo:exo = 3:1

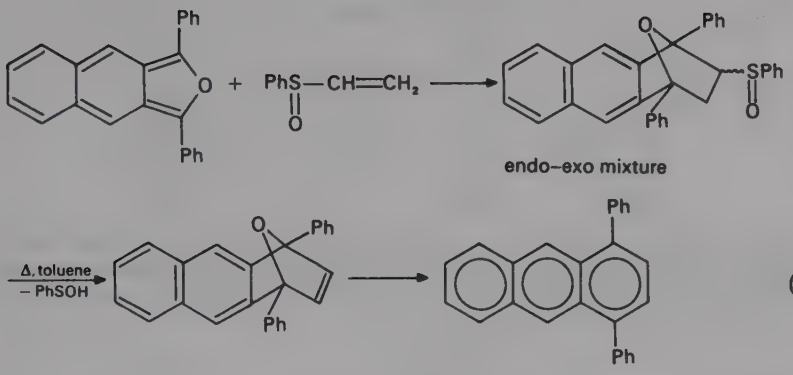
More detailed stereochemical studies on the Diels–Alder reaction between cyclopentadiene and 2-phenylsulphinylacrylic acid **560** revealed that the formation of endo-syn products **561** is strongly favoured (75–80%) over that of the endo-anti forms[661] (equation 359).



(560) **(561)**

(359)

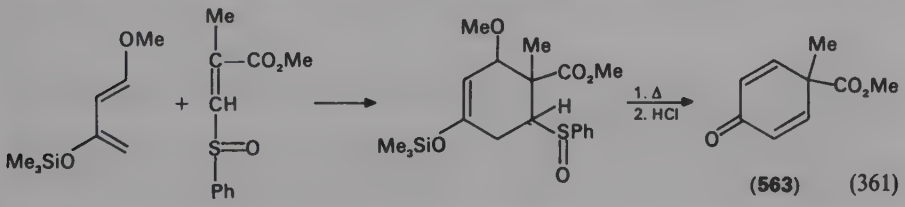
For a recent discussion on the stereochemical aspects of the Diels–Alder reaction with vinyl sulphoxides see References 662, 663. It should be pointed out that vinyl sulphoxides can be considered in [2 + 4]-cycloadditions as acetylene synthons since the sulphinyl moiety may be removed from the product by sulphenic acid elimination. Paquette and coworkers took advantage of this fact in the synthesis of properly substituted anthracenes **562**[664] (equation 360).



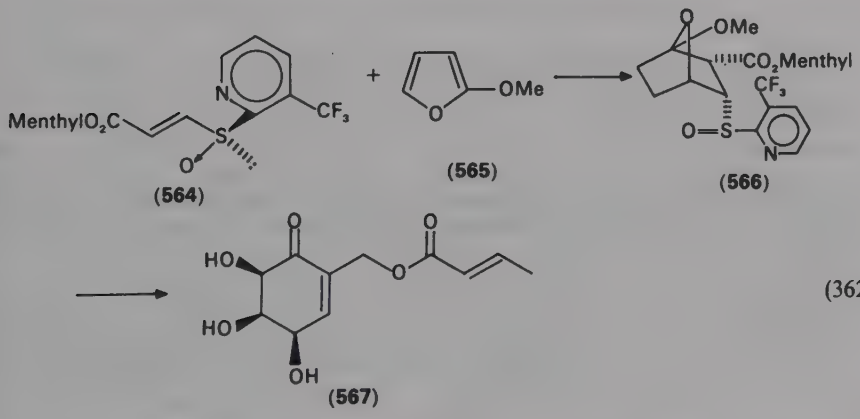
(360)

(562)

Danishefsky and coworkers using the same approach have synthesized substituted cyclohexadienones **563**[665,666] (equation 361). A highly stereoselective (96%) cycloaddition of diastereoisomerically pure (S_S)-menthyl 3-(3-trifluoromethylpyrid-2-ylsulphinyl)acrylate **564** to 2-methoxyfuran **565** leads to the cycloadduct **566** which was elaborated by Koizumi and coworkers to glyoxalase I inhibitor **567**[667] (equation 362).



(563) (361)



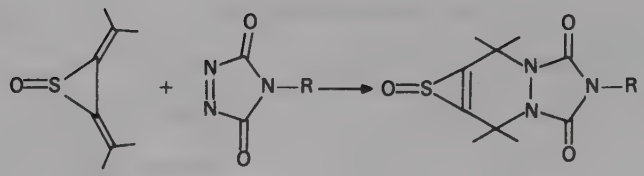
(564) (565) (566)

(567)

(362)

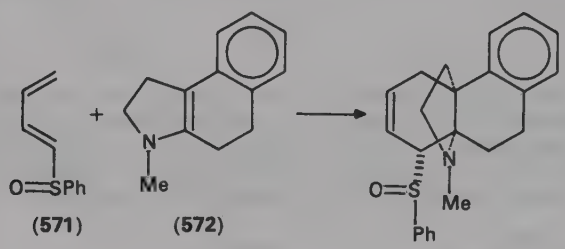
Divinyl sulphoxide was found to react with cyclopentadiene[668,669] or perchlorocyclopentadiene[670] to give a mixture of the monoaddition and diaddition products.

When the thiiranoradialene sulphoxide **568** was treated with an equimolar amount of 4-substituted 1, 2, 4-triazoline-3, 5-diones **569**, the adducts **570** were formed in quantitative yields[671] (equation 363).



(568) (569) (570) (363)

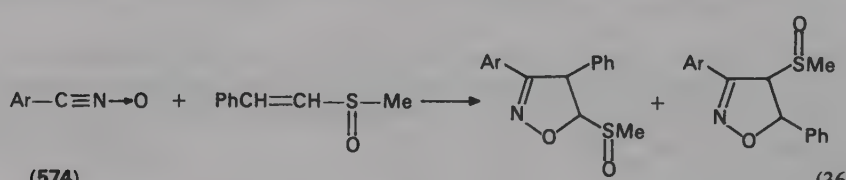
Butadienyl sulphoxides may be used as diene compounds in the Diels–Alder cycloadditions. For example, butadienyl phenyl sulphoxide **571** gives a mixture of diastereoisomeric sulphoxides **573** upon heating with an equimolar amount of *N*-methyl tetrahydrobenzindole **572**[672] (equation 364).



(571) (572) (573) (364)

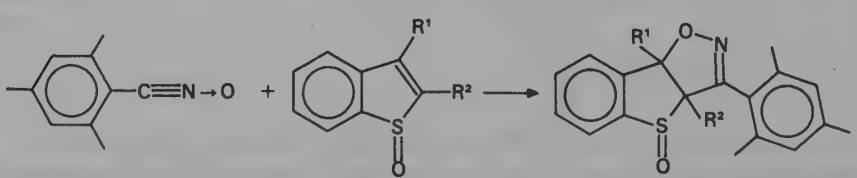
b. 1,3-Dipolar cycloadditions. Vinyl sulphoxides were also used as dipolarophiles in 1,3-dipolar cycloaddition reactions.

The cycloaddition of nitrile oxides **574** to vinyl sulphoxides usually produces a mixture of regio- and diastereoisomers. Their ratio is dependent on the nitrile oxide used and the configuration around the double bond in the starting sulphoxide (equation 365)[673].



(574) (365)

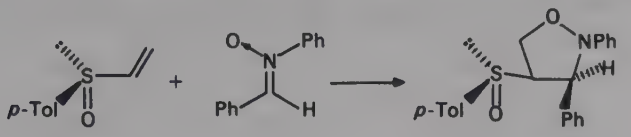
The 1,3-dipolar cycloaddition of mesitonitrile oxide **575** to benzo[*b*]thiophene *S*-oxides **576** in non-stereoselective and both *syn* and *anti* adducts **577** are obtained[674,675] (equation 366).



(575) (576) (577) (366)

On the other hand, a very high asymmetric induction was observed in the 1,3-dipolar cycloaddition of (*R*)-(+)-*p*-tolyl vinyl sulphoxide **578** with acyclic nitrones. The reaction

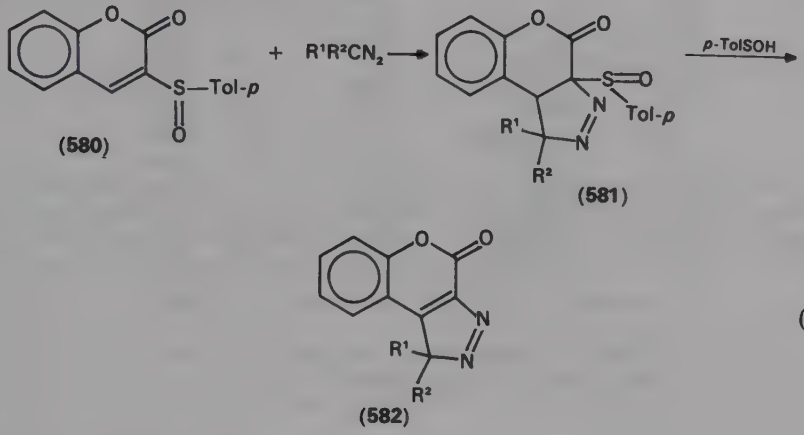
depicted in equation 367 affords the product **579** in 57% yield and with 90% e.e.[676].



(367)

(578) **(579)**

Diazoalkanes add to 3-*p*-toluenesulphinylcoumarin **580** to give the cycloaddition products **581**, which after elimination of *p*-toluenesulphenic acid afford 3-*H*-pyrazole derivatives **582**[677] (equation 368).



(368)

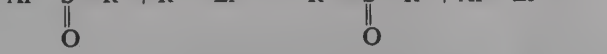
(580) **(581)** **(582)**

D. Other Transformations of Organic Substituents in Sulphoxides

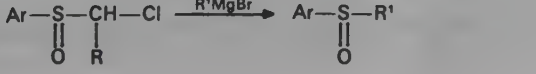
1. Exchange of organic substituents at the sulphinyl sulphur atom

The reaction of alkyllithium reagents with diaryl or alkyl aryl sulphoxides results in a displacement of the aromatic group by the alkyl group from the alkyllithium (equation 369)[380,381,479]. Johnson and coworkers[380] were the first to apply this reaction for the synthesis of optically active alkyl methyl sulphoxides. Later on, Durst and coworkers[381] found that the aromatic group which can best carry a negative charge is the most readily displaced, and that the lowest yields of displacement were observed when methyllithium was used as a nucleophilic reagent. The results are summarized in Table 28.

In the case of α-chloroalkyl aryl sulphoxides, the chloroalkyl group is easily replaced by an alkyl or aryl group of a Grignard reagent (equation 370). Bromomethyl sulphoxides react slowly and give the products in low yields, while iodomethyl sulphoxides are unreactive presumably due to steric hindrance (Table 29)[678].



(369)



(370)

TABLE 28. Displacement of aryl groups in sulphoxides by alkyllithiums

Aryl	R^1	R^2	Yield (%)	Refs.
p-Tol	Me	*n*-Bu	84	380
p-Tol	Me	*t*-Bu	75	380
p-Tol	*n*-Bu	*t*-Bu	76	380
Ph	Me	*n*-Bu	83	380
Ph	Me	*t*-Bu	66	381
Ph	Me	Me	3	381
Ph	Et	*n*-Bu	35	381
Ph	Et	*t*-Bu	50	381
Ph	*i*-Pr	Me	0	381
Ph	*i*-Pr	*t*-Bu	38	381
Ph	CH_2Ph	Me	7	381
Ph	CH_2Ph	*n*-Bu	40	381
Ph	CH_2Ph	*t*-Bu	50	381
p-Tol	$(CH_2)_5CHMe_2$	*t*-Bu	100	479
Ph	CH_2Cl	Me	12	381
Ph	CH_2Cl	*n*-Bu	4	381
Ph	CH_2Cl	*t*-Bu	5	381
Ph	CH(Cl)Me	Me	36	381
Ph	CH(Cl)Me	*n*-Bu	22	381
Ph	CH(Cl)Me	*t*-Bu	9	381

TABLE 29. Displacement of chloroalkyl groups in sulphoxides by Grignard reagents[678]

Aryl	R	R^1	Yield (%)
Ph	H	Et	99
Ph	H	*i*-Pr	55
p-Tol	H	Et	93
Ph	H	Ph	96
p-ClC_6H_4	H	Ph	97
Ph	Me	*i*-Pr	80
p-Tol	Et	Et	80
Ph	H	CH_2Br	81

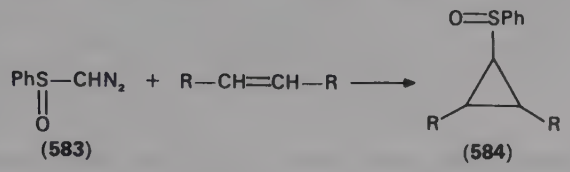
With α-ketosulphoxides a displacement of the enolate grouping by an excess of a Grignard reagent takes place only when the reaction is performed in THF (equation 371)[679].

$$Ar{-}\overset{\overset{O}{\|}}{S}{-}CH_2{-}\overset{\overset{O}{\|}}{C}{-}Ph \;+\; 4\,R{-}MgX \xrightarrow{THF} Ar{-}\overset{\overset{O}{\|}}{S}{-}R \qquad (371)$$

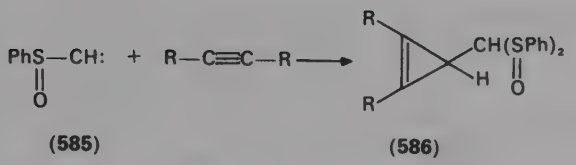
2. Formation and reactions of α-sulphinyl carbenes

Phenyl diazomethyl sulphoxide **583** formed *in situ* from diazomethane and benzenesulphinyl chloride undergoes addition to olefins affording the corresponding cyclopropyl

sulphoxides **584** in 35–40% yield[680,681] (equation 372). The addition proceeds in a *trans*-manner and most probably via a singlet carbene. Reaction of the same carbene **585** with alkynes leads, however, to an unexpected product **586**[682] (equation 373).

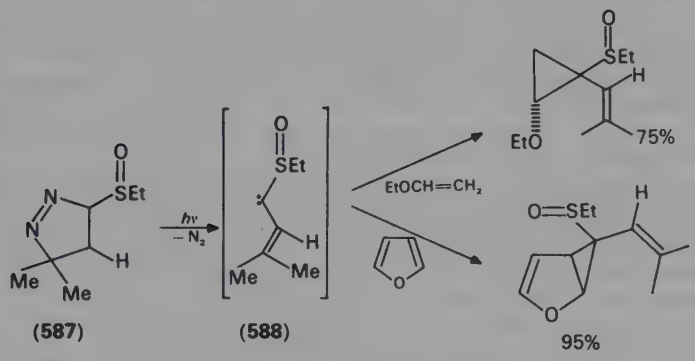


(372)



(373)

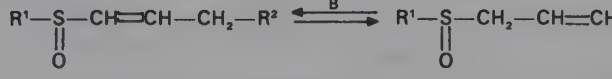
Photolysis of the sulphinyl-3*H*-pyrazole **587** in ether or methylene chloride leads to the formation of a relatively stable carbene **588** that can be identified by physical methods. When the irradiation is performed in ethyl vinyl ether or in furan, the expected cyclopropanes are formed smoothly and stereospecifically[683] (equation 374).



(374)

3. *Rearrangement of substituents in sulphoxides*

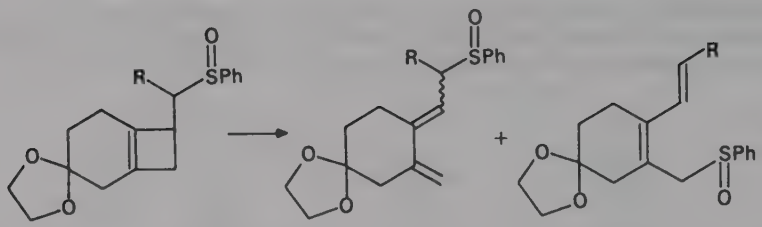
Double bond migration in vinylic and allylic sulphoxides can be achieved by using proper bases B (equation 375).



(375)

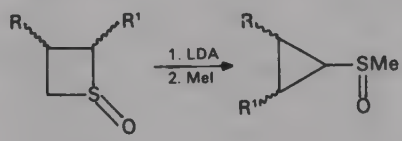
This reaction and its synthetic applications have been already described in previous sections (Section IV.A.2.d, References 475, 520, 521; Section IV.C.2.a, Reference 629).

Arenesulphinyl groups have been found to facilitate ring opening of cyclobutanes (equation 376)[684].



(376)

Anions of thietane-1-oxides **589** undergo ring contraction to give cyclopropyl sulphoxides **590**[685] (equation 377).



(377)

(589) **(590)**

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CHAPTER 4

Appendix to 'Synthesis of sulphoxides'†

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† The material in this appendix is divided in the same manner as the original Chapter 8 in 'The chemistry of sulphones and sulphoxides' (1988). Corresponding section numbers in this Appendix are preceded by an asterisk. Note that some section numbers are omitted while some new ones (not preceded by an asterisk) have been added. Structures, equations, tables, schemes and references run continuously in the original chapter and in this Appendix.

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*I. INTRODUCTION

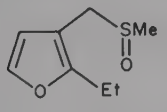
Since the appearance in 1988 of the original volume of *The Chemistry of Sulphones and Sulphoxides* interest in the chemistry of sulphoxides has been growing even more rapidly than during the previous two decades. Many studies are related to application of optically active sulphoxides in asymmetric synthesis, especially in asymmetric carbon–carbon bond formation. During these years the search for new synthetically useful approaches and modifications of existing procedures has been the subject of intensive investigations carried out both in academia and in industrial laboratories. While preparing the original chapter it was our intention to include also the results reported in 1986. This was not fully achieved. Therefore, the present chapter will be based on literature reports for the 1986–1992 period. A limited number of papers which appeared early in 1993 will also be included.

*II. SYNTHESIS OF ACHIRAL AND RACEMIC SULPHOXIDES

*A. Oxidation of Sulphides

*1. Oxidation by hydrogen peroxide

*a. *Hydrogen peroxide.* The mild oxidation with hydrogen peroxide alone in methanol[14] was successfully applied for the preparation of acid-sensitive sulphoxides such as 2-ethyl-3-(sulphinylmethyl)methylfuran **591**[686] and *N*-(sulphinylmethyl)methylphthalimide **592a**[687a]. In the latter case the corresponding sulphone **592b** was also formed.



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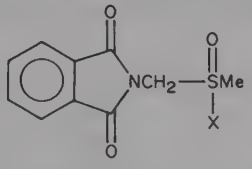
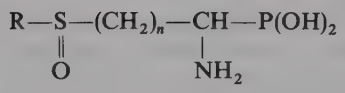


(592) (a) X = :
(b) X = O

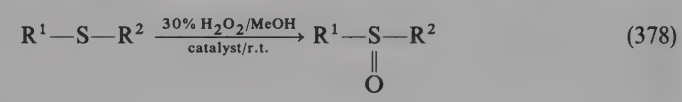
A few dialkyl and aryl alkyl sulphides were also converted into the corresponding sulphoxides using this procedure[687b].

In DMSO as a solvent, the use of hydrogen peroxide allowed the selective synthesis of 1-amino-2-alkylsulphinylalkanephosphonic acids **593** from the corresponding sulphide derivatives[688].



(593) (a) R = Me, $n = 1$ (c) R = Et, $n = 1$
(b) R = Me, $n = 2$ (d) R = Et, $n = 2$

**b. Oxidation by hydrogen peroxide in the presence of catalysts.* A selective and efficient method for the oxidation of sterically hindered sulphides to sulphoxides involves the use of hydrogen peroxide in methanol in the presence of catalytic amounts of a mixture of sulphuric acid and isoamyl, isopropyl or *t*-butyl alcohol (equation 378)[689]. Table 30 shows that sulphides are smoothly oxidized to sulphoxides in high yields varying from 77 to 100%. TLC analysis of the crude reaction products showed that the oxidation is quantitative in each case and sulphones were not formed.



(378)

catalyst: H_2SO_4/*i*-PrOH or H_2SO_4/*t*-BuOH

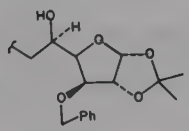
Telurium dioxide–hydrogen peroxide was found to be an efficient and selective reagent for the oxidation of sulphides to sulphoxides[690]. The presence of other common functional groups can be tolerated and over-oxidation to sulphones was not observed even with one equivalent of TeO_2. However, when catalytic amounts of TeO_2 are used, the reaction time is relatively long (8–48 h at room temperature). This drawback could be easily overcome by the addition of a small amount of concentrated hydrochloric acid (1/100 molar ratio of the sulphide). Table 31 clearly indicates that the oxidation under the above catalytic conditions is rapid, especially in the presence of HCl.

It was suggested that the true oxidizing species in the TeO_2–H_2O_2 system would be peroxytellnious acid, which would be reduced back to H_2TeO_3 and quickly regenerated

TABLE 30. Oxidation of sulphides, R^1SR^2, to sulphoxides, $R^1S(O)R^2$, by hydrogen peroxide catalysed by isopropyl alcohol/H_2SO_4[689a]

R^1	R^2	Time (h)	Yield (%)
Et	*t*-Bu	2	85
i-Pr	*t*-Bu	3	79
t-Bu	*t*-Bu	3	77
Ph	*t*-Bu	4	82
$PhCH_2$	*t*-Bu	24	100
Ph	Me	3	94
Ph	Ph	36	100
4-MeC_6H_4	Me	5	100
Me	$(EtO)_2P(O)CH_2$	8	86
Ph	$(EtO)_2P(O)CH_2$	36	90
$(EtO)_2P(O)CH_2$	$(EtO)_2P(O)CH_2$	12	92
Me	$Ph_2P(O)CH_2$	8	92
Ph	$Ph_2P(O)CH_2$	48	95

TABLE 31. Oxidation of sulphides, R^1SR^2, to sulphoxides, $R^1S(O)R^2$, with TeO_2–H_2O_2 system without and in the presence of hydrochloric acid[690]

R^1	R^2	Reaction time (h)/Yield of sulphoxide		
		1 equiv. of TeO_2	0.1 equiv. of TeO_2	0.1 equiv. of TeO_2 0.01 equiv. of HCl
Ph	Et	8/90	12/90	2/90
4-ClC_6H_4	Ph	16/80	24/84	2/85
n-Bu	Me	4/90	8/95	1/95
Ph	$MeCH{=}CHCH_2$	16/85	24/75	4/85
n-$PrCCH_2$ (O)	Ph	48/67		2/82
$PhCCH_2$ (O)	Ph	48/71		2/82
Ph		0		2/83

by H_2O_2. The proposed catalytic cycle is shown in equations 379 and 380.

$$TeO_2 + H_2O_2 \rightleftharpoons HO{-}TeOOH \quad (\parallel O) \tag{379}$$

$$R^1{-}S{-}R^2 + HO{-}TeOOH \rightleftharpoons R^1{-}S{-}R^2 + H_2TeO_3 \tag{380}$$

(S=O in both; $H_2TeO_3 \rightleftharpoons H_2O + TeO_2$)

A simple and convenient method for the synthesis of sulphoxides involves treatment of the parent sulphides with acetonitrile/hydrogen peroxide and potassium carbonate in methanolic solution (equation 381)[691]. In this case hydrogen peroxide under the correct pH conditions adds to acetonitrile to form *in situ* a highly reactive peroxyimidic acid intermediate, a very powerful oxidizing agent that is effective in the oxidation of a variety of sulphides (Table 32).

$$R^1{-}S{-}R^2 \xrightarrow[K_2CO_3,\ MeOH,\ 0\,^\circ C]{1.5\ equiv.\ MeCN,\ 1.1\ equiv.\ H_2O_2} R^1{-}S(O){-}R^2 \tag{381}$$

A quite rapid but non-selective formation of sulphoxides occurs under neutral conditions upon treatment of the corresponding sulphides with hydrogen peroxide in methanolic solution in the presence of trichloroacetonitrile[689b].

An addition compound (UHP) of hydrogen peroxide and urea, which is an inexpensive, stable and easy-to-handle source of anhydrous H_2O_2, when combined with phthalic anhydride acts as a very mild oxidizing system for organic sulphides[692]. The reaction is very simple and proceeds within 1–4 h upon addition of the starting sulphide to a suspension of UHP and phthalic anhydride in the appropriate solvent at room temperature (equation 382). The optimum molar ratio of reagents (sulphide, UHP and phthalic

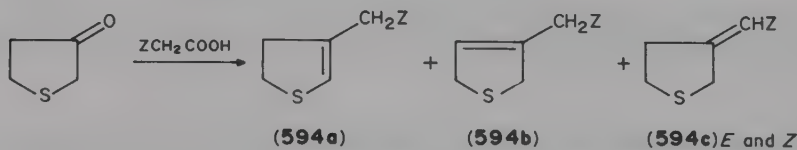
TABLE 32. Oxidation of sulphides, R^1SR^2, to sulphoxides, $R^1S(O)R^2$, with the H_2O_2/MeCN/K_2CO_3 system[691]

R^1	R^2	Time (h)	Yield (%)
Me	Me	0.5	63
Me	Et	2.0	71
Me	Ph	2.0	82
Me	$PhCH_2$	2.0	80
Et	Et	0.5	76
n-Bu	*t*-Bu	0.5	84
t-Bu	*t*-Bu	1.0	75
$PhCH_2$	$PhCH_2$	2.0	69
2-Phenyl-1,3-dithiane		2.0	91

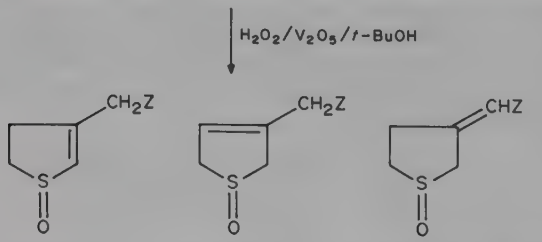
anhydride) is 1:4:2 and methanol is the solvent of choice. Several examples illustrating the efficiency of this procedure are listed in Table 33.

$$R^1—S—R^2 \xrightarrow[\text{MeOH or MeCN}]{\text{UHP/phthalic anhydride}} R^1—\underset{\underset{O}{\|}}{S}—R^2 \qquad (382)$$

The Knoevenagel condensation product **594**, which exists as a mixture of three tautomers, can be oxidized by an $H_2O_2/V_2O_5/t$-BuOH reagent to yield the corresponding mixture of three tautomers of the sulphoxide **595** (equations 383 and 384)[693].



(383)



(384)

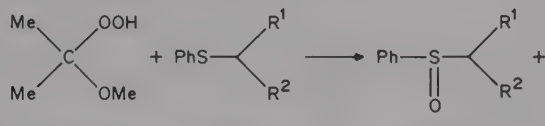
Z	% a	% b	% c
CN	6	24	70
CO_2Me	22	35	43
CO_2Et	23	35	42

TABLE 33. Oxidation of sulphides, R^1SR^2, to sulphoxides, $R^1S(O)R^2$, in methanol by the UHP/phthalic anhydride system[692a]

R^1	R^2	Time (h)	Yield (%)
n-Pr	*n*-Pr	2	84
n-Bu	*n*-Bu	2	94
t-Bu	*t*-Bu	3	92
t-Bu	Me	2	89
$PhCH_2$	$PhCH_2$	2	92
$PhCH_2$	Ph	3	94
Ph	Ph	3	95
$2\text{-}O_2N\text{-}C_6H_4$	Ph	4	92

**2. Oxidation with organic peroxides*

Aryl alkyl sulphoxides **596** are easily prepared in quantitative yields by chemoselective oxidation of the corresponding sulphides **597** with a molar equivalent of 2-hydroperoxy-2-methoxypropane (**598**) which is generated from 2, 3-dimethyl-2-butene by ozonization in methanol (equation 385)[694].

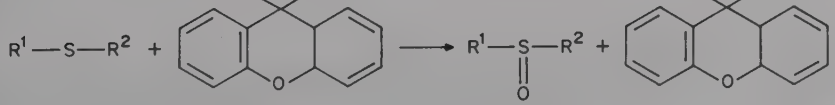


(385)

(**598**) (**597**) (**596**)

	R^1	R^2
(**a**)	H	H
(**b**)	H	H
(**c**)	$—CO(CH_2)_3—$	
(**d**)	$—CO(CH_2)_4—$	
(**e**)	$—CO(CH_2)_6—$	

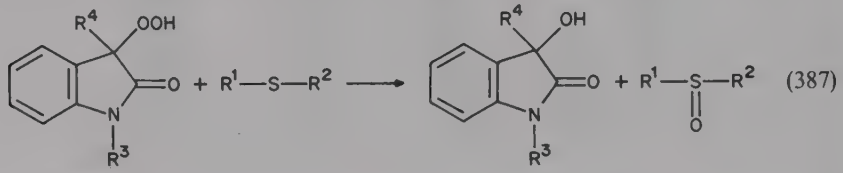
Selective conversion of sulphides to sulphoxides has also been achieved with 9-hydroperoxy-9-phenylxanthene (**599**) at ambient temperature[695]. Excellent yields of dialkyl sulphoxides were obtained. However, diaryl sulphides gave moderate to poor yields of sulphoxides. Selective oxidation of allyl phenyl sulphides to form sulphoxides without epoxidation of the unsaturated bond was also accomplished with **599**, which has a relatively high stability as compared to other known peroxide reagents (equation 386).



(**599**)

(386)

The 3-hydroperoxyindolin-2-ones **600**, prepared in moderate yields by the dye-sensitized photooxidation of the parent indolin-2-ones, were found to be useful reagents for the selective oxidation of sulphides to the corresponding sulphoxides without overoxidation to the sulphones (equation 387). Oxidations with these very stable hydroperoxides take place upon treatment of their dichloromethane solutions with a series of sulphides at reflux temperature. The corresponding sulphoxides were isolated in moderate to very good yields (see Table 34)[696].

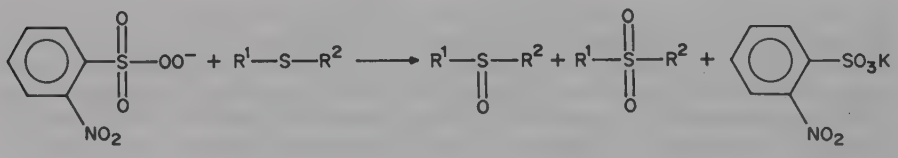


(600) (387)

TABLE 34. Oxidation of sulphides, R^1SR^2, with 3,4-hydroperoxyindolin-2-ones **600**[696]

600		Sulphoxide			
R^3	R^4	R^1	R^2	Time (h)	Yield (%)
Ph	Me	Ph	Me	2	82
Ph	Ph	Ph	Me	5	66
n-Bu	Ph	Ph	Me	5	44
Ph	Me	4-MeC_6H_4	Me	2	87
Ph	Me	4-ClC_6H_4	Me	2	69
Ph	Me	$PhCH_2$	$PhCH_2$	3	91
Ph	Me	$PhCH_2$	Me	3	81
Ph	Me	*n*-Bu	*n*-Bu	2	85
Ph	Me	*t*-Bu	*t*-Bu	3	37

A 2-nitrobenzenesulphonyl peroxyanion **601**, (equation 388), generated *in situ* upon treatment of 2-nitrobenzenesulphonyl chloride wih potassium superoxide at $-30\,^{\circ}C$ in dry acetonitrile, was found to be an efficient electrophilic oxidizing agent for the oxidation of various sulphides to sulphoxides in good yields (63–86%). However, the formation of the corresponding sulphones (4–32%) cannot be avoided [697].

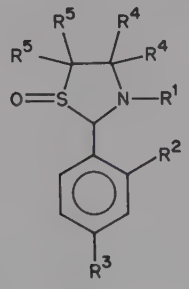


(601) (388)

*3. Oxidation with peracids

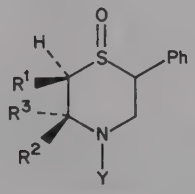
Oxidation with peracids has been much studied, but most procedures suffer from a number of disadvantages. For instance, *m*-chloroperbenzoic acid (MCPBA) is widely

used for the oxidation of sulphides to sulphoxides, but safety and cost considerations discourage its large-scale use. In spite of these facts, due to its mildness, this peracid has been very often used for the preparation of not very stable sulphoxides, such as the heterocyclic ones **602**[698] and **603**[699].



(602)

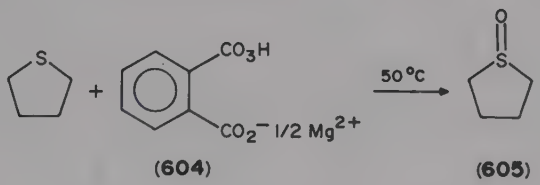
	R^1	R^2	R^3	R^4	R^5
(a)	Me	H	NMe_2	H	Me
(b)	Me	SPh	NMe_2	H	Me
(c)	Me	S(O)Ph	NMe_2	H	Me
(d)	Me	H	NO_2	H	Me
(e)	Me	H	NO_2	Me	H



(603)

	R^1	R^2	R^3	Y
(a)	Ph	H	H	H
(b)	Ph	H	H	Me
(c)	H	Ph	H	H
(d)	H	Ph	H	Me
(e)	Ph	Ph	H	H
(f)	Ph	Ph	H	Me

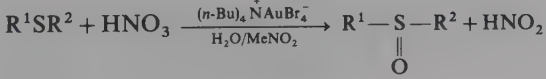
Magnesium monoperoxyphthalate hexahydrate (HMPP) **604** is an attractive alternative to MCPBA, and has been found to be useful for the quantitative oxidation of tetrahydrothiophene to the corresponding S-oxide **605** (equation 389)[700].



(604) **(605)** (389)

*4. *Oxidation with nitrogen-containing compounds*

**a. Nitric acid.* Tetrabromoaurate(III) was found to be an efficient catalyst for the oxidation of sulphides to sulphoxides by nitric acid in a biphasic system nitromethane/water (equation 390). This system allows the selective oxidation of all types of dialkyl, alkyl aryl and diaryl sulphides activated by electron-attracting substituents (Table 35)[701a].



(390)

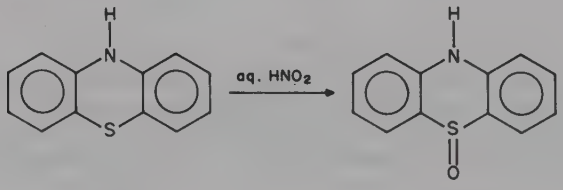
TABLE 35. Oxidation of sulphides, R^1SR^2, to sulphoxides, $R^1S(O)R^2$, with nitric acid in the presence of 5% of tetrabutylammonium tetrabromoaurate[701a]

R^1	R^2	Time (h)	Yield (%)
Ph	Et	0.5	91
Ph	$C_{18}H_{37}$	1.5	93
Ph	CH_2CH_2Ph	2.0	92
Ph	CH_2Ph	2.0	91
Ph	*c*-C_6H_{11}	2.0	89
4-$O_2NC_6H_4$	Et	48.0	94
4-$O_2NC_6H_4$	Me	28.0	87
4-ClC_6H_4	Me	2.0	88
t-Bu	*t*-Bu	0.3	93

c. Inorganic nitrates. A variety of sulphides are oxidized by cerium ammonium nitrate in a H_2O/CH_2Cl_2 two-phase system in the presence of tetra-*n*-butylammonium bromide at room temperature to give sulphoxides in yields varying between 90 and 100%[701b].

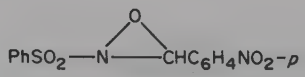
The selective conversion of sulphides to sulphoxides by molecular oxygen is also catalysed by cerium ammonium nitrate[701c].

e. Nitrous acid. The preparation of gram quantities of phenothiazine sulphoxide **606** is based on the oxidation of the corresponding sulphide **607** by aqueous nitrous acid (equation 391)[702].

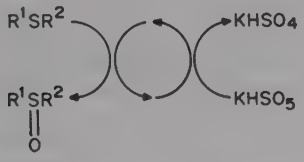


(607) (606) (391)

f. N-Sulphonyloxaziridines. *N*-Sulphonyloxaziridines, commonly known as the Davis, reagents, have been used for the selective oxidation of sulphides to the corresponding sulphoxides since 1978[703]. Recently, selective catalytic oxidation of sulphides to sulphoxides by *N*-sulphonyloxaziridine **608**, generated *in situ* from *N*-(*p*-nitrobenzylidene) benzenesulphonamide **609** (Scheme 9) using a buffered potassium peroxymonosulphate (oxone), has been reported[704].



(608)

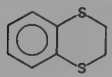
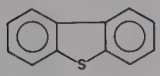
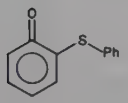


(609)

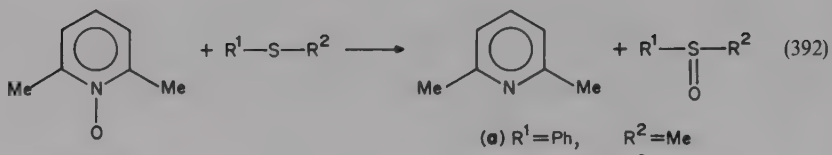
SCHEME 9

The results collected in Table 36 show that this system is able to selectively oxidize a variety of sulphides to sulphoxides in high yield and that it is remarkably chemoselective, tolerating functionalities such as alkene, halide and carbonyl groups. For the more nucleophilic sulphides oxidation was completed within 10–30 min, while the less nucleophilic diaryl sulphides required several hours.

TABLE 36. Selective catalytic oxidation of sulphides, R^1SR^2, by **609** (0.2 equivalent) and buffered oxone in CH_2Cl_2 at 25 °C[704]

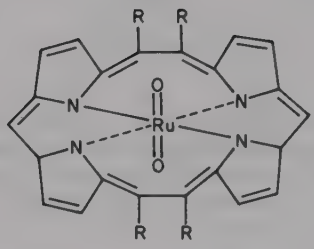
R^1	R^2	Equiv. of oxone	Time (h)	Isolated yields (%) sulphoxide/sulphone
Me	*p*-Tol	1.5	0.5	91/5
Me	Ph	1.5	0.5	91/5
Ph	CH_2Ph	1.5	18.0	95/0
Ph	Ph	1.5($CHCl_3$)	24.0	92/3
Ph	Ph	4.5($CHCl_3$)	8.0	90/0
Ph	Ph	4.5(K_2CO_3)	0.5	90/0
Ph	$CH=CH_2$	1.5	24	90/3
Ph	CH_2CH_2Cl	1.5	0.5	92/0
n-Bu	*n*-Bu	1.5	0.5	95/0
s-Bu	*s*-Bu	1.5	0.5	95/0
t-Bu	*t*-Bu	1.5	0.5	95/0
		1.5	18	90/0
		7.5	8	88/0
		7.5	18	89/0

g. 2,6-Lutidine N-oxide. 2,6-Lutidine-N-oxide **610** was found to oxidize a series of sulphides to the corresponding sulphoxides in the presence of [dioxo(tetramesitylporphyrinato)ruthenium(VI)] **611** as the oxygen transfer catalyst (equation 392)[705]. This reaction is also catalysed by $Ru(PPh_3)_4Cl_2$.



(610)

(a) R^1=Ph, R^2=Me
(b) R^1=$PhCH_2$, R^2=Me

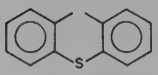
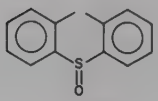


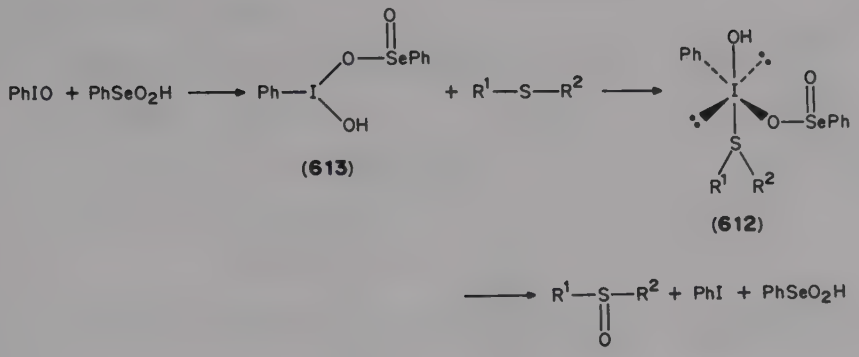
(611) R=Mesityl

**5. Oxidation with trivalent iodo compounds*

a. Iodosobenzene.* Iodosobenzene has been found to be a very effective oxidant for a variety of sulphides in the presence of a catalytic amount of benzeneseleninic acid or benzeneseleninic anhydride. The reaction affords sulphoxides in excellent yields (Table 37) and was proposed to proceed through a ligand-coupling of the hypervalent intermediate **612 which is formed from the sulphide with [hydroxy(benzeneseleninyloxy)iodo]benzene **613** as shown in Scheme 10[706].

TABLE 37. Oxidation of sulphides, R^1SR^2, to sulphoxides, $R^1S(O)R^2$, using iodoxobenzene and benzeneseleninic acid as a catalyst[706]

R	R^1	$PhIO/R^1SR^2$ ratio	Catalyst	Temp (°C)	Time (h)	Yield (%)
Me	Ph	1.1	$PhSeO_2H$	45	1	86
Et	Ph	1.1	$PhSeO_2H$	45	1	92
Me	4-MeC_6H_4	1.1	$PhSeO_2H$	45	1	95
Me	4-MeC_6H_4	1.1	$PhSeO_2H$	25	7	96
Et	4-MeC_6H_4	1.1	$PhSeO_2H$	45	1	90
4-ClC_6H_4	CH_2Ph	1.1	$PhSeO_2H$	45	0.15	91
4-$NO_2C_6H_4$	Me	1.4	$PhSeO_2H$	45	48	95
Me	*t*-Bu	1.1	$(PhSeO)_2O$	45	1	95
		1.1	$(PhSeO)_2O$	45	1.93	93
		1.1	$(PhSeO)_2O$	45	4.82	82
		1.2	$(PhSeO)_2O$	45	4.88	88

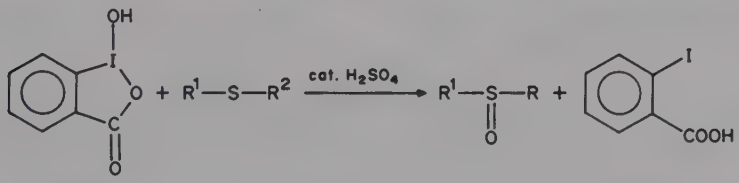


SCHEME 10

Iodosobenzene itself is able to oxidize vinyl sulphides to vinyl sulphoxides in methanol at room temperature (equation 393)[707].

$$RSCH{=}CH_2 + PhIO \xrightarrow[r.t.]{MeOH} RSCH{=}CH_2 \quad (393)$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad \| \; O$$

o-Iodosobenzoic acid, for which the cyclic structure of 1,3-dihydro-1-hydroxy-3-oxo-1,2-benzoiodoxole (**614**) was proved by X-ray analysis[708], is able to oxidize sulphides to the corresponding sulphoxides in acetic acid containing some sulphuric acid as a catalyst (equation 394)[709]. Yields are better than 90% and the crude products were shown to be free of the corresponding sulphones. Furthermore, the reduced form of this reagent can be very easily recovered and reconverted into the oxidizing agent.



(394)

**6. Oxidation with metaperiodates*

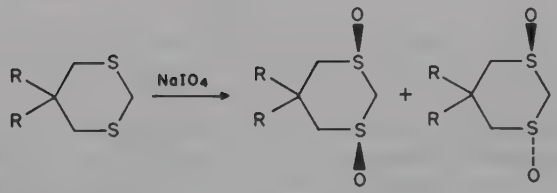
2-Trimethylsilylethyl sulphides **616**, prepared by the radical addition of thiols to vinyltrimethylsilane **617**, have been oxidized to the corresponding sulphoxides **618** with sodium metaperiodate (equation 395)[710].

1,3-Dithiane-1,3-dioxides **619** have been prepared as a mixture of diastereoisomers by the oxidation of thioacetals **620** with the same reagent (equation 396)[711,712].

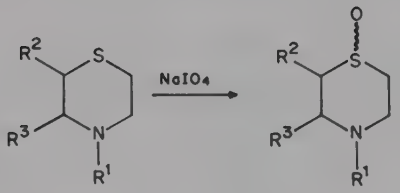
Similarly, oxidation of 1,4-thiazines **621** afforded the corresponding S-oxides **622** (equation 397)[699].

$$\text{RSH} + \underset{\text{(617)}}{\overset{\text{SiMe}_3}{\diagup\!=}} \xrightarrow[60\,^\circ\text{C}]{\text{AIBN}} \underset{\text{(616)}}{\text{R—S—CH}_2\text{CH}_2\text{SiMe}_3} \xrightarrow{\text{NaIO}_4} \underset{\text{(618)}}{\text{R—}\overset{\overset{\text{O}}{\|}}{\text{S}}\text{—CH}_2\text{CH}_2\text{SiMe}_3} \quad (395)$$

R	Yield (%)
Ph	98
4-MeC_6H_4	100
4-ClC_6H_4	80
2-$C_{10}H_7$	90
n-Pr	95
i-Pr	96
$PhCH_2$	100
$CH_2{=}CHCH_2$	99
c-C_6H_{11}	95
n-$C_{12}H_{23}$	95



(620) (a) R=Me (b) R=Et (619) (396)



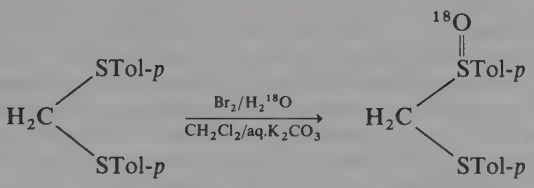
(621) (622) (397)

(a) $R^1 = R^2 = H, R^3 = Ph$
(b) $R^1 = R^3 = H, R^2 = Ph$
(c) $R^1 = CO_2Et, R^2 = H, R^3 = Ph$
(d) $R^1 = H, \quad R^2 = R^3 = Ph$
(e) $R^1 = CO_2Et, R^2 = R^3 = Ph$

*7. Oxidation with halogens and compounds containing 'electropositive' halogens

a. Halogens. ^{18}O-Labelled formaldehyde di-*p*-tolyl dithioacetal S-oxide **623** was prepared by oxidation of the dithioacetal **624** with bromine and $H_2{}^{18}O$ in dich-

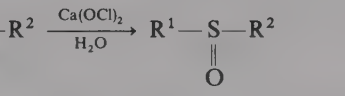
loromethane (equation 398)[713].



(398)

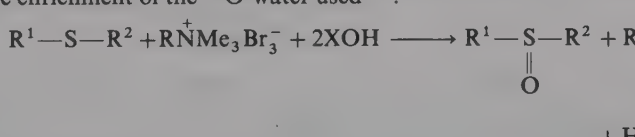
(624) **(623)**

**b. Hypochlorites.* Calcium hypochlorite is the second inorganic hypohalite which has been successfully used for the selective oxidation of sulphides to sulphoxides (equation 399)[714].



(399)

f. Ammonium tribromides. The reaction of sulphides with a stoichiometric amount of benzyltrimethylammonium tribromide **625** and aqueous sodium hydroxide in dichloromethane at room temperature or 1,2-dichloroethane under reflux gave the corresponding sulphoxides as the sole reaction product[715]. Various sulphides can also be oxidized selectively to the corresponding sulphoxides using phenyltrimethylammonium tribromide **626** in aqueous pyridine solution[716]. Both procedures, which can be presented by the general equation 400, afforded sulphoxides in high yields (see Table 38). Of interest is that the latter procedure allows ^{18}O-labelled sulphoxides to be prepared with no loss of isotope enrichment of the ^{18}O-water used[716].



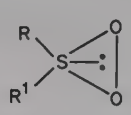
(400)

TABLE 38. Oxidation of sulphides, R^1SR^2, with ammonium tribromides **625** or **626**

R^1	R^2	Oxidant/solvents	Time (h)	Temp (°C)	Yield (%)	Ref.
n-Pr	*n*-Pr	**625**/H_2O/CH_2Cl_2	1	r.t.	89	715
n-Pr	*n*-Pr	**626**/H_2O/pyridine	3	r.t.	84	716
$PhCH_2$	$PhCH_2$	**625**/H_2O/CH_2Cl_2	2	r.t.	84	715
$PhCH_2$	$PhCH_2$	**626**/H_2O/pyridine	2	r.t.	88	716
$PhCH_2$	Ph	**625**/H_2O/CH_2Cl_2	3	r.t.	53	715
$PhCH_2$	Ph	**625**/H_2O/$C_2H_4Cl_2$	4	reflux	80	715
$PhCH_2$	Ph	**626**/H_2O/pyridine	2	r.t.	96	716
Ph	Ph	**625**/H_2O/CH_2Cl_2	6	r.t.	32	715
Ph	Ph	**625**/H_2O/$C_2H_4Cl_2$	4	reflux	73	715
Ph	Ph	**626**/H_2O/pyridine	24	r.t.	89	716
Me	2-$O_2NC_6H_4$	**626**/H_2O/pyridine	3	r.t.	82	716
Me	Ph	**626**/H_2O/pyridine	3	r.t.	85	716
Ph	4-$HO_2CC_6H_4$	**626**/H_2O/pyridine	18	r.t.	93	716

**8. Photochemical oxidation*

Photochemical oxidation of sulphides has been a subject of recent extensive investigations devoted to mechanistic[717] and biological[718] aspects of this reaction. As a rule, sulphoxides are formed as the primary products. However, their instability under the reaction conditions and, especially, rapid overoxidation to the corresponding sulphones limit very strongly the scope of this method for the preparation of sulphoxides. Detailed kinetic investigations[719–722] and theoretical calculations[723] support the earlier proposal[111] that thiadioxirane intermediates **627** are formed via a non-polar reaction in competition with the persulphoxide **628** formation. It was also shown that persulphoxides **628** are stabilized by coordinating solvents as well as by protic ones[720].



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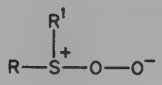


(628)

**9. Electrochemical oxidation*

The electrochemical oxidation of organic sulphides leads usually to a mixture of sulphoxides, sulphones and sulphonium salts. In some cases, however, this procedure can be successfully used for the preparation of sulphoxides. Thus, the electrochemical oxidation of 1,*n*-chloroalkyl(alkylthio)alkanes **629** (equation 401) is a good method for the preparation of the corresponding sulphoxides **630** with $n > 2$ in satisfactory yield[724].

$$R^1—S—(CH_2)_nCl \longrightarrow R—\underset{\underset{O}{\|}}{S}—(CH_2)_nCl \qquad (401)$$

(629) **(630)**

Similarly, 2-(4-nitrophenylthio)ethyl carboxylates **631** yield the corresponding sulphoxides **632** (equation 402) by facile electrolyses in good yields[725].

$$p\text{-}O_2NC_6H_4SCH_2CH_2COOR \xrightarrow{\text{E. oxidation}} p\text{-}O_2NC_6H_4\underset{\underset{O}{\|}}{S}CHCH_2COOR \qquad (402)$$

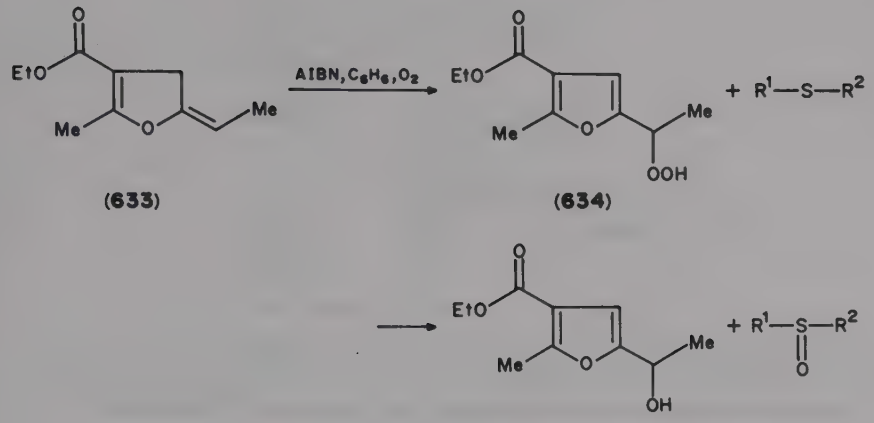
(631) (**a**) R = Me
(**b**) R = $PhCH_2OC(O)NH—CH(Me)$—

(632) 90% yield

**10. Oxidation by miscellaneous reagents*

Furyl hydroperoxide **634** generated *in situ* from the unsaturated precursor **633** was found to oxidize selectively sulphides into the corresponding sulphoxides in moderate yields as shown in Scheme 11[726].

DMSO was applied for oxidation of alkyl 2-chloroethyl sulphides **635a, b** and bis(2-chloroethyl)sulphide **635c** to the corresponding sulphoxides **636a–c** under relatively mild conditions (25–70 °C) (equation 403)[727].



(633) (634)

R^1	R^2	Yield (%)
p-Tol	Me	56
Ph	Me	53
$PhCH_2$	Me	61

SCHEME 11

$$R—S—CH_2CH_2Cl + Me_2S{=}O \longrightarrow RS(O)CH_2CH_2Cl + Me_2S \qquad (403)$$

(635) (a) R = Me
(b) R = Et
(c) $R = CH_2CH_2Cl$

(636)

Alkyl aryl sulphides are selectively oxidized by potassium peroxydisulphate in aqueous acetic acid to afford the corresponding sulphoxides in 75–90% yield[728]. However, potassium hydrogen persulphate under biphasic reaction conditions, in the presence of a phase transfer catalyst, converts diaryl sulphides to a mixture of sulphoxides and sulphones[729].

Selective oxidation of sulphides to sulphoxides can be achieved with the use of zinc bismuthate as an oxidant[730].

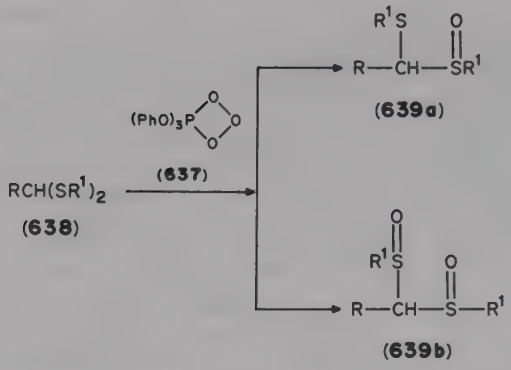
Reasonable yields (54–88%) of the sulphone-free sulphoxides were observed in the oxidation of sulphides with barium permanganate under non-aqueous conditions[731].

High-purity sulphoxides have been prepared by treating sulphides with solid sodium bromate in the presence of Al_2O_3 or silica gel in aqueous inert organic solvent systems[732].

Triphenylphosphite ozonide **637** has been found to oxidize thioacetals **638** in methylene chloride solution at −78 °C to give the monoxides **639a** and the dioxides **639b** (equation 404)[733]. The yields of **639b** increase with increase in the ozonide–thioacetal ratio.

Non-selective formation of sulphoxides was also observed in oxidation of sulphides with titanium silicate molecular sieves[734].

A similar lack of selectivity was observed when sulphides were oxidized by iodylarenes ($ArIO_2$) in the presence of vanadyl acetylacetonate as a catalyst. Beside sulphoxides, the corresponding sulphones and S-dealkylated products were formed in substantial yields[735a]. The selective oxidation of sulphides to sulphoxides with molecular oxygen was observed with the use of Ru(III)–dimethyl sulphoxide as a catalyst[735b].

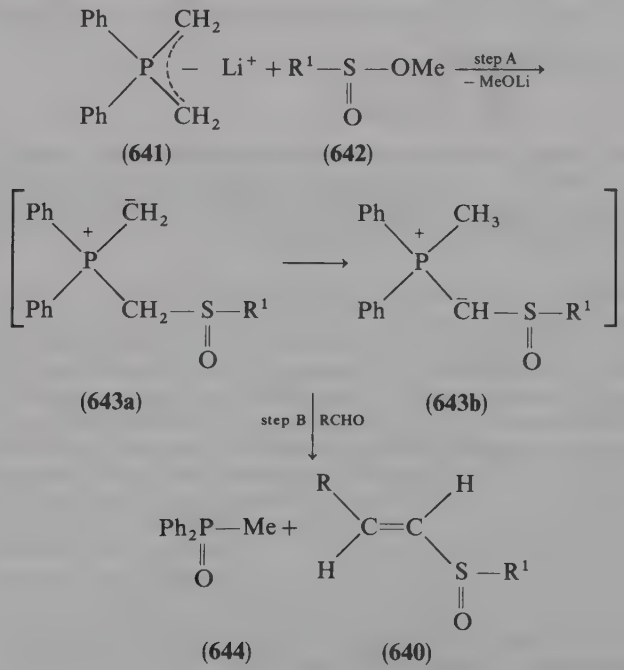


(404)

*D. Reaction of Organometallic Compounds with Sulphinic Acid Derivatives

*1. Sulphinic acid esters

Racemic, α,β-unsaturated sulphoxides **640** with (*E*)-geometry were effectively synthesized by a one-pot reaction of lithium dimethyldiphenylphosphonium diylide **641** with racemic sulphinates **642** followed by treatment of the formed α-sulphinylmethyl(methyl) diphenylphosphonium ylide (**643**) with aldehydes (Scheme 12)[736]. The results in Table 39 indicate that this preparation of sulphoxides **640** is very efficient and the yields usually exceed 70%. Synthesis of optically active analogues of **640** using this methodology will be discussed in the second part of this chapter.

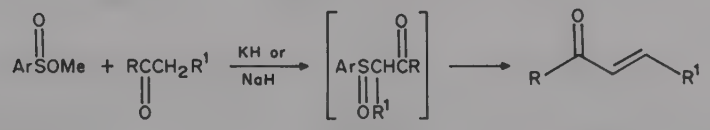


SCHEME 12

TABLE 39. Racemic α,β-unsaturated sulphoxides **640** prepared according to Scheme 12[736]

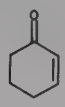
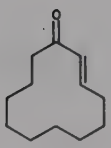
R	R^1	*E*/*Z* ratio	Yield (%)
Ph	Me	91/9	77.5
Ph	Et	100/0	70.0
Ph	*n*-Pr	100/0	71.0
Ph	*i*-Pr	100/0	75.0
Ph	*t*-Bu	100/0	48.0
Ph	Ph	96/4	68.8

A few α-pyridyl β-ketosulphoxides **645** have very recently been prepared from methyl 1-pyridinesulphinate **646** and ketone enolate anions and thermolysed without isolation to enones **647** (Scheme 13)[737].



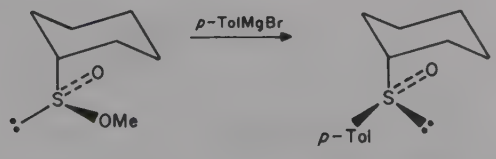
(646a) **(645)** **(647)**

Ar =

647	R	R^1	Yield (%)
a	*c*-C_6H_{11}	H	86
b	Me	C_6H_{13}	90 (only *E*)
c	CO_2Me	C_6H_{13}	57 (only *E*)
d			53
e			95

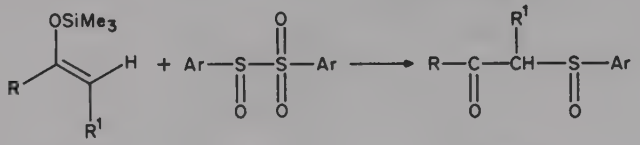
SCHEME 13

Reaction of diastereoisomeric methyl sulphinates **648** (90:10) with *p*-tolylmagnesium bromide (equation 405) furnished a mixture of sulphoxides **649** (89:11) in which the major diastereoisomer **649a** showed a ^{1}H-NMR spectrum very similar to those already reported[738a].



(648a, b) 90:10 **(649a, b)** 89:11 (405)

A few β-ketosulphoxides **645f–i** were prepared by the reaction of trimethylsilyl enol ethers **650** with *p*-toluenesulphinyl *p*-toluene sulphone (Scheme 14)[739].



(650) **(645)**

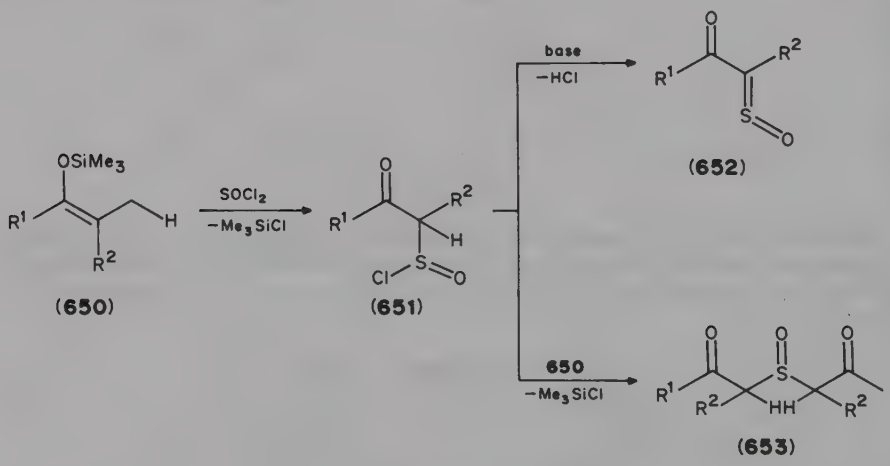
	Ar	R	R^1	Yield (%)
f	4-MeC_6H_4	$-(CH_2)_4-$		86
g	4-MeC_6H_4	$-CH_2CH_2CHCH_2-$ (Bu-*t*)		81
h	4-MeC_6H_4	$-CH-(CH_2)_2-$ (Me)		78
i	4-MeC_6H_4	*n*-Pr	*n*-Bu	78

SCHEME 14

*E. Reaction of Aromatic Derivatives and Compounds Containing Active Hydrogen with Sulphinyl Chlorides

*1. Thionyl chloride

The nucleophilic attack of silyl enol ethers **650** on thionyl chloride leads to β-oxosulphinyl chlorides **651**. The latter either undergo dehydrochlorination to oxosulphines **652** or react with an excess of the silyl enol ether to give β,β′-dioxo sulphoxides **653** as shown in Scheme 15[740].



(650) **(651)** **(652)** **(653)**

SCHEME 15

When the β,β′-dioxosulphoxide system **653** was the desired product, the best results were obtained by adding 0.5 equivalent of thionyl chloride to a solution of **650** in the

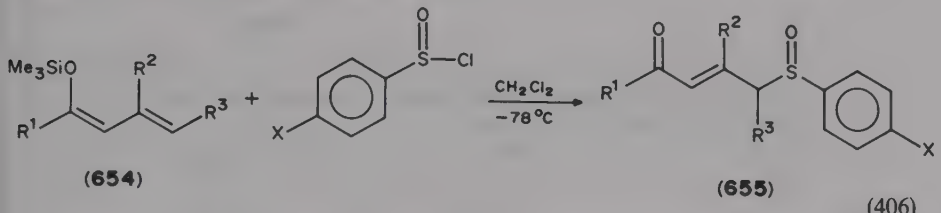
absence of base. Silyl enol ethers derived from esters and amides gave the corresponding products in good to moderate yields, while enol ethers derived from ketones did not produce **653** (Table 40).

TABLE 40. Preparation of β,β'-dioxo sulphoxides **653** by the reaction of thionyl chloride with silyl enol ethers **650**[740]

R^1	R^2	Yield (%)
MeO	Ph	70
MeO	Me	74
Me_2N	Et	18
Et	Me	0
Me	Ph	0
		0

*2. *Sulphinyl chlorides*

When 1-silyloxy-1,3-dienes **654** were treated.with arenesulphinyl chlorides, the reaction occurred exclusively at the γ-position (equation 406) and afforded δ-keto-β,γ-unsaturated sulphoxides **655** (Table 41)[740]. In all cases, except with the sulphoxides **655g–i**, only products with the *E*-geometry were isolated.



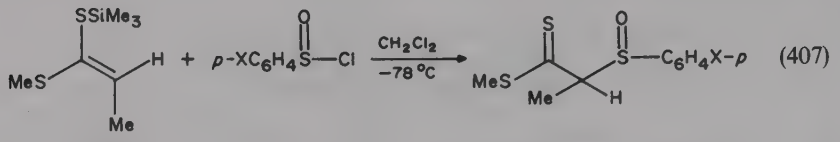
(406)

TABLE 41. Synthesis of δ-keto-β,γ-unsaturated sulphoxides **655** according to equation 406[740]

	R^1	R^2	R^3	X	Yield (%) isolated	(estimated)[a]
a	H	H	H	Me	—	(90)
b	H	H	H	H	30	(70)
c	H	H	H	Cl	26	(75)
d	Ph	H	H	Me	76	
e	Ph	H	H	H	86	
f	Ph	H	H	Cl	93	
g	MeO	Me	H	Me	84[b]	
h	MeO	Me	H	H	91[c]	
i	MeO	Me	H	Cl	63[c]	
j	H	H	Et	Me	—	(90)
k	H	H	Et	H	55	(75)
l	H	H	Et	Cl	35	(75)

[a] By ^{1}H NMR.
[b] *E*:*Z* = 75:25.
[c] *E*:*Z* = 7:3.

A closely related reaction of silyl enthiol ether **656** with arenesulphinyl chlorides proceeds smoothly at $-78\,^{\circ}C$ to give β-thioxo sulphoxides **657** in moderate yields (equation 407)[740].



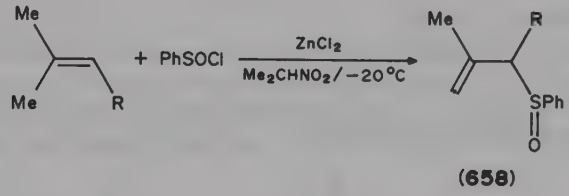
(407)

(656)

(657) (a) X=H (yield 25%)
(b) X=Cl (yield 40%)

*F. Addition of Sulphinyl Chlorides to Unsaturated Compounds

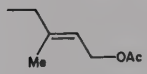
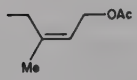
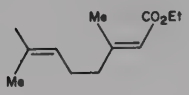
Synthesis of terminal isoprenoid sulphoxides **658** was achieved by the ene reaction of unsaturated hydrocarbons with benzenesulphinyl chloride in 2-nitropropane containing $ZnCl_2$ at $-20\,^{\circ}C$ (equation 408, Table 42)[741,742].



(408)

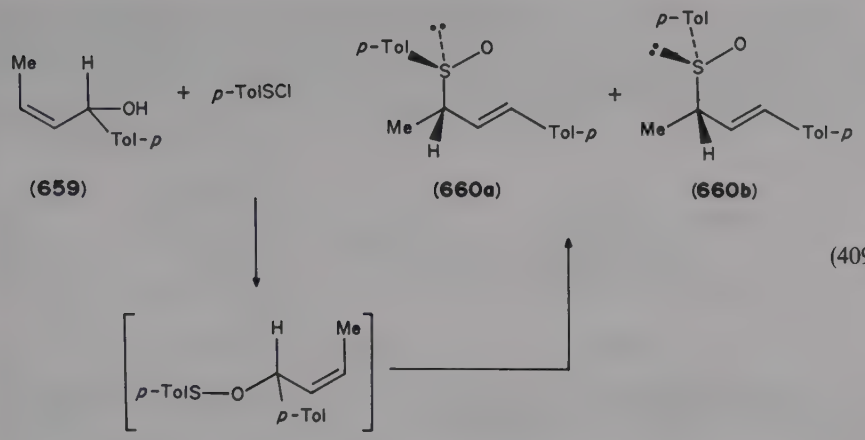
(658)

TABLE 42. Preparation of β,γ-unsaturated sulphoxides **658** from alkenes and benzenesulphinyl chloride

R	Yield (%)
	52
	61
	62
	65

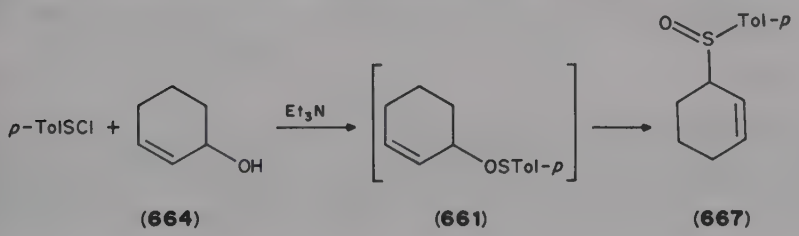
*H. Rearrangement of Sulphenic Acid Esters

When (Z) allylic alcohol **659** was treated with *p*-toluenesulphenyl chloride in the presence of triethylamine, the spontaneous [2,3] sigmatropic rearrangement of the allyl *p*-toluenesulphenate formed afforded the corresponding allyl *p*-tolyl sulphoxide **660** as a *ca* 55:45 mixture of diastereoisomers (equation 409)[718].

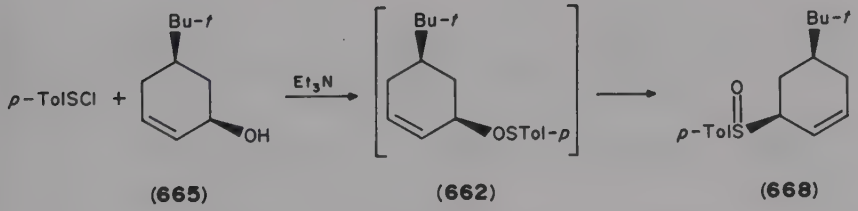


(409)

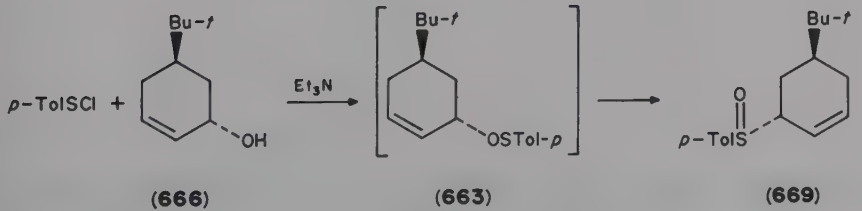
However, the rearrangement of the respective sulphenate esters **661**–**663** derived from cyclic allyl alcohols such as cyclohex-2-en-1-ol (**664**) and *cis*-5-*t*-butyl-cyclohex-2-en-1-ol (**665**) or its *trans*-isomer **666** is stereospecific and gives the corresponding sulphoxides **667**–**669** as single diastereoisomers (equations 410–412)[738b].



(410)

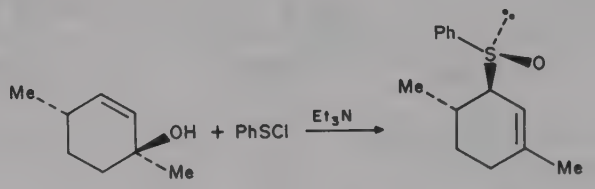


(411)



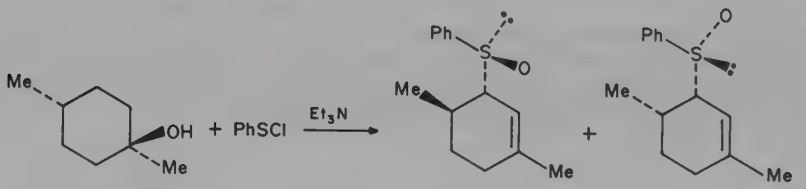
(412)

The analogous stereoselective formation of a single sulphoxide diastereoisomer **670a** was observed in the reaction of benzenesulphenyl chloride with (1*S*,4*S*)-*trans*-1,4-dimethylcyclohex-2-en-1-ol **671a** (equation 413)[743]. The absolute configuration at sulphur in **670a** was established to be *S*.



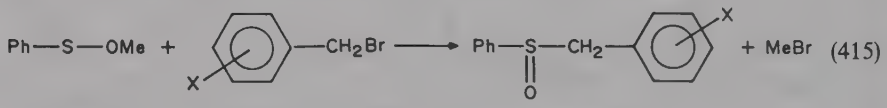
(671a) (670a) (413)

On the other hand, the reaction of the *cis*-alcohol **671b** under the same conditions gave a 1:1 mixture of **670b** and **670c** (equation 414)[743].



(671b) (670b) + (670c) (414)

Very recently, Kersten and Wenschuh reported[744] a new interesting approach for the preparation of unsymmetrical sulphoxides **672** from methyl benzenesulphenate **673** and benzyl bromides **674** (equation 415), which occurs upon heating the components dissolved in nitromethane at 75 °C for 8–10 h. It is of interest to note that perfluorobenzyl phenyl sulphoxide **679a** has also been prepared in 46% yield by this procedure.



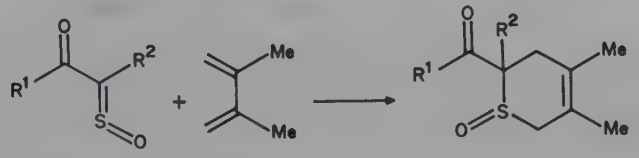
(673) (674) (672) (415)

X	Yield (%)
H	79
p-F	74
p-CF_3	65
m-CF_3	65
p-NO_2	57
m-NO_2	46
p-CN	69
p-OMe	55

Because of the similarity to the well-known Arbuzov reaction in phosphorus chemistry, this conversion of divalent organosulphur derivatives into tetravalent sulphinyl compounds was named by the above-mentioned authors a *thio*-Arbuzov reaction.

*I. Cycloaddition of Sulphur Monoxide and Sulphines to Unsaturated Compounds

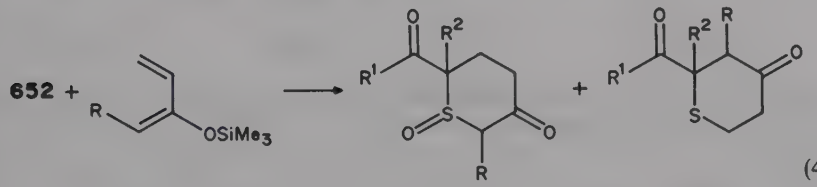
α-Oxosulphines **652**, prepared *in situ* from silyl ether **650** (Scheme 15), were trapped by 2,3-dimethyl-1,3-butadiene **675** in a cycloaddition reaction (equation 416) to give the cyclic unsaturated β-oxosulfoxides **676** listed in Table 43.



(416)

(652) **(675)** **(676)**

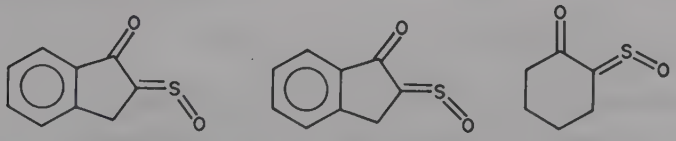
Similarly, the cycloaddition of the α-oxosulphines **652** and 2-trimethylsilyloxy-1,3-butadienes **677** proceeds rapidly at room temperature and is complete within a few minutes. The mixture of primary adducts upon hydrolysis using moist silica gel produced a mixture of thiacyclohexane S-oxide **678** and **679** (equation 417)[740].



(417)

(677) **(678)** **(679)**

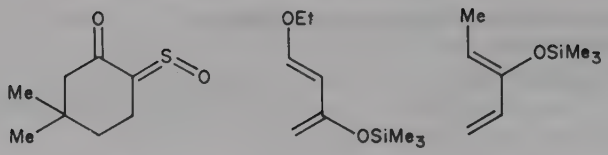
The analogous cycloaddition reactions were also observed for a few other sulphines (**680**–**683**) and dienes (**684** and **685**)[740].



(680) **(681)** **(682)**

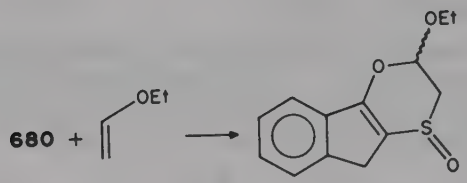
TABLE 43. Synthesis of dihydrothiapyran S-oxides **676** by cycloaddition of sulphines **652** to 1,3-butadiene **675**[740]

R^1	R^2	Temp (°C)	Time (h)	Yield (%)
MeO	Ph	0	2.5	87
MeO	Me	0	2.5	45
Et	Me	0	2.5	38
Me	Ph	0	2.5	72
H_2C=CH	Me	0→20	5.0	52
H_2C=CH	H	0→20	2.5	48
Ph	H	−78	0.5	84
H	Ph	0→20	14.0	14



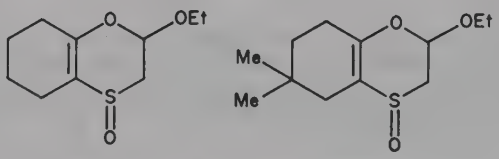
(683) (684) (685) (417)

An interesting aspect of sulphines **652** and **680–683** is that they can also be used as the diene component in cycloaddition reactions with electron-rich olefins. Thus, the stable α-oxosulphine **680** has been found to react with vinyl ether to give the sulphoxide **686** (equation 418)[745].



(686) (418)

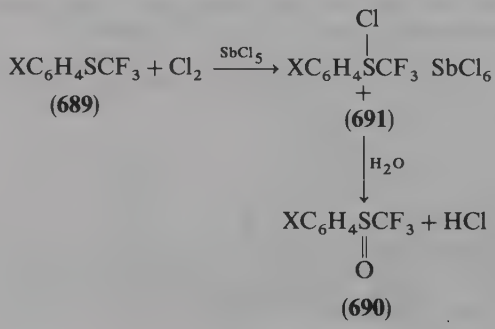
Similar reactions of sulphines **682** and **683**, generated *in situ* from the corresponding silyl enol ethers, with vinyl ether afforded 1,4-oxathiin S-oxides **687** and **688**, respectively[740].



(687) (688)

*K. From Organic Sulphur Compounds of Higher Oxidation State

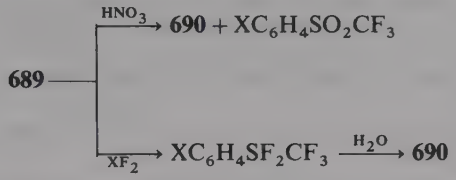
A few aryl trifluoromethyl sulphides **689** have been converted selectively to the corresponding sulphoxides **690** by hydrolysis of the appropriate chlorosulphonium salts **691** prepared by the reaction of the sulphides **689** with chlorine in the presence of $SbCl_5$ (equation 419)[746].



(419)

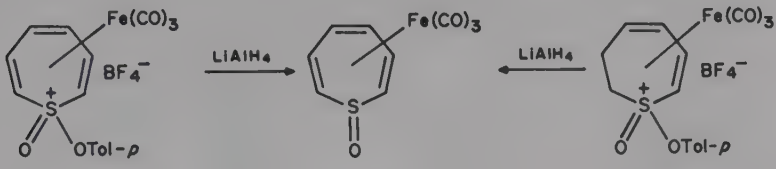
(a) X = H
(b) X = *p*-Cl
(c) X = *p*-F
(d) X = *m*-F
(e) X = *p*-NO_2

The sulphoxides **690** were prepared earlier, by oxidation of the sulphides **689** with nitric acid[747] or by hydrolysis of difluorosulphuranes **692**[748] (equation 420), but in a non-selective way, and they were contaminated with the corresponding sulphones.



(420)

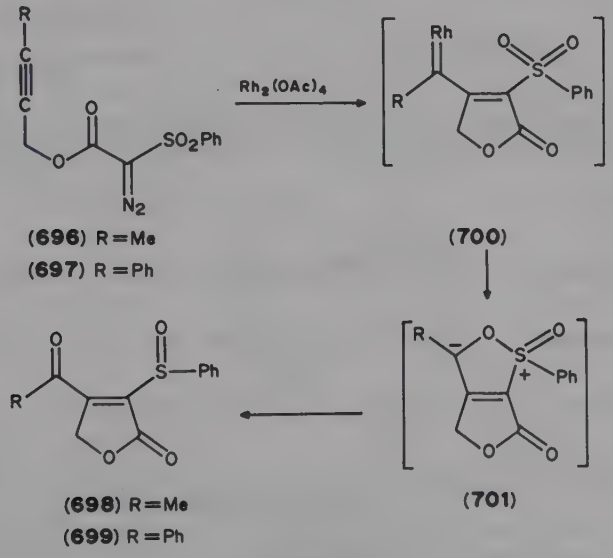
Lithium aluminium hydride reduction of a mixture of the diastereoisomers of the *p*-tolyloxysulphoxonium salt **693** at −100 °C for 30 min gave the 6,7-dihydrothiepine 1-oxide complex **694**, which was also prepared by the reduction of the sulphoxonium salt **695** (also a mixture of diastereoisomers) under the same conditions (equation 421)[749].



(693) (694) (695)

(421)

Treatment of diazo alkynyl sulphones **696** and **697** with Rh(II) acetate at 80 °C gave sulphoxides **698** and **699** in 60 and 90% yield, respectively[750]. To explain this novel oxygen transfer reaction, the sulphone oxygen attack onto the vinyl carbenoid **700** producing the dipolar species **701** was assumed. The latter collapses to ring-opened butenolide sulphoxides **698** and **699**, as shown in Scheme 16.



(696) R = Me
(697) R = Ph

(700)

(698) R = Me
(699) R = Ph

(701)

SCHEME 16

***M. Miscellaneous Methods**

In a simple one-pot reaction, mono, di, tri and polyalkylbenzenes, isomeric alkylhalobenzenes and fluoro(trifluoromethyl)- and 1,3,5-trifluorobenzene were converted into diaryl sulphoxides **702** upon treatment with $FSO_3H \cdot SbF_5$ (1:1)/SO_2[751]. The corresponding sulphides **703** are formed as minor by-products (equation 422).

$$ArH + FSO_3H \cdot SbF_5 \cdot SO_2 \longrightarrow \underset{\underset{O}{\|}}{ArSAr} + ArSAr \qquad (422)$$

(703)

Table 44 clearly indicates the synthetic utility of this one-pot procedure, and also shows that both steric and electronic factors have an important influence on the reaction course.

This procedure allows also the preparation of unsymmetrical diaryl sulphoxides. Selected examples are presented in Scheme 17.

TABLE 44. Synthesis of symmetrical diaryl sulphoxides, $Ar_2S{=}O$, **702**, by the reaction between the appropriate arene, Ar and $FSO_3H \cdot SbF_5/SO_2$ system[751]

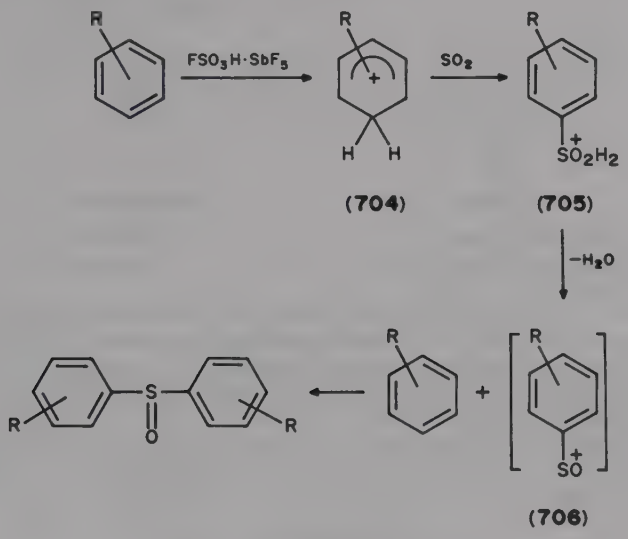
Arene	Ar	Yield (%)	m.p. (°C)
Toluene	4-MeC_6H_4	87(95)	94–96
Ethylbenzene	4-EtC_6H_4	90(97)	oil
Fluorobenzene	4-FC_6H_4	55(100)	oil
m-Fluorotoluene	2-Me-4-FC_6H_3	60(74)	115–117
o-Fluorotoluene	3-Me-4-FC_6H_3	64(72)	62–63.5
o-Chlorotoluene	3-Me-4-ClC_6H_3	66(69)	77–78
m-Xylene	2,4-$Me_2C_6H_3$	61(65)	167–169
Mesitylene	2,4,6-$Me_3C_6H_2$	26(48)	198–200
m-Diethylbenzene	2,4-$Et_2C_6H_3$	27(32)	oil
1,3,5-Trifluorobenzene	2,4,6-$F_3C_6H_2$	10(30)	oil
Pentamethylbenzene	1,2,3,4,5-Me_5C_6	(15.5)	95–97

$$ArH + Ar^1H + FSO_3H \cdot SbF_5/SO_2 \longrightarrow \text{Products}$$

Substrates	Products
Toluene + benzene	*p*-Tol—S(=O)—Ph (61%)
Toluene + fluorobenzene	*p*-Tol—S(=O)—C_6H_4F-*p* (71%) + *p*-Tol—S(=O)—Tol-*p* (29%)
Benzene + fluorobenzene	*p*-Tol—S(=O)—C_6H_4F-*p* (14%) + *p*-Tol—S(=O)—Tol-*p* (86%)
α,α,α-Trifluorotoluene	*m*-$CF_3C_6H_4$—S(=O)—C_6H_4F-*p* (73%) + *p*-FC_6H_4—S(=O)—C_6H_4F-*p*
+ fluorobenzene	+ *m*-$CF_3C_6H_4$—S(=O)—$C_6H_4CF_3$-*m* (14%)

SCHEME 17

The mechanism proposed involves sulphination of the arenium ion **704**, O-protonation of the resulting sulphinic acid to form the species **705** and its dehydration to the oxonium ion **706** which undergoes arylation (Scheme 18).



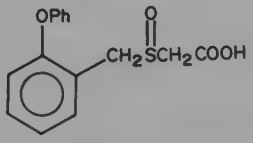
SCHEME 18

*III. SYNTHESIS OF OPTICALLY ACTIVE SULPHOXIDES

*A. Optical Resolution

*1. Classical resolution

The racemic [(*o*-phenoxyphenyl)sulphinyl] acetic acid **707** was resolved into the pure enantiomers by fractional crystallization of its diastereoisomeric salts with optically active bases[752].

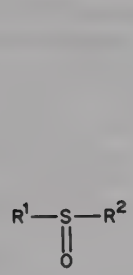


(707)

*2. Non-classical resolution

A few *o*-substituted phenyl alkyl sulphoxides have been resolved partially by the formation of inclusion complexes with β-cyclodextrin[753].

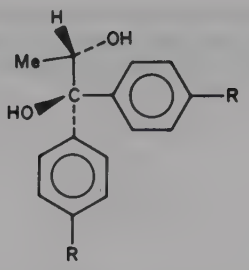
A new non-classical procedure of the resolution of sulphoxides **708** uses the fact that some sulphoxides form crystalline complexes with the optically active alcohol **709**[754]. However, both sulphoxides **708a** and **708b** were poorly resolved by the use of **709a** (e.e. *ca* 30%).



(708)

(a) R^1=Ph, R^2=Me

(b) R^1=Ph, R^2=CH_2=CH



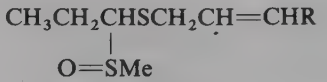
(709) (a) R=H

(b) R=Me

(c) R=*t*-Bu

Enantiomers of several sulphoxides can be easily separated by using a new chiral stationary phase containing the 3,5-dinitrobenzoyl derivatives of (*R*,*R*)-(−)-1,2-diaminocyclohexane as a selector covalently bound to the matrix. The easy operative conditions and the high enantioselectivity value allow one to extend this procedure to a semi-preparative and preparative scale[755,756].

Isolation of three diastereoisomers of 1-(methylsulphinyl)propyl alkenyl sulphides **710** isolated from Allium cepa was achieved by the use of chiral-phase HPLC with Chirocel OB column and hexane-isopropanol (9:1) as the mobile phase[757].

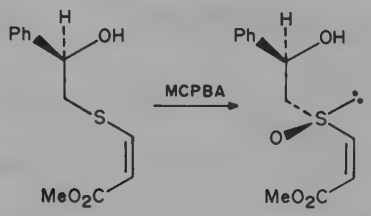


(710)

*B. Asymmetric Synthesis

Asymmetric oxidation of sulphides containing a chiral group with achiral oxidizing agents and prochiral sulphides by optically active oxidants still constitute simple and convenient routes to optically active sulphoxides.

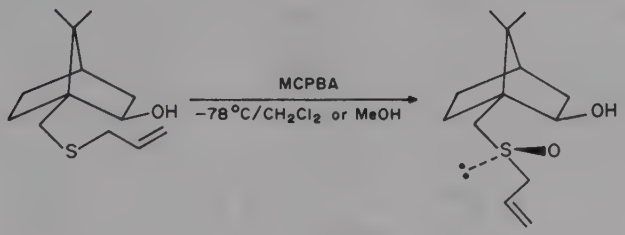
Oxidation of vinyl sulphide **711** with MCPBA acid in tetrachloromethane produces a 85:15 mixture of diastereoisomeric sulphoxides **712** in quantitative yield (equation 423). The two sulphoxides can be easily separated by fractional crystallization from the same solvent[758].



(711) (712a) m.p. 129–130 °C (85%) (423)

A low-temperature MCPBA oxidation of allylic sulphide **713** derived from (1*S*)-10-mercaptoisoborneol proceeds in a completely diastereoselective fashion to give a configurationally stable allylic sulphoxide **714a** (equation 424)[759]. When the oxidation was

carried out with $NaIO_4$ in CH_3OH/H_2O, a 66:34 mixture of separable sulphoxides **714a,b** was obtained.

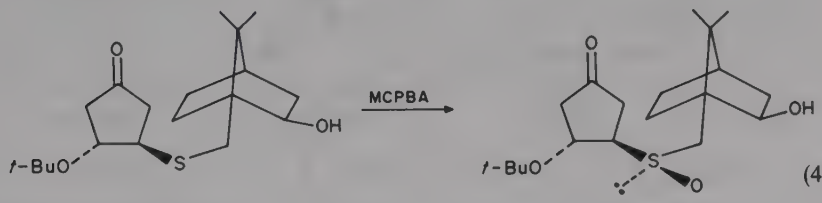


(424)

(713) **(714a)**

$[\alpha]_{589} = +28.9$ ($CHCl_3$)
m.p. 44.5–45 °C

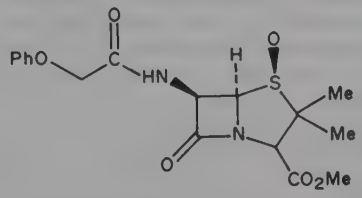
Oxidation of the hydroxy sulphide **715** derived from (1*S*)-10-mercaptoisoberneol with MCPBA also afforded a single diastereoisomeric sulphoxide **716** (equation 425)[760].



(425)

(715) **(716)**

Potassium peroxymonosulphate oxidation of sulphides to sulphoxides occurs also with very high selectivity. Thus, oxidation of pencillin V afforded the *syn* sulphoxide **717**[761].



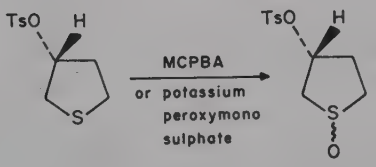
(717)

Oxidation of enantiomerically pure cyclic sulphide **718** with MCPBA provided mixtures of the *trans*- and *cis*-sulphoxides **719** and **720** in a ratio 10:1. When potassium peroxymonosulphate was used, the *trans* isomer **719** was isolated in 77% yield accompanied by minor amounts of **720** (equation 426)[762].

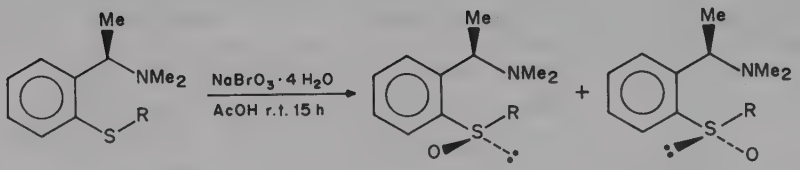
Oxidation of the sulphides **721**, derived from optically active *N,N*-dimethyl-1-phenylethylamine, with sodium perborate afforded two sulphoxides **722** and **723** (equation 427); their ratios are given in Table 45[763,764].

TABLE 45. Oxidation of sulphides **721** to sulphoxides **722** and **723**.

R	Ratio **722**/**723**	d.e. (%)
Me	11:89	78
Et	17:83	66
c-C_6H_{11}	18:82	64
$PhCH_2$	40:60	20



(718) **(719)** *trans*
(720) *cis*



(721) **(722)** **(723)** (427)

The simplest approach for the synthesis of optically active sulphoxides in which the sulphinyl sulphur atom constitutes a sole centre of chirality is via the asymmetric oxidation of prochiral sulphides with chiral oxidizing agents. This method has been actively developed during the past few years and many new procedures based on chemical and enzymatic oxidation have been more or less successfully applied.

Considering chemical oxidants, it should be noted that many studies during this period concentrated on the optimalization of the modified Sharpless asymmetric epoxidation procedure discovered by the research groups of Kagan[286] and of Modena[287].

Kagan and coworkers demonstrated the scope and limitations of their oxidizing system [Ti(OPr-*i*)$_4$: (+)DET(diethyl tartrate): H_2O in a ratio of 1:2:1][765], They found that the enantioselectivity of the oxidation (equation 428, Table 46) is enhanced by using cumene hydroperoxide (CHP) instead of *t*-butyl hydroperoxide. It was also observed that when aryl is replaced by 1-alkyne, the sulphoxide is still obtained with a high e.e. value. On the other hand, dialkyl sulphoxides are generally obtained with low enantioselectivity.

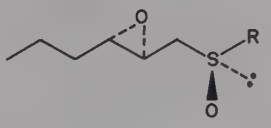
$$R^1—S—R^2 \xrightarrow[R^3OOH]{Ti(OPr-i)_4/(R,R)DET/H_2O} R^1—\overset{\overset{O}{\|}}{S}—R^2 \qquad (428)$$

The asymmetric oxidation was also carried out under catalytic conditions (with respect to the titanium complex). It was found that in the presence of 0.5 mol equiv. of titanium reagent the oxidation of methyl tolyl sulphide affords the same results as under the stoichiometric conditions.

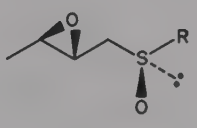
TABLE 46. Asymmetric oxidation of sulphides, R^1SR^2, to optically active sulphoxides, $R^1S(O)R^2$, with the modified Sharpless reagent[765]

R^1	R^2	R^3	Yield (%)	e.e. (%)
4-Tol	Me	*t*-Bu	90	89
4-Tol	Me	$PhCMe_2$	93	96
4-Tol	Me	Ph		16.3
4-Tol	Et	*t*-Bu	71	74
Ph	Me	*t*-Bu		88
Ph	Me	$PhCMe_2$	93	93
$PhCH_2$	Me	$PhCMe_2$	84	61.5
$PhCH_2$	Me	*t*-Bu		35
Me	*n*-C_8H_{17}	$PhCMe_2$	71	80
Me	*n*-C_8H_{17}	*t*-Bu		53
Me	2-$MeOC_6H_4$	$PhCMe_2$	97	93
Me	2-$MeOC_6H_4$	*t*-Bu		74

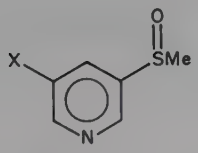
The Kagan modification has been successfully used for the synthesis of optically active 2,3-epoxy sulphoxides **724** and **725**[766], chiral 3-methylsulphinyl pyridines **726** and **727**[767a] and for the asymmetric oxidation of bis(methylthio)benzene derivatives **728**[767b].



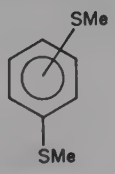
(724)
(a) R=Me
(b) R=Ph



(725)
(a) R=Me
(b) R=Ph



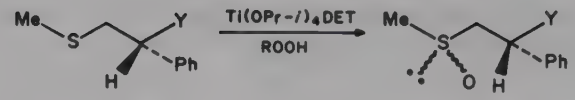
(726) X=H
(727) X=Cl



(728)

The Modena modification works very well in the case of β-hydroxysulphides. Oxidation of various, suitably blocked *S*-methyl-β-hydroxythioethers **729–732** afforded the corresponding sulphoxides **733–736** characterized by e.e. values up to 80%, which may be further increased (> 98%) by crystallization[768] (Scheme 19).

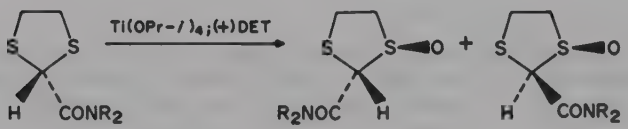
Using this modification (−)-trans-2-*N*,*N*-dialkylacetamido-1,3-dithiolane-*S*-oxides **736a–c** have been obtained in a very high diastereoisomeric ratio and enantiomeric excess by enantioselective oxidation of the starting 1,3-dithiolanes **738a–c** (equation 430)[769].



+ **(729–732)** **(733–736)** (429)

Sulphide	Y	ROOH	Yield (%)	Sulphoxide	d.r. a:b	e.e.$_a$	e.e.$_b$
(±)**729**	OH	*t*-BuOOH	20	**733**	68:32	3	5
(±)**730**	$OSiMe_3$	*t*-BuOOH	78	**734**	56:44	70	64
(±)**731**	$OSiPh_3$	$PhCMe_2OOH$	85	**735**	50:50	80	75
(±)**732**	$OSi(t\text{-}Bu)Ph_2$	*t*-BuOOH	90	**736**	55:45	75	71

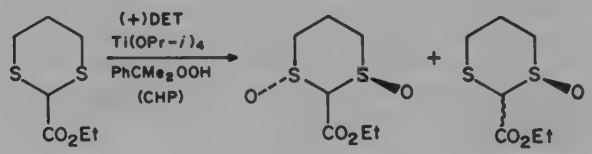
SCHEME 19



(738) **(737)** *trans* **(737)** *cis* (430)

R_2	Yield (%)	Ratio *trans*:*cis*	e.e. (%) for *trans*
Me_2	70	>99:1	63
Et_2	87	>99:1	94
$(CH_2)_4$	62	>99:1	77

The Modena modification was found to be superior to the Kagan procedure for the oxidation of 1-carboethoxy-1,3-dithiane **739** to the corresponding *trans*-1,3-dioxide **740** (equation 431)[770].

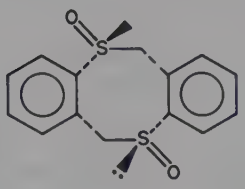


(739) **(740)** **(741)** (431)

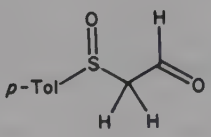
2 equiv.	38% (>97% e.e.)	60% (85% e.e.)
4 equiv.	68% (>97% e.e.)	28% (82% e.e.)

The optically active bis-sulphoxide **742** with an e.e. of 94% was also prepared from the corresponding bis-sulphide by this procedure[769b]. The Kagan and Modena modifications

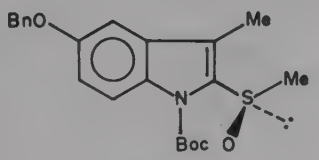
were used also for a very efficient preparation of optically active sulphinylaldehyde **743**[765b] and the indolyl sulphoxide **744** (e.e. 85%)[771].



(742)

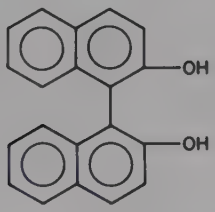


(743)

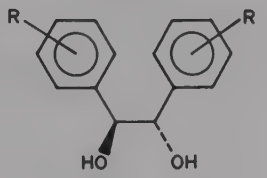


(744)

Two other modifications of the Sharpless reagent applied for the asymmetric oxidation of sulphides are based on the use of (+)-(*R*)-binaphthol **243**[772] and 1,2-bis(methoxyphenyl) ethane 1,2-diol **745**[773] as chiral auxiliaries.



(243)

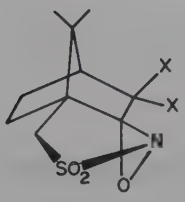


(745) (a) R = *o*-OMe
(b) R = *p*-OMe

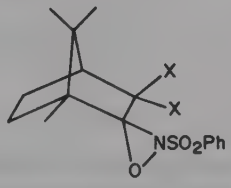
Both procedures afford optically active aryl methyl sulphoxides in high chemical yields and in good e.e. values (up to 73% for **243** and up to 84% with **745a**).

Enantiomerically pure *N*-sulphonyloxaziridines are asymmetric oxidizing agents which are able to convert prochiral sulphides to optically active sulphoxides of very high optical purity (see equation 135). During the past few years some new members of this family of chiral oxidants have been applied.

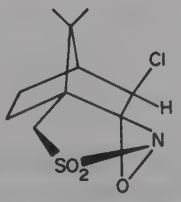
Davis and coworkers have used for these oxidations camphorsulphonyloxaziridines **746–753** and 2-sulphamyloxaziridines **754** and **755**.[774–779].



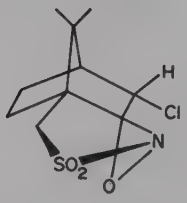
(746) (a) X = H
(b) X = Cl
(c) X = Br
(d) X = F



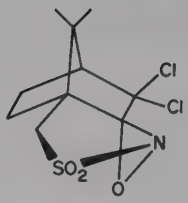
(747) (a) X = H
(b) X = Cl



endo-(748)

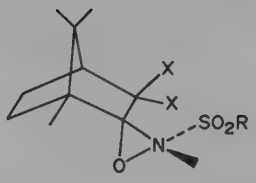


exo-(**749**)

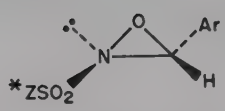


(**750**)

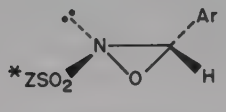
(**751**) R = Ph
(**752**) R = $PhCH_2$
(**753**) R = *o*-$MeOC_6H_4$



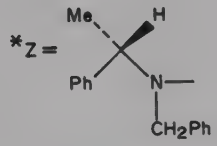
(**a**) X = H
(**b**) X = F
(**c**) X = Cl
(**d**) X = Pr



(**754**)

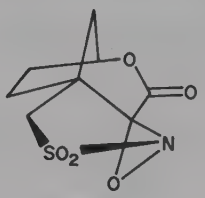


(**755**)



(**a**) Ar = 4-nitrophenyl
(**b**) Ar = 3-nitrophenyl
(**c**) Ar = 2-nitrophenyl
(**d**) Ar = 2-chlorophenyl
(**e**) Ar = 2-chloro-5-nitrophenyl
(**f**) Ar = 3, 5-dinitrophenyl
(**g**) Ar = pentafluorophenyl

Other authors have reported on the use of (3-oxocamphorsulphonyl)oxaziridine **746a**[780] and the camphyl derivatives **756**[781].



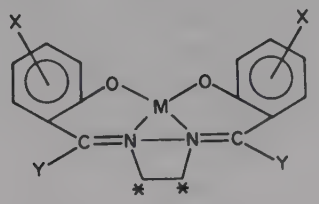
(**756**)

Table 47 shows that these oxidants exhibit remarkably high enantioselectivity for the asymmetric oxidation of prochiral sulphides to sulphoxides.

Asymmetric oxidation of sulphides to sulphoxides was found to occur with achiral oxidizing agents in the presence of optically active catalysts. Thus, the oxidation of dialkyl, alkyl aryl, diaryl and heterocyclic sulphides with various oxidants and a catalytic amount of metal *N*-salicylidene derivatives having the general structure **758** affords the corresponding sulphoxides with enantiomeric excess values varying from 2% to 73% (Table 48).

TABLE 47. Asymmetric oxidation of sulphides, R^1SR^2, to sulphoxides, $R^1S(O)R^2$, using oxaziridines **746–755**

				Sulphoxide			
R^1	R^2	Oxaziridine	Solvent	Yield (%)	Abs. conf.	e.e.	Ref.
Me	4-Tol	**746b**	CCl_4	80	*S*	67	778
Me	4-Tol	**747b**	CCl_4	95	*S*	95	775
i-Pr	4-Tol	**751c**	CCl_4	95	*S*	66	779
i-Bu	4-Tol	**751c**	CCl_4	91	*S*	90	779
n-Bu	4-Tol	**754c**	$CHCl_3$	—	*R*	68.4	777
$PhCH_2$	4-Tol	**751c**	CCl_4	88	*S*	94	779
$PhCH_2$	Et	**746a**	toluene	75	*R*	45	780
$PhCH_2$	*t*-Bu	**751c**	CH_2Cl_2	80	*S*	94	779
Ph	*c*-C_3H_5	**751c**	CCl_4	90	*S*	92	779
Ph	$CH{=}CH_2$	**751c**	CCl_4	60	*S*	85	775
Ph	CH_2CH_2Me	**751c**	CCl_4	65	*S*	94	775
Ph	CH_2CN	**751c**	CCl_4	45	*S*	95	775
2-Naph	Me	**751c**	CCl_4	84	*S*	94	779
9-Anth	Me	**751c**	CH_2Cl_2	90	*S*	95	779
Me	*t*-Bu	**751c**	CH_2Cl_2	90	*S*	93	779
Me	*n*-C_8H_{17}	**751c**	$CHCl_3$	57	*S*	58	779



(758)

'Twin cornet' iron porphyrines, that are modified on both faces chiral elements, catalysed the asymmetric iodobenzene-mediated oxidation of sulphides to sulphoxides in 17 to 73% enantiomeric excesses[787,788]. Similar results were noted in the oxidation of sulphides with iodobenzene catalysed by other catalysts derived from the antibodies of a C_2-chiral 1,4-xylylene-strapped porphyrin (e.e. varying from 18 to 71%)[789].

TABLE 48. Asymmetric oxidation of sulphides to sulphoxides catalysed by metal salicylidene derivatives **758**

		Sulphoxide		
Catalyst	Oxidant	Yield (%)	e.e. (%)	Ref.
Titanium-*N*-salicylidene-L-amino acids	*t*-BuOOH	27–54	2–21	782
(salen) titanium	*t*-BuOOH	32–87	5–53	783
(salen)vanadium	*t*-BuOOH	50–89	5–45	784
(salen) oxavanadium	*t*-BuOOH	70–96	1–40	785
(salen) manganium(III)	H_2O_2	80–95	34–68	786

The β-cyclodextrin-mediated oxidation of prochiral sulphides by achiral oxidation reagents has been thoroughly investigated. In pyridine containing hydrogen peroxide some experiments afforded sulphoxides with an e.e. as high as 90%. However, these results cannot always be reproduced and the reasons for this are not fully recognized[790]. In contrast, some alkyl aryl sulphides undergo enantioselective oxidation in crystalline cyclodextrin (CD) complexes under various conditions[791,792]. The highest optical yield (81%) was achieved in the combination of peracetic acid and methyl 1-naphthyl sulphide in the crystalline β-CD complex suspended in water. Other experiments gave sulphoxides with e.e. values ranging from 1 to 62%.

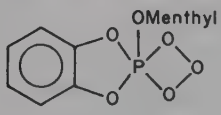
Oxidation of β-CD complexes of thioacetates **759** with sodium hypochlorite in aqueous media gave optically active α,α-dichlorosulphoxides **760** in 50–83% yield with e.e. values between 3.7 and 53.8% (equation 432)[793].

$$\underset{\textbf{(759)}}{XC_6H_4{-}(CH_2)_n{-}SCH_2\overset{\overset{O}{\|}}{C}OR} \xrightarrow[H_2O]{NaOCl} \underset{\textbf{(760)}}{XC_6H_4{-}(CH_2)_n{-}S\overset{\overset{O}{\|}}{C}HCl_2} \qquad (432)$$

$n = 0, 1$

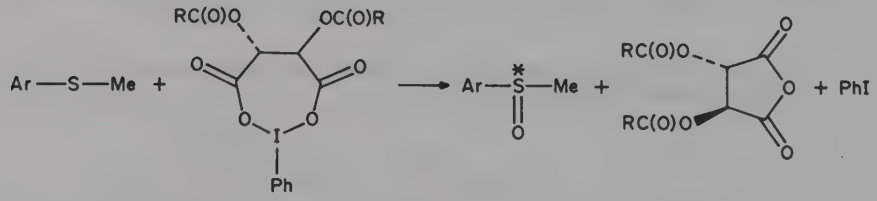
A variety of phenyl alkyl sulphides were selectively oxidized with $NaIO_4$ in a chiral micellar system prepared from chiral surfactants to form optically active sulphoxides with e.e. values from 1.6% to 15% [794].

A very low asymmetric induction (e.e. 3.7%) was noted when methyl phenyl sulphide was reacted with the chiral phosphate ozonide **761**[795]. Oxidation of *p*-tolyl methyl sulphide with hydrogen peroxide in the presence of optically active α-phenylethyl cyanide (e.e *ca* 50%) gave the corresponding sulphoxide with germinal optical activity[689b].



(761)

Moderate optical yields (30–53%) were observed in the asymmetric oxidation of *o*- and *p*-tolyl methyl sulphides with iodosobenzene in the presence of the *L*-tartaric anhydride[796]. It was suggested that the cyclic tartrates **762** generated *in situ* were responsible for the enantioselective course of the oxidation presented by equation 433.



(762) (**a**) R = Me
(**b**) R = *t*-Bu
(**c**) R = Ph (433)

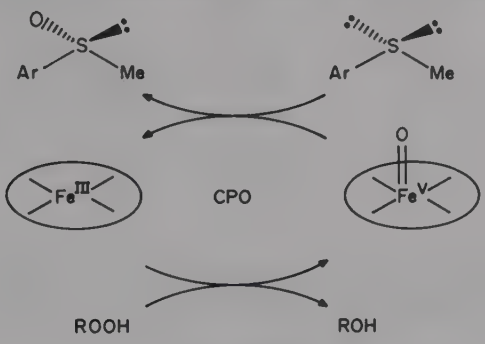
Later, the postulated iodine(III) tartrates **762** were produced and isolated as non-cyclic polymers capable of effecting the asymmetric oxidation of methyl *p*-tolyl sulphide

and the degree of chiral induction achieved by these polymers was comparable to that already reported for the *in situ* generated reagent[797].

A low asymmetric induction was observed in the electrochemical oxidation of alkyl phenyl sulphides on an anode coated with the optically active complex $Ru(phen)_3$ (phen = 1,10 phenantroline)[798].

The enzymatic conversion of sulphides to sulphoxides (equation 137) has been actively investigated during the past few years and has been comprehensively reviewed by Holland[799]. As a rule, microbiological methods do not provide a general, high-yielding route to sulphoxides with high e.e., but almost full enantioselectivity can be achieved with certain substrates.

It was recently reported that the chloroperoxidase-(CPO)-catalysed oxidation of prochiral sulphides, using H_2O_2, *t*-BuOOH or chiral hydroperoxides as stoichiometric oxidation reagents is very effective in providing a variety of aryl methyl and heteroaryl methyl sulphoxides with high e.e. (Scheme 20 and Table 49)[800 - 803].



SCHEME 20

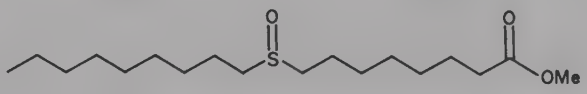
TABLE 49. Chloroperoxidase catalysed oxidation of sulphides, R^1SR^2, to sulphoxides, $R^1S(O)R^2$, using various oxidants ROOH

R^1	R^2	R	Yield (%)	e.e. (%)	Abs. conf.	Ref.
Ph	Me	H	100	98	*R*	802
Ph	Me	H	90	99	*R*	803
Ph	Me	*t*-Bu	100	76	*R*	800
4-Tol	Me	H	98	91	*R*	802
4-Tol	Me	H	92	99	*R*	802
4-Tol	Me	*t*-Bu	60	86	*R*	800
4-An	Me	H	66	100	*R*	803
4-An	Me	*t*-Bu	70	91	*R*	800
4-An	Me	PhCHMe	66	61	*R*	803
2-An	Me	*t*-Bu	33	25	*R*	800
$4\text{-}ClC_6H_4$	Me	H	87	97	*R*	803
$4\text{-}ClC_6H_4$	Me	*t*-Bu	44	85	*R*	800
$4\text{-}FC_6H_4$	Me	H	86	97	*R*	803
$4\text{-}FC_6H_4$	Me	*t*-Bu	100	97	*R*	802
2-pyridyl	Me	H	100	99	*R*	802
$PhCH_2$	Me	*t*-Bu	51	91	*R*	802

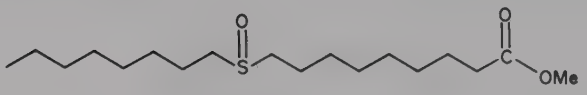
The hydrocarbon monooxygenase from *Pseudomonas oleovarans* (POM) and cyclohexanone monooxygenase (CMO) were found to be very effective for the stereoselective sulphoxidation of methyl alkyl and methyl aryl sulphides (Table 50) [804].

Oxidative conversion of sulphides to optically active sulphoxides was also observed with the pig liver microsomal FAD containing monooxygenase[805].

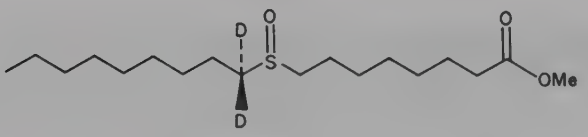
It was also shown that the Δ^9-desaturase of *Saccharomyces cerevisiae* can behave as a regio- and enantioselective sulphoxidation agent[806]. Thus, methyl 9-thiastearate *S*-oxide **763** having optical purity above 96% and the *R* absolute configuration at the sulphinyl sulphur atom was obtained via incubation of the corresponding sulphide with *S. cerevisiae* ATCC 12341. Similarly (*R*)-methyl 10-thiastearate *S*-oxide **764** (91% e.e.) was produced from the corresponding sulphide. The Δ^9-desaturase-produced sulphoxide **765**, containing two deuterium atoms at C-10, obtained by administering the corresponding sulphide to growing cultures of *S. cerevisiae* ATCC 2134, had an e.e. above 96%. This approach allows also the preparation of chiral *S*-benzyl-8-mercaptooctanoic acid methyl ester S-oxide **766** (e.e. > 98%) and *S*-benzyl 9-mercaptononanoic acid methyl ester *S*-oxide **767** (e.e. = 88%).



(763)



(764)



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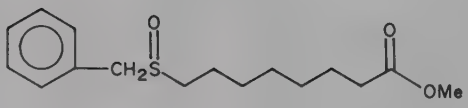
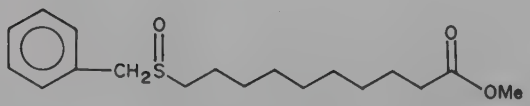
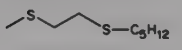


(766)

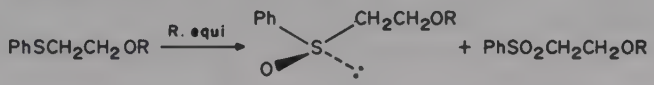


(767)

TABLE 50. Asymmetric sulphoxidation of methyl alkyl sulphides, Me—S—R, to optically active methyl alkyl sulphoxides, MeS(O)R, with monooxygenases

POM		CMO	
R	e.e.(%)	R	e.e.(%)
Et	88	*t*-Bu	99
n-Pr	80	Ph	99
n-Bu	60	4-FC_6H_4	92
n-C_5H_{11}	30	2-Tol	87
n-C_6H_{13}	70	2-An	51
n-C_7H_{15}	48	4-An	51
Hexen-3-yl	86	4-ClC_6H_4	51
Hepten-3-yl	88		
Hexen-2-yl	6		
Hepten-2-yl	4		
$(CH_2)_5CHMe_2$	2		
$CH(Me)(CH_2)_4Me$	52		
	30		
	52		

A very high enantioselectivity was also observed in the oxidation of 2-alkoxyethyl phenyl sulphides **768** to the corresponding sulphoxides **769** by incubation with a microorganism, *Rhodococcus equi* (*R. equi*) IFO 3720 (equation 434, Table 51)[807].



(434)

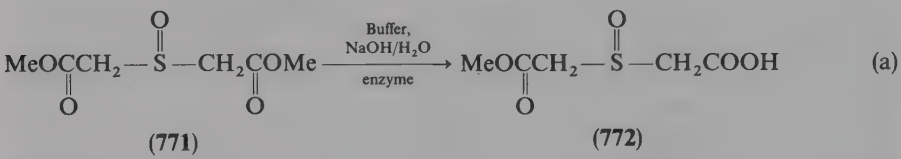
(768) **(769)** **(770)**

The biotransformation of properly functionalized prochiral sulphoxides has recently opend a new approach for the asymmetric synthesis of sulphoxides. Thus, methoxycarbonylmethyl carboxymethyl sulphoxide **772** and 2-acetoxyethyl 2-hydroxyethyl sulphoxide **774** have been produced with high enantiomeric purity by the enzyme-

TABLE 51. Asymmetric oxidation of 2-alkoxyethyl phenyl sulphides, $PhSCH_2CH_2OR$, with *R. equi*

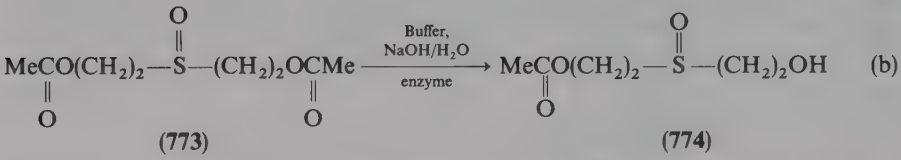
	Yield			
R	**768**	**769**	**770**	e.e.(%) of **769**
H	81	7	0	32
Me	0	80	13	> 99
n-Bu	29	42	17	99
Allyl	27	73	0	98
$MeOCH_2$	5	72	10	> 99.5
n-$BuOCH_2$	22	32	39	> 99.5

mediated hydrolysis of sulphinyldicarboxylates **771** and **773**, respectively. Both enantiomers of **772** have been obtained in a pure state by crystallization of the crude products obtained after hydrolysis and absolute configuration has been ascribed on the basis of an X-ray analysis to be (−)-(*R*) (equation 435, Table 52)[808].



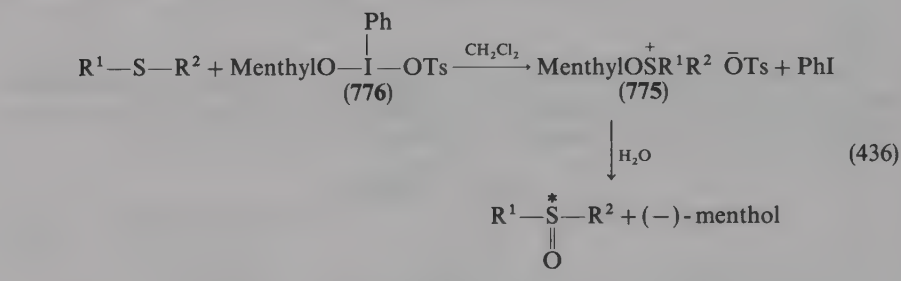
(771) (772) (a)

pure enantiomers: $[\alpha]_D \pm 20$ (435)



(773) (774) (b)

Optically active sulphoxides were formed by hydrolysis of the corresponding arylalkyl or dialkyl menthoxysulphonium salt **775** prepared from the appropriate sulphide and [(−) menthyloxy](tosyloxy)iodo] benzene **776** (equation 436)[809].



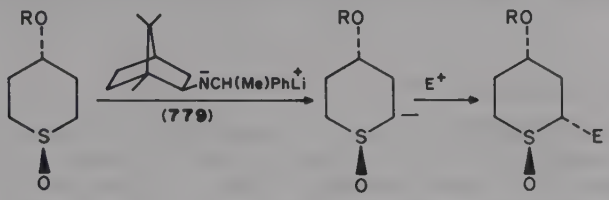
(436)

TABLE 52. Enzymatic hydrolysis of prochiral sulphinyldicarboxylates **771** and **773**

Sulphoxide substrate	Enzyme (concentration)	pH	Time (h)	Sulphoxide product			
					Yield (%)	$[\alpha]_D^{20}$	o.p. (%)
771	PLE(25)[a]	7.0	20	**772**	70	+ 14.6[c]	73
771	PLE(26)[a]	7.15	16.5	**772**	61	+ 14.1[c]	71
771	PLE(8)[a]	7.2	16	**772**	60	+ 13.5[c]	68
771	PLE(12)[a]	7.2	16	**772**	70	+ 15.8[c]	79
771	PLE(25)[a]	7.3	16	**772**	75	+ 14.5[c]	73
771	α-CT(4)[b]	7.4	14	**772**	63	− 16.3[c]	82
771	α-CT(3.9)[b]	7.5	16	**772**	63	− 18.3[c]	92
771	PPL(11)[b]	7.2	72	**772**	35	− 6.9[c]	35
773	PLE(25)[a]	7.5	40	**774**	70	+ 14.7[d]	67

[a] In μl/mmol.
[b] In mg/mmol.
[c] In MeOH, $c = 1$.
[d] In acetone, $c = 1.23$; PLE—porcine liver esterase, α-CT—α-chymotrypsin, PPL—lipase from hog pancrease.

Formation of a non-racemic product **777** was observed when achiral cyclic sulphoxide **778** was deprotonated by chiral lithium amide **779** and the α-sulphinyl anion **780** formed *in situ* was quenched with suitable electrophiles (equation 437)[811].



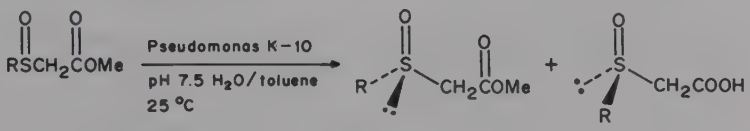
(437)

R = $SiPh_2Bu$-*t*

E	Yield(%)	e.e.(%)
Me_3Si	91	60
Me	85	67

*C. Kinetic Resolution of Sulphoxides

The already mentioned[338] enzyme-mediated hydrolysis of some racemic sulphinyl acetates has recently been extended[810] by the use of *Pseudomonas* K-10. It was found that, with this more readily available biological system, enzymatic hydrolysis of a number of arene or alkanesulphinyl acetates afforded both the unreacted sulphinyl acetate and the acids **783–788** with excellent e.e. (equation 438 and Table 53). Similar results were observed in the enantioselective transesterification with alcohols in hexane. Both procedures are suitable for the preparation of sulphinyl alkanoates where the ester and sulfoxide groups are separated by one or two methylene groups. However, the compounds with three methylene groups are not substrates for *Pseudomonas* K-10.



(438)

(781–786) **(787–792)**

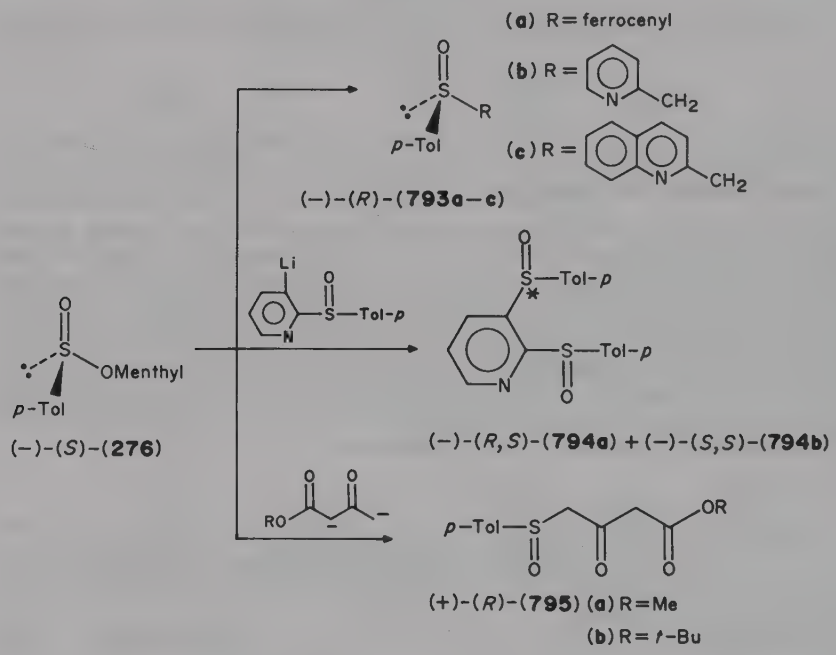
TABLE 53. Kinetic resolution of methylsulphinyl acetates **781–786** by the *Pseudomonas* K-10-mediated hydrolysis

	Ester			Acid		
R	No	Yield(%)	e.e.(%)	No	Yield(%)	e.e.(%)
Ph	**781**	48	>98	**787**	17	92
4-ClC_6H_4	**782**	48	>98	**788**	38	91
4-$MeOC_6H_4$	**783**	48	>98	**789**	34	88
4-$O_2NC_6H_4$	**784**	33	>98	**790**	22	97
n-Bu	**785**	33	>98	**791**	—	—
c-C_6H_{11}	**786**	49	>98	**792**	18	98

The kinetic resolution of racemic phenyl methyl sulphoxide was accomplished in the oxidation of its crystalline complex with β-cyclodextrin with NaOCl. It was shown[791], that when the conversion of racemic sulphoxide to sulphone reached 90% after 60 h, the observed optical purity of the recovered sulphoxide with the *R* configuration increased up to 90%.

*D. Stereospecific Synthesis

The Andersen synthesis of optically active sulphoxides still constitutes the most important and widely used method for the preparation of sulphoxides with high optical purity. The most commonly used precursor, diastereoisomerically pure (−)-(*S*)-menthyl *p*-toluenesulphinate **276** has recently been used for the preparation of some, not so common, optically active sulphoxide structures shown in Scheme 21.

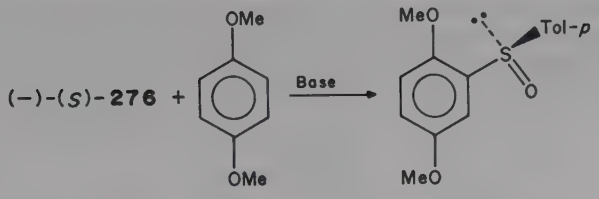


SCHEME 21

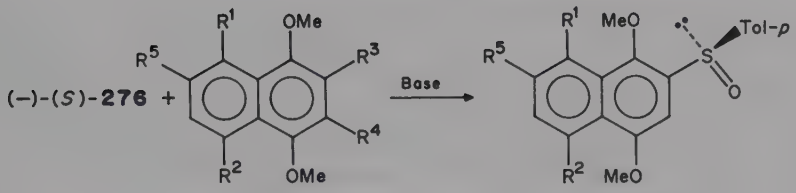
This sulphinate has also been applied as the starting material for the preparation of (*S*)-2-*p*-toluenesulphinyl-1,4-dimethoxybenzene **796** or the naphthalene derivatives **797b–c** in 68–81% yield (equation 439 and Scheme 22)[815–818].

The sulphinylation reaction of 1,4-dimethoxybenzene **798a** or the naphthalene derivatives **798b, d, e** is carried out by direct metallation with *n*-butyllithium, without previous bromination, to give the corresponding (*S*)-**796** or (*S*)-**797b,d,e.** The isomer **797c** is not available by direct lithiation. The starting material for **797c** is 2-bromo-1,4,5-trimethoxynaphthalene **798c** which is lithiated with *n*-butyllithium at −78 °C.

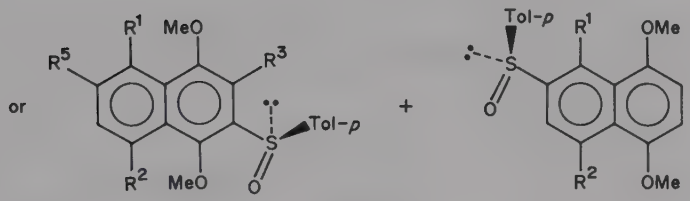
Two optically active α,β-unsaturated sulphoxides **640g,h** were prepared according to the already presented one-pot procedure (Scheme 12) based on the reaction of phosphonium diylide **641** with this sulphinate[736].



798a (−)-S-(796) (439)



(798) (−)-(S)-(797b,c)



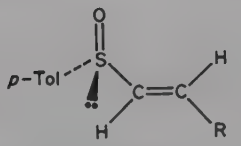
(−)-(S)-(797d) (−)-(S)-(797e)

798	R^1	R^2	R^3	R^4
b	H	H	H	H
c	H	OMe	Br	H
d	H	OMe	H	H
e	OMe	OMe	H	H

or

797	R^1	R^2	R^3	R^4	R^5
b	H	H		H	H
c	H	OMe		H	H
d	H	OMe	H		H
e	OMe	OMe	H	H	

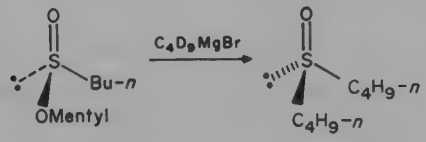
SCHEME 22



(+)-(R)-(640)

(g) R = H $[\alpha]_{589} = +258.8$ (e.e. 64.4%)
(h) R = Ph $[\alpha]_{589} = +144.25$ (97% E)

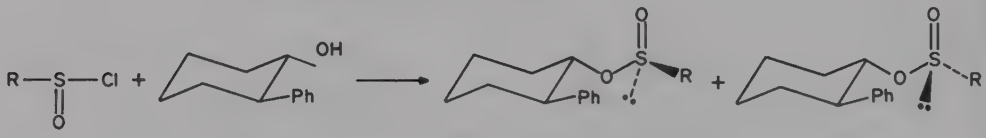
Diastereoisomeric *O*-methyl *n*-butanesulphinate **799** prepared by the reaction of *n*-butanesulphinyl chloride with (−)-menthol [343] afforded, upon treatment with *n*-butylmagnesium bromide-d_9, optically active *n*-butyl *n*-butyl-d_9 sulphoxide **800** with an e.e. of 47% (equation 440)[806a].



(440)

(−)-(**799**) (*R*)-(**800**)

Arene (alkane) sulphinates **801**–**803** derived from the readily available *trans*-2-phenylcyclohexano **804** have recently been prepared[819] in good yields and with a considerably better [(4–10):1] kinetic selectivity than that observed with menthol [(2–3):1][343] (Scheme 23). Moreover, the diastereoisomers can be readily separated by chromatography and, in all four examples reported, the major diastereoisomer is crystalline. These sulphinates afforded, for example, upon treatment with Grignard reagents the corresponding optically active sulphoxides **806** and **807** with an e.e. of above 90% (equations 441 and 442).

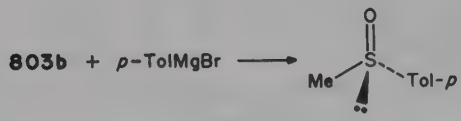


(**805**) (**804**) (**a**) (**b**)

(**a**) R = *p*-Tol
(**b**) R = 2-Naphthyl
(**c**) R = Me
(**d**) R = *i*-Pr

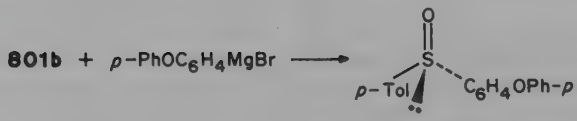
801, R = *p*-Tol
802, R = 2-Naphthyl
803, R = Me
804, R = *i*-Pr

SCHEME 23



(441)

(−)-*S*-(**806**)

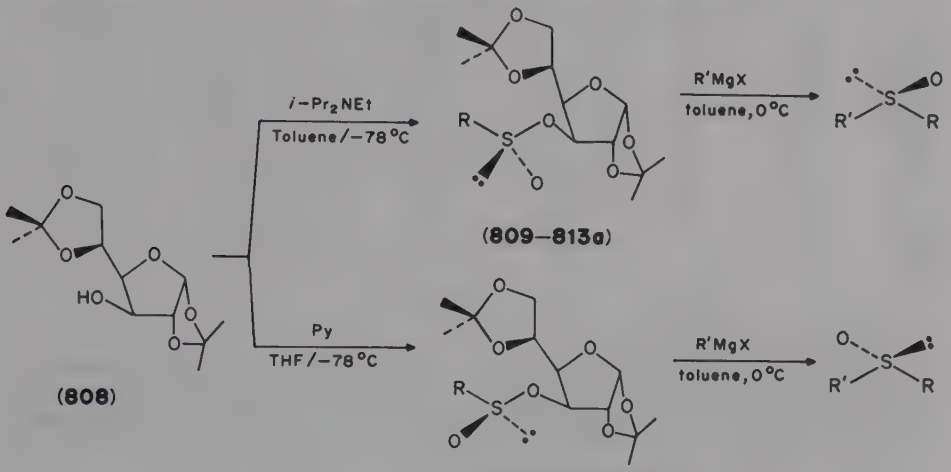


(442)

(−)-*S*-(**807**)

Diacetone-*S*-glucose (DAG) **808**, a commercially available sugar-derived secondary alcohol, was found to react with alkane- and arenesulphinyl chlorides in the presence of

i-Pr_2NEt to form (−)-(*S*)-alkane- and arenesulphinates **809–813a** in 50–90% yield with 89–⩾95% die. The diastereoisomers **809–813b** having opposite configuration at the sulphinyl sulphur atom were produced with 70–95% by the use of pyridine as a base. Diastereoisomerically pure DAG sulphinates were obtained either by recrystallization or by column chromatography. They were used as substrates for the synthesis of both enantiomers of a given sulphoxide (Scheme 24 and Tables 54 and 55)[820].



809, R = *p*-Tol
810, R = Me
811, R = Et
812, R = *n*-Pr
813, R = *i*-Pr

SCHEME 24

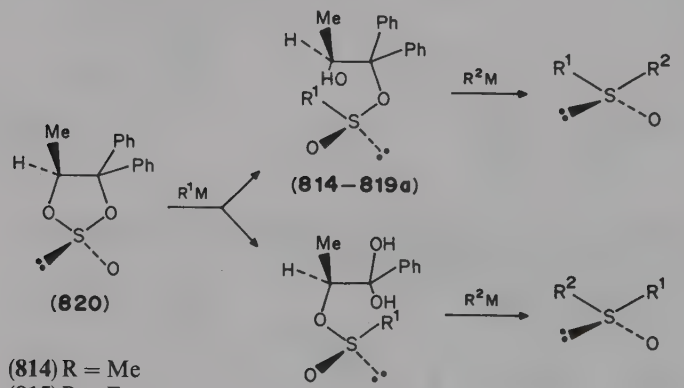
TABLE 54. Synthesis of optically active methyl sulphoxides, MeS(O)R, from DAG methanesulphinates **810** and $RMgX$[820]

Methanesulphinates			Sulphoxide		
Compd.	(Config. at S)	R	Yield (%)	$[\alpha]_D$	Config. (e.e. %)
810b	*R*	*p*-Tol	84	+145(*ca* 8.3, Me_2CO)	*R*(100)
810b	*R*	Ph	78	+149(*ca* 2.0, EtOH)	*R*(100)
810b	*R*	$PhCH_2$	83	−105(*ca* 6.0, EtOH)	*R*(100)
810b	*R*	*n*-Pr	66	−137(*ca* 6.0, EtOH)	*R*(100)
810b	*R*	*t*-Bu	62	+4.3(*ca* 1.64, Me_2CO)	*S*(100)
810a	*S*	*p*-Tol	90	−145(*ca* 1.0, Me_2CO)	*S*(100)
810a	*S*	Ph	80	−143(*ca* 1.0, Me_2CO)	*S*(100)
810a	*S*	$PhCH_2$	83	+104(*ca* 0.15, EtOH)	*S*(100)
810a	*S*	*n*-Pr	69	+136(*ca* 0.31, EtOH)	*S*(100)
810a	*S*	*t*-Bu	50	−4.3(*ca* 3.83, Me_2CO)	*R*(100)
810a	*S*	Vinyl	37	+229(*ca* 0.41, $CHCl_3$)	*S*(100)

TABLE 55. Synthesis of optically active sulphoxides, RS(O)R′, from DAG alkene- or arenesulphinates **809–813** RS(O)ODAG and R′MgX[820]

Sulphinate				Sulphoxide		
Compd.	R	(Config. at S)	R in R′MgX	Yield (%)	$[\alpha]_D$	Config. (e.e.%)
810b	Me	*R*	*p*-Tol	84	+ 145 (*ca* 8.3, Me_2CO)	*R*(100)
810a	Me	*S*	*p*-Tol	90	− 145 (*ca* 1.0, Me_2CO)	*R*(100)
811b	Et	*R*	*p*-Tol	96	+ 196 (*ca* 4.0, Me_2CO)	*R*(99)
811a	Et	*S*	*p*-Tol	90	− 195 (*ca* 2.9, Me_2CO)	*S*(99)
812b	*n*-Pr	*R*	*p*-Tol	88	+ 203 (*ca* 1.2, EtOH)	*R*(100)
812a	*n*-Pr	*S*	*p*-Tol	89	− 200 (*ca* 0.4, EtOH)	*S*(100)
813b	*i*-Pr	*R*	*p*-Tol	98	+ 188 (*ca* 4.0, EtOH)	*R*(100)
813a	*i*-Pr	*S*	*p*-Tol	89	− 187 (*ca* 2.4, EtOH)	*S*(100)
809b	*p*-Tol	*R*	Et	87	− 137 (*ca* 5.0, Me_2CO)	*S*(70)
809a	*p*-Tol	*S*	Et	80	+ 196 (*ca* 0.3, Me_2CO)	*R*(100)

Another general route to enantiomerically pure sulphoxides is based on stereospecific conversion of the diastereoisomerically pure β-hydroxysulphinates **814–819** with organometallic reagents. The starting sulphinates were found to be conveniently prepared by the reaction of cyclic sulphites **820** derived from optically active diols with organolithium or organomagnesium compounds (Scheme 25)[821].



(814) R = Me
(815) R = Et
(816) R = *n*-C_8H_{17}
(817) R = *t*-Bu
(817) R = CH_2Ph
(818) R = $CH{=}CH_2$
(819) R = 2,4,6-C_6H_2

SCHEME 25

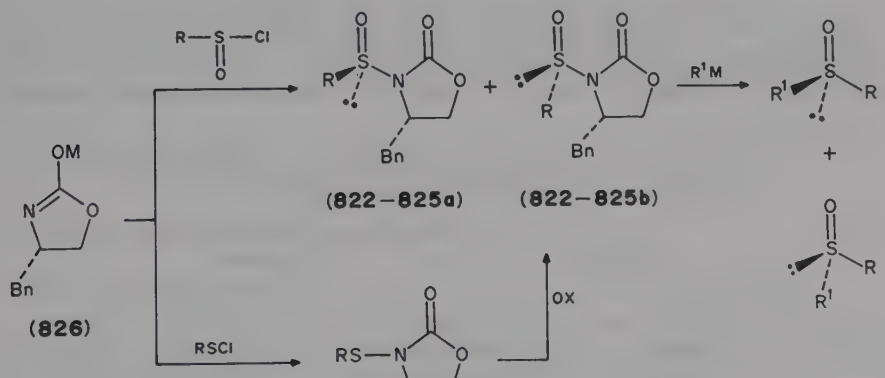
By using 2 molar equivalents of various organometallics in THF at room temperature or at 0 °C, a variety of chiral sulphoxides listed in Table 56 were produced and isolated in quantitative yields by flash chromatography. In all cases the sulphoxides obtained were enantiomerically pure.

TABLE 56. Synthesis of enantiomerically pure sulphoxides, $R^1S(O)R^2$, from sulphinates **814–819** and organometallics, R^2M[821]

Sulphinate			$R^1S(O)R^2$		
No	R^1	R^2M	T(°C)	e.e.	Config.
814a	Me	n-$C_8H_{17}MgBr$	0	100	*R*
815a	Et	PhLi	0	100	*R*
816a	n-C_8H_{17}	MeMgI	25	100	*S*
817b	*t*-Bu	MeLi	25	100	*R*
817b	*t*-Bu	PhLi	25	100	*S*
817b	*t*-Bu	*n*-BuLi	25	100	*R*
817b	*t*-Bu	$PhCH_2MgBr$	25	100	*R*
817b	*t*-Bu	$PhCH_2CH_2MgBr$	25	100	*R*
819b	2,4,6-$Me_3C_6H_2$	MeLi	0	100	*R*
819b	2,4,6-$Me_3C_6H_2$	PhMgBr	0	100	*R*

It should be noted that the absolute configurations discussed by Kagan and coworkers for *t*-butyl alkyl sulphoxides collected in Table 56 are based on the assumption that they are formed from the proper sulphinates with inversion of configuration at the sulphinyl sulphur atom. However, it was recently found that the reactions of alkyl *t*-butanesulphinates with alkylmagnesium halides may proceed with a predominant retention of configuration at the sulphinyl sulphur atom[822]. Therefore, the assigment of Kagan and coworkers[821] should be taken with care.

A few diastereoisomerically pure *N*-sulphinyloxazolidinones **822–824**, readily prepared by sulphinylation of the metallated oxazolidinones **826** with the appropriate sulphinyl chloride or by oxidation of the derived *N*-sulphenamides **827–830**, were found to react with organometallics with inversion of configuration at the sulphinyl sulphur atom to afford chiral sulphoxides listed in Table 57 (Scheme 26)[823].



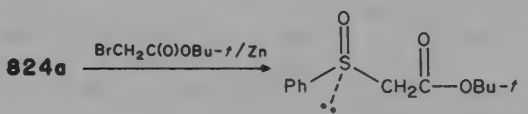
(**822, 827**) R = Me
(**823, 828**) R = *t*-Bu
(**824, 829**) R = Ph
(**825, 8330**) R = *p*-Tol

SCHEME 26

TABLE 57. Synthesis of optically active sulphoxides, $R^1S(O)R^2$, from *N*-sulphinyloxazolidinones **822–825** and organometallic reagents R^2M[823]

N-Sulphinyloxazolidinone			Sulphoxide $R^1S(O)R^2$			
No	R^1	RM	Yield (%)	$[\alpha]_D$	e.e. (%)	Abs. config.
822a	Me	PhMgBr	87	+120	90	*R*
822a	Me	*t*-BuMgCl	78	−7.3	93	*R*
822a	Me	$PhCH_2MgCl$	82	+50	91	*R*
822a	Me	n-$C_8H_{17}MgCl$	92	−79.7	100	*R*
823a	*t*-Bu	MeMgI	92	+7.8	100	*S*
823a	*t*-Bu	*n*-BuMgBr	91	−129	100	*S*
825a	4-Tol	MeMgI	90	−132	99	*S*
825a	4-Tol	EtMgBr	90	−204	98	*S*
825a	4-Tol	*i*-PrMgBr	91	−81	97	*S*
825a	4-Tol	*t*-BuMgCl	88	−185	97	*S*
825a	4-Tol	$PhCH_2MgCl$	86	−213	99	*S*

It is interesting to note that the Reformatsky reagent, prepared from *t*-butyl bromoacetate and activated zinc, afforded in the reaction with **824a** (*S*)-*tert*-butyl (α-phenylsulphinyl)acetate **831** in 81% yield and with e.e. of > 98% (equation 443)[823].



(443)

(*S*)-(**831**)

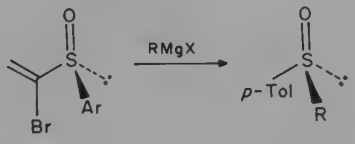
Optically pure sulphoxides can also be prepared in good-to-excellent yields by the modification[824] of the procedure reported in the mid-70's[373] which involves sequential displacement reactions of organometallic reagents on the 1,2,3 -oxathiazolidine S-oxides **309a** and **309b** derived from ephedrine[37] (Scheme 5). The oxides **309a** upon treatment with

TABLE 58. Synthesis of optically active sulphoxides, $R^1S(O)R^2$, from sulphinamides **310** and organometallics R^2M in the presence of $AlMe_3$[824]

ulphinamide			Sulphoxide		
No	R^1	R^2M	Yield (%)	$[\alpha]_D$	e.e. (%)
a	Me	PhMgBr	71	−139	> 99
a	Me	C_6F_5MgBr	30	−50	60
a	Me	*n*-BuMgCl	76	+113	> 99
a	Me	*t*-BuMgCl	63	+22	> 99
b	CD_3	C_6D_5MgBr	50	−114	> 99
c	$CH_2=CH$	PhMgBr	75	−376	> 99
d	$CH_2=CHCH_2$	PhMgBr	62	−225	> 99
e	*i*-Pr	PhMgBr	82	+207	> 99
f	Et	PhMgBr	44	−199	> 99

freshly prepared Grignard reagents in toluene afforded the sulphenamides **310** in excellent yields. Addition of $AlMe_3$ to **310**, followed by addition of the appropriate Grignard reagent at $-70\,°C$, gave the corresponding sulphoxides exhibiting a very high e.e. value (Table 58).

When optically active bromovinyl aryl sulphoxides **832** were subjected to reactions with organomagnesium reagents in THF at $-30\,°C$, the corresponding optically active aryl alkyl and unsymmetrical diaryl sulphoxides were formed in an enantioselective way (equation 444)[825].



(444)

(832)

Ar	R	Yield	$[\alpha]_D$	e.e. (%)
p-Tol[a]	Ph	77	−21.4	100
p-Tol[a]	*n*-Bu	81	−185	99
p-Tol[a]	*n*-Pr	78	−193	100
p-Tol[a]	*i*-Pr	86	−178	100
p-Tol[a]	Et	73	−184	98
2-Naph[b]	Me		+110	78
	n-Pr		+130	80

[a] e.e. = 100%.
[b] e.e. = 80%.

*IV. FUNCTIONALIZATION OF SULPHOXIDES

In recent years a great number of papers have been devoted to transformations of organic substituents adjacent to the sulphoxide moiety. In most cases such functionalizations were aimed at the synthesis of natural, biologically active compounds. Several reviews appeared which cover particular areas of application of sulphoxides in asymmetric synthesis[826–833].

In this chapter some new developments in the synthesis of special classes of sulphoxides via functionalization of other, more simple sulphoxides will be described.

*A. Reactions of the Sulphoxide α-Carbanions

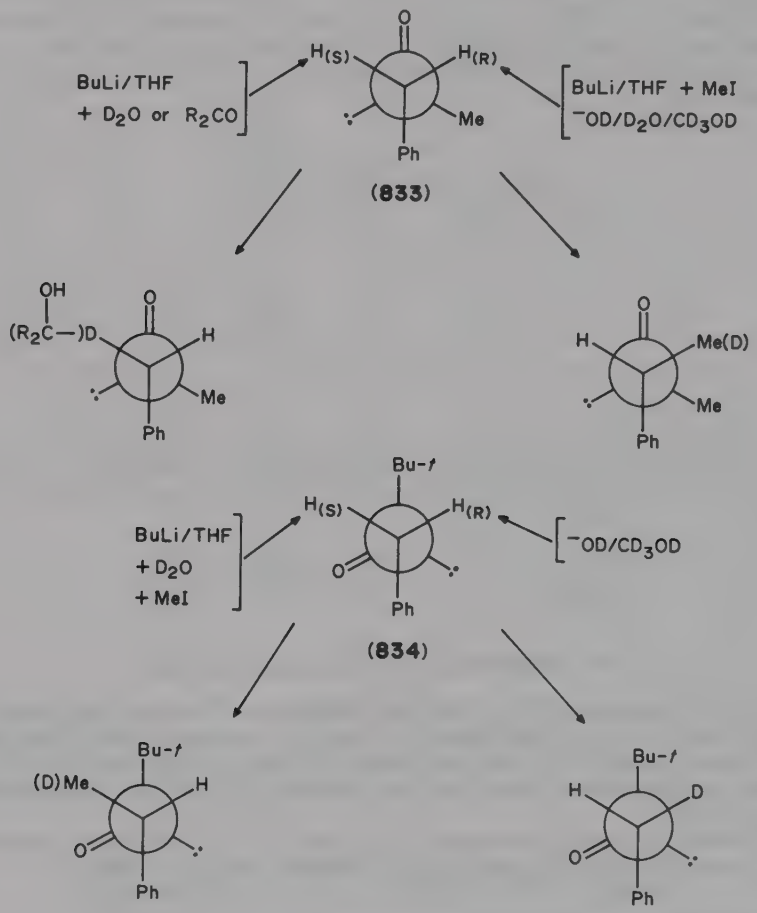
*1. Generation of carbanions

New studies concerning the structure and stereochemistry of α-sulphinyl carbanions have recently been reported. They need to be mentioned here particularly because aged and incorrect data are still often cited in recent papers and reviews.

Thus, until recently it was commonly accepted that the H/D exchange and alkylation of benzyl methyl sulphoxide **833** and benzyl *t*-butyl sulphoxide **834** proceed in a THF solution with a different stereochemistry[834].

However, X-ray analysis[835] of deuterated **834** and precise investigations of Ohno's group[836] showed that this is true only for **833**, while in the case of **834** both reactions proceed with the same stereochemistry. Moreover, the reaction medium has also a pronounced effect. For instance, the stereochemistry of the H/D exchange reaction performed

in polar protic solvents is opposite to that performed in THF. Some attempts at an explanation of the observed stereoselectivity in generation and reactivity of α-sulphinyl carbanions have been undertaken[836,837] and are briefly illustrated in Scheme 27.



SCHEME 27

The molecular structure of the α-sulphinyl carbanion has also been found to be completely different from the so far accepted four-centre chelate **315**. Two independent X-ray analyses have been performed, one by Boche and coworkers[838,839], using the dimeric TMEDA-complex of α-lithio-α-methyl benzyl sulphoxide **835** (Figure 1), and the other by Floriani and collaborators[840], using a 'naked' carbanion of methyl phenyl sulphoxide **836** (Figure 2), obtained by treatment of potassiomethyl phenyl sulphoxide with 18-crown-6. In both cases metal cations have been found to be linked exclusively to the sulphinyl oxygen atom, the distance between the 'anionic' carbon atom and the metal being very large (e.g. C1—Li in **835** is equal to 400 pm, while the normal C—Li bonds are shorter than 250 pm). The distances between the 'anionic' carbon atoms and sulphur are shorter, and between oxygen and sulphur longer than the corresponding bonds in DMSO

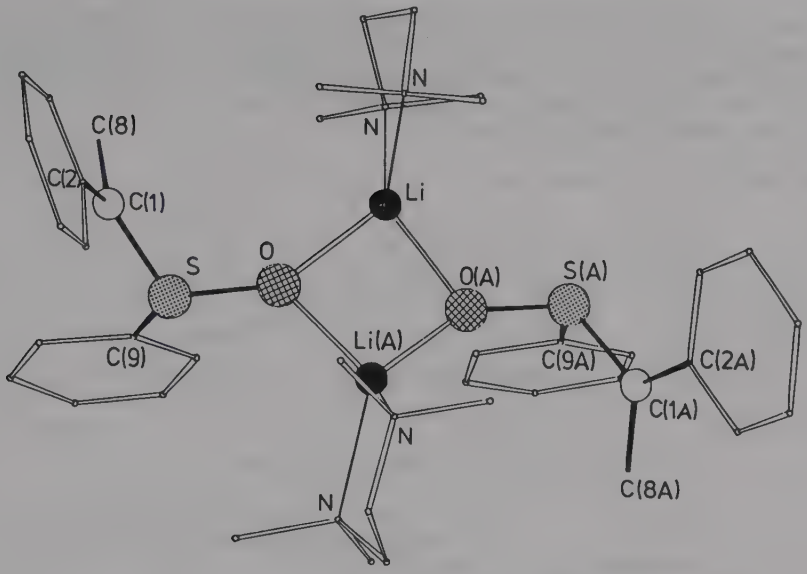


FIGURE 1. Crystal structure of dimeric **835** TMEDA. Reproduced by permission of VCH Verlags-gesellschaft mbH, Weinheim from Reference 838

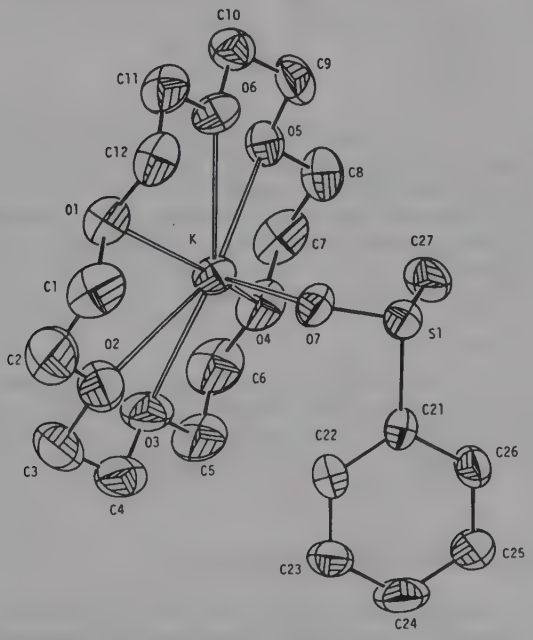
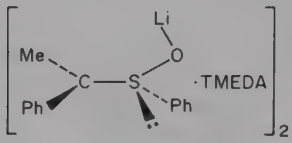
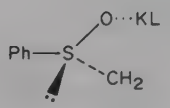


FIGURE 2. ORTEP view of complex **836**[840]. Reprinted with permission from Floriani *et al.*, *Organometallics*, **12**, 253. Copyright (1993) American Chemical Society

(see Table 59). Moreover, the Li atom in **835** does not lie in the C(1),S,O plane since the torsional angle C(1),S,O,Li is 12°. The 'anionic' carbon atom C(1) is non-planar and projects out of the S—C(2)—C(8) plane. The substituents at C(1) are bent towards the oxygen atom. Finally, the lone electron pair at C(1) is bent 16° away from the anti-periplaner position to the S—O bond[838,839].



(835)



(836)

TMEDA = tetramethylethylenediamine L = 18-Crown-6

TABLE 59. Bond lengths in **835**, **836** and DMSO[a]

Compound	Bond lengths (pm)		
	M—O	S—O	S—C
DMSO	—	147	180[b]
835	—	158	163
836	266	152	166

[a] Taken from References 838–840.
[b] S(O)—CH_3.

Thus, the two cases investigated are certainly not α-metallated sulphoxides. $^{7}Li^{+}$ and ^{17}O NMR spectral studies also indicate that the carbanions derived from benzyl sulphoxides behave in solutions as the oxylate form[837].

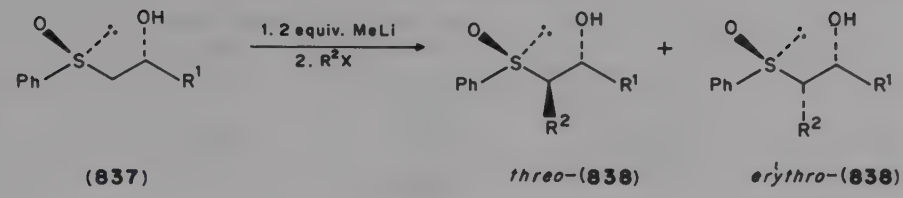
It should be stressed, however, that it is possible to obtain a C–metal bonded form of the α-sulphinyl anion, when chromium or palladium derivatives are used as complexing agents (equation 445)[840].

$$ArS(CH_2)O \cdots KL + Cr(CO)_5THF \longrightarrow [ArS(O)CH_2Cr(CO)_5 \cdots KL] \quad (445)$$
(L = crown ether)

In the light of the facts presented above, all previous explanations concerning the stereochemical outcome of the reactions of α-sulphinyl carbanions and involving structures which assume a direct carbon–metal bond should be verified. A critical review and further experimental investigations supported by theoretical calculations would be very desirable.

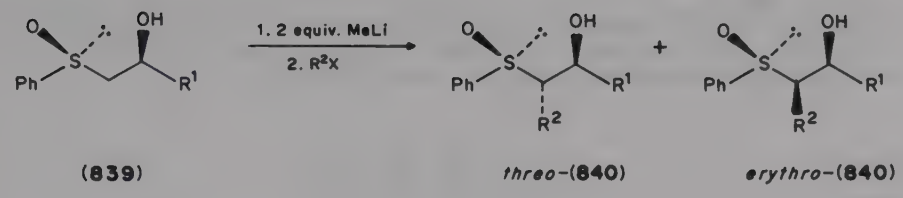
*2. *Reaction of α-sulphinyl carbanions with electrophiles*

b. *Alkylation of α-sulphinyl carbanions.* α-Alkylation of the dianions of β-hydroxy sulphoxides has been found to proceed with a high extent of 1,2-asymmetric induction to give *threo*-α-alkyl-β-hydroxy sulphoxides as main products. Stereoselectivity of the alkylation has been assumed to be controlled mainly by the stereochemistry of the hydroxy group and not by that of the sulphinyl group (equations 446a and b; Table 60)[841].



(837) *threo*-(838) *erythro*-(838)

(446a)



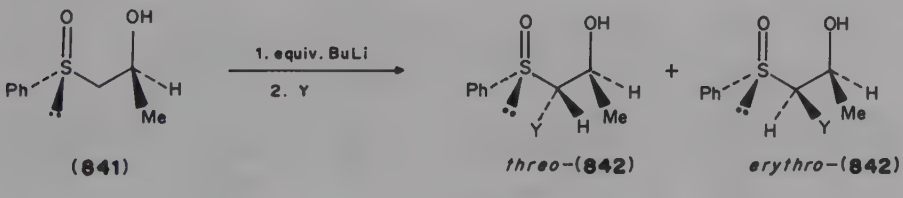
(839) *threo*-(840) *erythro*-(840)

(446b)

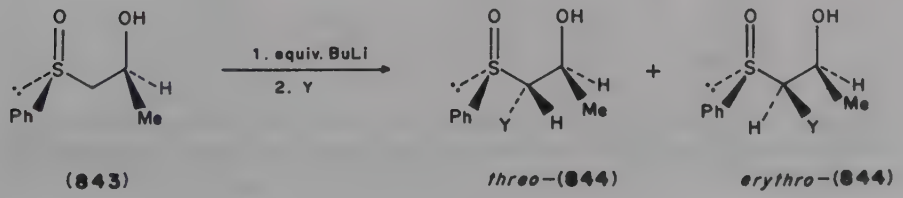
TABLE 60. Alkylation of β-hydroxy sulphoxide dianions[841]

β-Hydroxy sulphoxide	R^2X	Yield (%)	Ratio *threo*:*erythro*
837, R^1 = Me	MeI	**838** (87)	16:1
837, $R^1 = i\text{-}C_7H_{15}$	$n\text{-}C_{10}H_{21}I$	**838** (58)	4:1
839, R^1 = Me	MeI	**840** (76)	11:1
839, R^1 = Me	$(MeO)_3P{=}O$	**840** (50)	10:1
839, $R^1 = i\text{-}C_7H_{15}$	$n\text{-}C_{10}H_{21}I$	**840** (75)	20:1

Tanikaga and coworkers[842] found that the reaction of β-hydroxy sulphoxide dianions with electrophiles is more complicated. They observed that the dianions undergo configurational interconversion which causes the final products ratio to depend on the electrophile. Since the ratio of *threo*/*erythro* carbanions varies with reaction time, the small and reactive D_2O as electrophile reflects the initial *threo*/*erythro* ratio, while the bulky and moderately reactive *n*-iodooctane reflects the thermodynamic ratio (Scheme 28)[842].



(841) *threo*-(842) *erythro*-(842)

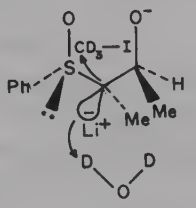


(843) *threo*-(844) *erythro*-(844)

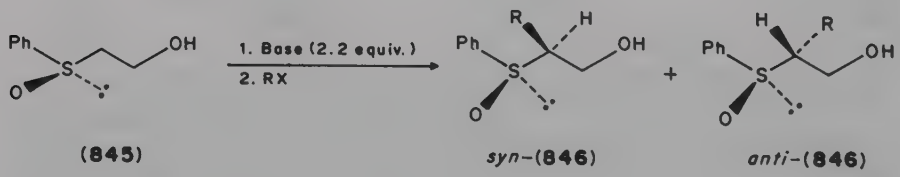
	threo:*erythro* **842**	*threo*:*erythro* **844**
(a) Y = n-C_8H_{17}	66:34	96:4
(b) Y = CH_3	78:22	
(c) Y = D	25:75	50:50

SCHEME 28

The same group[843] also found that the carbanion generated from α-methyl-β-hydroxy sulphoxide *threo*-**842b** is approached by a water molecule with retention of configuration while by CD_3I, with predominant inversion, and that in the latter case configurational interconversion of the carbanion occurs to a certain extent[843].



Finally, Ohta and coworkers have established the net effect of the sulphoxide group on the alkylation of β-hydroxy sulphoxides by using R-2-phenylsulphinylethanol **845** as a substrate (equation 447; Table 61)[844].



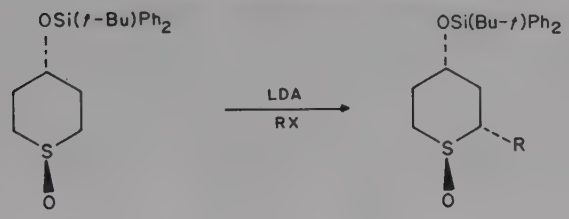
(**845**) *syn*-(**846**) *anti*-(**846**)

(447)

TABLE 61. Alkylation of R-2-phenylsulphinylethanol dianion[844]

Base	RX	Yield (%)	*syn*:*anti*
LDA	MeI	85	7:1
LDA	$MeOSO_2CF_3$	95	6.9:1
BuLi	MeI	59	6.9:1
LDA	$CH_2{=}CHCH_2Br$	78	6.9:1
LDA	$PhCH_2Br$	85	6.6:1
LDA	$C_8H_{17}I$	64	1:1

Alkylation of a strongly hindered *trans*-4-silyloxy thiane-1-oxide **778** occurs with high preference for the equatorial products which are formed as single diastereoisomers (equation 448)[845].

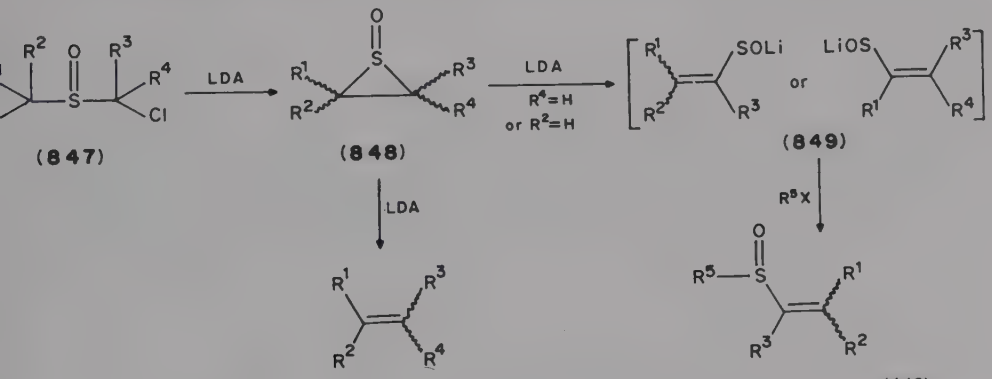


(778) (777) (448)

RX	Yield (%)
MeI	70
$PhCH_2Br$	80
Me_3SiCl	90

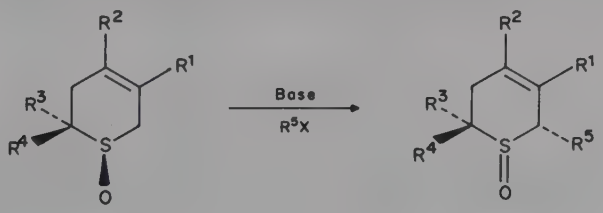
For the use of a homochiral base in this reaction, see equation 437 in Section III.B.

When α-chloro sulphoxides **847** are treated with two equivalents of LDA, a cyclization occurs with the intermediary formation of thiirane-1-oxides **848**. The attack of the second equivalent of a base causes ring opening to form lithium ethenesulphenates **849**. The latter react with added alkyl halides to give vinyl sulphoxides **850** in moderate yields. The alternative pathway leading to alkenes becomes pronounced in few cases only (equation 449; Table 62)[846].



(847) (848) (849) (850) (449)

The anions derived from 3,6-dihydro-*2H*-thiapyran *S*-oxides **851** react with alkylating agents at − 78 °C to give exclusively the products of α-alkylation[740, 847]. In most cases the



(851) (852) (450)

TABLE 62. Synthesis of vinyl sulphoxides **850** from α-chlorosulphoxides **847**

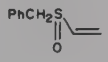
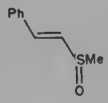
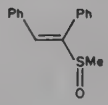
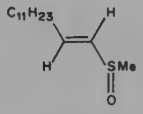
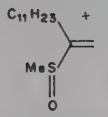
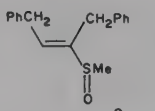
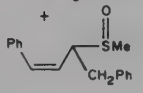
Substrate				R^5—X	Product		
R^1	R^2	R^3	R^4		Structure	Yield (%)	Remarks
H	H	H	H	$PhCH_2Br$		35	
Ph	H	H	H	MeI		60	+ 8% styrene
Ph	H	Ph	H	MeI		43	+ 21% *t*-stilbene
$n\text{-}C_{11}H_{23}$	H	H	H	MeI		32	
					as above	49	
H	H	$n\text{-}C_{11}H_{23}$	H	MeI		31	
$PhCH_2$	H	$n\text{-}C_{11}H_{23}$	H	MeI		56	
						10	
Me	Me	Me	Me	—		—	90% $Me_2C{=}CMe_2$

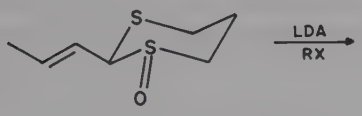
TABLE 63. Alkylation of 3,6-dihydro-2*H*-thiapyran *S*-oxides

R^1	R^2	R^3	R^4	R^5—X	Base	Yield (%)	Ref.
H	H	H	H	MeI	LDA	69	847
H	Ph	H	H	MeI	LDA	93	847
H	Ph	H	H	$PhCH_2Br$	LDA	59	847
H	Ph	H	H	$p\text{-}O_2NC_6H_4CH_2Br$	LDA	35	847
H	Ph	H	H	EtI	LDA	78	847
H	Ph	H	H	*i*-PrI	LDA	*trans* + *cis* yield not given	847
Me	Me	MeCH(OMe)	Ph	MeI	BuLi	65	740
Me	Me	MeCH(OMe)	Ph	EtI	BuLi	77	740

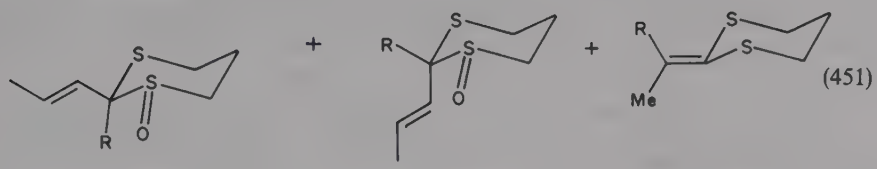
reaction is stereospecific and leads to *trans* isomers (an exception is the reaction with *i*-PrI, which gives a mixture of *cis*- and *trans*-**852** (equation 450; Table 63)[740, 847].

It should be added that 2, 5-dihydrothiophen *S*-oxides give, under similar conditions, polymeric or open-chain products[848].

Alkylation reactions of the anion of 2-propenyl-1, 3-dithiane oxide **853** show a preference for the attack at the face *syn* to the sulphinyl oxygen. Almost complete α-regioselectivity is observed, the only exception being the reaction with allyl halides (equation 451)[849].



trans-(**853**)

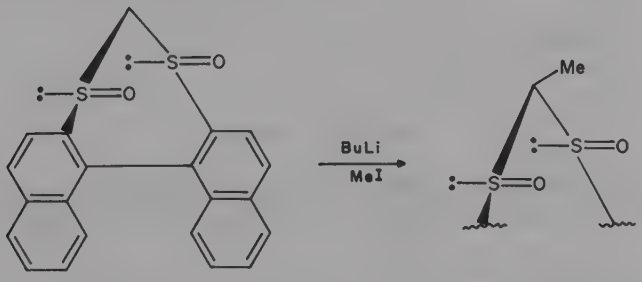


(451)

(**854**)	(**855**)	(**856**)
50%	40%	—
57%	33%	5%
84%	—	—

R = Me
R = CH_2=$CHCH_2$
R = $PhCH_2$

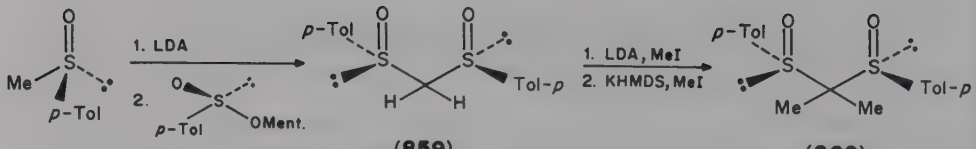
In a search for new sulphinyl derivatives, which would lead to products with higher stereoselectivity, a cyclic dithioacetal monoxide **857** has been constructed on the basis of the binaphthyl moiety. In fact, alkylation of the anion of **857** proceeds stereospecifically to give one diastereoisomer of **858** (equation 452)[850].



(452)

(**857**) (**858**)

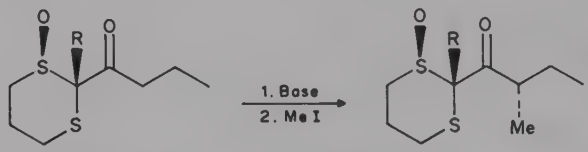
Optically active sulphoxides **859** and **860** with a C_2 symmetry have been synthesized (equation 453) and used as chiral catalysts in Diels–Alder reactions to give, in some cases, enantioselection up to 56%[851].



(859) **(860)**

KHMDS=KN(SiMe$_3$)$_2$ (453)

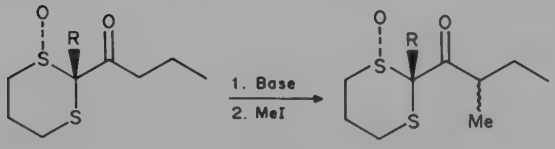
Stereochemical control of enolate alkylation in *cis* and *trans* acyl dithiane monoxides has been investigated. In some cases very high diastereoselectivity has been observed (equations 454 and 455)[852].



(454)

trans-(**861**) (**862**) major diastereoisomer, from x-ray

Base	R	Temp.	Ratio of isomers
LHMDS	Et	−100 °C	exclusive
LHMDS	*i*-Pr	−100 °C	25:1



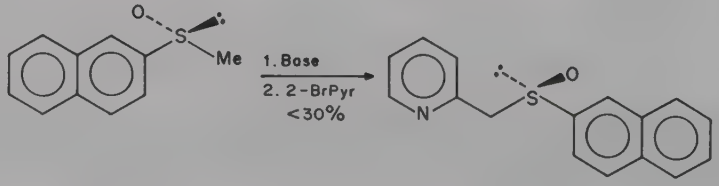
(455)

cis-(**861**) (**863**)

Base	R	Temp.	Ratio of isomers
LHMDS	Me	−78 °C	25:1
LHMDS	Et	−100 °C	20:1

LHMDS = LiN(SiMe$_3$)$_2$

2-Naphthyl 2-pyridylmethyl sulphoxide **865** has been obtained in low yield from a direct reaction of the sulphoxide **864** anion with 2-bromopyridine (equation 456)[765b].



(456)

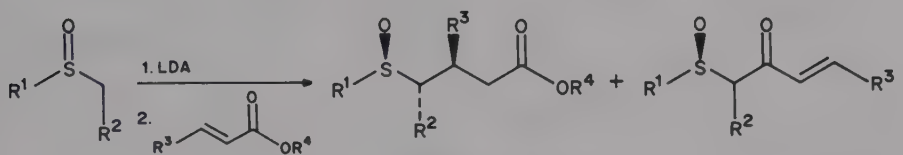
(**864**) (**865**)

DMSO cuprates **866** are readily prepared *in situ* by sequential treatment of DMSO with butyllithium followed by CuI and one equivalent of alkyllithium. Compounds **866** (equation 457) are used as common organocopper–lithium reagents where DMSO constitutes a non-transferable ligand[853].

$$CH_3SCH_3 \xrightarrow[2\ CuI]{1\ BuLi} CH_3SCH_2\ Cu \xrightarrow{R\text{—}Li} Li\ (CH_3SCH_2\ CuR) \quad (457)$$

(866)

**c. Michael addition of α-sulphinyl carbanions.* The reaction of lithiated alkyl *t*-butyl and benzyl sulphoxides with α,β-unsaturated exters gives conjugate addition products usually with a high stereoselectivity[854,855]. In the case of benzyl sulphoxides[855] (unlike in the case of alkyl sulphoxides[854]) the unreacting group connected with sulphur has relatively little influence on the stereoselectivity. *p*-Tolyl and *t*-butyl benzyl sulphoxides both give high selectivity and the methyl derivative gives only slightly worse results (equation 458; for selected examples see Table 64).

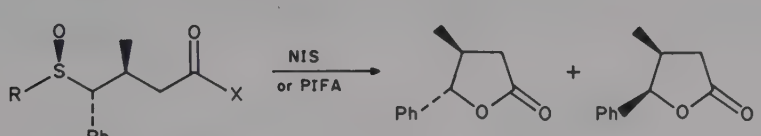


(867)

major diastereoisomer minor by-product

(458)

Treatment of products **867** with soft electrophiles results in intramolecular displacement of the sulphinyl groups by the carbonyl oxygen atom to give *trans*-β,γ-disubstituted butyrolactones with high stereoselectivity (e.g. equation 459[856]).



(459)

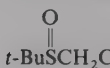
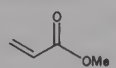
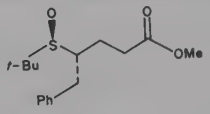
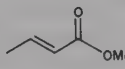
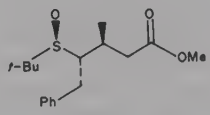
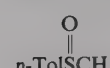
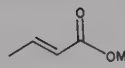
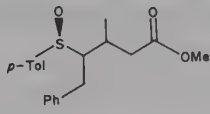
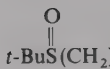
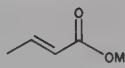
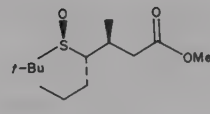
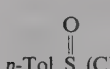
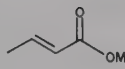
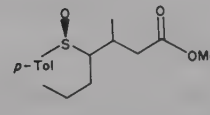
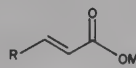
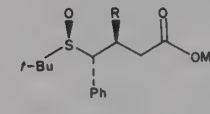
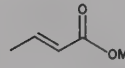
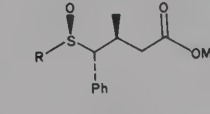
(867) **(868a)** **(868b)**

R	X	Reagent	Ratio **868a** : **868b**	Yield **868a** (%)
t-Bu	OH	NIS	97:3	69
t-Bu	OH	PIFA	100:0	71
p-Tol	OMe	NIS	98:2	98

NIS = *N*-iodosuccinimide.
PIFA = phenyliodonium bis(trifluoroacetate).

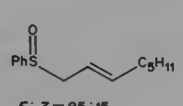
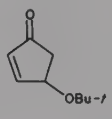
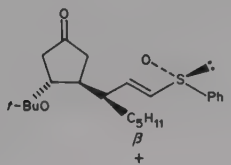
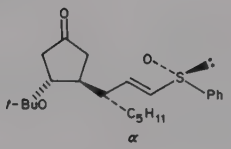
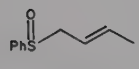
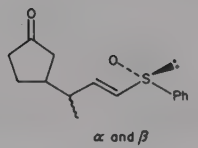
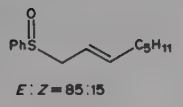
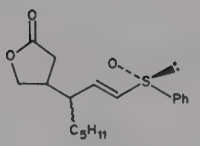
The Michael addition of allyl sulphoxide anions to α,β-unsaturated carbonyl compounds has recently been the subject of very intensive studies. It has been found that of four possible products (1,4α; 1,4γ; 1,2α and 1,2γ) only two are formed: 1,4γ and 1,2γ, the former

TABLE 64. Michael addition of α-lithio sulphoxides to α,β-unsaturated esters[854,855]

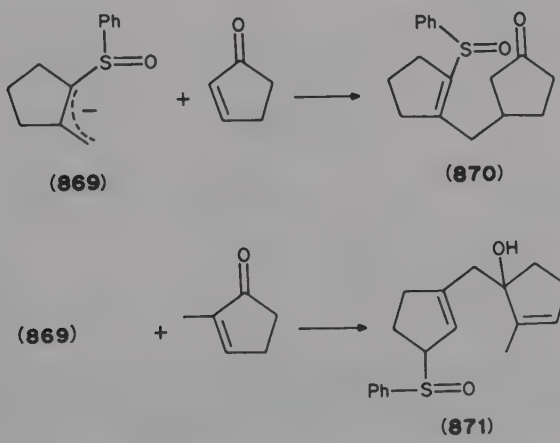
Sulphoxide	α,β-Unsaturated ester	Product **867**	Yield(%) of pure diasteresisomers
			64
			68
			89 (1.5:1 mixture of diastereoisomers)
			64
			68 (1.5:1 mixture of diastereoisomers)
			R = H 78 R = Me 80 R = Ph 86
 R = *t*-Bu R = *p*-Tol R = Me			R = *t*-Bu 80 R = *p*-Tol 62 R = Me 79 (a 84:7:5:4 mixture of stereoisomers)

being in most cases prevailing. When five-membered ring enones are used, only 1,4γ adducts are found, while six- and seven-membered ring systems provide both 1,4γ and 1,2γ products[857,858] (Table 66). The reaction proceeds in a highly stereoselective manner to give (*E*)-vinyl sulphoxides as single diastereoisomers [the β-diastereoisomers from (*E*)-allylic sulphoxides and the α ones from (Z) sulphoxides (for selected examples see Table 65)[857]. Allylic sulphoxides substituted at C-1 and C-2 give adducts with much poorer diastereoselectivity[859]. For mechanistic considerations concerning this reaction see References 860 and 861. It should be stressed that the 1,4-addition of *cis*-sulphinylallyl

TABLE 65. Conjugate addition of allyl sulphoxide anions to cyclic enones[857]

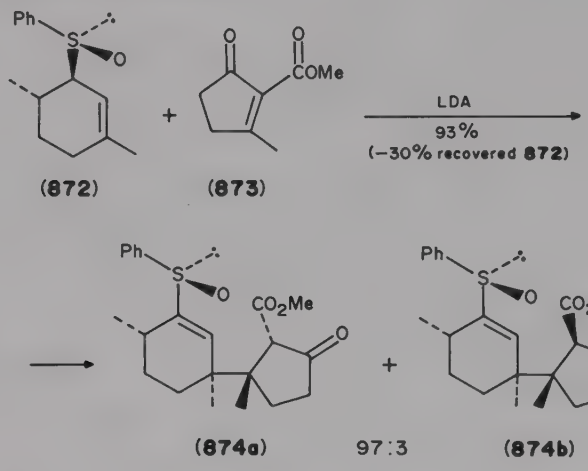
Sulfoxide	Enone	Products	Ratio β:α	Yield
 E:Z = 85:15			83:17	83
E:Z = 17:83			21:79	79
 E:Z = 80:20			80:20	64
 E:Z = 85:15			83:17	83

anion, e.g. **869**, can be performed only with unsubstituted cyclopentenone while with 2-methyl-2-cyclopentenone, almost exclusive formation of the 1,2γ products **871** is observed (equation 460)[862].



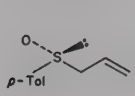
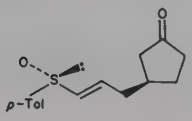
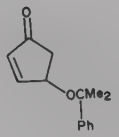
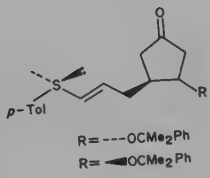
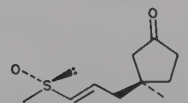
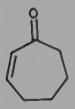
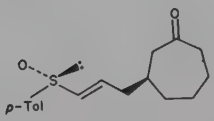
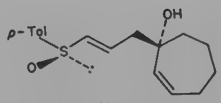
(460)

To circumvent this problem an activated enone **873** has been used for the reaction with optically active cyclohexenyl sulphoxide **872**. The adducts obtained have been used as substrates in the total synthesis of an antibiotic and antitumor agent, (+)−12,13-epoxytrichothec-9-ene (equation 461)[743].



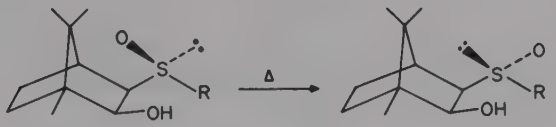
(461)

TABLE 66. Enantioselective conjugate addition of (+)-(*R*)-allyl *p*-tolyl sulphoxide to cyclic enones[858]

Sulphoxide	Enone	1,4-γ Adduct	Yield (%)	(e.e.) (%)	1,2-γ Adduct
			91	(96)	none
			68 7	(95) (90)	none
			80	(95)	none
			25	58 (50)	

When the anion of optically active *p*-tolyl vinyl sulphoxide was used, the 1,4-γ adducts were obtained with very good enantioselectivity. In the case of racemic enones kinetic resolution was observed. Only the (*S*)-enones underwent addition reaction indicating that the carbanion approaches 2-cyclopentenone from the *si* face (Table 66)[858].

In a search for more stable allyl sulphoxides (which would not undergo a [2,3] sigmatropic rearrangement nor thermal *syn*-elimination of allylsulphenic acid), a series of optically active isobornyl allyl sulphoxides has been synthesized[863,864]. It has turned out that both epimers of each sulphoxide can be obtained by simple thermal epimerization of the S_s isomer (equation 462).

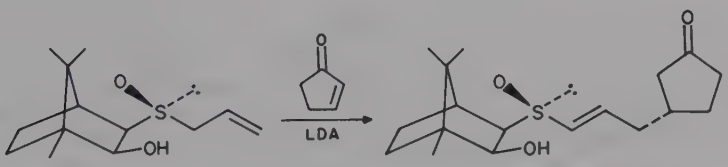


(462)

(S_s)-(**875**) (R_s)-(**875**)

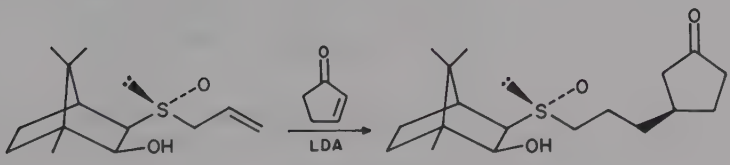
R = (**a**) allyl
(**b**) (*E*)-but-2-enyl
(**c**) dimethylallyl
(**d**) (*E*)-oct-2-enyl

Addition of their anions to cyclopentenone proceeds stereospecifically with yields of 50 to 60% (equations 463 and 464)[863].



(463)

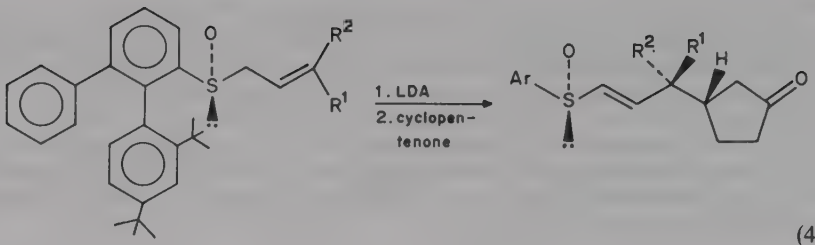
(S_S)-(**875a**) $[\alpha]_D + 31.8$ $[\alpha]_D - 69.2$



(464)

(S_R)-(**875a**) $[\alpha]_D + 92$ $[\alpha]_D + 162.8$

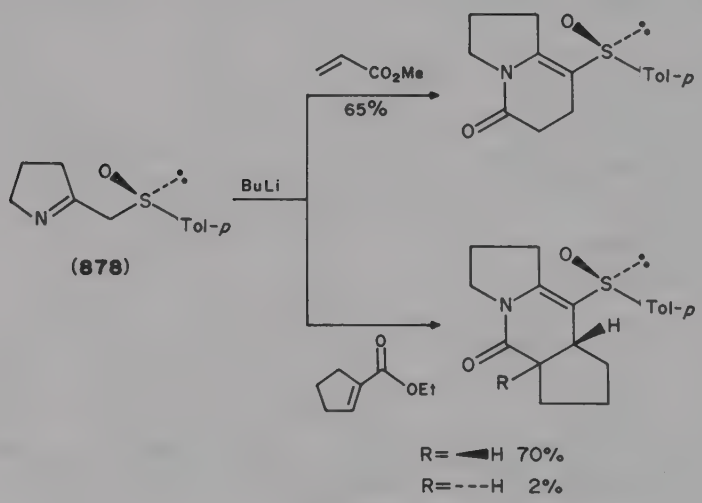
Swindell and coworkers prepared a strongly hindered allylic sulphoxide **876**, which was found to add to cyclopentenone with greater regio- and diastereoselectivity than those exhibited by simpler reagents (equation 465)[865].



(465)

R^1	R^2	Yield (%)	Diastereoisomeric ratio
H	H	80	92:8
Me	H	54	85:15
Ph	H	60	90:10
Me	Me	86	93:7

Cyclic α-sulphinyl ketimines **878**, when treated with BuLi and α, β-unsaturated esters, undergo smoothly 1,4-addition followed by cylization to give substituted derivatives of indolizidinone (Scheme 29)[866,867].



SCHEME 29

This procedure has been applied among others in the total synthesis of yohimban[867].

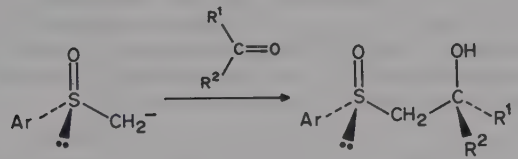
**d. Hydroxyalkylation of α-sulphinyl carbanions and synthesis of vinyl sulphoxides.* In the aldol-condensation-type reaction of α-sulphinyl carbanions with aldehydes and ketones, a new chiral centre at the β carbon atom is created. It has been found that diastereoselectivity of this process is rather low[868], the only exception being 2-pyridyl

TABLE 67. Hydroxyalkylation of α-sulphinyl carbanions

Ar	R^1	R^2	Base	Yield ($R,R+R,S$) (%)	Diastereoisomeric excess (%)	Ref.
p-Tol	Ph	H	LDA	95	0	468
p-Tol	Ph	H	LDA + $ZnBr_2$	35	60	468
p-Tol	Ph	H	LDA + $ZnCl_2$		80[a]	469
α-Naph	c-Hex	Me	LDA	60	4	468
2-Pyridyl	Ph	H	LDA	90	60	468
2-Pyridyl	Ph	H	LDA + $MgBr_2$	88	60	468
2-Pyridyl	c-Hex	Me	LDA	77	20	468

[a] Pure (*R*, *R*)-**879** was obtained by crystallization in 28% yield and exhibited $[\alpha]_D + 88.2$ ($CHCl_3$).

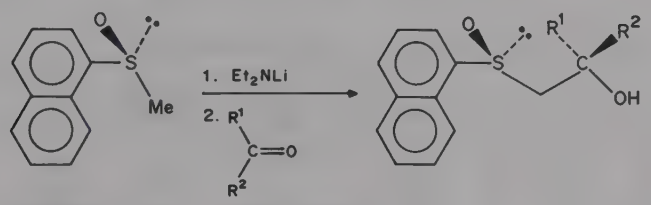
sulphoxides, and that it can be substantially increased by the addition of zinc salts (equation 466; Table 67)[868,869].



(466)

(*R*, *R*)-(**879**)
prevailing diastereoisomer

In a more recent paper[870] it has been shown that when the anion of (*S*)-(−)-methyl 1-naphthyl sulphoxide **880** reacts with alkyl phenyl ketones, the products **881** are formed stereospecifically or with very high stereoselectivity. Surprisingly, there is a trend of decreasing stereoselectivity on increasing the size and branching of the alkyl substituents. Dialkyl ketones give bad results (equation 467; Table 68)[870].



(467)

(*S*)-(**880**)
$[\alpha]_D$-459.8

yields 96–98%

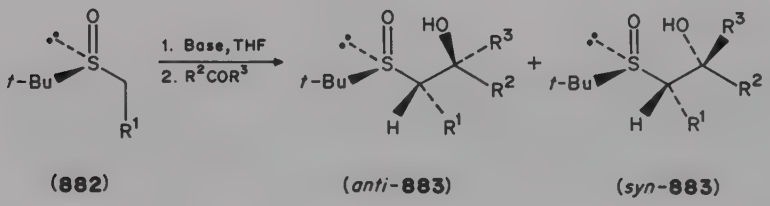
(S_S, S_C)-(**881**)
prevailing diastereoisomer

When sulphoxides possessing α-methylene group are used as substrates, the situation becomes more complex since a new chiral centre is created also at the α-carbon atom. However, it has been found that in the case of *tert*-butyl sulphoxides **882** the reaction with carbonyl compounds leads to the formation of only two of four possible diastereoisomers

TABLE 68. Hydroxyalkylation of (*S*)-(−)-methyl 1-naphthyl sulphoxide

R^1	R^2	Diastereoisomeric excess (%)
Ph	Me	100
Ph	Et	100
Ph	Pr	100
Ph	Bu	100
Ph	*i*-Pr	44
Ph	*i*-Bu	52
Ph	*t*-Bu	50
Ph	*n*-Hex	60
Et	Me	6

883. Complete steric control on the carbon α to sulphur and only a moderate one at the β-carbon are observed (equation 468; Table 69)[871,872]. The results reveal some consistent trends. Thus, addition of unhindered aldehydes gives poor stereoselectivity. However, increasing the bulk of the sulphoxide results in improved stereoselectivity. Good results are obtained in the addition to more hindered aldehydes and particularly ketones. Temperature, solvent, precomplexation with Lewis acids, transmetallation and the kind of base used have only moderate influence on diastereoselectivity[872].



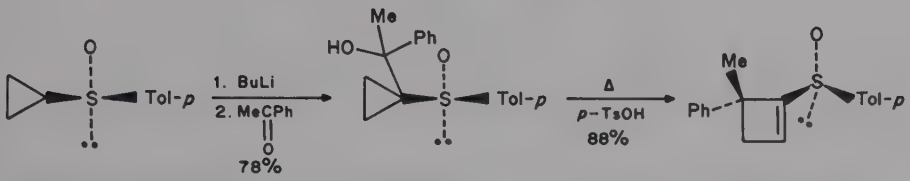
(882) (*anti*-883) (*syn*-883) (468)

TABLE 69. Hydroxyalkylation of *tert*-butyl sulphoxides **882**

R^1	R^2	R^3	Base (addition)	Yield of **883** (%)	*anti*/*syn* ratio **883**	Reference
n-Pr	Ph	H	LDA	85	1.2	872
n-Pr	*i*-Pr	H	LDA	81	5.0	872
$PhCH_2$	Et	H	LDA	85	2.0	871
$PhCH_2$	Et	H	LDA(Zn^{2+})	85	4.0	871
$PhCH_2$	Ph	H	LDA	81	1.7	871
$PhCH_2$	Ph	H	LDA(Zn^{2+})	98	5.3	871
$PhCH_2$	*i*-Pr	H	LDA	90	4.0	871,872
$PhCH_2$	*i*-Pr	H	LDA (Zn^{2+})	72	10.0	871
$PhCH_2$	Ph	Me	LDA	90	3.0	872
i-Pr	*i*-Pr	H	LDA	76	8.0	872
i-Pr	Ph	Me	LDA	98	5.0	872
Ph	Ph	Me	LHMDS	83	5.0	872

Several prochiral sulphoxides have been metallated at low temperatures (preferably at −100 °C) with (+)-menthyllithium and the enantiomerically enriched anions thus obtained reacted with benzophenone. Only in the case of sulphoxides possessing diastereotopic α-protons was stereoselectivity observed. The maximum e.e. value obtained is 40% [873].

Addition of the carbanion derived from (R_S)-(+)-*p*-toluenesulphinylcyclopropane **884** to acetophenone affords the product **885** as a 3:2 mixture of diastereoisomers, which have been separated by t.l.c. When heated in refluxing benzene in the presence of catalytic amounts of *p*-toluenesulphonic acid they give the same product of a rearrangement—cyclobutene **886** (equation 469)[874]. An explanation of such a stereochemical outcome has been proposed[874].



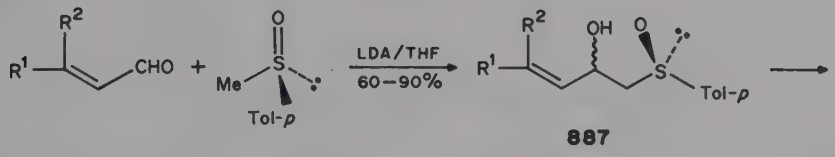
(R_S)-(+)-(**884**)
e.e. = 100%

(**885**)

(S_S, 4*R*)-(**886**)
e.e. > 94%

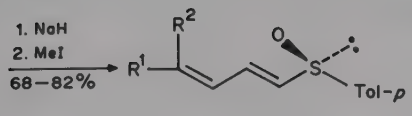
(469)

Enantiomerically pure 4-substituted (1*E*, 3*E*)-1[(*R*)-*p*-tolylsulphinyl]-1,3-butadienes **888** have been prepared in two steps by the condensation of the (*R*)-(+)-methyl *p*-tolyl sulphoxide anion with α,β-unsaturated aldehydes (1,2-addition) followed by a one-pot dehydration of the resulting mixture of diastereoisomers of β-hydroxysulphoxides **887** (equation 470)[875].



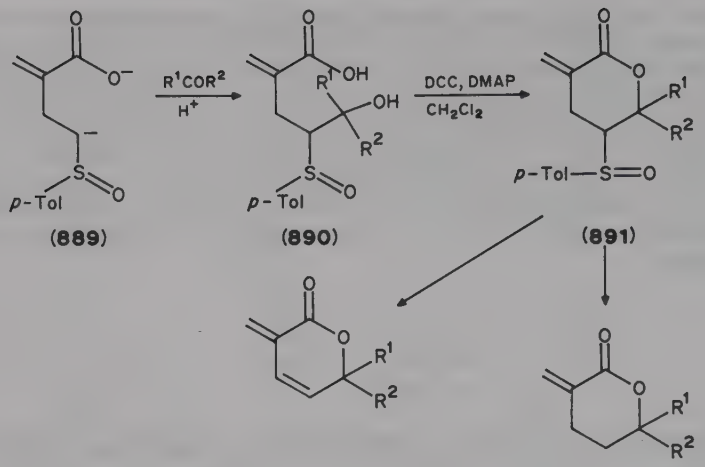
887

(470)



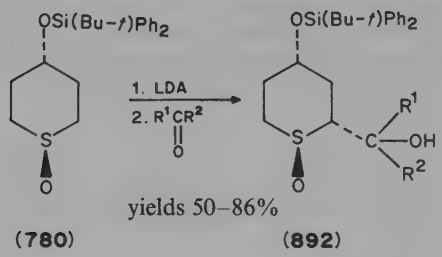
888

The dianion **889** derived from 2-methylene-4-*p*-toluenesulphinylbutyric acid reacts with carbonyl compounds to give the hydroxy carboxylic acids **890**. Crystallization of the latter gives sulphinyl lactones **891**, which can be further converted into sulphur-free α-methylene lactones (equation 471)[876].



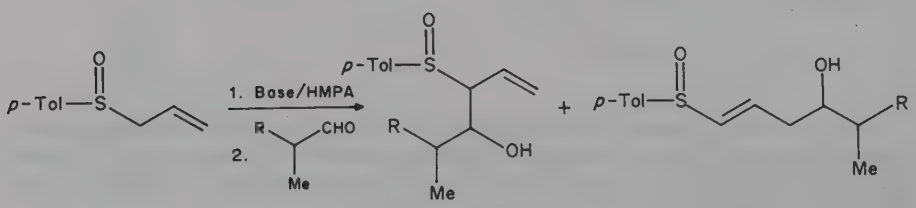
(471)

The anion of the strongly hindered thiane oxide **780** was found to react with aldehydes and ketones to give exclusively *trans* products, being a 1:1 mixture of isomers diastereoisomeric at the newly formed carbinol centre (equation 472)[845].



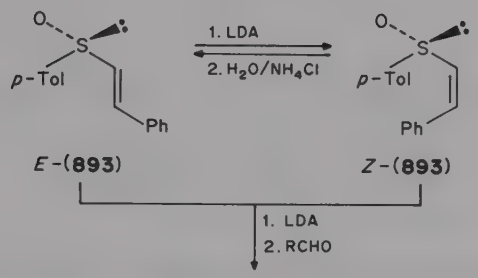
(472)

In contrast to the data contained in References 426 and 483 (equations 240 and 241), the anion of *p*-tolyl allyl sulphoxide has been found to react with aldehydes to form predominantly the products of α-addition. The increase of the α:γ ratio is a result of addition of HMPA during the reaction (equation 473)[877].



(473)

Optically active *E* and *Z* α-lithiovinyl sulphoxides **893** react with aldehydes to give β-hydroxy sulphoxides **894** and **895** with moderate selectivity. The product ratio **894**:**895** is almost the same irrespective of the configuration of the double bond in the substrate. This is due to the fact that vinyl anions bearing an adjacent electron-withdrawing group are configurationally unstable (equation 474; Table 70)[878].



(474)

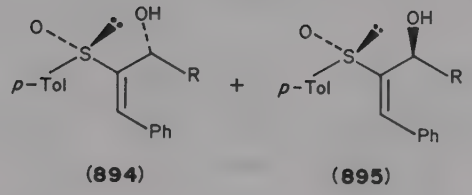
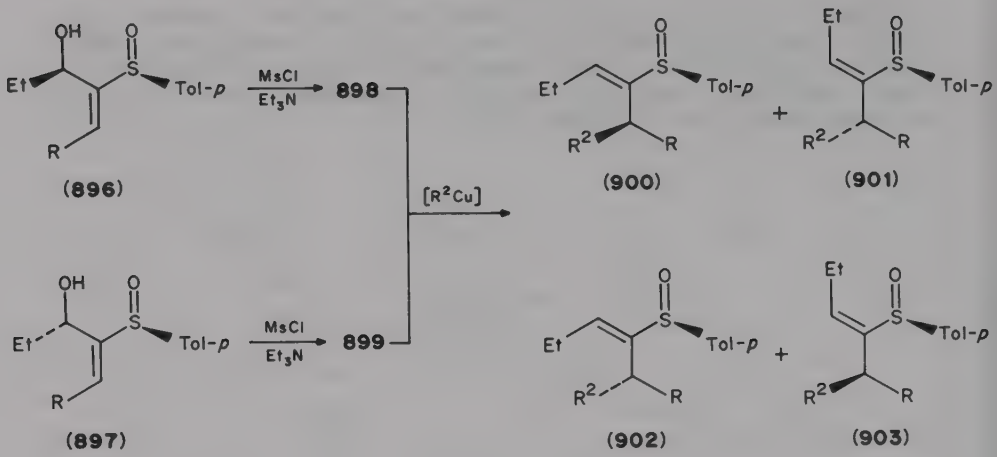


TABLE 70. Hydroxyalkylation of vinyl sulphoxide anions

				Yield (%)	
		R	Ratio **894**:**895**	**894**	**895**
E-**893**	**a**	Me	45:55	18	34
	b	*i*-Pr	34:66	16	44
	c	*t*-Bu	15:85	—	59
Z-**893**	**a**	Me	47:53	18	25
	b	*i*-Pr	41:59	25	35
	c	*t*-Bu	14:86	71 (both diast)	

Mesylation of optically active sulphoxides **896** and **897** and subsequent treatment with organocyanocuprates leads exclusively to the S_N2' substituted products, i.e. enantiomerically pure substituted vinyl sulphoxides **900**–**903** with high *E*/*Z* stereoselectivity (equation 475, Table 71)[879].



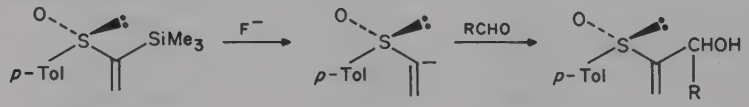
(475)

(**a**) R = Ph, R^2 = Me; (**b**) R = *n*-Bu, R^2 = Me; (**c**) R = Me; (**d**) R = Ph, R^2 = *t*-Bu

TABLE 71. S_N2' Displacements of acyclic sulphinylallylic mesylates **898** and **899**

Substrate Symbol	R	$[R^2Cu]$	Products ratio				Yield (%)
			900	**901**	**902**	**903**	
898a	Ph	MeCu(CN)Li	**900a** 6	**901a** 94	—	—	81
899a	Ph	MeCu(CN)MgBr	—	—	**902a** 6	**903a** 94	80
898a	Ph	*t*-BuCu(CN)Li	**900d** 9	**901d** 91	—	—	69
899a	Ph	*t*-BuCu(CN)MgCl	—	—	**902d** 6	**903d** 94	71
898b	*n*-Bu	MeCu(CN)Li	**900b** 9	**901b** 91	—	—	86
899b	*n*-Bu	Me_2CuLi	—	—	**902b** 90	**903b** 10	80
899c	Me	PhCu(CN)MgBr	**900a** 9	**901a** 91	—	—	80
899c	Me	$Ph_2CuMgBr$	**900a** 6	**901a** 94	—	—	70
898c	Me	BuCu(CN)Li	—	—	**902b** 15	**903b** 85	74
898c	Me	PhCu(CN)Li	—	—	**902a** 0	**903a** 100	—

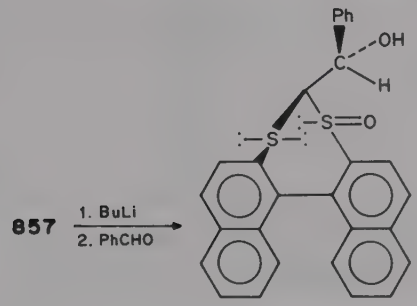
p-Tolyl 1-(trimethylsilyl)vinyl sulphoxide **904** can serve as a source of the vinyl carbanion **905** which is formed *in situ* upon treatment with tetra-*n*-butylammonium fluoride (equation 476)[880].



(476)

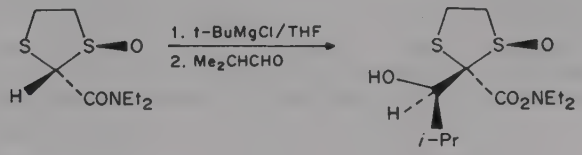
R:	Ph	*n*-Pr	*i*-Pr	*i*-Bu		Me
Yield of **906** (%):	75	50	60	80	70	95	40

The anions of various sulphoxides bearing at the α-carbon atom different substituents have also been applied for the reaction with carbonyl compounds. Among these, various kinds of dithioacetal monoxides are of special importance. Thus, the cyclic dithioacetal monoxide **857** mentioned earlier reacts with benzaldehyde to give the product **907** as a single diastereoisomer (two new chiral centres are stereospecifically created in one reaction) (equation 477)[850].



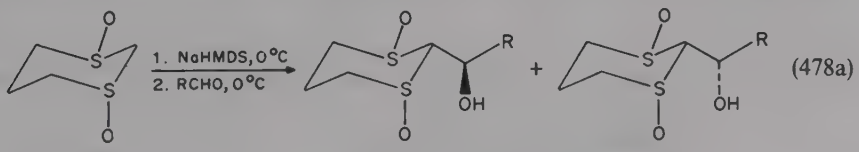
(907) (477)

Similarly, the enolate generated from the optically active dithiolane monoxide **737** gives with isobutyraldehyde the product **908** as a single diastereoisomer (equation 478)[789a].



(737) $[\alpha]_D^{25}$-13.3 (478)

The anion of *trans*-1,3-dithiane-*S*,*S'*-dioxide **619** is generated either with butyllithium in a pyridine/THF system[881] or with $NaN(SiMe_3)_2$ (NaHMDS) in THF[882]. The diastereoselectivity of the reaction of this anion with aldehydes is strongly dependent on the conditions, being surprisingly low at −78 °C and increasing substantially when equilibration occurs at 0 °C. NaHMDS gives generally better diastereoselectivity than BuLi/pyridine (equation 478a, Table 72)[881,882].



(619) (909) (910) (478a)

The open-chain bis-sulphoxide **911**, having also a C_2 axis of symmetry, gives the products of condensation with carbonyl compounds with moderate to good diastereoselectivity. The use of magnesium-containing base improves the diastereoisomer ratio (even to > 98:2), however, it lowers the yields to 25% (equation 479, Table 73)[883].

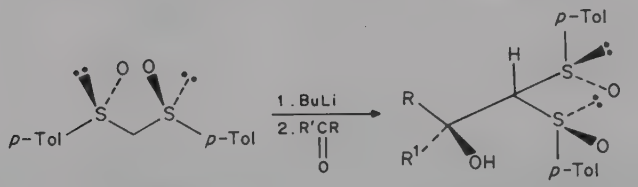
TABLE 72. Hydroxyalkylation of 1,3-dithiane-*S*,*S*'-dioxide **619** (NaHMDS as a base)

R	Ratio **909**:**910**	Isolated yield of **909** (%)
Ph	96:4	87
3-An	95:5	64
3,4-di[Me_2(*t*-Bu)SiO]C_6H_3	96:4	74
2-An	95:5	76
4-$O_2NC_6H_4$	95:5	42
2,4,6-$Me_3C_6H_2$	70:30	47
3-Pyridyl	97:3	71
n-Bu	77:23	—
i-Pr	60:40	—
t-Bu	40:60	—
t-Bu	13:87	71[a]

[a] Yield of **910**; BuLi/pyridine used as a base.

TABLE 73. Hydroxyalkylation of *β*-disulphoxide **911**

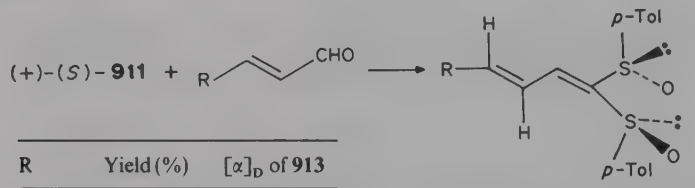
R	R'	Yield (%)	Diaster. ratio
Ph	H	70	90:10
p-$O_2NC_6H_4$	H	93	85:15
p-An	H	37	84:16
3,4-$Cl_2C_6H_3$	H	85	74:26
p-$MeO_2CC_6H_4$	H	75	85:15
C_5H_{11}	H	60	60:40
i-Pr	H	56	55:45
EtO_2C	Me	60	75:25



(479)

(+)-(*S*,*S*)-(**911**) (*S*,*S*,*S*)-(**912**) major diastereoisomer

The same substrate has been used for the synthesis of disulphinyl butadienes **913** (equation 480)[883].

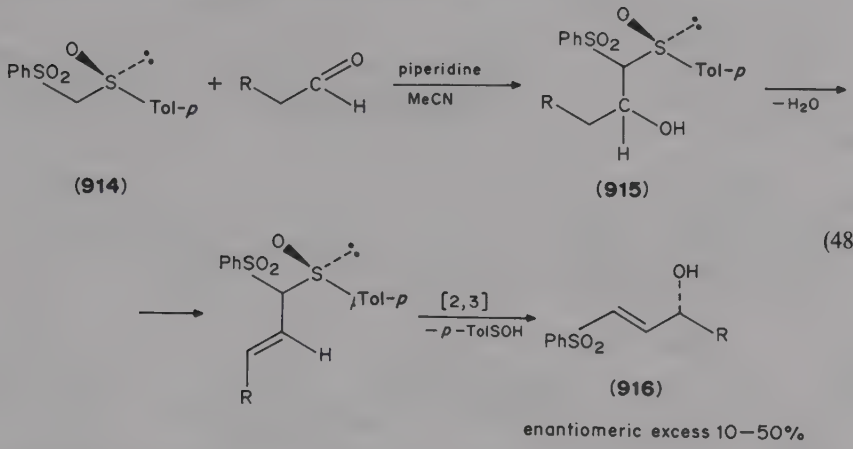


(480)

R	Yield (%)	$[\alpha]_D$ of **913**
Me	64	−22
Et	81	−24
Ph	80	−94
2-An	81	−109

(**913**)

In contrast to dithioacetal mono- and bis-sulphoxides, the α-sulphonyl sulphoxide **914** does not give in the reaction with aldehyde the corresponding hydroxyalkyl derivatives **915**, but γ-hydroxy-α, β-unsaturated sulphones **916**, the products of their dehydration and subsequent [2,3] sigmatropic rearrangement (equation 481)[884].



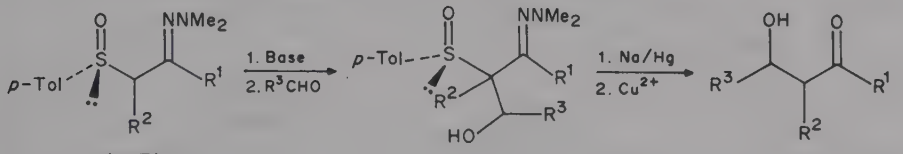
(914) (915) (916)

(481)

enantiomeric excess 10–50%

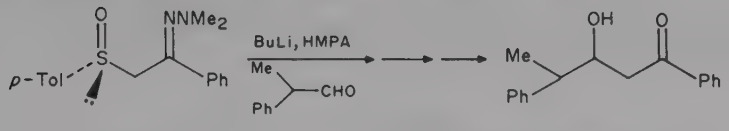
Among other α-substituted sulphoxides, the following have been reacted with carbonyl compounds in the presence of bases:

A. α-Sulphinyl hydrazones **917**; enantioselectivity of the aldol condensation is 48–88%; the products have been transformed into optically active β-hydroxy hydrazones and ketones (equation 482)[885]. When chiral racemic aldehydes are used in this reaction, a double stereoselection is observed which results in the formation of optically active β-hydroxyketones with very high stereoselectivity (equation 483)[886].



(917)

(482)

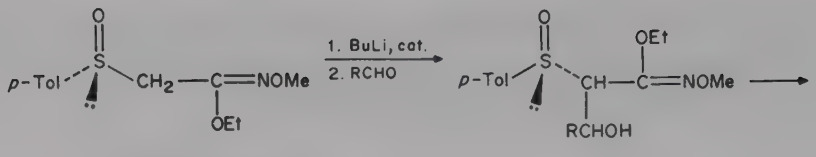


(483)

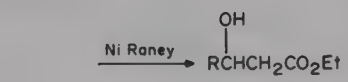
(−)-(*R*)-(**917**) overall yield 38% diast. ratio ≥ 30:1 e.e. = 100%

B. Ethyl (*R*)-(+)-*p*-toluenesulphinyl-*N*-methoxyacetimidate **918**; the products are transformed into optically active β-hydroxy esters with e.e. = 76–94% (equation 484)[887].

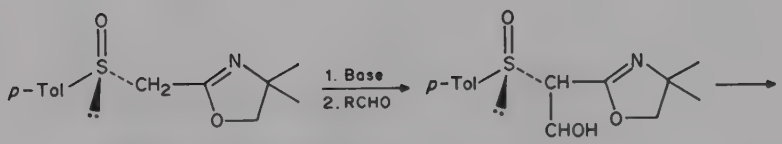
C. 2-Arylsulphinylmethyl oxazolines **919**; the products are transformed into optically active β-hydroxyalkyloxazolines in overall yields of 60–85% with e.e. = 24–53% (equation 485)[888].



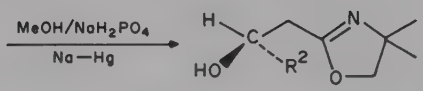
(**918**)



(484)

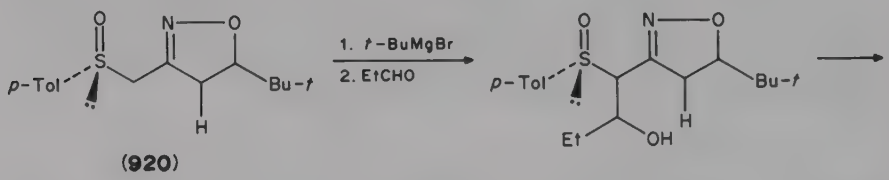


(**919**)

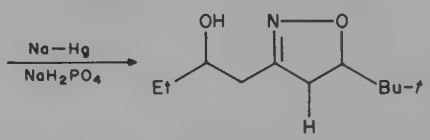


(485)

D. Stereoisomerically pure sulphinyl-4,5-dihydroisoxazoles **920**; diastereoisomeric ratio up to 50:1 (equation 486)[889].

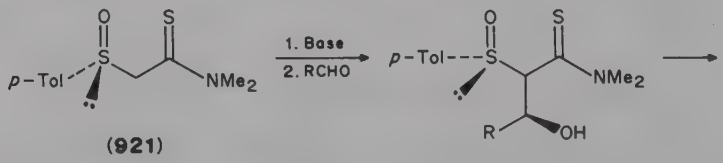


(**920**)

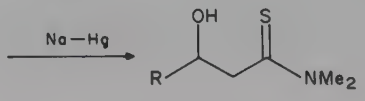


(486)

E. Enantiomerically pure *p*-tolylsulphinyl-*N*,*N*-dimethylthioacetamides **921**; the products are converted into optically active *β*-hydroxythioacetamides with e.e. = 40–90% (equation 487)[890].

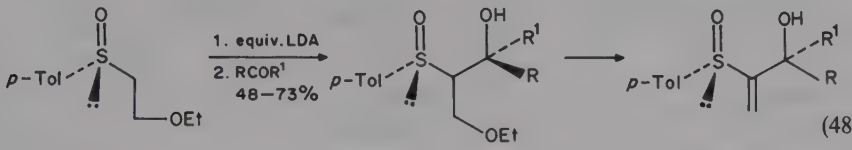


(**921**)



(487)

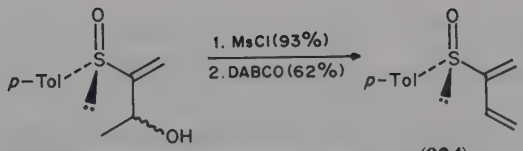
The adol condensation of β-ethoxyethyl *p*-tolyl sulphoxide **922** performed in the presence of two equivalents of base leads to very interesting α-methylene β-hydroxy sulphoxides **923** (equation 488)[891]. The latter can be used as substrates for the synthesis of optically active 2-sulphinylbutadienes **924** (equation 489)[892].



(488)

(922)
$[\alpha]_D + 169$

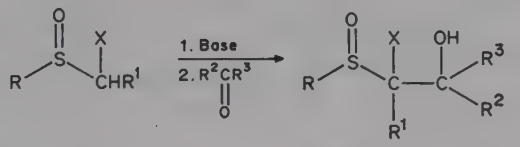
(923)
$R^1R = (CH_2)_5$; $[\alpha]_D + 127$
$R^1 = R = Me$; $[\alpha]_D + 277$
when $R^1 \neq R$, mixture of diastereoisomers



(489)

(923) **(924)**
$[\alpha]_D + 174$

The hydroxyalkylation of α-halosulphoxides **925** leads to sulphinylhalohydrines **926** (equation 490), which are very useful substrates for further transformations.



(490)

(925) **(926)**

The stereochemistry of this reaction is completely controlled by the chirality at the sulphur centre. Thus, when a symmetrical ketone is used, only a single stereoisomer of a chlorohydrin **927** is formed irrespective of the diastereoisomeric ratio of the starting chloroalkyl sulphoxide **926a** (equation 491)[893]. This fact is explained in terms of the equilibration of the anion of α-chloroalkyl sulphoxide[894]. The anion **A** is assumed to be more stable due to the *gauche* repulsions and dipole–dipole interactions (Figure 3)[894].

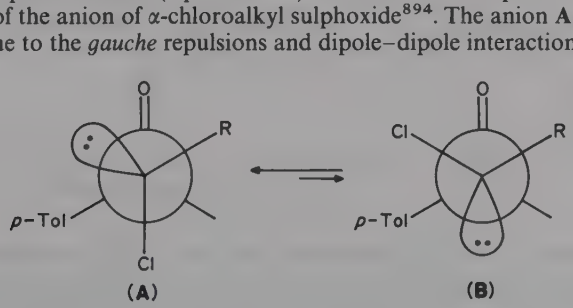
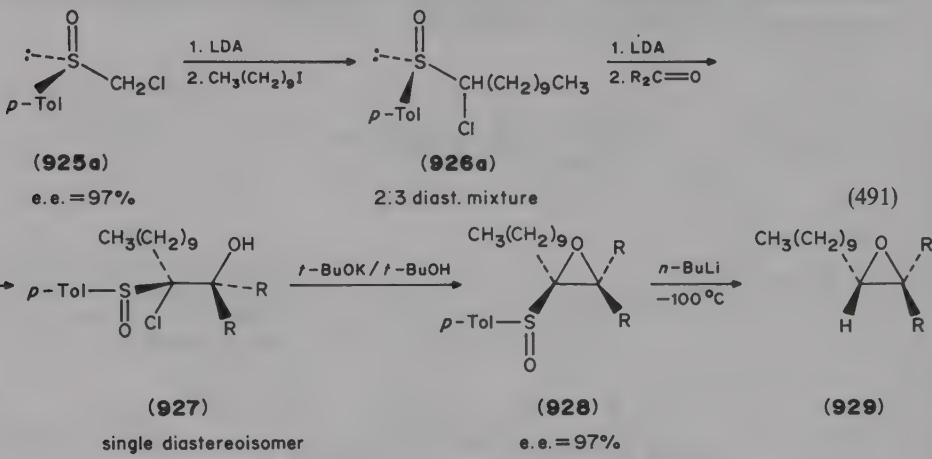
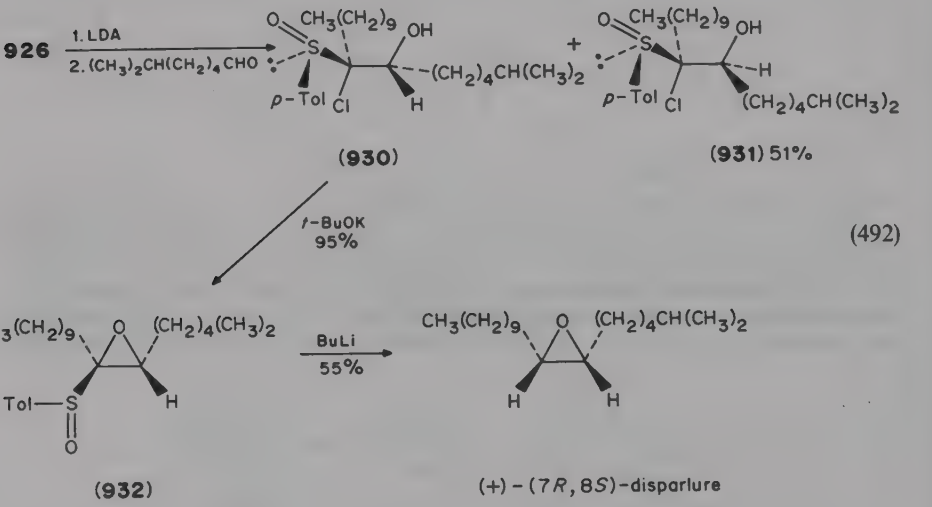


FIGURE 3. Equilibration of α-chloroalkyl sulphoxide anion

Treatment of chlorohydrins with a base gives sulphinyloxiranes **928** in almost quantitative yields and with full stereoselectivity (equation 491, Table 74)[893].



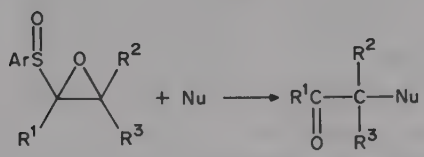
When aldehydes or unsymmetrical ketones are used in the reaction with **926**, a mixture of diastereoisomers (at the newly created carbinol centre) **930** and **931** is formed. They can be separated and each of them transformed into different enantiomers of a sulphur-free oxirane. This procedure has been applied for the synthesis of the sex attractant (+)-disparlure (equation 492)[893].



Sulphinyloxiranes are very interesting substrates, since they react with various nucleophiles at the epoxy ring and at the sulphinyl group to afford sulphur-free products in high yields (equation 493). This subject has been exhaustively investigated by Satoh and Yamakawa[828].

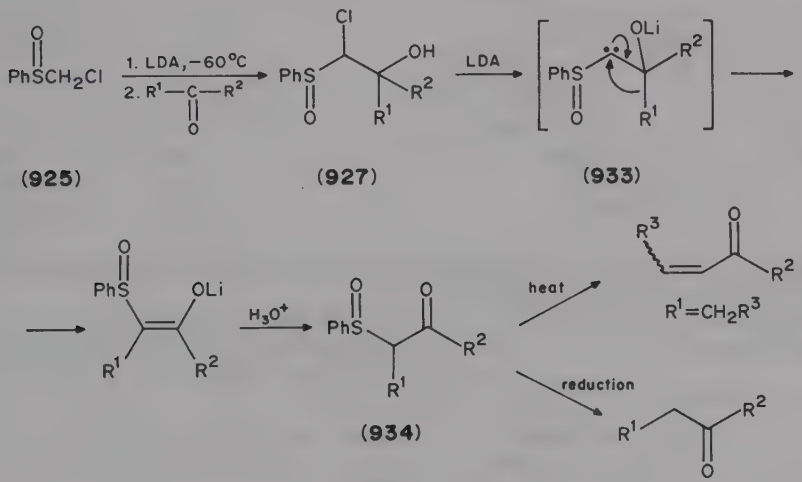
TABLE 74. Hydroxyalkylation of chloromethyl *p*-tolyl sulphoxide **925a**[893]

	927	**928**		**929**	
R_2	Yield (%)	Yield (%)	$[\alpha]_D$	Yield (%)	$[\alpha]_D$
Me_2	100	98	+ 8.9	73	−13.7
Ph_2		99	−91.7	89	−28.6
$-(CH_2)_5-$	93	95	+13.7	85	−14
$-(CH_2)_6-$	84	86	+18.5	61	−13.7



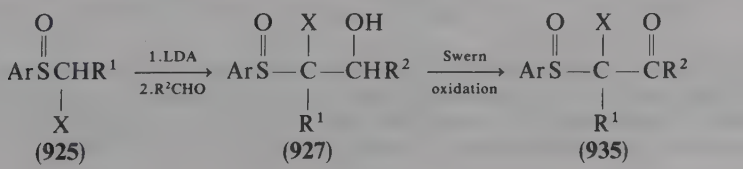
(493)

Sulphinylhalohydrins **927** have also been applied for the synthesis of different kinds of sulphoxides. Thus, treatment of **927**, obtained from **925** and aldehydes[895] or ketones[896], with an excess of LDA, gives β-oxo-sulphoxides **934** via the formation of α-sulphinyl carbenoids **933** and subsequent rearrangement. In the case of ketones this reaction has been applied for a one-carbon homologation of ketones[896] (equation 494, Table 75).



(494)

Oxidation of **927** gives α-halo-β-oxosulphoxides **935** (equation 495, Table 76)[897].



(495)

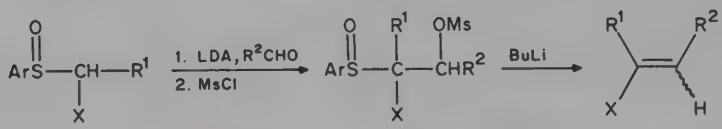
TABLE 75. Synthesis of β-oxosulphoxides **934** from chloromethyl phenyl sulphoxide

R^1	R^2	Yield of **927**(%)	Yield of **934**(%)	Reference
H	$CH_3(CH_2)_8$	98	95	895
H	Et	85	71	895
H	$Ph(CH_2)_2$	87	91	895
H	*c*-Hex	87	98	895
H	*t*-Bu	96	93	895
H	Ph	92	78	895
H	*o*-An	98	93	895
$—(CH_2)_3—$		92	95	896
$—(CH_2)_4—$		82	81	896
$—(CH_2)_5—$		91	47	896
n-Hex	*n*-Hex	90	61	896
Ph	Ph	87	91	896

TABLE 76. Synthesis of α-halo-β-oxosulphoxides **935**

X	Ar	R^2	Yield of **927**(%)	Yield of **935**(%)
F	Ph	$PhCH_2CH_2$	97	93
		$CH_3(CH_2)_8$	95	85
		Ph	94	97
		c-Hex	80	89
Cl	*p*-Tol	$PhCH_2CH_2$	99	96
		$CH_3(CH_2)_8$	82	92
		Ph	92	83
		c-Hex	91	94
Br	*p*-Tol	$PhCH_2CH_2$	95	73
		$CH_3(CH_2)_8$	99	90
		Ph	90	74
		c-Hex	90	72

Mesylation of **926** gives *O*-mesyl derivatives **936** which, on treatment with BuLi, give haloalkenes in good yields (equation 496)[898].

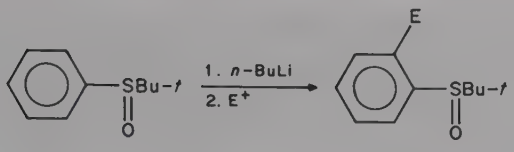


(496)

(936)

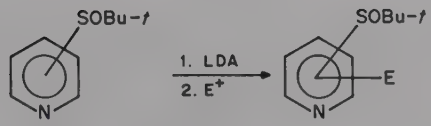
Ar = Ph, *p*-Tol (mixture of R^1 = Me, *n*-Pr
X = F, Cl diastereoisomers) R^2 = $PhCH_2CH_2$, *n*-Pr, $CH_3(CH_2)_8$

When diaryl, *t*-butyl aryl and pyridyl aryl (*t*-butyl) sulphoxides are treated with BuLi or LDA, regiospecific *ortho* metallation in the aryl or pyridyl moiety takes place[899–901]. The lithioaryl sulphoxides thus formed react with various electrophiles to give *ortho*-substituted aryl (pyridyl) sulphoxides (equations 497 and 498, Table 77)[901].



(497)

(937)



(498)

(938) (939)

regioisomers not specified[901]

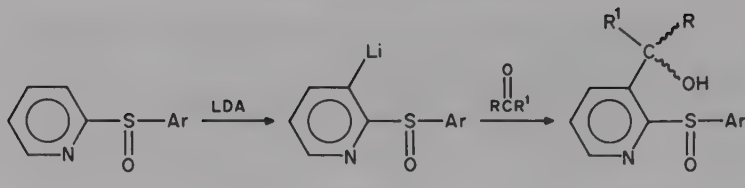
TABLE 77. Reaction of *ortho*-lithiated aryl and pyridyl sulphoxides with electrophiles[901]

E^+	**937**, *E*	Yield (%)	**938** substitution	*E*	**939**, *E*	Yield (%)
MeOD	D	88		MeOD	D	75
MeI	Me	96		MeI	Me	82
EtI	Et	87	2 –	PhCHO	$HOCH_2Ph$	74
$BrCH_2CH{=}CH_2$	$CH_2{-}CH{=}CH_2$	41		I_2	I	35
PhCHO	HOCHPh	82		Me_3SiCl	Me_3Si	70
$ClCONEt_2$	$CONEt_2$	54		Bu_3SnCl	Bu_3Sn	90
	OH	48	4 –	MeOD	D	72
$(TMSO)_2$	OH	44		MeI	Me	74
$BrCH_2CH_2Br$	Br	85		Me_3SiCl	Me_3Si	66
$B(OMe)_3/HCl$	$B(OH)_2$	69		Bu_3SnCl	Bu_3Sn	74
Me_3SiCl	Me_3Si	89				
Me_3SnCl	Me_3Sn	85				

Reaction of the α-anion **940** obtained from aryl 2-pyridyl sulphoxides with carbonyl compounds takes place regiospecifically at the pyridine ring affording a mixture of two diastereoisomeric products **941** (equation 499, Table 78)[899].

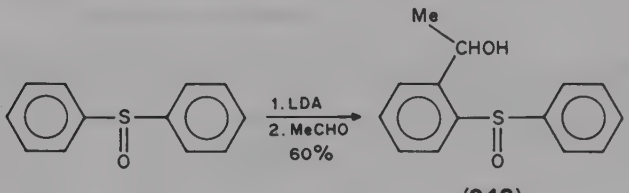
TABLE 78. Hydroxyalkylation of 3-lithio-2-pyridyl aryl sulphoxides **940**[899]

Ar	R	R^1	Yield of **941** (%)	Diast. ratio
Ph	Me	H	81	1:1.1
Ph	Ph	H	87	3.3:1
Ph	Ph	Me	90	1:1.1
1-Naph	Ph	H	93	6.7:1
1-(2-MeO)Naph	Ph	H	81	2.4:1



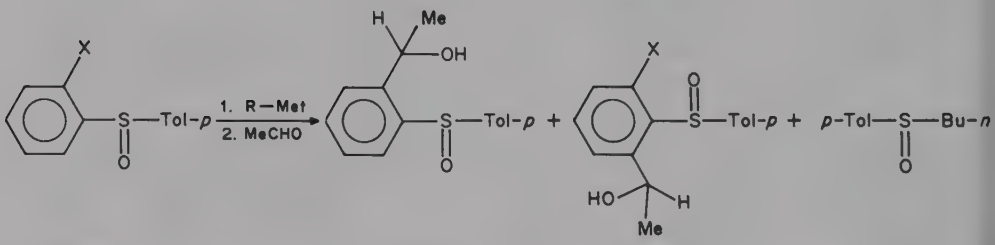
(940) (941) (499)

In the case of diphenyl sulphoxide the *ortho*-hydroxyalkylation product **942** is formed with low stereoselectivity (diastereoisomer ratio 63:37; equation 500)[900]. The stereoselectivity is also low to moderate when *ortho*-halophenyl *p*-tolyl sulphoxides **943** are lithiated and subsequently treated with acetaldehyde. The reaction is, however, strongly dependent on the base applied and on the halogen atom which allows one to obtain each of two regioisomers **944** and **945** (equation 501, Table 79)[900].



(942)

diast. ratio 63:37 (500)



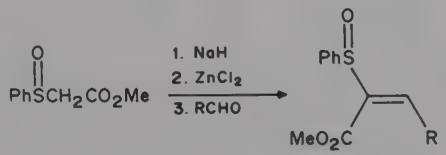
(943) (944) (945) (946) (501)

TABLE 79. Hydroxyalkylation of *ortho*-halophenyl *p*-tolyl sulphoxide **943**

X	R-Met	Yield (%) 944	945	946	Diast. ratio
Cl[a]	*n*-BuLi	—	—	90	—
Cl[a]	LDA	—	94	—	69:31
Br[b]	*n*-BuLi	40	—	34	65:35
Br[b]	LDA	—	95	—	71:29
I	*n*-BuLi	92	—	—	65:35
I	LDA	—	59	—	72:28

[a] 100% optical purity.
[b] 58% optical purity.

The reaction of α-sulphinyl carbanions with aldehydes and ketones has also been used for a direct synthesis of vinyl sulphoxides. However, this is only possible in the case when the α-sulphinyl carbanion centre is adjacent to another electron-withdrawing group. For example, the condensation of the anion formed from methyl benzenesulphinylacetate **947** with a series of aldehydes, performed in the presence of zinc chloride, produces α,β-unsaturated α-carbomethoxy sulphoxides in low-to-moderate yields (equation 502)[902]. Under these conditions formation of the intermediate β-hydroxy sulphinyl ester is usually not observed.

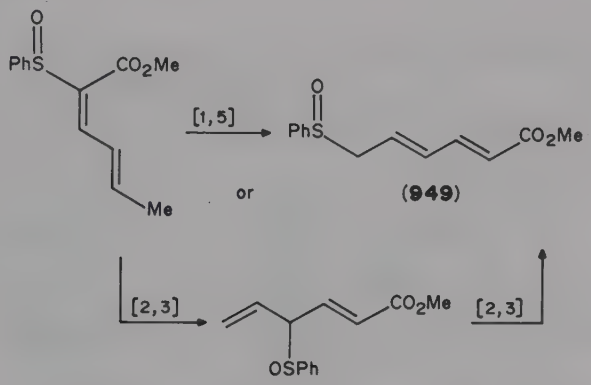


(502)

(947) **(948)**

R	Ph	n-C_5H_{11}	n-Bu	t-MeCH=CH	Me	i-Pr	$PhCH_2CH_2$
Yield (%)	20	38	35	39	34	12	48

Rearrangement of the conjugated ester obtained from crotonaldehyde leads in a high yield (72%) to the dienoic sulphoxide **949** probably via a double [2,3]-sigmatropic process (equation 503)[902].



(503)

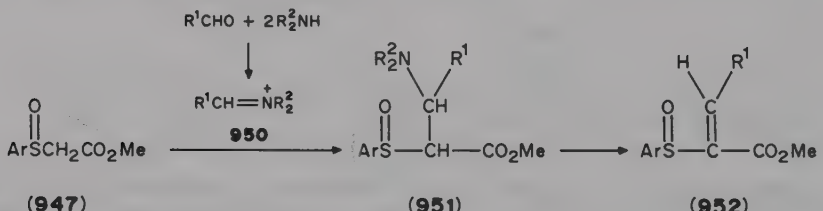
Another possibility of a direct formation of vinyl sulphoxides under mild basic conditions is the Knoevenagel reaction. Tanikaga and coworkers have proved that this reaction proceeds via a preliminary formation of the iminium salts **950** which, being more electrophilic than the starting aldehyde, react with the enolate anion formed from the sulphinylacetate **947** to give the isolated amino compounds **951**. The latter eliminate amine to give the thermodynamically more stable *E*-vinyl sulphoxides **952** (equation 504, Table 80)[903].

It should be added that elimination of amine from **951** performed in acetic acid produced both (*E*)- and (*Z*)-**952** in variable proportions[903].

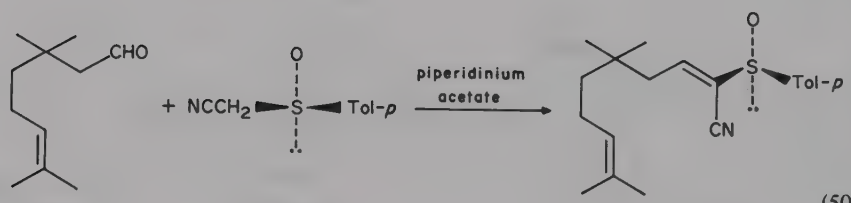
Chiral cyanovinylic sulphoxide **955** has been obtained stereoselectively in 86% yield by the Knoevenagel reaction of optically active cyanomethyl *p*-tolyl sulphoxide **954** and 3-methylcitronellal **953** (equation 505)[904,905].

TABLE 80. Preparation of (*E*)-**952** by the Knoevenagel reaction

Ar	R^1	Temp(°C)	Time (h)	Yield (%)	*E*:*Z*
Ph	*n*-Pr	0	24	57	98:2
p-ClC_6H_4	*n*-Pr	0	24	70	98:2
p-$O_2NC_6H_4$	*n*-Pr	0	24	74	98:2
p-ClC_6H_4	*n*-Hex	0	24	75	98:2
p-ClC_6H_4	*i*-Pr	20	24	90	99:1
p-ClC_6H_4		20	48	83	99:1
p-ClC_6H_4	Ph	60	6	88	99:1



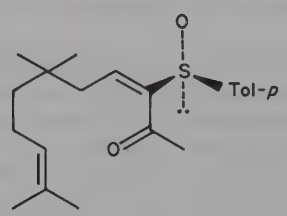
(947) (951) (952) (504)



(953) (*R*)-(**954**) (*S*)-(**955**) (505)

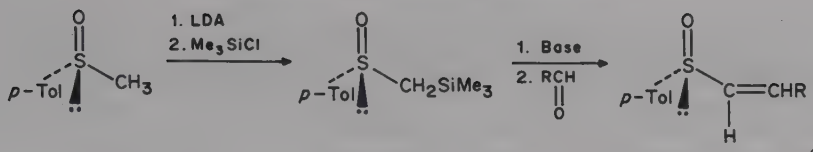
$[\alpha]_D + 252.7$

In a similar way the ketovinylic sulphoxide (*S*)-**956** has been prepared[906].



(**956**)

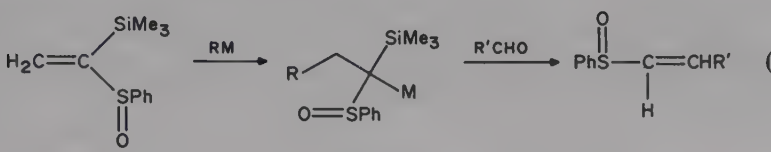
The well-known Peterson olefination reaction has also been applied for the synthesis of vinyl sulphoxides. Cinquini and collaborators using the *in situ* formed α-silyl sulphoxide **957** have obtained in this way a series of optically active *p*-tolyl vinyl sulphoxides **958** usually as a mixture of (*E*) and (*Z*) diastereoisomers (equation 506)[907].



(449) (957) (958) (506)

R	*n*-Pr	*i*-Pr	*i*-Bu	*t*-Bu	*c*-Hex	Ph
Yield	62	55	58	50	60	65
E/*Z* ratio	2:1	1:3	1.1:1	only Z	1:2.9	2:1

A better diastereoselectivity was observed when 1-silylethenyl sulphoxide **959** is used as a Michael acceptor for a variety of organometallic reagents and the anion thus formed reacts with aldehydes (equation 507, Table 81)[908].

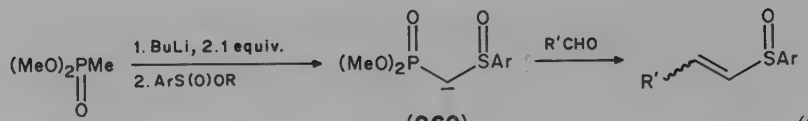


(959) (507)

TABLE 81. Vinyl sulphoxides from tandem Michael addition–Peterson olefination[908]

R—M (equiv.)	R'CHO	Yield	*E*:*Z*
PhLi (1.5)	PhCHO	71	*E*
PhMgBr (1.2)	PhCHO	50	*E*
Ph_2CuLi	PhCHO	56	*E*
PhCuMgBr (1)	PhCHO	68	*E*
PhLi (1.5)	*p*-$MeOC_6H_4CHO$	92	*E*
PhLi (1.5)	MeCH=CHCHO	87	*E*
PhLi (1.5)	*n*-PrCHO	86	*E*
MeLi (1.5)	PhCHO	76	1.7
MeLi (1.5)	*p*-$MeOC_6H_4CHO$	73	2.3
t-BuMgBr (1.2)	PhCHO	26	*E*
i-$Pr_2CuMgBr$ (1.1)	PhCHO	44	*E*
CH_2=C(OLi)OEt (1)	PhCHO	66	1.8
	p-$MeOC_6H_4CHO$	73	2
	2-Furyl CHO	75	2
	n-PrCHO	60	*E*
	MeCH=CHCHO	73	*E*

A one-pot procedure of a widely used Horner–Wittig (Horner–Emmons) olefination[515] has been developed for the preparation of vinyl sulphoxides which consists in the *in situ* formation of α-phosphoryl sulphinyl carbanion **960** and its subsequent reaction with aldehydes (equation 508)[909].



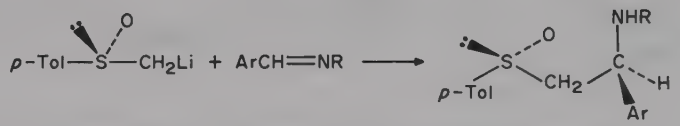
(960) (508)

R = alkyl, menthyl

yields 61–94%
mixtures of (*E*) and (*Z*)

e. *Aminoalkylation of α-sulphinyl anions.* The authors of some recent papers claim that the results of Tsuchihashi and coworkers[524,910], concerning stereospecific asymmetric additions of α-sulphinyl carbanions to imines, cannot be reproduced since always a mixture of diastereoisomers is formed[911,912]. More detailed studies of Kagan have revealed that the diastereomeric ratio (d.r.) of the products formed is strongly dependent on the temperature of the carbanion formation (T_1) and on the temperature of the condensation with an imine (T_2), the optimum conditions being $T_1 = 0$ °C, $T_2 = -78$ °C.

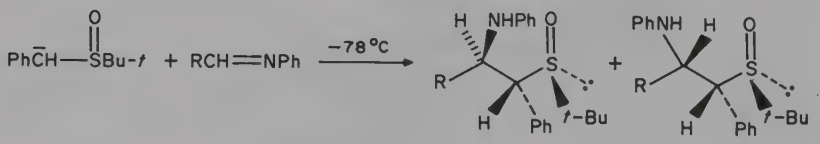
The best results have been obtained for the following imines: R = Ar = Ph, yield 99%, d.r. = 92:8; R = Ar = *p*-An, yield 74%, d.r. = 95:5 and Ar = Ph, R = *n*-Pr, yield 76%, d.r. = 90:10. The major diastereoisomer can be easily purified by crystallization to give enantiomerically pure β-aminosulphoxides **962** (equation 509) [911].



(449)–Li (961) (962) (509)

major diastereoisomer

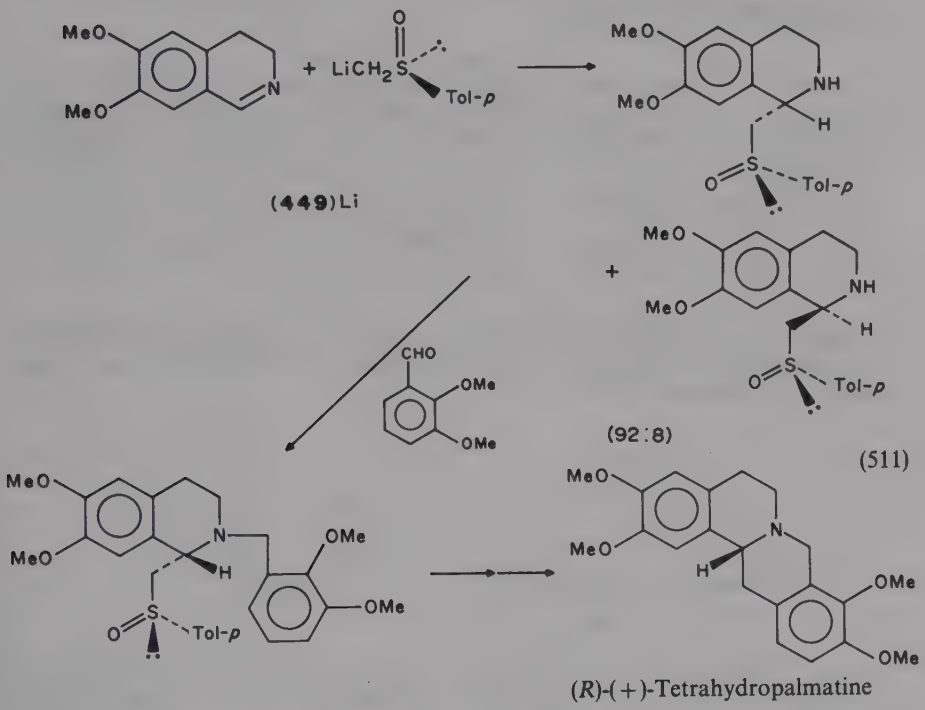
In turn, Pyne and Dikic[912] have found that **449**-Li undergoes addition to imines having at least one aryl substituent to give, under kinetic control conditions, β-aminosulphoxides **962** with good-to-modest diastereoselectivity (best results: when R = Ph and Ar = furyl, yield 96%, d.r. = 91:9; R = Me and Ar = Ph, yield 89%, d.r. = 91:9). However, under equilibrium conditions poor diastereoselection is observed, e.g. in the case of R = Me and Ar = Ph the diastereoisomeric ratio drops to 51:49 when the reaction time is increased from 10 min to 12 h[912]. Finally, Pyne and Boche[871] have found that the *t*-butyl phenyl sulphoxide **963** carbanion adds to *N*-phenyl imines, in which the substituent R is alkenyl or aryl, with a high *anti*-diastereoselection (equation 510).



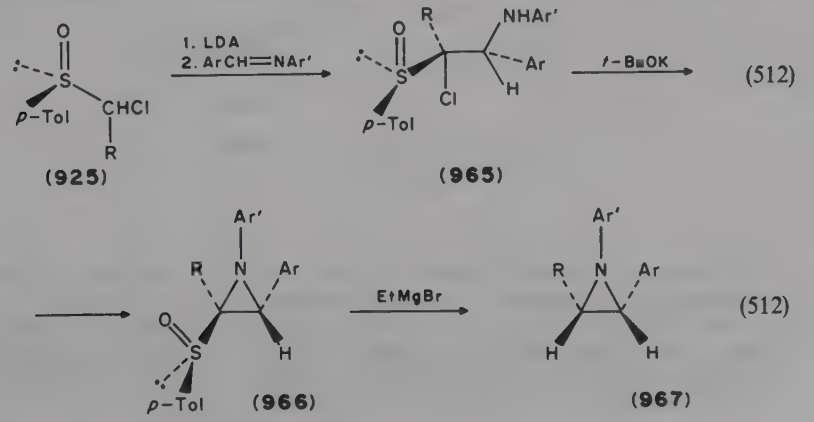
(963) *anti*-(964) *syn*-(964) (510)

R	Ph	(*E*)-PhCH=CH	2-Furyl
anti: syn	>97:3	>97:3	97:3
Yield (%)	94 (Li^+)	52 (Li^+)	100 (Li^+)
(counter cation)		82 (Zn^{+2})	

In summary, the reaction is apparently very sensitive to the conditions applied and thus very capricious. Therefore, the results taken from different papers are in certain cases inconsistent and — because of using different conditions and substituents — incomparable. Nevertheless, this reaction has been successfully applied for the synthesis of some natural products, e.g. (*R*)-(+)-tetrahydropalmatine where the asymmetric centre has been stereoselectively formed during the addition step (equation 511)[912].



The carbanions of α-chlorosulphoxides **925** react with imines to give the corresponding chloroamines **965** as single diastereoisomers (thus with full 1,2- and 1,3-asymmetric

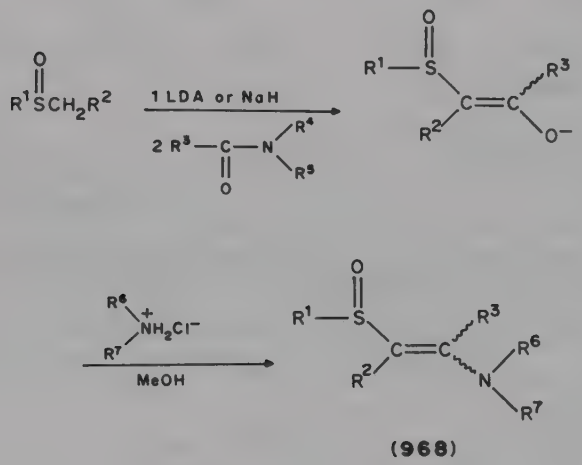


induction). Treatment of the latter with potassium *t*-butoxide gives sulphinylaziridines **966** which, in turn, can be converted into aziridines **967** on reacting with an excess of ethylmagnesium bromide (equation 512, Table 82)[913].

TABLE 82. Synthesis of optically active β-amino-α-chloro sulphoxides **965**, sulphinylaziridines **966** and aziridines **967**

			965		**966**		**967**	
R	Ar	Ar'	Yield (%)	$[\alpha]_D$	Yield (%)	$[\alpha]_D$	Yield (%)	$[\alpha]_D$
n-$C_{10}H_{21}$	Ph	Ph	94	−217.4	87	−301.4	95	−159.5
n-$C_{10}H_{21}$	Ph	p-Br-C_6H_4	88	−250.5	98	−277.4	85	−132.6
Me	Ph	Ph	91	−177.6	92	−385.2	89	−271.3
Me	*p*-ClC_6H_4	Ph	74	−196.1	90	−384.8	91	−313.3

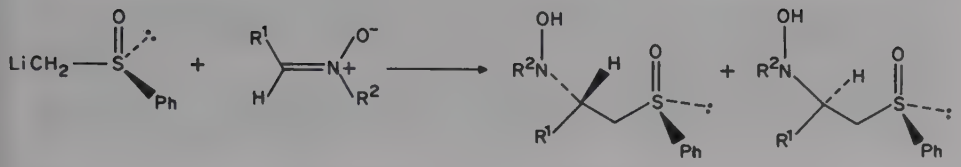
β-Enamino sulphoxides **968** have been synthesized in moderate-to-good yields (22–72%) from metallated dialkyl and alkyl aryl sulphoxides, tertiary amides and amine hydrochlorides (equation 513)[914].



(513)

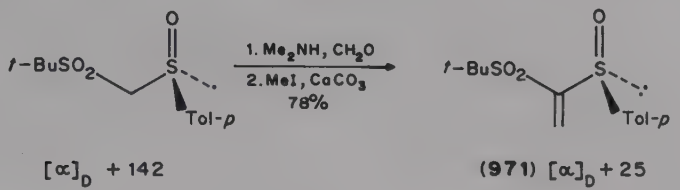
(968)

The reaction of α-sulphinyl carbanions with nitrones was reported by Cinquini and collaborators to proceed with a very high β-stereoselectivity (equation 274)[526]. The recent work of Pyne and Hajipour showed that the diastereoselectivity is moderate and the diastereoisomeric ratio **969**:**970** varies from 67:33 (for R^1 = Ph and R^2 = Me) to 85:15 (for R^1 = Ph and R^2 = *t*-Bu) and 86:14 (for R^1, R^2 = isoquinoline), being 50:50 for R^1 = Me and R^2 = *t*-Bu (equation 514)[915].

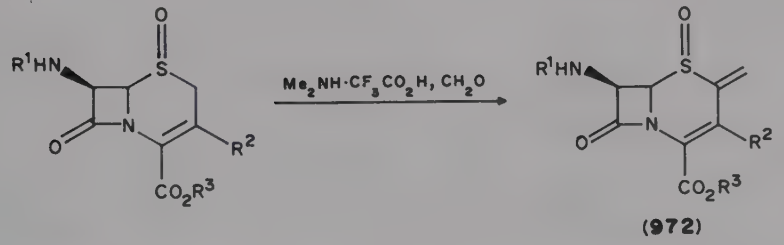


(969) (970) (514)

The Mannich reaction has recently been applied for the synthesis of the optically active α-sulphonylvinyl sulphoxide **971**, used as a dienophile in a Diels-Alder cycloaddition (equation 515)[916a] and for the synthesis of 2-methylene-3-cephem sulphoxides **972** (equation 516)[916b].

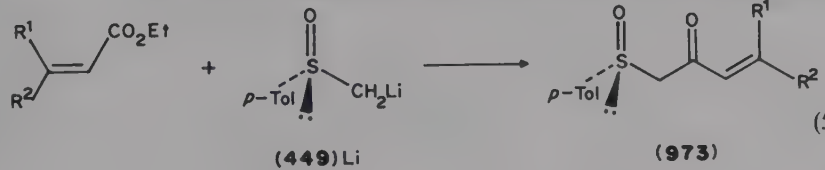


(515)



(516)

*f. Acylation of α-sulphinyl carbanions. Synthesis of β-oxosulphoxides**. The α-sulphinyl carbanion **449**-Li has been reported to react with α,β-unsaturated esters to give opti-



(517)

R¹	R²	Yield (%)	$[\alpha]_D$ of **973**
H	Me	65	+241
H	*n*-C_5H_{11}	61	+177
H	Ph	85	+278
Me	Me	88	

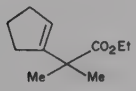
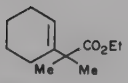
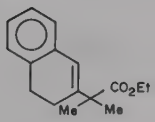
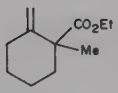
* In our original chapter the name 'α-ketosulphoxides' instead of 'β-oxosulphoxides' was sometimes used. However, this appeared to be misleading since other authors named these compounds 'β-ketosulphoxides'. Therefore, only the name 'β-oxosulphoxides' will be used in the present chapter.

cally active β-oxo-γ,δ-unsaturated sulphoxides **973** in high yields (equation 517)[917, 918] (for a competing Michael addition of α-sulphinyl carbanions to α,β-unsaturated esters, see equation 458 and Table 64)[854,855].

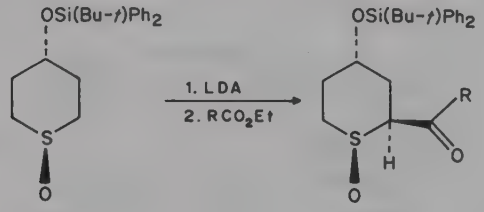
The dimsyl anion undergoes acylation by a variety of cycloalkenylacetates (β,γ-unsaturated esters) to give the corresponding products **974** in high yields (equation 518)[919].

$$CH_3SCH_2Na \xrightarrow{RC(O)OEt} RCCH_2SCH_3 \quad (518)$$

(**974**)

R-CO_2Et	Yield of **974** (%)
	81
	63
	87
	58

Acylation of the carbanion derived from **778** gives exclusively the products **975** in which the aryl group is introduced *cis* to the sulphinyl oxygen (equation 519)[920].

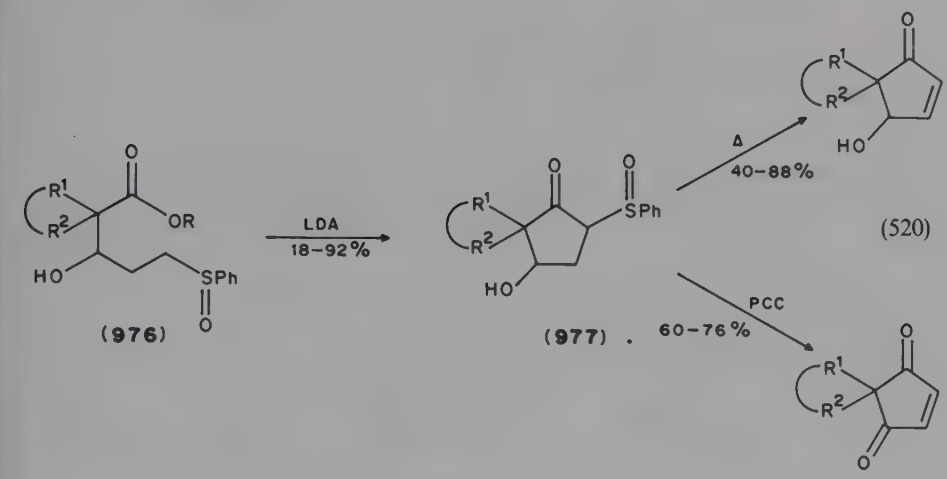


(**778**) (**975**) (519)

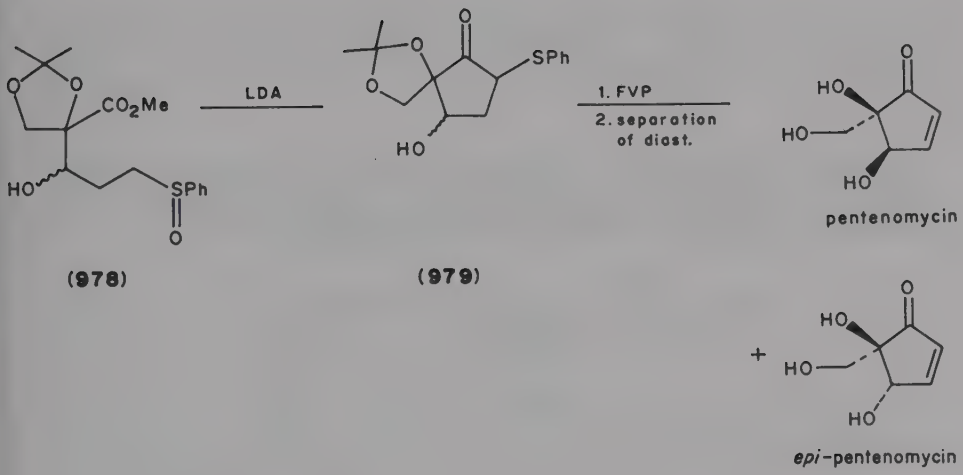
975	R	Yield (%)
a	Me	73
b	*t*-Bu	82
c	Et	86
d	*i*-Pr	52
e	Ph	81

It should be added that **975b** has been obtained directly from **778** in 55% e.e. by using a homochiral lithium amide base **779** for the deprotonation and then quenching with t-$BuCO_2Et$[920].

Intramolecular acylation of the α-sulphinyl carbanion derived from **976** and **978** has been used for the preparation of spirocycloalkenones (equation 520)[921] and pentenomycins (equation 521)[922].

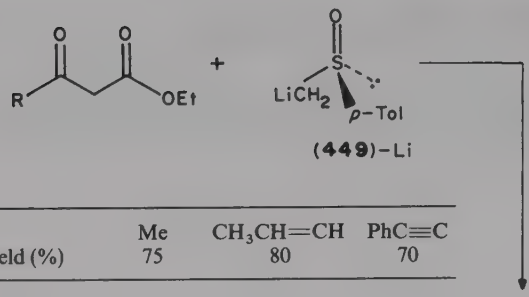


(520)



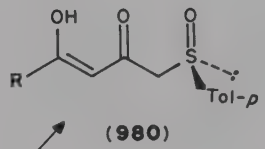
(521)

Optically active β,γ-dioxoallyl p-tolyl sulphoxides **980** have been synthesized either by acylation of **499**-Li with β-oxocarboxylic esters or by direct condensation of the dianion of (+)-(*R*)-1-(*p*-tolylsulphinyl)-propan-2-one **981** with carboxylic esters (equation 522)[923].



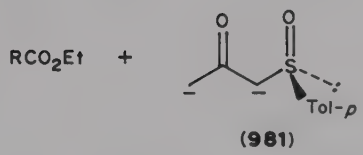
(449)-Li

R	Me	$CH_3CH{=}CH$	$PhC{\equiv}C$
Yield (%)	75	80	70



(980)

(522)



(981)

R	$CH_3CH{=}CH$	EtO_2CCH_2
Yield (%)	85	77

Recently, a one-pot synthesis of β-oxosulphoxides from carboxylic acids has been developed. It consists in the preliminary formation of the acylimidazole **982** which, without previous isolation, is reacted with dimsyl anion (equation 523)[924].

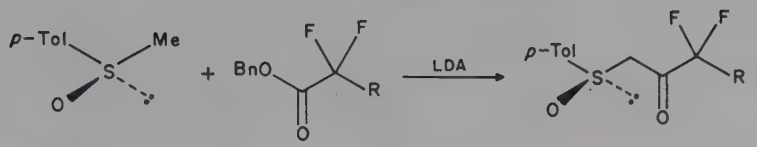
$$RCO_2H \xrightarrow{Im_2CO} RC(=O)\text{-}Im \xrightarrow[THF]{Me_2SO/MeLi} RC(=O)CH_2SCH_3 \qquad (523)$$

(982)

Im = Imidazolyl

R	neo-Pent	n-C_5H_{11}	Ph	Ph_3C	*p*-An	2-quinolyl	8-isoquinolyl
Yield (%)	65	78	81	88	78	56	65

α,α-Difluoroesters react smoothly with α-sulphinyl carbanions to give the β-oxo-γ, γ-difluorosulphoxides **983** (equation 524)[925].

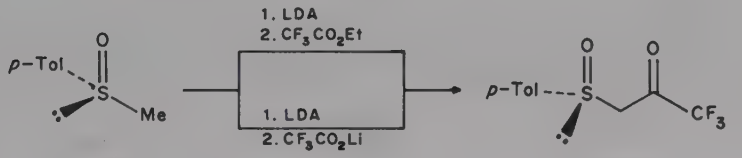


(524)

(449) (983)

R	Ph	Me
Yield (%)	92	94

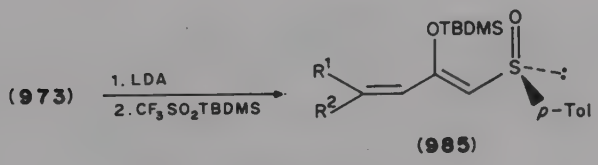
β-Oxo-β-trifluoromethyl sulphoxides, e.g. **984**, have been obtained by acylation of α-sulphinyl carbanions either with ethyl trifluoroacetate[926,927] or directly with trifluoroacetic acid lithium salt (equation 525)[928].



(525)

(449) (984)

Acylation of α-sulphinyl carbanions has found some practical applications in organic synthesis. Thus, the products **973** have been transformed into enantiomerically pure 4-substituted (1*Z*, 2*E*)-[(*R*)-*p*-tolylsulphinyl]-2-*t*-butyl dimethylsilyloxy-1, 3-butadienes **985** (equation 526)[918].



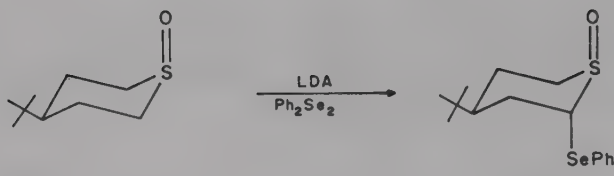
(526)

(985)

R^1	R^2	Yield (%)	$[\alpha]_D$
H	Me	85	−201
Me	Me	70	−119
H	Ph	70	−118

For the synthesis of optically active 3-sulphinyldihydropyridine see Reference 929, and of optically active 3-(*p*-tolysulphinyl) chromone see Reference 930.

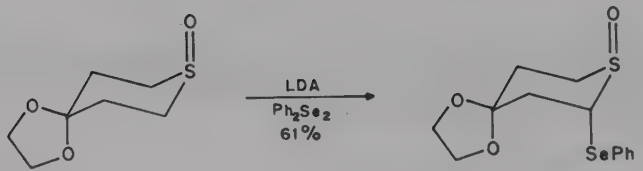
g. Other reactions of α-sulphinyl carbanions.* α-Sulphinyl carbanions react with selenylating agents to give α-selenenyl sulphoxides. In this way α-benzeneselenenyl thiane-1-oxides **986–988 have been obtained (equations 527–529)[931].



(527)

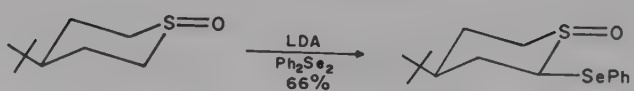
(986)

64%, diast. pure after crystallization



(528)

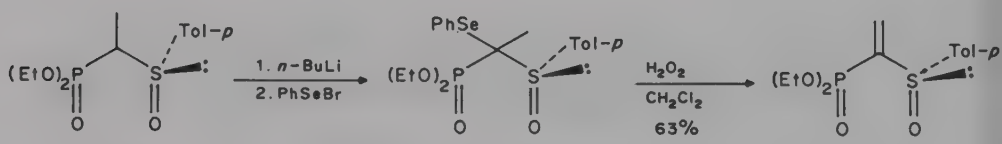
(987)



(529)

(988)

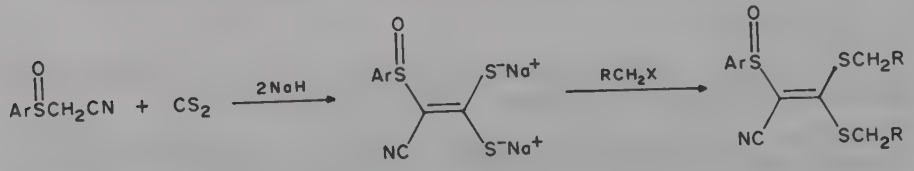
A two-step procedure—selenenylation of a carbanion of **989** and deselenenylation of **990** by oxidative benzeneselenenic acid eliminations—has been used for the synthesis of the enantiomerically pure (+)-(*S*)-α-diethoxyphosphorylvinyl *p*-tolyl sulphoxide **991** (equation 530)[932].



(989) **(990)** (*S*)-(**991**) $[\alpha]_D$ +157

(530)

Reaction of arylsulphinylacetonitriles **992** with carbon disulphide in the presence of NaH and subsequent alkylation yield sulphinylketene dithioacetals **993** (equation 531)[933].



(992) **(993)** (531)

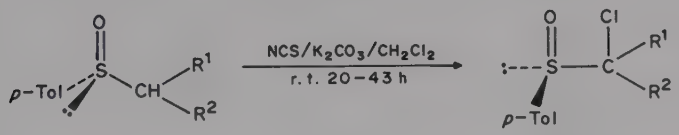
Ar	R	Yield (%)
Ph	H	74
Ph	Ph	48
Ph	CO_2Me	47
p-ClC_6H_4	COPh	10
Ph	$—(CH_2)_2—$[a]	50
Ph	$—(CH_2)_3—$[a]	14

[a] RR

*B. Introduction, Substitution, Transformation and Elimination of Heteroatomic Groups at Organic Substituents in Sulphoxides

*1. α-Halogenation of sulphoxides

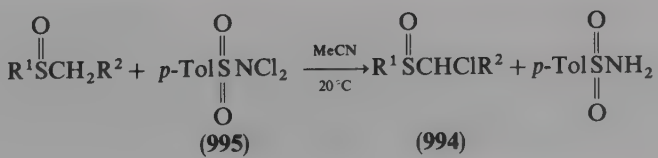
To a great variety of methods of α-halogenation of sulphoxides two new improved procedures have recently been added. Thus, optically active alkyl *p*-tolyl sulphoxides have been chlorinated with *N*-chlorosuccinimide (NSC) in the presence of K_2CO_3 in CH_2Cl_2 to give 1-chloroalkyl *p*-tolyl sulphoxides **994** with high stereoselectivity. Crystallization of enaniomerically enriched samples allows one to obtain pure enantiomers of **994** (equation 531)[934].



(994) (531)

	R^1	R^2	Yield (%)	e.e. (%)	remarks
a	H	H	91	87	
b	H	Me	94	93	(3:1 diast. mixt.)
c	H	CH_2Ph	88	87	(6.6:1 diast. mixt.)
d	Me	Me	92	94	

When *N*,*N*-dichloro-*p*-toluenesulphonamide **995** is used as a chlorinating agent, a variety of α-chloro sulphoxides are obtained from the corresponding sulphoxides. The reaction is performed under mild and neutral conditions and exhibits a high regioselectivity of monochlorination at the α-position of sulphoxides (equation 532, Table 83)[935].

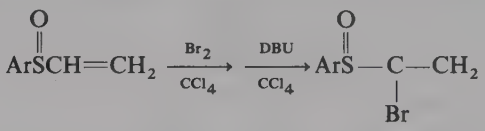


(995) (994) (532)

TABLE 83. Chlorination of sulphoxides with *N,N*-dichloro-*p*-toluenesulphonamide **995**

R^1	R^2	Time (h)	**994** Yield (%)
Me	H	10	80
n-Pr	Et	10	94
p-An	H	5	98
Ph	H	5	91
p-ClC_6H_4	H	5	95
p-$O_2NC_6H_4$	H	10	92
β-Naph	H	5	93
p-Tol	Me	5	93
p-ClC_6H_4	Me	5	91
p-BrC_6H_4	Et	5	89
Et	Ph	5	81
$PhCH_2$	Ph	5	70

α-Bromovinyl sulphoxides **996** have been obtained by treating vinyl sulphoxides with bromine and subsequent hydrogen bromide elimination (equation 533)[825].

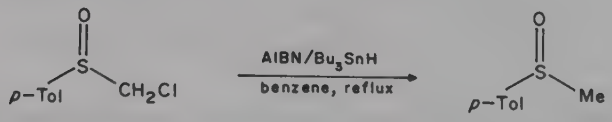


(533)

(996)

**2. Substitution of heteroatomic groups by hydrogen atoms*

(*R*)-Chloromethyl *p*-tolyl sulphoxide **994a** has been quantitatively and without racemization at sulfur reduced to methyl *p*-tolyl sulphoxide under free-radical conditions (equation 534)[936].

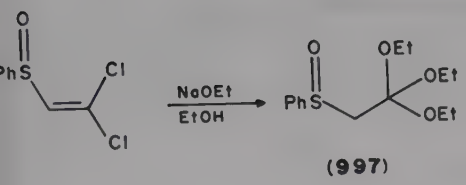


(534)

(*R*)-(994a)

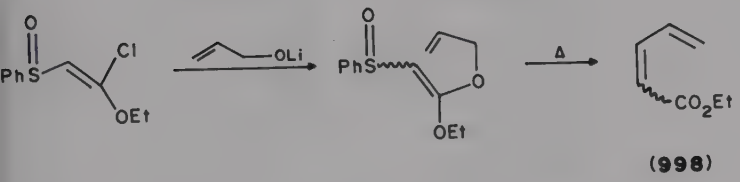
**4. Nucleophilic substitution in halogenosulphoxides having a halogen atom in another position.*

β-Chlorovinyl sulphoxides react with alkoxy anions to give the products of a formal substitution[937]. However, they are most probably formed via a nucleophilic addition–elimination process. In some cases the products of a final 1,4-addition are obtained, e.g. sulphinyl orthoesters **997** (equation 535)[937a]. When allylic (equation 536 a)[937a] or propargylic (equation 536 b)[937b] alkoxides are used, the conjugate dienoate esters **998** or 4-oxo-2-alkenoate esters **999** are obtained, respectively.



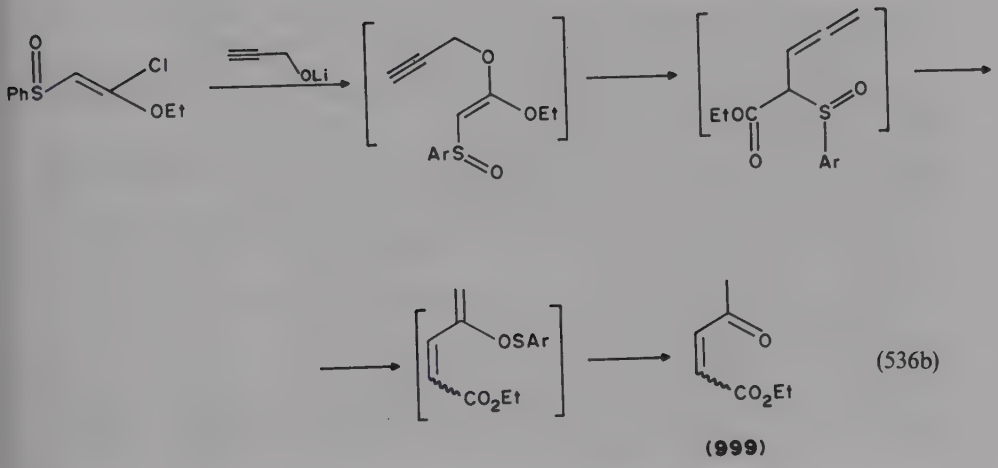
(535)

(997)



(536a)

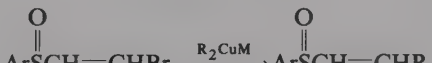
(998)



(536b)

(999)

β-Bromovinyl aryl sulphoxides **1000** react with organocuprates to give the products **1001** of cross-coupling reactions (probably also according to the addition–elimination mechanism) (equation 537, Table 84)[938].



(537)

(1000) (1001)

*7. *Reduction of β-oxosulphoxides*

Recently, the reduction of β-oxosulphoxides to β-hydroxysulphoxides has attracted much interest, mainly due to the fact that the use of proper reducing agents allows for a highly stereoselective synthesis of the desired diastereoisomeric products. Particularly important reducing agents are *i*-Bu_2AlH (DIBAL) and the DIBAL/$ZnCl_2$ system, each of

TABLE 84. Reaction of β-bromovinyl sulphoxides with organocuprates [938]

Ar	Olefinic bond configuration in **1000**	R_2CuM	Temp. (°C)	*E*/*Z* ratio	Product yield (%)
Ph	*E*	*n*-Bu_2CuLi	−5	80:2	65
Ph	*E*	*n*-$Bu_2CuMgBr$	0	100:2	71
Ph	*Z*	*n*-Bu_2CuLi	−5	25:75	70
Ph	*Z*	*n*-$Bu_2CuMgBr$	0	10:90	64
Ph	*E*	Ph_2CuLi	−5	100:0	35
Ph	*E*	$Ph_2CuMgBr$	0	100:0	54
Ph	*Z*	Ph_2CuLi	−5	80:20	51
Ph	*Z*	$Ph_2CuMgBr$	0	100:0	52
Ph	*Z*	$Ph_2CuMgBr$	−80	50:50	—
2-Naph	*Z*	*n*-$Bu_2CuMgBr$	0	0:100	63
2-Naph	*Z*	*s*-$Bu_2CuMgBr$	0	0:100	69

them leading to the opposite epimer of β-hydroxysulphoxide (see equation 321). These reagents have been simultaneously introduced by Solladie[616] and Kosugi[939].

The detailed studies on the stereoselectivity of the reduction of acyclic and cyclic, six-membered β-oxosulphoxides with various reducing agents[940] have led to the following general mechanistic conclusions:

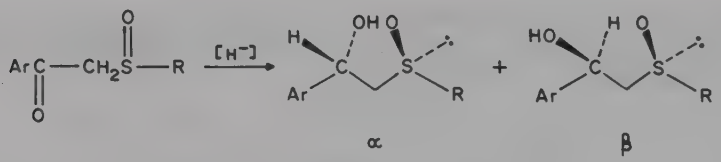
(i) When DIBAL is used as a reducing agent, the hydride transfer takes place intramolecularly from the pre-formed Al—O=S associate, the high stereoselectivity being determined by the relative stability of the chair-like transition states.

(ii) In the presence of $ZnCl_2$ a chelated species is formed from $ZnCl_2$ and β-oxosulphoxide. The hydride transfer occurs in this case intermolecularly in the half-chair conformation adopted by this species.

(iii) The reduction with $LiAlH_4$ involves a lithium chelate, to which hydride is intramolecularly transferred from associated AlH_4^-.

(iv) A very important role is played by the lone electron pairs of the sulphinyl oxygen and sulphur in controlling the approach of all hydrides.

The results of the reductions of acyclic β-oxosulphoxides (equation 538) are collected in Table 85 (in the case of cyclic compounds the results are too spacious to be presented here).

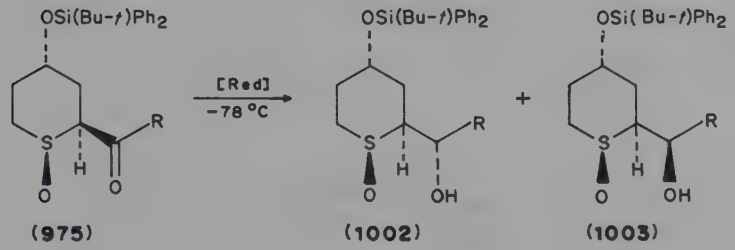


(538)

TABLE 85. Reductions of β-oxosulphoxides[940]

Ar	R	α:β					
		n-Bu_4NBH_4	$NaBH_4$	$LiBH_4$	*i*-Bu_2AlH	*i*-$Bu_2AlH/ZnCl_2$	$LiAlH_4$
Ph	*p*-Tol	51:49	59:51	43:57	>95:5	<5:95	16:84
Ph	Me	43:57	55:45	47:53	84:16	20:80	36:64
2-Pyr	Me	44:56	50:50	50:50	92:8	49:51	40:60
2-Pyr	*p*-Tol	50:50	56:44	33:67	100:0	56:44	44:56
2-Pyr	*P*-Tol	50:50	48:52	43:57	100:0	50:50	33:67

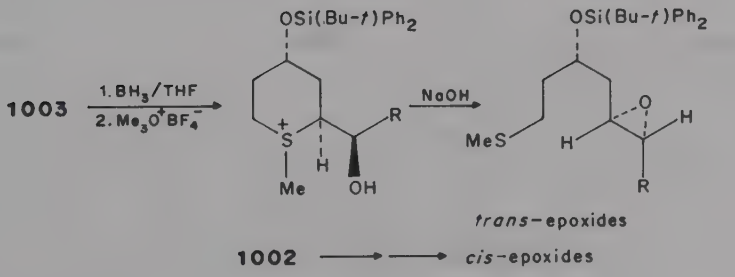
Cyclic β-oxosulphoxides **975** have been reduced with DIBAL and the DIBAL/$ZnCl_2$ system to give opposite epimers of β-hydroxy sulphoxides **1002** and **1003**, in some cases with a very high diastereoselectivity (equation 539, Table 86)[920]. The pure diastereoisomers have been stereoselectively transformed into epoxides (equation 540).



(975) (1002) (1003) (539)

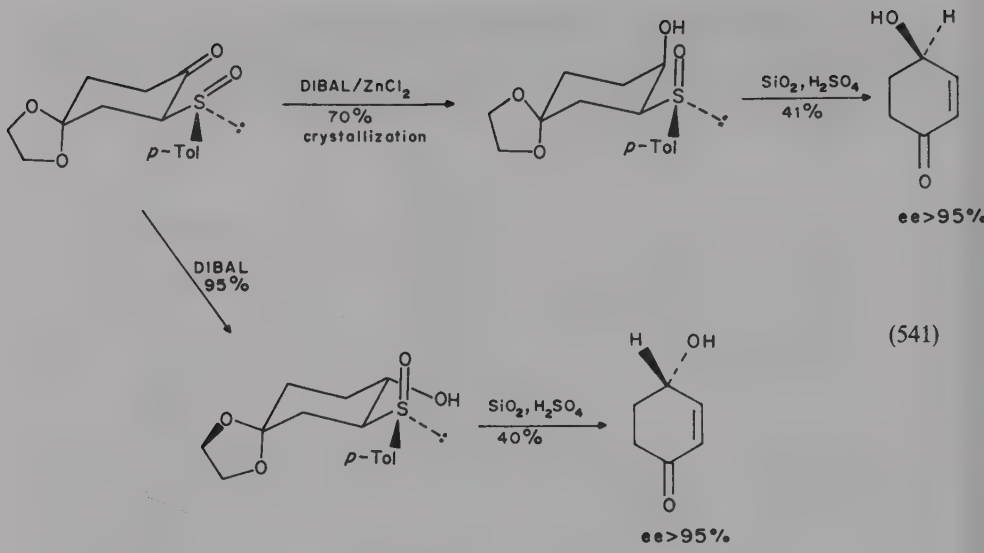
TABLE 86. Reduction of β-oxosulphoxides **975**

R	[Red]	Yield (%)	**1002**:**1003** ratio
Me	DIBAL	57	1:1.6
Me	DIBAL/$ZnCl_2$	67	0:100
t-Bu	DIBAL	88	100:0
t-Bu	DIBAL/$ZnCl_2$	65	0:100
Et	DIBAL	72	1.9:1
Et	DIBAL/$ZnCl_2$	75	0:100
i-Pr	DIBAL	50	100:0
i-Pr	DIBAL/$ZnCl_2$	60	0:100
Ph	DIBAL	—	unsuccessful
Ph	DIBAL/$ZnCl_2$	74	0:100



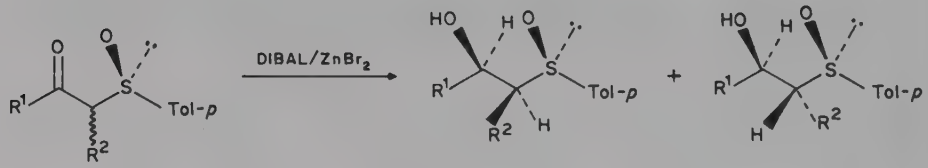
(540)

Stereoselective reduction of cyclohexanone sulphoxide has been used for the synthesis of both enantiomers of 4-hydroxy-2-cyclohexenone (equation 541)[941].



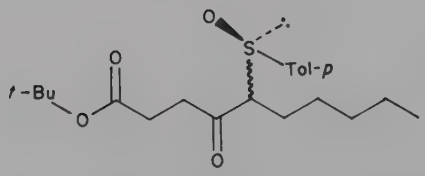
(541)

Garcia Ruano and coworkers have found that the highly stereoselective reduction of chiral α-alkyl-β-oxosulphoxides **1004** with the DIBAL/$ZnBr_2$ system is governed by the configuration at sulphur (1,3-induction) and not by that of the α-carbon, since the reduction gives usually only two diastereoisomers **1005** and **1006** in a ratio identical with that of the starting β-oxosulphoxide (equation 542)[942]. In fact, the stereochemical stability of the chiral centre at the α-carbon atom must be very low due to a high acidity of the α-hydrogen atom, which was observed by Bravo and collaborators on *t*-butyl-4-oxo-5-*p*-tolylsulphinyl decanoate **1007**[943].



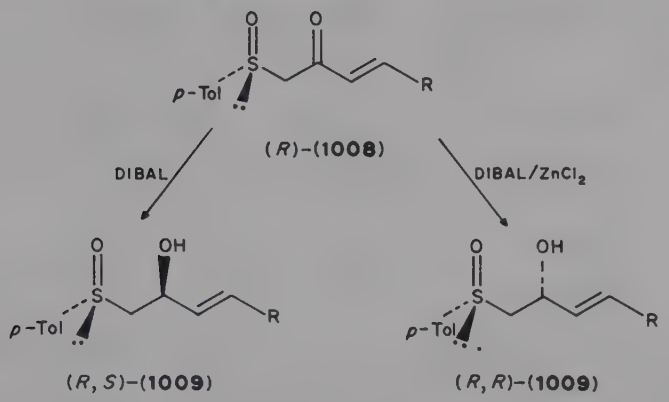
(1004) **(1005)** **(1006)**

(542)



(1007)

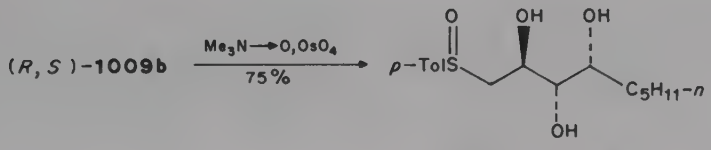
Optically active allylic β-hydroxysulphoxides **1009** are particularly interesting because of a possible double hydroxylation leading to vicinal triols. They have been obtained with very high diastereoselectivity from corresponding allylic β-oxosulphoxides **1008** (equation 543)[917].



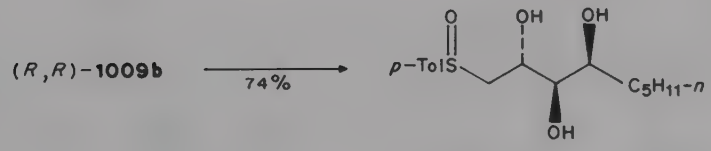
(543)

	DIBAL		DIBAL/$ZnCl_2$	
R	RS/RR	Yield (%)	RS/RR	Yield (%)
(a) Me	94:6	91	<5:>95	90
(b) n-C_5H_{11}	93:7	96	<5:>95	97
(c) Ph	>95:5	95	<5:>95	95

The sulphoxides **1009** have been found to undergo *cis*-hydroxylation with very high asymmetric induction to give triols of high diastereoisomeric purity (eqyatuibs 544 and 545)[917].



(544)



(545)

This method has been used for the synthesis of arabinitol[944,945] and the C-1/C-12 unit of amphotericin B[946].

(*R*)-β,δ-Dioxosulphoxides **1010** have been reduced with DIBAL to give (S_2,R_S)-δ-oxo-β-hydroxysulphoxides **1011** with almost full diastereoselectivity (equation 546)[947].

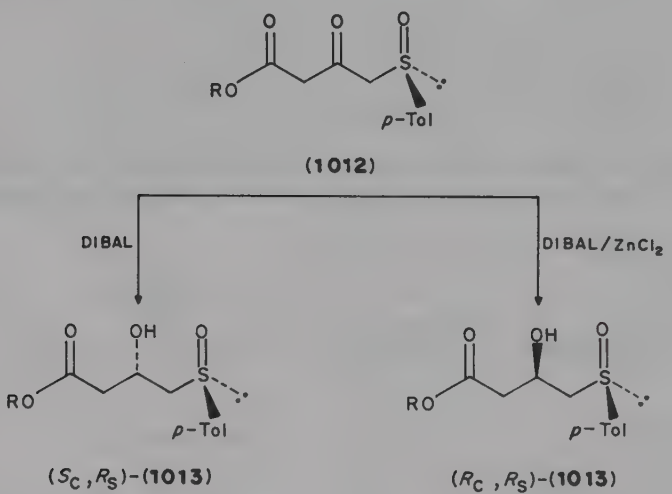
(546)

(*R*)-(**1010**) (S_C,R_S)-(**1011**)

R	Yield (%)	$[\alpha]_D$	d.e. (%)
Me	85	+243	>99
EtO_2CCH_2	80	+169	>98
Ph	80	+160	>98
$CH_3CH{=}CH$	70	+162	>98

The δ-oxo group has been reduced with tetramethylammonium triacetoxyborohydride to give stereoselectively the *anti* diol.

In turn, methyl and *t*-butyl 3-hydroxy-4-*p*-tolylsulphinylbutyrates **1013** have been prepared by stereoselective reduction of (*R*)-3-oxo-4-*p*-tolylsulphinylbutyrates **1012** (equation 547)[984].



(547)

(S_C,R_S)-(**1013**) (R_C,R_S)-(**1013**)

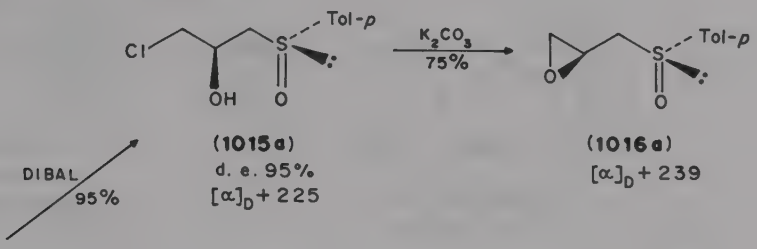
R	Yield (%)	$[\alpha]_D$	d.e. (%)
Me	69	+224	>95
t-Bu	78	+191	>95

R	Yield (%)	$[\alpha]_D$*	d.e. (%)
Me	60	+160	78
t-Bu	68	+126	90

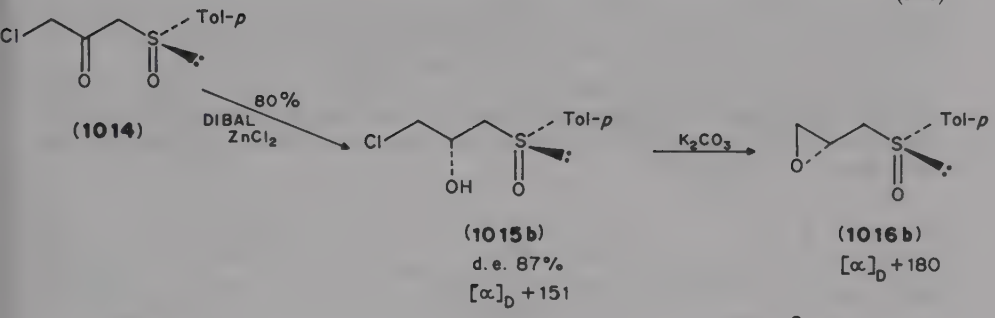
* after recrystallization

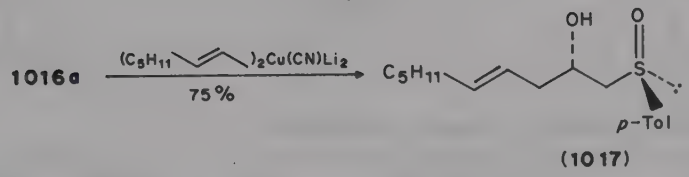
γ-Halo-β-oxosulphoxides can also be effectively reduced with DIBAL and DIBAL/$ZnCl_2$. Thus, optically active γ-chloro-β-oxopropyl *p*-tolyl sulphoxide **1014** gives either of

two diastereoisomeric hydroxy sulphoxides **1015** when treated with DIBAL or DIBAL/$ZnCl_2$. The latter have then been transformed into optically active β-sulphinyl oxiranes **1016** which, in turn, are opened with cuprates to give unsaturated β-hydroxy sulphoxides **1017** (equations 548 and 549)[949].



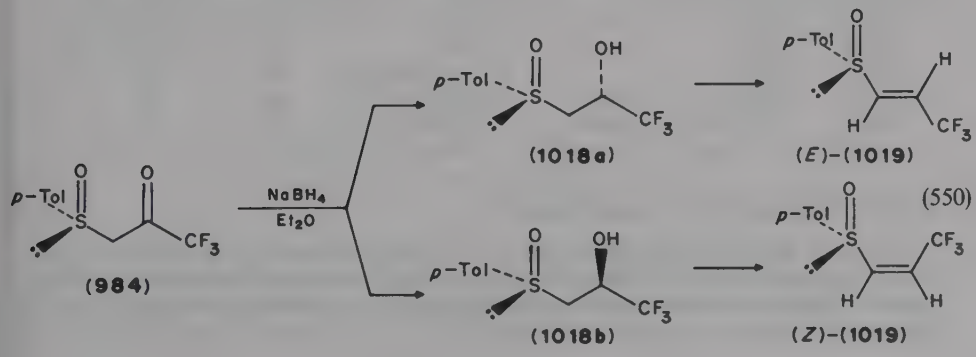
(548)





(549)

The perfluoro derivatives, e.g. **984**, when reduced with borohydrides give the corresponding hydroxy sulphoxides **1018** with low-to-moderate stereoselectivity (diast. ratio 70:30 to 85:15)[926, 928, 950]. This is due to the fact that compounds of type **984** exist in both the keto and hydrated forms. They have been, however, converted stereoselectively into β-trifluorovinyl sulphoxides (equation 550)[927].



(550)

However, when the difluoro compounds **983** are reduced with DIBAL, only (S_C,R_S) alcohols **1020** are produced (equation 551)[925]. Similar results are obtained in the case of the corresponding monofluoro derivatives[951].

(551)

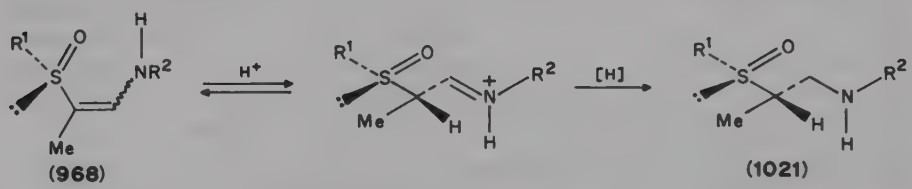
(983) **(1020)**

R = Me, yield 86%
R = Ph, yield 89%

(optically pure)

A highly diastereoselective reduction of β-oxosulphoxides has been widely used for the synthesis of natural products, for example, leukotriene B_4[952], butanolides[953], (*R*,*R*)-pyrenophorin and (*R*)-patulolide[954], (−)-(*R*)-yashabushiketol[955] and others.

Reduction of β-sulphinyl enamines **968** with borohydrides in aqueous ethanol solution results in the formation of two diastereoisomers of β-aminosulphoxides **1021** in comparable amounts. However, in the presence of acid a pronounced stereoselectivity is observed (equation 552, Table 87)[956].



(968) **(1021)**

(552)

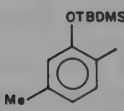
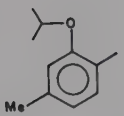
TABLE 87. Reduction of β-sulphinyl enamines **968**

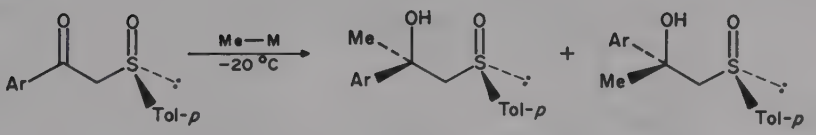
R^1	R^2	Borohydride	Acid	Yield (%)	d.e. (%)
Me	*t*-Bu	$NaBH_4$	AcOH	87	70
Ph	*t*-Bu		AcOH	92	42
p-Tol	*t*-Bu		AcOH	98	62
t-Bu	*t*-Bu		AcOH	93	31
p-Tol	$PhCH_2$		AcOH	90	54
p-Tol	$PhCH_2$		TFA	48	22
Ph	*t*-Bu		TFA	92	77
p-Tol	*t*-Bu		TFA	64	92
Ph	*t*-Bu		Ph_2CHCO_2H	90	59
p-Tol	$PhCH_2$	$Zn(BH_4)_2$	AcOH	94	34
p-Tol	$PhCH_2$	Bu_4NBH_4	AcOH	75	30

8. Other transformation of β-oxosulphoxides

Normally, when methyllithium is added to a β-oxosulphoxide, no methylation takes place owing to enolization. However, the diastereofacially controlled addition of a methyl group to optically active β-oxosulphoxides has been achieved by using special organometallic reagents (equation 553, Table 88)[957].

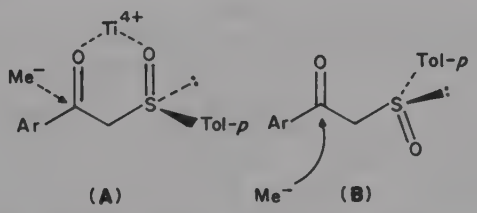
TABLE 88. Addition of organometallics to the carbonyl group in β-oxosulphoxides[957]

Ar	Me—M	Solvent	Yield of **1022** (%)	Ratio $(R_S,R_C):(R_S,S_C)$
Ph	$MeTiCl_3$	Et_2O	79	82:18
Ph	Me_3Al	PhMe	66	26:74
Ph	$MeMgBr–CeCl_3$	PhMe	30	16:84
p-Tol	$MeTiCl_3$	Et_2O	60	80:20
p-Tol	Me_3Al	PhMe	50	16:84
	$MeTiCl_3$	Et_2O	96	97:3
	Me_3Al	PhMe	71	13:87
	$MeMgBr/CeCl_3$	PhMe	36	34:66
	$MeTiCl_3$	Et_2O	77	94:6
	Me_3Al	PhMe	48	4:96

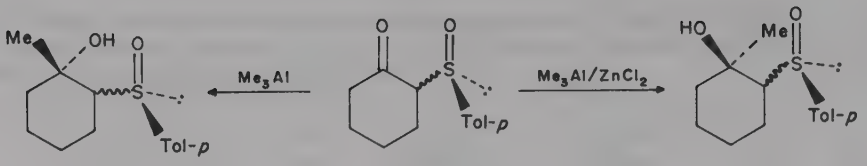


(553)

The different stereochemistry is explained in terms of different conformations of the β-oxosulphoxide depending on the nature of the alkylating reagent. In the presence of titanium chloride the β-oxosulphoxide adopts the chelated conformation **A** and the nucleophilic addition occurs from the less hindered lone pair side (*si* face) of the sulphoxide. Trimethylaluminium attacks from the *re* face in the conformation **B** caused by dipolar interactions[957].



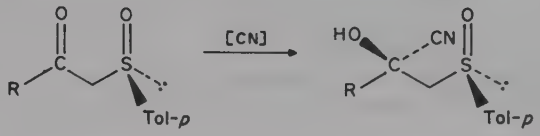
A similar effect is observed when, instead of titanium derivatives, a $Me_3Al/ZnCl_2$ system is applied (equation 554)[958].



(1023) (554)

Secondary and tertiary hydroxy sulphoxides, obtained by reduction of **1023**, and by Me_3Al addition to **1023**, respectively, have been used as chiral catalysts in the enantioselective addition of diethylzinc to benzaldehyde to give products with moderate e.e. values (up to 55%)[959].

Reaction of β-oxosulphoxides with cyanodiethylaluminium affords cyanohydrins **1024** with diastereoisomeric excess $\geq 96\%$. The newly created chiral centre is controlled only by the sulphur configuration (1,3-induction) (equation 555)[960, 961].



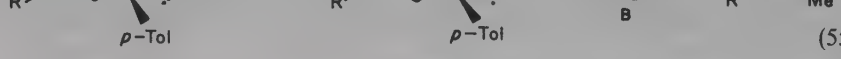
(555)

(R)-(465) **(1024)**

d.e. 96%

R	Yield of **1024** (%)		
	Et_2AlCN	Et_2AlCN/ZnX_2	Et_2AlCN/MgX_2
Ph	87	87	90
Et	85	86	89
t-Bu	87	92	90

Optically pure β-iminosulphoxides **1025** are obtained from the reaction of chiral β-oxosulphoxides with amines or by condensation of the imine α-carbanions with (−)-menthyl *p*-toluenesulphinate (equation 556)[962].

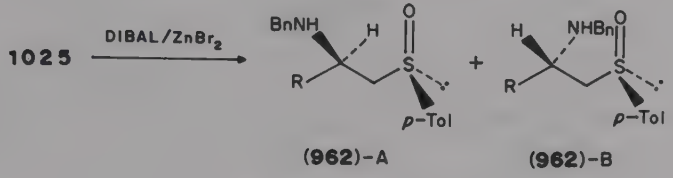


(556)

(R)-(465) **(1025)**

R	Yield (%)	
	Method A	Method B
Me	94	83
n-Pr	90	75
i-Pr	55	81
t-Bu	55	40
Ph	65	92

The DIBAL/$ZnBr_2$ reduction of **1025** gives β-amino sulphoxides **962** with very high diastereoselectivity (equation 557)[962] (*cf* synthesis of β-aminosulphoxides **962** by amino-alkylation of sulphinyl carbanions, equation 509, and of **1021** by reduction of enamines, equation 552).



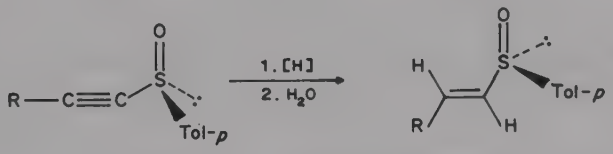
(557)

(962)-A (962)-B

R	Yield (%)	A:B ratio
Me	80	>97:<3
n-Pr	72	>97:<3
i-Pr	82	>97:<3
t-Bu	15	>97:<3
Ph	75	>97:<3

9. Hydrogenation of unsaturated sulphoxides

Hydroalumination of acetylenic sulphoxides **1026** proceeds in a fully stereoselective manner to afford optically pure (*E*) vinyl sulphoxides **1027** (equation 558, Table 89)[963,964]. When the Wilkinson catalyst, $RhCl(PPh_3)_3$, is used for catalytic hydrogenation, (*R*)-(−)-(*Z*) isomers are produced almost quantitatively[964].



(558)

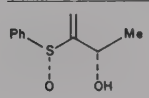
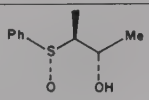
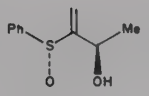
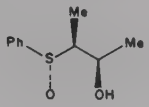
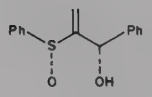
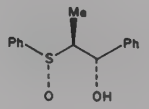
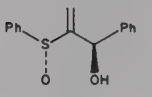
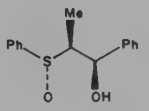
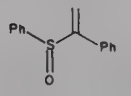
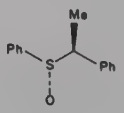
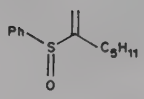
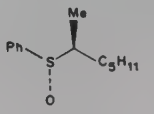
(1026) (1027)

Rhodium-complex catalysed directed hydrogenation of (α-hydroxyalkyl)vinyl sulphoxides gives the saturated products in high yields (up to 100%) and with very high diastereoselectivity (Table 90). Hydrogenation of these sulphoxides is directed by the S=O coordination (unlike in the case of sulphones where the H—O coordination is more important)[965].

TABLE 89. Hydroalumination of acetylenic sulphoxides **1026**

R	Yield of **1027** (%) DIBAL	$LiAlH_4$	$[\alpha]_D$
n-Pr	84	87	+177.9
n-Bu	87	94	+158.2
n-C_5H_{11}	88	95	+148.2
n-C_6H_{13}	81	94	+138.2

TABLE 90. Hydrogenation of (α-hydroxyalkyl)vinyl sulphoxides

Substrate	Product	Diastereoisomeric excess (%)
		99
		98
		99
 *for comparison*		97
		99.5
		93

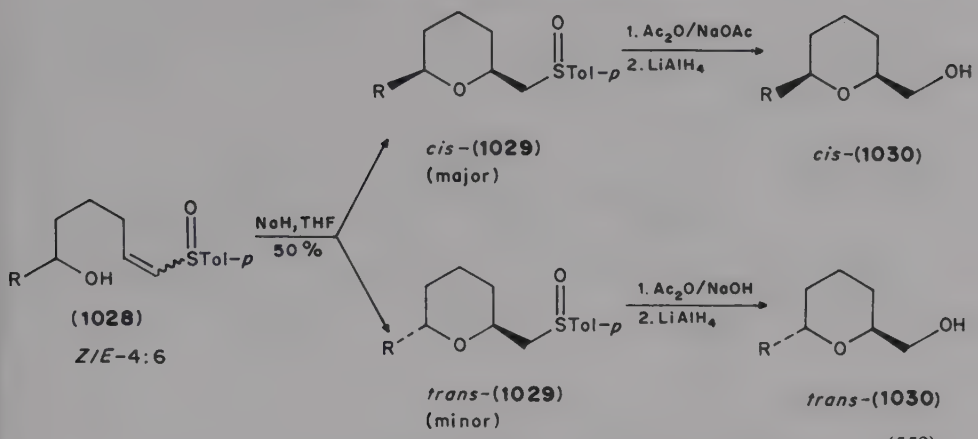
*C. Additions to Unsaturated Sulphoxides

*2. Nucleophilic additions

*a. *Addition of heteroatomic nucleophiles.* The intramolecular 1,4-addition of the alcoholic group to the α,β-unsaturated sulphoxide in compound **1028** proceeds in a highly stereoselective manner to give *cis*-2,6-disubstituted pyranes **1030**. The reaction gives best results under thermodynamically controlled conditions (equation 559)[966]. This method has been used for the synthesis of dioxospirodecanes[967]. The ω-hydroxy allenyl sulphoxide **1031** undergoes intramolecular addition of the hydroxy group across the α,β-double bond to give the pyran derivative **1032**. Its subsequent transformations yield the spiroketal **1033** (equation 560)[968].

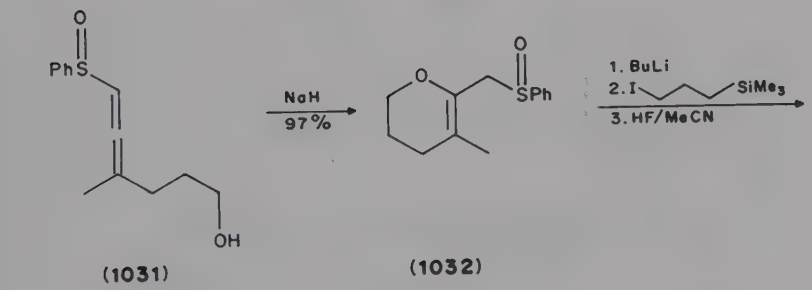
The kinetically controlled conjugate addition of benzylamine to isomeric *E* and *Z* vinyl sulphoxides **1034** is a diastereoconvergent process and gives the same major diastereoisomeric adduct (equation 561)[969].

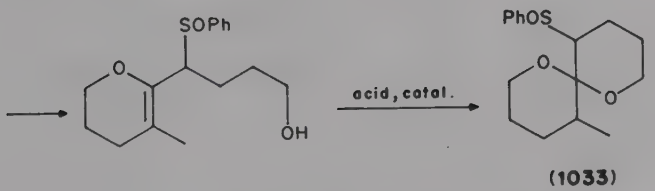
On the contrary, the intramolecular addition of amines to vinyl sulphoxides **1037** proceeds in the same diastereofacial sense for *E* and *Z* sulphoxides and hence leads to different diastereoisomers in each case (equation 562)[970].



(559)

R	*cis*:*trans* **1030**	Yield *cis* + *trans* **1030** (%)
PhCH=CH	18:1	78
n-C_5H_{11}	35:1	80
MeCH=CH	25:1	60
Ph	71:1	83

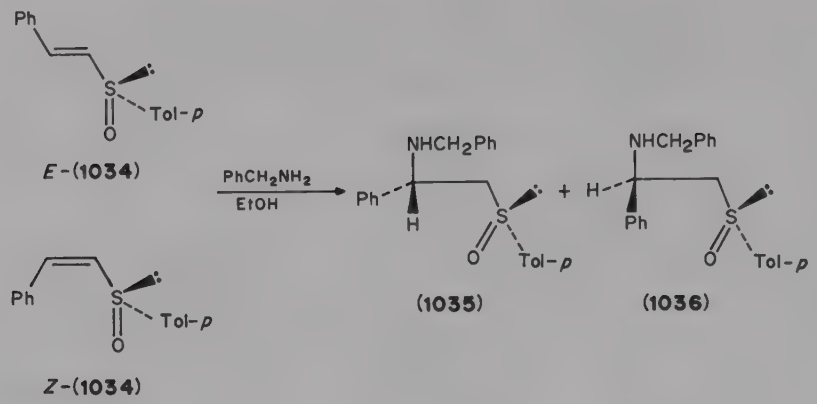




(560)

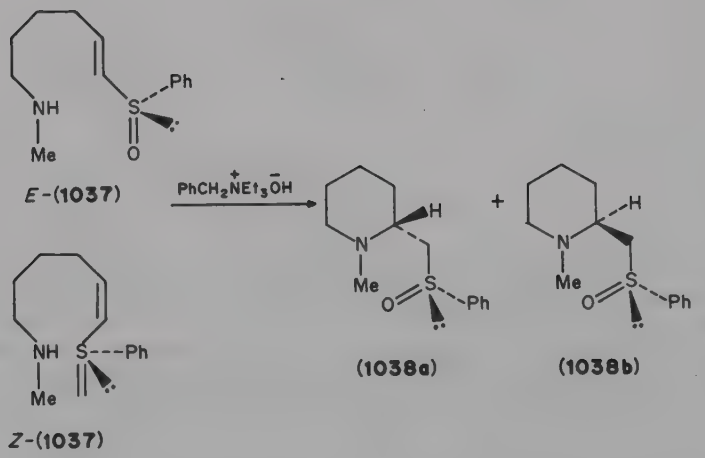
Similar behaviour has been observed in the conjugate intramolecular addition of the amido group to vinyl sulphoxide moiety in **1039** (equation 563)[971].

Synthesis of the enantiomerically pure *Z*-2-haloalkenyl sulphoxides **1040** has been achieved by the addition of the halide anion to acetylenic sulphoxides **1026** (equation 564, Table 91)[972].



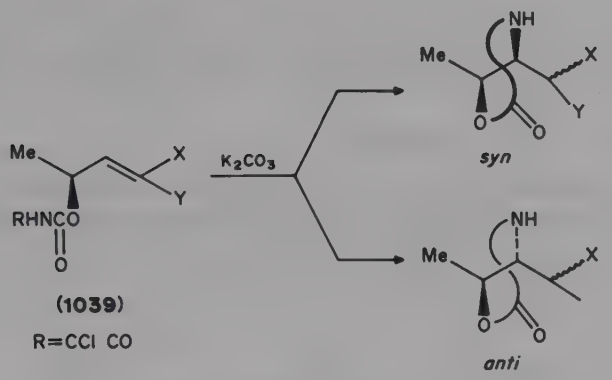
(561)

Substrate	Product ratio **1035**:**1036**
E-**1034**	87:13
Z-**1034**	85:15



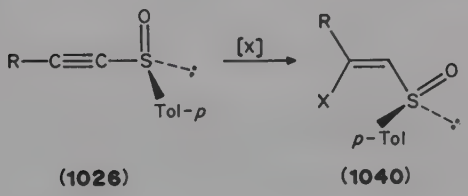
(562)

Substrate	Product ratio **1038a**:**1038b**
E-**1037**	91:9
Z-**1037**	16:84



(563)

Substrate	X	Y	Ratio *syn*:*anti*	Yield (%)
1039a	S(O)Ph (*S*)	H	3.3:1	81
1039b	S(O)Ph (*S*)	H	23:1	93
1039c	H	S(O)Ph (*S*)	110:1	98
1039d	H	S(O)Ph (*S*)	20:1	100



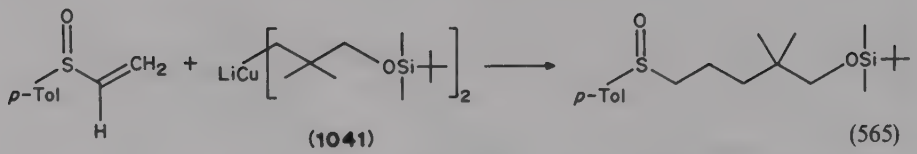
(1026) (1040)

(564)

TABLE 91. Synthesis of *Z*-2-haloalkenyl sulphoxides **1040**

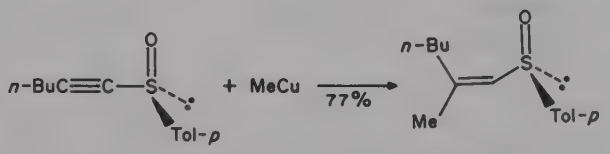
R	[X]	X	Product yield (%)	$[\alpha]_D$
H	ZnI_2	I	87	−483.3
H	$ZnBr_2$	Br	75	−473.5
H	$ZnCl_2$	Cl	83	−453.9
n-Bu	NaI/AcOH	I	82	−294.5
H	NaI/AcOH	I	87	−477.4

b. Michael additions to α,β-unsaturated sulphoxides.* Organocopper reagents have been widely used as the Michael donors in the conjugate addition to α,β-unsaturated sulphoxides. Thus, it is necessary to use the cuprate **1041 to achieve the desired Michael addition to *p*-tolyl vinyl sulphoxide (the lithio derivative gives the product of substitution at sulphur) (equation 565)[862].



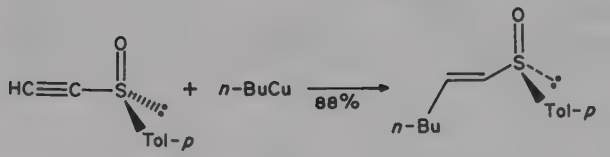
(565)

Acetylenic sulphoxides undergo a facile 1,4-conjugate addition with organocopper reagents in a stereoselective manner (*cis*-addition) to give vinyl sulphoxides (equations 566 and 567)[963].



(566)

Z; $[\alpha]_D$ +260



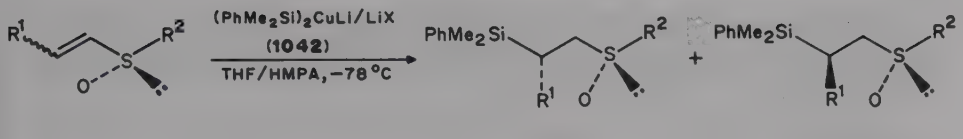
(567)

E, $[\alpha]_D$ +154

The use of bis(dimethylphenylsilyl)cuprate **1042** in the Michael addition to vinyl sulphoxides allows for asymmetric carbon–silicon bond formation, in moderate-to-good diastereoselectivity. It should be emphasized that both *E* and *Z* vinyl sulphoxides give the same total yield of products but with opposite diastereoisomer ratios (equation 568, Table 92)[973].

TABLE 92. Michael addition of silylcuprate **1042** to vinyl sulphoxides

R^1	R^2	Total yield (%)	Product ratio **1043**:**1044**	
H	Ph	70	—	
(*E*) Me	Ph	48	88:12	
(*Z*) Me	Ph	47	6:94	
(*E*) *n*-C_5H_{11}	Ph	82	80:20	
(*Z*) *n*-C_5H_{11}	Ph	73	25:75	
(*E*) Ph	Ph	72	79:21	
(*Z*) Ph	Ph	67	20:80	
(*E*) *n*-C_5H_{11}	*p*-Tol	67	75:25	optically active
(*Z*) *n*-C_5H_{11}	*p*-Tol	70	20:80	
(*E*) Ph	*p*-Tol	78	85:15	
(*Z*) Ph	*p*-Tol	70	23:77	

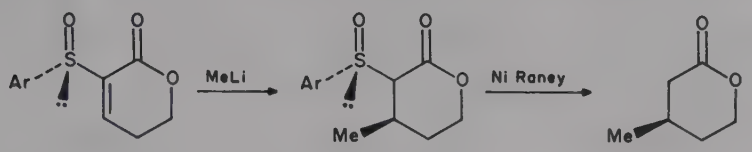


(1043) (1044)

(568)

For Michael addition to 1-silylethenyl sulphoxides see equation 507 and Table 81.

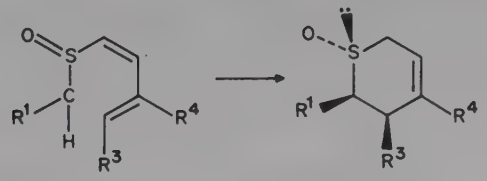
In many cases organolithium and organomagnesium derivatives have also been used as Michael donors. Thus, Michael addition of methyllithium to the sulphinyl lactone **1045** was the crucial step in the asymmetric synthesis of the sesquiterpene (−)-β-vetivone (equation 569)[974].



(1045) (569)

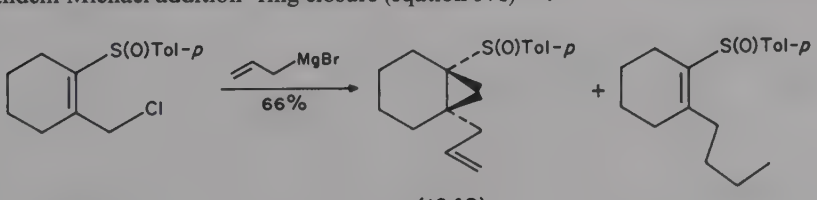
Ar	Yield (%)	e.e. (%)
p-Tol	44	95
p-Anisyl	51	93

A stereospecific cyclization of substituted α′-lithiated α(Z), γ-butadienyl sulphoxides **1046** leads to the formation of thiane-1-oxides **1047** (equation 570)[975].



(1046) (1047) (570)

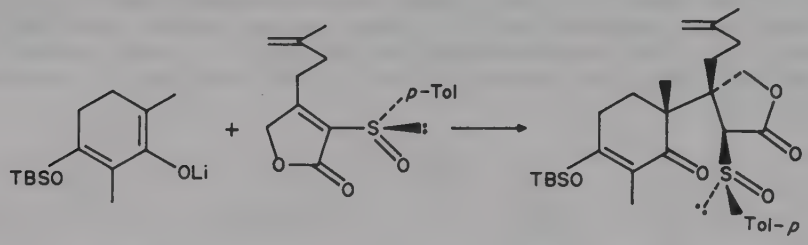
The vinyl sulphoxide **1048** gives, on treatment with 3 equivalents of allylmagnesium bromide, a single diastereoisomer of the cyclopropane derivative **1049**, as a result of a tandem Michael addition–ring closure (eqation 571)[976].



(1048) (1049) (571)

The solid–liquid phase transfer catalysis in the absence of any solvent has been found to promote Michael additions of nitroalkanes and of diethyl *N*-acetylaminomalonate to phenyl vinyl sulphoxide. The yields of products depend on the reaction conditions and are usually very high (up to 97%)[977].

Lithium enolate **1050** adds to (+)-(*S*)-sulphinyl butenolide **1051** to give a 7.4:1 mixture of diastereoisomeric sulphinyl lactones in 75% yield, from which **1052** was obtained in a pure form via crystallization (equation 572)[978] and used in the enantioselective total synthesis of Aphidicolin.



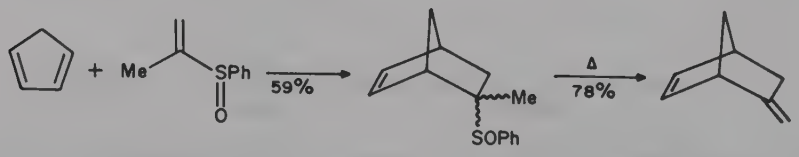
(1050) **(1051)** **(1052)**

$[\alpha]_{Hg}^{25} + 132$ (572)

*3. Cycloadditions

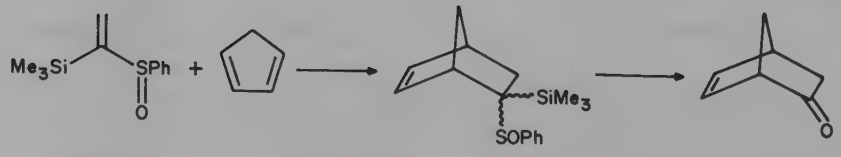
**a. Diels–Alder reactions.* In recent years the application of vinyl sulphoxides as dienophiles has been the subject of a great number of publications. The results have been exhaustively and critically reviewed[826,829,832,833]. For this reason only selected examples of general importance will be presented here.

Olefins substituted only with a sulphinyl moiety as a sole electron-withdrawing group are rather poor dienophiles. Nevertheless, α-methylvinyl phenyl sulphoxide **1053** and α-trimethylsilylvinyl phenyl sulphoxide **1054** have been successfully used as alkene[979] and ketene[980] equivalents, respectively, in the Diels–Alder reaction with cyclopentadiene (equations 573 and 574).



(1053) **(Ref. 979)**

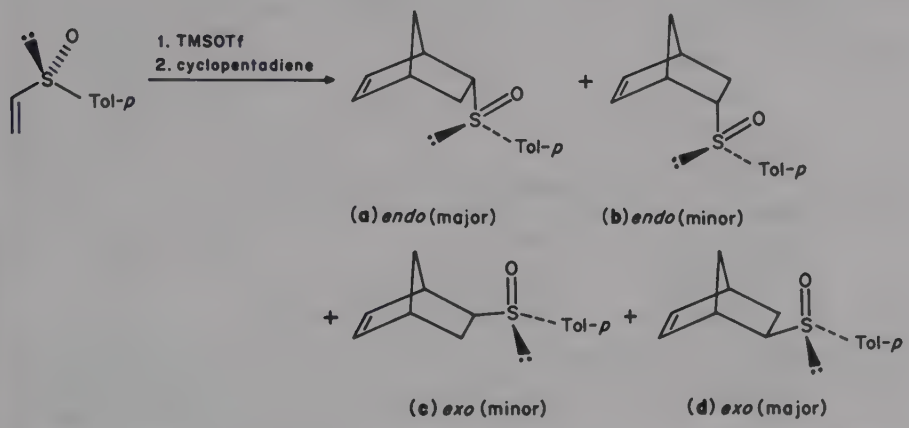
(573)



(1054) **(Ref. 980)**

(574)

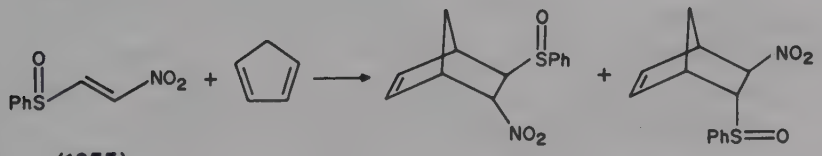
Recently, trimethylsilyl trifluoromethanesulphonate (TMSOTf) has been used as an effective catalyst in the cycloaddition of *p*-tolyl vinyl sulphoxide with cyclopentadiene to give mainly the *endo*-product in a good yield (equation 575)[981].



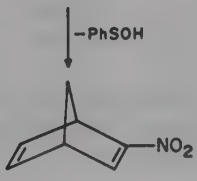
(575)

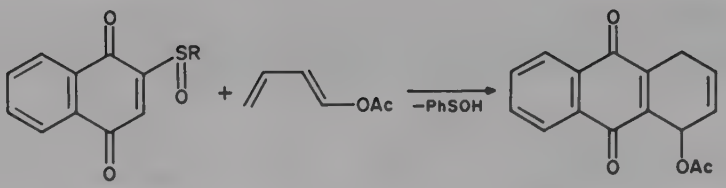
Mol. equiv.	Time	Total yield (%)	*Endo* d.e.	*Exo* d.e.	*Endo/Exo*
0.05	15	20	57	—	99:1
0.20	15	60	96	63	92:8
1.00	3	61	92	99	89:1

Regardless of the substituents, vinyl sulphoxides generally represent a synthetic equivalent of alkynes in the Diels–Alder reaction and therefore they are often used to introduce a moiety which would have to be obtained from substituted alkynes difficult of access. For example, instead of nitroacetylene, which is unstable, β-nitrovinyl phenyl sulphoxide **1055** can be used (equation 576)[982]. Similarly, the sulphoxide **1057** as a dienophile plays the role of the unknown naphthynoquinone **1056** (equation 577)[983].



(576)





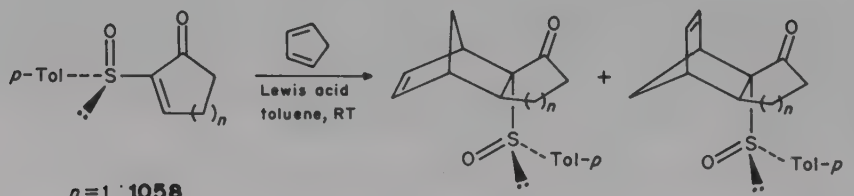
(1057)

(577)

(1056)

In order to enhance the dienophilicity of vinyl sulphoxides, additional electron-withdrawing groups are introduced to the molecule. This is particularly important in the case of optically active sulphoxides, since the transfer of chirality from sulphur to newly created asymmetric centres may be observed.

For example, the Diels–Alder reaction of optically active 2-*p*-tolylsulphinyl-2-cycloalkenones (C=O as the second electron-withdrawing group) with cyclopentadiene gives the corresponding cycloadducts with virtually complete diastereofacial selectivity, showing the outstanding efficiency of the *p*-tolylsulphinyl group as a chiral auxiliary. However, the *exo/endo* selectivity was only moderate (13–60% d.e.) (equation 578)[984].



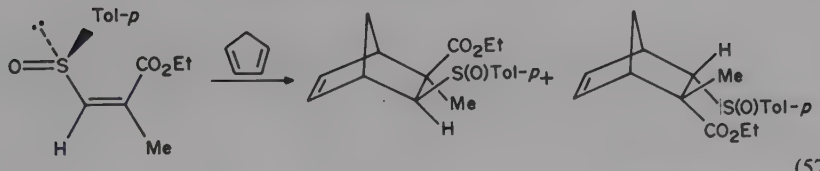
n=1 : **1058**
n=2 : **1059**

exo *endo*

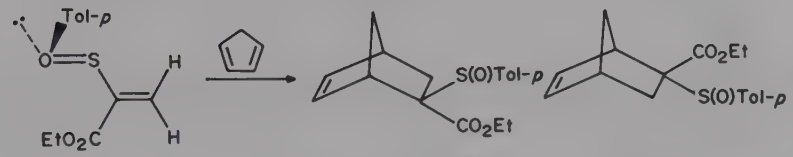
(578)

Dienophile	Lewis acid	Yield (%)	*exo/endo*
1058	$AlCl_3$	73	38/62
1059	$AlCl_3$	75	68/32
1058	$EtAlCl_2$	92	60/40
1059	$EtAlCl_2$	77	83/17
1059	$ZnBr_2$	25	57/43

Introduction of the ethoxycarbonyl function to the α or β position enhances the reactivity of vinyl sulphoxides and the selectivity of the cycloaddition (e.g. equations 579 and 580)[829].



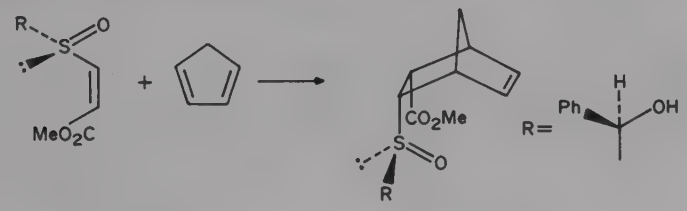
30% (100:0) 61% (95:5) (579)



(580)

r.t. 6h	75% (15:85)	25% (8:92)
0 °C 3 h $ZnCl_2$	79% (97:3)	21% (91:9)

Similarly, the Diels–Alder reaction of optically active β-hydroxy β′-carbomethoxyvinyl sulphoxide **1060** and cyclopentadiene proceeds highly stereoselectively and gives the product **1061** in 98% yield (equation 581)[758].



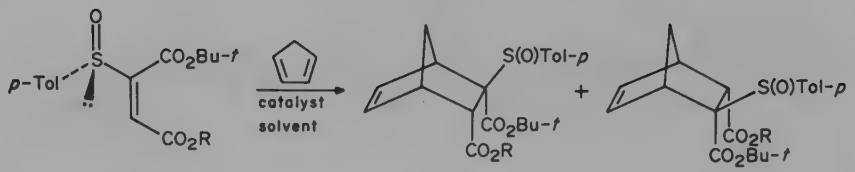
(581)

(1060) **(1061)**

A high reactivity towards cyclopentadiene was also observed when sulphinylmaleates **1062** are used as dienophiles. The *endo/exo* and facial selectivities depend on the solvent and catalyst used (equation 582, Table 93)[985].

TABLE 93. Cycloaddition of sulphinylmaleates to cyclopentadiene

Dienophile	Catalyst	T(°C)	Reaction time (h)	Products		
				1063 *endo*	**1064 endo**	*exo*
1062a	—	0	3	88	7	5
1062a	—	−20	12	91	5	3
1062a	$ZnBr_2$	−20	−20	complex mixture		
1062a	$BH_3 \cdot THF$	−10	20	84	9	7
1062a	$H_2O/NaHCO_3$	r.t.	28	30	47	—
1062b	—	r.t.	41	58	17	25
1062b	$ZnBr_2$	0	2	9	82	9
1062b	$ZnBr_2$	−20	7	6	89	5
1062b	$LiClO_4/Et_2O$	r.t.	4	31	48	21
1062b	$BF_3 \cdot Et_2O$	−20	7	43	37	20

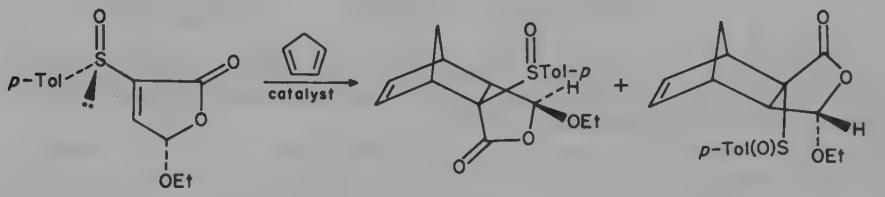


(1062) **(1063)**-*endo* **(1064)**-*endo* *exo*

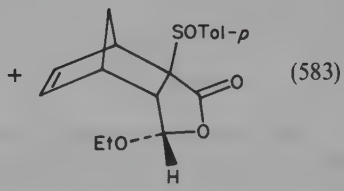
(a) R = H
(b) R = Me

(582)

Similarly, α-sulphinylbutenolides **1065** undergo cycloaddition with cyclopentadiene to give a mixture of diastereoisomers, the ratio of which depends on the catalyst applied (equation 583)[986].



(1065) **(1066)** **(1067)**

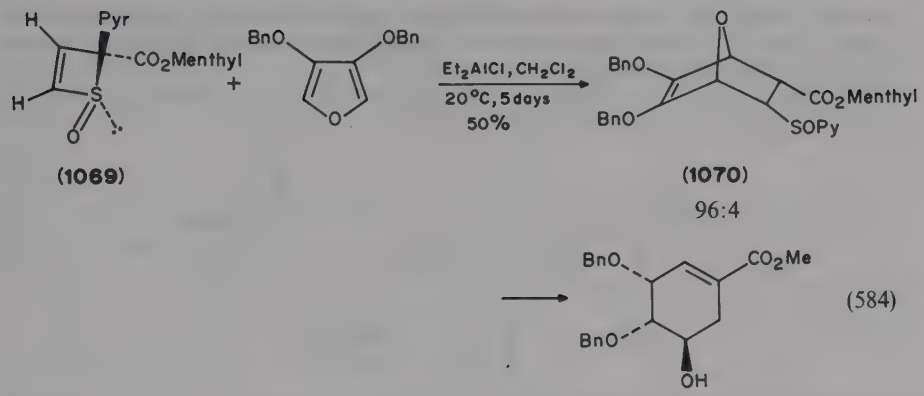


(1068)

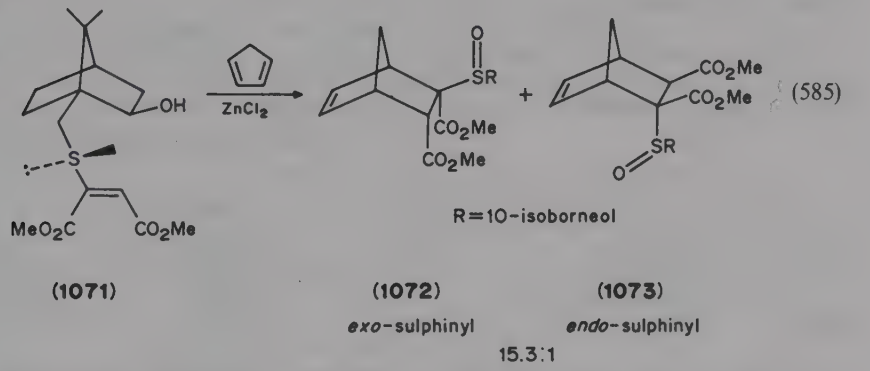
(583)

Catalyst	T(°C)	Adducts ratio		
		1066	**1067**	**1068**
—	r.t.	79	10	11
$ZnBr_2$	0	83	17	0
$Eu(fod)_3$	0	75	19	6
$TiCl_4$	−78	decomposition		

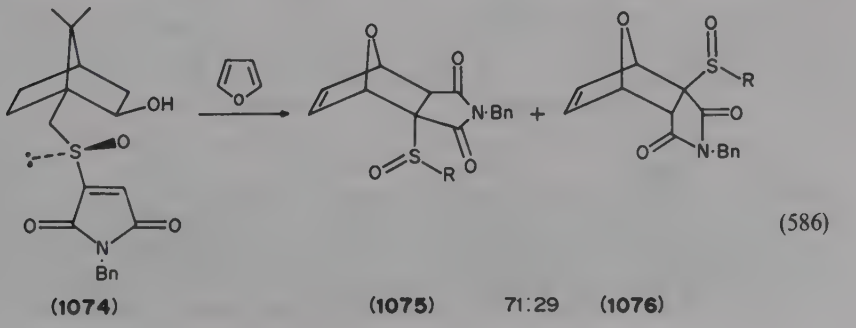
Remarkable interest has been devoted to the cycloadditions with furan, which is a much less reactive diene than cyclopentadiene (e.g. it does not react with **1062**). To achieve such a cycloaddition special substituents have been introduced to the vinyl sulphoxide moiety. For example, carbomethoxyvinyl pyridyl sulphoxide **1069** reacts smoothly with 3,4-dibenzyloxyfuran to give the cycloadduct **1070**, which has been used in the synthesis of (+)-methyl 5-epishikimate (equation 584)[987,988].



Recently, new types of vinyl sulphoxides containing the 10-isoborneol moiety as a chiral auxiliary have been introduced. The sulphinylmaleate **1071** containing the isoborneol group reacts with cyclopentadiene in the presence of Lewis acids with diastereoselectivities of *exo* and *endo* adducts equal to 100% and stereoselectivity *exo*:*endo* of 15.3:1 (equation 585)[989].

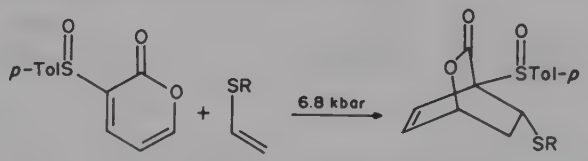


The sulphinylmaleimide **1074** containing the isoborneol group has been synthesized with the aim of improving reactivity of the vinyl sulphoxide, since the sulphinylmaleate **1071** has appeared to be entirely unreactive towards furan. As anticipated, **1074** reacts very



smoothly with furan (and, of course, also with cyclopentadiene). The product ratio depends on the reaction temperature: at 0 °C single diastereoisomers of both *endo* and *exo* sulphinyl adducts are produced (equation 586)[832,990].

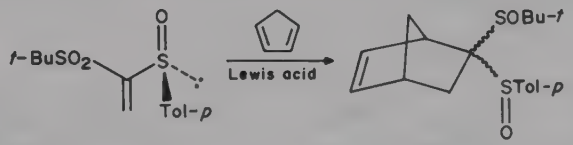
To achieve cycloaddition of pyrone sulphoxide **1077** with vinyl sulphides it is necessary to use a high-pressure technique (equation 587)[991].



(587)

(1077) R = Me yield 98%
R = Ph yield 73%

Other electron-withdrawing groups attached to the α-carbon atom of vinyl sulphoxides also enhance their reactivity. For example, α-*t*-butylsulphonylvinyl *p*-tolyl sulphoxide **971** reacts with cyclopentadiene in the presence of a catalyst to give the adducts in good yields and with high diastereoselection (equation 588)[916].



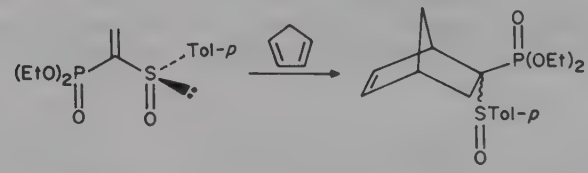
(588)

(971) **(1078)**

a + b + c + d (config. not given)

Lewis acid	Yield (%)	a:b:c:d
none	36	9:23:35:23
$ZnBr_2$	68	12:0:88:0
$Eu(fod)_3$	70	8:0:92:0
SiO_2	72	10:0:84:6

α-Diethoxyphosphorylvinyl *p*-tolyl sulphoxide behaves similarly (equation 589)[932].

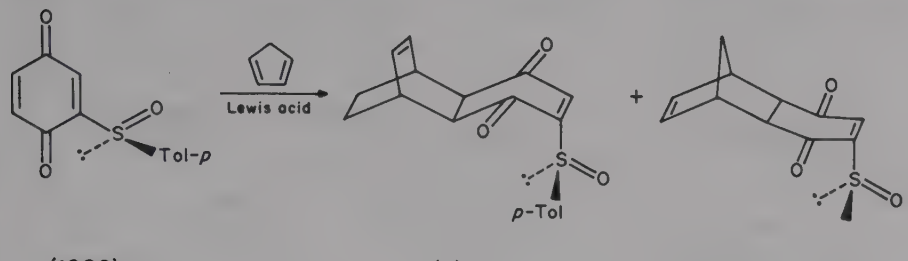


(589)

(+)-(*S*)-(991) **(1079) a + b + c + d**

Catalyst	Solvent	Temp. (°C)	a:b:c:d
—	CH_2Cl_2	r.t.	9.8:54.4:30.1:5.7
—	H_2O/Me_2CO	r.t.	13.2:53.6:27.5:5.7
$ZnCl_2$	CH_2Cl_2	−20	25.5:74.5:0:0
$BF_3 \cdot Et_2O$	CH_2Cl_2	−20	46.4:10.7:24.5:18.4

The Diels–Alder reaction of (*S*)-2-*p*-tolylsulphinyl-1,4-benzoquinone **1080** with cyclopentadiene proceeds across the less activated double bond of a dienophile (equation 590)[816].

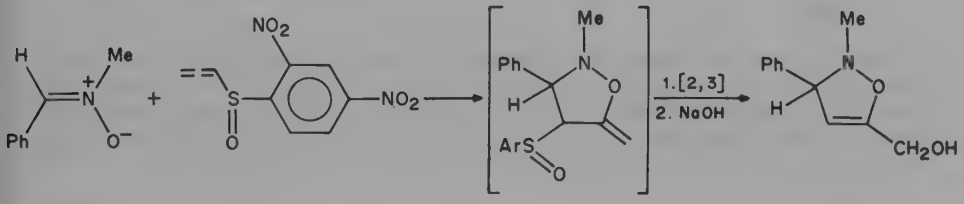


(1080) **(a)** **(b)**

Lewis acid	a:b
$Eu(fod)_3$	91:9
$BF_3 \cdot OEt_2$	10:90

(590)

c. [3 + 2] Cycloaddition. The reaction of 2,4-dinitrophenylsulphinylpropadiene **1081** with *N*-methyl-*C*-phenylnitrone **1082** gives a [3 + 2] cycloadduct as an intermediate which undergoes a [2,3] sigmatropic rearrangement to give the isoxazoline **1083**. The same reaction course is observed with other nitrones. However, when the aryl group attached to the sulphinyl moiety contains no electron-withdrawing substituents, the reaction does not proceed at all (equation 591)[992].



(1082) **(1081)** **(1083)**

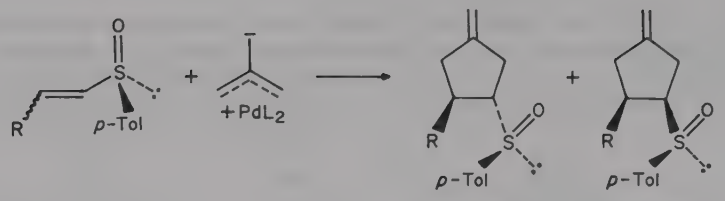
Ar=2,4-$(O_2N)C_6H_3$ yield 95%

(591)

The palladium-catalysed [3 + 2] cycloaddition of trimethylenemethane with a variety of optically active vinyl sulphoxides leads to a mixture of only two diastereoisomers of 3,4-disubstituted *exo*-methylenecyclopentane **1084** in good chemical yields (equation 592)[993].

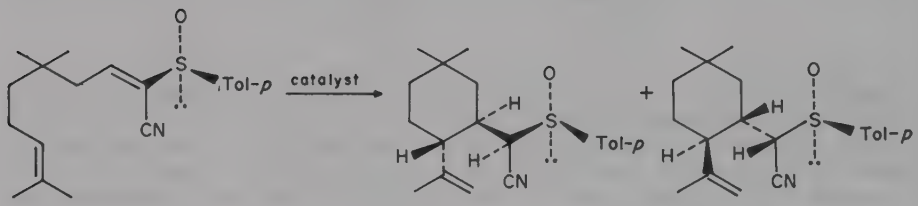
4. Ene reactions

The chiral cyanovinyl sulphoxide (*S*)-**955** undergoes an intramolecular asymmetric ene reaction to afford a diastereoisomeric mixture of optically active cyclohexane derivatives **1085** and **1086** in which the newly created three asymmetric centres are enantiomeric. The d.e. is very high and depends on the catalyst used. Et_2AlCl at $-20\,^{\circ}C$ in CH_2Cl_2 has proven to be the most effective one, the major product being **1085** (equation 593, Table 94)[905].



(1084a) (1084b) (592)

R	Diast. ratio **1084a**:**1084b**	Yield(%)
(*E*) Ph	90:10	80
(*Z*) Ph	25:75	47
(*E*) C_5H_{11}	77:23	62
(*E*) *t*-Bu	82:18	82



(**1085**) (**1086**) (593)

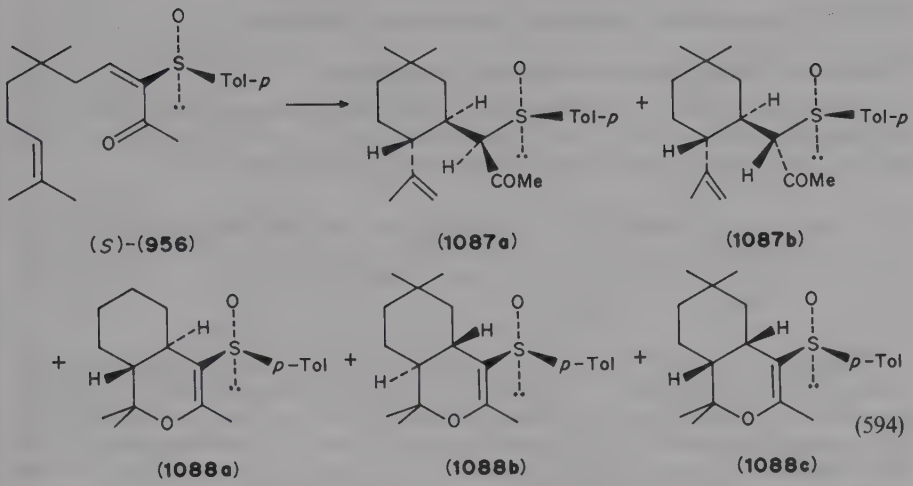
(*S*)-(**955**) 1*R*, 2*R*, α *R*, R_s 1*S*, 2*S*, α *R*, R_s

When the ketovinylic sulphoxide (*S*)-**956** is used, apart from the ene reaction products **1087**, also the products of the intramolecular Diels–Alder cycloaddition **1088** are formed. The use of bidentate Lewis acids ($ZnCl_2$, $ZnBr_2$, ZnI_2, $SnCl_4$) provides a mixture of all **1087** and **1088** isomers, while monodentate ones (Et_2AlCl, $EtAlCl_2$, $BF_3 \cdot Et_2O$) yield exclusively the products of the Diels–Alder cycloaddition (equation 594)[906].

TABLE 94. Intramolecular ene reaction of cyanovinylic sulphoxide **955**

Lewis acid	Solvent	Temp. (°C)	Time (h)	Yield (%)[a] **1085** + **1086**	Diast. excess (%)
$ZnCl_2$	CH_2Cl_2	r.t.	12	61(68)	78.2
$ZnBr_2$	CH_2Cl_2	r.t.	18	82(92)	76.8
$ZnBr_2$	PhMe	r.t.	20	76(89)	73.9
Et_2AlCl	CH_2Cl_2	0	1	77(91)	96.6
Et_2AlCl	CH_2Cl_2	−20	2	62(89)	97.3
Et_2AlCl	hexane	0	2	42(51)	80.8
$EtAlCl_2$	CH_2Cl_2	−20	1	52(88)	94.9
$EtAlCl_2$	CH_2Cl_2	−78	12	34(71)	95.2
Me_3Al	CH_2Cl_2		4	22(73)	20.6

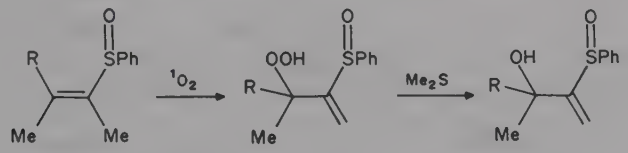
[a] The yields based on the recovered substrate are given in parentheses.



(S)-(956) (1087a) (1087b)

(1088a) (1088b) (1088c) (594)

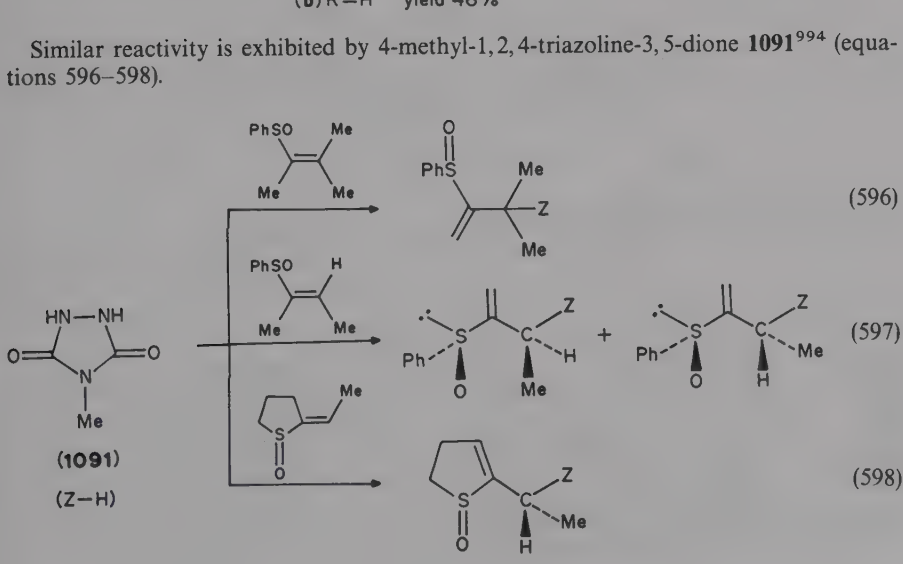
The ene-type reaction of singlet oxygen with vinyl sulphoxides **1089** followed by reduction with Me_2S gives the corresponding 2-hydroxy-α-methylene sulphoxides **1090**. The reaction is limited to the sulphoxides specified in equation 595—others give sulphones or do not react at all[994].



(595)

(1089) (a) R=Me yield 80% (1090)
(b) R=H yield 46%

Similar reactivity is exhibited by 4-methyl-1,2,4-triazoline-3,5-dione **1091**[994] (equations 596–598).



(596)

(597)

(598)

(1091)

(Z–H)

*D. Other Transformations of Organic Substituents in Sulphoxides

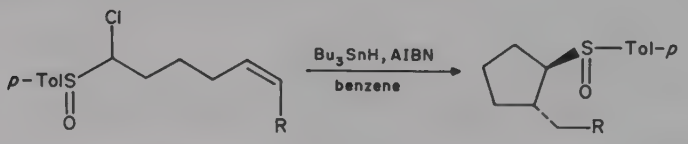
4. Reaction of radicals located on carbon atoms in sulphoxides

a. α-Sulphinyl radicals. *p*-Tolylsulphinylmethyl radical, generated from chloromethyl *p*-tolylsulphoxide **994a**, reacts with electron-rich olefins in the presence of tributyltin hydride to give the corresponding addition products, e.g. equation 599[936].

$$p\text{-Tol}\underset{\underset{\text{O}}{\|}}{\text{S}}\text{CH}_2\text{Cl} + \rightleftharpoons\!\!\!\!\!\!\diagup\!\!\!\!\!\!\diagdown \text{SiMe}_3 \xrightarrow[\text{AIBN, benzene}]{\text{Bu}_3\text{SnH}} p\text{-Tol}\underset{\underset{\text{O}}{\|}}{\text{S}}\text{CH}_2\text{CH}_2\text{CH}_2\text{SiMe}_3 \qquad (599)$$

(994a)

Cyclization of the α-sulphinyl radical was described in 1990 almost simultaneously by Renaud[936] and by Tsai and coworkers[995]. The two teams obtained, however, different stereochemical results. Thus, Renaud claims that the cyclization proceeds with a high *trans* stereoselectivity (equation 600)[936]. In contrast to this, Tsai and coworkers report that in this cyclization there is no *cis/trans* selectivity and only a low selectivity with respect to the sulphur atom. What is interesting, however, is that even the presence of an electron-withdrawing group attached to the olefin does not hamper the reaction of the (presumably) electron-deficient α-sulphinyl radical (equation 601, Table 95)[995].



(600)

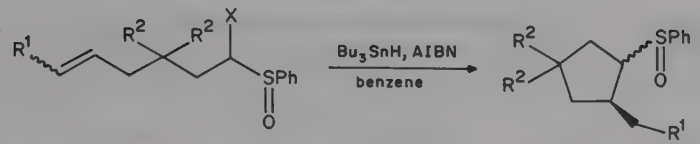
(1092) **(1093)**

	R	Yield (%)	*trans/cis*
(a)	H	40	86:14
(b)	OMe	94	> 95:5

TABLE 95. Cyclization of α-sulphinyl radicals

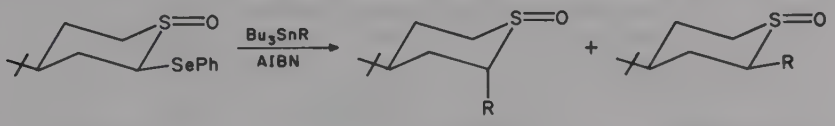
				1093			
						Diast. ratio	
Substrate	R^1	R^2	X	Yield (%)	*cis/trans*	*cis*	*trans*
1092c	H	H	Cl	46[a]	50/50	2/3	1/2
1092d	H	CO_2Me	Br	60	65/35	1/2	2/3
1092e (*E*)[b]	CO_2Et	H	Cl	70	75/25	1/4	1/2
1092f (*Z*)[b]	CO_2Et	H	Cl	88	70/30	1/5	4/5

[a] 43% of dechlorination product was also obtained.
[b] Mixtures of diastereoisomers: 3/7 in *E* and 1/3 in *Z*.



(1092) (1093) (601)

α-Sulphinyl radicals have also been generated from 2-phenylselenenylthian-1-oxides (**986**–**988**). Depending on the substituent in the organotin reagent used, the corresponding 2-deuterated or 2-alkyl derivatives have been obtained (for example, see equation 602)[931].

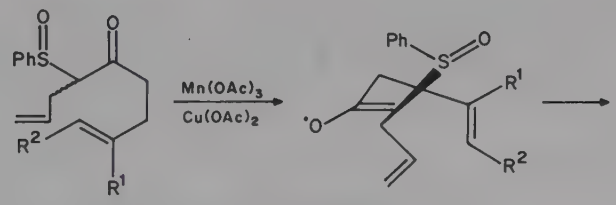


(**988**) (**1094**)-*cis* (**1094**)-*trans*

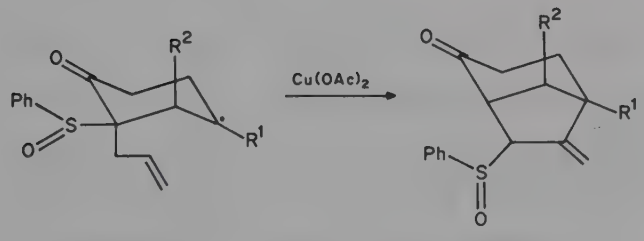
R	Yield (%)	Conditions	*cis*:*trans*
allyl	92	benzene, reflux	1:15
D	95	benzene, reflux	6.7:1
D	82	CH_2Cl_2, −78, *hv*	19:1

(602)

Manganese(III) acetate oxidation of the unsaturated β-oxosulphoxides **1095** gives the enol radicals **1096** which undergo a stereoselective cyclization to produce the cyclohexyl radicals **1097**, which in turn yield the bicyclic sulphoxides **1098** as the sole diastereoisomers. From the optically active sulphoxides **1095** the enantiomerically pure products **1098** are obtained (equation 603)[996].

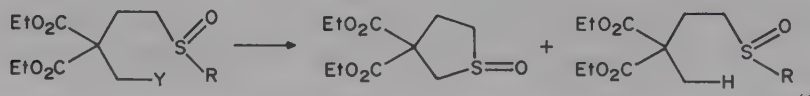


(**1095**) (**1096**)



(**1097**) (**1098**) (603)

b. γ-Sulphinyl radicals. Alkyl radicals having a sulphoxide function at the γ-position form five-membered cyclic sulphoxides as a result of a nucleophilic attack of the radical on the sulphur atom (equation 604)[997].



(604)

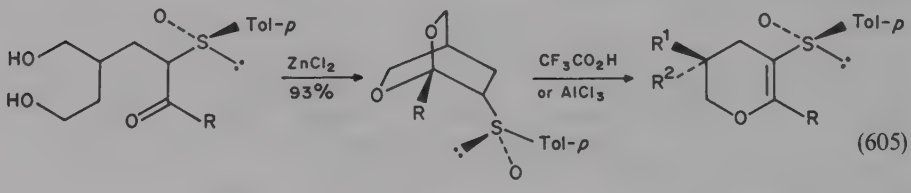
(1099) **(1100)** **(1101)**

Y = Br, radical generated by *hv*, $Bu_3SnSnBu_3$
Y = alkyl-bis-(dimethylglyoximato)pyridinecobalt(III), generates a pair of alkyl and cobaloxime(II) radicals

R	Solvent	Product ratio **1100**:**1101**	Total yield (%)
t-Bu	Benzene	92:8	74
t-Bu	$CHCl_3$	54:46	51
$PhCH_2$	Benzene	96:4	45
$PhCH_2$	$CHCl_3$	85:15	53

5. Miscellaneous

Intramolecular acetalization of **1102** on treatment with $ZnCl_2$ leads to a mixture of diastereoisomers of **1103** which can be easily separated. Exposure of the separated isomers to CF_3CO_2H or $AlCl_3$ results in the predominant formation of one of the diastereoisomers of 5-sulphinylpyrans **1104** (equation 605, Table 96)[998].



(605)

(1102) **(1103)** **(1104)**

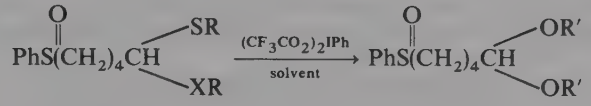
3(*S*): $R^1 = H$, $R^2 = CH_2OH$ (**a**) R = Me
3(*R*): $R^1 = CH_2OH$, $R^2 = H$ (**b**) R = *i*-amyl

TABLE 96. Synthesis of 5-sulphinylpyrans **1104**

Substrate	Conditions	Product	Yield (%)	Ratio 3*S*/3*R*
1103a (mixt.)	CF_3CO_2H/C_6H_6	**1104a**	78	2.7/1
(7*S*)-**1103a**			79	2.4/1
(7*R*)-**1103a**			76	3.7/1
1103a (mixt.)	$AlCl_3$/THF	**1104a**	89	1/2.5
(7*S*)-**1103a**			90	1/2.9
(7*R*)-**1103a**			84	1.2/1
1103b (mixt.)	CF_3CO_2H/C_6H_6	**1104b**	77	2.3/1
1103b (mixt.)	$AlCl_3$/THF	**1104b**	99	1/4

This approach, using a chiral sulphinyl auxiliary, has been applied for the total synthesis of optically active talaromycins[999] and for all four isomers of the insect phermone, 2-methyl-1,6-dioxaspiro[4,5]decane[1000].

Dethioacetalization of ω-sulphinyl mono- and dithioacetals **1105** can be achieved without destroying the sulphoxide moiety by using bis(trifluoroacetoxy)iodobenzene (equation 606)[1001].



(606)

(1105)

R	X	R′	Solvent	Yield (%)
Et	S	Me	MeOH	97
Ph	S	$-CH_2CH_2-$ [b]	$HOCH_2CH_2OH$	91
$-(CH_2)_3-$ [a]	S	Me	MeOH	86
$-(CH_2)_2-$ [a]	S	Me	MeOH	93
$-(CH_2)_2-$ [a]	O	Me	MeOH	90

[a] RR
[b] R′R′

*V. REFERENCES

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CHAPTER 5

Cyclic sulfones and sulfoxides

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Edited by S. Patai and Z. Rappoport © 1988, 1994 John Wiley & Sons Ltd

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The following chapter constitutes a walk on the trail of cyclic sulfones and sulfoxides, an intriguing and interesting class of compounds, that displays a variety of novel and unique properties, particularly when of small ring size.

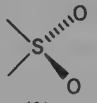
Several theoretical and experimental characteristics of the sulfone and sulfoxide groups are substantially modified when these are incorporated within a cyclic array. As a rule, the smaller the ring size the larger the deviation from the 'normal' expected properties and behavior of the sulfone and sulfoxide groups.

This chapter is an attempt to present a balanced treatment of the subject, concentrating on recent developments in the area and emphasizing the chemistry of small-ring sulfones and sulfoxides as a particular distinct category within the chemistry of the sulfone and sulfoxide functional groups.

Section III in the chapter is based on Reference 2, whereas Section V is relatively short since a recently published book[279] adequately covers the relevant topics.

I. PREFACE

The generation, structure, physical and chemical properties of the closely-related sulfone (**1**) and sulfoxide (**2**) functional groups have been thoroughly described and discussed in this volume.



(1)

(2)

In view of the fact that the chemistry of ring compounds has played a considerable role in the development of modern organic chemistry, the following question is definitely relevant: Do *cyclic* sulfones and sulfoxides envisioned as a particular distinct category within this class of compounds contribute uniquely—in their own right—to the understanding of the characteristics and chemistry of the sulfone and sulfoxide functionalities and their role in organic chemistry?

Small ring compounds represent a fair portion of strained organic systems[1] in which the geometry of sp^3 and that of sp^2 carbons have been distorted from the ideal configurations. Foremost among these reactive molecules are the small ring heterocycles, such as thiirane and thiirene oxides and dioxides[2].

The introduction of heteroatoms into cyclic systems produces significant variations in the molecular geometry that reflect the changes in covalent radii, relative electronegativity and effective hybridization. Consequently, there are changes in the bonding and the physico-chemical characteristics of these heterocyclic systems—particularly in small ring systems.

Cyclic systems have frequently been used in studies of chemical bonding and reactivity, reaction mechanisms and a variety of other problems of interest to chemists[3]. Their utility depends on the changes in the carbon–carbon and the carbon–heteroatom bonds as well as on steric and electronic effects that result from the introduction of heteroatoms into the system. Indeed, the carbon–heteroatom bond length in small rings shows an effective increase with increasing heteroatom electronegativity[4], in line with a

potential facile ring opening involving these bonds. Thus, the presence of a heteroatom, coupled with the strain in the system, makes the hetero-three- to five-membered rings (relatively) easily cleavable: both electrophiles and nucleophiles as well as thermally and photochemically induced reactions are expected to initiate facile ring opening.

The presence of one or more sulfone and/or sulfoxide functions within a ring system also adds a new dimension of intrinsic difficulty concerning the synthesis, the stability–reactivity, and the stereo- and regio-selectivity of the reactions of these heterocycles. Clearly, the geometrical constraints impart particular features to these molecules in terms of structural and conformational chemistry, energy, strain energy, bonding, charge distribution and, consequently, in terms of the potential unique characteristics of the sulfone and sulfoxide groups incorporated in them. Based on accumulated evidence, the special contribution of cyclic sulfones and sulfoxides to the understanding of the various aspects of the chemistry of these two closely-related functional groups deserves a special treatment. Correlations and/or discrepancies between theoretical or 'educated' predictions and experimental results concerning the cyclic sulfone and sulfoxide systems will be described, and this treatment will provide an excellent setting for studying and understanding the following:

(a) The consequences of the inclusion of the sulfone and sulfoxide groups in a cyclic array as far as generation, structural-physical/spectral properties, bonding, energies, activating and directive effects, chemical stability and chemical reactivity are concerned.

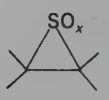
(b) The nature and some fundamental aspects of carbon–carbon and carbon–sulfur bonds in general, and in sulfur-containing small-ring heterocycles in particular.

(c) The particular role played by d-orbitals in cyclic strained systems containing the sulfoxide and/or sulfone functional group.

II. INTRODUCTION: SCOPE AND LIMITATIONS

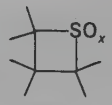
The first member of the three-membered ring sulfones was synthesized about 70 years ago[5], and its unsaturated analogue has been known for only 20 years[6]. Since the mid-sixties, an explosive expansion in the chemistry of some of these small- to middle-sized sulfone and sulfoxide heterocycles has taken place.

To date, all saturated and unsaturated three- and larger-membered ring sulfones and sulfoxides (e.g., thiirane (**3**), thiirene (**4**), thietane (**5**), thiete (**6**), dithietane (**7**), thiolane (**8**), thiolene (**9**), thiane (**10**), thiene (**11**), dithiane (**12**), thiepane (**13**), thiocane (**14**), and their unsaturated analogues as well as isomers and closely-related systems) have been synthesized and their chemistry well-established.



(**3**)

(**4**)



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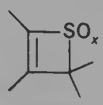

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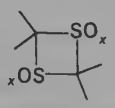

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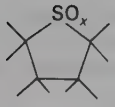

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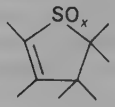

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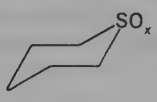
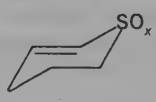
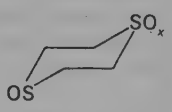


(**10**)



(**11**)



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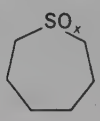
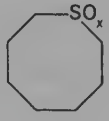


(**13**)



(**14**)

($x = 1$ or 2)

Heterocycles of type **3–14** containing either additional nonsulfur heteroatom or nonsulfone/sulfoxide functional groups (other than double bonds) within the ring skeleton, have been excluded from being treated because of the overwhelming amount of material and since we wanted to emphasize the effects which these two functional groups exert on the chemical and physical properties of the systems.

Similarly, only selected cyclic systems containing more than one sulfoxide or sulfone groups have been included and discussed here, primarily in the thietane (i.e. 1,2- and 1,3-dithietanes) and thiane (i.e. 1,2-, 1,3- and 1,4-dithianes) series. The criterion for the inclusion of these multifunctional heterocycles was their contribution to the understanding of the physical properties and chemical reactivity of cyclic sulfones and sulfoxides, and the effects of these groups on either their immediate vicinity or on the behavior of the whole molecule.

Three-membered saturated and unsaturated sulfone and sulfoxide rings comprise a unique class of compounds[2] among the cyclic sulfone and sulfoxide series, due to the greatest distortion from the optimal (normal) bond lengths and angles of their counterparts in the open-chain and/or greater than eight-membered heterocycle series. Consequently, their preparation constitutes a special synthetic challenge, and their physicochemical properties are expected and, indeed, have been found to be different from those of other cyclic sulfones and sulfoxides. Therefore, the three-membered sulfones and sulfoxides are to be treated together. Cyclic sulfones and sulfoxides having a ring size of greater than eight have not been included, assuming that beginning with nine-membered rings the chemistry of the acyclic sulfones and sulfoxides has actually been approached.

The field of cyclic sulfones and sulfoxides also provides a challenge for further investigations. Four possible directions for future research are as follows:

(a) the synthesis and study of three-membered rings incorporating sulfone or sulfoxide and an additional heteroatom (e.g. **15a**)[7,8];

(b) the synthesis and study of small-ring sulfamides and sulfurous diamides (e.g. **15b**) and closely related systems[9];

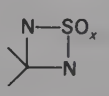
(c) the synthesis and study of thiapropellanes (e.g., **15c**)[10];

(d) the use of cyclic sulfones and sulfoxides as synthons in organic synthesis.

(15a)

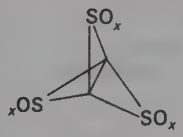
($x = 1$ or 2)

Z = NR, O, S, etc.



(15b)

($x = 1$ or 2)



(15c)

($x = 1$ or 2)

III. THREE-MEMBERED RING SULFOXIDES AND SULFONES

A. Introduction

The incorporation of the sulfoxide and sulfone functional groups within three-membered saturated and unsaturated ring systems (e.g. **3** and **4**) turns the latter into extremely interesting candidates for both theoretical and experimental investigation. The geometrical constraints are such that a unique combination of angles (tetrahedral, trigonal and dihedral), bond lengths (carbon–carbon, carbon–sulfur and sulfur–oxygen), strain energy and regio-proximity is obtained and reflected in the consequent physical and

chemical properties of these systems. In addition, some kind of 'aromaticity' can, in principle, be assigned to the unsaturated systems of type **4**[11], whereas the sulfoxides **4** ($x = 1$) can be considered as both pseudo-aromatic and 'classically' nonaromatic simultaneously[12] since they have, at least formally, a cyclic array or $4n\pi$ electrons predicted by theory to be highly unstable[13,14].

Although it may be experimentally impossible to distinguish and quantify the effect of each of the above factors separately within given three-membered ring systems, a comparison with the properties of higher ring systems (i.e., **5**–**14**) may provide an estimate of the contribution of the sulfone or the sulfoxide function to these properties.

The chemistry of three-membered rings containing oxidized sulfur starts with the work of Staudinger and Pfenninger[5] (equation 1).

$$R^1R^2CN_2 + SO_2 \longrightarrow [R^1R^2C{=}SO_2] \xrightarrow{R^1R^2(CN)_2} \underset{\text{(3a)}}{R^1R^2C(\text{—}SO_2\text{—})CR^1R^2} \qquad (1)$$

The base-induced Ramberg–Bäcklund rearrangement[15] later initiated extensive mechanistically[16]- and synthetically[17]-oriented investigations, and played a significant role not only with respect to the study of thiirane dioxides (**3b**), but also contributed substantially to the present state of the art concerning three-membered rings containing sulfur[2] (equation 2).

$$\underset{\text{X = halogen}}{R^1R^2CSO_2CR^3R^4} \xrightarrow[-\,HX]{\text{base}} \underset{\text{(3b)}}{R^1R^2C(\text{—}SO_2\text{—})CR^3R^4} \xrightarrow{(-\,SO_2)} R^1R^2C{=}CR^3R^4 \qquad (2)$$

R^1, R^2, R^3, R^4 = H, alkyl, aryl

Following the pioneering mechanistic studies conducted by Bordwell[18] and Neureiter[19], the physical and chemical properties of the thiirane dioxides could be established, as well as several significant aspects of their chemistry.

Thiirane oxides (**3**; $x = 1$) were rather rare and not well characterized until about 20 years ago[20]. Since 1965 synthetic methods for their preparation have been consistently and systematically explored[2]. They are rather thermodynamically stable compounds—compared to their closely-related thiirane dioxides—provided they have an *anti*-configuration with respect to the substituents and the sulfinyl oxygen. Also they are more resistant than the corresponding sulfones toward ring opening by either nucleophiles or electrophiles.

The first substituted thiirene dioxides[21] and thiirene oxides[22] (e.g. **4**; $x = 2$ and $x = 1$, respectively) were synthesized and characterized by Carpino and coworkers, while the parent thiirene oxide and dioxide are not known to date. However, the successful syntheses of the substituted unsaturated systems **4** opened the door to an extensive research involving the theoretical and experimental aspects of this class of intriguing compounds[2], particularly as far as the unique role and characteristics of their sulfone and sulfoxide groups are concerned.

Regardless of the question concerning the 'Hückel aromatic nature' of these nonbenzenoid systems, in which aromatic effects, if any, would require transmission through d-orbitals of the sulfur atom[11,23], the accumulated chemical and spectral evidence clearly suggests that both thiirene dioxides and thiirene oxides are unique systems with regard to their fundamental molecular structure and electronic configuration[2]. Thus, both the fascinating question of π-d bonding in conjugative unsaturated sulfone systems and the aromatic or nonaromatic nature of sulfone- and sulfoxide-containing unsaturated

heterocycles may be addressed and studied using thiirene dioxides and oxides as a model. It is noteworthy that thiirene oxides are remarkably stable, both thermally and toward electrophiles, relative to their saturated analogues (3) in spite of their additional strain[12]. It should be pointed out, however, that three-membered rings containing a sulfur atom are generally more stable than other three-membered rings. This is probably due to a lower strain energy for the former, apparently associated with the capacity of the sulfur atom to better accommodate the extra strain of the small ring compared with either the carbon atom or other second-row heteroatoms[2].

B. Structure and Physical Properties

1. Molecular orbital calculations

Ab initio molecular orbital calculations[24] of the parent cyclic thiirane oxide and dioxide (3; $x = 1$ and 2) have been carried out recently[25], using the Gaussian 76 program[26]. The geometries were optimized at the STO-3G* level[27] in which a manifold of five d-type functions, consisting of one second-order Gaussian each, was added to the minimal STO-3G basis set[28] for the second-row sulfur atom. The r(CH) and ⟨HCH have been fixed at their experimental values. The results were compared with those obtained for the equilibrium geometries of the open sulfones XSO_2Y where X = Y = H or CH_3[25]. The relevant data are summarized in Table 1 together with data obtained from previous theoretical studies of cyclic sulfoxides and sulfones in which the structural parameters were determined by using *ab initio* MO-SCF[29], extended Hückel[30], and MNDO[31,32] calculations. In all of these theoretical studies, the importance and the necessity of including d-functions of the hypervalent sulfur (as a second-row atom) in the sulfone or sulfoxide group in the calculations was clearly demonstrated[29,32,33]. In fact, in those cases in which the 3d AO's of the sulfur atom were neglected in the calculations, the results obtained are clearly unsatisfactory compared to the results obtained either by alternative theoretical calculation procedures (which include the d-orbitals) or by experiment.

Two major trends are apparent from the data in Table 1. First, in both the acyclic and cyclic series, there is a lengthening of the sulfur–oxygen bond in going from the sulfones to

TABLE 1. Calculated bond lengths[a] and angles[b] in three-membered ring sulfone and sulfoxide and their acyclic analogues

	Geometrical parameters					
Molecule[c]	r(SO)	r(CS)	r(CC)	⟨OSO	⟨CSC	⟨CSO
Thiirane 1,1-dioxide	1.456 (1.452)[f]	1.757 (1.755)	1.560 (1.590)	—	52.7	115.0
Thiirane 1-oxide	1.474 (1.504)	1.788 (1.822)	1.515 (1.505)	—	50.1	114.9
Dimethyl sulfone[d]	1.455	1.818	—	124.3	98.5	107.8
Dimethyl sulfoxide[e]	1.522	1.791	—	—	141.8	123.8

[a] Bond lengths in Å.
[b] Angles in deg.
[c] Ref. 25 for the first three molecules and Ref. 32 for the fourth one.
[d] Point group C_{2v}.
[e] Point group C_s.
[f] Data in parentheses are from a previous study[29] in which a medium-size contracted Gaussian basis set was used in the calculations.

the sulfoxides, although this tendency is less pronounced in the cyclic series. Second, the carbon–carbon bond in the thiirane dioxide is substantially longer than that of the thiirane oxide or that of ordinary carbon–carbon σ bonds, whereas the carbon–sulfur bond in the cyclic oxide is longer than that of the cyclic sulfone, in contrast to the trend in the acyclic counterparts. The first feature should manifest itself in the increased capacity of the three-membered sulfoxides—compared with that of the three-membered sulfones—to serve as nucleophiles via the sulfoxide oxygen in appropriately designed chemical reactions. The second feature should lead to a relatively easy opening of the carbon–carbon bond in thiirane dioxides.

The group of Hoffmann and coworkers[30] concluded that the long C—C bond of thiirane dioxide is due to the effective population of the π^* level of the ethylene fragment through a low-lying orbital ($3b_2$ of π symmetry) in SO_2, and to the action of the 3d-orbitals in SO_2 as effective acceptors, thus depopulating the orbital of C_2H_4. The combination of these two effects leads to a weakening of the carbon–carbon bond. Consequently, the cleavage of this bond in the thiirane dioxide should be disrotatory, but conrotatory in the thiirane itself. The binding mechanism in the thiirane 1-oxide was also interpreted in terms of a donor-acceptor complex between ethylene and the SO fragment. It turns out that two factors are important in explaining the calculated structural features in thiirane oxides and dioxides: the donor–acceptor strength of the sulfoxide and the sulfone moieties, respectively, and the 3d sulfur orbital participation[29,30]. The extraordinary length of the carbon–carbon bond, which has been quoted to be the longest known[34], is best explained in terms of the latter. However, there is no evidence for an increased 3d S population in strained sulfur compounds like thiirane oxides. Although, in principle, the lowest-energy conformations of sulfones as well as sulfoxides would assume a staggered arrangement about the carbon–sulfur bond, the unique geometrical constraints applied when these groups are incorporated in a three-membered ring array should be reflected in both the total energy of the strained systems and in the net atomic charges of all the atoms involved. These two parameters may be used for predicting the relative thermodynamical stability and chemical reactivity of the cyclic sulfones and sulfoxides, on the one hand, in comparison to their acyclic counterparts, on the other. Selected relevent STO-3G* total energies and net atomic charges based on the Mulliken population analysis procedure[35] are given in Table 2. As could be expected, the total energy content of the cyclic molecule increases and the polarity of its sulfone group decreases compared with those of the acyclic counterpart dimethyl sulfone. Given the changes in carbon–carbon and the carbon–sulfur bond lengths and the strain energy embodied in the cyclic sulfone, which is clearly reflected in its total energy, it is not simple to estimate the 'net effect' of the decreased polarity of the

TABLE 2. Calculated total energies (au) and atomic charges of three-membered ring sulfone and sulfoxide and their acyclic counterparts (after Reference 25)

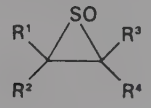
		Net atomic charges			
Molecule	Total Energy	S	O	C	H
Thiirane 1,1-dioxide	−617.98137 −624.678[c]	+0.35	−0.24	−0.12	+0.09
Thiirane 1-oxide	−544.15393 −549.994[c]	+0.27	−0.31	−0.14	+0.08[a] 0.09[b]
Dimethyl sulfone	−619.11196	+0.40	−0.27	−0.19	+0.08

[a]The hydrogen atoms on the oxygen side of the CSC plane.
[b]The hydrogen atoms on the opposite side of the CSC plane.
[c]Ref. 29. MO-SCF calculations using medium-size contracted Gaussian basis set.

sulfonyl group on the predicted chemical reactivity of the whole system including the functional group itself, nor to test experimentally the conclusions reached.

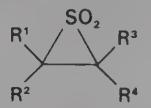
2. Experimental geometrical parameters

The geometric parameters of the three-membered ring sulfones and sulfoxides have been determined via X-ray diffraction techniques and gas-phase microwave spectroscopy. The accumulated data for some selected thiirane and thiirene oxides and dioxides (**16**–**19**) as well as for the corresponding thiirane (**20**) and the acyclic dimethyl sulfone (for the sake of comparison) are given in Table 3, together with the calculated values.



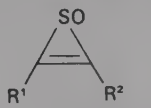
(**16**)

(**a**) $R^1 = R^2 = R^3 = R^4 = H$
(**b**) $R^1 = R^3 = CH_3$; $R^2 = R^4 = H$



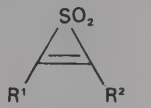
(**17**)

(**a**) $R^1 = R^2 = R^3 = R^4 = H$
(**b**) $R^1 = R^3 = CH_3$; $R^2 = R^4 = H$



(**18**)

(**a**) $R^1 = R^2 = C_6H_5$

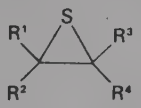


(**19**)

(**a**) $R^1 = R^2 = CH_3$
(**b**) $R^1 = R^2 = C_6H_5$

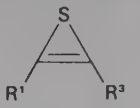
As in the acyclic series, there is a lengthening of the sulfur–oxygen bond as the sulfur is oxidized from the sulfoxide to the sulfone in both the thiirane (i.e. **16a** → **17a**) and the thiirene (i.e. **18a** → **19b**) series. Unexpected, however, is the substantial decrease in the OSO angle of the sulfone group in thiirenes compared with that of the thiiranes (e.g. ⟨OSO of **19a** is smaller than ⟨OSO of **17a**) and that of the corresponding acyclic dimethyl sulfone. There appears to be no simple explanation for this trend.

A unique characteristic feature of the cyclic three-membered ring sulfones and sulfoxides is the dramatic increase in the length of the carbon–carbon single bonds and the carbon–carbon double bonds in the series of thiirane–thiirane oxide–thiirane dioxide (**20a** → **16a** → **17a**), and thiirene–thiirene oxide–thiirene dioxide (**21** → **18a** → **19b**).



(**20**)

(**a**) $R^1 = R^2 = R^3 = R^4 = H$
(**b**) $R^1 = R^3 = CH_3$; $R^2 = R^4 = H$



(**21**)

$R^1 = R^2 = Ph$

There is a concomitant decrease in the length of the carbon–sulfur bonds in the thiirene series, but irregularity is apparent in the decrease of the carbon–sulfur bond in the thiirane series. Thus, *r*(CS) **19b** ⟨ *r*(CS) **18a** and *r*(CS) **17a** ⟨ *r*(CS) **16a**, but the carbon–sulfur bond lengths of **20a** and its oxide (**16a**) are essentially identical.

The above relationships between the thiiranes (**20**) and their dioxides (**17**) are reminiscent of those between cyclopropane and cyclopropanone[44]. The entire phenomena of the C—C bond lengthening and the concomitant C—S bond shortening in the three-membered ring sulfones and sulfoxides can be accounted for in terms of the sulfur 3d-orbital participation and the variation in the donor–acceptor capacities of the S, SO and SO_2[29,30]. The variations of the calculated valence-state orbital energies, together with the corresponding variations of the C—C overlap populations, can be used to understand the discontinuous variations of the C—C and the C—S bond lengths in the series thiiranes –

TABLE 3. Experimental geometries of selected acyclic and three-membered sulfones and sulfoxides (**16–19**)

Molecule	Functional group	Geometrical parameters							Method of determination[a]	Ref.
		r(SO)	r(CS)	r(CC)	∠OSO	∠CSC	∠CCS	∠CSO		
17a	SO_2	1.439	1.731	1.590	121.26	54.7	62.7		M	36
			1.76	1.586					M	34
		(1.456)[b]	(1.757)[b]	(1.560)[b]		(52.7)[b]				
17b	SO_2	1.720	1.588			54.6	62.0		X	4
		(1.730)[b]	(1.60)[b]						X	37
16a	SO	1.483	1.822	1.504		48.8	65.6		X	38
		(1.474)[b]	(1.788)[b]	(1.515)[b]						
19a	SO_2	1.449	1.692	1.333	114.8	46.4			X	39
19b	SO_2	1.444; 1.453	1.703; 1.716	1.354	116.1	46.7	66.2; 67.2		X	39
18a	SO	1.467	1.784	1.305		42.9	68.5; 68.6	114.9; 115	X	39
$(CH_3)SO_2$	SO_2	1.432; 1.435	1.777; 1.771		121.0; 119.7	103.3; 102.6			M	40
		(1.455)[b]	(1.818)[b]		(124.3)[b]	(98.5)[b]				
SO_2[c]		1.431			119.3					41
$(CH_3)_2SO$	SO	1.477	1.810			96.4		106.7		38,42
20a[d]	S		1.815	1.484		48.3	65.9		M	4,43
20b[d]	S		1.820	1.492		48.4	65.8		X	4

[a] X = X-ray diffraction technique; M = microwave spectroscopy.
[b] Values in parentheses are the calculated geometries (see Table 1).
[c] Point group C_{2v}.
[d] Data for this ring are included for comparison.

thirane oxides – thiirane dioxides[29]. In contrast, extended Hückel calculations[30] showed continuous changes along this series, the C—S population increasing and the C—C population decreasing.

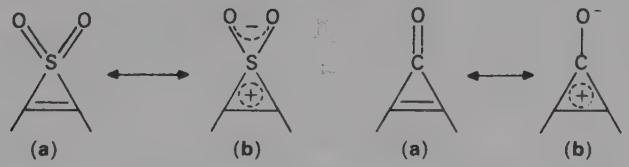
Clearly, there exists a good agreement between theoretical predictions (and calculations) based on the participation of sulfur 3d-orbitals and available experimental results. Thus, the important role of the sulfur d-orbitals in determining the structure and, consequently, the chemistry of sulfones and sulfoxides in general, and of strained small-ring sulfones and sulfoxides in particular, has been established.

It is illuminating to note that only very minor (and probably insignificant) differences can be detected as far as the r(SO) and ⟨OSO in the cyclic and acyclic sulfones and sulfoxides [i.e. **17a** versus $(CH_3)_2SO_2$ and SO_2; and **16a** versus $(CH_3)_2SO$] are concerned. The same is true concerning the r(SO) in the sulfoxide and sulfone groups in the thiirene series (i.e. **18a** and **19a**), compared with that of the acyclic analogues [i.e. $(CH_3)_2SO$ and $(CH_3)_2SO_2$, respectively].

The apparent insensitivity of the SO_2 bond lengths (and CNDO/S[45] and CNDO/2[46] calculations of oxygen charge densities) to structural variations in the carbon skeleton portion of the molecule might well be due to an 'insulating effect' of the LUMO sulfur d-orbitals; that is, that electronic interactions between the carbon framework and sulfur can occur without appreciable change in the oxygen–sulfur interactions. Consequently, the sulfur–oxygen bond distance provides an unsatisfactory measure of, e.g., d-π electron interactions. In contrast, the dramatic changes in the carbon–carbon bond lengths (from 1.305 Å in **18a** to 1.354 Å in **19b** and from 1.784 Å for the carbon–sulfur bond in **18a** to 1.709 Å for this bond in **19b**) were interpreted in terms of substantial π-delocalization[39]. It should be pointed out, however, that several 'ordinary' cyclic sulfones have been found to have shorter carbon–sulfur lengths than those of the corresponding sulfoxides[47].

3. *Theoretical treatment and interpretations*

The structural features and the spectroscopic characteristics of the thiirene dioxide system (**22**) are of special theoretical interest since, on the basis of analogy with cyclopropenone (**23**), it is a possible nonbenzenoid aromatic system with all the physical and chemical implications involved. Aromatic and/or conjugative effects, if any, require transmission through the d-orbitals of the sulfur atom.



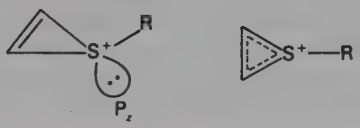
(22) (23)

Conjugation of the π-electrons of the carbon–carbon double bond with the LUMO sulfur 3d-orbitals would be expected to stabilize the Hückel $4n + 2$ ($n = 0$) array of π-electrons in the thiirene dioxide system. No wonder, therefore, that the successful synthesis of the first member in this series (e.g. **19b**)[21] has initiated and stimulated several studies[11,39,45,46,48,49], the main objective of which was to determine whether or not thiirene dioxides should be considered to be aromatic (or 'pseudo-aromatic') and/or to what extent conjugation effects, which require some sort of π-d bonding in the conjugatively unsaturated sulfones, are operative within these systems. The fact that the sulfur–oxygen bond lengths in thiirene dioxides were found to be similar to those of other SO_2-containing compounds, *does not* corroborate a Hückel-type π-delocalization

illustrated by structure **22b**. Understandably, the chemistry and reactivity of the thiirene dioxides and their sulfone functional group are contingent on the structural characteristics.

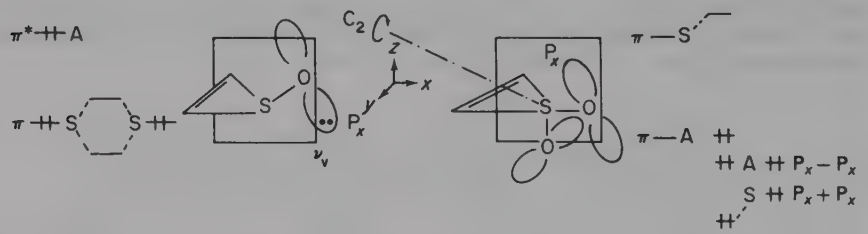
Similar considerations apply to the thiirene oxide system (**18**), since in this case too the sulfur's 3d-orbitals have the potential of interacting with the 2p-orbitals of both the adjacent carbon and oxygen atoms. Such an interaction should facilitate some kind of conjugation of the carbon–carbon double-bond π-electrons with the formally unoccupied 3d-orbitals, which in turn would give rise to Hückel-type stabilization associated with cyclic array of $4n + 2$ ($n = 0$) π-electrons.

The question of sulfur d-orbital involvement in chemical bonding centers about their 'size' (radial distribution) in potential bonding situations. This size depends mainly upon the net charge (oxidation state)[50]: the greater the oxidation state of sulfur, the greater the importance of d-orbitals in overlap transmission of electronic effects via π-conjugation. The high-lying d_{xz}-orbital of proper symmetry contracts in volume and descends in energy as the oxidation state of the thiirene sulfur increases[51]. Thus, the available d_{xz}-orbital would permit electron delocalization from the ethylene fragment into sulfur and might permit a thiirenium cation (**24**) as a potential nonbenzenoid 'aromatic' molecule with a nonzero carbon–sulfur π-bond order (cf. **25**), whereas the lower order of geometry would allow the p_z electron pair to mix in the not large orthogonal *S*-function and assume a nonbonding rather than antibonding role.



(24) **(25)**

Analogous effects may allow 'aromatic' assignments to the thiirene 1-oxide and dioxide, and may be demonstrated through the interaction diagrams given below[52].

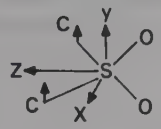


Employing a C_2 symmetry in the case of the thiirene 1-dioxide and remembering that the spiro-operator that mixes the fragment orbitals gives nonzero matrix elements only if these orbitals are symmetric to the C_2 operation[53], the net result is stabilizing. On the other hand, thiirene 1-oxide suffers a homoconjugative destabilization.

Based on experimental results and complementary calculations, an out-of-plane π-delocalization is suggested for thiirene dioxides[39]. As far as the thiirene oxide is concerned, theoretical calculations[11] predict possible spiroconjugative-type[53] interaction between the $\pi^*_{C=C}$ orbital of the ring and the π-orbitals of the SO (which leads to aromatic stabilization and a π charge transfer backward from the SO to the C=C). There exists, however, a rather strong destabilization effect, due to the $\pi^*_{SO}(d_{xz})$-orbital.

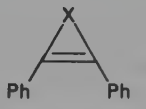
In order to justify the validity of ketone–sulfone analogies, a series of CNDO/2 calculations on a number of model cyclic unsaturated sulfones and ketones was

undertaken[46]. It was found that: (a) only little charge separation occurs in thiirene dioxides; (b) the difference in charge density on oxygen in the series of ketones is not reproduced by the sulfones; and (c) in contrast to cyclopropenone, thiirene dioxide is a weak acceptor in hydrogen bonding. It was concluded[46] that a comparison of cyclic unsaturated sulfones and ketones is of little value, and that although the d_{yz}-orbital of the sulfur atom (**26**) can and does promote resonance structures (e.g. **22b**) analogous to the predominant polar resonance structures in ketones (e.g. **23b**), the d_{xy}-orbital has a contrary effect of comparable magnitude.



(26)

The thiirene dioxide system was investigated by an analysis of the inductive and conjugative interactions between the carbon–carbon (C=C) and the sulfonyl (SO_2) subunits and consideration of the possible 'aromaticity' of this species[45]. By using a method which makes it possible to distinguish inductive from conjugative effects[48], the C=C—SO_2 interactions could be evaluated and compared to the results obtained by analyzing the UV photoelectron spectra of thiirene dioxides[45]. Both approaches revealed a strong hyperconjugative interaction between the occupied C=C MO and an occupied SO_2 σ-MO_1, and a modest mixing between the former and a vacant SO_2 σ^* which is a nearly pure sulfur d-AO. The π-σ^* interaction is responsible for a small π charge transfer from the carbon–carbon double bond to the sulfonyl unit. In spite of this charge transfer being much smaller in magnitude than in the corresponding cyclopropenone, it was concluded that thiirene dioxide does have a tendency to exhibit properties expected of an 'aromatic' model. However, the degree (but not the nature) of this tendency is much smaller for thiirene dioxides than for the corresponding ketones. In a complementary study[49], the photoelectron spectra of 2,3-diphenyl-substituted compounds (**27**) were interpreted and analyzed in terms of inductive and conjugative interactions between the subunits C=C and X. The values obtained were compared with theoretical data obtained by using the 'cut-off' procedure[48,54].



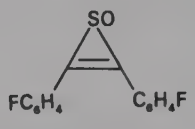
X = CH_2, CO, C=S, SO, SO_2

(27)

The calculated CNDO/2 inductive (I) and CNDO/2 conjugative (C) effects of **27** were found to be -0.35 and 0.04, -0.45 and 0.1, and -0.95 and 0.06 eV for X = CO, SO and SO_2, respectively. The corresponding aromaticities (conjugation energies) and the π charge transfer from the PhC=CPh segment to X were calculated to be -52.84 and 245.4×10^{-3}, -22.05 and 82.2×10^{-3}, and -21.84 and 81.4×10^{-3} kcal mol^{-1}, respectively[49]. Although the values obtained for either the sulfoxide or the sulfone (**27**, X = SO and X = SO_2) are surprisingly comparable in magnitude, the results suggest that these phenyl-substituted molecules are likely (somewhat) aromatic as their parent systems are. Interestingly, the corresponding experimental I and C values for **27** (X = CO and SO)[49] were found to be at least 1.5–2.5 times greater than the calculated spiroconjugation in

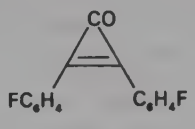
thiirene dioxide which was found to be negligible relative to hyperconjugation, and the influence of d-orbitals of sulfur on the electronic structure of this system was shown to be rather pronounced. Both aromaticity orders derived from the *ab initio* and CNDO/S charge transfer values concur and agree with the CNDO/S conjugation energy order, and both suggested thiirene dioxides to be aromatic in nature at least to some extent[11].

Following the work of Taft[55] and coworkers on fluorobenzenes which permitted the isolation of the inductive (σ_I) and conjugative (σ_R) effects, the σ values of 2, 3-di-*meta*- and *para*-fluorophenylthiirene oxides (**28a,b**) were calculated (based on the measured shielding parameters of these compounds)[56] and compared with the σ values of corresponding bis(*meta*- and *para*-fluorophenyl) cyclopropenones (**29a,b**).



(28)

(a) *m*-FC_6H_4
(b) *p*-FC_6H_4



(29)

(a) *m*-FC_6H_4
(b) *p*-FC_6H_4

These comparisons of σ_R (0.16 and 0.25 for **18** and **29**, respectively) showed, as expected, that the extent of the electron-withdrawing conjugative effect increases in the order thiirene oxide < thiirene dioxide < cyclopropenone. Although this result agrees with earlier studies on the relative order of conjugative interaction in simple vinyl sulfoxides and sulfones compared with that of enones, it is not pertinent to the question of whether these are simple conjugative interactions or *cyclic* conjugative effects with transmission through the sulfur atom[11,23c,45,46,56].

Standard CNDO/2 calculations on models of thiirenes have been performed[39] in an attempt to obtain a picture of their bonding. Both the atomic charge densities and bond indices of the parent thiirene, thiirene oxide and thiirene dioxide have been calculated using model parameters. While the trends in the carbon–carbon and carbon–sulfur bond indices agree qualitatively with the trends observed in the experimental bond lengths, the sulfur–oxygen indices predicted that the sulfoxide distance should be smaller than the sulfone distance—in contrast to the experimental results. Thus, it was concluded[39] that the calculated oxygen charge densities and sulfur–oxygen bond orders provide an insensitive measure of d-π electron interactions, and that the in-plane carbon p_z-orbitals are primarily responsible for the bond-length variations. The contributions of the out-of-plane carbon p_y–sulfur interactions to the carbon–sulfur bond orders in the thiirene series suggest that π-delocalization may be of a magnitude comparable to that of the cyclopropenones.

Based on the geometries of three-membered ring heterocycles as determined by X-ray and gas-phase methods, it could be demonstrated[4] that in saturated three-membered heterocycles similar to **3**, the carbon–carbon bond length decreases linearly with increasing heteroatom electronegativity whereas the carbon–heteroatom bond shows an effective increase as the electronegativity of the heteroatom increases. The above is applicable to the series sulfones–sulfoxides **3** if the relative electronegativities of the two functional groups are being considered. These effects are explicable in terms of interaction of the heteroatom with ethylene[29,30,57] and are analogous to the formation of metalacyclopropanes[58,59].

The experimental carbon–carbon and carbon–sulfur bond-length values for the series **3** and **4** are in good agreement with the calculated values both in the saturated and unsaturated sulfones and sulfoxides (Table 1 and 3). Thus, it appears that the carbon–

carbon double bonds in the series **4** also vary with electronegativity in a systematic manner. Clearly, variations in the electronic distribution in the three-membered ring sulfones and sulfoxides leave their trace in the molecular geometry and ultimately in the chemistry of these systems.

On the basis of a naive analogy with cyclopropenones, the ground-state aromatic stabilization of which has been recently reconfirmed, some kind of 'aromaticity' can, in principle, be assigned to these systems when Z = SO or SO_2, assuming a possibility for transmission of electronic effects via π-conjugation.

The thiirene oxide system is of particular interest due to it being simultaneously both a potentially nonbenzenoid aromatic $(4n + 2)\pi$ and antiaromatic $4n\pi$ Hückel system.

Since it is clear that the presence of an unshared pair of electrons on the sulfur of the sulfoxide group leads to no special instability in the case of the known thiirene oxides (i.e., **18a**, **28a,b** and the first alkyl-substituted thiirene oxide **30** recently synthesized[60]), the reduced antiaromatic properties of the thiirene oxides relative to that of thiirenes have been manifested experimentally. As far as the possibility of electron-attracting conjugative stabilization involving the sulfur atom in thiirene oxides is concerned, the experimental evidence accumulated so far is not decisive. Thus, the chemical shift of the vinylic carbon of 2,3-diphenylthiirene 1-oxide (**18a**) was found to be 137.3 ppm (downfield from Me_4Si) and those of the corresponding diphenyl and dimethyl sulfones (**19b**, **19a**) to be 158.9 and 167.4 ppm, respectively[12], compared with the reported values of 148.5 and 157.9 for the 2,3-diphenyl- and 2,3-dimethylcyclopropenones.

To summarize, based on both theoretical and experimental results, the following conclusions emerge[12]:

(i) Conjugative interactions and/or cyclic π-delocalizations are small compared with closely related systems.

(ii) No significant antiaromatic destabilizing effects can be ascribed to the sulfur unshared pair of electrons.

(iii) The oxygen moiety in the sulfoxide function should not be expected to be highly reactive.

4. Spectroscopic characteristics and characterization

a. Infrared. The infrared spectrum is the best available technique for determining the presence of both the sulfone and the sulfoxide functional groups within a given molecule. Although the sulfur–oxygen stretching frequencies of both the sulfone and the sulfoxide groups give rise to absorption peaks within the fingerprint region (that is $<1400\,cm^{-1}$), their location is characteristically fixed, and they are typically strong so as to dominate the spectrum and thus are easily identifiable.

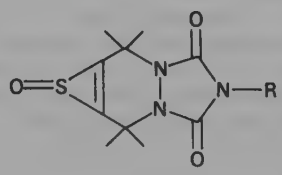
As in the acyclic series, saturated three-membered ring sulfones and sulfoxides (i.e. thiirane dioxides and thiirane oxides) exhibit stretching frequencies typical of sulfones and sulfoxides: at about 1320 (asymmetric) and $1160\,cm^{-1}$ (symmetric) for the former[61,62] and $1050–1090\,cm^{-1}$ for the latter[63], with the exact location being somewhat dependent on the nature of substituents on the α-carbons. Some representative data of IR absorptions of the SO_2 and SO groups in thiirane and thiirene oxides and dioxides are given in Table 4. It appears that the constraints of the three-membered saturated ring have little effect on the stretching frequencies of both sulfone and sulfoxide groups incorporated in it. The situation is entirely different, however, as far as the IR spectra of both thiirene dioxides and thiirene oxides are concerned (Table 4). Thus, the most striking feature of the data in Table 4 is, undoubtedly, the anomalous asymmetric stretching[64] frequency of the SO_2 group in thiirene dioxides. Usually, an internal correlation is observed between the asymmetric and symmetric stretching frequencies of the SO_2 group in sulfones as well as in

TABLE 4. Selected IR stretching frequencies of sulfone and sulfoxide groups in thiirane and thiirene dioxides and oxides

Compound		IR frequencies[a] Asymmetric		Symmetric	Ref.
Thiirane dioxide	**17a**	1310		1160	2,36,62
Thiirane dioxide	**17c** ($R^1 = Cl$; $R^2 = R^3 = R^4 = H$)	1328[c]		1168[c]	61
Thiirane dioxide	**17d** ($R^1 = R^3 = Ph$; $R^2 = R^4 = H$)	1346[b]		1160[b]	21
Thiirane dioxide	**19a**	1256		1166	6
Thiirene dioxide	**19b**	1279[b]		1167[b]	6,21
Thiirene dioxide	**28a**	1250[c]		1149[c]	2,22
Thiirane oxide	**16a**		1060		63
Thiirane oxide	**16b**		1080, 1065[d]		63
Thiirane oxide	**16c** ($R^1 = R^3 = Ph$; $R^2 = R^4 = H$)		1065		63
Thiirene oxide	**18a**		1061		22
	18b		1065		22
	30[e]		1115[f]		60

[a] cm^{-1}.
[b] In CCl_4.
[c] In Nujol.
[d] Two isomers; *syn*; *anti*.
[e] Dialkyl-substituted thiirene oxide (six-membered ring fused)[60].
[f] In KBr.

other compounds containing the sulfonyl group. In contrast, thiirene dioxides show a marked shift of the asymmetric absorption to lower frequencies (compared with other sulfones) without a correlated shift of the symmetric band to higher frequencies. The net result is that the Bellamy–Williams correlation[65] no longer holds for these compounds. Although the reason for this phenomenon is not yet clear, it appears that the ring strain alone cannot be responsible for this effect[6]. However, the π-d interactions of the type discussed in the previous section may provide a satisfactory explanation. It is interesting to note that a characteristic feature of the cycloadducts of thiirene oxide with 4-substituted 1,2,4-triazoline-3,5-diones (e.g. the six-membered ring fused thiirene *S*-oxide **30**) is that their stretching vibrational absorption due to the sulfur–oxygen bond appears at the unusually high frequency of 1115 cm^{-1}. This value indicates a surprisingly short S—O bond length, the shortest found for any type of sulfoxide (1.4583 Å by X-ray analysis)[60]. Apparently, this S—O bond shortening reflects the combined effect of ring fusion and alkyl substitution.



(30)

(a) R = Me

(b) R = Ph

b. ^1H *and* ^{13}C *NMR spectroscopy.* Proton- and carbon-13 NMR spectroscopy have found wide application in organosulfur chemistry[63,66,67]. In both cases, as expected, the inductive- and the directionally-dependent anisotropic effects of the sulfonyl and the sulfoxyl groups play a major role[67,68] cyclic systems included[2,69,70].

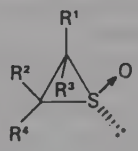
The order of magnitude of α-proton shifts for a particular ring size is generally S < SO < SO_2, in accord with the inductive effects of these functional groups[66]. Shielding in the three-membered series is probably dominated by bond and group anisotropies that distinguish it from the other sulfur-containing ring systems[70].

Thus, the positions of the three-membered ring proton signals of thiirane dioxides depend upon the environment of these protons[71] and the solvents used[72] and are not uniquely indicative of this class of compounds. The high field shift of the three-membered ring protons of thiirane dioxides compared with the α-protons in the four- and higher-membered sulfone rings may be partly due to the diamagnetic anisotropy of the three-membered ring[73].

^1H NMR techniques have been extensively used in determining both the configuration and the stereochemistry of thiirane oxides, e.g., in making the choice between isomers obtained in the preparation of the oxides. Configuration assignments have been made, based on the expected anisotropy effect of the S—O bond. In certain six-, five- and four-membered ring sulfoxides, a β-hydrogen which is *syn* to the S—O bond experiences a profound deshielding effect, while a β-hydrogen which is *anti* to the S—O (i.e. *syn* to the lone pair of the sulfur atom) suffers from a shielding effect as compared with the same protons of the parent sulfide[69,74].

Indeed, the validity of this approach and analogy was unequivocally demonstrated[63] by an examination of the NMR characteristics of 2,2-dimethylthiirane (**31a**), *cis*-2,3-dimethylthiirane (**31b**), *trans*-2,3-dimethylthiirane (**31c**), and their corresponding sulfoxides (**32a–c**).

(31)



(32)

(a) $R^1 = R^3 = CH_3$, $R^2 = R^4 = H$

(b) $R^1 = R^2 = CH_3$, $R^3 = R^4 = H$

(c) $R^1 = R^4 = CH_3$, $R^2 = R^3 = H$

The chemical shifts of the H-methyl groups in thiiranes **31a**, **31b** and **31c** were found to be $\delta = 1.59$, 1.44 and 1.45, respectively. The chemical shifts of the β-anti-methyl hydrogens (i.e. those of R^3) where found to be $\delta = 1.25$, 1.23 and 1.27 in **32a–c** compared with $\delta = 1.74$ and 1.64 for *syn*-R^1-hydrogens in **32a** and **31c**, respectively[63,75]. The consistency of the deshielding effect in accordance with the position of the β-hydrogens in ring sulfoxides is thus apparent. These observations validate the applicability of the S—O anisotropy rule to the three-membered ring system.

Although a remarkable upfield or downfield shift of a β-proton in a rigid system depending on the direction of the S—O bond was established in many cases, the same behavior was not observed for the hydrogens directly attached to the three-membered thiirane oxide ring (e.g. $\delta = 1.85$ and 1.89 for R^3 in **31b** and **32b**, respectively). Occasionally, the shielding and deshielding effects of the S—O bond are compensating each other at these hydrogens. The principle has been used successfully, however, to assign the configuration of a number of aryl-substituted thiirane oxides.

All the above chemical shift-based assignments were further confirmed by solvent-induced shift studies[63,76]. The geminal coupling constants in thiirane oxide (− 6.4 Hz) and 2-methylthiirane oxide (− 6.0 Hz) were appreciably more negative than those in thiirane (− 0.7 Hz) and 2-methylthiirane (− 0.8 Hz), respectively[76]; the trend to greater negative value of J_{gem} with increasing group electronegativity of the heteroatom is the converse of the usual NMR behavior of three-membered heterocycles. The vicinal coupling constants for the *syn*-protons, namely 11.5 and 11.7 Hz, in thiirane oxide were also abnormal[77]. These facts were interpreted in terms of the Pople–Bothner-By model for spin coupling[78]. However, the larger ^3J values for thiirane oxide were ascribed to greater electronegativity of the SO compared with that of S in thiiranes. In general, the opposite effect is found in other three-membered heterocycles: an increase in ^3J is found as the electronegativity of the heteroatom decreases[79] and the magnitude of $^3J_{CH}$ roughly parallels $^3J_{HH}$ in this series of compounds[80].

The vinylic hydrogen in 2-methylthiirene dioxide resonates at $\delta = 8.99$[81], a particularly low magnetic field. This low value may reflect the combined inductive and anisotropic effects of the sulfone group with the anisotropic effect of the carbon–carbon double bond. Consequently, this high deshielding of the ring hydrogen cannot be considered as evidence for the assumed partial aromaticity assigned to the thiirene dioxides[6,11,39].

Several trends have emerged in the extensive carbon-13 NMR spectroscopy data that have been accumulated for sulfones and sulfoxides. Based on many studies of cyclic systems—particularly five- and six-membered ring sulfur compounds—these trends were shown to generally apply equally to both the cyclic and acyclic systems[70]. Thus: (a) oxidation of a sulfide to a sulfone results in a 20–25 ppm downfield chemical shift for sp^3-hybridized α-carbon atoms and 4–9 ppm upfield shift for β-carbons[82,83], and (b) there is very little difference between the chemical shifts of α-carbon atoms of sulfones and sulfoxides[84,85] despite the difference in the inductive effects of these two functional groups[70]. A difference is observed, however, in the ^1H chemical shift of related cyclic sulfoxides and sulfones[70].

The ^{13}C NMR data for representative three-membered sulfones and sulfoxides are given in Table 5. The chemical shifts of the sp^3-hybridized α-carbon in the parent thiirane[70] and the five-membered ring[86] sulfide, sulfoxide and sulfone are 18.1, 31.7, 54.3 and 51.1, respectively, whereas those of cyclopropenone, diphenylcyclopropenone and dimethylcyclopropenone are 169.0[87], 148.7[88] and 157.9, respectively.

In contrast to the insignificant differences between the carbon chemical shifts of cyclic

TABLE 5. Ring carbon-13 chemical shifts of three-membered sulfones and sulfoxides

Compound	Chemical shift (ppm)[a]	Ref.
Thiirane oxide **16a**	33.8	70
Thiirane dioxide **17a**	31.6	70
2,3-Diphenylthiirene oxide **18a**	137.3	12
Alkyl-substituted fused thiirene oxide **30a**	15.3	60
2,3-Diphenylthiirene dioxide **19b**	158.9	12
2,3-Dimethylthiirene dioxide **19a**	167.4	12

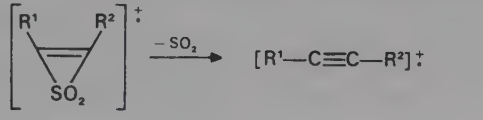
[a]Downfield from $(CH_3)_4Si$ in $CDCl_3$.

sulfones and sulfoxides in the saturated series, there is a noticeable downfield shift (14–22 ppm) of the α-carbon in the sulfones compared to sulfoxides in the thiirene series. In comparing the carbon shifts of the thiirene oxides and dioxides with the cyclopropenone system, we note very similar patterns (e.g., about 9 ppm difference in the shifts of alkyl- and aryl-substituted vinylic carbons). Similarly, the positions of the methyl and H absorption in the NMR spectrum of 2-methylthiirene dioxides are comparable to those observed for methylcyclopropenone (2.70 and 8.70, respectively)[89]. Hence, the differences in the ^{13}C chemical shift values found for the thiirene oxides and dioxides suggest a higher degree of aromaticity of the dioxides compared with that of the sulfoxides[12]. However, the magnitude of this conjugative effect (and, consequently, the relative degree of 'aromaticity') remains an open question, since the inductive effect (and, also, possibly the anisotropic effect)[70] is clearly reflected in the observed difference.

Interestingly, the oxygen-17 chemical shifts for the thiirane oxide (**16a**) and thiirane dioxide (**17a**) were found to be 71 and 111 ppm (downfield from natural-abundance ^{17}O in H_2O), respectively. The oxygen-17 shift reveals that this oxygen is the most highly shielded oxygen atom so far reported[80,70].

c. Mass spectroscopy. The extrusion of sulfur dioxide and of sulfur monoxide is a characteristic of these systems[2,6,15–18,63] and should be reflected in their mass spectra.

Verification of the molecular weight of thiirene dioxides by mass spectrometry, employing the conventional electron-impact (EI) ionization method, has been unsuccessful due to the absence or insignificant intensity of molecular ion peaks in their mass spectra. The base peak is rather characteristic, however, and corresponds to the formation of the disubstituted acetylene ion by loss of sulfur dioxide[91] (equation 3).



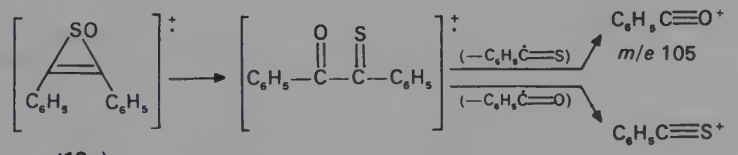
(3)

(**19**)

In fact, considerable thermal decomposition may precede ionization as suggested by the fact that only the relatively volatile 2, 2-dimethylthiirene dioxide gave any evidence for the molecular ion. Retention of the positive charge with the sulfone function is responsible for the ion at *m/e* 64 (SO_2^+).

Similarly, a common feature in the mass spectrum of thiirene oxides is the high abundance of the substituted acetylene ion (e.g. $[PhC{\equiv}CPh]^+$) formed by elimination of sulfur monoxide. In fact, this ion constitutes the base peak in the spectrum of **18a** whereas the molecular ion has a rather insignificant intensity (0.25% Σ of M^+)[91].

The other ions are products of the further decomposition of the diphenylacetylene ion (*m/e* 178), or the fragmentation products of the monothiobenzyl[92] ion as depicted in equation 4[93].



(4)

(**18a**)

The use of the chemical ionization (CI) mass spectrometry technique[94] in the case of

thiirene dioxides proved to be very useful, in that by using different reagent gases (i.e. methane, isobutane, ammonia and dimethylamine) the relative abundance of molecular adduct ions have been enhanced and thus the molecular weight of the thiirene dioxides investigated could be established[91]. Thus, the formation of $(R^1C{\equiv}CR^2 + H)^+$ and $(SO_2 + H)^+$ in the methane CI spectra occurred via the elimination of SO_2 from $(M + H)^+$. Here, too, the acetylenic ion dominated the spectra. Similar results were obtained with the other reagent gases.

Similarly, methane CI spectrum of **18a** was found to be dominated by the $(C_6H_5C{\equiv}CC_6H_5 + H)^+$ ion. A distinct molecular ion species at *m/e* value corresponding to $(M + H)^+$ was observed in the methane mass spectra of this thiirene oxide (26% Σ 40). Furthermore, the relative intensity of the $(M + H)^+$ peak of **18a** was shown to increase substantially in the isobutane and dimethyl amine CI mass spectra[91].

C. The Sulfone and Sulfoxide Functionality in Three-Membered Ring Systems: Activating and Directive Effects

There are several unique features associated with the sulfone and the sulfoxide groups relating to their activating, directive, stabilizing and destabilizing effects as well as to their interrelationships with adjacent functional groups. The incorporation of these groups within a cyclic array imparts some extra strain-originated conformational-torsional constraints as well as steric-originated rigidity (and/or enhanced proximity between certain atoms) to these systems, the ultimate result being a substantial modification of the sulfone and sulfoxide functionality compared with that of acyclic systems.

The following features associated with the sulfoxide and sulfone functional groups in thiirane and thiirene oxides and dioxides are to be discussed:

1. Thermal elimination of SO_2 and SO (SO_2 and SO as leaving groups).
2. Acidity of α-hydrogens (sulfonyl and sulfoxy carbanions).
3. Electrophilicity of the SO_2 and SO groups (reaction with bases/nucleophiles).
4. Nucleophilicity of the SO_2 and SO groups (the reaction of the sulfoxy oxygen with electrophiles).
5. The (formal) Michael addition of nucleophiles to thiirene oxides and dioxides (formally vinyl sulfoxides and sulfones).
6. Miscellaneous (formation of complexes, and configuration induced by the sulfoxide group).

In all of the above, the activating, directive and stabilizing–destabilizing effects are similar in principle to those in the acyclic systems. However, the *magnitude* of these effects *per se*, or in conjunction with other characteristics of the systems in point, are considerably different and, consequently, the ultimate chemical results may be different.

1. Thermal elimination of SO_2 and SO

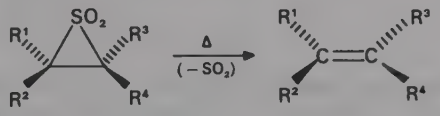
In principle the higher the oxidation state of the sulfur atom, the better its 'leaving capacity'; that is, the sulfonyl group is a better leaving group than the sulfoxy group, which in turn is a better leaving group than the unoxidized divalent sulfur. The enhanced polarizability of the oxidized groups, combined with the high electronegativity of the attached oxygen atom(s) which generates a partial positive charge on the sulfur atom, turn these groups into efficient 'sink' for the bonding electrons of the adjacent carbon atoms. Furthermore, the carbon–sulfur bond is weaker than ordinary carbon–carbon bonds, sulfur dioxide is a resonance-stabilized unit, and sulfur monoxide in its triplet ground state can easily be generated from suitable sulfoxides[95], possibly through the thermally allowed concerted nonlinear chelatropic process[96].

Hence, one would expect the thermal elimination of sulfur dioxide or of sulfur monoxide

to be a facile process. However, elimination of SO_2 or SO from acyclic sulfones and sulfoxides is not ordinarily observed. Both are very stable compounds, and elimination requires either appropriate chemical modifications in the case of sulfones or the presence of a β-carbon carrying at least one hydrogen atom in the case of sulfoxides[97].

The situation is entirely different in the three-membered ring sulfones and sulfoxides: the facile thermolytic elimination of SO_2 from the former is probably their most distinctive (and dominant) chemical reaction, whereas the loss of SO from the latter characterizes both the thiirane and thiirene series[2].

Thus, most thiirane dioxides slowly decompose near room temperature and rapidly at about 80° or above their melting points to give, stereospecifically, the related alkenes and sulfur dioxide[2,18,19,71] (equation 5).



(5)

(17) (33)

(c) $R^1 = R^3 = H$, $R^2 = R^4$ = alkyl or aryl

(d) $R^1 = R^4 = H$, $R^2 = R^3$ = alkyl or aryl

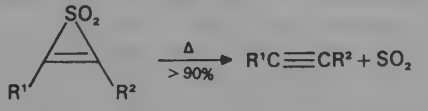
This thermal fragmentation is so facile that only under inert atmosphere and very low temperatures can the rate of decomposition be reduced sufficiently so as to make the systematic study of these molecules possible.

Several mechanistic explanations[98]—including both concerted symmetry-allowed nonlinear chelatropic paths[96], and nonconcerted stepwise mechanisms (such as that in which a diradical species is involved[99])—have been advanced to accommodate the stereospecific experimental results[2,17a,73,99].

The SO_2 eliminations follow first-order rates and were found to correlate surprisingly well with the ionizing power of the medium. Also, the rates are base-accelerated, albeit the effect is rather small[99].

The formation of alkenes from thiirane dioxides may not be stereospecifically controlled in the presence of a sufficiently strong base and sufficiently acidic protons in the three-membered ring. Under such conditions (essentially those typical for the Ramberg–Bäcklund reaction), epimerization via a carbanion intermediate produces an equilibrium mixture of thiirane dioxides[19,99] and consequently a mixture of *cis*- and *trans*-alkenes.

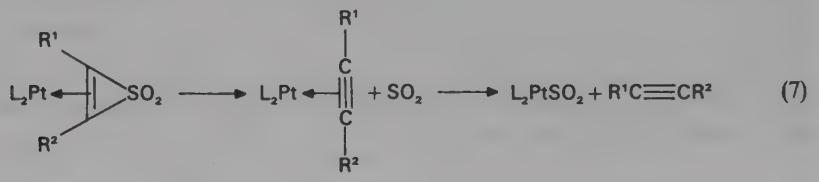
Thermal decomposition of thiirene dioxides results in the extrusion of sulfur dioxide and the formation of the corresponding acetylenes in high yields[6,21,100,101] (equation 6). Kinetic studies[100,101] of this thermally-induced extrusion showed it to be facilitated by electron-donating substituents (e.g. alkyl groups). In addition, the data which correlate best with the sum of σ_p^+ substituent constants suggest that a free radical, stepwise, rather than a nonlinear, symmetry-allowed, concerted extrusion mechanism[96] is operable. Interestingly, the thermal elimination of SO_2 from the thiirene oxide **19b** to give diphenylacetylene was found to be 10^4 slower than the elimination of SO_2 from the thiirane dioxide analogue **17** to give *trans*-stilbene[102].



(6)

(19) (34)

The transition-metal catalyzed decomposition of thiirene dioxides has been also investigated primarily via kinetic studies[103]. Zerovalent platinum and palladium complexes and monovalent iridium and rhodium complexes were found to affect this process, whereas divalent platinum and palladium had no effect. The kinetic data suggested the mechanism in equation 7.



(7)

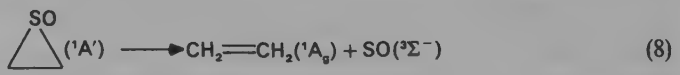
(35) (36) (34)

Since a similarity between the rates of decomposition of thiirene dioxide complexes and those of thiirane dioxides was found, it was suggested[103] that upon coordination the carbon–carbon bond order of thiirene dioxides decreases and the ligand becomes thiirane dioxide-like. The role of the metal is thus to 'saturate' the carbon–carbon double bond so that the reactivity of the coordinated thiirene dioxide approaches that of the thermally less stable thiirane dioxide.

The higher strain energy in thiirene dioxides (**19**) compared to thiirane dioxides (**17**) is obvious. Yet, the elimination of sulfur dioxide from the latter is significantly faster than one would expect for a thermally allowed concerted process. Consequently, either aromatic-type conjugative stabilization effects are operative in thiirene dioxides[2,12] or the relative ease of SO_2 elimination reflects the relative thermodynamic stability of the (diradical?)[99] intermediates involved in the nonconcerted stepwise elimination process.

It has been generally assumed that thermal decomposition of thiirane oxides proceeds stereospecifically to the corresponding olefins by elimination of sulfur monoxide, possibly through a concerted nonlinear chelatropic reaction[96] with retention of configuration of the liberated olefin.

Pyrolysis of the parent thiirane oxide **16a** monitored by microwave spectroscopy led to the conclusion that the sulfur monoxide is generated in its triplet ground state, although the singlet state ($^1\Delta$) cannot be excluded completely[38] (equation 8). A later study presented evidence, based on the stereoselective addition to dienes of sulfur monoxide generated from thiirane oxide as well as thermochemical data, that the ground state $^3\Sigma^-$ is formed exclusively[104].

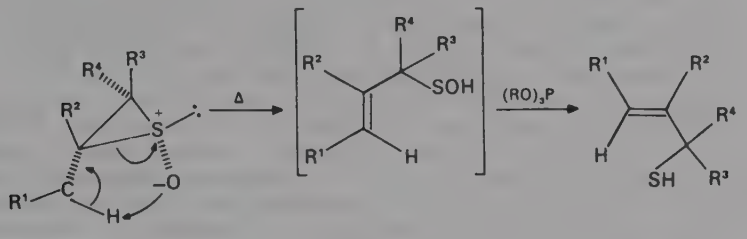


(8)

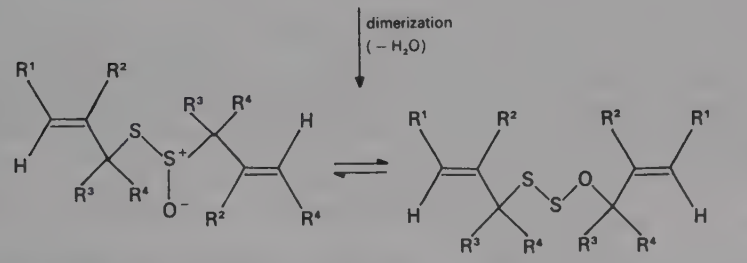
(16a)

In the presence of a suitably disposed β-hydrogen—as in alkyl-substituted thiirane oxides such as **16c**—an alternative, more facile pathway for thermal fragmentation is available[63a,105]. In such cases the thiirene oxides are thermally rearranged to the allylic sulfenic acid, **37**, similarly to the thermolysis of larger cyclic[106] and acyclic[97] sulfoxides (see equation 9). In sharp contrast to this type of thiirane oxide, *mono*- and *cis*-disubstituted ones have no available hydrogen for abstraction and afford on thermolysis only olefins and sulfur monoxide[63a]. However, rapid thermolysis of thiirane oxides of type **16c** at high temperatures (200–340 °C), rather than at room temperature or lower, afforded mixtures of *cis*- and *trans*-olefins with the concomitant extrusion of sulfur monoxide[105]. The rationale proposed for all these observations is that thiirane oxides may thermally

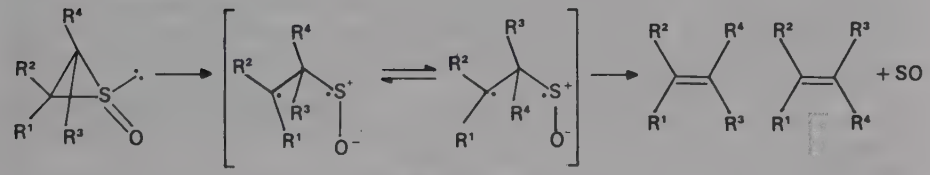
decompose by two routes: the first is a facile rearrangement to a sulfenic acid when the stereochemistry is favorable (as shown in equation 9), and the second is a pathway of higher activation energy which leads through a partially stereospecific route to the olefins and sulfur monoxide[105] (equation 10).



(16c) (37) (38)



(9)



(16) (A) (39) (B) (40) (41)

(d) $R^1 = R^4 = CH_3$, $R^2 = R^3 = H$ (g) $R^1 = R^4 = H$, $R^2 = R^3 = C_6H_5$

(e) $R^1 = R^3 = H$, $R^2 = R^4 = D$ (h) $R^1 = R^3 = H$, $R^2 = R^4 = C_6H_5$

(f) $R^1 = R^4 = H$, $R^2 = R^3 = D$ (10)

Thermolysis of **16e,f** in either solution or gas phase (150–350 °C) gave deuteriated ethylenes (i.e. **40e** from **16e** and **41f** from **16f**) with about 95% retention of stereochemistry[107]. Similarly, pyrolysis of the stereoisomeric 2,3-diphenylthiirane oxides **16g,h** proceeded smoothly to yield stilbenes and sulfur monoxide in more than 70% yield[108]. The extrusion of SO from the *trans*-isomer proceeds almost stereospecifically, while that from the *cis*-isomer occurs with complete loss of stereochemistry. This indicates the intervention of a stepwise mechanism, and not a symmetry-allowed nonlinear chelatropic reaction[96]. Based on the fact that all attempts to trap the intermediate with 1,3-dipolarophiles were in vain, whereas a 1:1 adduct was obtained in good yield (about 60%) with the carbon radical scavenger di-*p*-anisyl thioketone, a mechanistic scheme as depicted in equation 10 has been proposed[108]. Although the radical intermediates are capable of internal rotation about the carbon–carbon bond, for the 2,3-diphenyl case (i.e. **16g,h**), the rotation would be

restricted owing to the steric repulsion of the two phenyl groups, with the *trans*-conformer of **39** being thermally favored.

All the above indicates that thiirane oxides are not unusual in their thermal behavior when compared with their higher or lower oxidized analogues, and suggests analogous modes of extrusion of S, SO and SO_2 from the sulfur-containing three-membered rings. Although a stereochemically rather rigid 'biradical' **39** of the type proposed in the thermolysis of thiiranes[109] and thiirane dioxides[99] may account mechanistically for the results, a significant contribution of a concerted process cannot be ruled out.

The symmetric diarylthiirene oxides (**18**) are much more thermally stable than the corresponding saturated thiiranes and unsaturated thiirene dioxides. Thus, the thiirene oxide **18a** shows only slight decomposition after 24 hours of reflux in benzene, whereas the analogous sulfone **19b** fragments completely to SO_2 and diphenylacetylene after less than six hours under the same conditions[110]. Irradiation of the oxide **18a**, however, does result in the elimination of sulfur monoxide and formation of diphenylacetylene. Its thermolysis at 130 °C afforded benzil as the only isolable product[22], implying that SO is not being eliminated in this thermolytic process.

It is highly probable that the lesser stability of thiirene dioxides compared with that of the thiirene oxides simply reflects the more facile extrusion of sulfur dioxide relative to that of sulfur monoxide. In fact, the same effect is probably operative in the case of the *cis*- and *trans*-diphenylthiirane oxides (**16g,h**)[110] compared with *cis*- and *trans*-diphenylthiirane dioxides (**17d,e**)[99]: the former were found to be more stable toward thermal decomposition than the latter.

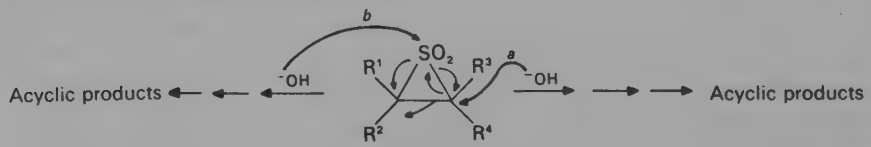
2. *Acidity of (sulfonyl and sulfoxy) α-hydrogens*

Two major factors are responsible for the acidity of the hydrogens attached to carbon atoms alpha to sulfonyl and sulfoxy groups. The first is the strong inductive effect of these highly electronegative functional groups (the effect of the sulfone being greater than that of the sulfoxide), and the second is the capacity of the adjacent partially positively charged sulfur atom to stabilize the developing α-carbanion via the expansion of its valence shell involving p–d orbital interaction.

The question arises whether there are any unique characteristics associated with the acidity of α-hydrogens when the sulfone or the sulfoxide group is incorporated within a three-membered ring system.

Based on extensive studies associated with the Ramberg–Bäcklund rearrangement[15] and its mechanism[2,16–19,111,112], including the treatment of thiirane oxides with bases, the following conclusions emerge:

The nucleophilic attack of strong bases (e.g. hydroxide ion, alkoxide ions and carbanions) on either the α-carbon[111] or the sulfur atom of the sulfone group[99,113] of the thiirane dioxides is the initial key step that is responsible for the subsequent ring opening and further reaction. The formation of a three-membered α-sulfonyl carbanion is not observed in these cases (equation 11).

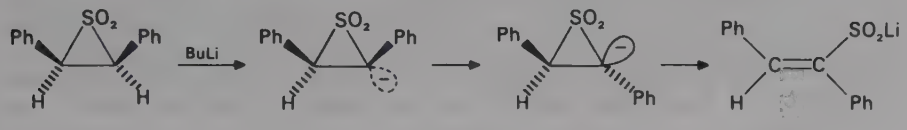


(17)

R^1 or R^2 or R^3 or R^4 = H (11)

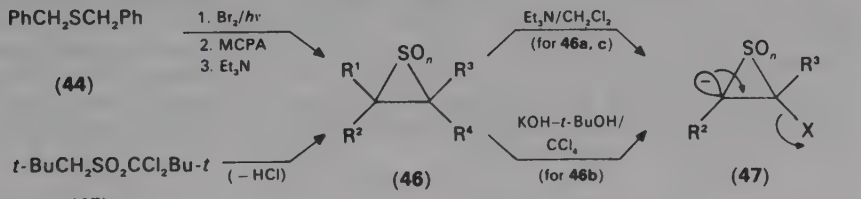
The reaction of thiirane dioxides with reagents that are weak nucleophiles but strong

bases, however, does lead to the formation of α-carbanions. Thus, for example, the formation of the sulfinate **43** was interpreted[99,111] in terms of a carbanion intermediate (**42**) which rearranges with inversion of configuration as illustrated in equation 12.



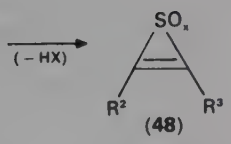
(16c) (a) (42) (b) (43) (12)

Clearly, strain energy, the unique sp^3 hybridization of both carbons and sulfur in the three-membered ring thiiranes, the relative stability of α-carbanions, and the substitution pattern on the one hand, and both the nucleophilicity/basicity ratio and steric hindrance of the attacking base on the other, play significant roles in determining the course of reaction between three-membered sulfones containing α-hydrogens and bases[2]. With weakly nucleophilic bases and thiirane dioxides whose substituents either stabilize an adjacent carbanion (e.g. aryl groups), or sterically hinder nucleophilic attack on the substituted carbon (e.g. *t*-butyl groups), the α-sulfonyl carbanion forms, leading to a product in which the three-membered ring skeleton is preserved intact. The above explains the accessibility of the thiirene dioxide[6] and thiirene oxide[22] systems when a modified Ramberg–Bäcklund procedure is used under mild conditions. This leads to several unique compounds otherwise difficult to obtain[112] as illustrated in equation 13. In all of these cases, the formation of α-sulfonyl or α-sulfoxy carbanions (**47**) is the key step.



R^4 = H, R^4 = Br or Cl
(a) $n = 2$; $R^2 = R^3$ = Ph
(b) $n = 2$; $R^2 = R^3$ = *t*-Bu
(c) $n = 1$; $R^2 = R^3$ = Ph

X = Br or Cl
n = 1 or 2 (13)



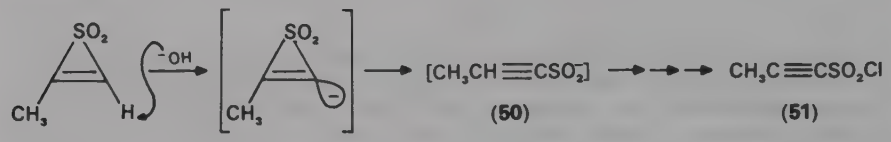
(48)

(a) $n = 2$; $R^2 = R^3$ = Ph
(b) $n = 2$; $R^2 = R^3$ = *t*-Bu
(c) $n = 1$; $R^2 = R^3$ = Ph

Significantly, (a) α-sulfonyl carbanions of thiirane dioxides, generated from the latter in the presence of strong bases such as potassium *t*-butoxide[19] and alkoxide ions[99], do epimerize to relieve steric repulsion between substituents as in **42** above; and (b) the α-hydrogen in aryl-substituted three-membered sulfoxides (e.g. **46c**) are sufficiently acidic to

form carbanions, in spite of the decreased capacity of the sulfoxide group to stabilize an adjacent carbanion compared to sulfones[2].

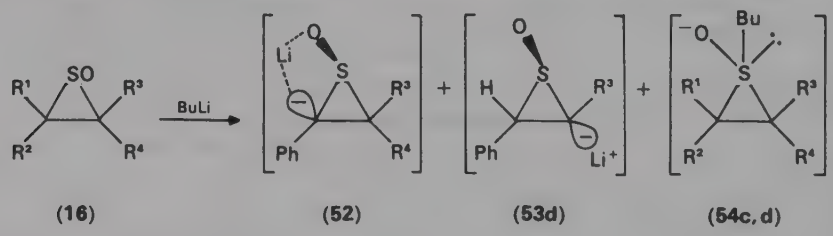
The issue of the acidity of α-hydrogens in thiirene oxides and dioxides is dealt with only in the dioxide series, since neither the parent, nor any mono-substituted thiirene oxide, is known to date. Thus the study of the reaction of 2-methylthiirene dioxide (**19c**) with aqueous sodium hydroxide revealed that the hydroxide ion is presumably diverted from attack at the sulfonyl group (which is the usual pattern for hydroxide ion attack on thiirene dioxides) by the pronounced acidity of the vinyl proton of this compound[113] (see equation 14).



(19c) (49) (50) (51) (14)

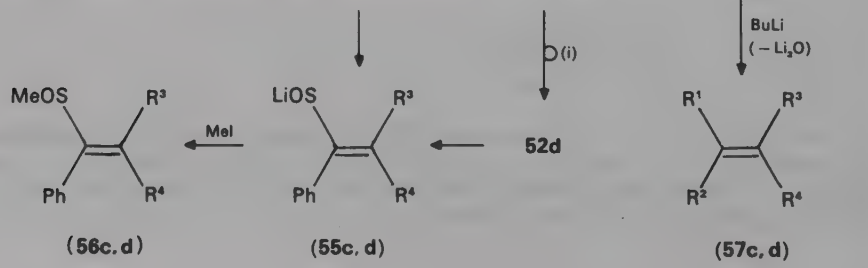
Although sulfinate (**50**) was not actually isolated, its intermediacy was established by trapping as the isolable sulfonyl chloride **51**, which suggests the formation of the α-sulfonyl vinyl carbanion **49** as the first species along the reaction route.

The formation of α-sulfoxy carbanions in thiirane oxides is possibly analogous to the formation of α-sulfonyl carbanions in the thiirane dioxide series. The reaction of the three-membered ring oxide (e.g. **16**) with a weakly nucleophilic strong base such as BuLi will provide the sulfoxy carbanion (i.e. **52** and **53**) competitively only in the presence of carbanion stabilizing substituents (e.g. aryl groups) since: (a) the capacity of the sulfoxide group to stabilize an α-carbanion is less than that of the sulfone; and (b) the competing route, in which the sulfur is being attacked nucleophilically by the base, is evidently more favorable in sulfoxides than in sulfones. On the other hand, the chelation of the Li^+ to the sulfoxide oxygen would give preference to the formation of *syn* carbanion and to epimerization (inversion) of the sterically unfavorable carbanion. An illustrative example for all the above is given in equation 15[114].



(16) (52) (53d) (54c, d)

(c) $R^1 = R^3 = H$, $R^2 = R^4 = Ph$ (c) $R^3 = H$, $R^4 = Ph$
(d) $R^1 = R^4 = H$, $R^2 = R^3 = Ph$ (d) $R^3 = Ph$, $R^4 = H$ (15)



(56c, d) (55c, d) (57c, d)

To summarize: under favorable conditions the acidity of α-hydrogens facilitates the generation of α-sulfoxy and α-sulfonyl carbanions in thiirane and thiirene oxides and dioxides as in acyclic sulfoxides and sulfones. However, the particular structural constraints of three-membered ring systems may lead not only to different chemical consequences following the formation of the carbanions, but may also provide alternative pathways not available in the case of the acyclic counterparts for hydrogen abstraction in the reaction of bases.

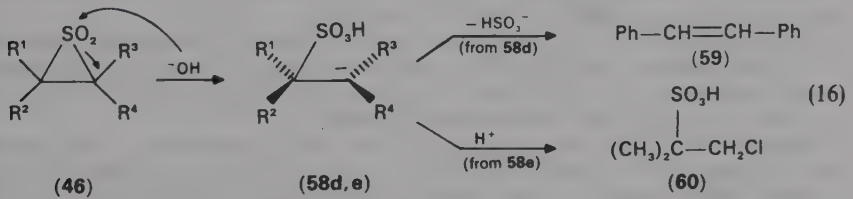
3. *Electrophilicity of the SO_2 and SO group (reaction with bases/nucleophiles)*

A direct attack of nucleophiles on the sulfur atom of the sulfone or sulfoxide group in acyclic or large-ring sulfones and sulfoxides is rather rare, or unknown, excluding metal hydride reductions and/or reductive deoxygenations. The situation is completely different in the three-membered ring systems.

The elimination of sulfur dioxide from thiirane dioxides leading to the corresponding alkenes is not the only result of base-induced reactions; other products are also formed. This fact raises the question of the mechanistic pathway of this reaction. In general, the thiirane dioxide is treated with a large excess of the base in an appropriate solvent for several hours at room temperature or below. Bases commonly used are 2N NaOH (in water), $NaOCH_3$ (in methanol), *t*-BuO^-K^+ (in *t*-BuOH) and BuLi (in tetrahydrofuran) or KOH–CCl_4 (in *t*-BuOH)[16–19,99,112,113].

A nucleophilic attack of the hydroxide (or the alkoxide) ions on the *sulfur* atom of the thiirane dioxide ring to give sulfonic acids or similar intermediates, which then decompose to alkenes and bisulfite ion, has been suggested for these reactions[16–17,99].

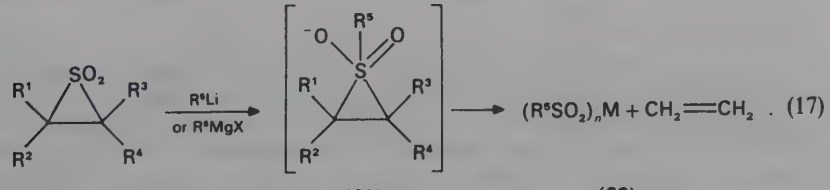
Sulfonic acids (e.g. **58**) should be sufficiently stable to be isolated and identified, as proved to be the case in the Ramberg–Bäcklund rearrangement of 2-halothiirane dioxide[115] (equation 16).



(16)

(**d**) $R^1 = R^3 = H$; $R^2 = R^4 = Ph$
(**e**) $R^1 = R^2 = CH_3$; $R^3 = H$; $R^4 = Cl$

Similarly, the reaction of the parent thiirane dioxide, the 2-chloro- and 2,3-*cis*-dimethylthiirane dioxides with either Grignard or alkyl lithium reagents, has been studied extensively. The fair-to-good yields of the sulfinates (**62**) obtained (48–82%), accompanied by ethylene (or the corresponding alkenes for substituted thiirane dioxide), have been interpreted in terms of initial nucleophilic attack of the base on the sulfur atom as depicted in equation 17[116].

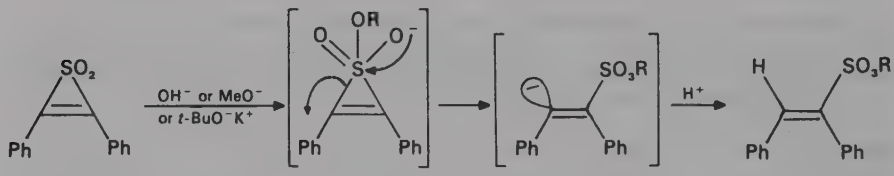


(17)

(**17a**) $R^1 = R^2 = R^3 = R^4 = H$ (**61**) $R^5 = CH_3$ or *n*-C_4H_9 (**62**) M = Li or Mg

An initial attack of a lithium reagent on the sulfur atom of **16**, leading to alkenes, has been discussed in the previous section. The similarity in the chemical consequences of the electrophilicity of both the sulfone and sulfoxide functional groups in strained three-membered ring systems is thus established.

As expected, the treatment of thiirane dioxides with strong bases resulted in ring opening to give the corresponding alkenesulfonic acids (or sulfonates) with retention of the original stereochemistry. These results are best accounted for in terms of initial attack of the nucleophilic base on the electrophilic sulfur with concomitant ring opening as shown in equation 18[99,102].



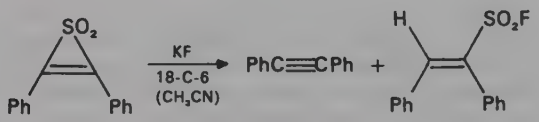
(19b) **(63)** **(64a–c)** **(65a,b)**

(a) R = H
(b) R = CH_3
(c) R = *t*-Bu (18)

Although a radical mode of ring opening cannot be excluded[102], the initial formation of the common sulfurane intermediate **63** does take account of both products obtained, the sulfonic acids/sulfonates **65** and the diphenylacetylene (**66**), and the expected temperature dependence of the ratio **65/66**. Also, the formation of the sulfurane (**63**) explains the similar results obtained in applying the KOH–CCl_4 system to the *in situ*-generated *n*-butyl- and *t*-butyl-substituted thiirene dioxides[117].

Treatment of **19b** with phenylmagnesium bromide gives diphenylacetylene (**66**) and the salt of benzenesulfinic acid[6,21]. Lithium aluminium hydride reacts with **19b** similarly. These ring-opening reactions are similar to the reactions of organometallic reagents with the analogous thiirane dioxides (equation 17 above).

Finally, the reaction of **19b** with potassium fluoride in the presence of a crown-ether phase-transfer agent[118] to yield the sulfonyl fluoride **67** and diphenylacetylene[119] belongs to the same category in which a nucleophile (F^- in this case) attacks the electrophilic sulfur of the sulfone group (equation 19).



(19)

(19b) **(66)** **(67)**

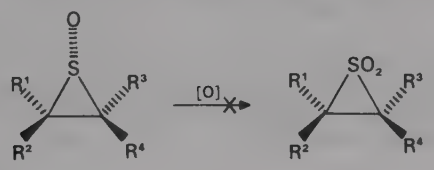
To summarize: in contrast to the observed nucleophilic attack of strongly basic nucleophiles on the sulfonyl and sulfoxy sulfur of the three-membered ring sulfones and sulfoxides, the acyclic sulfone and sulfoxide groups are attacked by nucleophiles only with difficulty[120]. Although the precise reason for this difference is as yet not clear, it is most probably associated with the geometry, electronic structure, bonding and strain energy of the cyclic compounds.

4. Nucleophilicity of the SO_2 and SO groups

Both the sulfone and the sulfoxide groups are characteristically electrophilic based on the increasing electropositivity of the sulfur atom in proportion to its oxidation state. Therefore, the nucleophilicity of these groups can be discussed only in terms of the nucleophilicity of either the trivalent sulfur atom, still having a pair of nonbonding electrons, or the oxygen atom in the sulfoxides.

Oxidation of thiirane and thiirene oxides to the dioxides is the best method to obtain the sulfones. Indeed, in the acyclic, or large-ring systems, the sequence sulfide → sulfoxide → sulfone is by far the easiest method to prepare sulfoxides and sulfones. The situation is different in the three-membered ring series: Thus, oxidation of thiiranes to the oxides by either perbenzoic acid or *m*-chloroperbenzoic acid under mild conditions affords the corresponding thiirane sulfoxides in almost quantitative yield[2,63,75,121]. However, further oxidation to the sulfone is rather limited since the thermally and/or chemically sensitive sulfones cannot survive the reaction conditions employed. With more stable thiirane oxides having the *anti*-configuration of the substituent(s) and the sulfinyl oxygen, steric hindrance may prevent a smooth oxidation under mild conditions. The following constitutes an illustrative example.

All attempts to oxidize either *cis*- or *trans*-di-*t*-butylthiirane oxides failed[122] (see equation 20). Reagents investigated included *m*-chloroperbenzoic acid, sodium peroxide, hydrogen peroxide, ozone and aqueous potassium permanganate. The *cis* oxide was resistant to oxidation (apparently steric hindrance), and the *trans* isomer was consumed with excess oxidizing agent but no identifiable products could be isolated.



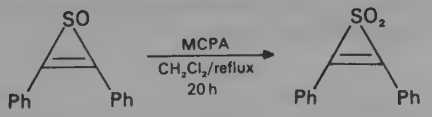
(20)

(16i,j) (17i,j)

(i) $R^1 = R^3 = H$, $R^2 = R^4 = t\text{-Bu}$

(j) $R^1 = R^4 = H$, $R^2 = R^3 = t\text{-Bu}$

In contrast to thiirane oxides, the electrophilic oxidation of thiirene oxides to thiirene dioxides is feasible, probably because both the starting material and the end product can survive the reaction conditions (equation 21).



(20–30% yield) (21)

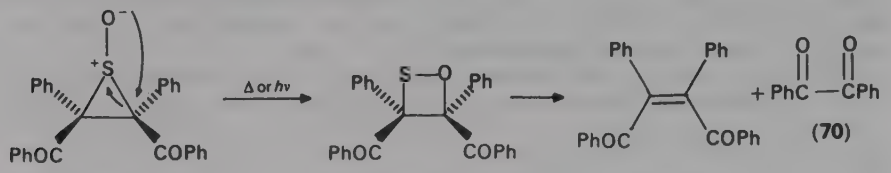
(18a) (19b)

To what extent the above suggests that the sulfoxide sulfur of thiirene oxides is more nucleophilic than that of thiirane oxides remains an open question.

There are several reactions in which the sulfoxy *oxygen* exhibits its nucleophilicity, the most noticeable being the thermal rearrangement of thiirane oxides (in the presence of a suitable disposed β-hydrogen) to allylic sulfenic acids[2,63,105] (see equation 9 in Section III.C.1).

In the following transformations, the nucleophilic oxygen of the sulfoxide group plays a

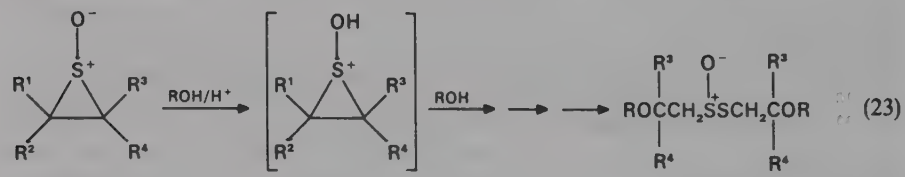
key role. Thus, a mechanism which involves ring expansion of the sulfoxide was suggested[123] to account for the formation of the products in the thermolysis and photolysis of the thiirane oxide **16k**. The stereochemistry around the sulfur atom has no effect on the ultimate results (see equation 22).



(22)

Expansions of cyclic sulfones to cyclic sulfinates are known[124], and a similar mechanistic pathway of the expansion of the three-membered ring to a four-membered ring has been suggested for the photolytic fragmentation of the 2, 3-diphenylthiirene oxide **18a**[22].

The first step in the acid-catalyzed ring opening of thiirane oxides[125,126] is the proton attachment to the oxygen as illustrated in equation 23. The ring opening is generally stereospecific, with inversion occurring at the ring-substituted carbon attacked by the nucleophile[126]. A preferential attack on the unsubstituted carbon was observed with thiols as nucleophiles.



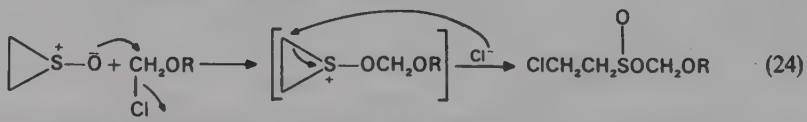
(23)

(m) $R^1 = R^2 = H$, $R^3 = R^4 = Me$

(n) $R^1 = R^2 = R^3 = H$, $R^4 = Ph$

R = Me, Et, *i*-Pr, etc.

A mechanism analogous in many ways to that of the acid-catalyzed ring opening reaction was advanced for the reaction of the thiirane oxide with alkyl chloromethyl ethers[127]. The first step is the displacement of the chloride by the sulfoxy oxygen (equation 24). In view of the above mechanistic interpretation, it is quite surprising that the parent thiirane oxide (**16a**) was found to be protonated on sulfur and *not* at oxygen in FSO_3H–SbF_6 at $-78\,^{\circ}C$, according to NMR studies[128].

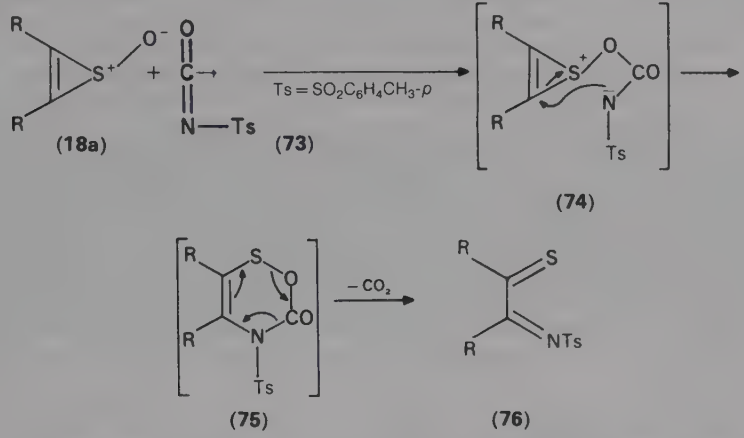


(24)

Theoretical considerations (previously discussed in Section III.B.3) predict the oxygen moiety in the sulfoxide function of thiirene oxides to be relatively nonreactive[12], that is, less nucleophilic than the sulfoxy oxygen of either thiirane oxides or ordinary acyclic sulfoxides.

The sulfoxide function in the diphenylthiirene oxide (**18a**) did react with the particularly-

electrophilic[129] *p*-toluenesulfonyl and chlorosulfonyl isocyanates[12]. Hence, refluxing **18a** with isocyanate **73** in methylene chloride for 24 hours resulted in the isolation of imine **76** due, most probably, to the mechanistic sequence given in equation 25[12].



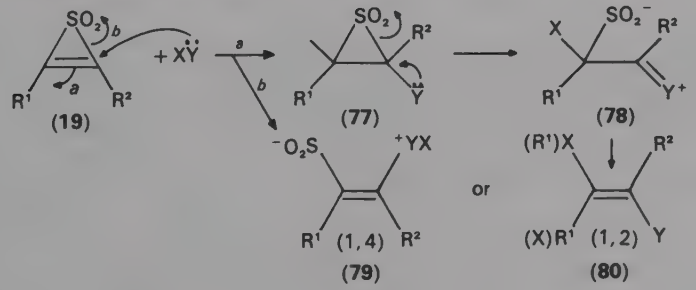
(25)

The successful deoxygenation of the sulfoxide **18a**[12] by either hexachlorodisilane as the reducing agent, or diiron nonacarbonyl according to the deoxygenation–complexation route[130], can also be rationalized in terms of electrophilic attack of the reagents used on the nucleophilic sulfoxy oxygen.

In conclusion, any electrophilic attack on the sulfoxide function in thiirene oxides must overcome a substantial energy barrier. Indeed, many oxidative reagents that proved to react smoothly with acyclic sulfoxides[131] left the thiirene oxides intact under comparable reaction conditions. Thus, there is a good correlation between theoretical predictions and experimental results in this case[2,12].

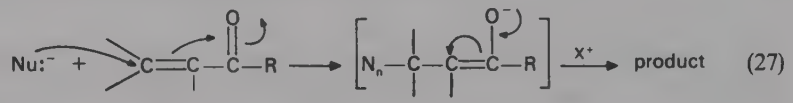
5. *The (formal) Michael addition of nucleophiles to thiirene oxides and dioxides*

α,β-Unsaturated sulfones[132], like other alkenes substituted with electron-withdrawing groups[133], are susceptible to nucleophilic additions across the carbon–carbon double bond. Thiirene dioxides are no exception and they do undergo the expected addition with soft nucleophiles. Formally, these may be categorized as Michael additions. However, these additions in the thiirene dioxide series are accompanied by ring cleavage (of one of the carbon–sulfur bonds) *sometimes* followed, as a consequence, by a loss of a sulfur dioxide unit, as shown in equation 26. The mechanistic patterns in the scheme, however, should not be considered as proven.



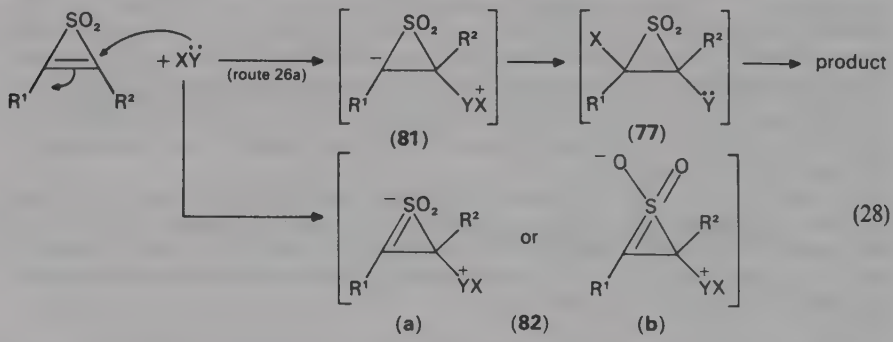
(26)

Michael addition is a 1,4-addition reaction of a nucleophile to an α,β-unsaturated system in which the double bond is conjugated with a carbonyl group, enabling the formation of the corresponding enolate as an intermediate (equation 27).



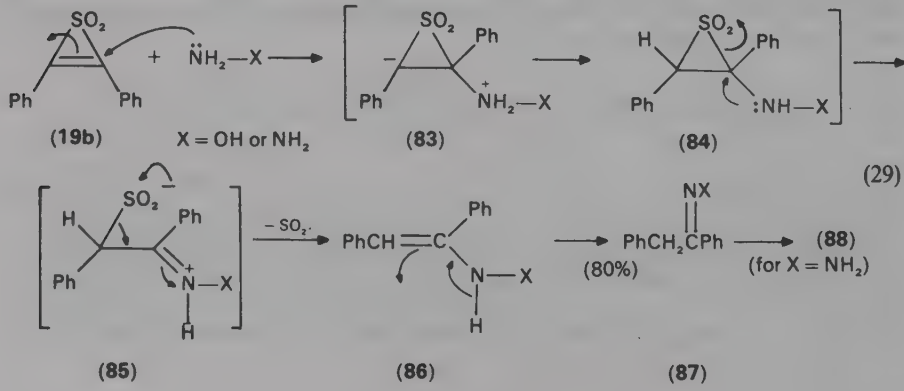
(27)

Clearly, an analogous 1,4-type conjugation cannot be operative in the three-membered ring thiirene dioxides for two major reasons: (a) there is an 'insulating effect' of the LUMO sulfur d-orbitals; that is, electronic interactions between the carbon framework and sulfur are not extended into the sulfur–oxygen interactions (see Sections III.B.2, 3); and (b) the intermediacy of a carbon–sulfur double bond (i.e. **82a**) within the three-membered ring framework is highly unlikely (equation 28). Consequently, the nucleophilic addition of XŸ proceeds either by route *a* or route *b* (equation 26) with the intermediacy of the stabilized α-sulfonyl carbanion **81** along route *a*. Therefore, only 1,2-additions to the double bond via route *a* (equation 26) may be categorized as 'Michael additions' and will be treated as such.



(28)

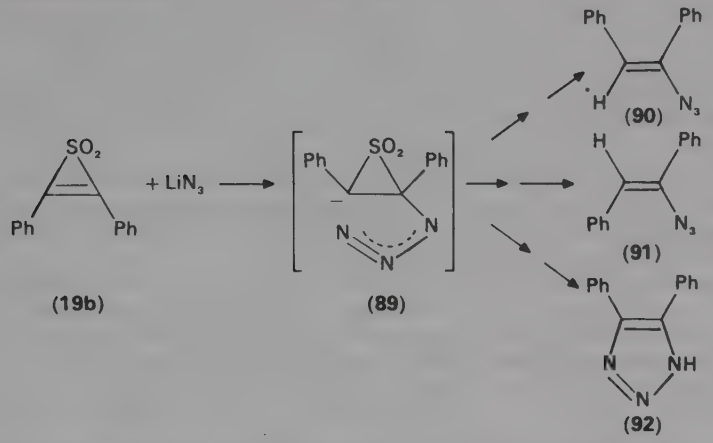
An illustrative example of the Michael reaction is that of the thiirene dioxide **19b** with either hydroxylamine or hydrazine to give desoxybenzoin oxime (**87**) and desoxybenzoin azine (**88**), respectively, in good yields[6] (see equation 29). The results were interpreted in terms of an initial nucleophilic addition to the α,β-unsaturated sulfone system, followed by loss of sulfur dioxide and tautomerization. Interestingly, the treatment of the corresponding thiirene oxide (**18a**) with hydroxylamine also afforded **86** (as well as the dioxime of benzoin), albeit in a lower yield, but apparently via the same mechanistic pathway[6].



(29)

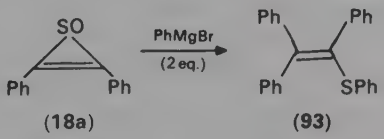
Although the nucleophilic addition of secondary amines to thiirene dioxides can be interpreted as following the same mechanistic pathway, the reaction was found to be second order in amine[119] (which is typical for the addition of amines to olefins in appropriate solvents[132,133]), and the addition is *syn*. As a result, mechanisms with a cyclic-concerted addition across the carbon–carbon bond, or a stepwise addition involving two molecules of amine per one molecule of thiirene dioxide, have been proposed.

In a similar manner, the reaction of **19b** with lithium azide[135] to give the *cis*- and *trans*-vinyl azides (i.e. **90, 91**) and triazole **92** can be rationalized by assuming an initial stepwise 'Michael-type' nucleophilic addition of the azide ion to the carbon–carbon double bond, followed by protonation or rearrangement/transformations including inversion of the initially formed α-sulfonyl carbanion[134] (equation 30). The products obtained in the reaction of **19b** with equimolar acyl-substituted sulfonium ylids such as $(CH_3)_2\overset{+}{S}\overset{-}{C}HCOAr$[135] were also rationalized in terms of an initial attack of the ylid carbon on the vinylic carbon of the thiirene dioxide leading to an α-sulfonyl carbanion analogous to **89**, which through further transformations results in a novel ring enlargement of the original thiirene dioxide.



(30)

Finally, obtaining olefin **93** from the reaction of thiirene oxide **18a** with two equivalents of phenylmagnesium bromide may be a consequence of the initial nucleophilic 'Michael-type' addition of the latter across the carbon–carbon double bond of the cyclic sulfone[22] (see equation 31).



(31)

Thus, like α,β-unsaturated ketones and sulfones, both thiirene dioxides and thiirene oxides are preferentially attacked by the less basic nucleophiles on the vinylic carbon atom[2]. This would lead to formally 1,4 Michael-type adducts and/or other products resulting from further transformations following the initial formation of the α-sulfonyl and α-sulfoxy carbanions.

6. *Miscellaneous*

a. Complexation with transition metal complexes. Zerovalent platinum and palladium complexes of the thiirene dioxides can be easily prepared by ligand exchange with

platinum complexes of the type L_2PtX at ambient temperature[81] (see equation 32).

(32)

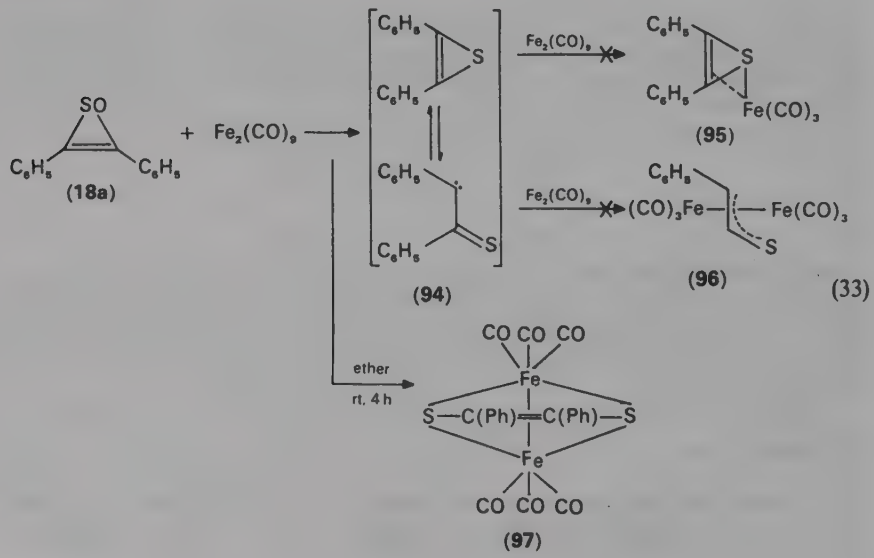
(19) **(35)**

(a) $R^1 = R^2 = CH_3$
(b) $R^1 = R^2 = Ph$
(c) $R^1 = H$, $R^2 = CH_3$
(d) $R^1 = CH_3$, $R^2 = Ph$

$L = Ph_3P$
$X = Ph_3P$, $CH_2{=}CH_2$, CS_2

Of all attempted thiirene dioxides, only **19c** coordinated to Vaska's complex [*trans*-$IrL_2(CO)Cl$]. The structural assignments were based on both IR and NMR spectroscopy (i.e. coupling constants), according to which both the platinum and the palladium complexes of thiirene dioxides **19a,c** were isolated at temperatures below 0 °C. Attempts to isolate the complexes with **19b,d** failed, presumably due to the reduced availability of the π-electrons of the carbon–carbon double bond in these substituted thiirene oxides for interaction with the vacant LUMO of the metal, or their enhanced tendency to lose SO_2 thermally. Indeed, the zerovalent palladium and platinum complexes as well as monovalent rhodium and iridium complexes were found[81] to catalyze the decomposition of thiirene dioxide, whereas divalent platinum and palladium complexes had no effect. The capacity of SO_2 to serve as a ligand in metal complexes is well known, and obtaining the stable complex L_2PtSO_2 in the above-catalyzed SO_2 elimination from thiirene dioxides (see equation 7) is probably a major driving force for the reaction to occur. At any rate, the sulfone group appears to be only indirectly involved in the complexation of thiirene dioxides to transition metals.

Unexpectedly, neither direct complexation nor the deoxygenated complexes **95** or **96**[136,137] were observed in the reaction of diphenylthiirene oxide (**18a**) with iron nonacarbonyl. Instead, the red organosulfur–iron complex **97**[138] was isolated[12], which required the cleavage of three carbon–sulfur bonds in the thiirene oxide system (see equation 33). The mechanism of the formation of **97** from **18a** is as yet a matter of speculation.

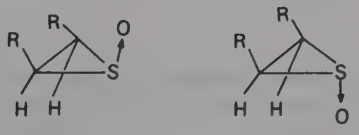


(33)

b. Configuration induced by the sulfoxide group. The asymmetry of the sulfoxide group gives rise to *syn–anti* configurations in cyclic substituted sulfoxides involving the sulfoxy oxygen and the substituents.

A systematic study[63a] in which substituted thiiranes were oxidized to the corresponding thiirane oxides determined the geometrical position of the oxygen atom by complete NMR and microwave analysis.

Mono- and *cis*-di-substituted thiirane oxides can theoretically exist in the *syn*- (*s*) and *anti*- (*a*) configurations shown below:



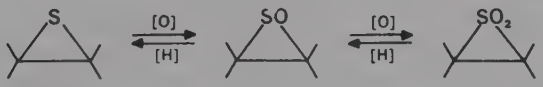
(s) (a)

The oxidizing agent (organic peracid) usually attacks the sulfur from the less hindered side of the substrate to produce the less hindered oxidation product as a major isomer[139].

Thus, the observed stereoselectivity means the exclusive formation of the *anti*-isomer (*a*). This conclusion was confirmed by NMR analysis[63] (see Section III.B.4.b) and, clearly, can be extended and generalized with respect to larger cyclic sulfoxide systems.

D. The Synthesis of Three-Membered Ring Sulfones and Sulfoxides

Oxidation of the sulfur in thiiranes (**20**) to the corresponding sulfoxides (i.e. **16**) and further oxidation to the sulfones (**17**) is formally analogous to the sequence sulfides → sulfoxides → sulfones in the acyclic or large ring series (equation 34).

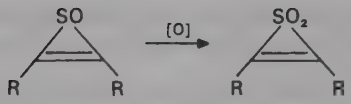


(20) (16) (17) (34)

Also, the reduction of sulfones **17** to the sulfoxides **16** would seem to be the method of choice for the preparation of the latter, provided the former are readily available.

Unfortunately, although sulfoxides **16** are accessible via the oxidation of thiiranes **20** under controlled mild reaction conditions[2,63,121,122], their direct oxidation to the sulfones **17** is impractical, since the thermodynamically unstable sulfones would lose SO_2 under the reaction conditions. On the other hand, the treatment of the sensitive three-membered ring sulfones with either appropriate reducing agents (e.g. metal hydrides like $LiAlH_4$) or deoxygenation agents (e.g. $Cl_3SiSiCl_3$[140], $Et_3N{\cdot}SO_2$[141], $Fe(CO)_9$[12,130]) would result in reduction up to the sulfide state (i.e. **20**) followed, possibly, by the destruction of the three-membered ring system. In fact, there is no known method available for reducing the sulfones to sulfoxides even in the acyclic series, due to the very fast reduction of the sulfoxide to the sulfide.

The situation is even more problematic in the unsaturated series: the elusive thiirenes[2,142] cannot serve as starting materials for the synthesis of thiirene oxides **18** via direct oxidation, and the laborious synthetic method used to prepare the most commonly known and studied aryl-substituted thiirene oxides[2,22] **18** does not make the latter attractive as starting materials for preparing the corresponding thiirene dioxides[19]. Fortunately there are much better and versatile methods available[2] for the synthesis of the sulfones **19** (equation 35).

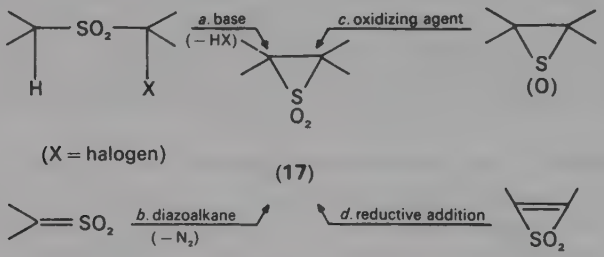


(18) (19) (35)

Similarly, also for the transformation **18** → **19**, different strategies have been developed, which will be presented and discussed below.

1. Thiirane dioxides

Due to the instability of thiirane dioxides, only a few methods are available for their practical preparation. Of the routes summarized in the scheme below[2] (equation 36), only *a* and *b* have practical value and generalizability. Route *b* appears to be the method of choice.



(36)

Route *a* represents the classic Ramberg–Bäcklund reaction, the most thoroughly studied of all the routes[2,15–19,99,117]. Under the basic reaction conditions employed, the *in situ* generated three-membered ring would undergo further transformations, mainly loss of SO_2. This route, however, turns out to be very productive in the preparation of aryl-substituted thiirene dioxides[6] and oxides[22] due to the relative thermal stability and survivability of the latter in the presence of weakly nucleophilic organic bases (see later).

Route *b* involves the formation of one carbon–carbon bond and one carbon–sulfur bond. It belongs to the category of sulfene chemistry[143]. Sulfene intermediates react readily with diazoalkanes to produce, after the loss of nitrogen, thiirane dioxides. So far, this appears to be the method of choice for the preparation of thiirane dioxides of all types.

Route *c* involves the oxidation of thiiranes through the corresponding sulfoxides to the dioxide stage. The problems associated with this route have been discussed above, and its scope was shown to be rather limited.

Route *d* is a hydrogenation of thiirene dioxides. Since the preparation of thiirene dioxides is rather laborious, and many of them are prepared from the corresponding thiirane oxides[6], this method has practically no preparative value, and the only example reported is the reduction of **18a** to *cis*- **17d** in a very low yield (8%)[21].

a. From α-halosulfones and strong bases. Typically, the bases applied are sodium hydroxide, sodium alkoxides and *t*-BuO^-K^+. The reaction is generally depicted as in Scheme 37[17b].

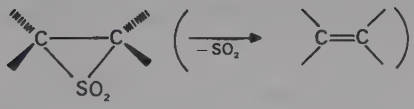
Actually, thiirane dioxides (**17**) have so far never been isolated in these reactions; *cis*- and *trans*-olefins were the main products, and all attempts to obtain the three-membered ring system and prevent the loss of SO_2 failed. Hence, the method can be used only for the *in situ* formation of intermediates.

(i)

(ii)

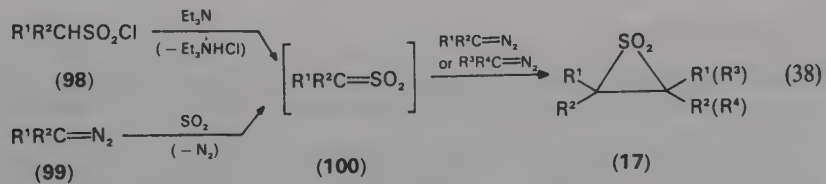
(37)

(iii)



(17)

b. Via sulfenes and diazoalkanes. The best method for the synthesis of thiirane dioxides is the interception with diazoalkanes of sulfenes generated *in situ* through dehydrohalogenation of sulfonyl chlorides containing α-hydrogens[143]. Alternatively, sulfenes can be generated by the reaction of diazoalkanes with sulfur dioxide[5], and with a second mole of a diazoalkane give thiirane dioxides (equation 38).



(38)

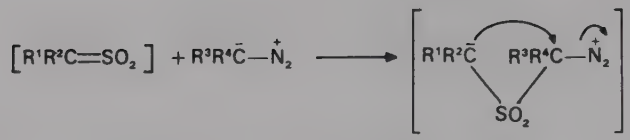
In a typical procedure[61,144] the sulfonyl chloride in ether is added to an etheral solution of the diazoalkane and triethylamine. Filtration and evaporation gives the relatively pure thiirane dioxide. Further purification can be easily achieved by recrystallizations preferentially *below* room temperature in order to avoid fragmentation of the product into sulfur dioxide and the olefin. In general, when the temperature of the above reaction is lowered, the yields are improved without a drastic decrease in reactivity[144]. Many thiirane dioxides have been successfully synthesized through this method and a detailed list of them can be found elsewhere[2].

The use of excess diazoalkane in its reaction with sulfur dioxide will necessarily lead to symmetrically substituted thiirane dioxides. When monoalkyl or monoaryl diazoalkanes are used, mixtures of *cis*- and *trans*-isomers are formed[18,19,99].

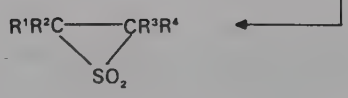
The *cis/trans* ratio of the products varies significantly with the polarity of the reaction medium: the higher the polarity of the solvent, the lower is the yield of the *cis*-product.

Another procedure[145] consists of bubbling of sulfur dioxide through a chilled solution of diazomethane in ether[146]. Evaporation of the solvent leaves the crude thiirane dioxide, which can be further purified by either distillation under reduced pressure or recrystallization. The formation of the thiirane dioxides is usually accompanied by formation of the corresponding olefins, along with small amount of ketazines.

The mechanism of this reaction is not known. However, some evidence[18,98,143] suggests the mechanism (equation 39) with the zwitterion **101** as a key intermediate. This is in accord with the known favored attack of nucleophiles at the sulfur atom of sulfenes[143].



(100) (101) (39)



(17)

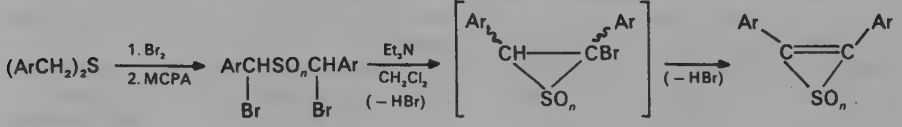
The stereochemistry of the ring product (17) was rationalized in terms of the attraction and repulsion between the involved substituents[98]. The accompanying olefins may be formed via carbene intermediates (arising from α-elimination of SO_2 from sulfene), and the intermediacy of thiadiazoline dioxide (from sulfene and diazoalkane) explains the formation of the ketazine side-products. Thiadiazoline, on its part, may be formed directly by the cyclization of zwitterion **101**.

As stated before, routes *c* and *d* (equation 36)[6,21] have very limited value.

2. *Thiirene dioxides*

a. Via modified Ramberg–Bäcklund reaction. The Ramberg–Bäcklund method is extremely useful for the preparation of thiirene dioxides[6,147] as well as of thiirene oxides[21] and other three-membered ring sulfone systems (e.g. thiadiaziridine dioxides)[100,101].

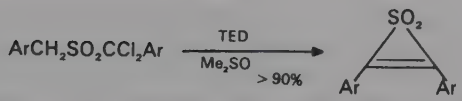
Most thiirene dioxides (and oxides) have been prepared through a modified Ramberg–Bäcklund reaction as the last crucial cyclization step, as illustrated in equation 40 for the benzylic series[6,22]. Synthesis of thiirene dioxides requires two major modifications of the originally employed reaction: first, the inorganic base has to be replaced by the less basic and less nucleophilic triethylamine[6,21]; and second, the aqueous media has to be substituted by an aprotic organic solvent (e.g. methylene chloride). Under these mild reaction conditions the isolation of aryl-substituted thiirene dioxides (and oxides) is feasible[6,22]. In fact, this is the most convenient way for the preparation of the aryl-disubstituted three-membered ring sulfones and sulfoxides[2].



(102) (103) (18) $n=1$
(19) $n=2$

(40)

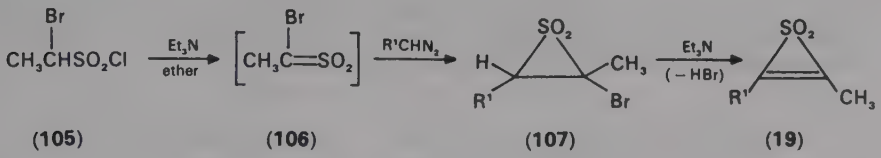
In a similar way, diarylthiirene dioxides can be prepared by the reaction of triethylenediamine (TED) or DABCO with α,α-dichlorobenzyl sulfones at ambient temperatures[100] (equation 41).



(104) (19) (41)

Ar = C_6H_5, *p*-ClC_6H_4, *p*-MeC_6H_4

b. Via sulfenes and diazoalkanes. This route for the preparation of alkyl-substituted thiirene dioxides is based on the interception of *in situ*-generated sulfenes with diazoalkanes[143,144]. The 2-halo-substituted thiirane dioxide ring thus formed is treated with a base to yield the required thiirene dioxide through dehydrohalogenation[6,113] (see equation 42).



(105) (106) (107) (19)

(a) $R^1 = CH_3$
(c) $R^1 = H$
(d) $R^1 = C_6H_5$

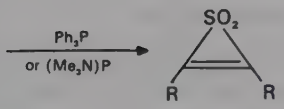
(42)

However, alcohol-free solutions of diazomethane[146] must be used to avoid destruction of the intermediate sulfene and a stronger base such as 1, 5-diazabicyclo [4.3.0] non-5-ene is required for the final dehydrohalogenation step to obtain sulfones **19a,d**.

c. By debromination of tetrabromosulfones. This route to dialkylthiirene dioxides from tetrabromosulfones (see equation 43) is of particular significance, since it can be used on a large scale, and makes dialkylthiirene dioxides as easily obtainable as the diaryl-analogues. Both dimethyl- and diethyl-thiirene dioxides have been thus prepared[148].

$$\underset{\textbf{(108)}}{CH_3SOCH_3} \xrightarrow{Br_2{}^{149}} \underset{\textbf{(109)}}{CBr_3SO_2CBr_3} \xrightarrow{(RO)_3P{}^{150}} \underset{\textbf{(110)}}{RCBr_2SO_2CBr_2R} \qquad (43)$$

(a) R = Me
(e) R = Et



(19a, e)

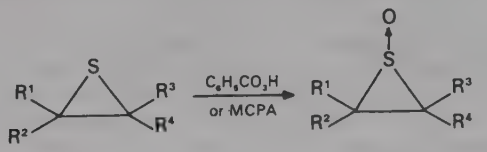
3. Thiirane oxides

To date, several well-established methods are available for the convenient preparation of thiirane oxides, the two main ones being the controlled oxidation of thiiranes[63a] and the reaction of sulfenes with diazoalkanes[63b].

a. By oxidation of thiiranes. The controlled oxidation of thiiranes to the corresponding thiirane oxides is a well-established process[63a,65].

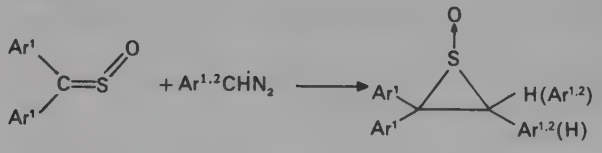
Following the isolation of the parent thiirane oxide **16a** by the oxidation of thiirane with either sodium metaperiodate[95] or with the *t*-BuOH–H_2O–V_2O_5 system[151], a systematic study was undertaken[63a,75] to establish a reliable and general method for the oxidation of thiiranes to thiirane oxides. Iodosobenzene, *t*-butyl hypochlorite, N_2O_4, H_2O_2 and organic peracids have been examined.

Either perbenzoic acid or *m*-chloroperbenzoic acid are the reagents of choice and methylene chloride is the preferred solvent for the oxidation under mild conditions[63a,75] (equation 44). Equimolar amounts of the reactants are used and the oxidation is completed within minutes. The reaction affords an essentially pure solution of the sulfoxide in almost quantitative yield[63a,75]. The thiirane oxides have the *anti*-configuration with respect to the substituent(s) and sulphinyl oxygen[63a,75]. Considering the steric hindrance of substituents in the peracid oxidation, the preferential formation of the *anti*-isomer is to be expected. However, there is no significant deuterium isotope effect on the regioselectivity of the sulfoxidation of *cis*-dideuteriothiirane; both stereoisomers of the corresponding thiirane oxide are formed in equal amounts[107].



(20) (16) (44)

b. Via sulfines and diazoalkanes. This is the most important nonoxidative method for the preparation of thiirane oxides, particularly aryl-substituted ones. Thus, diaryl sulphines dissolved in aprotic solvents such as pentane or ether give the thiirane oxides in good yields in a smooth reaction with aryldiazomethanes, as illustrated in equation 45[2,63b]. A mechanism analogous to that operative in the reaction of sulfenes with diazoalkanes to give thiirane dioxides (equation 39) is probable.



(111) (112) (16) (45)

(*syn* and *anti*)

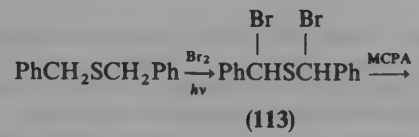
If reaction conditions are chosen in such a way that the products crystallize from the cooled reaction mixture, it is possible to obtain pure products even in the cases of sensitive three-membered ring sulfoxides.

All the asymmetric thiirane oxides which have been obtained through this procedure are mixtures of the two possible *cis*- and *trans*- (*syn*- and *anti*-) configurations, but the *anti*-isomer predominates.

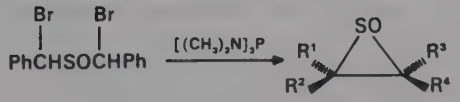
Any attempt to separate the two components by the usual chromatographic methods failed owing to the instability of the thiirane oxides, which easily lose sulfur monoxide to give the corresponding olefins[152].

c. By ring closure of α,α′-dibromobenzyl sulfoxides. A general, efficient nonoxidative route for the preparation of diaryl-substituted thiirane oxides involves the photolytic

bromination of dibenzyl sulfide followed by the oxidation of the isolable intermediate dibromosulfide (**113**) to the corresponding mixture of benzylic α,α'-dibromosulfoxides (**114**). 1,3-elimination of bromine from the dibromide by treatment with *tris*(dimethylamino)phosphine provides the three-membered ring sulfoxide stereospecifically[153] (equation 46).



(**113**)



(46)

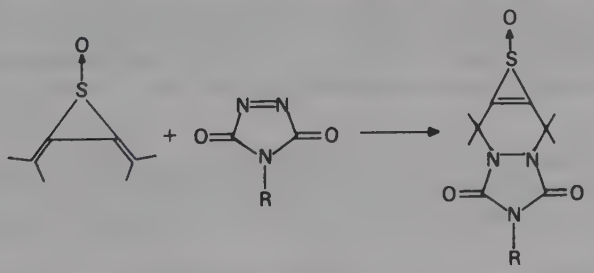
(**114**) (**16**)

(**a**) *meso*-dibromo (*anti*) (**c**) $R^1 = R^3 = Ph$ (from **114a**)
(**b**) (±)-α,α'-dibromo (*trans*) (**d**) $R^1 = R^4 = Ph$ (from **114b**)

4. Thiirene oxides

a. Aryl substituted. A general route for the preparation of thiirene oxides involves the reaction of benzylic α,α'-dibromosulfoxides with excess triethylamine in refluxing methylene chloride for 24–48 hours[22]. In fact, all known aryl-substituted thiirene oxides have been synthesized through this modified Ramberg–Bäcklund procedure (equation 40). This route, however, is laborious, lengthy, and the overall yield is rather low (16–20%)[2].

b. Alkyl substituted. The first (and so far the only known) synthesis of alkyl-substituted thiirene oxides[60] involves the [2 + 4] cycloaddition of equimolar amounts of thiiranoradialene sulfoxide **115**[154] and the superdienophile **116**, to yield the sulfoxide system **30**[60] (equation 47).



(47)

(**115**) (**116**) (**30a, b**)

(**a**) $R = CH_3$
(**b**) $R = C_6H_5$

All attempts to prepare other [2 + 4] cycloadducts of sulfoxides **115** with dienophiles such as maleic anhydride, ethyl azodicarboxylate, etc., have failed[60]. A method for preparing ordinary alkyl-substituted thiirene oxides (e.g. **18**; $R^1 = R^2 =$ alkyl) is still lacking.

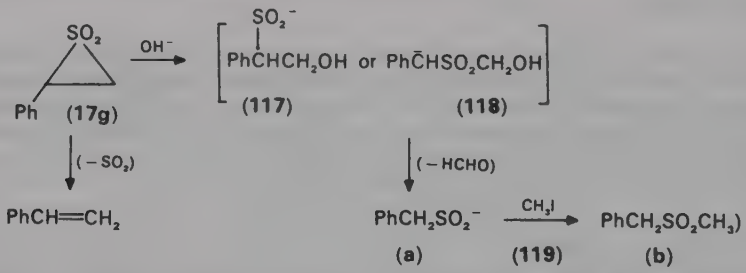
E. Selected Chemical Reactions and Transformations

Selected additional reactions, transformations, or rearrangements of three-membered ring sulfones and sulfoxides will follow. The criteria for selection is the direct or indirect involvement of the functional groups in the reaction.

1. Nucleophilic attack on carbon in thiirane and thiirene dioxides and oxides

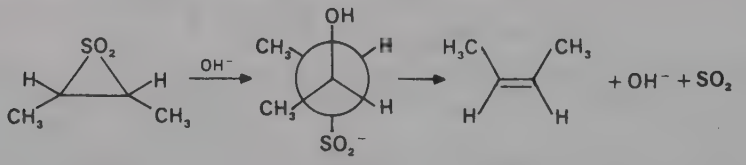
a. With strong bases. The rupture of thiirane and thiirene dioxides generated *in situ* under the Ramberg–Bäcklund rearrangement conditions has been extensively studied[15-19,99,112] and thoroughly discussed[2,154], alkenes and acetylenes, respectively, being the major products. The involvement of the sulfone group in these transformations is obvious either as the site of primary attack by the base, or as an 'electron sink' for the bonding carbon–sulfur bond electrons, following the nucleophilic attack of the base on the carbon or the initial formation of the corresponding α-sulfonyl carbanion. Of all the above, only the base-induced formation of α-sulfonyl carbanions is known in the acyclic systems.

In the presence of aqueous sodium hydroxide, 2-phenylthiirane dioxide gives styrene and the sulfinate **119**. These results have been interpreted[111] in terms of initial *nucleophilic* attack of hydroxide ion at the *carbon atom* in the 3-position of the three-membered ring in addition to sulfur dioxide elimination (see equation 48).



(48)

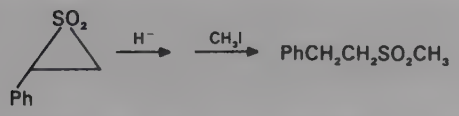
Similarly, the stereospecific formation of *cis*-2-butene from *cis*-2,3-dimethylthiirane dioxide[19] may be rationalized in terms of a stereospecific ring opening to give the threo-sulfinate **120** which, in turn, decomposes stereospecifically to yield the *cis*-alkene, hydroxide ion and sulfur dioxide[73]. The parent thiirane dioxide fragments analogously to ethylene, hydroxide ion and sulfur dioxide (equation 49).



(49)

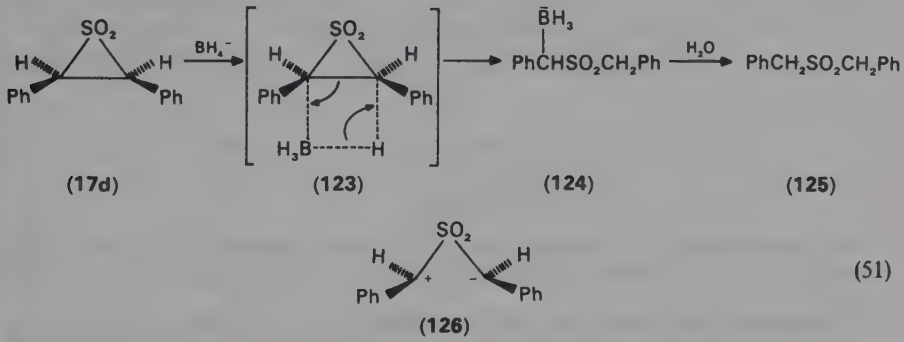
It was further confirmed that although the fragmentation pattern is dependent on the substitution pattern, most thiirane dioxides formed *in situ* decompose rapidly and stereospecifically under alkaline conditions to yield the corresponding alkenes with *retention* of configuration[156].

b. With metal hydrides. A closely related nucleophilic ring opening is the selective attack on the 2-carbon atom by the hydride ion ($LiAlH_4$ or $LiBH_4$)[115] as shown in equation 50.



(17g) (122) (50)

In general, reductive cleavage of the carbon–carbon bond in thiirane dioxides can be accomplished[115] by the typical nucleophilic reducing agents, lithium and sodium borohydrides, and lithium aluminium hydride. Thus, 2,3-*cis*-diphenylthiirane afforded 45% yield of dibenzyl sulfone with either $LiBH_4$ or $NaBH_4$, but only between 0–10% with $LiAlH_4$. The reduction of 2,2,3,3-tetraphenylthiirane dioxide gave the corresponding open sulfone in 68% yield, whereas the reduction of 2-phenylthiirane dioxide with the same reagents (equation 50) gave no carbon–carbon cleavage product, but rather a carbon–sulfur fission product (a sulfinic acid salt). Based on these results and solvent effects, the mechanism shown in equation 51 has been proposed[155], although others involving either an activated zwitterion (**126**) or a simple S_N2 hydride attack on the phenyl-substituted carbon cannot be excluded.

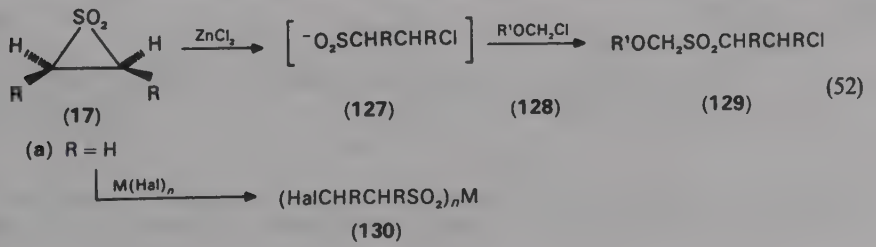


(17d) (123) (124) (125)

(126) (51)

There is no clear reason to prefer either of these mechanisms, since stereochemical and kinetic data are lacking. Solvent effects also give no suggestion about the problem. It is possible that the carbon–carbon bond is weakened by an increasing number of phenyl substituents, resulting in more carbon–carbon bond cleavage products, as is indeed found experimentally. All these reductive reactions of thiirane dioxides with metal hydrides are accompanied by the formation of the corresponding alkenes via the 'usual' elimination of sulfur dioxide.

c. With metal halides. Reaction of the parent thiirane dioxide with chloromethyl ethers in the presence of zinc chloride gave alkoxymethyl 2-chloroethyl sulfones (**129**), presumably through the intermediacy of the chlorosulfinate (**127**)[128] (equation 52).



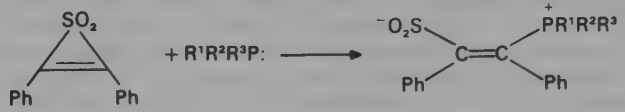
(17) (127) (128) (129) (52)

(a) R = H

(130)

The zinc chloride is acting here as a Lewis acid. Similarly, thiirane dioxides react with metal halides such as lithium and magnesium chlorides, bromides and iodides in ether or THF to give the halo-metal sulfinates (**130**) in fair yields[157].

d. With soft nucleophiles. Phosphines react rapidly with thiirene dioxides to give the corresponding betaines (**132**) in essentially quantitative yield[119,158] (equation 53).

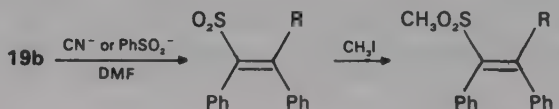


(53)

(19b) **(131)** **(132)**

(a) $R^1 = R^2 = R^3 = NMe_2$ **(c)** $R^1 = R^2 = Et$; $R^3 = Ph$
(b) $R^1 = R^2 = R^3 = Bu$ **(d)** $R^1 = R^2 = Ph$; $R^3 = CH_3$

Cyanide and benzenesulfinate ions react with thiirene dioxides in an analogous manner (equation 54).



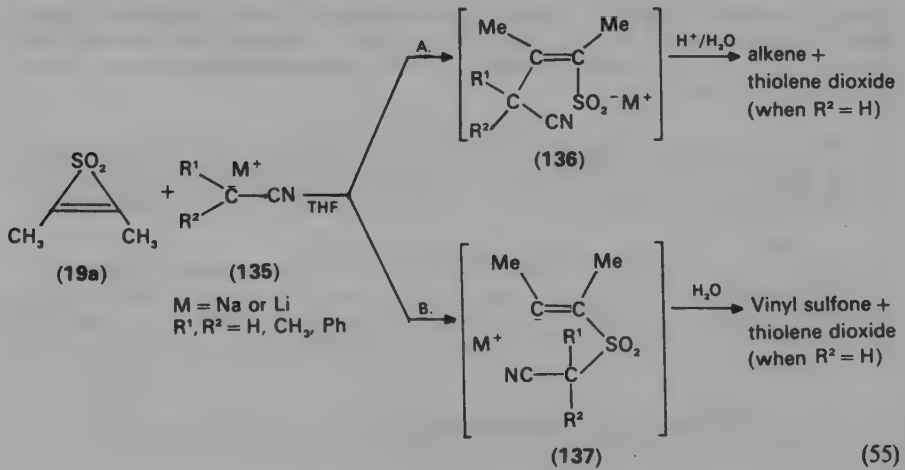
(54)

(133) **(134)**

(a) R = CN
(b) $R = PhSO_2$

The stereochemistry of the electrocyclic ring opening following the attack of the nucleophile on the vinylic carbon appears to be governed by the principle of least motion[159,60].

α-Metalated nitriles (**135**) attack thiirene dioxides nucleophilically; the latter act as ambident electrophiles. The two intermediates formed (**136** and **137**) yield both alkenes and sulfur-containing heterocycles, depending on whether or not the starting metalated nitriles contain an α-hydrogen atom[135] (equation 55).

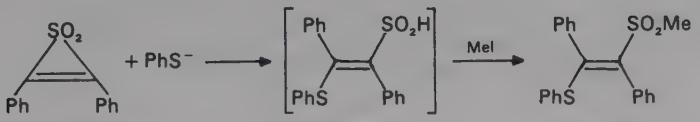


(19a) **(135)**
M = Na or Li
R^1, R^2 = H, CH_3, Ph

(136) **(137)**

(55)

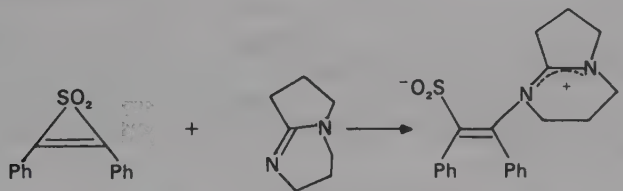
The softer, less basic potassium bromide and iodide did not react with the thiirene dioxide **19b**. The latter was also inert towards potassium thiocyanate, selenocyanate or nitrile. It did react, however, with potassium thiophenoxide in DMF at room temperature to yield, most probably, the vinyl sulfinate **138** isolated as the corresponding sulfone[39] (equation 56).



(19b) (138) (139) (56)

The isolation of the *E*-isomer **139** was in fact unexpected, since all tetrasubstituted olefins previously obtained from thiirene dioxide have been assigned the *cis*-configuration with respect to the two phenyl substituents based on the principle of least motion during the ring opening to olefins[159,160]. It might well be, therefore, that the *E*-isomer is obtained through the isomerization of the initially formed *Z*-isomer.

Although thiirene dioxides do not react with typical tertiary amines like triethylamine, they do react with the amidine 1,5-diazobicyclo-[4.3.0]-non-5-ene (DBN) to give a 1:1 adduct betaine[119,158] **141**, analogously to the reaction of thiirene dioxides with soft nucleophiles (equation 57).

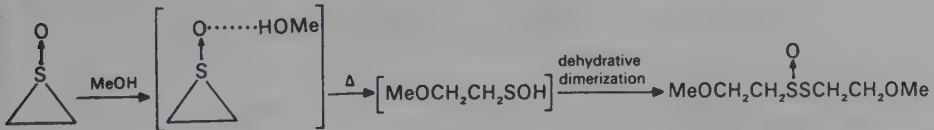


(19b) (140) (141) (57)

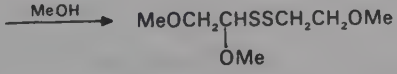
Interestingly, it appears that thiirene oxides also react with amidines (e.g. DBU) in a similar way[2].

2. Acid-catalyzed ring opening of thiirane oxides

The reaction of **16a** on heating with methanol to give the sulfenic acid intermediate **142** and the sulfinate **143** (which was further transformed into the disulfide **144**) was interpreted in terms of the mechanism shown in equation 58[161].



(16a) (142) (143) (58)



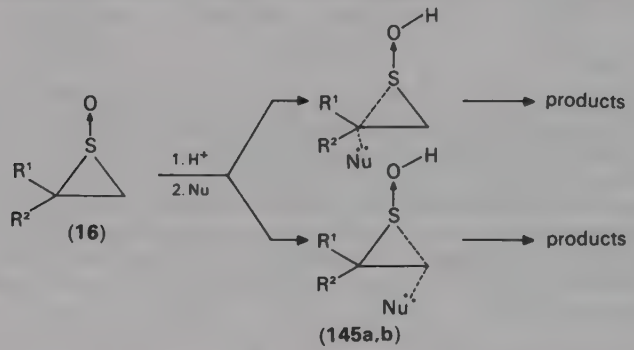
(144)

Presumably, the heterolytic scission of the carbon–sulfur bond in the oxide is assisted by the hydrogen bonding, in addition to the inherent strain of the three-membered ring.

Under the reaction conditions the initially formed thiosulfinate (**143**) is quantitatively transformed into the disulfide **144** by a Pummerer-type rearrangement[125].

The above reaction is a convincing example of an intermolecular hydrogen abstraction leading essentially to the same result as obtained in the pyrolysis of alkyl-substituted thiirane oxides through an intramolecular β-elimination of hydrogen.

The mechanistic interpretation of the acid-catalyzed ring opening reaction of thiirane oxides[125] is based on the push–pull mechanism[162] with a transition state in which the bonded hydrogen atom plays a major role (see equation 59).

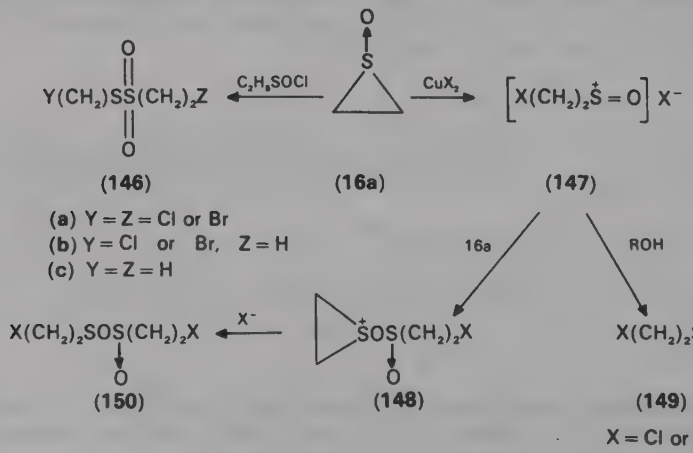


(16) (145a,b) (59)

The above explains the key roles of: (a) the nucleophilicity of the nucleophile; (b) the substituent(s); (c) the polarity of the reaction medium; and (d) the the bulkiness of the nucleophile, in determining the regio- and stereo-specificity of the reaction. The reaction of alkyl chloromethyl ethers with thiirane oxides to give sulfenic esters[128] appears to be mechanistically analogous.

3. *Reactions of thiirane oxides with metal salts*

Whereas acyclic sulfoxides form complexes with various metal salts, thiirane oxides react with copper(II) chloride or bromide[163] in benzene at room temperature to give the thiolsulfonate **146a**. In alcoholic solution below 0 °C the major products are sulfinates (**149**). Similar results are obtained in the reaction of thiirane oxides with ethanesulfinyl chloride[163] as summarized in equation 60.



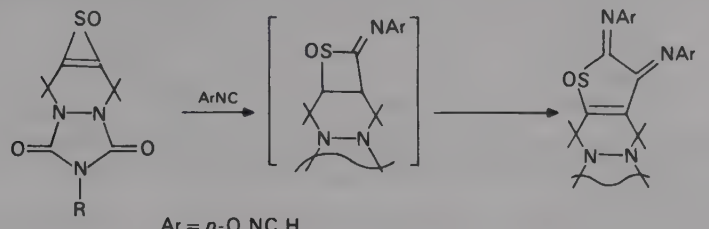
(146) (16a) (147)

(a) Y = Z = Cl or Br
(b) Y = Cl or Br, Z = H
(c) Y = Z = H

(150) (148) (149)

X = Cl or Br (60)

The formation of the 2, 3-diiminosulfoxide **152** by the insertion of two moles of isonitrile into the carbon–sulfur bond of **30**[164] (equation 61) can be naively considered as related to the transformation **16a** → **147** → **148**.



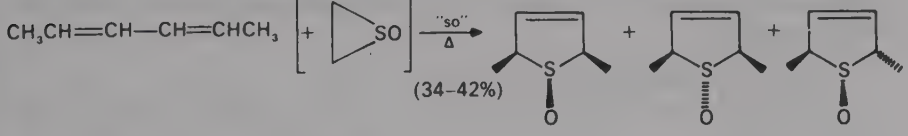
(30) (151) (152) (61)

4. Thermolysis of thiirane and thiirene oxides

The thermolysis of acyclic- and/or six- and larger ring sulfoxides to yield olefins and sulfenic acids is well documented[97,106]. The formation of allylic sulfenic acids and thiosulfinates in the thermolysis of thiirane oxides containing hydrogen on the α-carbon of the ring substituent (which is *syn* to the S—O bond) has been discussed previously in terms of β-elimination of hydrogen, which is facilitated by relief of strain in the three-membered ring (Section III.C.1).

The thermolysis of thiirane oxides not having β-hydrogens available for extraction has been shown, through an elegant study[104], to generate triplet sulfur monoxide[95] that could be trapped stereospecifically with dienes[165].

Thus the reaction of the three geometrical isomers of 2, 4-hexadiene with thiirane oxide afforded the three related 3-thiolene *S*-oxides **154** depicted in equation 62[104].



(153) (16a) (154)

(a) *trans–trans*	0	87	13
(b) *cis–trans*	*Trace*	5	95
(c) *cis–cis*	20	19	61

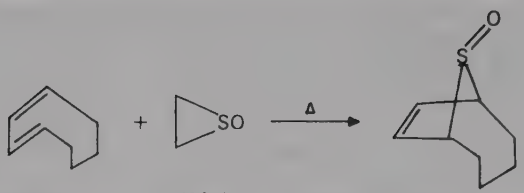
(% extrapolated to zero reaction time)

(62)

The above stereoselective additions of SO to dienes could have been predicted from its ground triplet state.

Stereochemical control at sulfur is detectable only in methyl *cis*-sulfoxide, of course, but it is noteworthy that the methyl *cis*-sulfoxide from **153a** is exclusively the less-stable isomer **154**-*t*, *t*.

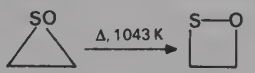
The high stereoselectivity of the SO—diene reaction is further demonstrated in reaction 63, where essentially only one sulfoxide (**156**) was formed[104].



(155) (16a) (156) (63)

Interestingly, preliminary calculations (3–21G* basis set) estimate the ΔH_f of the triplet SO (and ethylene) generation from the parent thiirane oxide (**16a**) to be about 18 kcal mol^{-1} [166].

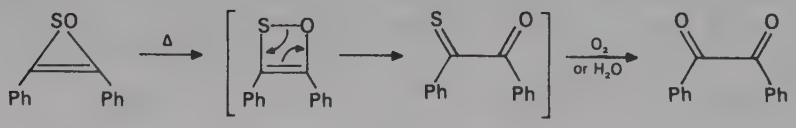
The thermolysis of **16a** has been studied[167] by the flash vacuum thermolysis-field ionization mass spectrometry technique[168] in the temperature range 1043–1404 K. Evidence was presented that the ring enlargement product 1,2-oxathietane **157** is being formed (sulfoxide–sulfenate rearrangement) alongside atomic oxygen extrusion and sulfur monoxide elimination (among others; see equation 64). The extrusion of atomic oxygen from organic sulfoxides has been previously reported[169]. It should be pointed out, however, that the rupture of the semipolar S—O bond requires about 90 kcal mol^{-1} [170], compared to about 18 kcal mol^{-1} [166] required for the extrusion of the triplet SO.



(16a) (157) (64)

Also, the isolation of benzil **160** as the only product in the thermolysis of thiirene oxide **18a** at 130 °C was rationalized[22] in terms of initial ring expansion (sulfoxide–sulfenate rearrangement) followed by rearrangement to monothiobenzil **159**. The latter might be expected to undergo hydrolysis or air oxidation to give benzil **160** (equation 65).

Support for the initial ring expansion (**18a** → **158**) can be inferred from the fact that benzil was also isolated (although in low yield) in the electrochemical reduction of the thiirene oxide **18a**[171].



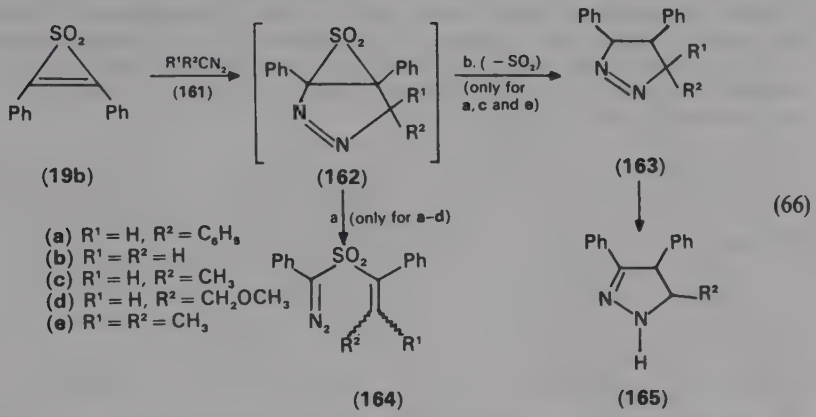
(18a) (158) (159) (160) (65)

5. Cycloaddition reactions

As formal α,β-unsaturated sulfones and sulfoxides, respectively, both thiirene dioxides (**19**) and thiirene oxides (**18**) should be capable, in principle, of undergoing cycloaddition reactions with either electron-rich olefins or serving as electrophilic dipolarophiles in 2 + 3 cycloadditions. The ultimate products in such cycloadditions are expected to be a consequence of rearrangements of the initially formed cycloadducts, and/or loss of sulfur dioxide (or sulfur monoxide) following the cycloaddition step, depending on the particular reaction conditions. The relative ease of the cycloaddition should provide some indication concerning the extent of the 'aromaticity' in these systems[2].

a. Thiirene dioxides. The [2 + 2] and [2 + 3] cycloaddition capability of thiirene dioxides (**19**) has been extensively explored[2,6,134,135,172–175].

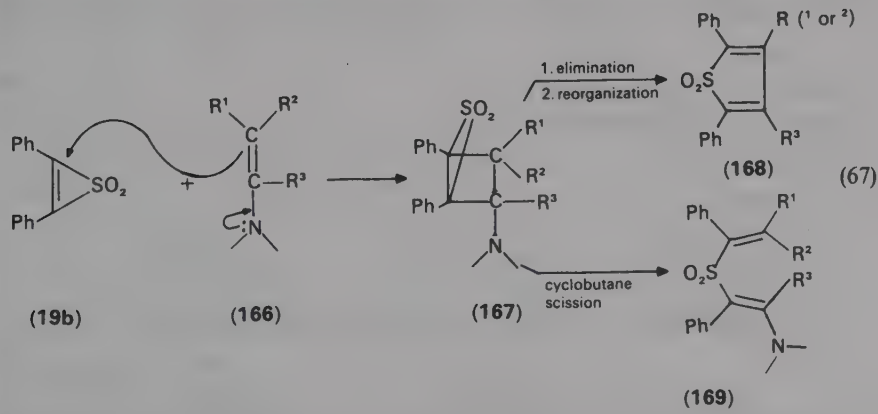
The cycloaddition of thiirene dioxide with phenyldiazomethane gave 3,4,5-triphenylpyrazole (**165a**) and the acyclic α-diazobenzyl 1,2-diphenylvinyl sulfone (**164a**), both suggested to originate in the common 1,3-dipolar cycloaddition intermediate **162**[6] (equation 66). Diphenylthiirene dioxide reacts similarly with other diazoalkanes (**161b–e**).



(66)

The ring-opening process leading to **164** (route a) is analogous to that which has been demonstrated to follow the cycloadditions of tosyl azide to certain enamines[176]. Similar results have been reported for the reaction of 2,3-diphenylcyclopropenone with 2-diazopropane[177]. Other 1,3-dipolar cycloadditions with thiirene dioxides could also be affected (see below).

Thiirene dioxides readily react with an entire spectrum of enamines to provide novel acyclic and cyclic systems[172]. These products result mostly from carbon–carbon or carbon–sulfur bond cleavage in the intermediate 'fused' thiirane dioxide **167** (equation 67).



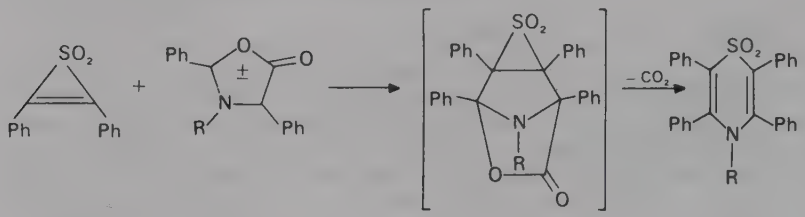
(67)

The synthetic potential of such transformations for the preparation of medium-size heterocycles[172] has been discussed elsewhere[2]. It is generally accepted that the reaction between thiirene dioxides and enamines is a stepwise (nonconcerted) thermal [2 + 2] cycloaddition. However, a concerted [4 + 2] cycloaddition, in which the lone pair of the enamine nitrogen atom participates, cannot be excluded.

In general, the above cycloadditions are exothermic and occur much faster than those of

enamines with cyclopropenones. Perhaps this is further evidence for the lack of substantial aromatic character of thiirene dioxides (at least compared to cyclopropenones).

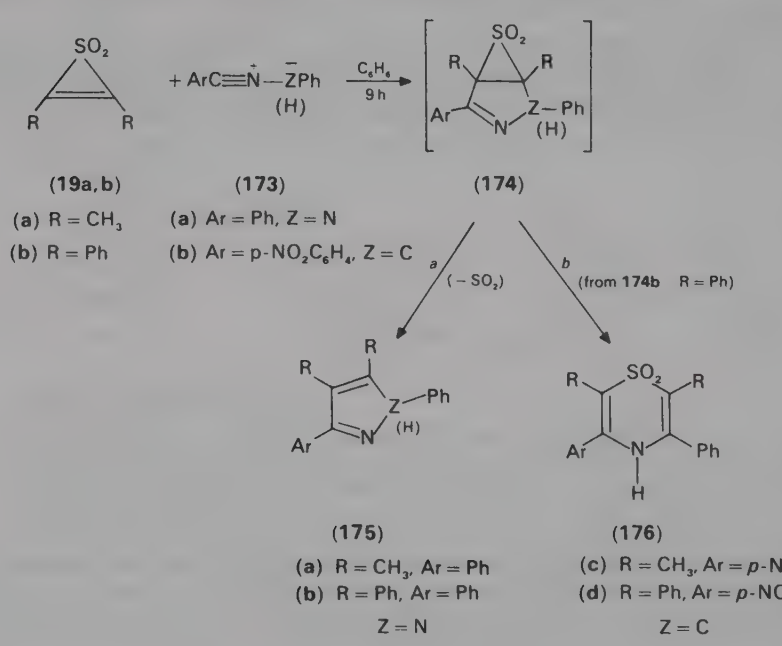
1,3-Dipolar cycloadditions with thiirene dioxides as dipolarophiles have been conducted, leading (after extrusion of various small stable molecules) to a variety of heterocycles as illustrated in equation 68[174]. These results suggest the cycloaddition of **170** across the 2,3-double bond of the thiirene dioxide to give the intermediate **171** which is followed by both carbon dioxide extrusion (preferentially to sulfur dioxide extrusion), and cleavage of the three-membered ring. In contrast, the reaction of thiirene dioxide **19b** with a six-membered mesoinoic compound[178] or with pyridinium ylids[173] is known to give adducts resulting from extrusion of sulfur dioxide.



(68)

(19b) (170) (171) . (172)

Similar cycloadditions between thiirene dioxides and 1,3-dipoles generated *in situ* give heterocycles which result from either loss of sulfur dioxide or from the three-membered ring opening of the initially formed adduct (e.g. **174**). Such cycloadditions with nitrilium imides (**173a**) and nitrile ylids (**173b**) are illustrated in equation 69[175].



(69)

(19a,b) (173) (174)

(a) R = CH_3 (a) Ar = Ph, Z = N

(b) R = Ph (b) Ar = p-$NO_2C_6H_4$, Z = C

(175)

(a) R = CH_3, Ar = Ph

(b) R = Ph, Ar = Ph

Z = N

(176)

(c) R = CH_3, Ar = p-$NO_2C_6H_4$

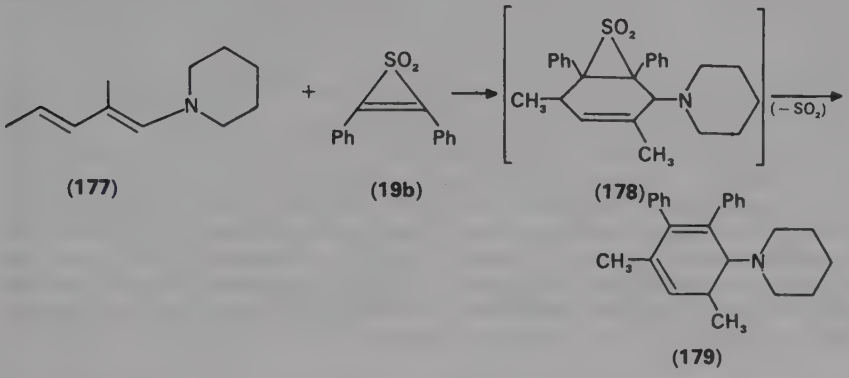
(d) R = Ph, Ar = p-$NO_2C_6H_4$

Z = C

Ready extrusion of sulfur dioxide from fused thiirane dioxides is well known and was observed in the formation of pyrazoles from **19b** and diazoalkanes[6,179]. A ring expansion

similar to that depicted in route *b* (equation 69) was reported for the 1:1 cycloadduct of **19b** and azide ion[134] as well as in analogous cycloadditions[174].

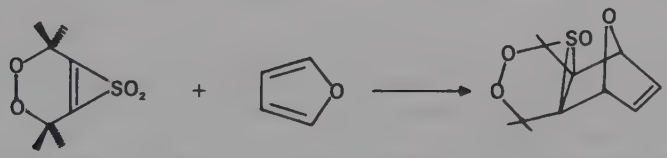
Interestingly, benzonitrile oxide does not react with thiirene dioxide **19b** even in boiling benzene, whereas the electron-rich diene 1-piperidino-2-methyl-1, 3-pentadiene (**177**) does react under the same reaction conditions to give the expected six-membered [4 + 2] cycloadduct **178**, accompanied by sulfur dioxide extrusion and 1, 3-hydrogen shift to form the conjugated system **179**[175] (equation 70).



(70)

b. Thiirene oxides. Treatment of thiirene oxide **18a** with phenyldiazomethane in ether results in the formation of the pyrazole **165** which arises by loss of sulfur monoxide from a labile cycloadduct analogous to **162**[6], which in turn is obtained from the cycloaddition of the corresponding thiirene dioxide (i.e. **19b**) with the diazoalkane[6].

When the bicyclic thiirene oxide **180**[164] is dissolved in excess furan, a single crystalline *endo*-cycloadduct (**182**) is formed stereospecifically (equation 71)[164]. This is the first propellane containing the thiirane oxide moiety. Clearly, the driving force for its formation is the release of the ring strain of the starting fused-ring system **180**. In contrast, **18a** did not react with furan even under 'forcing' conditions.



(71)

IV. FOUR-MEMBERED RING SULFOXIDES AND SULFONES

A. Introduction

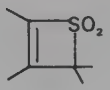
The unique characteristics of three-membered ring sulfoxides and sulfones raise the question: Are the major features observed in the three-membered ring series extended into the still small and strained four-membered ring series, or will the latter be more reminiscent of the larger ring and acyclic sulfoxides and sulfones?

The less strain energy inherent in the four-membered ring sulfoxides and sulfones, their less distorted geometries and the lack of potential 'aromatic'-type conjugation effects make the comparison of their physical and chemical properties with other cyclic and

acyclic counterparts meaningful and susceptible to experimental testing, and also turn them into interesting candidates for theoretical investigation. Thus, for example, the puckered structure established for this class of oxides and dioxides[180] imparts a unique dimension to the uncertainty regarding the role of d-orbitals acting as polarization functions[3,24] in molecules containing second-row atoms, particularly sulfur[181]. In certain cases, such as the four-membered ring thietane and dithietane (oxides, dioxides, trioxides and tetroxides included), the special symmetry of d-functions may be required to span the irreducible representations of occupied orbitals in the molecule[182], and to determine whether or not d-orbitals are used in bonding in these puckered bent or planar cyclic systems[183].

The preparation and investigation of the thietane oxide system (**5a**) is largely associated with stereochemical and conformational studies[66,74,184,185]. The investigation of the thietane dioxides (**5b**) is substantially related to the chemistry of sulfenes[143,186,187], the [2 + 2] cycloaddition of which with enamines is probably the method of choice for the synthesis of **5b**[186,187]. The study of the thiete dioxide system (**6**) evolved, at least in part, from the recognition that the unstable thiete system **183** can be uniquely stabilized when the sulfur in the system is transformed into the corresponding sulfone[188,189], and that the thiete dioxide system is very useful in cycloadditions[190] and thermolytic[191] reactions. The main interest in the dithietane oxides and dioxides (**7**) appears to lie in the synthetic challenge associated with their preparation, as well as in their unique structural features and chemical behavior under thermolytic conditions[192].

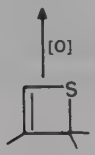
(5)
(a) $n = 1$
(b) $n = 2$



(6)

(184)
(a) $n = 1$
(b) $n = 2$

(7)
(a) $n = 1$
(b) $n = 2$



(183)

Whereas the transformations thietane → thietane oxide → thietane dioxide are easy to perform[192], as is the reverse transformation thietane dioxides → thietanes[188], no method of reducing the sulfonyl group to a sulfoxy group is available as yet.

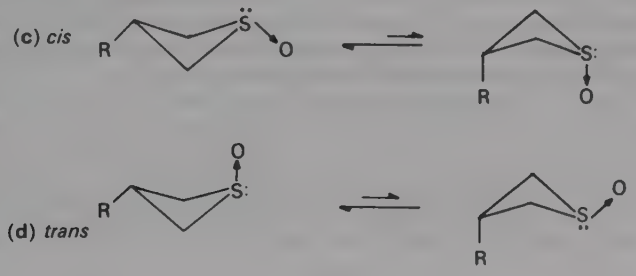
Although one finds, as expected, a regular change of physical and chemical properties in going from thietanes to their oxides and dioxides, or in going from thiirane oxides and dioxides to the four-, five- and six-membered sulfoxides and sulfones, there are some unusual effects associated with the four-membered ring series. An example is the unusual sulfonyl-oxygen deshielding and β-carbon shielding[70], as revealed by carbon-13 and oxygen-17 NMR spectroscopy. This suggests unique structural characteristics, which may be relevant to structure, bonding and charge distribution in these systems.

B. Structure and Physical Properties

1. Conformation and stereochemistry of thietane oxides and dioxides

It is well-documented that the thietane ring is puckered[193] and an energy barrier exists to planarity. Hence two conformations must be considered for each isomer of the *cis*- and

trans-3-substituted thietane oxides; the sulfinyl oxygen, nonetheless, exerts equatorial preference[74]. This preference may be attributed to a 1,3-cross ring, nonbonded interaction between the axial β-hydrogen and axial sulfinyl oxygen in the less-favored isomer. Apparently the nonbonded electron pair on sulfur has a lesser steric requirement. Stereochemical assignments could be made for a series of 3-substituted thietane oxides based on their NMR spectra[66]. Both isomers prefer conformations with the ring-substituent equatorial, as shown in equation 72. Interestingly, this preference is not affected significantly by changes of substituents in the 3-position[184], although the nature of the substituent may have a small effect on the degree of ring puckering. Based on dipole-moment studies, it was concluded[193b] that ring puckering decreases in the order: sulfide (axial)1, 1-sulfoxide, sulfone.



(72)

(5c,d)

The same equatorial preference is also manifested in the 3,3-disubstituted thietane oxides[66,194]. Thus, the NMR spectra of **5e,f** contain two Me singlets at 1.23 and 1.30 ppm and two methylene multiplets at 3.03 and 3.53 ppm (in $CDCl_3$). The large difference in the chemical shifts of the axial and equatorial α-methylene hydrogens is characteristic of an axial nonbonded electron pair on sulfur (conformation **5e**; equation 73). This conformational preference is corroborated by the *small* differences in the chemical shifts of the two methyl groups, and fits the contention that 1,3-diaxial interactions are responsible for this ultimate result. Certainly, these interactions are greater in the conformer **5f**.

(73)

(e) **(5)** **(f)**

The preference for conformer **5e** has also been established for 3-alkyl-3-aryl thietane oxides[194], based mainly on the analysis of the AA'BB' spin system of the ring hydrogens in the NMR spectrum.

The NMR spectra of the corresponding dimethyl sulfide and dimethyl sulfone consist of two singlets at 1.27, 2.92 and 1.43, 3.80 ppm, respectively (in $CDCl_3$), most probably implying a rapid interconversion of puckered conformations[66].

The proton spectra analysis of thietane, thietane oxide and thietane dioxide at 100 and 300 MHz in the temperature range -140 to 190 °C confirmed the puckered structure for the oxide (**5a**) with the sulfinyl oxygen in the equatorial orientation, as inferred from chemical-shift considerations[180]. It appears that the repulsive-type 1,3-interactions between the oxygen and the 3-substituents[184] are operating between oxygen and the axial proton on C-3 in the unsubstituted thietane oxide (**5a**). For the thietane dioxide (**5b**;

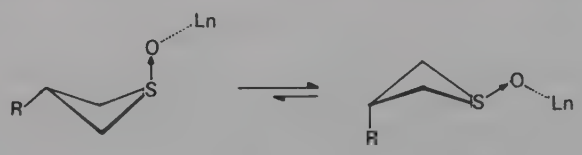
equation 74), the NMR data are in agreement with either a planar structure or, more likely, a rapid interconversion between two equivalent conformers, as is the case for the unsubstituted thietane[180].

(74)

(5b)

Interestingly, the crystal structures of 3-substituted thietane and thietane dioxides[180] showed that in the solid state they exist in the puckered structure, with the S—O bond equatorial in the oxides and the 3-substituent *axial* for the *trans*-isomers, contrary to what has been quoted before[66,195]. Thus, the claim that conformer **5c** is predominant in the solutions of the *trans*-isomer needs to be re-examined.

A study[195] based on the NMR lanthanide-induced shifts (LIS) for a series of *cis*- and *trans*-3-substituted, and 3,3-disubstituted thietane oxides concluded that all *cis*-substituted oxides (**5c**; R = CH_3, *t*-Bu and aryl) exist *exclusively* in the diequatorial conformation. The *trans*-3-substituted isomers (**185**) prefer the equatorial oxygen conformation (R = CH_3, 86%; *t*-Bu, 65–75%; aryl, 75%), which means an *axial* preference for the substituents (e.g. **185d**), at least when they are bound to a shift reagent (equation 75).



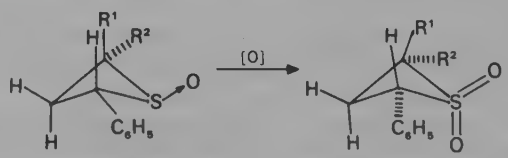
(75)

(c) **(d)**

(185)

Based on NMR chemical shift assignments and the use of recorded spin–spin coupling constants ($J_{m,n}$), it was determined[193c] that in both 2,4-diphenyl-substituted thietane oxides (**186a,b**) the dominant conformers are those in which the S—O bond is *equatorial* and, therefore, in the *trans*-2,4-isomer[186] one phenyl group (i.e. R^1) is *syn*-axial to the S—O bond, whereas in the *cis*-2,4-diphenyl isomer **186b** both phenyls are *anti*-equatorial to the S—O bond.

The consequences with respect to the corresponding thietane dioxides are straightforward: in the *trans*-isomer, **187a**, one phenyl group (i.e. R^1) is necessarily axial, whereas in the isomer **187b** both substituents are equatorial (equation 76). Clearly these preferred conformations minimize the potential repulsive interaction between 1,3-diaxial substituents[66].



(76)

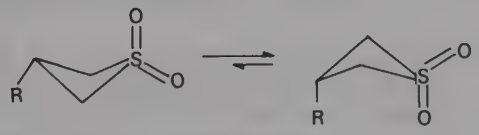
(186) **(187)**

(a) $R^1 = C_6H_5$, $R^2 = H$
(b) $R^1 = H$, $R^2 = C_6H_5$

The crystal structure of the *cis*-oxide **186b**[196] was shown (as expected) to be a flattened molecule as the benzene rings extend in an equatorial direction from the puckered thietane ring. The latter has a pucker angle of 41.9°, which is in good agreement with the value of 39.7° calculated for this molecule[193c] by using the Barfield–Karplus (spin–spin, coupling-based) equation[197].

It might well be that, compared with other thietane oxide systems, the larger pucker angle here is due to the two bulky 2,4-phenyl substituents that tend toward equatorial conformation.

The NMR spectra of 3-substituted thietane dioxides (**188**; equation 77) have been analyzed at 300 and 100 MHz using a LAOCN program, and provided evidence for a slight puckering of the four-membered ring and a preferred *axial* orientation (i.e. **188b**) of the 3-substituents[198]. The NMR measurements in the range between − 135 and + 150 °C indicate an increase in the population of the less-stable equatorially substituted isomer with increasing temperature. These results are in accord with an axial preference of the substituents in the analogous *trans*-3-substituted thietane oxides, as previously established[185].



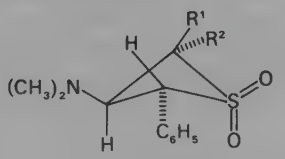
(77)

($a_{(1-3)}$) **(188)** ($b_{(1-3)}$)

R = OH, Cl, OCOMe

X-ray analyses of solid **188** have shown that the angles of the puckering of the four-membered sulfones are small and that the substituents are always axial, as in solution[198]. As far as the 3-substituted thietane dioxide is concerned, the axial preference of the substituent is unexpected (although not unprecedented[199]) and difficult to account for, since the equatorial preference (i.e. **188a**) would have been predicted based on steric considerations; that is, the 1-O, 3-R diaxial repulsive interactions. Attractive-type interactions between the electronegative 3-substituents and the axial sulfonyl-oxygen are very difficult to advocate. It is, therefore, noteworthy that NMR study of the parent thietane dioxide (**5b**) in a nematic phase solvent[200] showed the four-membered sulfone to have a *planar* or slightly distorted average vibration conformation with a low barrier to ring planarity. The thietane oxide, however, exists preferentially in one strongly puckered conformation (angle of puckering about 38°) with the oxygen in equatorial orientation.

As one would expect, the tri-substituted *cis–trans*-2,4-diaryl-3-dimethylaminothietanes (**187c,d**) were shown by NMR to have all three substituents in pseudoequatorial positions with the remaining hydrogens in axial positions[202].



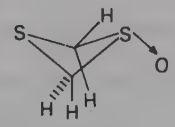
(187)

(c) R¹ = H, R² = Ar (*cis*)

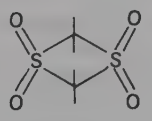
(d) R¹ = Ar, R² = H (*trans*)

The structures of four-membered rings are of considerable interest, owing in part to the low-frequency ring puckering vibration[203]. The comparison of the structures and conformational preferences of thietane oxides and dioxides discussed above with those of dithietane oxides and dioxides is therefore appropriate and will follow.

The gas-phase structure of 1,3-dithietane 1-oxide (**189**) has been determined from its microwave spectrum and the spectra of eight isotopic modifications[192]. The ring is puckered, the angle between the two CSC planes being 39.3° with the oxygen equatorial.



(189)



(7b)

The oxide **189** displays short nonbonded sulfur–sulfur and carbon–carbon distances (2.600 and 2.372 Å, respectively). Nonetheless, the sulfur–oxygen bond (1.473 Å) and the angle of pucker appear to be normal compared to the data presented above for the thietane oxides[180,197,200,204].

The structure of 1,3-dithietane tetroxide **7b** has been shown by X-ray diffraction methods to be planar and almost square[192], the molecule being located on a crystallographically required center of symmetry at the center of the four-membered ring, with the planes of the SO_2 and CH_2 groups essentially perpendicular to the plane of the four-atom ring (89.9° and 85°, respectively). Again, these results are in accord with previous studies that established the planarity (or near planarity) of the analogous thietane dioxides[180,198]. It appears that the inclusion of a second sulfur atom, a sulfoxide, or a sulfone group in the four-membered ring thietane oxides and dioxides (in a 1,3 relationship) does not alter the conformational preferences of the latter, nor does it cause any unusual anomalies as far as the particular geometrical parameters (e.g. bond lengths and angles) of these molecules are concerned (see Section IV.B.2 below).

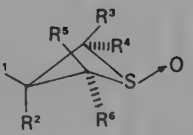
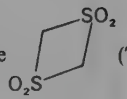
2. *Experimental geometrical parameters*

The crystal structures of several thietane oxides have been determined. Bond lengths and angles are given in Table 6.

The data indicate no exceptional intermolecular contacts nor any unusual bond lengths and bond angles in the compounds studied. The structures and conformational preferences are consistent with those derived from NMR studies. The slight deviation of the pucker angle in the thietane oxide **186b** (41.9°), compared to that of the other oxides cited, may be accounted for by the two bulky phenyl substituents tending toward equatorial conformations. Interestingly, however, the pucker angles of 3-substituted thietane dioxides (i.e. $\mathbf{188}_{(1-3)}$; R = OH, Cl, OCOMe) were found by X-ray studies[198,208] to be 6.8°, 9.3° and 7.9°, respectively. This means that the ring of thietane dioxides is approaching planarity, whereas that of the 1,3-dithietane tetroxides is actually planar and almost square[192], at least in the case of the parent tetroxide **7b**. Intramolecular nonbonded S···S and C···C distances are 2.590 Å and 2.524 Å, respectively. The former short value is similar to what was found for the nonbonded S···S distance in the oxide **189**[192].

3. *Theoretical treatment and interpretations*

a. NMR-based calculations. Both the dihedral angles HCCH and the angles of pucker of *cis*- and *trans*-2-4-diphenylthietane oxides (**186a,b**) have been calculated[193c] by using

TABLE 6. Bond lengths[a] and bond angles[b] in selected thietane oxides  (**5;186**) and 1,3-dithietane tetroxide  (**7b**)

Compound	*r*SO	*r*SC	*r*CC	⟨CSC	⟨OSC	⟨SCC	⟨CCC	⟨OSO	Pucker angle	Ref.
5d; $R^1 = R^3 = R^4 = R^5 = R^6 = H$, $R^2 = CO_2H$	1.52	1.835[c]	1.59[d]	78	110.5[e]	89.5[f]	94	—	35	205
	1.526	1.842	1.529	76.6	112.0	90.2	96.6	—	27	206
5c; $R^2 = R^3 = R^4 = R^5 = R^6 = H$, $R^1 = p\text{-}BrC_6H_4$	1.482	1.84[c]	1.54	—	118	—	—	—	33	195
5d; $R^1 = R^3 = R^4 = R^5 = R^6 = H$, $R^2 = p\text{-}BrC_6H_4$	1.492	1.83[c]	1.52	—	116	—	—	—	32	195
5e; $R^1 = R^2 = CH_3$, $R^3 = R^4 = R^5 = R^6 = H$	—	—	—	—	—	—	—	—	27	206
186b; $R^1 = R^2 = R^3 = R^5$, $R^4 = R^6 = C_6H_5$	1.466	1.847	1.565	76.5	114.1	86.9	93.9	—	41.9	196
186c; $R^1 = R^4 = R^5 = H$, $R^2 = C_6H_{13}$, $R^3 = CH_3$, $R^6 = CH_2OH$	1.502	1.844[c]	1.552[d]	76.5	112.5[e]	90.4[f]	94.7	—	29	207
7b	1.434[g]	1.808[c]	—	88.5	111.1	91.5[h]	—	119.4		

[a] In Å.
[b] Degrees (°).
[c] An average of value obtained from the S—C_2 and S—C_4 distances.
[d] An average value obtained from the two relevant C—C bonds.
[e] An average value obtained from the two (or four) relevant OSC angles.
[f] An average value obtained from the relevant SSC angles.
[g] An average value obtained from the two relevant S—O bond lengths.
[h] ⟩SCS.

their NMR spectra, some previously published data concerning bond lengths and angles in the thietane–thietane oxide series[205,209], and the Karplus–Barfield equation[197] of the form $^3J_{H,H'} = A\cos^2\phi + B\cos\phi + C$.

Thus, the dihedral angles of the *trans*-oxide (**186a**) were calculated to be 91.0°, 36.5°, 26.5° and 154° for $\langle R^2CCH^3$, $\langle R^2CCH^4$, $\langle H^2CCH^3$ and H^2CCH^4, respectively; and 31.6° and 159.1° for $\langle R^1CCH^3$ and R^1CCH^4, respectively, in the *cis*-oxide **186b**.

The pucker angle of **186b** was calculated to be 39.7° and that of **5d** ($R^2 = CO_2H$) to be 29.7°[193c]. These results are in excellent agreement with the experimental values of 41.9° and 27° obtained via X-ray studies[196,206] as can be seen in Table 6. For the corresponding *cis*-thietane dioxide (i.e. **187b**) the above procedure gave an angle of pucker of 35°, a value that is highly questionable in view of the tendency toward planarity of the four-membered ring in thietane dioxides.

Similar calculations have been applied to the 3-substituted thietane dioxide series (i.e. $\mathbf{188}_{(1-3)}$)[198], assuming that only the constant C in the Karplus equation should be significantly affected by the substituents and by the oxidation state of sulfur. The results thus obtained were in poor agreement with X-ray data.

It is difficult to decide whether the discrepancy between the calculated and experimental data is due to a different conformational preference of the thietane dioxides in the liquid and the solid phase, or to the crude approximations included in the Karplus–Barfield equation. However, the relationship between vicinal coupling constants and dihedral angles appears qualitatively valid in thietane oxides and dioxides, particularly if trends instead of exact values are discussed[193c]. At any rate thietane dioxides, 1,3-dithietane dioxides and tetroxides maintain either planarity[192] or a slightly distorted average vibrating conformation with a low barrier to ring planarity[198].

b. Photoelectron (PE) spectra and their assignments. The PE spectrum of 1,3-dithietane 1-oxide **189** is best discussed by comparison with thietane oxide, since the large perturbation S → SO can be replaced by the isovalent and electronic one, $CH_2 \rightarrow S$[192].

The three highest occupied orbitals of sulfoxides are the lone pairs n_s and n_o, as well as the π_{SO} bond[210]. The 1,3-dithietane 1-oxide adds a 'lone-pair' ionization and destabilizes the n_o and π_{SO} radical-cation states compared with thietane oxide. According to a hyperconjugative MO model, the n_s^+ combination in 1,3-dithietane is destabilized by about 1 eV relative to the basis orbital energy $\alpha(n_s)$ due to the combination with the

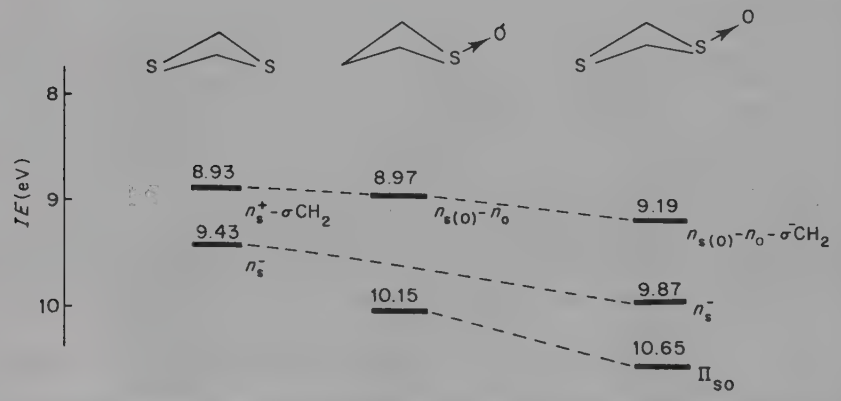
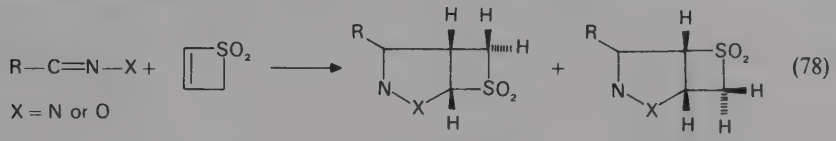


FIGURE 1. Sulfur lone-pair and π_{SO} ionization patterns in 1,3-dithietane, thietane oxide and 1,3-dithietane oxide.

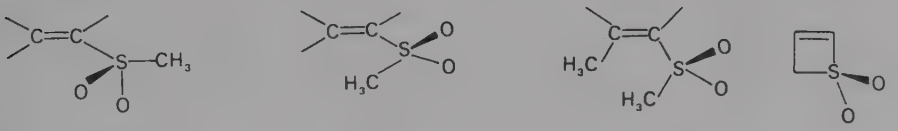
$\sigma_{CH_2}(b_{2u})$ orbital[210]. In the 1,3-dithietane 1-oxide both sulfur 'lone-pair' ionizations are further increased by the oxygen substitution. In thietane oxide both n_o and π_{SO} ionizations are lowered by the $S \rightarrow CH_2$ substitution, whereas a $CH_2 \rightarrow SO$ replacement splits the n_o and π_{SO} ionizations and increases their center of gravity. The radical-cation-state correlation shown in Figure 1[192] is supported both by EHMO and modified CNDO calculations based on the known structural parameters[211]. Similar considerations and interpretations have been applied for the PE spectra of 1,3-dithietane dioxide and 1,3-dithietane tetroxide (**7b**) and their assignments.

c. Theoretical investigation on cycloaddition of thiete dioxides. Cycloaddition of nitrile oxides, diazoalkanes and nitrones with thiete dioxide[213] (**6b**) show regiochemical characteristics markedly different from those observed for acyclic vinyl sulfones[212]. This difference constituted a good basis for a theoretical study of regioisomerism of these cycloaddition reactions[214].



(**190**) (**6b**) (**A**) (**191**) (**B**)

The charge-transfer stabilization energy, calculated according to the Klopman–Salem perturbational approach in the CNDO/2 approximation[215], provided results that are able to account for the experimental trends of the ratio between the two isomers (i.e. **191A,B**; equation 78)[214]. The change of regiochemistry in the cycloadditions of the four-membered cyclic sulfone (**6b**) compared to that of the acyclic vinyl sulfone, can be explained in terms of its locked *cis–syn*-structure. Such a *cis–syn*-structure occurs also in open vinyl sulfones (**193**), but is not locked in them. An example of predicted regiochemistry differences between the 'open' and the cyclic sulfones in the cycloaddition reaction with $PhC{\equiv}N \rightarrow O$ is given below [based on the calculated stabilization energy differences $\Delta\Delta E = \Delta E(\mathbf{B}) - \Delta E(\mathbf{A})$][214]:



(**192a**) (**192b**) (**193**) (**6b**)

$10^{-3}\Delta\Delta J\,mol^{-1}$: +2.84(**A**) +0.402(**A**) + (**B**) −1.548(**B**) −0.963(**B**)

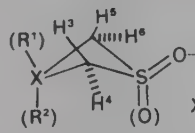
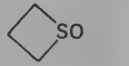
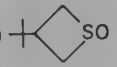
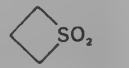
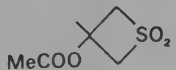
Thus, formation of one isomer only in the cycloaddition is expected when the following holds: $-0.84 > \Delta\Delta E > 1.25 \times 10^3\,J\,mol^{-1}$, whereas $-0.84 < \Delta\Delta E < 1.25 \times 10^3\,J\,mol^{-1}$ corresponds to a mixture of variable isomer ratios.

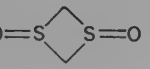
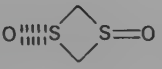
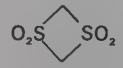
Predictions obtained by using the frontier orbital approximation[213] were unsuccessful, apparently due to inadequacies in these MO calculations mostly involving the energy gap between HO of the dipole and LU of the dipolarophile.

4. Spectroscopic characteristics and characterization

a. ^1H and ^{13}C NMR spectroscopy. NMR spectroscopy is the technique most often applied to the study and characterization of four-membered ring sulfoxides and

TABLE 7. ^{1}H and ^{13}C NMR chemical shifts and coupling constants of four-membered sulfoxides and sulfones

 X = C or S	Chemical shifts δ			Coupling constants							Refs.
	$^{1}H_{(\alpha-C)}$	$^{13}C_{\alpha}$	$R^{1\,or\,2} = H$	gemH^3H^4	*trans*H^3H^6	*cis*H^4H^6	*cis*H^3H^5	gemH^1H^2 (X = C; $R^1 = R^2 = H$)	*trans*H^2H^3 (X = C; $R^1 = R^2 = H$)	*cis* H^1H^3	
	3.09[a], 3.46[a]	52.7[b]	1.95, 2.27[a]	−10.29	−0.95	6.10	−0.57	−12.69[a]	+12.53[a]	+12.53[a]	180, 192
(*cis* & *trans*-) 	{*cis*- 2.83[c], 3.42[c] {*trans*- 3.52, 3.62[d]		1.93 3.07								66 66
	4.09[a]	65.6[b]	2.14	−14.0	−1.24		2.24(av.)	−12.63[a]	+6.33[a]	+10.34[a]	180,192
	3.80[d], 3.56[e]										66
	4.19[d], 4.57[d]	71.73[d]		−14.48	−1.19	3.76	2.87			7.93	198

	4.23[f], 3.37, 3.73[g],	53.1		−7.53[h]	0.73[i]	5.56	0.005[i]		192
	5.27[f,j]	68.4							192
(*cis*-) 	4.78, 5.72[j]	69.1		−13.40[h]	1[i]	3.76[i]	1[i]		192
(*trans*-) 	4.97[j]	69							192
	6.40[h]	92.1							192

[a] In $(CD_3)_2CO$.
[b] α-Carbon.
[c] Multiplet in CCl_4.
[d] In $CDCl_3$.
[e] In C_6H_6.
[f] In $(CD_3)_2SO$.
[g] In C_6D_6.
[h] Negative sign assumed.
[i] Sign unknown.
[j] In CF_3COOH.

sulfones[66,70,74,180,184,185,192–203,216]. Chemical shifts and coupling constants have been used for structural, conformational and stereochemical assignments and preferences and for the establishment of the four-membered ring sulfone effect[70,216].

^1H and ^{13}C chemical shifts and coupling constants of some selected representative four-membered ring sulfoxides and sulfones are given in Table 7.

Stereochemical assignments for a series of 3-substituted thietane oxides (**5c,d**) were made, based on the equatorial preference of the oxygen–sulfur bond[76] and on the large chemical-shift-difference characteristic of the α-methylene hydrogens in the *cis*-isomer, and the significant relative deshielding of the β-hydrogen in the *trans*-isomer[66]. The stereochemical assignments were confirmed by the aromatic solvent-induced shifts (ASIS)[217]. Protons on the opposite side of the ring to the sulfinyl oxygen in thietane oxides undergo larger ASIS than those on the same side of the ring[194]. The preference of the equatorial orientation by the sulfur–oxygen bond has also been established for 3,3-disubstituted thietane oxides based on similar interpretation of the NMR data including the appearance of the resonance of the axial hydrogens (in line with that of the hydrogen *anti* to the 'lone pair' on sulfur) in the sulfoxide at higher field compared with the resonance of the equatorial hydrogens. Indeed, the α-proton *trans* diaxial to the nonbonded electrons on sulfur always appears at higher field than the equatorial α-proton in cyclic sulfoxides[66].

The proton spectra of thietane oxide (**5a**) and thietane dioxide (**5b**) have been studied in order to evaluate whether the oxidation at the sulfur atom changes the established 35° puckering of the ring[218], and whether a correlation is possible between structure and NMR parameters[180].

The analysis of the spectral data indicates for thietane oxide a preferred puckered structure with the sulfinyl oxygen in the equatorial orientation. The ring inversion rate is fast enough to average the coupling constant values, but the strongly puckered structure is the most populated. The data for thietane dioxide are in agreement with either a planar structure, or with two rapid interconverting equivalent conformers.

Thorough analysis of the coupling constants suggests that vicinal and cross-ring coupling can be valuable when used for stereochemical assignments in thietane oxides and dioxides, provided one takes into consideration the conformational changes and the substituent effects[180].

All of the above conclusions have been confirmed in an NMR study of **5a** and **b** in the nematic phase[201]. The results confirmed the effective C_{2v} symmetry of the dioxide as expected for a planar-ring geometry or for rapidly interconverting slightly bent structures, with a low barrier to ring planarity. The NMR-based experimental values and the calculated ring parameters (D_{ij}) were found to be in very good agreement in both the oxide and the dioxide ring systems. The angle of puckering for **5a** has been estimated to be approximately 38°[201] as compared with 34.67° obtained from microwave results[219].

Following a detailed NMR study of the 3-substituted thietane dioxides **188** it was concluded that the three-bond coupling constants ^3J can be safely used for stereochemical assignments in this series; in particular the $^3J_{R^1H^4} < 4$Hz (Table 7, $R^1 = H$, $X = C$) is consistent with an equatorial–equatorial interaction. This indicates an axial preference for the 3-substituent R (i.e. **188b**) in both liquid and solid phases, and also suggests that the ring is puckered[198].

The previously discussed conformational study of 3-substituted thietane oxides using lanthanide shift reagents[185] corroborates the conclusions derived from other NMR studies and suggests that all *trans*-3-substituted thietane oxides prefer an equatorial oxygen conformation when the thietane oxides are bound to shift reagents.

A useful comparison of the ^{13}C shifts for acyclic and cyclic five- and six-membered sulfur compounds has been made[86,220], but data on cyclic sulfur compounds of other ring sizes are rather limited. Typically, oxidation of sulfide to a sulfone results in 20–25 ppm

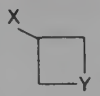
downfield shift for the α-carbon and 4–9 ppm upfield shift for the β-carbon[70]. Surprisingly, there is very little difference between the α-carbon shifts of sulfoxides and sulfones.

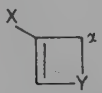
The chemical shifts of the unsubstituted α-carbons of thietane oxides and dioxides (Table 7) are about 53 ppm for the former and about 67 ppm for the latter. The value of the α-carbon chemical shifts of the 1, 3-dithietane disulfoxides (*cis* and *trans*) is about 69 ppm [near that of the four-membered thietane(mono)-dioxide], whereas the chemical shift of the α-carbon of the parent 1, 3-thietane tetroxide is about 92 ppm. In comparing the above values with the chemical shift of the α-carbon in thietane, which is about 26 ppm[70], one can see that there is about 40 ppm downfield shift in going from the thietane to its dioxide and an additional 25 ppm downfield shift in going to the tetroxide. The difference between the α-carbon chemical shifts of the sulfones and sulfoxides is 13–15 ppm. The shift of 28.0 ppm for the β-carbon in thietane decreases to 10.4 ppm in the sulfoxide and to 5.8 in the sulfone. Effects of this order of magnitude are not observed in other cyclic sulfones and sulfoxides. There is some parallel to this anomalous 'four-membered ring-sulfone effect'[216] in the downfield chemical shifts of the α-protons and upfield chemical shift of the β-protons in the four-membered ring sulfones (4.09 and 2.14 ppm, respectively, compared with 3.21 and 2.94 ppm for the thietane[221]). In the other ring systems the order of α-proton shifts is in accord with the inductive effect: sulfenyl < sulfinyl (average) < sulfonyl[70]. The 'four-membered ring effect'[192] is also reflected in the considerable deshielding of the sulfonyl oxygens in the thietane dioxide as determined via the oxygen-17 chemical shifts (182 ppm compared with 111 and 165 ppm in three- and five-membered ring sulfones, respectively[70]). It should be pointed out that the nonequivalence of the two sulfone oxygens may be observed[70]. For oxygen-17 shifts, the sulfoxides also show the same trend. The effect appears to be general for other sulfonyl and sulfoximino groups in saturated four-membered rings[70]. In contrast, carbon-13 shifts in cycloalkanes[222] and thiacycloalkanes[70] and nitrogen-15 shifts in azacycloalkanes[223] do not show an anomaly at the four-membered ring. The origin of the 'four-membered ring sulfone effect' remains an unanswered question, but it may be related to perturbation of the sulfur atoms, which might have an unusual dependence on the state of oxidation when incorporated in four-membered rings.

Carbon-13 chemical shifts of the α- and β-carbon atoms of various unsubstituted and 3-substituted thietane oxides and dioxides have been recorded and correlated by the equations $\delta_\alpha = a_y + b_x$ and $\delta_\beta = a_x + b_y$ where a and b are parameters characteristic of the sulfoxide or sulfone (y) and the substituent (x)[216]. The values of the substituent parameters were found to parallel those which determine the effect on the ^{13}C chemical shifts when hydrogen is replaced by a substituent[224].

In four-membered ring sulfones, the α-carbon–hydrogen coupling constants J(CH) were shown to be similar to those of the corresponding sulfoxides and sulfides. The β-carbon–hydrogen coupling constants are sensitive to the nature of the substituent X, but no special β effect is observed. Interestingly, thietes (**6b**) also reveal the 'four-membered ring sulfone effect'. *Trans*-3-substituted thietane oxides show a greater downfield shift for the β-carbon atom than the *cis*-isomer (Table 8). Except for the four-membered ring anomaly, the experimental data are in accord with the expected trends in cyclic sulfides, sulfoxides and sulfones.

b. Infrared, mass and UV spectra. The strong IR absorptions are 1030–1070 for sulfoxides and 1130–1160 and 1300–1350 cm^{-1} for sulfones[225]. Here the four-membered

TABLE 8. Chemical shifts (ppm)[a] and coupling constants for selected thietanes, thietane oxides and dioxides  (after Reference 216)

Y	X	α-C	β-C	^1J(α-CH)	^1J(β-CH)	a_y	b_y
S	H	26.16	28.17	145.7	135.9	27.95	24.13
SO	H	52.80	10.40	148.1	139.4	50.39[b]	18.67[b]
SO_2	H	65.57	5.8	145.2	144.3	64.97	7.17
S	Ph	32.00	44.07	146.7	131.4		
SO	Ph	56.24[b]	33.39[b,c]	147.7[b]	—		
SO_2	Ph	71.87	24.46	147.7	146.6		
S	OH	38.67	67.33	147.4	150.7		
SO	OH	59.90[b]	63.80[b]	149.1[b]	151.3[b]		
SO_2	OH	74.09[b]	52.67[d]	145.8	161.6		
							
S	Ph	35.79					
SO_2	Ph	69.87					

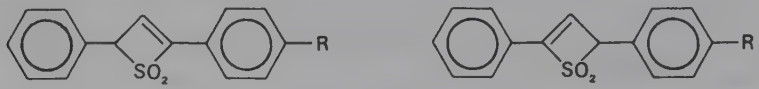
[a]In $CDCl_3$.
[b]For the *trans*-isomer.
[c]27.11 ppm for the *cis*-isomer.
[d]In $(CD_3)_2CO$.

ring sulfoxides and sulfones were found to be within the 'normal' ranges[66,185,193c,202,216,226,227]

Mass spectrometry was applied in conjunction with thermolysis studies leading mainly to sulfines[192,228] and rearranged products[229] with four-membered sulfoxides and to a loss of sulfur dioxide with sulfones[192,193c,230]. The fragmentation pattern of thietes under electron impact can be explained by the sequential loss of the elements of sulfur monoxide and oxygen from an intervening cyclic sulfinate intermediate[189].

The combination of the flash vacuum pyrolysis (FVP) technique[169] with mass spectrometry proved to be particularly useful in identification and characterization of both the fragmentation/rearrangement patterns, intermediates and/or final products formed (see Section IV.E.1). Usually, no structures are indicated in the mass spectra, although ionization and appearance potential can, in principle, provide structural information.

In view of the limited capacity of the sulfur atom in the sulfoxide and sulfone functional groups to transmit conjugative effects due to the 'insulating effect' of the LUMO sulfur d-orbitals[45,46,56], the application of the UV technique even in the case of the cyclic vinyl sulfones (e.g. thiete dioxides **6b**) cannot be expected to find extensive use. UV spectra of substituted thiete dioxides in which an extended conjugated system (e.g. **194**) exists in the molecule, did provide useful information for structure elucidation[231]. However, the extent



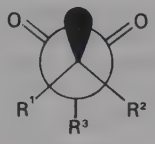
(a) **(194)** (b)

R = H, Cl, NO_2

of participation (if at all) of the sulfone group in the chromophoric conjugated system (and consequently in determining λ_{max} and ε) in **194** cannot be estimated without further UV studies with similar or closely related thiete dioxide systems.

C. Acidity and p*K* Values

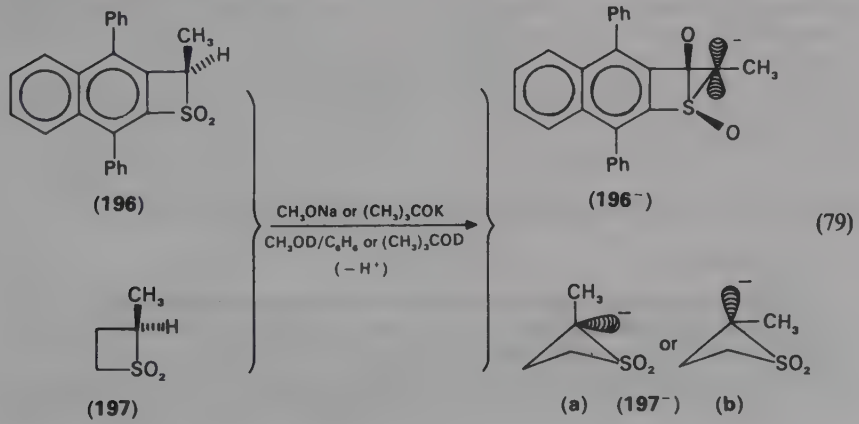
The inductive and electrostatic effects, steric constraints and conjugative interactions are the major factors that determine the configurational stability of α-sulfonyl carbanions[227]. These are thought to be pyramidal with appreciable electrostatic inhibition to racemization by way of inversion[232]. LCAO-MO-SCF calculations have indicated the conformer **195** in which the lone pair is directed along the bisector of the OSO angle to be the most stable in acyclic sulfones[232c].



(**195**)

Stereochemical constraints in cyclic sulfones and sulfoxides impart increased weight to strain and conformational factors in the generation of carbanions and their stability, causing distinct differences between the behavior of cyclic and open-chain systems[233], due primarily to the prevention of extensive rotation about the C_α—S bond, which is the major way that achiral carbanions racemize. Study of the α-H/D exchange rate k_e and the racemization rate k_α may provide information concerning the acidity-stereochemical relationships in optically active cyclic sulfone and sulfoxide systems.

Rate constants for H/D exchange and activation parameters (k_e and k_α) have been measured for the optically active thietane dioxides **196** and **197**[227]. The k_e/k_α values for ethoxide and *t*-butoxide-catalyzed reactions were found to be 0.88–1.02 and 0.6–0.67, respectively, with **197** undergo ring exchange/racemization about 10^5 times slower than the former. Racemization occurs concurrently with exchange in **196** in which extensive delocalization by the aromatic system stabilizes the negative charge of the α-sulfonyl carbanion (**196**$^-$). Also, the shift of the α methyl group from an eclipsed to a staggered conformation (with respect to the sulfonyl oxygen) in passing from **196** to its carbanion results in a relief of steric strain that contributes to the rate acceleration compared with the process in **197** (equation 79).

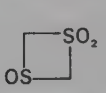


(79)

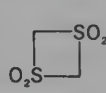
197 enjoys greater conformational mobility than **196**, and the k_e/k_α values (0.60–0.67) are in agreement with two mechanistic possibilities reflecting either exchange with net inversion (from **197**⁻**a**) or a blend of inversion without exchange (*iso*inversion), inversion and racemization processes (from **197**⁻**b**). Both enthalpy and entropy factors are involved in these processes, which are solvent-dependent. Nevertheless, it might well be that the dominance of k_α over k_e in the thietane dioxide series reflects the low barrier to ring planarity in the four-membered ring[180,198,200] once the α-sulfonyl carbanion has been formed.

Both the isomerization and the H/D exchange rates were shown to be dependent on the nature of the α-halogen substituent (I > Br > Cl) in a series of *cis*- and *trans*-2-halo-3-morpholino-4,4-dimethylthietane dioxides[234]. The observed k_e/k_α values of about 1 for the *cis*-isomers demonstrate that the relief of strain energy (particularly in the more sterically hindered *cis*-series), through the formation of the α-sulfonyl carbanion and its inversion, promotes both exchange and isomerization. A plausible explanation for the greater H/D exchange rate in the *trans*-isomers can be envisaged in the particular position of the exchanging proton with respect to the sulfonyl OSO angle. The dependence of the H/D exchange rate of a proton α to sulfonyl or sulfinyl groups on its orientation relative to these groups is well established[232d].

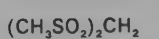
Ring-strain effects are known to enhance the acidity of hydrogens in α positions to functional groups capable of stabilizing a negative charge[233]. A comparison of the pK_a values[192] (in DMSO) of the sulfoxide-sulfone **7c** and the disulfone **7b**, 13.8 and 12.5 ± 0.08 respectively, with 15.0 ± 0.02 for **198** and 15.5 for **199**[235], demonstrates that similar effects are most probably operative in the cyclic thietane sulfoxide and sulfone systems. Both the 1,3-dithietane oxide (**184a**)[192] and the tetroxide **7b**[236] have been shown to undergo ready H/D exchange with $NaOD/D_2O$. Analysis of deuteriated **184a** indicated a 6:1 preference of 'axial' monodeuteriation over 'equatorial' monodeuteriation, in contrast to the predictions of the 'gauche effect theory' of greater reactivity for the quasi-equatorial protons gauche to both the S—O bond and the lone pair of sulfur[237].



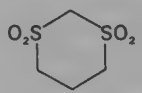
(7c)



(7b)



(198)



(199)

(184a)

Both thermal- and acid-induced equilibrations of 3,3-disubstituted thietane oxides were very slow ($K_{eq} \approx 10^{-5}\,s^{-1}$)[194]. The results suggest that thietane oxides are similar to the various acyclic sulfoxides with respect to the rates of thermally induced pyramidal inversion at sulfur[238], and that this inversion process, therefore, does not interfere significantly in the above exchange/racemization studies.

It is noteworthy that in spite of the demonstrated acidity of the α-hydrogens in thietane oxides and dioxides, attempted mono- or dialkylations of these systems have been unsuccessful thus far.

D. The Synthesis of Four-membered Ring Sulfoxides and Sulfones

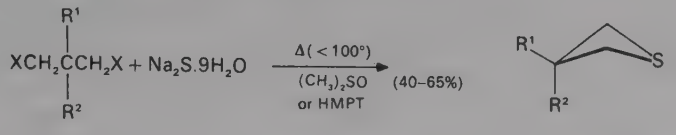
1. Thietane oxides

The method of choice for preparing thietane oxides is the oxidation of thietanes. This can be conducted using hydrogen peroxide, sodium hypochloride[194], sodium metaperiodate[66], $NaIO_4$[74c] and *m*-chloroperbenzoic acid[185].

The thietanes are most often prepared through ring closure of 1,3-dibromides or 1,3-disulfonate esters[193c,239,240], through fusion of cyclic carbonate esters of 1,3-diols with

thiocyanate ion[241], by base-induced cyclization of substituted 1,3-chlorothiols[193c], or by reduction of thietane 1,1-dioxides[74,143,242].

A typical sequence is described in equation 80[194,243].



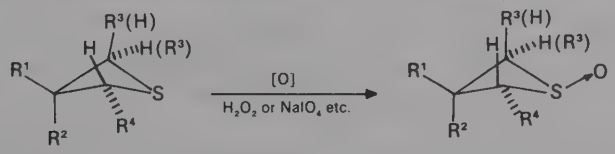
(80)

(200)

X = Br or $OSO_2C_6H_5$

(201a)

Oxidation of the thietanes provides thietane oxides (equation 81).



(81)

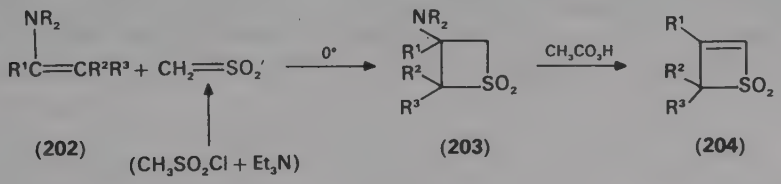
(201b, c)

(5)

The oxidation results in mixtures of *cis*- and *trans*-isomers, the ratio of which is primarily sterically controlled[74]. The oxidant appears to approach the sulfur atom preferentially from the least-sterically hindered direction, so that the thermodynamically least stable isomers may occasionally predominate[74,194,244].

The base-induced cyclization of 1,3-chlorothiols to thietane[193c,226] followed by the oxidation of the latter is analogous in all respects to the strategy described above.

Thiete sulfones may be[74b] converted to the corresponding saturated thietanes and followed by oxidation of the latter to the desired sulfoxides[185] (equation 82). By chromatography, the mixture (**207**) can be separated to the *cis* and *trans* isomers.

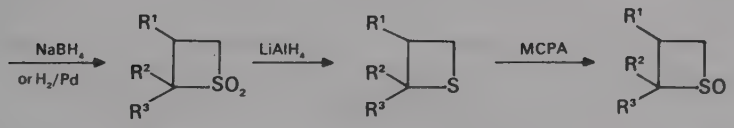


(202)

(203)

(204)

(82)

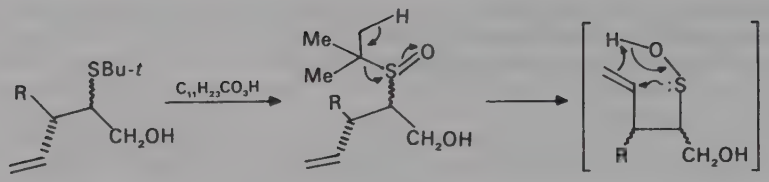


(205)

(206)

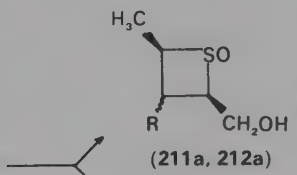
(207)

The addition of sulfenic acids to olefins[207] has been successfully applied in the synthesis of thietanoprostanoids, the thietane analogues of prostaglandin[245]. The general synthetic scheme is presented in equation 83[207]. The key step is the thermolysis of either *erythro*- or *threo*-2-*t*-butylsulphinyl-3-vinyl-1-ol (**209**) to give the corresponding alkenesulfenic acids **210**, which cyclize spontaneously to a mixture of stereoisomeric thietane oxides.

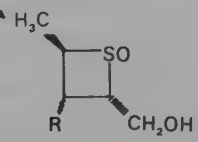


(208) (erythro or threo) R = C_6H_{13} (209) (erythro or threo) (210)

(83)



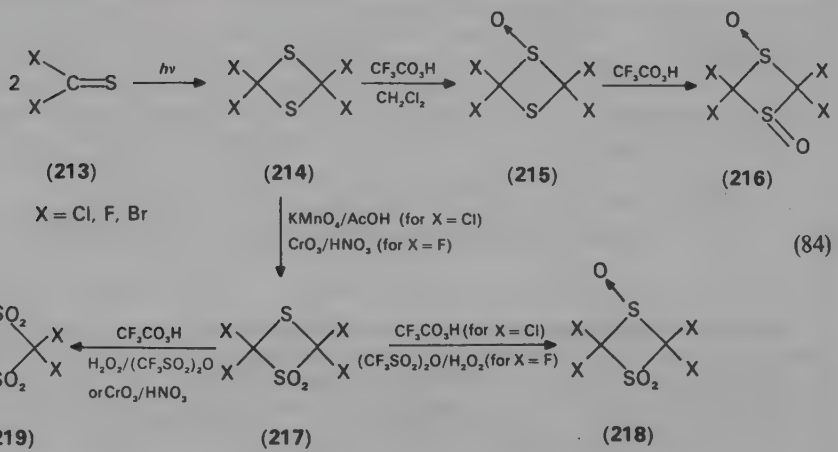
(211a, 212a)



(211b, 212b)

The synthesis takes advantage of the well-documented sulfoxide → sulfenate rearrangement[97,106], as well as of its retro-process, leading to cyclization and formation of the desired four-membered ring sulfoxide system (i.e. **211**, **212**). A closely related ring enlargement is based on the reversibility of this rearrangement and has found wide use in penicillin chemistry[246].

The syntheses of perhalogenated dithiethanes and their oxidation products (**214**–**219**) have been recently reported[247]. The method is based on the photochemical dimerization of thiophosgen or its fluoro- and bromo-analogues followed by partial oxidation with trifluoroperacetic acid to the desired sulfoxides (or sulfones)[248] as shown in equation 84.



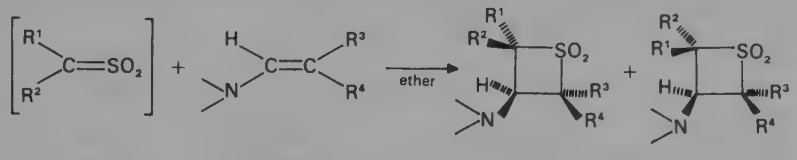
(213) X = Cl, F, Br (214) (215) (216) (219) (217) (218)

(84)

2. *Thietane dioxides*

Given any thietane, oxidation of the sulfur to a sulfone with peracids[202,203] or H_2O_2[74c] is straightforward and in most cases neither intervenes chemically with other sites nor alters the structural features or stereochemistry of the thietane ring.

It appears, however, that the most used strategy for the preparation of thietane dioxides is the [2 + 2] cycloaddition of enamines (**202**) with *in situ*-generated sulfenes (**220**)[74,143,186–188,202,242] to give *β*-aminothietane sulfones (equation 85).



(**220**) (**202**) (**a**) (**221**) (**b**)

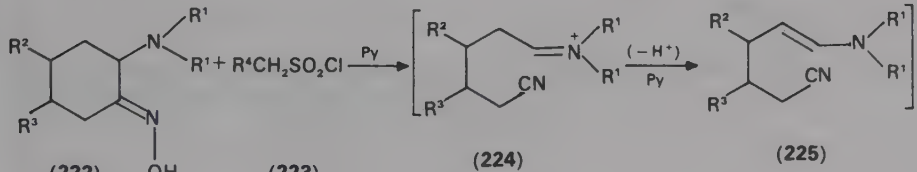
R^1 = Ar, Alkyl, ArCO, CO_2Et, CN, Hal $R^3 = R^4$ = Alkyl (*trans*) (*cis*)

$R^2 = CH_3$ or H (85)

Although the yields of the above reactions are high and the procedure is simple[186], there are some apparent disadvantages: the selection of the sulfene substituents R^1 and R^2 is limited, depending on the availability of the sulfonyl chloride precursors; the cycloaddition leads to a mixture of *cis*- and *trans*-substituted thietane dioxides; the cycloaddition reaction is reversible[202]; and several further transformations are necessary if a dioxide without 3-*N*-substituent is required.

The steric outcome in the above cyclization can be explained on the basis of either a zwitterionic intermediate[186,202] or a concerted [π2s + π2s] process[248], depending on the nature of the reactants[186]. Definite predictions are practically impossible as yet. The more stable *trans*-isomers (i.e. **221a**) can be obtained by stirring the isomeric mixture with catalytic amounts of potassium *t*-butoxide in *t*-butyl alcohol for several days[186].

A closely related procedure for preparing thietane dioxides is the one-step conversion of cyclic α-amino ketoximes (**222**) to 2-(ω-cyanoalkyl)-3-dialkylaminothietane dioxides (**226**), with *trans*-orientation of the substituents[249] (equation 86).



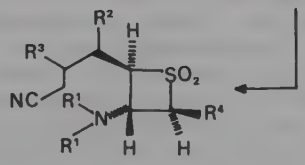
(**222**) (**223**) (**224**) (**225**)

(**a**) $R^2 = R^3 = H$

(**b**) $R^2 = H$, $R^3 = t$-Bu

(**c**) $R^2 = t$-Bu, $R^3 = H$

R^4 = H or C_6H_5 (86)

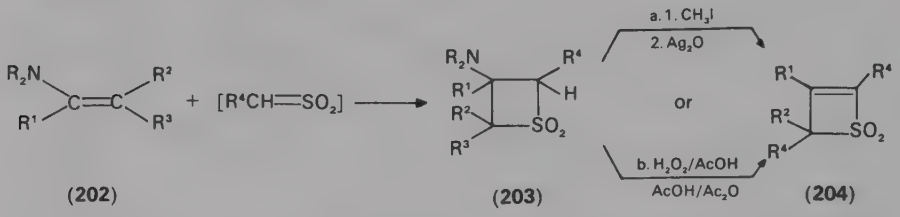


(**226**)

The scope of the above is rather limited, mainly because of the need to prepare the starting ketoximes **222** and the resultant specific pattern of the sulfone product.

3. *Thiete dioxides*

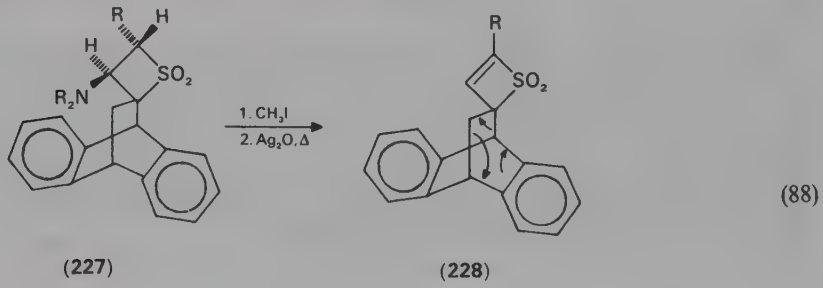
Practically speaking, almost all syntheses of these systems are based on the enamine–sulfene cycloaddition reaction[143,250]. The thietane sulfone thus obtained yields, by elimination of R_2NH, the desired unsaturated, four-membered sulfone system[187–189,231,250,251] (equation 87).



(202) (203) (204)

(87)

An attempted synthesis via a retro Diels–Alder route failed, due to the instability of the thiete sulfones at the temperatures required to remove the anthracene blocking group[189] (equation 88).

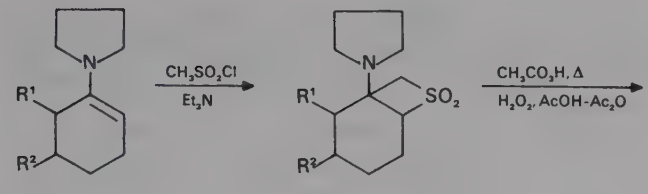


(227) (228) (229)

(88)

The Hofmann degradation approach (equation 87a) suffers from the fact that some aminothietane dioxides (**203**) display a propensity for ring cleavage when treated with methyl iodide, particularly when R^2 or R^3 are electron-withdrawing substituents[189]. *N*-oxide degradation, on the other hand, appears to be quite general, albeit giving rise to mixtures of isomeric thiete dioxides [189,250]. Hofmann degradations readily take place in water suspensions even without heating[188] and this method is probably the most convenient (and most used) to prepare thiete dioxides.

Thiete dioxides, in which the double bond is incorporated into an aromatic system (i.e. **234**), are made via the same strategy depicted in equation 87, except that the system is aromatized only at the last step[250–253] (equation 89).

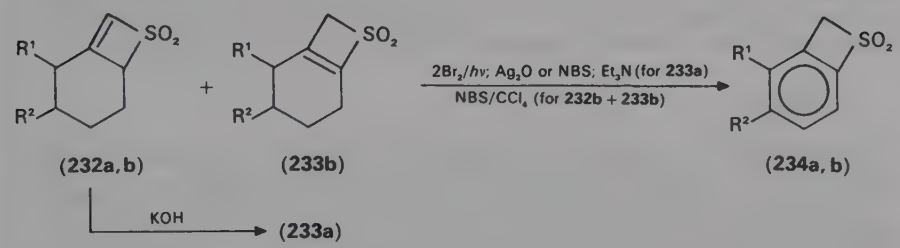


(230) (231)

(a) $R^1 = R^2 = H$

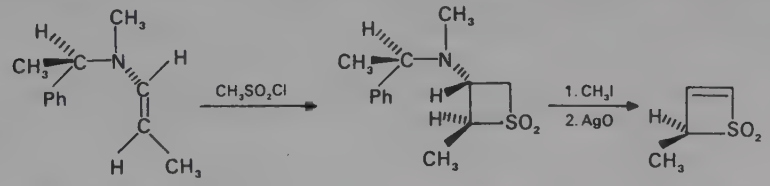
(b) $R^1R^2 =$

(89)



(232a,b) (233b) (234a,b) (233a)

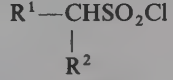
Asymmetric induction and the synthesis of optically active thietane and thiete dioxides can be achieved via the basic strategy depicted above (equation 87), by using optically active enamine in the first (2 + 2) cycloaddition[187] (equation 90). α-Halo and α,α-dihalo



(90)

R(+) (235) (236) *S*(+) (237)

thiete dioxides can be readily prepared by using α-halo and α,α-dihalosulfonyl chlorides (**238**) within the scheme of equation 87[254].

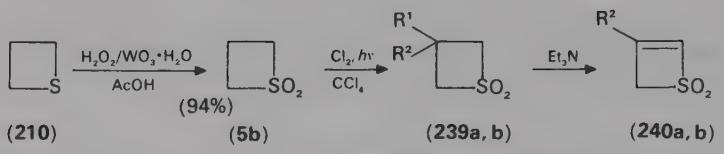


(**238**)

R^1 = H, Cl, Br

R^2 = Cl, Br, I

A preparation of 3-substituted thiete dioxides takes advantage of the commercial availability of the parent four-membered thietanes. The latter is oxidized to the sulfone, which in turn is photochemically mono- or di-chlorinated in the 3-position. The 3-chlorothietane dioxide (**239a**) can be easily transformed into the thiete dioxide, whereas the 3,3-dichloro homolog is transformed into the 3-chloro-2*H*-thiete 1,1-dioxide (**240b**)[255] (equation 91). **240b** reacts with carbanions, amines, alcohols and thiols to give the corresponding 3-substituted thiete dioxides[255].



(91)

(62%) (**a**) $R^1 = Cl$, $R^2 = H$
(82%) (**b**) $R^1 = R^2 = Cl$

E. Selected Chemical Reactions and Transformations

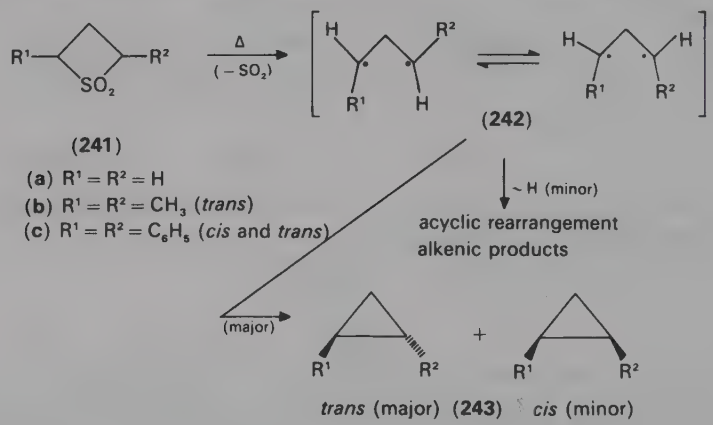
Several typical reactions of cyclic sulfoxides or sulfones are not observed in the acyclic and large-ring sulfoxide and sulfone analogues, or if they are, they take a different path. In such cases the effect of the cyclic sulfoxide or sulfone function is at least partially a consequence of the particular stereochemical constraints of the cyclic array.

1. Thermolysis

Acyclic sulfoxides fragment into olefins and sulfenic acids on thermolysis[97]. Cyclic sulfoxides exhibit essentially the same ready mode of fragmentation[106].

The main result of the thermolysis of the three-membered ring sulfoxides and sulfones is the extrusion of the sulfur monoxide and the sulfur dioxide moieties (Section III.C.1)[99,105]. Only in the presence of a suitably disposed β-hydrogen does the ordinary sulfoxide-sulfenic acid fragmentation take place in the thiirane oxide series (equation 9).

The dominant pattern for the thermal fragmentation of thietane dioxides involves extrusion of sulfur dioxide leading to a 1,3-diradical (i.e. **242**) which closes to final products, mainly cyclopropanes, accompanied by rearrangement products resulting from hydrogen migration within the diradical[191,193c,230,256–258] (equation 92).

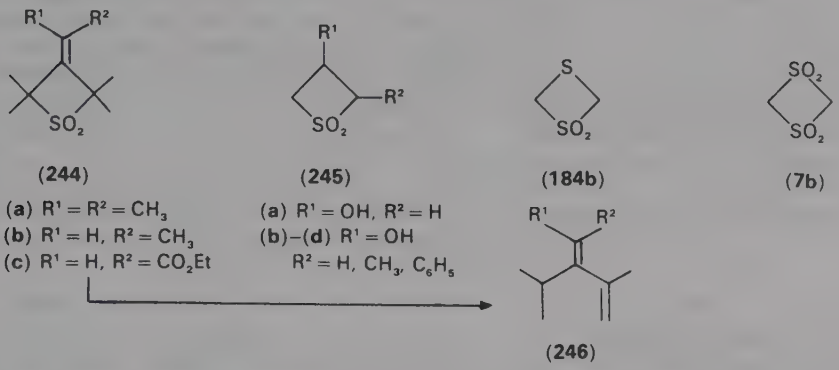


(92)

The reaction is not stereospecific and the product mixture of the *cis*- and *trans*-cyclopropane isomers (when applicable)[193c,230] approximates the expected equilibrium mixture at the temperatures of the pyrolysis[259].

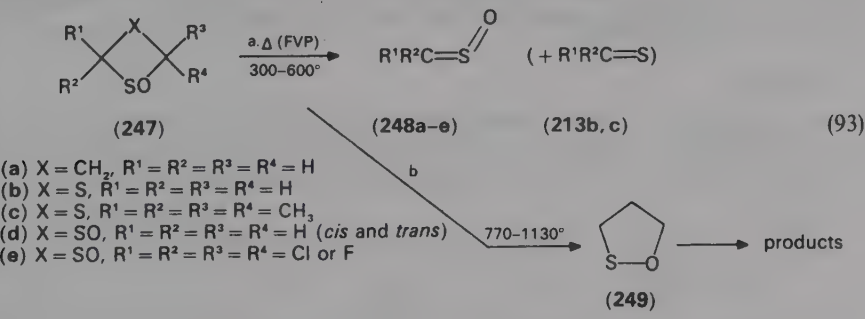
Analogous results are obtained in the pyrolysis of 3-alkylidene-2,2,4,4-tetramethylene-thietane dioxides[256] (**244**), 3-hydroxy and 3-keto thietane dioxides (**245**)[191], and 1,3-dithietane dioxides and tetroxides (**184b** and **7b**)[192]. The extrusion of both CO and SO_2 and the two SO_2 moieties in **245b–d** and **7b**, respectively, to give ethylene, the formation of

diene **246** in the pyrolysis of **244a–c**, of acetone in the pyrolysis of **245a**, and of thirane in the pyrolysis of **184b**, are all consistent with a mechanism involving a trimethylene radical intermediate.



The reaction appears to take place via homolysis of the carbon–sulfur bond, facilitated by both ring strain and the relative ease of the SO_2 extrusion, to give the 1, 3-diradical in an overall retro 3 + 1 process[258]. The latter can either ring close to form cyclopropanes (or cyclopropanones, or thiiranes, or thiirane dioxides, that may undergo further transformations) or, depending on the substitution pattern, give rise to hydrogen migrations (and/or other rearrangements) to yield stable unsaturated acyclic products.

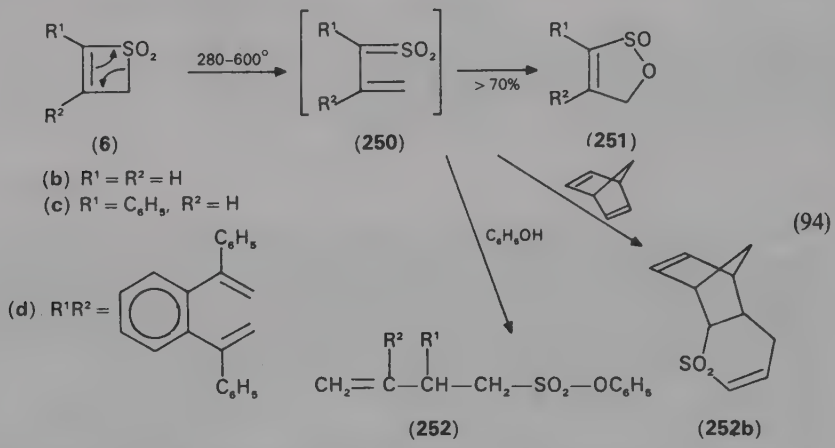
In contrast, thermolyses of the four-membered ring sulfoxides do not eliminate sulfur monoxide[260] but undergo, almost exclusively, a retro 2 + 2 decomposition [simultaneous for a concerted ($\sigma_a^2 + \sigma_s^2$) process or stepwise for a process involving 1, 4-diradical] leading to the generation of sulfines (i.e. **248**)[192,228,247a]. The formation of these low-molecular-weight, reactive, short-lived species can be detected by either mass spectrometry, microwave or photoelectron spectroscopy techniques[192], or through the actual trapping, isolation and identification of the final products (equation 93).



One exception to the above general fragmentation pattern is the formation of the ring-rearranged sulfenate (**249**) in the gas-phase thermolysis of thietane oxide (**247a**) at elevated temperatures[229]. Although the temperature of this thermolysis is considerably higher than those used in the other studies, it is difficult to account for the (not totally unprecedented[191]) difference in the results.

Stepwise decomposition of thietane oxides should be influenced by the relative stabilities of the developing radical centers, whereas the subsequent selection between

retro (3 + 1) and (2 + 2) routes should be influenced by the relative stability of the developing π systems. The stabilization of an adjacent (α-) radical center is in the order $S > SO > SO_2$, while the order of leaving abilities is the reverse, $SO_2 > SO > S$. Based on what is known of thermal ring opening of cyclobutenes (retro 2 + 2 intramolecular cycloaddition)[96], and on the behavior of thietane oxides and dioxides under pyrolytic conditions, the thermolyses of thiete sulfones have been explained in terms of a retro (2 + 2) concerted process, leading initially to sulfene intermediates, which can be trapped or are further rearranged under the reaction conditions to yield the observed final products[191,257,261] (equation 94).

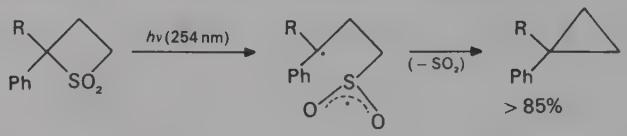


(94)

The formation of cyclic sulfinic esters (sultines) from vinyl sulfenes is known[191], and the trapping of the expected intermediate vinyl sulfene in the thermolysis of thiete dioxide (**6b** and **194**) has been convincingly achieved[231,262]. Specifically, thermolysis of thiete dioxide **6b** in the presence of norbornenes gave cycloadducts of the Diels–Alder type (i.e. **252b**), resulting from the trapping of the vinyl sulfene formed. The accumulated evidence thus supports the proposed mechanism for these thermolytic reactions.

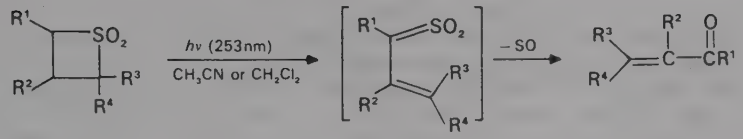
2. *Photolysis*

The photolyses of several 2-alkyl-2-phenylthietane dioxides in dichloromethane or methanol afforded excellent yields of 1-substituted 1-phenylcyclopropanes apparently via the same mechanism as in the parallel thermolyses[263a] (equation 95).



(95)

The phenyl substitution provides both the chromophore necessary for photoactivity and the stabilization of the initially formed radical. The reported photochemical extrusion of SO from 2,2,4,4-tetraacetylthietane[263b] to give the corresponding cyclopropane appears to be a unique case associated with the particular features of the irradiated molecule.



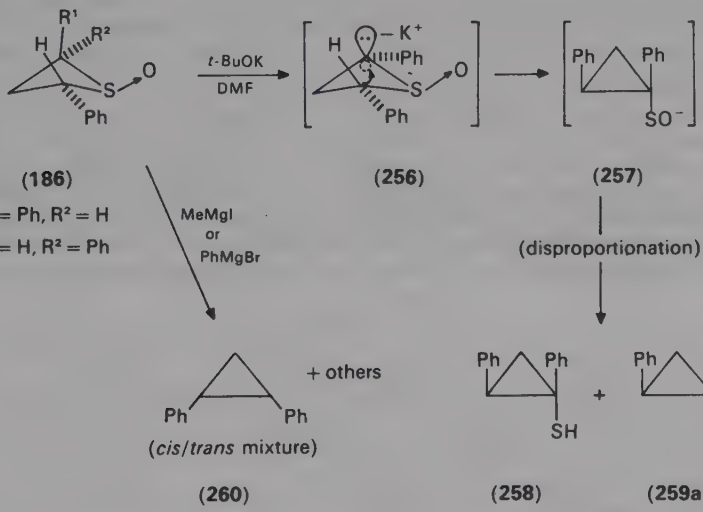
(6e) (250b) (255) (96)

The photolysis of various substituted thiete dioxides under similar conditions resulted in the formation of the unsaturated ketones (**255**)[264], most probably via a vinyl sulfene intermediate followed by a loss of sulfur monoxide as shown in equation 96. The same results were obtained in the thermolysis of **6e** ($R^1 = R^3 = Ph$; $R^2 = R^4 = H$)[231], which further demonstrates that similar mechanisms are operative in thermolyses and photolyses of thietane dioxides and thiete dioxides.

3. Rearrangements

Molecular rearrangements such as that of Stevens[248,265] or the sulfoxide → sulfinic acid, Ramberg–Bäcklund[15] or sultone → sultine rearrangements, are quite common in these classes of compounds.

Rearrangements closely resembling the Stevens rearrangement[248,265] have been investigated by applying Grignard reagents or potassium *t*-butoxide in dimethylformamide (low availability of protons) to *cis*- and *trans*-2,4-diphenylthietane oxides and dioxides[266,267]. The main results are summarized in equation 97 and 98.



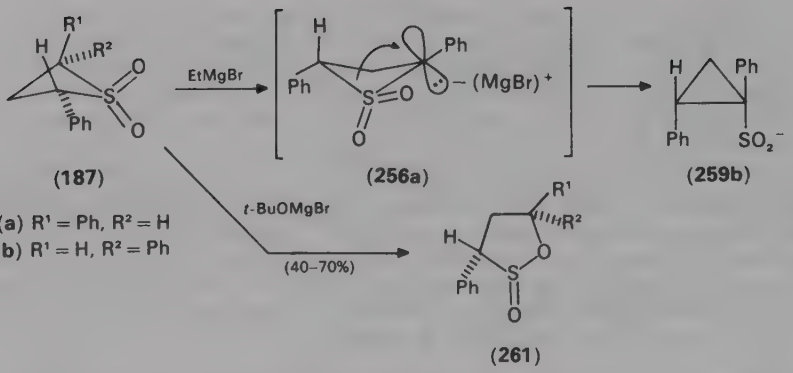
(**186**)
(**a**) $R^1 = Ph$, $R^2 = H$
(**b**) $R^1 = H$, $R^2 = Ph$

(**256**) (**257**) (97)

(**260**) (**258**) (**259a**)

Both (*cis*- and *trans*-) isomers rearrange stereospecifically to the *cis*-rearranged cyclopropane product (i.e. **257**), the processes being apparently controlled by the same *cis*-anion intermediate (i.e. **256**)

The α-sulfonyl carbanion (**256a**) rapidly formed from either isomer is stabilized by rearrangement to the *trans*-1,2-diphenylcyclopropane sulfinate (**259b**), so that the overall result is a highly stereoselective rearrangement process. In line with previous results, the ring enlargement (i.e. **187** → **261**) induced by the *t*-BuOMgBr is an example of a stereospecific sulfone → sultine rearrangement in a cyclic system.



(187)
(a) $R^1 = Ph$, $R^2 = H$
(b) $R^1 = H$, $R^2 = Ph$

(256a)

(259b)

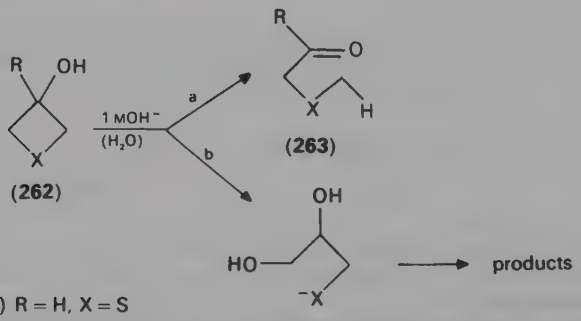
(261)

(98)

The relative stabilities of the species involved appear to be responsible for the stereochemical outcomes. Relief of ring strain must play a role in determining the course of the reaction. An explanation for the different reaction paths on using different Grignard reagents must wait further experimentation.

4. Eliminative fission of the thietane ring

The role of strain in determining reactivity in base-induced eliminative fission of the thietane ring (equation 99a), the nature of the transition state for ring opening, and the competition between eliminative fission and nucleophilic substitutive ring fission (equation 99b) have been recently studied[268]. The rates of eliminative fission were found to be 5×10^{-5} and $6 \times 10^{-1} - 6 \times 10^{-3}$ $M^{-1} s^{-1}$ for the thietane oxides (**262b,d**) and thietane dioxides (**262c,e**), respectively. The thietane **262a** under these conditions undergoes the substitutive ring fission alternative (equation 99b) at higher temperatures and at a slower rate. Thus, the reactivity is to be associated with the capacity of the functional group to stabilize a carbanion adjacent to the carbon that is detached in the ring cleavage. The observed accelerations, compared with rates of about 10^{-9} in the cyclobutanol series[269], are presumably offset by the lower strain energy of thietane (81.9 kJ mol^{-1}) compared with that of cyclobutane (106.2 kJ mol^{-1}). By comparison of the reactivities of the cyclic sulfoxide and sulfone (**262d,e**) with those of their acyclic counterparts [e.g., about 10^{-8} and



(262)

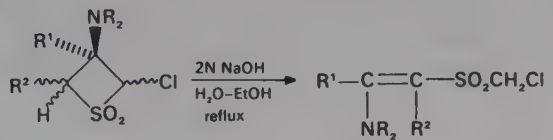
(263)

(264)

(99)

(a) R = H, X = S
(b) R = H, X = SO
(c) R = H, X = SO_2
(d) R = C_6H_5, X = SO
(e) R = C_6H_5, X = SO_2

10^{-5} for $C_6H_5C(OH)HCH_2XCH_3$; X = SO and SO_2, respectively], the effect of ring strain is estimated at about 5×10^4 for the sulfoxide and sulfone [268]. The increased rate of fission in the phenyl-substituted thietanes reflects the apparent relief of larger amounts of ring strain in these cases (as a result of increased initial steric interactions between ring hydrogens and substituents). Other 3,3-disubstituted thietane dioxides were shown to undergo base-induced eliminative ring fission similar to that discussed above. The ring opening is observed only if position 4 is mono-substituted (so that a carbanion can be formed there), and position 3 is di-substituted (to make the α,β dehydrohalogenation impossible)[270] (equation 100).

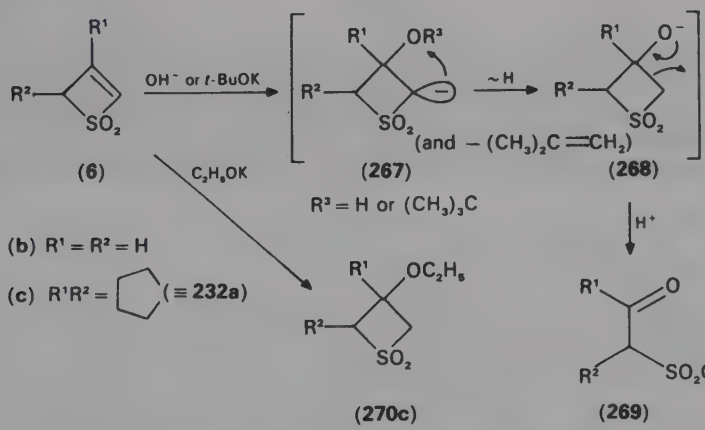


(100)

(265) (266)

(a) $R^1 = C_6H_5$, $R^2 = H$
(b) $R^1 = C_6H_5$, $R^2 = CH_3$

Base-induced eliminative ring fission, in which both the double bond and the sulfone function take part, has been observed in thiete dioxides[253]. The reaction can be rationalized in terms of initial Michael-type addition to the double bond of the ring vinyl sulfone, followed by a reverse aldol condensation with ring opening. The isolation of the ether **270c** in the treatment of **6c** with potassium ethoxide (since the transformation **267** → **268** is not possible in this case) is in agreement with the reaction mechanism outlined in equation 101[253].



(101)

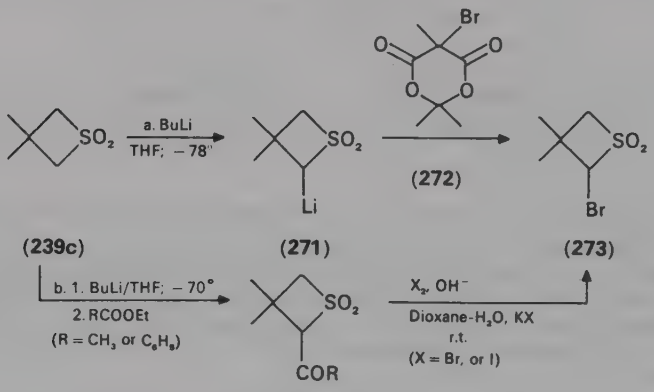
Interestingly, isomerization of the double bond in thiete sulfones can be accomplished by their treatment with strong bases (e.g. KOH) in aprotic solvents[253].

5. α-Halogenation

The α-halogenation of sulfones is not a straightforward reaction, since (a) the carbon is at best partially positively charged due to the strong electron-withdrawing capacity of the

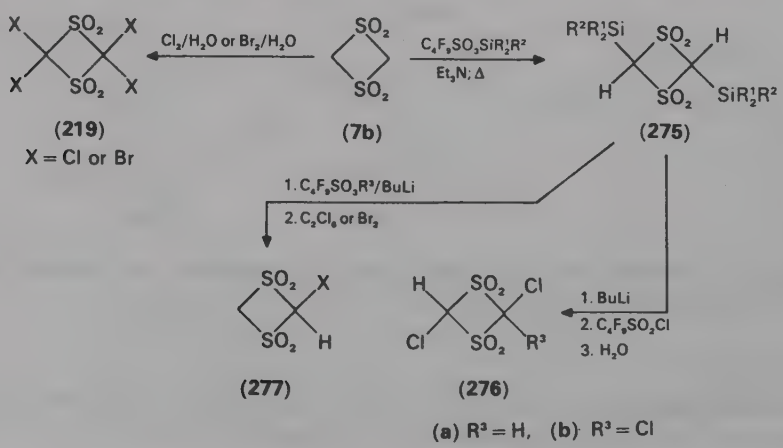
adjacent sulfone group; (b) the α-hydrogens are nonenolizable; and (c) some steric hindrance is expected to be exerted by the sulfone oxygens on the approaching halogenating agent. The α-halogenation of various acyclic and bicyclic sulfones can be achieved, however, by the halogenation of the initially generated α-sulfonyl carbanions[271].

The lithio-α-carbanion readily generated by the treatment of thietane dioxides with BuLi failed to react with all conventional halogenating agents (Br_2, Cl_2, NBS or *N*-chlorobenzotriazole)[272]. Successful halogenation could be affected, however, by treating the α-carbanion with the 5-methyl, 5-bromo derivative of Meldrum's acid **272**[272,273]. Thietane dioxides can be monoacylated by using esters and employing essentially the same procedure. The resulting monoacylthietane dioxides (i.e. **274**) can be easily transformed to the corresponding α-halothietane dioxides by treatment with basic aqueous solutions of the desired halogen (equation 102b)[274].



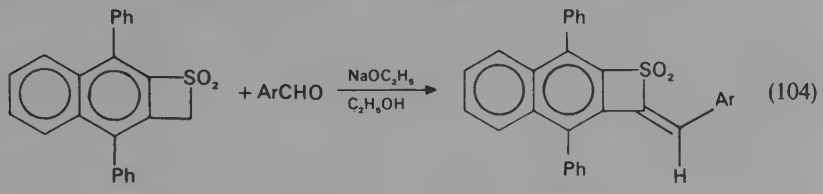
(102)

The 1,3-dithietane tetroxides (**7b**) readily undergo tetra-α-halogenation[275] with either Br_2 or Cl_2, but not with I_2. Partial α-halogenation in this series can be accomplished indirectly by starting from either 2,4-bis(trimethylsilyl)- or 2,4-bis(*t*-butyldimethylsilyl)-1,3-dithietane tetroxides (**275**) as shown in equation 103[275]. In all of the above reactions one takes advantage of the highly acidic α-hydrogens and, consequently, the



(103)

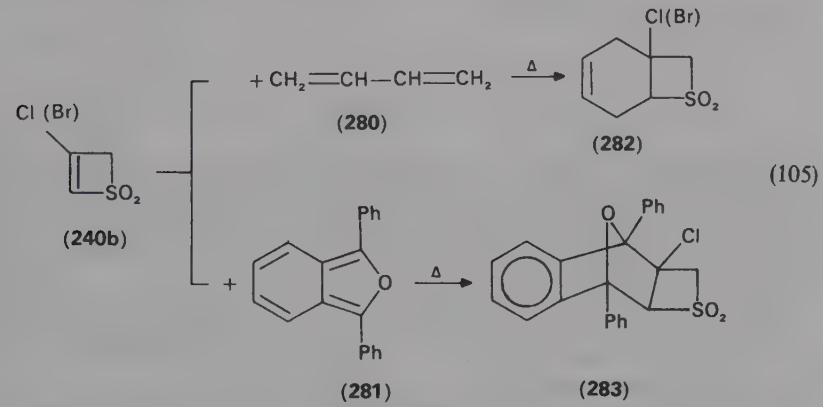
facile *in situ* formation of the reactive α-sulfonyl carbanions. By analogy to α-halogenation, condensations of thiete dioxides with aldehydes yields α-methylidene thiete sulfones (**279**). Here again the particularly acidic α-hydrogen and the formation of the stabilized α-carbanion[227] have been utilized[276] (equation 104).



(196a) (278) (279) (104)

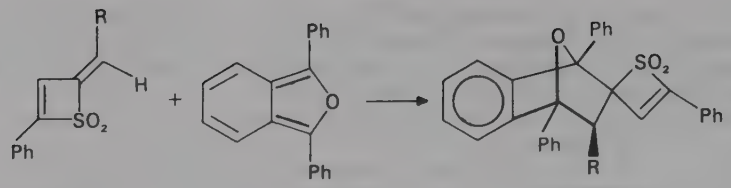
6. Cycloaddition reactions

Based on the high dienophilicity of acyclic vinyl sulfones one should expect thiete dioxides to exhibit similar properties. Indeed, several Diels–Alder (2 + 4) cycloadditions with thiete dioxide as dienophile are known. For example, 1,3-butadiene and 1,3-diphenylisobenzofuran react with 3-chloro- or 3-bromo-thiete dioxides to afford the corresponding 1:1 Diels–Alder cycloadducts[255,277] (equation 105).



(105)

Equimolar quantities of methylidene thiete (**284a**) and phenylisobenzofuran afforded a *single* crystalline spiro-cycloadduct (**285a**), and a similar result was obtained with thiete **284b**[242b] (equation 106). Clearly, the Diels–Alder additions with these thietes prefer (essentially exclusively) the involvement of the exocyclic double bond as the dienophile, which suggests steric control (associated with the bulky sulfone group) in the transition states. Inspection of the two theoretically possible transition states[242b] indeed corroborates this conclusion. Irradiation of thiete dioxide **284a** afforded a single crystalline *trans*-photodimer (as far as the two sulfonyl groups are concerned) with the cycloaddition having occurred between the two *exo*cyclic double bonds of the monomers. This photodimerization is a symmetry-allowed (2 + 2) cycloaddition[248] in which the high degree of symmetry observed in the process is a consequence of an arrangement with the minimal steric interference of the two sulfone groups in the most favorable transition state.



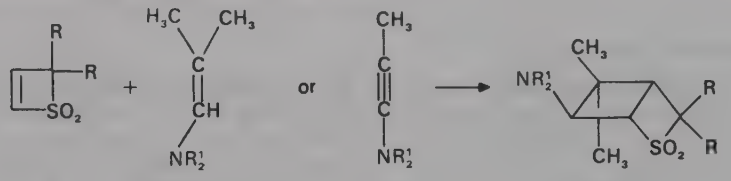
(106)

(284)
(a) R = H
(b) R = Ph

(281)

(285a,b)

As expected, 1:1 (2 + 2) cycloadducts are obtained in the reactions of thiete dioxides with some typical electron-rich olefins, e.g. enamines and ynamines, although this cycloaddition has not proven to be general[190].

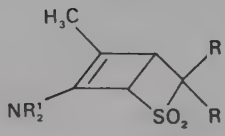


(107)

(6)
(b) R = H
R = CH_3

(286)
R^1 = CH_3 or C_2H_5

(287)



(288)

The steric effect generated by the gem-dimethyl group of the thietane ring on the adjacent sp^2 carbon atom makes the cycloaddition in these cases more sluggish compared with those of the parent thietane dioxide (**6b**)[190]. These cycloadditions provide a convenient entry into the strained thiabicyclo [2.2.0] hexane system (e.g. **287**, **288**; equation 107).

Cycloadditions of the 1,3-dipolar nitrile oxides and diazoalkenes to acyclic vinyl sulfones are in general highly selective, the particular regioisomer formed depending on the substituents of both reactants[213,214]. Nitrones, on the other hand, tend to yield mixtures of the two possible isomers (see equation 78).

3 + 2 Cycloadditions of nitrones, nitrile oxides or diazo compounds to thiete dioxides do not show the high stereoselectivity observed with acyclic vinyl sulfones, and mixtures of the two possible adducts are formed[213,214,278]. The charge-transfer stabilization energy calculated according to the Klopman–Salem perturbational approach[215] is able to account for the experimental trends of the isomer ratio in terms of the major stereochemical structural differences between the acyclic vinyl sulfones and the four-membered ring sulfones[214] (see Section IV.B.3).

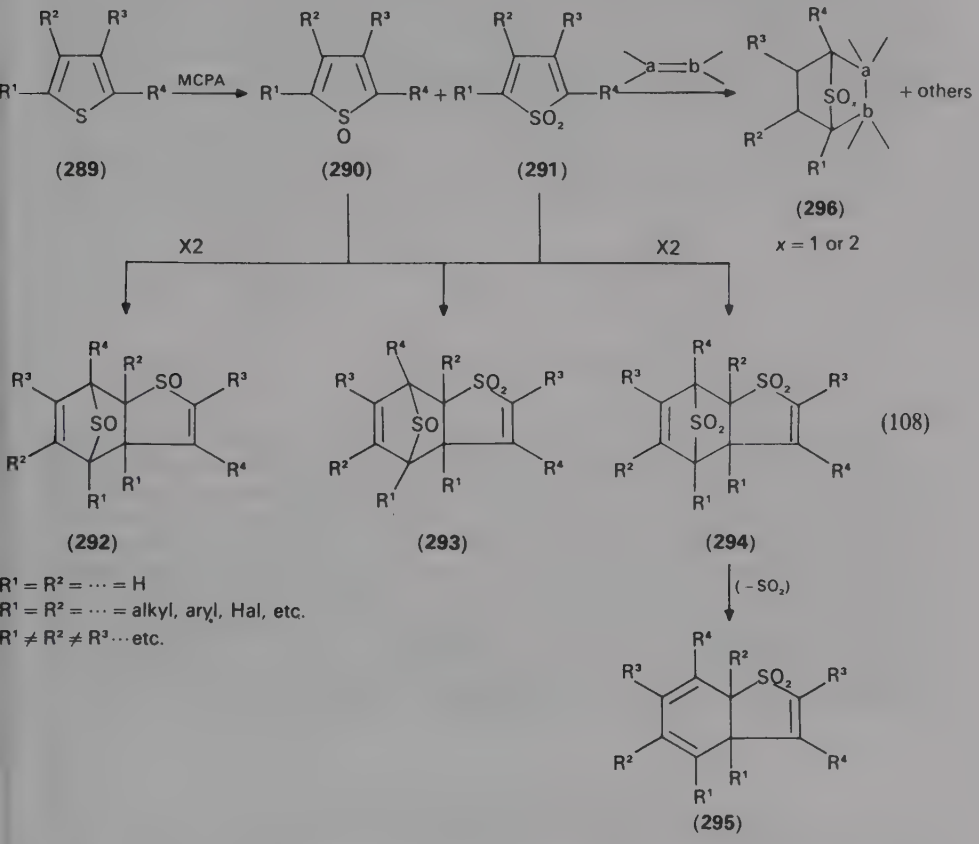
V. FIVE-MEMBERED RING SULFOXIDES AND SULFONES

A. Introduction and Scope

The enormous literature of five-membered ring systems containing sulfur primarily describes the synthesis, properties and chemistry of thiophene and its derivatives[279].

Thiophene oxides and dioxides have recently been thoroughly reviewed[280,281].

Oxidation of thiophene to the corresponding oxide and dioxide, i.e. **290** and **291** (MCPA appears to be the reagent of choice[282,283]) results in loss of aromaticity in the latter, giving rise to the formation of reactive electron-deficient diene systems 'locked' in the cisoid configuration. It is not surprising, therefore, that the bulk of the chemistry associated with these molecules involves either self-Diels–Alder-type cycloadditions of the *in situ*-generated oxidized reactive species, or their facile cycloaddition with both dienophiles and dienes as illustrated in equation 108[280,281]. Diene character and tendency toward Diels–Alder additions were calculated to be less for thiophene oxides than for thiophene dioxides[284], the ready dimerization of the latter being rationalized in terms of second-order perturbation theory[285] and spiro-conjugation[53a]. Experimentally, however, thiophene oxide is much more reactive as a diene than thiophene dioxide[286,287].



The existence or nonexistence of conjugative effects involving the sulfone group in thiophene dioxides (a problem analogous to that in thiirene oxide and dioxide systems[2,11]) has been the subject of many studies resulting, nonetheless, in no unequivocal conclusion[280].

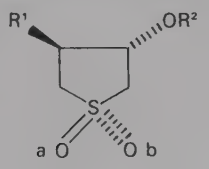
Here, only few selected aspects associated with these systems, particularly those having generalizability and/or which provide a better understanding of the sulfoxide and sulfone functionality within cyclic systems (and/or not dealt with in References 280 and 281) will be

briefly reviewed. The discussion of five-membered ring sulfoxides and sulfones containing additional heteroatom(s) and/or sulfoxide or sulfone groups is beyond the scope of this chapter.

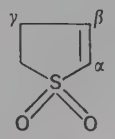
B. Physical Studies (NMR, IR and p*K*)

Oxygen-17 NMR spectroscopy has an immense potential for structural analysis of cyclic sulfoxides and sulfones as well as for providing insight into the nature of bonding within these two functional groups[288]. Indeed, in addition to data concerning the ^{17}O NMR chemical shifts for several cyclic sulfoxides and sulfones, ^{17}O NMR chemical shift differences between several diastereotopic sulfonyl oxygens in both cyclic and acyclic systems have been reported[70,289].

The ^{17}O NMR spectra of 4-alkoxythiolane dioxides (**297**) indicate that the sulfonyl oxygens have little influence on the chemical shifts of the 'etheral' oxygen, but that the sulfonyl oxygens are diastereotopic, with the chemical shift differences ($\Delta\delta_{a,b}$) being independent of the structure of the alkyl group in the moiety[280]. The oxygen *cis* to the alkoxy *oxygen* (O_b) was shown to be the more deshielded.



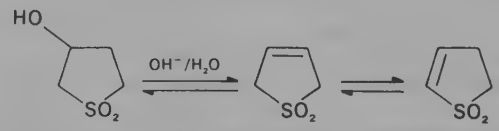
(**297**)



(**298**)

$R^1 = H$, OCH_3, OC_2H_5, $OC_3H_7^i$, etc.
R^2 = alkyl

Although the $\Delta\delta_{a,b}$ (i.e. $\delta O_b - \delta O_a$) was rather small (≈ 1.55 ppm), the shift-reagent $Eu(fod)_3$ enhances the ^{17}O chemical difference substantially, and shifts both oxygens upfield (the least sterically hindered sulfonyl oxygen is more responsive to the shielding). α,β but not β,γ unsaturation in the molecule [i.e., the double bond in thiolene (**298**)] deshielded the sulfonyl oxygens, in both five- and six-membered rings[290]. The utility of ^{17}O NMR in the thiolene dioxide series was further demonstrated by the determination of the base-induced equilibrium in equation 109. ^1H NMR has been used to assign configuration to stereoisomeric sulfoxides. The chemical shift of the β-hydrogen was found to be strongly dependent on the spatial relationship between the β-hydrogen and the sulfoxide group. The field effect and the magnetic anisotropy of the sulfoxide group result in deshielding of the β-proton in the *cis*-position to the sulfoxide oxygen[291].



(109)

(6%) (56%) (38%)

(**297b**) (**299**) (**298**)

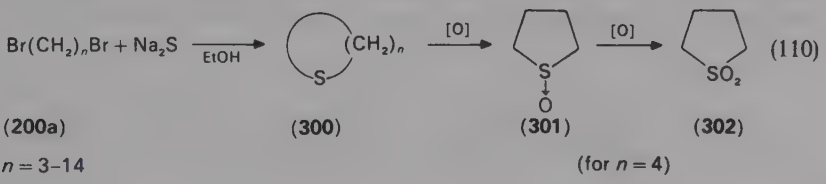
A long-range proton coupling, which was found to be transmitted by a sulfone group in thiolane dioxide systems[292], is apparently facilitated by a nonbonding *p*-orbital on one of the sulfone oxygen atoms. This phenomenon is of interest for saturated cyclic systems.

IR spectra of thiolane oxides in the solid phase were shown to be most outstandingly different in the sulfoxide region depending on the particular crystalline state/structure[291b], a fact which can be used to advantage for conformational analysis. Also, as one could expect, the sulfoxide absorptions indicate strong hydrogen bonding.

Finally, since besides the inductive effect of the sulfoxide and the sulfone functional groups, hydrogen bonding, field effects and steric effects to solvation may or may not work in the same direction, the pK_α values can be useful in assigning configurations of suitable pairs of stereoisomeric sulfoxide and sulfone carboxylic acids[291].

C. The Synthesis of Five-membered Ring Sulfoxides and Sulfones

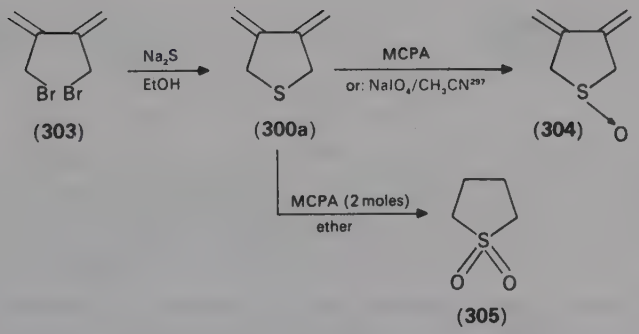
The reaction of α,ω-dihaloalkanes with sulfide ion under high dilution conditions is the method of choice for the synthesis of five- and six-membered ring sulfides[243,293]. The oxidation of the formed thiolanes to the corresponding thiolane sulfoxides and/or sulfones by common oxidizing agents is simple and straightforward. This synthetic sequence constitutes the common route for the synthesis of sulfur-containing cyclic systems having ring size of four up to fifteen[243] (and most probably even more; see equation 110). The method has been successfully applied to prepare several 3,4-dimethylenethiolanes[294] that are interesting as starting materials in numerous cycloadditions or as potential precursors of the tetramethylenemethane biradical[295] through the thermal or photolytic extrusion of sulfur monoxide or dioxide[296] (equation 111).



(110)

(200a) (300) (301) (302)

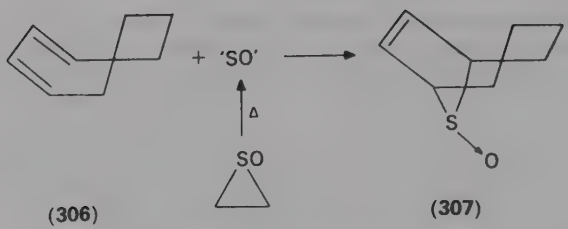
$n = 3$–14 (for $n = 4$)



(303) (300a) (304) (111)

(305)

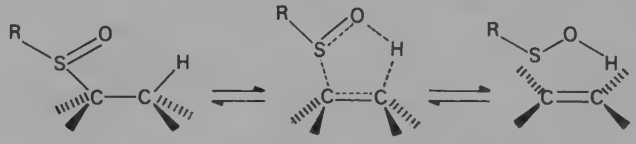
Two attractive routes to thiolene oxide and dioxide are the diene-SO[104] and diene-SO_2[298] cycloadditions, respectively. These cycloadditions are highly stereoselective at both carbons of the diene systems and at sulfur (see equation 62 for specifics) which, in the case of sulfoxide formation, proceed via attack of triplet SO on the diene. Equation 112 shows an example of such a cycloaddition[104]. The overall yields are significantly improved by running the cycloadditions in the absence of oxygen and by the use of excess diene.



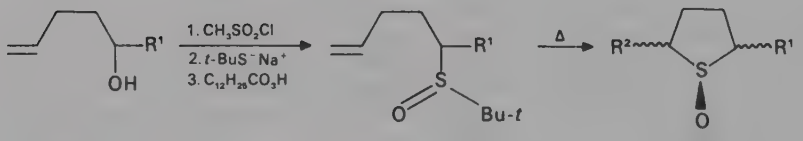
(306) (307) (112)

Since sulfoxides and sulfones are versatile synthetic intermediates, and since in both the thiolene oxide and dioxides the reverse dethionylation[114] (−SO), and cheletropic extrusion of sulfur dioxide[296], respectively, readily take place thermally, these cycloadditions are expected to find a useful place in organic synthesis. It should be kept in mind, however, that the retrograde SO-diene reaction and interconversion of the thiolene oxides compete effectively against SO extrusion on heating, and that diene isomerization accompanies the forward reaction (SO + diene).

A method for the stereospecific synthesis of thiolane oxides involves the pyrolysis of derivatives of 5-*t*-butylsulfinylpentene (**310**), and is based on the thermal decomposition of dialkyl sulfoxides to alkenes and alkanesulfenic acids[299] (equation 113). This reversible reaction proceeds by a concerted *syn*-intramolecular mechanism[246,300] and thus facilitates the desired stereospecific synthesis[301]. The stereoelectronic requirements preclude the formation of the other possible isomer or the six-membered ring thiane oxide (equation 114). Bicyclic thiolane oxides can be prepared similarly from a cyclic alkene[301].



(308) (113)



(309) (310) (301) (114)

(a) $R^1 = H$

(b) $R^1 = CH_3$

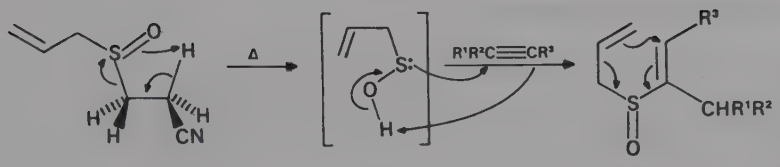
(a) $R^1 = H$, $R^2 = cis\text{-}CH_3$ (with reference to O)

(b) $R^1 = R^2 = cis\text{-}CH_3$

(c) $R^1 = trans\text{-}CH_3$, $R^2 = cis\text{-}CH_3$

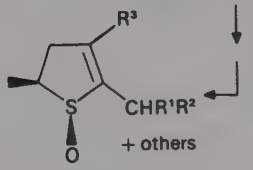
A closely related method is the thermolysis of 1-allylsulfinyl-2-cyanoethane in alkynes, which leads to the formation of thiolane oxide derivatives via consecutive pericyclic reactions[302]. The low yield and formation of mixtures are somewhat compensated for by the convenience, but its practicality is as yet rather limited (equation 115).

It is noteworthy that, based on the sulfoxide–sulfenic acid rearrangement, the readily accessible 1,3-dithiolane systems (**316**) may be utilized (equation 116) as an efficient entry into the 1,4-dithiane series[303], including the construction of carbocyclic fused systems[304]. The oxidation of the dithienes **318** to the corresponding sulfoxides (**319** and **320**) and sulfones is a simple, straightforward process.

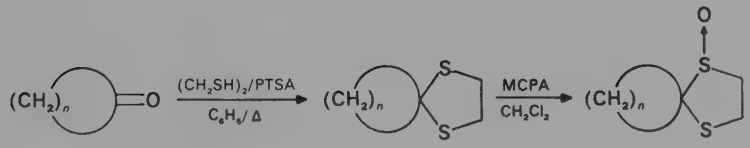


(311) (312) (313) (115)

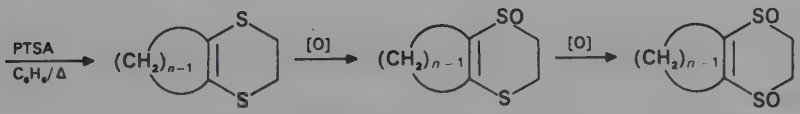
$R^1 = H$, $R^2 = C_6H_{11}$
$R^3 = H$ or CO_2Me



(314)

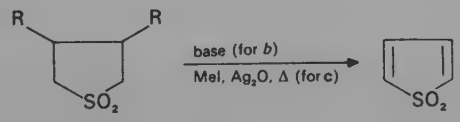


(315) (316) (317) (116)



(318) (319) (320)

Similarly, the most common method of preparing the substituted, fully unsaturated thiolane system, e.g. thiophene dioxides, is by direct oxidation of the readily available substituted thiophenes with hydrogen peroxide, perbenzoic acid and *m*-chloroperbenzoic acid[280–283]. Alternatively, thiophene dioxides are conveniently prepared via the 'double elimination' methodology[280,305] illustrated in equation 117.



(321) (117)

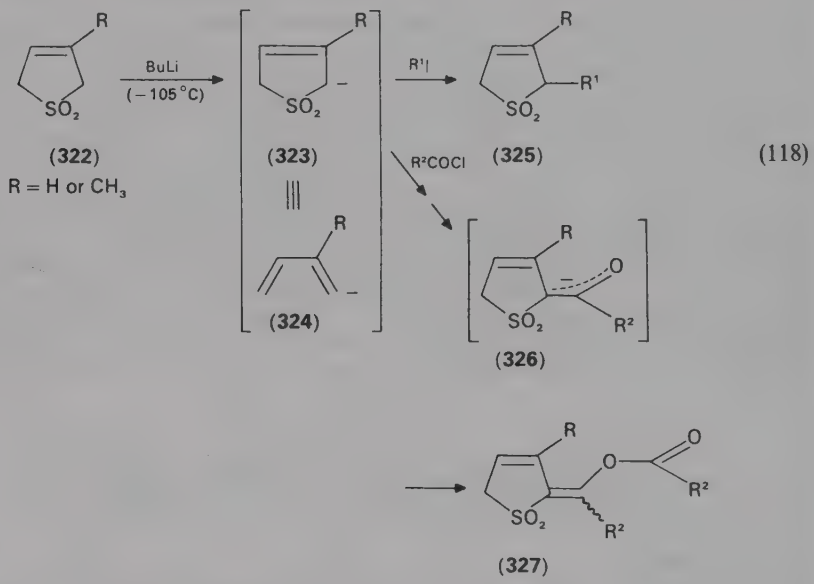
(302a) R = Br or Cl

(302b) R = NMe_2

D. Selected Chemical Reactions

1. Alkylation/acylation of 3-thiolenes

Treatment of 3-thiolenes with BuLi provides the 2-anion **323**, which may act as a butadiene 1-anion equivalent (i.e. **324**)[306]. Treatment of **323** with alkyl halide gives the 2-alkylated product (**325**) in high yield[306,307] (see equation 118). Acylation of **323** leads to the products **327** in which the acylated anions formed *in situ* under the basic conditions have undergone further acylation[306].



(118)

The success of the above alkylation and acylations, without obtaining ring-opening products[308], extends the usefulness of this method particularly when the anion **323** is being used in a regio- and stereo-specific manner[306,309]. Thus, the combination of direct alkylation and thermal extrusion of sulfur dioxide provides an ideal route for the preparation of terminally substituted conjugated dienes.

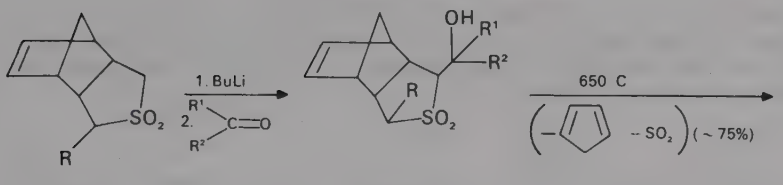
2. Functionalization of conjugated dienes

Based on the facile formation and reactivity of **323**, and the retro Diels–Alder reaction of **325**[306,310], a simple procedure has been developed for the stereoselective synthesis of functionalized conjugated dienes as well as vinylallenes[311] (see equation 119).

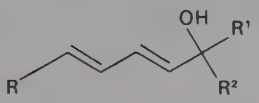
3. Epoxidation of thiolene dioxides

When 3-thiolene dioxide is treated with hydrogen peroxide, the corresponding epoxide is obtained[313]. The 3,4-*trans*-diols can be obtained by hydrolysis under acidic conditions (equation 120).

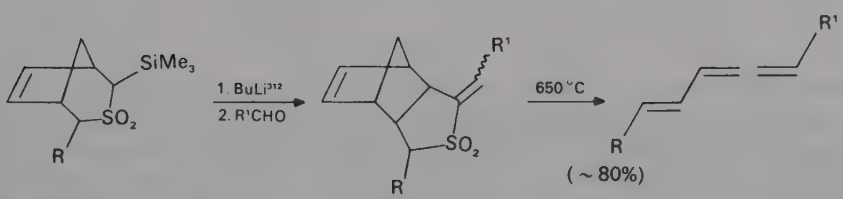
The cycloaddition reactions of thiophene oxides and dioxides (**290** and **291**[280,281]) have already been discussed (Section V.A).



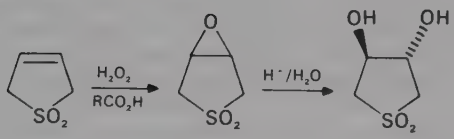
(328) (330)



(332) (119)



(329) (331) (333)



(322a) (334) (302d) (120)

VI. SIX-MEMBERED RING SULFOXIDES AND SULFONES

The distorted sp^3 angles at both carbon and sulfur atoms in small ring sulfoxides and sulfones approach their 'normal' size beginning with the thianes. Consequently, the characteristics and chemical behavior of six- and higher-membered sulfoxides and sulfones are expected to be similar to those of the acyclic counterparts. However, in view of the constraints imposed by the cyclic array, three issues deserve study:

(a) The chair (twist) boat conformational preference/equilibrium once the sulfur atom is incorporated into the cyclohexane ring skeleton, and the physical-chemical consequences of the various conformations adopted by the molecule.

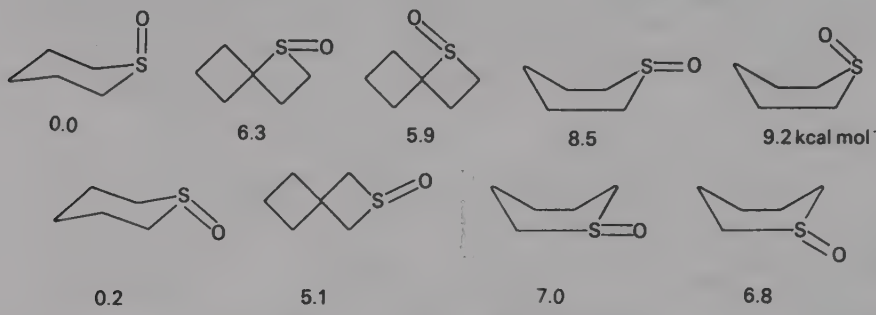
(b) The axial/equatorial orientation of the sulfur–oxygen bond in thiane sulfoxides and the direction/orientation preferences in reactions in which sulfoxide or sulfone groups are involved.

(c) The role of steric hindrance in modifying and/or altering the course of reactions in thianes compared to those in analogous acyclic systems.

A. Conformational Analysis

The molecular mechanics method[314] has been applied to the calculation of conformational properties of the thiane, dithiane and trithiane oxide systems[315], which are

expected to differ considerably from those of cyclohexane[316]. It was calculated that the chair form of thiane oxide is more stable than the twist form by more than 5 kcal mol^{-1}, and for the chair, the axial orientation of the oxygen atom is more stable than the equatorial by about 0.15 kcal mol^{-1} [315].



Other studies have also established the preference of the chair conformation with the oxygen in the axial position[317,318]; the rationale for this preference is different from the 'attractive interaction between the sulfoxide oxygen and the *syn*-axial hydrogens' proposed previously[318b]. Rather, a *repulsion* effect is advocated[315]: the equatorial oxygen is squeezed between four vicinal hydrogens, while there are only two corresponding repulsions if it is in the axial position. The correlation between the predicted[315] and observed[318a] conformational/orientational preferences in 3,3-dimethylthiane oxide (e.g., equatorial preference in the chair conformation) corroborates this interpretation. The axial preferences of the sulfur–oxygen bond in the thiane oxide is reversed in 3,3-dimethylthiane oxide because of the *syn*-axial interaction. 4,4-Dimethylthiane oxide, however, maintains a predominance of the axial isomers as deduced from the analysis of NMR data[318a].

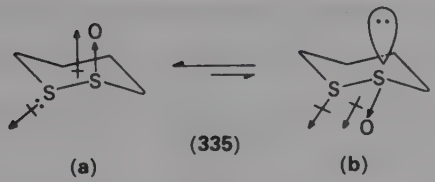
The same preferences have been calculated[315] and observed[319] in the 1,2-dithiane oxide system. Although the chair forms are also more stable than the twist or boat in 1,3-, 1,4-dithianes and 1,3,5-trithianes, the preference of the oxygen is highly variable, depending on steric and electronic interactions.

Examination of the NMR spectrum of thiane 3,3,5,5-d_4 oxide enabled the estimation of the axial/equatorial equilibrium constant[317]. The value was found to be 1.62 (at -90 °C), corresponding to a free-energy difference of 0.175 kcal mol^{-1}, which is in good agreement with field force calculations[315].

The substitution of a heteroatom for an α-sulfoxy methylene group substantially increases the preference for an axial orientation of the sulfoxide oxygen[320], despite the smaller space requirement of the sulfur with its lone pairs, compared to that of a methylene group[321], at least in the case of 1,3-dithiolane oxides. The substituting heteroatom, therefore, should decrease the conformation stability (i.e. lower the barrier to chair–chair interconversion).

Based on NMR data that were interpreted in terms of one conformationally pure form of the 1,2-dithiane oxide **335** that is not undergoing interconversion, it was suggested[319] that the strong axial preference of the sulfur–oxygen bond results from a dipolar interaction; that is, an unfavorable dipolar arrangement in the case of the equatorial orientation is relieved with the sulfur–oxygen bond adopting an axial configuration (an anomeric effect; equation 121).

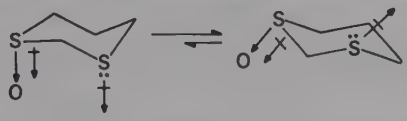
The conformational preferences of six-membered cyclic sulfoxides are strongly dependent upon the nature of the other ring atoms, especially in 1- and 3-positions[322]. Indeed, molecular mechanics calculations indicate that most of the energy difference between the



(121)

(a) (335) (b)

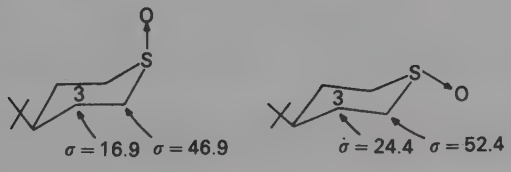
equatorial and axial conformations of **336** arises from dipole–dipole interactions[315], which explains the preference for conformation **336b** (see equation 122).



(122)

(a) (336) (b)

X-ray structure determination of *cis*- and *trans*-2-phenyl-1,3-dithiane oxides showed them to adopt chair conformations with equatorial phenyl groups, and demonstrated the importance of transannular dipolar interactions as structure determinants[323]. The analysis of ^{1}H- and ^{13}C-NMR parameters of the thiane-3-one oxides reveals the chair conformation and axial preference of the sulfur–oxygen bond[85,324]. Introduction of a sulfur at the remaining β-position of these systems increases the amount of the equatorial conformer. It was concluded that orbital–orbital interactions may well be dominant factors in these systems, since simple steric and dipolar effects are not sufficient to account for the observed differences[324]. ^{1}H- and ^{13}C-NMR studies showed that the *axial* S=O conformers indeed dominate the conformational equilibria of 1,2- and 1,4-dithiolane oxides, whereas the *equatorial* is more stable than the axial by 0.64 kcal mol^{-1} ($\Delta G°$ at -80 °C) in 1,3-dithiolane oxides. Since a solvent effect was not observed, it appears that dipole/dipole interactions do not control this equilibrium[326]. The marked sensitivity of carbon-13 NMR shifts to the orientation of the sulfonyl oxygen in six-membered ring sulfoxides (**10**) (the largest effect being about 7.5 ppm shielding at C-3,5 of the axial conformer relative to the equatorial; i.e. **10b** vs. **10c**) permits facile stereochemical assignments within this series[326]. This upfield shift can be interpreted in terms of the 'gauche γ' steric shift[327]. The difference in the 'β' effect (shielding of C-2,6) must have a different origin. A difference in the shifts of the axial and equatorial oxygens was found in the ^{17}O-NMR spectra of 4-heterosubstituted thiolane dioxides[290]. However, incomplete knowledge regarding various effects on sulfonyl oxygen shifts weakens the stereochemical assignments of the sulfone oxygens. Nevertheless, the *cis*- and *trans*-isomers of methyl-substituted thiane oxides are readily identified by ^{13}C and ^{18}O NMR, the latter approach being particularly useful[327]. Thus, the ^{17}O signals of *axial* SO groups are found several ppm *upfield* of the equatorial counterparts. The fact that the axial/equatorial ratio of thiane oxides is solvent-dependent is relevant to the stereochemistry of α-methylation or chlorination of cyclic sulfoxides, which depend on the orientation of the sulfoxide oxygen (see Section VI.C below).

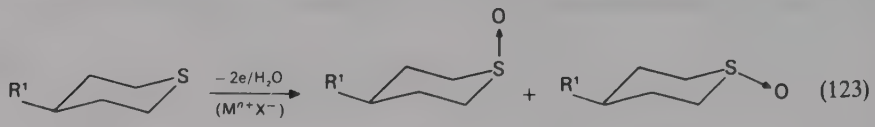


(b) (10) (c)

B. The Synthesis of Six-Membered Ring Sulfoxides and Sulfones

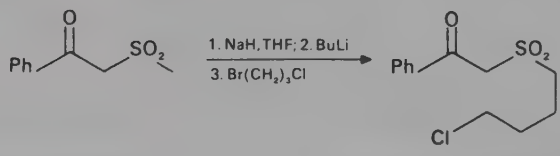
The oxidation of thianes to the corresponding sulfoxides and sulfones is a matter of routine.

Electrochemical oxidation of 4-aryl-substituted thiane in aqueous organic solvents containing various halide salts as electrolytes gave selectively the *trans*-sulfoxide (**10e**). Under acidic conditions a preferential formation of the *cis*-sulfoxide was attained[328]. The stereoselective potential of this method for the oxidation of cyclic sulfides[139,329] is apparent (equation 123).

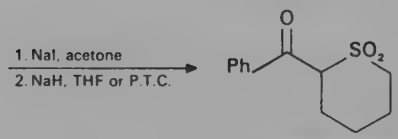


(123)

The 1,3-dianions formed across the sulfone[330] of β-ketosulfones may be selectively dialkylated[331] with an α,ω-dihalide and thus cyclize to give 2-ketothiane dioxides[332]. Due to its polarity, the 2-keto-substituent (or other polar group in the 2-position) adopts the axial orientation[332] (equation 124).

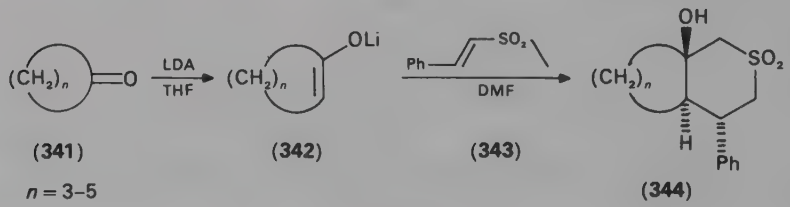


(124)



The application of vinyl sulfones as synthones has been restricted since conversion of the sulfonyl group to another functional moiety is generally difficult.

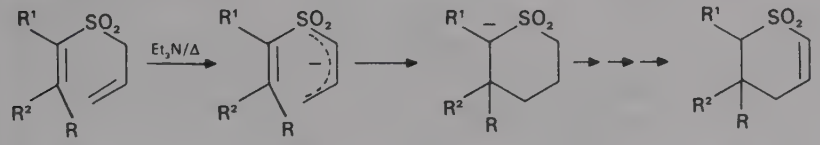
A useful method of utilizing vinyl sulfones (specifically methyl styryl sulfones) for the preparation of thiane dioxides in good yields is illustrated in equation 125[333].



(125)

It appears that the ketone enolates add to the vinyl sulfone, followed by a condensation that leads to the thiane sulfone. The latter may be desulfonylated to provide olefins[333,334].

Similarly, enamino vinyl sulfones (**345**) can undergo a thermally allowed electrocyclic reaction between the termini of the enaminic double bond and the allyl sulfonyl portion in the intermediate anion (**346**) to afford α,β-unsaturated thiene dioxides (**348**) as shown in equation 126[335].

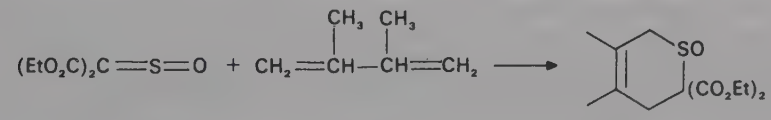


(126)

(345) (346) (347) (348)

R = Morpholine

β,γ-Unsaturated sulfoxides (e.g. 3-thiene oxides) can be prepared by trapping of the *in situ*-generated **349** with dienes in a Diels–Alder-type reaction (equation 127)[336].



(127)

(349) (350) (351)

The trapping of both sulfines and sulfenes with dienes is probably the method of choice for the preparation of 3-thiene oxides and dioxides, respectively[143,337].

C. Selected Chemical Transformations

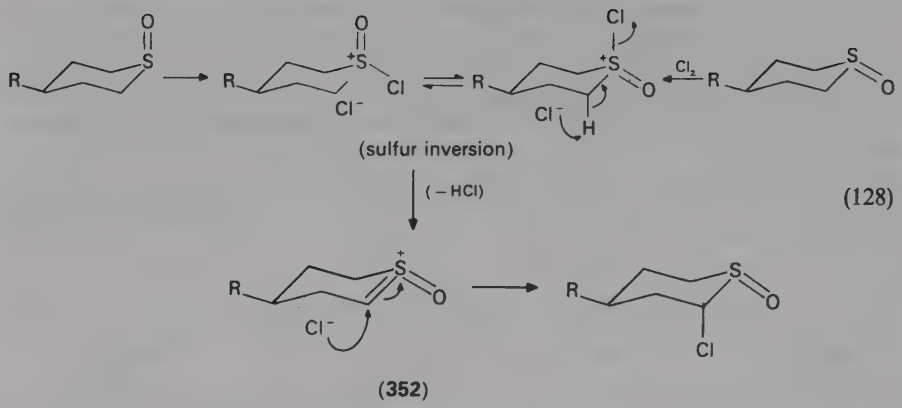
1. α-Halogenation of thiane oxides

Whereas α-chlorination of sulfones usually constitutes a problem, thiane oxides are easily chlorinated at the α-position by a wide spectrum of chlorinating agents[338]. The mechanism is similar to that with carbonyl groups[339].

Several studies[338,340–342] show that the chlorination does not proceed, as assumed previously[343], by proton abstraction followed by reaction of the carbanion thus formed, with electrophilic chlorine. A mechanism involving a chlorooxosulfonium ion formed by attack of a positive chlorine species on sulfur was shown to be more likely[344].

The chlorination gave α-chlorosulfoxides with the chloride atom in the *axial* and the oxygen atom in the *equatorial* position, independent of the configuration at the sulfur of the starting material[338,340,341]. Furthermore, thietane oxides containing small substituents undergo ring inversion to place the oxygen in the equatorial position before being halogenated axially[338,340]. The mechanism shown in equation 128 takes into account all the experimental results. The steric course is rationalized on the basis of *trans*-axial elimination of hydrogen chloride, followed by an *axial* addition of chloride ion to the α-carbon. The 'inverted ylide' **352** must have a nonplanar structure around sulfur[338].

The comparison of the results of α-halogenation with those of α-methylation of six-membered ring sulfoxides[345] reveals that similar factors are operative and determine the stereochemical outcomes in both cases.

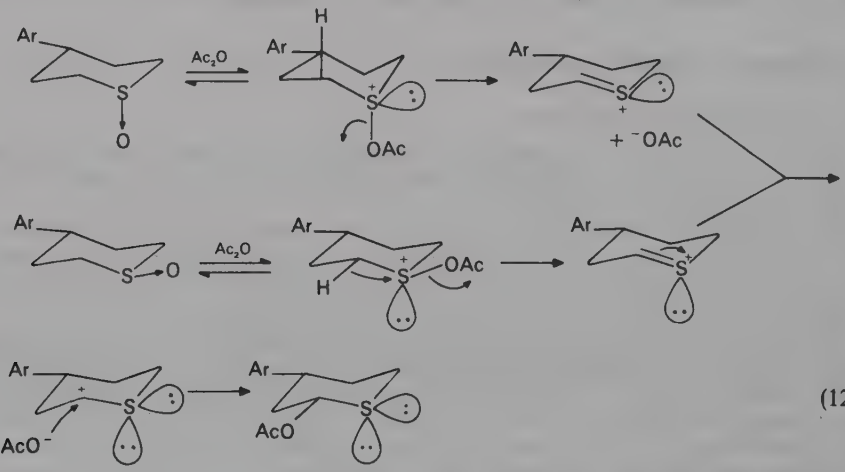


(128)

(352)

2. Pummerer rearrangement

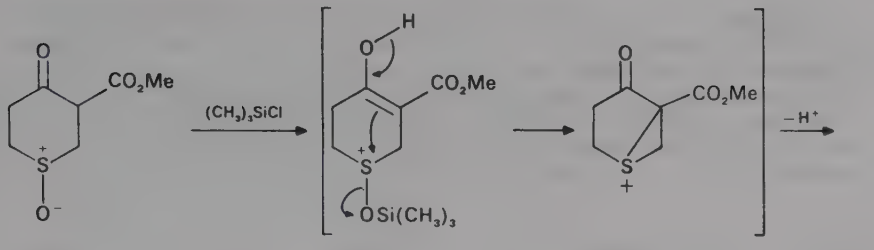
The Pummerer reaction[346] of conformationally rigid 4-aryl-substituted thiane oxides with acetic anhydride was either stereoselective or stereospecific, and the rearrangement is mainly intermolecular, while the rate-determining step appears to be the E2 1,2-elimination of acetic acid from the acetoxysulfonium intermediates formed in the initial acetylation of the sulfoxide. The thermodynamically controlled product is the axial acetoxy isomer, while the kinetically controlled product is the equatorial isomer that is preferentially formed due to the facile access of the acetate to the equatorial position[347]. The overall mechanism is illustrated in equation 129.



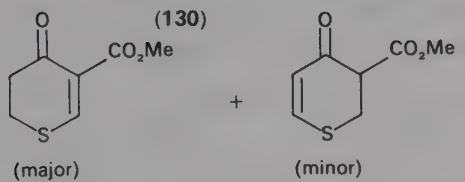
(129)

Chlorotrimethylsilane-induced Pummerer rearrangements effect the transformation of 4-ketothiane oxides into the corresponding α,β-unsaturated thianes[348], apparently via the formation and subsequent deprotonation of thiiranium intermediates rather than by the conventional sulfocarbonium mechanism depicted in equation 129.

The reaction appears to be facilitated by a γ-carbonyl group. In the absence of this activation, sulfoxide deoxygenation[349] appears to be the favored reaction pathway[348] (equation 130).



(353) (354) (355) (130)

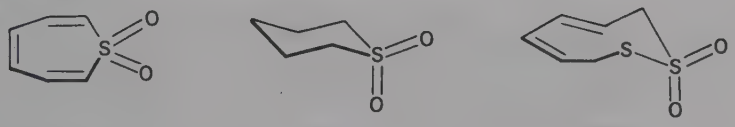


(356) (357)

VII. MEDIUM-SIZE RING SULFOXIDES AND SULFONES

In principle, the properties and chemical behavior of cyclic sulfoxides and sulfones having a ring size of seven and up are expected to be quite similar to those of the analogous acyclic systems.

This is actually observed, except when either potentially aromatic molecules such as thiepin dioxide (**358**) or when (relatively) sterically/conformationally rigid systems are involved.

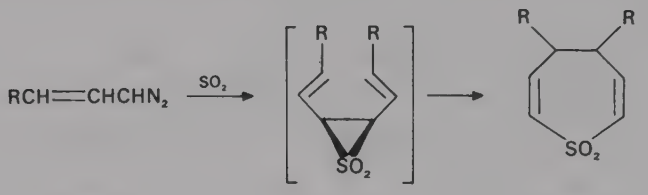


(**358**) (**10b**) (**359**)

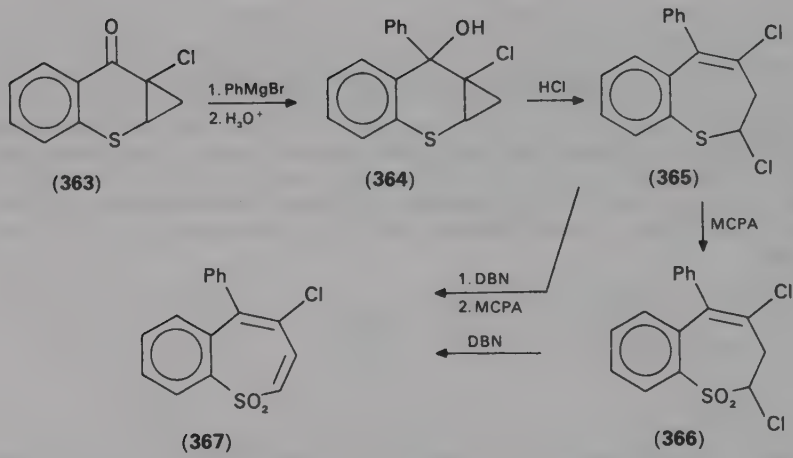
Thus, the crystal structure of the eight-membered ring dithiocin dioxide **359** indicates that the eight-membered ring is a pseudo-chair in which the 'pseudo-axial' sulfur–oxygen bond of the sulfone group is significantly shorter (1.352 Å vs. 1.475 Å) than the 'pseudo-equatorial' one[350]. *Ab initio* STO-3G* molecular orbital calculations for both this molecule and the six-membered thiane dioxide (**10b**) (for the sake of comparison) have been conducted[25]. Limited geometry optimization of the axial and equatorial S—O bonds in the chair conformations of the six- and eight-membered rings **10b** and **329** leads to bond lengths of 1.46 Å in *both* molecules, with the difference between the two S—O bonds in each molecule being less than 0.01 Å, in spite of the difference in ring size, and even when a sulfur atom has been incorporated adjacent to the sulfone group in the eight-membered ring. Consequently, axial and equatorial S—O bond lengths in these systems are predicted not to differ significantly in the gas phase[350]. Indeed, X-ray crystal structure determination of the seven-membered ring 1, 3-dithiazine tetroxide system indicates that all the S—O bonds of the two sulfone groups in the molecule are essentially identical[351]. If a difference does exist in the solid state, it must be associated with crystal packing forces, which lead to deformation of sulfur moieties as suggested by relevant molecular calculations[352].

The common route for the synthesis of medium-size ring sulfoxides and sulfones is oxidation of the corresponding cyclic sulfides[70], which are obtained from the interaction of α,ω-dihaloalkanes with sulfide ion in fair to good yields[243] (equation 110).

Other less general routes to the medium-size ring sulfoxide and sulfone systems do exist, but each one is specific to a particular ring size and to the specifically desired structural features of the target molecule. Equations 131 and 132 are two examples[353,354] of such syntheses.



(360) (361) (362) (131)



(363) (364) (365) (132)

(367) (366)

VIII. ACKNOWLEDGEMENTS

The hospitality of the Department of Chemistry and Professor James P. Kutney at the University of British Columbia, Vancouver, Canada, during the time of writing this chapter is highly appreciated. I am indebted to the secretarial staff of the Department, Ms. Carolyn Delheij-Joyce in particular, for their extensive and patient input in the typing and production, and to Professor Manfred Reinecke for his help and useful suggestions.

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CHAPTER 6

Appendix to 'Cyclic sulfones and sulfoxides'†

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*I. PREFACE

This is an updated account of the developments in the area of the synthesis and chemistry of cyclic sulfoxides and sulfones since the original chapter 'Cyclic sulfones and sulfoxides' was written. As such, it is an attempt to present a balanced treatment, not encyclopedic coverage of the subject, concentrating on the most important relevant developments in the 1987–1992 period. Following the 'guiding philosophy' of the original chapter, the emphasis is on small-ring sulfoxides and sulfones since they clearly represent a distinct category within the chemistry of these functional groups: the geometrical constraints of the small-ring systems have their consequences as far as bonding, strain, thermodynamics and stereochemistry are concerned and these, in turn, determine the resulting chemical properties and reactivity observed in relation to the incorporated sulfoxide and sulfone functional groups. In approaching the six-membered, and the medium-sized rings, the role and contribution of these functional groups is similar, in most respects, to those of acyclic systems.

The updating which is summarized in this supplement to the original chapter is based, mainly, on primary resources (i.e. *Journal of the American Chemical Society, Journal of Organic Chemistry, Tetrahedron, Tetrahedron Letters* and others) as well as on research results presented and later published[355a–c] at the recent three International Symposia on the Organic Chemistry of Sulfur (ISOCS). A recent relevant review-type chapter, covering the 1991 literautre on the extrusion of SO_2 from heterocyclic compounds, is also available[356].

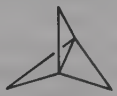
*II. INTRODUCTION: SCOPE AND LIMITATIONS

As was stated in the original chapter, all saturated and unsaturated three- and larger-membered ring sulfones and sulfoxides (i.e. thiiranes/thiirenes, thietanes/thietes, etc., **3**–**14**)

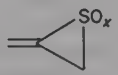
were prepared quite some time ago and their chemistry, in general terms, is well established. However, in view of the great distortion from the optimal (normal) bond lengths and, particularly, angles in the small-ring members of this series, (a) the predictions, based on theoretical calculations, of their experimental accessibility; (b) the actual synthesis of particularly strained (but, relatively, thermodynamically stable) and/or uniquely substituted molecules of this class of compounds; (c) the use of specially designed systems within these series, e.g. as synthons in organic synthesis; and (d) the in-depth understanding of their special nature and characteristics and their observed chemistry, have still remained as intriguing challenges and, therefore, 'organizers' and 'directives' of future research in this area.

Indeed, significant developments, particularly concerning (a), (c) and (d) above, have typified the last five years of research in the field. Thus, for example, the high-level *ab initio* calculations optimized at the MP2/6-31G* and MP2/6-311G(MC)*[357] levels of the structure, spectra and thermochemical properties have been carried out, together with a parallel set of calculations for [1.1.1] propellane **368**, cyclopropane and thiirane [359], and predicted the trithia [1.1.1] propellane **367** [358] to be experimentally accessible.

(367)



(368)



(369)

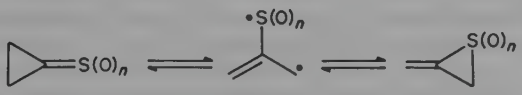
$x = 1$ or 2

The excellent agreement between theory and experiment for the latter molecules and later calculations on the oxide and dioxide analogues (i.e. **15c**[360]) lend confidence to the theoretically based predictions for both **367** and **15c** as well as for closely related, strained systems[361] (e.g. **369**). Yet, although the scope as far as the calculations are concerned appears to be (almost) unlimited, the real challenge appears to remain within the experimental domain [i.e. (b)], that is, to try to overcome the technical and physical limitations and constraints and actually prepare the targeted sulfoxide and sulfone molecules under optimal conditions which will enable their characterization and experimental study. Experimental verification of theoretical predictions, like in the cases mentioned above, lead to higher achievements both in the theoretical fundamentals and in the experimental molecular architecture.

* III. THREE-MEMBERED RING SULFOXIDES AND SULFONES

* B. Structure and Physical Properties

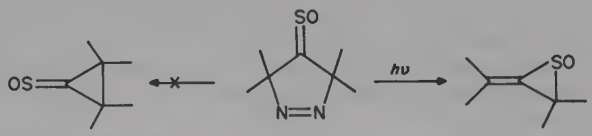
Because cyclopropanethione (**370a**) is unstable relative to its valence isomer methylene thiirane, all attempts to date to prepare the former, or its simple derivatives, have led instead to the latter [362]. In parallel to the pursuit of the elusive cyclopropanethione, the relative thermodynamic stabilities of the valence tautomeric pairs cyclopropanethione *S*-oxide (**370b**)/methylenethiirane *S*-oxide (**371b**) and cyclopropanethione *S,S*-dioxide (**370c**)/methylene-thiirane *S,S*-dioxide (**371c**) are questions of particular importance and practical consequences (equation 133).



(133)

(370) **a,b,c** $n = 0,1,2$ **(371)**

While the irradiation of peralkylated 1-pyrazoline-4-thione *S*-oxide (**372**) afforded the corresponding allene episulfoxides (**374**) rather than the 'expected' cyclopropanethione *S*-oxides (**373**)[363] (equation 134), it remained unclear whether this result is relevant to the question of the relative stabilities of the pairs **370a–c**/**371a–c**.



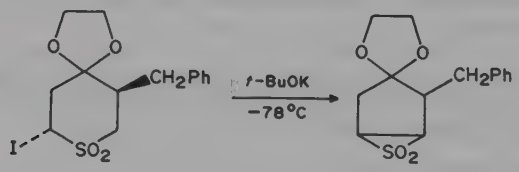
(373) (372) (374) (134)

Thus, the geometries of **370a–c**, and **371a–c**, respectively, were optimized at the SCF level by using *ab initio* molecular orbital theory with a polarized double-zeta basis set[361]. It was found that indeed **371a** is more stable than **370a** by 6.4 kcal mol^{-1} whereas in the sulfoxide–sulfone pairs the *S*-oxide **370b** is significantly more stable than its sulfoxide isomer **371b** by 8.2 kcal mol^{-1} and the reverse is true for the sulfone series in which the methylenethiirane *S*,*S*-dioxide **371c** is more stable, although by 0.2 kcal mol^{-1} only, compared with its cyclopropanethione *S*,*S*-dioxide counterpart **370c**. The intermediacies of both **370b,c** were demonstrated *experimentally* whereas **371b,c** were not observed[361].

*C. The Sulfone and Sulfoxide Functionality in Three-membered Ring Systems: Activating and Directive Effects

*1. Thermal elimination of SO_2 and SO

It is widely accepted that thiirane dioxides are intermediates during the Ramberg–Bäcklund reaction in which α-halo sulfones are treated with strong bases. Supporting evidence for the involvement of thiirane dioxides in this type of reaction was provided and discussed in the original chapter[364]. Further strengthening of this involvement is the recent actual isolation of the thiirane dioxide intermediate (**376**)[365] on the treatment of compound **375** with 1.5 equivalents of *t*-BuOk at −78 °C as depicted in equation 135.



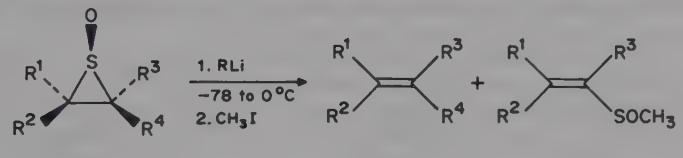
(375) (376) (135)

The sulfone **376**, which is stable for a period of months at 20 °C, loses SO_2 by heating to 100 °C to afford the corresponding alkene. Similarly, the treatment of primary sulfonyl chlorides, RCH_2SO_2Cl with Et_3N at −40 °C, gives the corresponding isolable thiirane dioxides. The latter slowly lose SO_2 to afford $CH_2{=}CHR$ on warming to room temperature[366]. The latter results are in full accord with those of previous studies in which the intermediacy of three-membered rings containing the SO_2 group was unequivocally established in the reaction of α,α- or α,α′-dihalo sulfones or sulfonamides with Et_3N in aprotic solvents under mild conditions[8]. Yet, whether the mechanism of the SO_2 extrusion is ionic, radical or else is still an open question[364].

** 3. Electrophilicity of the SO_2 and SO groups (reaction with bases/nucleophiles)*

Both the strong inductive effect of the electronegative sulfone and sulfoxide groups (that of the former stronger than that of the latter) and the capacity for the partially positively charged sulfur atom of these groups to stabilize a developing negative charge on the adjacent (α-)carbon (via the expansion of the sulfur valence shell involving p–d orbital interaction) should lead to reactions initiated by the easy abstraction of the sulfonyl and sulfoxy α-hydrogens. Strong bases, however (hydroxide and alkoxide ions as well as carbanions), were shown to attack, nucleophilically, either the α-carbon [111] or the sulfur atom of the sulfone group [99,113], whereas with strong bases, but weak nucleophiles (e.g. BuLi), the expected α-carbanion did form (equation 12). The rationale for these results has been already provided and discussed (e.g. equations 12–15) [364].

In a recent study [367] in which aryl-substituted thiirane oxides (**16**) were reacted with BuLi, PhLi, lithium di-isopropylamide (2.2 molar equivalents) and lithium dimethyl cuprate, two reaction paths could be observed: (a) attack at sulfur leading to olefins with complete retention of configuration at the carbon skeleton; and (b) initial abstraction of α-sulfoxy hydrogen at carbon, leading to a vinyl sulfenate **378** as depicted in equation 136.



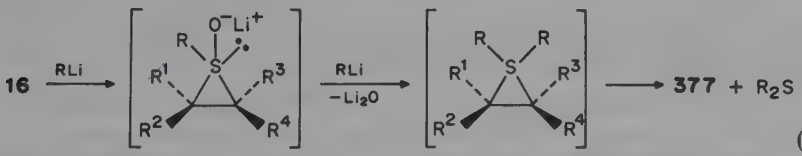
(136)

(16) **(377)** **(378)**

(**a**) R = *n*-Bu
(**b**) R = Ph
(**c**) R = N(*i*-Pr)$_2$
(**d**$_{1,2}$) R = $(CH_3)_2Cu$

(**a**) $R^1 = H$; $R^2 = R^3 = Ph$; $R^4 = H$
(**b**) $R^1 = R^3 = Ph$; $R^2 = R^4 = H$
(**c**) $R^1 = Ph$; $R^2 = R^3 = R^4 = H$
(**d**) $R^1 = Ph$; $R^2 = H$ or D; $R^3 = R^4 = H$
(**e**) $R^1 = R^2 = Ph$; $R^3 = R^4 = H$

Significantly, initial direct attack at carbon itself (rather than attack at *sulfur* or *α-hydrogen* abstraction) was observed only in the reaction of the phenylthiirane oxide **16c** with the more nucleophilic lithium dimethylcuprate, leading to a saturated sulfenate anion trapped as alkyl methyl sulfoxide together with the olefin **377c** and vinyl sulfoxides **378c,d**. Thus, in the attack of the lithium base at the sulfur atom in thiirane oxides **16**, the stereochemistry at the carbon skeleton of the resulting olefins **377** is completely retained; the sulfurane mechanism [364] for the final retrocheletropic concerted desulfurization seems to account satisfactorily for the observed stereochemistry [114] (equation 137).



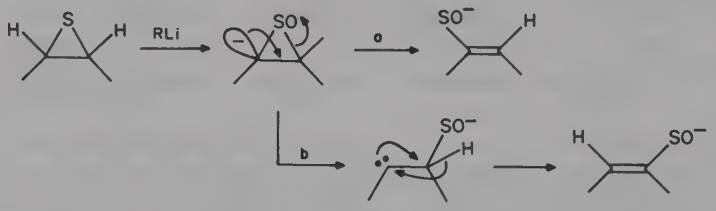
(137)

On the other hand, the formation of vinyl sulfoxides (**378**) should occur by hydrogen abstraction followed by ring opening to vinyl sulfenates, which are subsequently methylated to provide **378**. Similar results were obtained in the reaction of other cyclic sulfur compounds promoted by LDA [368].

Based on studies with deuteriated thiirane oxides **16** in which a decrease in the reactivity at the deuteriated positions was evident, combined with the irreversibility found for the

removal of the α-sulfoxy proton, it was concluded[367] that the deprotonation leading to the corresponding α-carbanion must occur in a rate-determining step which, most probably, precedes the ring-opening process. Although a carbanionic intermediate could not be put in evidence either by H/D exchange or by trapping with alkylating agents[368], the low activation energy found in an *ab initio* theoretical study of base-induced ring opening of the parent thiirane oxide as a model system[369] suggests the primary irreversible formation of a carbanionic species which rapidly rearranges to vinyl sulfenates.

In accord with the above, one concludes that the β-elimination mechanism (route a in equation 138) rather than the α-elimination followed by concerted carbenoid insertion into an adjacent C—H bond (route b) is the only one operating. Consequently, the methylsulfinyl group replaces the hydrogen or deuterium (in **16, 2-H** or **2-D**) removed by the base. The exclusiveness of the β-elimination mechanism is further corroborated by the fact that episulfoxide **16f** ($R^1 = R^2 = p$-Tol; R^3 = Ph; R^4 = H) in which only one hydrogen (R^4) is available for abstraction gave the vinyl sulfoxide **378g** ($R^1 = R^2 = p$-Tol; R^3 = Ph) exclusively. All the other stereochemical results can be explained by the stepwise mechanism proposed in which the removal of a proton by a base is followed by ring opening of the carbanion formed via a β-elimination route[367]. Apparently, the chelation of lithium with both the oxygen and the carbanionic center (i.e. **52**) is the main factor governing the stereochemistry in these base-induced transformations[114].



(138)

The detailed experimental results suggest that electronic activation at benzylic hydrogens (i.e. stabilization of a conjugated carbanion) plays a minor role compared to that of the combined electronic and chelating effect of the sulfinyl oxygen on both *syn*-hydrogens. As one would expect, the hydrogen atom *anti* to the phenyl group in **16** is the one which is preferentially abstracted by the base[367].

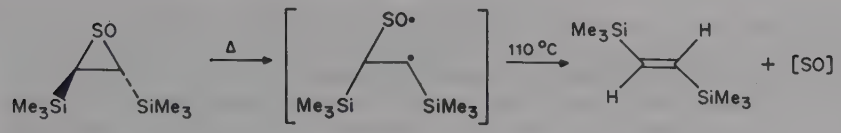
*E. Selected Chemical Reactions and Transformations

*4. Thermolysis of thiirane and thiirene oxides

Thermolysis of the parent thiirane oxide was shown to generate triplet sulfur monoxide[95] as well as the ring enlargement product 1,2-oxathietane **157** as an intermediate, if conducted in the temperature range of 1043–1404 K via the flash vacuum thermolysis techniques[167]. Ring expansion was also advocated in the thermolysis of the 2,3-diphenylthiirene oxide (**18a**)[22].

The *trans*-2,3-bis(trimethylsilyl) thiirane *S*-oxide **379** (obtained via oxidation of the corresponding thiirane by MCPBA) was recovered unchanged after heating at 80 °C for several hours. However, upon heating to 110 °C this oxide did decompose to afford the *trans*-1,2-bistrimethylsilyl ethene **381** and sulfur monoxide, apparently via a diradical intermediate (equation 139).

All other α-silyl groups *syn* to the sulfoxide oxygen in thiirane oxides undergo the Sila–Pummerer rearrangement even at low temperatures[371]. It might well be that the ring strain associated with the Pummerer intermediate may be responsible for the relative thermal stability of the bulky **379**. At higher temperatures, homolytic cleavage of the



(379) (380) (381) (139)

carbon–sulfur bond occurs (leading to the diradical **380**), similar to that observed in other thiirane oxides[370].

It is interesting to mention that the 2-trimethylsilylthiirane *S*-oxide—obtained via the oxidation of the corresponding thiirane with MCPBA—also undergoes ring-opening during the process of its formation. However, in this case it is an acid-catalyzed ring-opening which leads to other products. On heating, the expected sulfur monoxide extrusion takes place[372].

*IV. FOUR-MEMBERED RING SULFOXIDES AND SULFONES

*A. Introduction

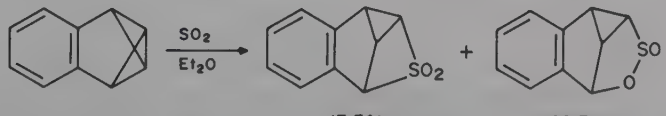
Although less strain energy is inherent in the four-membered ring sulfoxides and sulfones than in that of their three-membered ring counterparts, it appears to be still sufficient to facilitate their thermally or photolytically induced ring-opening leading to chemical transformations. In view of the well-established chemistry, unique structural features and physical properties and the synthetic methods of preparing the various members of this class of compounds (i.e. **5**,**6**,**7** and **184**)[373], it is not surprising that recent developments in the area of four-membered ring sulfoxides and sulfones are associated with either the use of thermolysis and photolysis for the generation of uniquely reactive intermediates, or the preparation of special structures within which the four-membered ring sulfoxides and sulfones are incorporated (*vide infra*).

*D. The Synthesis of Four-membered Ring Sulfoxides and Sulfones

*1. Thietane oxides

The spontaneous addition of sulfur dioxide to strained hydrocarbons including bridged bicyclo [1.1.0] butane derivatives[374] and quadricyclanes[375] to provide cyclic sulfones and sulfines has been investigated in several laboratories. The rationale behind this direction of research was taking advantage of the strong 'electrophilic-type' chemical reactivity of the SO_2 on the one hand, and of the relatively high-strain energy-derived 'extra' reactivity of the strained hydrocarbons on the other hand, to obtain particularly interesting cyclic heterocycles.

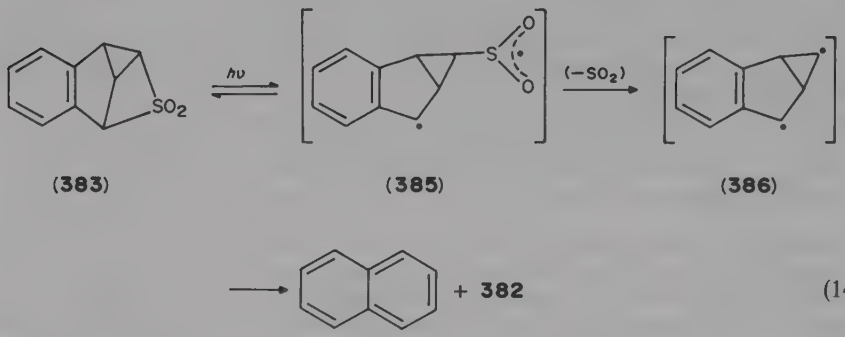
In accord with the above line of thought, benzobenzvalene (naphthvalene) **382** reacted smoothly with sulfur dioxide to give the crystalline adducts **383** and **384** in which the latter predominated[376] (equation 140).



13.5% 40.5% (140)

(382) (383) (384)

Both the four-membered sulfone **383** and the α-sulfine **384** are formally 2+2 cycloadducts, the former resulting from a cheletropic-type addition of the SO_2. The fact that the sulfur heteroatom is bound to a benzylic position. Combined with the inherent strain in the sulfone **383** is likely to confer a high photochemical reactivity on this compound. Indeed, photolysis of a deoxygenated solution of **383** at 254 nm provided both naphthalene and benzobenzvalene (**382**) via initial homolytic ring-opening (as expected) to provide the sulfinyloxy biradical **385**, which loses SO_2 to provide the C-centered benzoprefulvene biradical **386** [377] from which the final products are obtained by ring-opening or ring-closure [376] (equation 141).



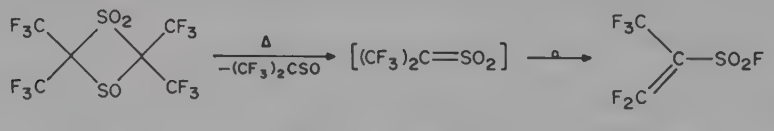
(141)

Not surprisingly, the sulfone **383** and the sultine **384** interconvert photochemically[378]. On thermolysis under flash vacuum pyrolysis (FVP) conditions, **383** gives naphthalene (major product), α-sultine **384**, the isomeric 1- and 3-indenecarboxaldehydes and a trace of indene[376]. The initial step here is the thermally-induced *ring-opening* of the highly strained heterocyclic four-membered ring system in **383**.

*E. Selected Chemical Reactions and Transformations

The synthesis of perhalogenated dithietanes and their oxidation products (e.g. **214**–**219**) has been well known for about a decade[247,275]. Recent developments in this area are associated with the successful attempt of their use as a source for stabilized perhalogenated sulfenes. Since sulfenes $R_2C=SO_2$ have so far not been isolated but only demonstrated to exist as transient trappable intermediates mainly in cycloaddition reactions[379], the targeting at stable sulfene species is of particular theoretical and practical importance.

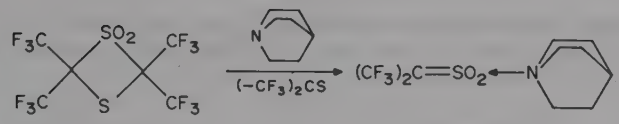
Thus, in parallel to the symmetrical cleavage of 1,3-dithietane *S*-oxides[380], the thermolysis of tetrakis (trifluoromethyl)-1,3-dithietane 1,1,3-trioxide **388** provided an indication of the existence of the perhalogenated sulfene **389** [381] (equation 142).



(142)

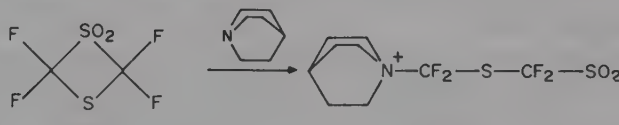
388 **389** **390**

When the analogous tetrakis (trifluoromethyl)-1,3-dithietane 1,1-dioxide **391** is treated with quinuclidine, the stable perhalogenated sulfene **392** precipitates as colorless crystals in 74% yield[382] (equation 143).



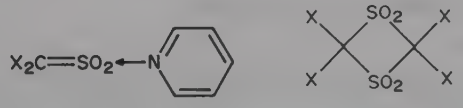
(391) (392) (143)

The analogous reaction (equation 144) with the tetrafluoro-1,3-dithietane 1,1-dioxide **217b** proceeds completely differently to give the sulfinate **393** due to the nucleophilic attack of the amine at the carbon atom rather than at the sulfur atom, as in the case with **391**[382]. Apparently, both steric and electronic effects are responsible for this difference: the 2-carbon in **217b** is less hindered than the 2-carbon in **391** and therefore should be more prone to nucleophilic attack of the amine; on the other hand, the sulfur atom of the sulfone group in **391** is apparently more electrophilic than the sulfur atom of this group in **217b**. The combined effects determine the preferred route of this reaction in each of the cases. As expected, the C—SO_2 bond was ruptured in **217b** and not the electron-richer C—S bond.



(217b) (393) (144)

Both **392** and the analogous stabilized pyridine-sulfene adduct (**394**) can be obtained by direct symmetrical splitting of the tetrakis (trifluoromethyl)-1,3-dithietane *S*-oxides **391** and **395a**[383].

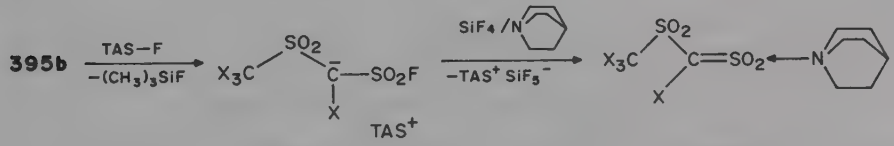


(394) (395)

(a) X=CF_3

(b) X=Cl or Br

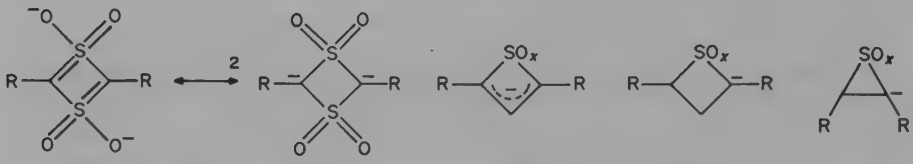
The perhalogenated thietane *S,S*-tetroxides **395b** are singly cleaved by tris(dimethylamino)sulfonium-trimethylsilyl difluoride (TAS-F) to form intermediate salts from which an abstraction of a fluoride ion provides the perhalogenated mesylsulfenes stabilized by S-coordinated quinuclidine (i.e. **397**)[384] (equation 145).



(396) (397) (145)

In view of the already prepared dianion of thietane *S,S*-tetroxides (i.e. **398**)[385], a recent gas-phase study of the anionic species derived from both three- and four-membered sulfoxides and sulfones (i.e. **399–401**) is of particular interest[386]. This should shed light not only on the relative stability/reactivity of the carbanions, but should provide insight into

the structure–reactivity relationships in these strained, small-ring sulfoxide and sulfone systems, including the particular role played by strain, electronic and stereochemical factors.



(398) (399) (400) (401)

$x = 1$ or 2

*V. FIVE-MEMBERED RING SULFOXIDES AND SULFONES

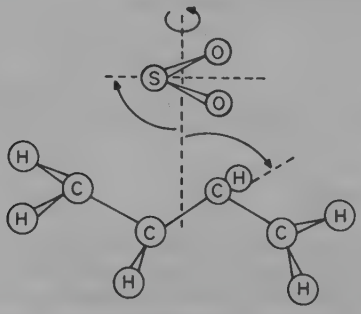
*A. Introduction and Scope

The synthesis, properties and chemistry of five-membered ring sulfoxides and sulfones are documented in many recent publications. Yet, as was the case when the original chapter was written, most papers deal with the chemistry of specially desisned and/or substituted thiophene dioxides and closely related systems. The recent developments in five-membered ring sulfoxides and sulfones will be reviewed in Section V. E. following the summary of developments concerning the chemistry of other members of this class of cyclic sulfoxides and sulfones.

*B. Physical Studies (NMR, IR, p*K* and others)

1. Microwave spectrum

The microwave spectrum of the butadiene–SO_2 complex has been observed and the rotational constants determined as $A = 2793.8856$ MHz, $B = 1325.4117$ MHz and $C = 1123.0275$ MHz. The structure of the complex was determined from the moments of inertia of the normal and of isotopic species. The centers of mass of the two components are separated by 3.32(5) Å with SO_2 located above the center of the butadiene plane. The two molecular planes are close to parallel with the C_2 axis of the SO_2 rotated 44°(5) relative to the C—C signle bond of the butadiene. The dipole moment was found to be $\mu_{total} = 1.475(15)D$[387]. The above determinations are important, since they provide infor-



(402)

mation on the intermolecular interactions which play a decisive role in chemical processes. Considering the microscopic reversibility principle, the study of complexes like that of the butadiene–sulfur dioxide (**402**), together with future refinements of the corresponding calculations, may pave the way not only for an understanding of the intermolecular interactions between reacting species and departing fragments (as well as the intramolecular interactions in the intermediate 'active complex'), but also for *a priori* predictions of the resulting products in both cyclo- and retrocyclo-addition reactions of cyclic sulfones, sulfoxides and others[388].

2. Hydrogen bonding

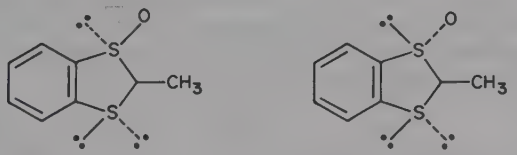
The capability for hydrogen bonding of sulfoxides and sulfones with various alcohols and phenols has been investigated by many workers and critically reviewed recently[389].

In order to test the relationship between the strength of the hydrogen bond and the OH frequency shift, phenol (in CCl_4) has been selected as a standard compound and the differences in the stretching frequency of the IR phenolic–OH bond ($\Delta\sigma_{OH}$ values) in and without the presence of the oxygen-bearing compound (base) were measured[390]. Accordingly, the corresponding capability of hydrogen bond formation, the equilibrium constants (K) and the relevant thermodynamic parameters (for the hydrogen bond) were calculated. The $-\Delta H^\circ$ values for the five-membered sulfoxides and sulfones were found to be 7.0 and 4.9 ± 0.3 kcal mol^{-1} respectively, suggesting, as expected, that the sulfones have lower capability for hydrogen bonding than the corresponding sulfoxides[390]. That the sulfone does not obey the proposed semiempirical relationship ($-\Delta H = 0.016\Delta\sigma_{OH} + 0.63$) can be accounted for by the formation of the hydrogen bond simultaneously with both its oxygen atoms.

3. Absolute configuration

The importance of chirality in determining the mode, course and stereochemical consequence of chemical and enzymatic reactions is well recognized. This applies to sulfoxidations which are very common biotransformation processes, so that their stereoselectivity is of particular interest.

In using a combination of chromatographic (CSPHPLC), spectral (^{1}H-NMR), chiroptical (circular dichroism), X-ray crystallographic, and stereochemical correlation methods, the absolute configurations of *cis*- and *trans*-2-alkyl-1,3-benzodithiole 1-oxides (e.g. **403 a,b**) have recently been established[391].

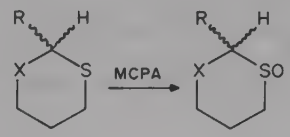


(a)(+)-*cis*-1*R*,2*S* **(403)** (b)(−)-*trans*-1*S*,2*S*

In starting with the 2-methyl-1,3-benzodithiole and using the above as reference compounds, it was shown that the *trans* isomers were in all cases preferentially formed (64–86%) using chemical oxidants whereas the fungal and bacterial oxidations showed a marked selectivity (87–96%) for the *cis* isomers[392].

In another study, 1,3-oxathianes and 1,3-dithianes were oxidized to the corresponding sulfoxides (equation 146)[393]. Resolution by chromatography followed by CD spectra

recording makes possible the assignment of the absolute configurations to the corresponding sulfoxide products (i.e. **405**) based on the known absolute configurations of the analogous 1,3-oxathiolanes.



(146)

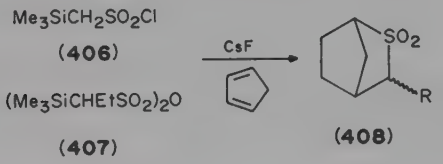
(404) **(405)**

(a,b) X = O or S; R = H or *p*-BrC_6H_4 — **(a,b)** X = O or S (*cis* or *trans*); **(c)** X = Y = SO (*trans*)

Thus, for example, oxidation of the (+)-enantiomer **404a** (R = H) gave α(+) and (−) sulfoxide **405a** in the ratio 1:7, and the latter was shown by X-ray crystallography to be the *trans*-(2*R*,3*R*) sulfoxide. CNDO/S-CI calculations, including d-orbitals for **405a** (R = H) and **405c** (R = *p*-BrC_6H_4) predicted one transition at *ca* 195 nm, polarized nearly parallel to the S=O bond, which corresponds to an experimental UV bond with ε in the range of 2000–4000. The signs of the dihedral angles between the S=O bond and the ^{1}La direction (from the corresponding crystal structures and MM calculations) showed agreement with the CD couplets, as expected, provided the coupled oscillator mechanism is operating[393]. Application of the same techniques would facilitate the determination of the absolute configurations of closely related sulfoxide systems.

*C. The Synthesis of Five-membered Ring Sulfoxides and Sulfones

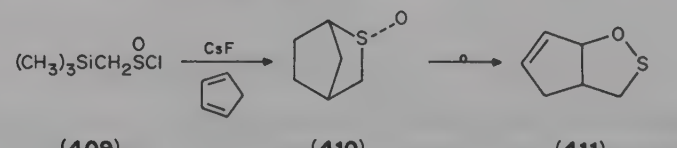
The treatment of starting materials, containing both sulfur and silicon atoms (α-silylated alkanesulfonyl chlorides or sulfonic anhydrides) with an equivalent of cesium fluoride (acting as a desilylation agent) in the presence of cyclopentadienes, led directly to the sulfene/cyclopentadiene Diels–Alder adducts in good yields[370] (equation 147).



(a) R = H; 64% (from **406**)
(b) R = *trans*-Et + **(c)** R = *cis*- Et (major) (minor)
Total: 76% (from **407**)

(147)

Similarly, the treatment of (trimethylsilyl)methanesulfinyl chloride (**409**) with one equivalent of CsF in the presence of cyclopentadiene led to a 9:1 mixture of the *exo*- and *endo*-sulfoxide analogues of **408** (R = H); the latter (i.e. **410**) is unstable and rapidly rearranges to the sultine **411**[394] (equation 148).

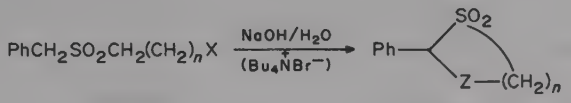


(148)

(409) **(410)** **(411)**

The use of sulfenes and sulfines, generated differently, as dienophiles in cycloadditions to produce heterocycles (mainly six-membered rings) is well-known and constitutes, perhaps, the method of choice for the preparation of 3-thiene oxides and dioxides[143,337].

Benzyl chloroalkyl sulfones and benzyl carboethoxyalkyl sulfones, on treatment with aqueous NaOH solution (50%) under phase-transfer catalytic conditions, provide, among other products, cyclic sulfones (3–7-membered rings) via an intramolecular substitution of the ε-halide by the α-sulfonyl/benzyl carbanion[395] (equation 149). However, the yields of the cyclic sulfones obtained (e.g. **413**) are rather low due to competitive elimination and hydrolysis reactions.



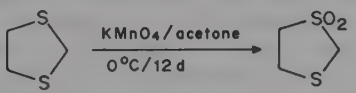
(149)

(412) **(413)**

$X = Cl$ or CO_2Et $Z = CH_2$ or $C{=}O$

$n = 1–3$ $n = 0$ $n = 1–3$ $n = 1–4$

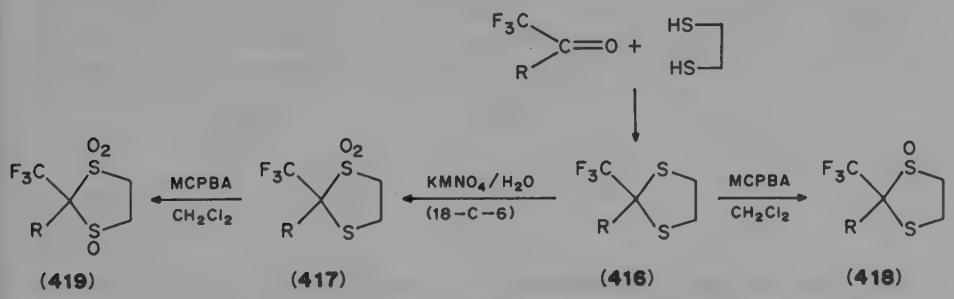
It is surprising that the parent five-membered monosulfone of 1,3-dithiolane (i.e. **415**) was not described in the literature until very recently, when it was prepared[396] from **414** by the method of Gokel[396a] (equation 150). It might well be that this is the oxidation method of choice whenever only one of the two sulfur atoms is to be oxidized to the corresponding sulfoxide and/or sulfone.



(150)

(414) **(415)**

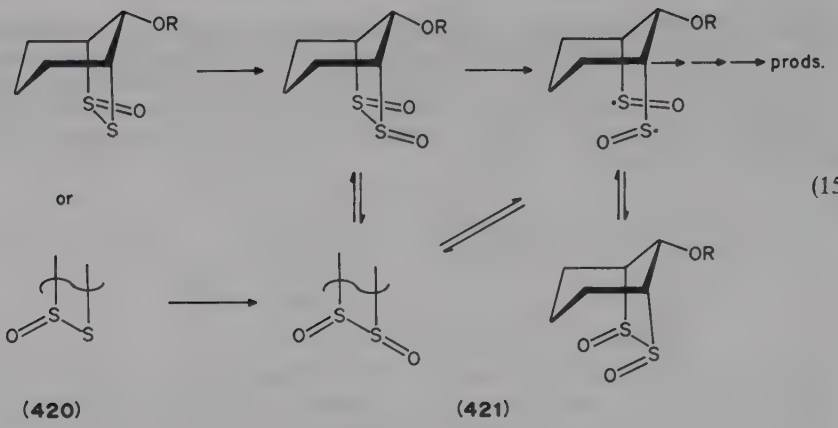
Indeed, in the preparation of a series of trifluoromethyl-substituted 1,3-dithiolane *S*-oxides and dioxides (i.e. **417**–**419**), potassium permanganate in water was used under phase-transfer reaction conditions (18-Crown-6) for the preparation of the mono-*S*-dioxides whereas the 'classic' MCPBA/CH_2Cl_2 oxidation of **416** was used for the preparation of the mono-*S*-oxides or the mixed *S*-oxides and *S*-dioxides from the oxidation products of the first series[397] (equation 151).



(419) **(417)** **(416)** **(418)**

(151)

Clear evidence, based on ^{13}C- and ^{1}H-NMR spectroscopy, for the formation of the elusive, long sought α-disulfoxides was recently reported[398]. Oxidation of the bridged bicyclic thiosulfinates **420** by MCPBA afforded the targeted bridged bicylic α-disulfoxides **421** as intermediates along the reaction coordinate (equation 152).



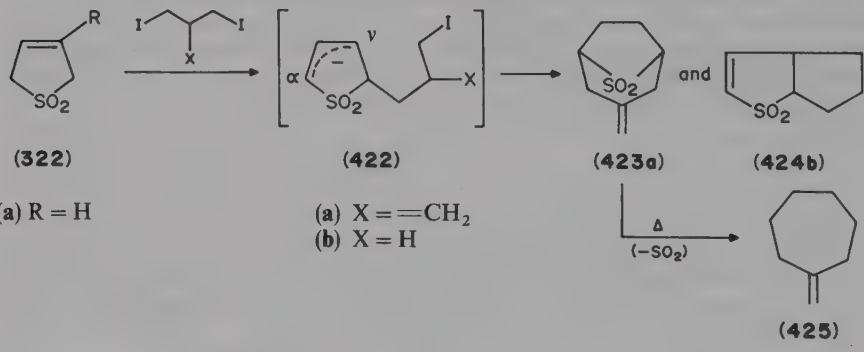
(152)

$R = C(O)(CH_2)_4CH_3$

***D. Selected Chemical Reactions**

4. Dialkylative cyclization reactions of 3-sulfolenes

The reaction of 3-sulfolene (**322a**) with 2-methylene-1,3-diiodopropane in the presence of a strong base gave the bridged bicyclic compound **423a**[399] whereas its undergoing dialkylative cyclization reaction with 1,3-diiodopropane produced the linearly fused bicyclic 2-sulfolene **424b**[400]. In the competition between α- and γ-alkylation of the monoalkylated anionic intermediates (i.e. **422a, b**), electronic effects should favor the α-alkylative cyclization, giving bridged bicyclic sulfones as indicated by the preferred formation of **423a** and **424b** in using the two different alkylating reagents (equation 153).

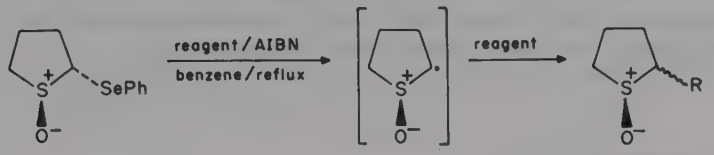


(153)

Since electronic effects, geometric factors, $\pi-\pi$ interactions and steric effects may all affect the mode of the dialkylative cyclization, 3-substituted sulfolenes (**322**; R = Me, Et, *t*-Bu,Cl) were treated with the same alkylating agents as well as with *o*-dibromomethylbenzene[401]. The results confirmed that the dialkylative cyclization reactions of 3-sulfolenes with dihalo substrates provide bridged bicyclic [3.2.1] and [4.2.1] systems; and that the competitive bicyclization reactions giving linearly fused [3.3.0] and [4.3.0] products can be reduced by placing a bulky substituent (e.g. *t*-Bu) on the 3-position of the sulfolene.

5. Reactions of sulfinylated radicals

Although control of the stereoselectivity of radical reactions is an important problem both theoretically[401] and synthetically[402], very little is known about controlling the stereochemical outcome of radical reactions by solvent effects and complexation. A study of the reactions of the five-membered thiolane *S*-oxide-2-yl radical (**427**) as a model system, with allyltributylstannane and vinyltrimethylsilane, revealed the radical to react from the less hindered face (*anti* to the $S^+—O^-$ bond) leading, preferentially, to the *trans*-substituted isomers with the overall yield of the products being low[403] (equation 154).



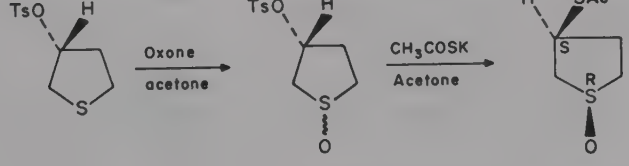
(154)

(**426**) (**427**) (**428**)

(**a**) R = CH_2=$CHCH_2$ (*trans/cis*, 6.0:1)
(**b**) R = $CH_2CH_2SiMe_3$ (*trans/cis*, 4.0:1)

Deuteriation of **426** with the smaller-sized reagent tributyltin deuteride afforded the deuteriated **428** (R = D) in 88% yield and very low selectivity (*trans/cis*, 1.1:1) in line with the expectation that the stereoselectivity will be governed only by steric effects. The lower selectivity observed for the reaction in benzene and THF compared to that obtained when methylene chloride was used, was attributed to complexation of the former with the positive end of the $S^+—O^-$ dipole[403]. The dramatic increase of anti-attack relative to the $S^+—O^-$ bond in the presence of lithium and zinc halides was explained by formation of complexes of lithium cations or other Lewis acids with the oxygen atom of the sulfinyl group (IV)[389].

Enantiomerically pure 3-substituted five-membered ring sulfoxides (e.g. **429**) in which X is a suitable leaving group (to be substituted nucleophilically) are very important in the synthesis of the antibacterial sulfopenem series. This goal could be partly achieved[404] by potassium peroxy-monosulfate (Oxone) oxidation of the corresponding sulfide precursor: the desired *trans*-isomer (**430a**) was produced in 77% yield accompanied by just minor amounts of the *cis*-isomer (**430b**)[405]. Treatment of **430a** with potassium thioacetate provided optically pure (1*R*, 3*S*) thioacetate **431** in > 80% yield[404] (equation 155).

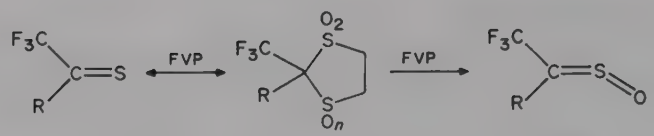


(155)

(**429**) (**430** -*trans* (**a**)/*cis* (**b**)) (**431**)

6. Thermolysis

Flash vacuum pyrolysis (FVP) of 1,3-dithiolane-*S*,*S*-dioxides (**417a**) and *S*,*S*-trioxides (**417b**) provided, in good yields, the corresponding thioketones (**432**) and sulfines (**433**), respectively[397] (equation 156).

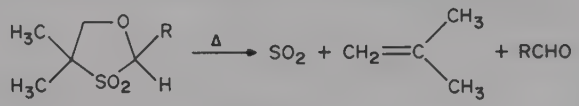


(156)

(432) (417) (433)

(a) $n = 0$
(b) $n = 1$

Thermolysis of cyclic 1,3-oxathiolane-*S*,*S*-dioxides results in fragmentation in which the sulfonyl group is removed as sulfur dioxide[396] (equation 157).

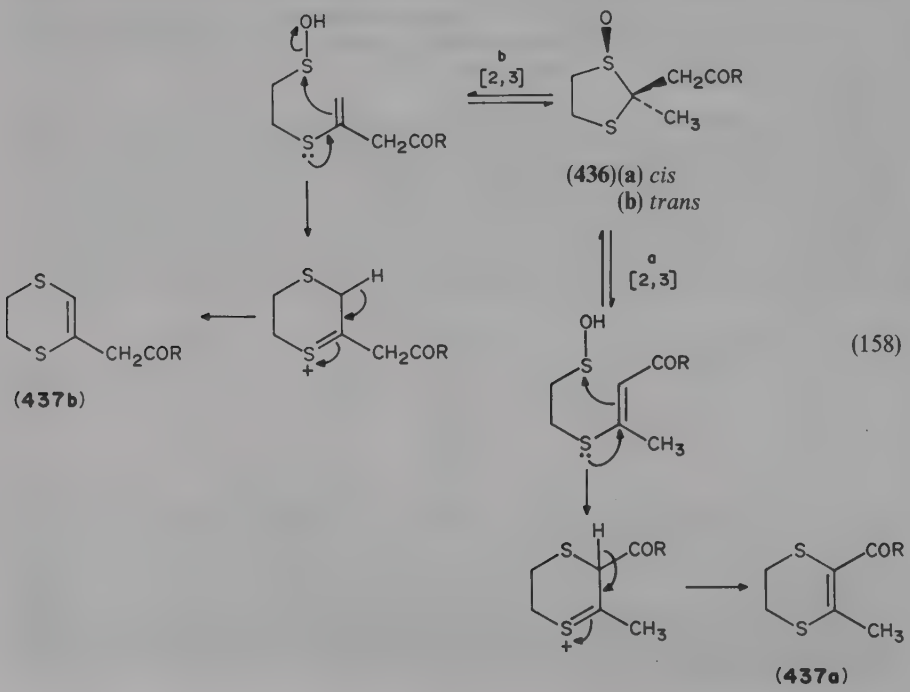


(157)

(434) (435)

7. Rearrangement

Under neutral conditions, thermolysis of *cis*- and *trans*-1,3-dithiolane sulfoxides **436a,b** in toluene or C_6H_6–DMF at reflux, produced the expected (based on previous studies with the analogous 1,3-oxathiolane and thiazolidine sulfoxides[406]) ring-enlarged dihydrodithiins **437a,b**, respectively[407], via the established sulfoxide–sulfenic acid equilibrium[408] (equation 158). Deuteration provided evidence that the sulfoxide–sulfenic acid equilib-



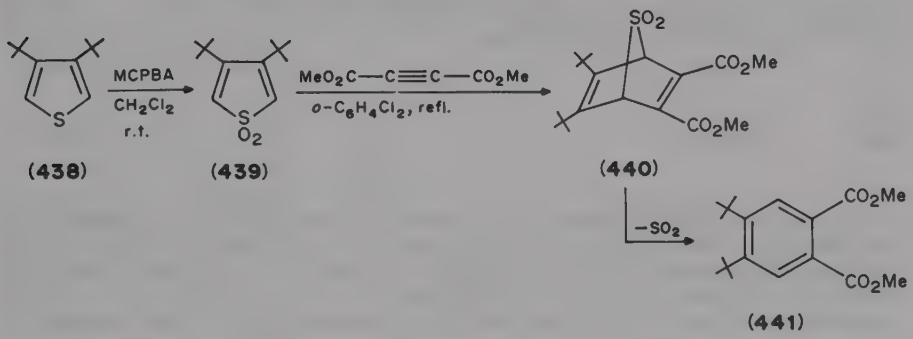
(158)

rium is operative in this transformation and that no isomerization occurs to interconvert the *cis*- and *trans*- sulfoxide precursors.

Kinetic studies of the deuterium isotope effect showed K_H/K_D to be within the range of the expected values for the relevant primary isotope effect in β-*cis*-elimination[409], substantiating the sigmatropic thermally-induced rearrangement of these cyclic sulfoxides[407].

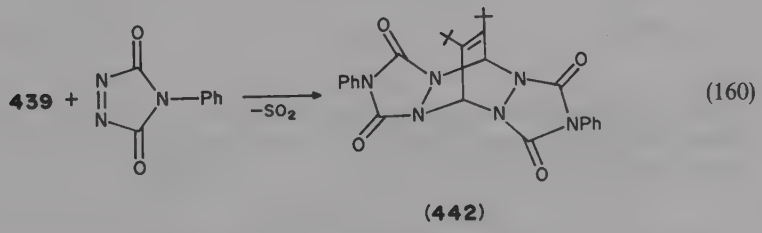
E. Synthesis and Chemistry of Thiophene 1,1-Dioxides

The MCPBA oxidation of the easily synthesized 3,4-di-*t*-butylthiophene (**438**) in high yield[410] provided smoothly the corresponding bulky thiophene *S*,*S*-dioxides **439**. The Diels–Alder reaction of the latter with acetylenes or their synthetic equivalents (e.g. benzynes) provides an easy entry into *o*-di-*t*-butylbenzene and its derivatives following the elimination of sulfur dioxide from the cycloaddition adducts (e.g. **440**) on thermolysis[411]. An illustrative example is given in equation 159.



(159)

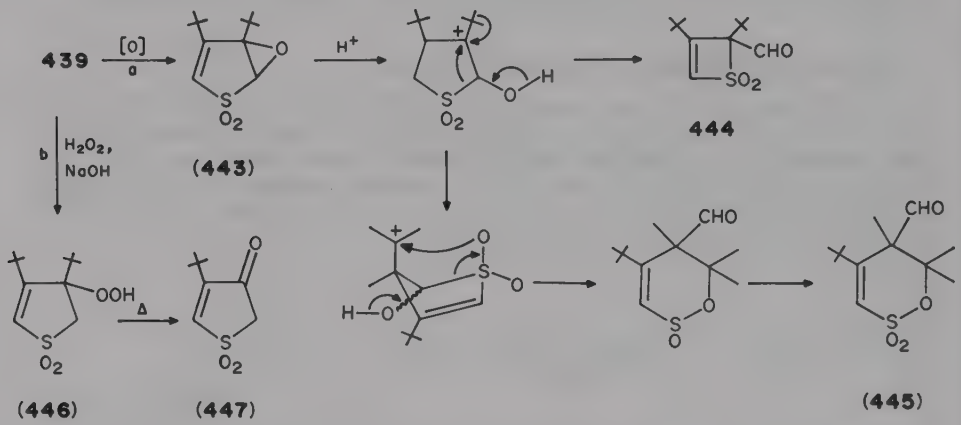
3,4-Di-*t*-butylthiophene 1,1-dioxide reacts with two equivalents of either maleic anhydride or 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) to give, following loss of SO_2, the *endo–endo* (73%) and *endo–exo* (23%) bisadducts in the first case and the bisadduct **442** (87%) in the second (equation 160), which have a highly hindered and strained double bond incorporated in a bicyclo [2.2.2] oct-2-ene ring system. The reaction of **439** with phenyl vinyl sulfone affords *o*-di-*t*-butylbenzene (the parent compound in the **441** series) following the loss of sulfur dioxide and benzenesulfinic acid from the initially formed Diels–Alder adduct.



(160)

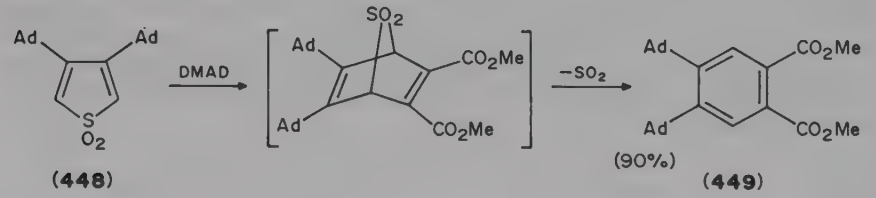
Oxidation of the thiophene dioxide **439** with either MCPBA or trifluoroperacetic acid affords the thiete 1,1-oxide **444** and the 5,6-dehydrosulfone **445** apparently via the mechanism depicted in equation 161a[413]. Under basic conditions the rearrangement is suppressed so that the initially formed epoxy sulfone **443**—a representative of a new ring

system—can be isolated in good yield. Oxidation of **439** with alkaline H_2O_2 (equation 161b) involves a smooth Michael addition of HOO^- to give the first isolable β-hydroperoxy sulfone (**446**) in a very high yield. Thermal decomposition of **446** affords the corresponding ketone **447**[413].



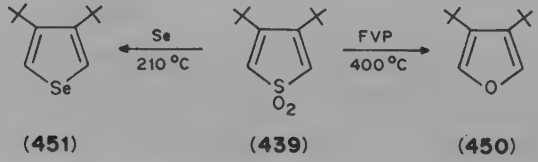
(161)

The synthesis of 3,4-di-1-adamantyl thiophene *S,S*-dioxide **448**[414] by using the same methodology as that applied in the synthesis of the analogous di-*t*-butylthiophene *S,S*-dioxide **439**, enabled one not only to obtain a thiophene substituted with bulkier (than *t*-butyl) substituents on its 3- and 4-positions, but also to obtain in high yield the adamantyl analogue of **441** (i.e. **449**) following the cheletropic loss of sulfur dioxide from the initially formed adduct[414] (equation 162). Since thiophene-1,1-dioxides are more stable than the corresponding cyclopentadienones and their Diels–Alder cycloadducts lose sulfur dioxide under the cycloaddition reaction conditions, they were reacted with benzynes to afford (following the loss of SO_2 from the cycloadduct) the corresponding naphthalene derivatives[415].



(162)

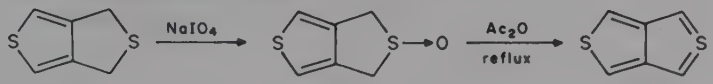
Interestingly, the crowded 3,4-di-*t*-butylfuran (**450**) and selenophene (**451**) could be obtained by flash vacuum pyrolysis of the dioxide **439** and by heating it with selenium powder, respectively[416] (equation 163).



(163)

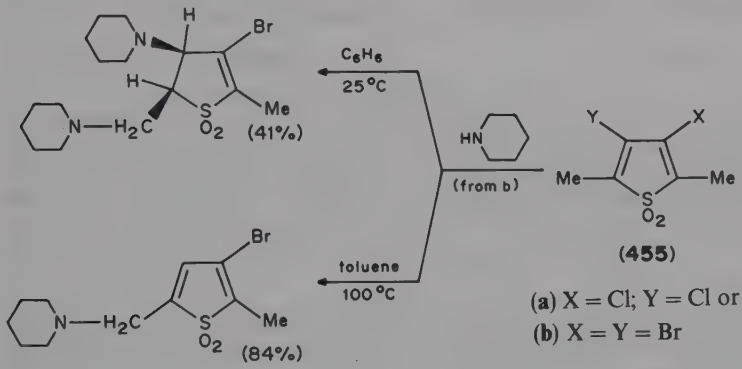
Of particular interest in the 3,4-substituted series is the successful generation, from **452** via **453**, of the parent [3,4-*c*]-thienothiophene **454**[417] (equation 164) which is effectively trapped with acetylenic and olefinic dipolarophiles in 1,3-dipolar cycloadditions.

All the chemistry associated with the 3,4-bulky-substituted thiophene *S*,*S*-dioxides was recently reviewed and summarized[418].



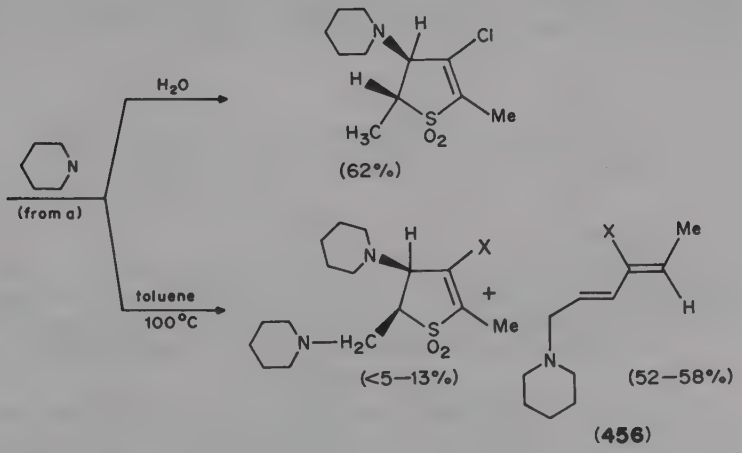
(452) (453) (454) (164)

Substituted thiophene-1,1-dioxides are rather stable and constitute useful starting materials for organic synthesis[279], but their reaction pattern with secondary amines is rather complex. Studies of the reactivity of 3-halo-[419] and 3,4-dihalo-[420] 2,5-dialkylthiophene-1,1-dioxides (**455a,b**) with aqueous piperidine and excess piperidine in benzene have been carried out, aimed at developing useful organic reactions. The results are summarized in equation 165.



(455)

(a) X = Cl; Y = Cl or Br
(b) X = Y = Br

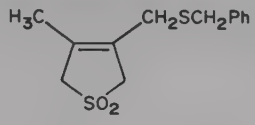


(456)

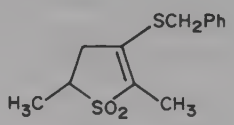
(165)

Similar results were obtained in the reaction of **455** with other secondary amines[420]. Of particular synthetic interest is the use of thiophene dioxides as templates for the introduction (via aromatic substitution or metallation) of various substituents in the α- and β-positions, followed by ring opening which leads, stereospecifically, to dialkylamino-substituted halobutadienes such as **456**.

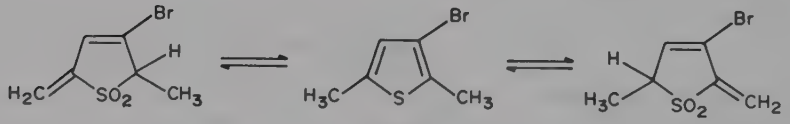
The reaction between 3,4- and 2,5-dimethyl-substituted thiophene *S,S*-dioxides with various nucleophiles such as thiolates and alkoxides was shown[422] to proceed through (a) addition to the exomethylene tautomer, leading to **457** in the case of the 3,4-dimethyl isomer; (b) a 'normal' 1,4-addition followed by double bond isomerization leading to **458** in the case of the 2,5-dimethyl isomer; and (c) a mixture of products—including substitution of the halogen—in the case of the 2,5-dimethyl-3-bromo isomer, depending on the reaction conditions and the particular nucleophile. Thus, in the latter case both possible exomethylene tautomers (equation 166) react whereas in protic solvents normal Michael addition to **459** occurs[419,420].



(457)

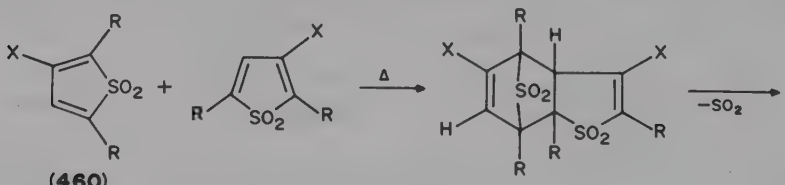


(458)

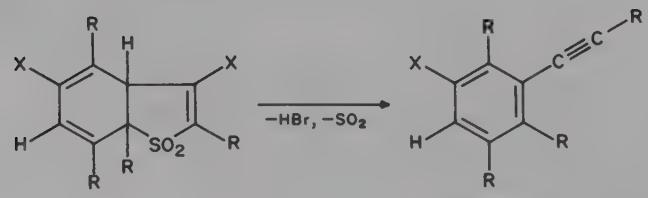


(459) (166)

Tandem cycloaddition (dimerization)-ring opening of 3-halo-2,5-dialkylthiophene 1,1-dioxides (**460**) under basic reaction conditions was shown to open a new short route to unsymmetrically penta-substituted benzenes (**461**) as depicted in equation 167[422]. Similarly, heating of 3,5-dibromo-2-methyl- (or phenyl-) thiophene 1,1-dioxides leads to dimerization followed by elimination of HBr to give benzo[*b*]thiophene 1,1-dioxides[423].

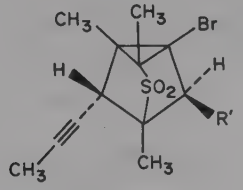


(460)



(461) (167)

The reaction of **460** ($R = CH_3$; $X = Br$) with Grignard reagents ($R'MgBr$) gave the condenseding sulfone system **462** the formation of which can be rationalized by the following sequence: 1,4-Michael addition of $R'MgBr$ to the 3-position of **460** gives a carbanion which, in a Michael fashion, adds to another molecule of **460** in the 3-position. Intramolecular attack of the resulting carbanion on the 4-position of the first sulfone molecule gives a new α-sulfone carbanion which, in nucleophilic substitution, attacks the 5-position. Elimination of sulfur dioxide (from the sulfinate leaving group) and bromide ion then gives **462**[424].

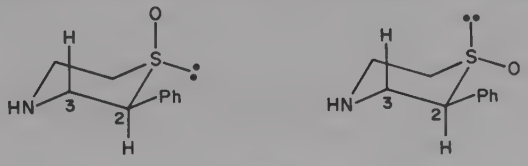


(462)

*VI. SIX-MEMBERED RING SULFOXIDES AND SULFONES

*A. Conformational Analysis

Most of the pioneering studies on conformational analysis within cyclic sulfoxides and sulfones were based on ^{1}H-NMR and/or ^{13}C-NMR data concerning the relevant chemical shifts and/or coupling constants–decoupling of the studied normal or partly deuteriated molecules. Recent studies of these and of closely related six-membered ring systems still rely heavily on significant chemical shifts and coupling constants to assign the stereochemistry of the involved functional group and, consequently, the conformations[425]. Thus, for example, the stereochemistry of the sulfinyl group in, and the conformation of, several phenyl-substituted, 1,4-thiazane derivatives (*N*-methyl and *N*-alkoxycarbonyl, *S*-oxides and *S,S*-dioxides; e.g. **463a,b**) were determined following their synthesis[426]. In the cases of the 2-phenyl (**463a**), 3-phenyl and *trans*-2,3 diphenyl derivatives, where the axial character of the H_{3ax} in the ^{1}H-NMR spectra of the thiazenes was identified and their axial orientation confirmed, it was possible to study the effect of oxidation of sulfur (sulfide → sulfoxide) based on the chemical shifts of these signals[425].



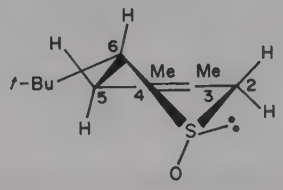
(a) **(463)** **(b)**

Recent conformational and configurational studies of cyclic sulfoxides and sulfones[427,429] are based on ^{17}O-NMR coupled with ^{13}C-NMR spectra, taking the advantage of the prochirality of the sulfoxide group on the one hand and of the potential non-equivalence of the two oxygen atoms in the cyclic sulfones on the other.

1. Oxygen-17 NMR-based conformation and configurational assignment

The assignment of the *cis*- and *trans*-configuration of 3,4-dimethyl-6-*t*-butyl-5,6-dihydro-2H-thiopyran-*S*-oxides (**464a,b**) was made by the use of ^{13}C and ^{17}O data and force

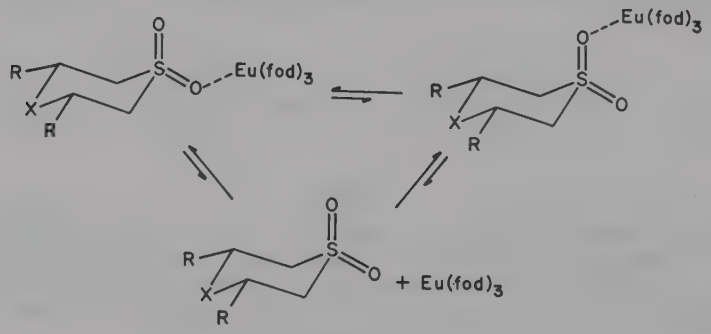
field calculations[427]. The chemical shifts of the oxygen atoms, −14 and 5 ppm for **464a** and **464b** respectively, compared with the values reported for rigid *trans*-1-thiadecalin (−11.4 and 5.6 ppm)[428] and of several pairs of thiane-*S*-oxides[327], indicate that, in this pair, one isomer has the substituent on sulfur which is equatorial and the other axial. However, knowledge of this orientation of the oxygen atom of the sulfoxide group is *per se* insufficient to assign the corresponding configurations. The large deshielding shown by H_{5ax} (2.09 ppm) in **464eq**, which has the equatorial oxygen, indicates that this proton and the oxygen in the sulfoxide group are *syn*-axial[427]. This can be only if the conformation of **464a** is half-chair. It follows that **464a** has the *cis*-configuration and, consequently, **464b** has the *trans* which, in turn, requires **464b** to be in the half-chair conformation too to allow the *t*-Bu and the oxygen on sulfur to be equatorial.



(464)

(**a**) ax (as in figure)
(**b**) eq (O and lone-pair on S reversed)

The ^{17}O-NMR shifts of diastereotopic sulfonyl oxygens within a series of conformationally homogeneous six-membered ring sulfones and sulfoxides have been determined[429], capitalizing on (a) the ^{17}O-NMR diastereotopicity (or chemical-shift non-equivalence) of the sulfonyl oxygens in both cyclic[430] and acyclic sulfones; and (b) the correlations between relative ^{17}O-NMR chemical shift differences caused by the influence of α-, β- and γ-substituent and differential shielding effects caused by conformer differences in diastereomeric relationships. The lanthanide-induced shifts (LIS) of **465a, c** resulting from competitive complexation with the europium metal ion [Eu(fod)$_3$], were also determined[429] for assessing the relative binding potential of the attached diastereotopic sulfonyl oxygens (equation 168).

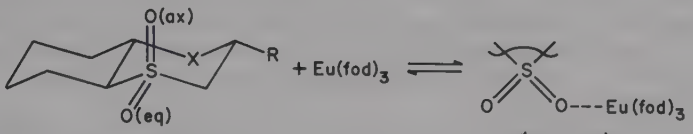


(168)

(465)

(**a**) X = NH; R = Ph
(**b**) X = NCH_3; R = Ph
(**c**) X = S; R = Ph

Thus, **465a–c** exhibited shifts at δ 140.6 and 155.1, 135.9 and 150.3, and 143.4 and 154.1, respectively, suggesting, by analogy with the ^{17}O spectra of other conformationally homogeneous sulfones, that the high-field sulfonyl oxygens are *axial*. When incremental quantities of $Eu(fod)_3$ were added to methylene chloride solutions of the sulfones **465a–c**, their ^{17}O resonances experienced varying degrees of differential shielding, the axial oxygens being less responsive than the equatorial ones: The corresponding slopes α_1(eq) and α_1(ax) of the lines (incremental shifts versus Ln^{3+}/substrate mole ratio) were 459.0, −209.3; −534.6, −132.9; and −452.3, −156.5 ppm for **465a,b** and **c**. From these data it is clear that Eu^{3+} binds to the equatorial sulfonyl oxygen significantly more strongly than to the axial sulfonyl oxygen[429]. The results of ^{17}O-LSR (lathanide shift reagents) studies of other heterocyclic sulfones (i.e. 1-thiadecalin, -1,4-dithiadecalin, -1,4-oxathiadecalin-dioxides and 2-alkylsulfonyl cyclohexanols) using $Eu(fod)_3$[431] were not always consistent with those obtained previously with **465a–c**. Thus, for example, the reversal binding preference of the Eu^{3+} (to an axial rather than to an equatorial oxygen) upon substitution of an oxygen atom for C_4 in **466c** (equation 169) can be accounted for by the resulting change in the geometry of the sulfonyl group, which in turn reverses the relative extent of exposure of the two diastereotopic oxygens for the metal complexation. The propensity of $Eu(fod)_3$ to bind as determined by ^{17}O NMR can thus be effectively used to distinguish between diastereotopic sulfonyl oxygens of cyclic dioxides in solution.



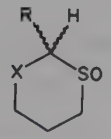
(169)

(466)

(**a**) X = CH_2; R = H
(**b**) X = S; R = H
(**c**) X = O; R = H

2. Absolute configuration

Similar to the use of CD in the determination of the absolute configuration of five-membered rings, the same technique and methodology were applied in determining the absolute configuration of 1,3-oxathiane and 1,3-dithiane oxides and dioxides **A**–**E**[393].

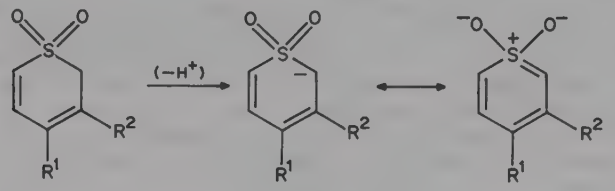


(**A**) X = O; R = H
(**B**) X = S; R = H
(**C**) X = SO (*trans*)
(**D**) X = O; R = *p*-BrC_6H_4 (*cis* and *trans*)
(**E**) X = S; R = *p*-BrC_6H_4 (*trans*)

CNDO/S-CI calculations on A–C showed agreement with the signs of the CD couplets, assuming that the coupled oscillator mechanism is working. Application of the same technique to **D** and **E** facilitated the assignments of absolute configurations to these compounds[393].

3. Aromatic stabilization energies and cycloconjugation

Aromatic stabilization energies (ASEs) for anions possessing $4\pi + 2$ electrons can be estimated by comparing their pK_{HA} values with those of open-chain analogues. Anions derived from thiopyran 1,1-dioxides (i.e. **467a**, see equation 170) were found to be more acidic than the acyclic model ($pK_{HA} = 20.2$) by 4.2–8.4 pK_{HA} units[432]. This is consistent with the suggestion[433] that the anions derived from these sulfones—all having 6π-electron systems—may possess considerable aromatic stabilization.



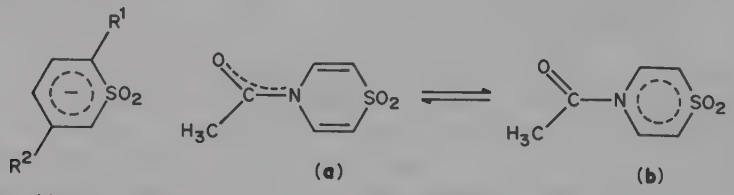
(170)

(467) **(467⁻)**

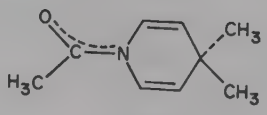
(a) $R^1 = H$; $R^2 = Ph$
(b) $R^1 = Me$; $R^2 = Ph$

In a related study, the extreme sensitivity of the electronic energy of cyclic π-electron species to the number of π electrons associated with the ring was exploited to assess the possible operation of orbital overlap (conjugative interactions) between second-row atoms (P,S) and the π-system.

In reference to anions such as **468**, the barrier to the amide rotation in **469** by NMR line-shape analysis[434] was determined and compared with the corresponding barrier in the reference compound **470**[435].



(468) **(469)**

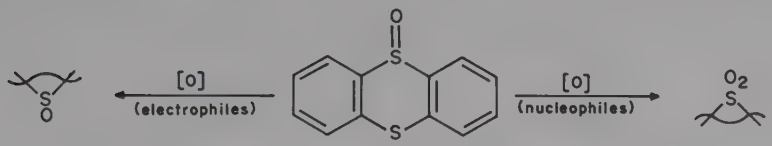


(470)

The amide barrier in **469** was found to be substantially *less* (>6 kcal) than in the reference compound **470** in which a saturated center interrupts the conjugation. This result, also supported by *ab initio* calculations at the Hartree–Fock level with the 3-21G(*) basis set, suggests that conjugative interactions stabilize the transition state for the amide rotation by cycloconjugation, but not the planar equilibrium states, compressing the barrier relative to reference **470**.

It is worth mentioning that thianthrene 5-oxide (**471**) was employed (equation 171) as a mechanistic probe to assess the electronic nature of oxygen-transfer reagents: those oxidants that attack preferentially the sulfide 'S' site to give the bisulfoxide (SO/SO) are

eletrophilic, and those that predominately react at the sulfoxide 'SO' site to give the sulfone (S/SO_2) are nucleophilic[436].

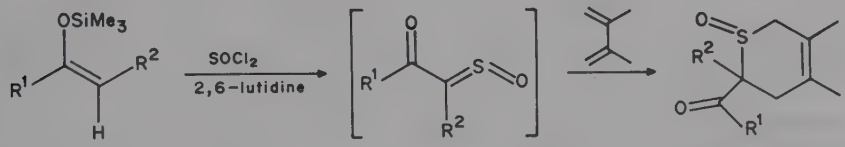


(171)

(471)

*B. The Synthesis of Six-membered Ring Sulfoxides and Sulfones

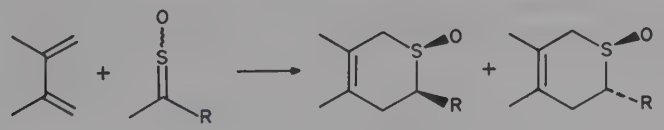
The trapping of sulfines by dienes is, perhaps, one of the best methods for the synthesis of six-membered ring sulfoxides. Indeed, the cycloaddition of a variety of differently substituted sulfines with dienes to give dihydropyran *S*-oxides (e.g., equation 172 has been demonstrated and is well documented[437]. Generally speaking, the stereochemical relationship of the unsymmetrically disubstituted sulfine counterparts is retained in the cycloadduct in accordance with concerted [4 + 2] cycloaddition reactions. α-Oxo sulfines **473**, best generated by reacting enol silyl ethers with thionyl chloride[438], also cycloadd smoothly with dienes to give—similarly to ordinary sulfines—the corresponding substituted six-membered ring sulfoxide systems **474**[437] (equation 172).



(472) (473) (474)

(172)

Unexpectedly, the reaction of butadienes **475** with the relatively labile *Z*-monoaryl sulfines (**476**) afforded *cis/trans* mixtures of the corresponding dihydrothiapyran *S*-oxides (**477**), the *Z/E* ratio being dependent upon the initial diene/sulfine ratio and the *Z* to *E* isomerization of the dienophile being responsible. In contrast, *Z/E* mixtures of the aliphatic *t*-butyl sulfine gave, with 2,3-dimethylbuta-1,3-diene, only the corresponding stereochemically more stable *trans*-(*E*)-cycloadduct[439]. The total isolated yields are within the range of 60–95% except in the case of the bulky *t*-butyl sulfine, which is 25–42% for the only obtained *trans* isomer. The absence of a solvent effect is consistent with a concerted mechanism for these uncatalyzed cycloadditions (equation 173).

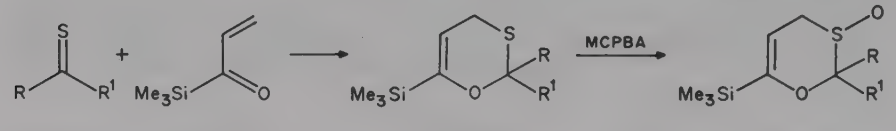


(475) (476) (*Z*) (477) (*E*)

(173)

R = Ph; *p*-Tol; *p*-ClC_6H_4; 2,4,6-$Me_3C_6H_2$; Me_3C

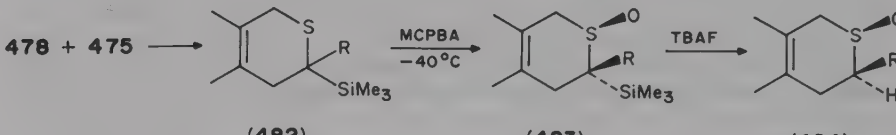
[4 + 2]-Cycloadditions of silylated and nonsilylated thiones (**478**) with vinyl trimethylsilylketone (**479**), behaving as heterodiene, provide 4*H*-1,3-oxathiins **480** and the latter can be easily oxidized to the corresponding *S*-oxides (equation 174). This synthetic methodology constitutes an additional entry to six-membered ring sulfoxide systems (i.e. **481**)[440].



(478) **(479)** **(480)** **(481)**

(**a**) $R = R^1 = Ar$
(**b**) $R = Ph$; $R^1 = SiZ_3$ ($Z = Me$ or Ph) (174)

Similarly, the cycloaddition reaction between the silylated alkyl thiones (i.e. **478c**, R = *t*-Bu or Me; $R^1 = Me_3Si$) and the diene **475** affords the adduct **482** from which the *trans*-sulfoxide **483** can be easily obtained via oxidation. Desilylation provides a 1:3 mixture of the *cis* and *trans* desilylated sulfoxides **484** (equation 175)[441].

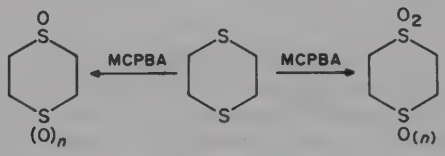


(482) **(483)** **(484)**

R = *t*-Bu *cis* and *trans*

(175)

MCPBA oxidation of sulfides to sulfoxides and sulfones is a very convenient method to convert the parent 1,4-dithiane **485** to the various corresponding oxides (**486**) and dioxides (**487**); see equation 176. The yields, however, are only fair.

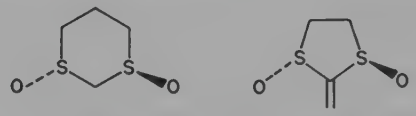


(176)

(486) **(485)** **(487)**

(**a**) $n = 0$ (1 eq. MCPBA) (**a**) $n = 1$ (3 eq. MCPBA)
(**b**) $n = 1$ (2 eq. MCPBA) (**b**) $n = 2$ (5 eq. MCPBA)

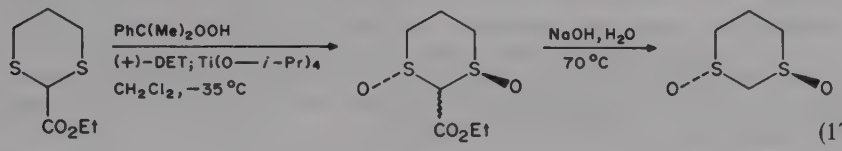
The chiral bifunctionalization of compounds is a powerful strategy for the preparation of C_2 symmetric reagents. The latter are finding increasing importance in asymmetric synthesis as a result of the generally high selectivities obtained with them[443]. Indeed, the 1,3-dithiane 1,3-dioxides **488** and **489** were found to be very useful C_2 symmetric reagents



(488) **(489)**

in their undergoing highly diastereoselective reactions, acting as potential chiral acyl anion and chiral ketene equivalents, respectively[444].

The asymmetric bisoxidation of the 2-substituted (to deliver good enantioselectivity in the oxidation process)[445] 1,3-dithiane **490** to **491** followed by alkaline hydrolysis afforded the (1*R*, 3*R*)-1,3-dithiane 1,3-dioxide **492** in enantiomerically pure form[446] (equation 177).



(177)

(490) **(491)** **((+)-(492)**

68%; > 97% ee 79%; 99% ee

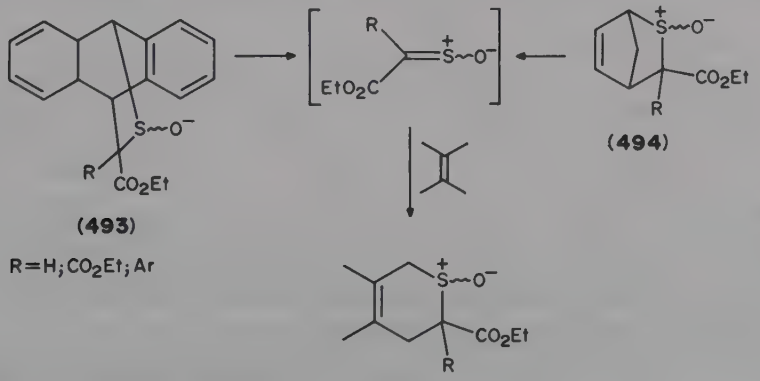
*C. Selected Chemical Transformations

3. Oxidation

In contrast to the vast majority of oxidation reactions with dimethyldioxirane (DMD) in which it functions as an electrophilic agent[447], its reaction with thianthrene-5-oxide (**471**) occurs predominantly at the sulfinyl (SO) rather than the sulfenyl (S) sulfur, reflecting the nucleophilic character of DMD in this case (equation 171)[448]. A very recent mechanistic study[449] ruled out the possibility of initial attack of DMD at the sulfinyl oxygen of **471** (but not of other sulfoxides) perhaps owing to its internal hydrogen bond donor nature. In using thianthrene-5-oxide as a probe for the electronic character of oxygen transfer agents[436, 450], it was recently demonstrated[451] that the peroxide intermediate derived from the $^1O_2$ oxidation of Ad=Ad acted exclusively as a nucleophile.

4. Thermolysis of S-oxides

The *S*-oxides of the cycloadducts of thioaldehydes and either anthracene (**493**) or cyclopentadiene undergo thermal cleavage to liberate sulfines under 'clean' conditions[452,453] although complications can arise from intramolecular rearrangements of *endo* sulfoxides of type **494**[454] (equation 178). Under FVP conditions, intramolecular cycliz-



(493) **(494)**

(178)

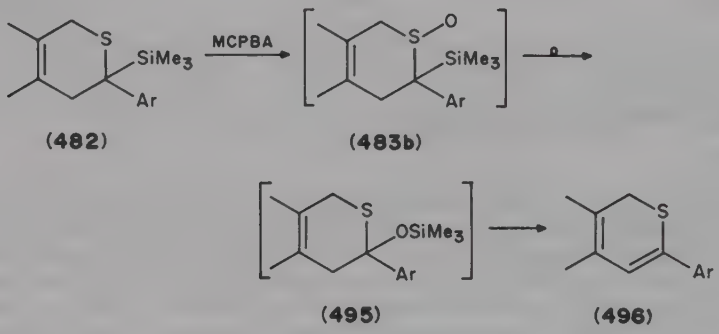
R=H; CO_2Et; Ar

484c

ation of the initially generated allyl and homoallyl sulfines from the alkene ester $(CO_2\text{-}[CH_2]_n\,CH{=}CH_2$; $n = 1$ or 2) adduct **494** gave furan-2(5*H*)-one and 5,6-dihydro-2-pyrone, respectively[455].

5. Sila-Pummerer rearrangement

Oxidation of the aryl silyl thioketone cycloadducts **482** (R = Ar) using MCPBA at −50 °C does not produce the corresponding *S*-oxides (i.e. **483b**; R = Ar). Rather, the expected, initially formed six-membered *S*-oxide undergoes a thermal sila-Pummerer rearrangement to give an *O*-silyl monothioacetal **495**, which on subsequent elimination of silanol leads to the diene **496**[456] (equation 179).

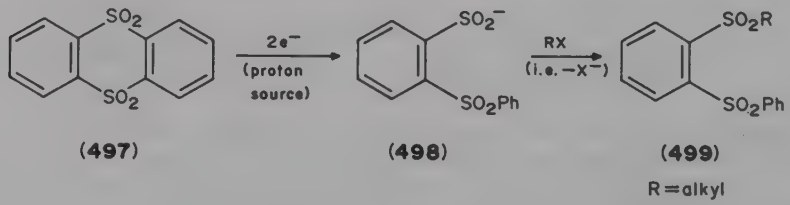


(179)

6. Cathodic behavior of sulfones

Electrochemical studies revealed that the 9,9,10,10-tetroxide **497** may afford surprisingly stable radical anions and dianions[457]. Based on the ESR spectrum of the anion and the observed low coupling constants, equal delocalization of the negative charge between the two aromatic nuclei can be deduced[458]. The capability of the dianion produced from **497** as a reducing species was demonstrated previously[459].

Under cathodic conditions the disulfone **497** is cleaved and an open sulfinate (**498**) is formed (equation 180). The addition of primary aliphatic halides RX at the end of the electrolysis is a facile synthesis of the 'mixed' disulfones **499** in high yields[458].



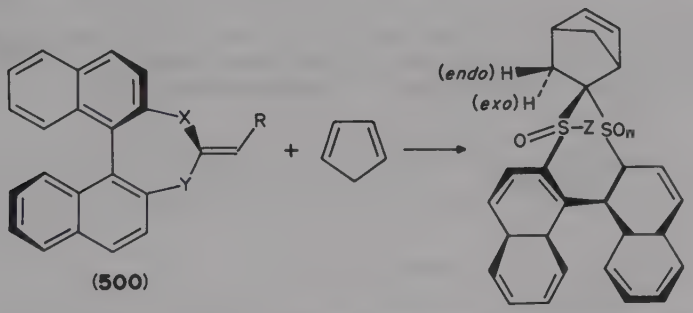
(180)

*VII. MEDIUM-SIZE RING SULFOXIDES AND SULFONES

A. Selected Chemical Reactions of Seven-membered Rings

Chiral ketene dithioacetal mono, di-, tri- and tetra-oxides **500** of C_2 symmetry were prepared starting from the corresponding dithiepin[460] by oxidation with MCPBA[461]. All

the sulfoxides were formed as single, pseudoequatorial diastereoisomers, showing the efficient transferability of the chirality of the binaphthyl residue. All the *S*-oxides **500a–c** (equation 181) gave diastereoselective cycloaddition to cyclopentadiene (as evidenced from the study of the relevant nuclear Overhauser effect[462] and lanthanide-induced shift complexes) in high yields (92–98%). The disulfone **500d** gave a mixture of diasteroisomers in a kinetically controlled cycloaddition[461].



(181)

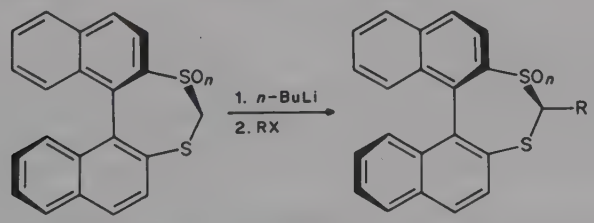
(500)

(**a**) X = SO; Y = S; R = H
(**b**) X = Y = SO; R = H
(**c**) X = SO; Y = SO_2; R = H
(**d**) X = Y = SO_2; R = H
(**e**) X = Y = SO_2; R = alkyl, vinyl, aryl

(501)

(**b**) Z = – :, *n* = 1; *endo*:*exo* = 3:1
(**c**) Z = – :, *n* = 1; *endo*:*exo* = 2:1
(**d**) Z = O, *n* = 2; *endo*:*exo* = 1:4.5

With **500e** the *endo*-adduct predominates[463]. Reaction of the anions derived from the chiral thiepine *S*-oxides and *S*-dioxides (**502a,b**) with carbonyl compounds or alkylating agents afforded the product effectively and stereoselectively, particularly with the sulfoxides **502a,b**, apparently due to the synergistic contribution of the chiral binaphthyl residue and the sulfoxide group[464]. An example is given in equation 182.



(182)

(502)

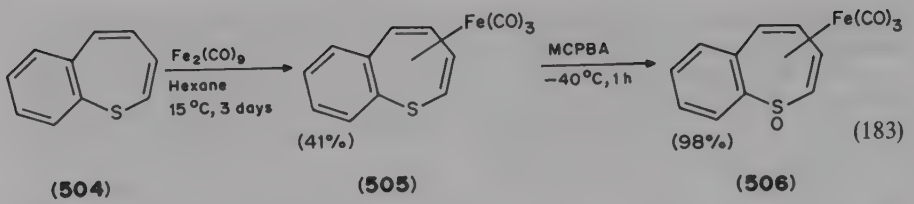
(**a**) *n* = 1
(**b**) *n* = 2

(503a,b)

R = CH_3; $C(OH)R^1$ (R^1 = H or CH_3)

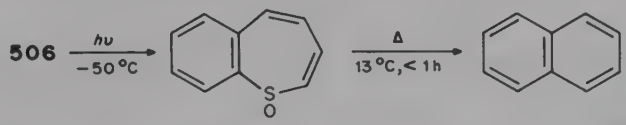
Thiepine itself and its *S*-oxide are unstable whereas 1-benzothiepine and its dioxide are well characterized. However, 1-benzothiepine 1-oxide has not yet been synthesized. In view of the precedents it should be less stable than the parent 1-benzothiepine (**504**). While direct MCPBA oxidation of **504** to provide the *S*-oxide was unsuccessful, an advantage of the transition complexation strategy[465] has been utilized[466] as illustrated in equation 183.

Further oxidation of the thiepine oxide–transition metal complex **506** with MCPBA gives the iron tricarbonyl dioxide complex and its reduction with LAH provides the corresponding 1-benzothiepine–metal complex [**504**–$Fe(CO)_3$]. Irradiation of a dilute



(504) (505) (506) (183)

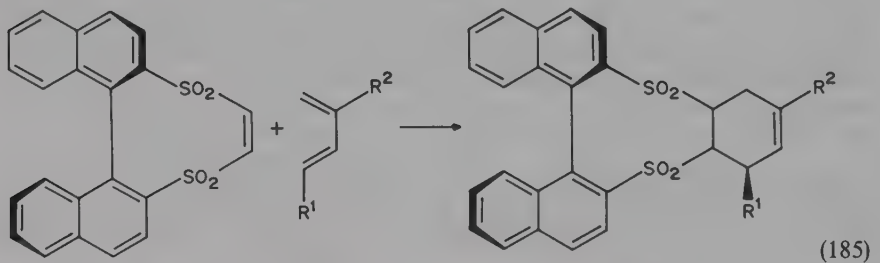
THF solution of **506** at $-50\,°C$ resulted in the formation of the unstable, metal-free sulfoxide **507** (photolytic decomplexation), as pale yellow needles at $-40\,°C$. Within one hour at 13 °C, **507** was transformed into naphthalene (equation 184)[466].



(507) (184)

B. Selected Chemistry of Eight-membered Rings

Similarly to its seven-membered ring counterparts[461], the C_2 symmetrical chiral, eight-membered ring, *S,S*-tetroxide **508** is a reactive dienophile and forms Diels–Alder adducts in high yield with symmetrical and unsymmetrical dienes (e.g. cyclopentadiene, furan, anthracene) producing a single diasteromeric adduct in most cases[467] (equation 185).



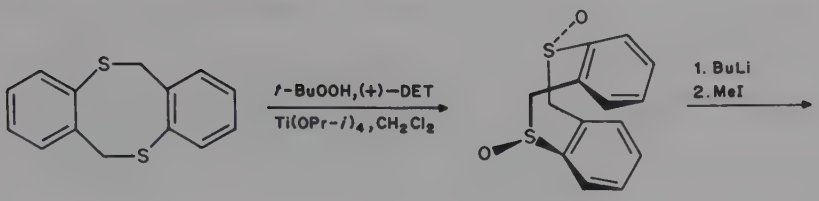
(508) (509) (185)

R^1 = OMe or OTMS or Me
R^2 = OTMS or H or Me

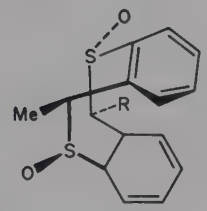
The arylsulfonyl groups can be removed with formation of a double bond, rendering **508** a chiral synthetic equivalent of acetylene[468] in the above [4 + 2] cycloaddition reactions[467].

Asymmetric oxidation of **510** afforded the disulfoxide **511** as a mixture of four products[469]. Stepwise treatment of **511** with BuLi followed by MeI afforded the mono- and dimethylation products **512a,b**, respectively[470] (equation 186).

Sensitized photoxidation of 1,5-dithiacyclooctane **511** in methanol produced more than 90% of the corresponding monosulfoxide **514** and a mixture of *cis*- and *trans*-bissulfoxides **515a,b**[471] (equation 187). In aprotic solvents (benzene, chloroform, acetonitrile) novel cleavage products are obtained in addition to **514** and **515a,b**. The cleavage products (i.e. **516–518**) derive mostly from the reaction of the monosulfoxide with singlet oxygen[471].

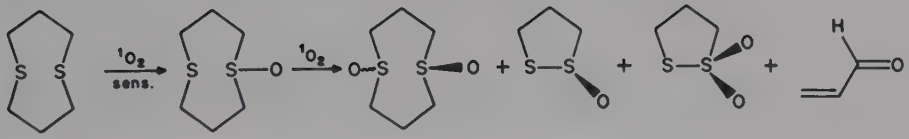


(510) (511)



(186)

(512)
(a) R = H
(b) R = Me

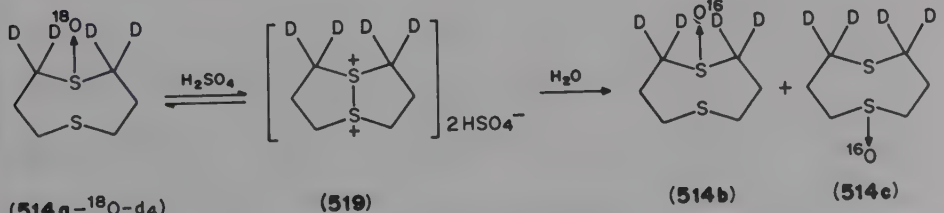


(513) (514) (515a,b) (516) (517) (518)

(187)

Transannular interaction in organic reactions is usually observed in medium-sized cyclic compounds. As a typical example, the two sulfur atoms in **513** and the related cyclic compounds approach close together due to the characteristic conformational property observed in eight-membered cyclic compounds and hence should have an attractive force even in the neutral state in **513**–**515**[472].

Thus, treatment of the mono-sulfoxide **514** with a concentrated sulfuric acid produces the dication **519**, which in turn provides a 1:1 mixture of the sulfoxides **514b** and **514c** on quenching with H_2O[472] (equation 188).

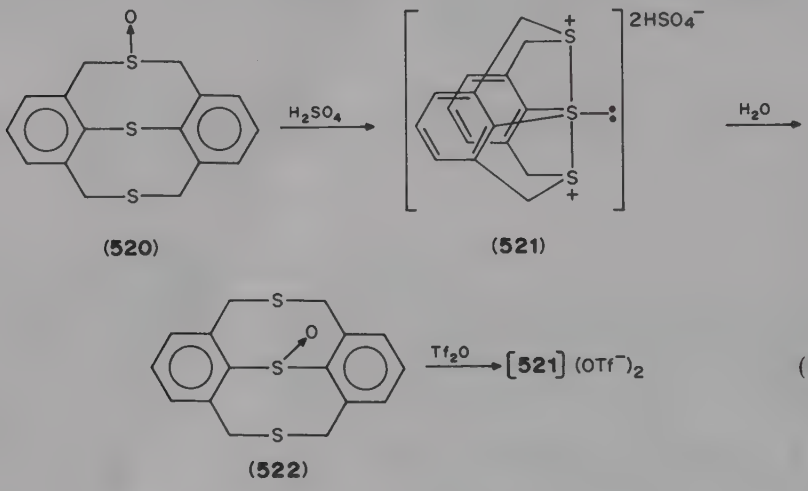


(514a-^{18}O-d4) (519) (514b) (514c)

(188)

A very stable disulfide dication salt is obtained from the sulfoxide **514** by its treatment with triflic anhydride $[(CF_3SO_2)_2O]$[473].

Other dithiadications could be obtained via transannular interaction on oxidation of other 1,5-dithiaannulenes (e.g. dithia-substituted naphthalene) or on treatment of the sulfoxide with concentrated sulfuric acid[474]. In concentrated H_2SO_4 the sulfoxide **520** undergoes an immediate conformational change (from chair–chair to boat–boat form) to give the hypervalent dication species **521** (equation 189). The latter could be isolated as a crystalline salt by treating the sulfoxide **522** with $(CF_3SO_2)_2O$ (Tf_2O)[475].



(189)

C. Transannular Cyclization and Ring Opening

Medium (eight- and nine-membered) ring γ-epoxy sulfones undergo desilylative transannular cyclization or epoxide ring opening, due to the unique conformation of these rings as well as to the proximity of the two reactive sites and functionality. The mechanism and synthetic potential of these reactions have been recently studied and reported[476].

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CHAPTER 7

Cyclic sulfides

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I. INTRODUCTION

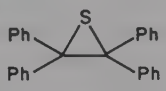
Several reviews on the chemistry of cyclic sulfides have appeared in the last decades. However, most of them deal with a single heterocycle. The aim of this chapter is to bring together the most important features of the cyclic sulfides from three- to eight-membered rings. For each class of cyclic sulfides the behavior of the saturated member has been mainly discussed; however, occasionally the unsaturated species have been also considered.

The chapter covers the most important findings which appeared in the literature of the last decade together with some important early results. References to previously published reviews have been inserted in each section to give the reader a tool for a deeper inspection of the specific argument.

II. THIIRANES

Thiirane is the IUPAC name of the saturated three-membered ring sulfide(**1**). Other names have also been used, such as episulfides, ethylene sulfides, thiacyclopropanes or thiaepoxides. The first thiirane, the tetraphenyl derivative **2**, was synthesized almost 80 years ago[1].

(1)



(2)

Since then the chemistry of thiiranes has attracted much attention due to the challenging synthetic problems, and to the peculiar reactivity of these sulfides which is related to the strained structure of the three-membered ring and to the presence of the sulfur atom.

Several reviews dealing with the synthesis and the reactivity of thiiranes are available[2–13]. Full coverage of the literature can be found in References 14–19.

A. Structure

Several molecular orbital calculations at various levels have been performed on thiiranes to predict their geometrical structure and their peculiar features[20–35]. The most recent calculation of the thiirane (**1**) structure computed at the Hartree–Fock SCF level, with the 6–31G(d) basis set[36], shows good agreement with bond lengths and angles determined on the basis of microwave measurements[37,38] (Table 1).

As in other three-membered ring compounds, the ring bonds of thiirane are bent as shown by the computed carbon–carbon and carbon–sulfur bent bond lengths which are 1.480 Å and 1.826 Å, respectively[36]. These data have been calculated using the path of maximum density connecting the two atoms.

A theoretical investigation on the structure of 2-phenylthiirane[39] has shown that the plane of the phenyl ring and that of the three-membered ring are orthogonal at the energy minimum. This preferred geometry has been attributed to conjugation effects.

It has been also observed by X-ray diffractometric analysis that substitution at carbon affects the bond length of the three-membered ring[40–45].

TABLE 1. Representative bond lengths (Å) and angles (deg) of thiirane

	SCF[a]	Microwave[b]
C—C	1.480	1.492 (1.484[c])
C—S	1.826	1.819
C—H	1.075	1.078
C—S—C	48.0	—
S—C—C	66.0	65.48
H—C—H	114.7	116.0

[a] Reference 36.
[b] Reference 37.
[c] Reference 38.

B. Nuclear Magnetic Resonance

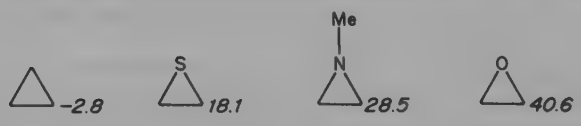
The proton chemical shifts of thiiranes vary from 2.27 for the parent compound to about 3.7 ppm depending on the nature of the substituents at the carbon atoms[46–48]. The geminal coupling constants $^2J_{HH}$ are of the order of magnitude of 1 Hz[46–48]. The value of this coupling constant, unusually low if compared with the same constant measured in oxiranes (5–6 Hz[46,48–60]), might be attributed to the different electronegativity of the two heteroatoms. For similar reasons the vicinal coupling constants $^3J_{HH}$ of thiiranes[46–48], ranging from 4 up to 7 Hz, are larger than those of oxiranes.

Like other saturated three-membered ring compounds, the vicinal coupling constants of thiiranes follow the Karplus rule, the *cis*-$^3J_{HH}$ being larger than the *trans*-$^3J_{HH}$ so that these values can be used for structure determination in the absence of other measurements.

The ^{13}C chemical shift of thiirane (**1**) is 18.1 ppm[51] and substitution usually has predictable effects on chemical shifts of the ring carbons. A comparison of the ^{13}C chemical shifts of three-membered rings (Table 2) shows the usual deshielding effect due to the heteroatom substitution which increases with increasing electronegativity of the atom.

Interestingly, the effect of three-membered ring anellation of the strained tricyclo-[3.1.0.0^{2,6}]hexane (**6**) follows a similar trend[61] (Table 3). The size of the effect on the carbons linked to the methylene group or to the heteroatoms depends upon the shielding due to the three-membered ring and upon the deshielding due to the heteroatom which increases with increasing electronegativity. For the cyclopropane derivative **7** the former effect is predominant and a net shielding is observed while anellation with the more

TABLE 2. ^{13}C chemical shifts (ppm) of cyclopropane (**3**), 1-methylaziridine (**4**), oxirane (**5**) and thiirane (**1**)



(**3**) (**1**) (**4**) (**5**)

TABLE 3. Selected ^{13}C chemical shifts (delta) of tricyclo-[3.1.0.0^{2,6}]hexane (**6**), and of the three-membered ring anellated **7**, **8**, **9** and **10**[61]

(**6**) (**7**) (**8**) (**9**) (**10**)

electronegative oxygen atom in **8** produces the highest deshielding[61]. The aziridine derivative **9** and the thiirane **10** show, as expected, a less pronounced deshielding.

The carbon–hydrogen one-bond coupling constant, $^1J_{CH}$, of thiirane is 170.6 Hz[51]. This value is higher than that found for $^1J_{CH}$ in aziridine (168.0 Hz) and lower than that of oxiranes (175.7 Hz). Since the $^1J_{CH}$ value is mainly determined by the electronegativity of the heteroatom and by the effect of ring strain on hybridization, the highest value is expected for oxirane.

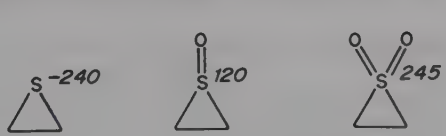
Recently, natural abundance ^{33}S nuclear magnetic resonance of thiirane (**1**) has been measured and the chemical shift compared with those of thiirane 1-oxide (**11**) and thiirane 1, 1-dioxide (**12**)[62] (Table 4). Furthermore, sulfur charges on **1**, **11** and **12** were calculated at the STO-3G* level, including d-orbitals, in order to verify whether it was possible to correlate ^{33}S chemical shifts of the three heterocycles with increasing oxidation at sulfur.

A good correlation between ^{33}S chemical shift and charge on sulfur has been found for the three heterocycles (Figure 1). However, such correlation seems a peculiarity of the three-membered ring system since it does not apply to other larger sulfur-containing heterocycles as well as to open-chain derivatives (Figure 1). This behavior has been interpreted in terms of a complex balance of various factors contributing to the ^{33}S chemical shift, among which the bond order term, in the case of three-membered rings, is the most important one[62].

C. Synthesis

The syntheses of thiiranes may be classified according to the last bond formed, when the main categories will be those where a carbon–sulfur or a carbon–carbon bond is the last bond formed. However, this classification requires knowledge of the correct reaction mechanism, which is sometimes not accessible. Hence, it may be more convenient to focus attention on the compound from which the thiirane derivative can be formed. Thus, we classify the syntheses of thiiranes according to the nature of the starting material used.

TABLE 4. ^{33}S chemical shifts (ppm) of thiirane (**1**), thiirane-1-oxide(**11**) and thiirane-1, dioxide (**12**)[a]



(**1**) (**11**) (**12**)

[a] CS_2 as internal standard.

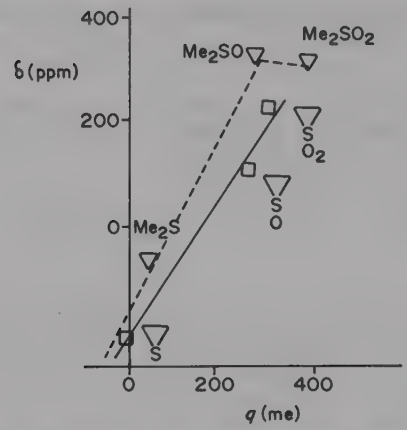
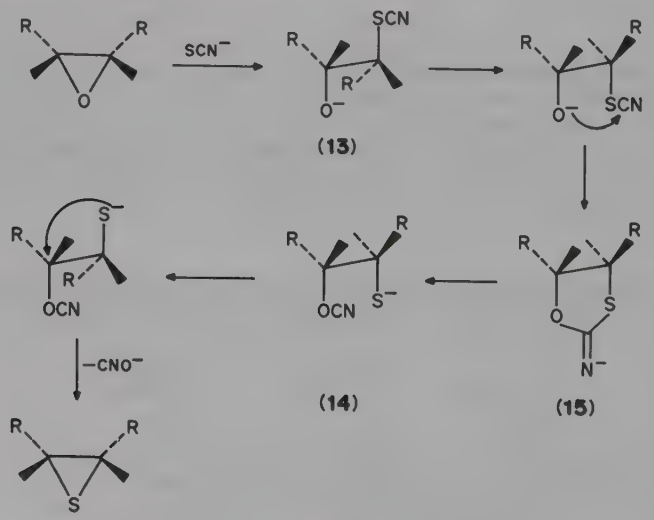


FIGURE 1. ^{33}S chemical shifts (ppm) of **1**, **11**, **12** and dimethyl disulfide, dimethyl sulfoxide and dimethyl sulfone against calculated charges on sulfur q (in millielectrons)[62].

1. *Thiiranes from oxiranes*

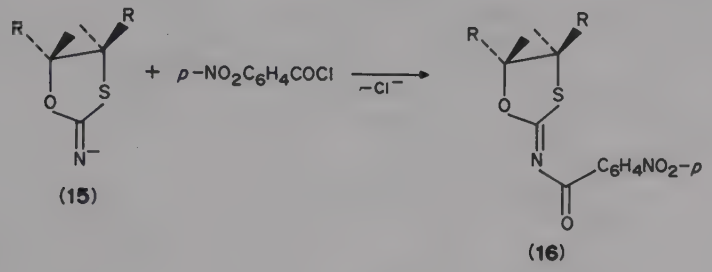
Several reagents containing an X=S functionality, in which the sulfur atom is nucleophilic enough to give ring opening of the epoxide and the group X contains an electrophilic center, have been used for the synthesis of thiiranes from epoxides. This is the case of thiocyanate ion[52–60, 63–77], thiourea and substituted thioureas [52, 57, 65, 66, 70, 78–98]. Other reagents which have a carbon–sulfur or a phosphorus–sulfur double-bond functionality, like 3-methylbenzothiazole thione[99,100], triazole-2-thione derivatives[101], triphenyl and tributylphosphine sulfide[102] and 1-phenyl-3,4-dimethyl-d^3-phospholene sulfide[103], have been successfully used. With these reagents the stereo-



SCHEME 1

chemistry of the oxirane is retained in the thiirane. This behavior has been explained assuming inversion at both carbons of the oxirane. The reaction sequence described in Scheme 1 is the generally accepted mechanism for the synthesis of thiiranes from oxiranes and thiocyanate ions.

The steps which control the stereochemical course of the reaction are the ring opening of the epoxide, occurring by an S_N2 mechanism with inversion at the carbon atom, which generates the intermediate **13**, the formation of the thiolate **14** through the oxathiolane **15**, and the subsequent ring closure to the thiirane derivative by nucleophilic displacement of the cyanate ion which also occurs with inversion of configuration. Indeed the oxathiolane derivative **15** has been trapped by acylation with *p*-nitrobenzoyl chloride to give **16**[60] (Scheme 2), and indirect evidence supporting the proposed mechanism arises from the finding that 1,2-hydroxyalkyl thiocyanates, under basic conditions, give the corresponding thiiranes[56, 68].



SCHEME 2

A similar mechanism has been proposed for the reaction of oxiranes with thiourea (Scheme 3). The isothiouronium derivative **17** can be isolated and purified as a salt of organic or inorganic acids; the thiirane derivative is then obtained by alkaline treatment of the thiouronium salt.

Usually, the reaction of oxiranes with thiourea gives a thiirane where the stereochemistry of the oxirane is preserved. However, in some instances contradictory results have been obtained[104]. In fact the reaction of *trans*-3-methylcyclohexene oxide **18** with thiourea gives *cis*-3-methylcyclohexene sulfide **19**[104] (Scheme 4). In this case steric effects can play a determining role in inverting the expected stereochemistry.

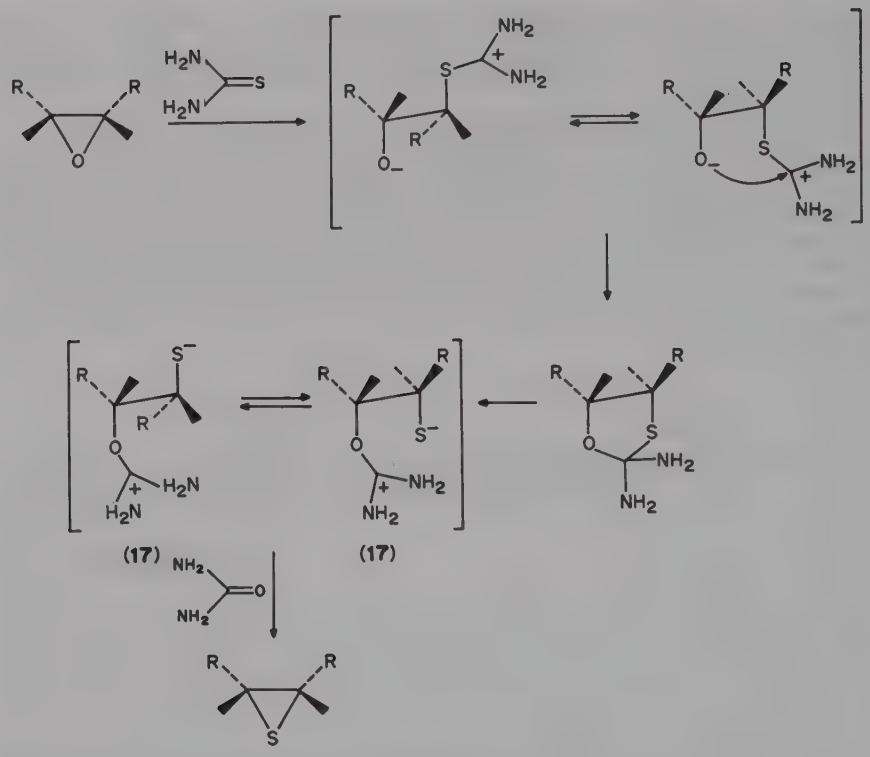
The reaction of phosphine sulfide derivatives[102, 103] with oxiranes needs acid catalysis and gives thiiranes with the same stereochemistry of the starting epoxides. The generally accepted mechanism for this reaction is reported in Scheme 5.

This mechanism accounts for the observed stereochemical course of the reaction and is also in agreement with the finding[102] that when an optically active phosphine sulfide was used, the recovered oxide was optically active with the same configuration as the starting sulfide.

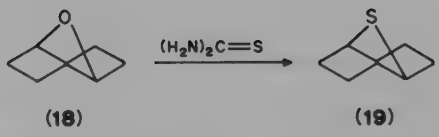
Another way to transform oxiranes into thiiranes is shown in Scheme 6 for the synthesis of the bis-thiirane **20** from the bis-oxirane **21**[104].

In this case the ring opening by thioacetic acid of the oxirane derivative gives the diol **22**, which has two protected thiol functions. The diol is then transformed into the tosylate **23**. In the last step the thiolate ions, generated by alkaline hydrolysis of the thioester functions of **23**, give rise to intramolecular nucleophilic substitution to yield the bis-thiirane **20**.

Other examples of synthesis of thiiranes from vicinal acetylthio tosylates, which however give low yields of cyclic sulfides, have been also reported[105].



SCHEME 3

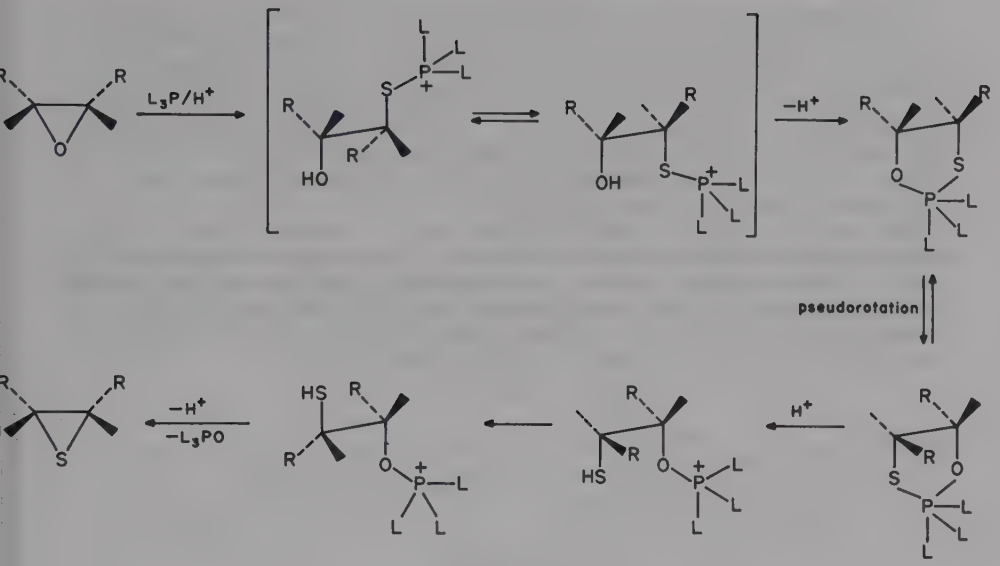


SCHEME 4

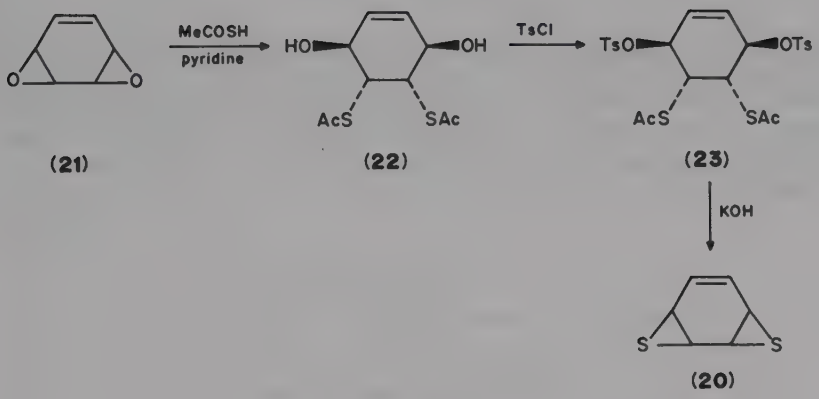
2. Thiiranes from olefins

In the following section, the direct oxidation of olefins into thiiranes by reaction with atomic sulfur will be taken into consideration, as well as reactions where the thiirane is obtained by means of simple transformations of suitable alkenes.

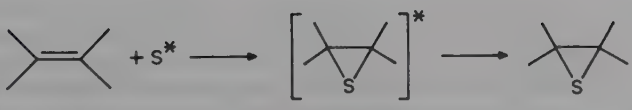
The direct oxidation of alkenes to thiiranes suffers from the lack of an easy source of atomic sulfur either in (^{1}D)S or (^{3}P)S excited states [106–108] (Scheme 7).



SCHEME 5



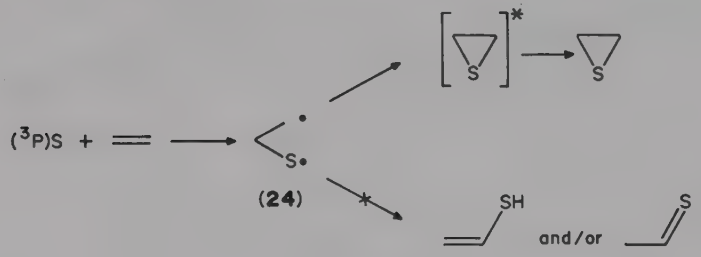
SCHEME 6



SCHEME 7

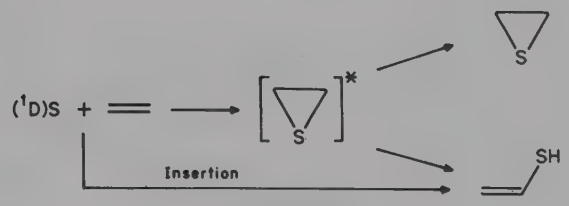
Excited sulfur atoms have been obtained in a number of different approaches, such as the heating of a mixture of H_2S and air at 410 °C in the presence of NaF–CSi as catalyst[109], electrical discharge through CS_2[110,111] and pyrolysis of diethyl tetrasulfide[107]. However, a more practical way to obtain excited sulfur atoms is vapor-phase irradiation[108,112] or electrical discharge[110,111] of carbonyl sulfide. The yields of thiiranes obtained from such species with olefins are usually not very high, because of the very low rate of conversion into the episulfide compared to the rate of decomposition of the three-membered ring in the reaction conditions[108,113,114].

The reactivity of both (^{1}D)S and (^{3}P)S, generated by irradiation of carbonyl sulfide, towards ethylene has been studied in argon matrix[112]. It has been demonstrated that (^{3}P)S reacts with ethylene affording thiirane as unique product. This result has been explained by the initial formation of the triplet biradical species **24**, which rearranges first to the thiirane in its excited triplet state and then to thiirane in the ground state without any decomposition to ethenethiol or thioacetaldehyde (Scheme 8).



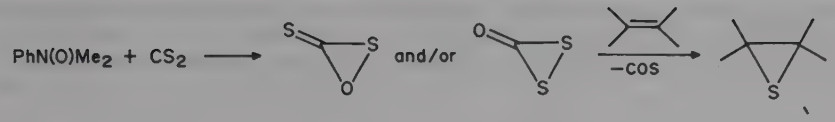
SCHEME 8

On the other hand, the reaction of (^{1}D)S with ethylene leads to the formation of both thiirane and ethenethiol. The formation of the latter can be due to the isomerization of vibrationally activated thiirane or to a direct insertion of (^{1}D)S into a C—H bond of ethylene, a process which has been demonstrated to be very sensitive to pressure[115] (Scheme 9).



SCHEME 9

Nevertheless, the direct oxidation of alkenes with atomic sulfur is synthetically not important, at least when one of the other common methods for the preparation of episulfides is accessible. Oxidation of a double bond with a sulfur atom can be performed also in solution. Moderate yields of thiiranes have been obtained by reaction of the tertiary amine *N*-oxide **25** with a large excess of carbon disulfide in the presence of an alkene[116] (Scheme 10).

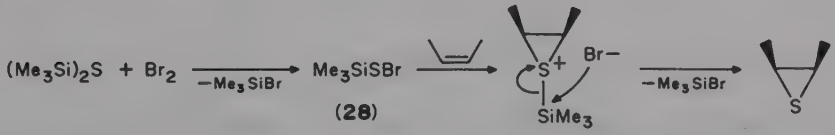


(25) (26) (27)

SCHEME 10

A mechanism involving the oxidation of carbon disulfide by **25** to both the cyclic species **26** and **27**, which in turn are able to transfer a sulfur atom to the alkene, has been suggested.

In a different approach, olefins are directly transformed into thiiranes by reaction with an unstable silylsulfenyl bromide[117] (Scheme 11).

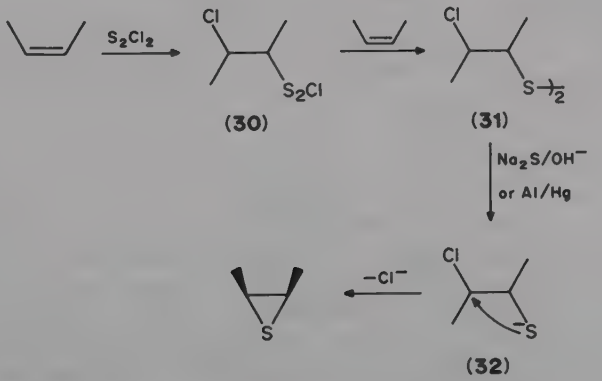


(28) (29)

SCHEME 11

Bromine with bis(trimethylsilyl)sulfide generates the trimethylsilylsulfenyl bromide (**28**), which reacts with olefins to give moderate yields of the corresponding episulfides with retention of configuration. The proposed mechanism involves the formation of the episulfonium ion **29** by attack of sulfenyl bromide on the double bond followed by the attack of bromide ion on the exocyclic silicon atom of **29** with formation of the episulfide and a second equivalent of trimethylsilyl bromide. The unusual attack of bromide ion at silicon rather than at carbon with ring opening is favored because of the low energy of the sulfur–silicon bond.

Several other methods involving electrophilic sulfur species and olefinic double bonds have been developed. Thus, addition of sulfur monochloride to olefins affords a mixture of mono- and polysulfides, the latter species being subsequently converted into thiiranes[118] (Scheme 12).

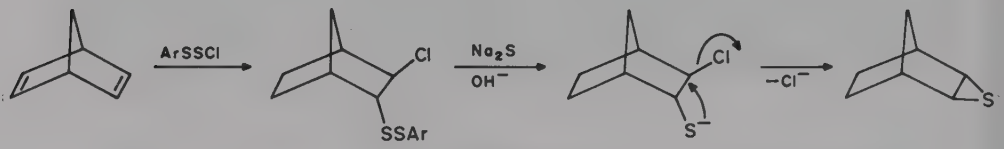


(30) (31) (32)

SCHEME 12

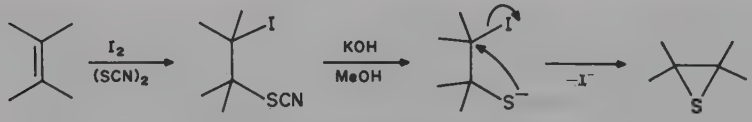
The accepted mechanism for this reaction involves attack of sulfur monochloride on the alkene with formation of the thiosulfenyl chloride **30**, which can react with a second molecule of olefin to give the dichloro disulfide **31**. Thiiranes were in turn obtained by treatment of **31** with sodium sulfide or with Al/Hg. Both the electrophilic attack of sulfur monochloride on the alkene and the intramolecular nucleophilic substitution affording the thiolate ions are *trans*-stereospecific, so that the geometry of the alkene is retained in the episulfide.

A closely related method is the reaction of a thiosulfenyl chloride with an alkene[119,120] (Scheme 13).



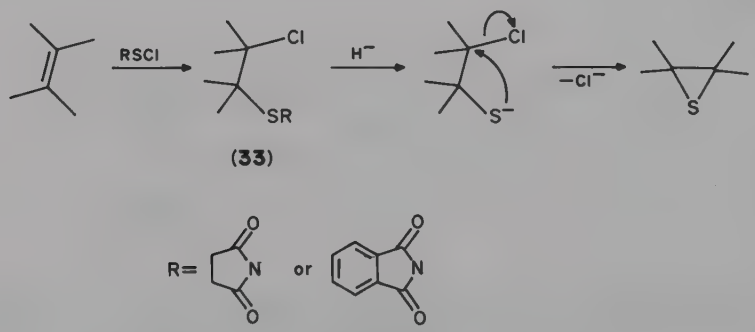
SCHEME 13

Among other approaches developed is the addition of acylsulfenyl chlorides to alkenes followed by basic hydrolysis[121], and the reaction of iodo thiocyanogen followed by basic treatment[122,123] (Scheme 14). Similarly, a chloro thiolate ion can be generated by hydride



SCHEME 14

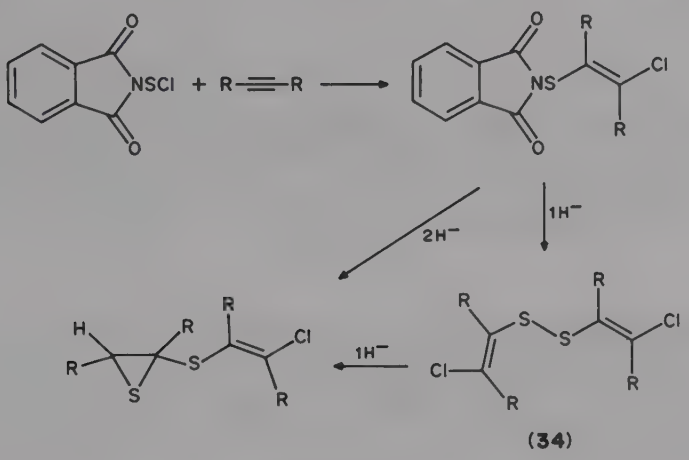
ion reduction of a sulfenamide of type **33**, which is simply prepared from addition of succinimidesulfenyl chloride or phthalimidesulfenyl chloride to suitable alkenes[124] (Scheme 15).



SCHEME 15

Due to the easy preparation and stability of these aminosulfenyl chlorides as well as the almost quantitative yield of both steps, this method is a most versatile way of transforming

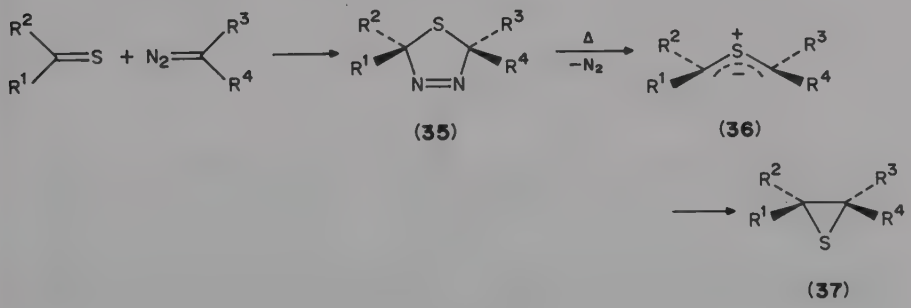
olefins into episulfides. Phthalimidesulfenyl chloride has also been successfully used for the synthesis of unusual vinylthiothiiranes starting from alkynes[125] (Scheme 16), where the disulfide **34** is the key intermediate.



SCHEME 16

3. Thiiranes from thiocarbonyl compounds

Thiocarbonyl compounds such as thioaldehydes, thioketones, thioesters or dithioesters can be transformed into episulfides. Probably the most versatile and widely used method of transforming a thiocarbonyl compound into a thiirane is the reaction with a diazo derivative[3,6–8,14–19] (Scheme 17).

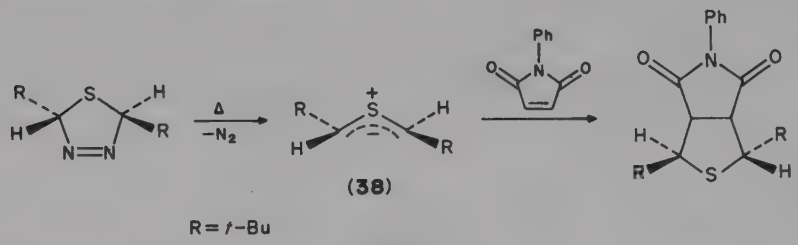


SCHEME 17

The most reasonable mechanism involves the formation of the 1,3,4-thiadiazolidine derivatives **35**, which are formed by cycloaddition of the thione to the diazo compound. The cycloadduct **35** thermally loses nitrogen to give the thiocarbonyl ylide **36**, which generates the episulfide **37** through a conrotatory 4π electrocyclic ring closure[126–134]. This mechanism has been fully demonstrated. First of all it has been possible to isolate the thiadiazolidine **35**, which in some cases is quite stable and gives **37** only in very drastic

reaction conditions[126]. Moreover, compounds of type **35** can be prepared following different routes and transformed into thiiranes by nitrogen extrusion[135,136].

The intermediacy of thiocarbonyl ylides **38** has also been proved by a trapping reaction with activated alkenes[126] (Scheme 18).

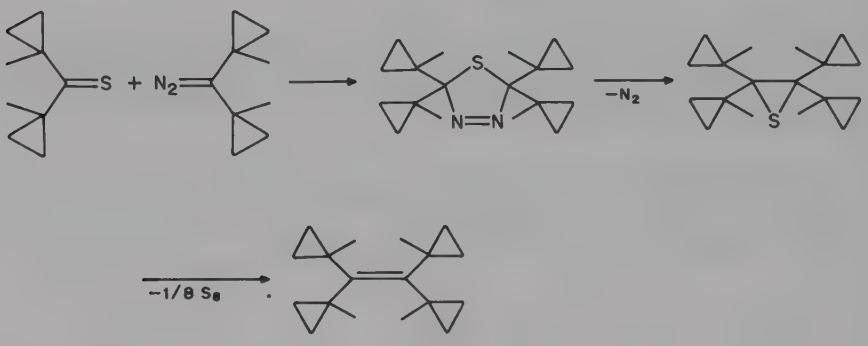


(38)

R = *t*-Bu

SCHEME 18

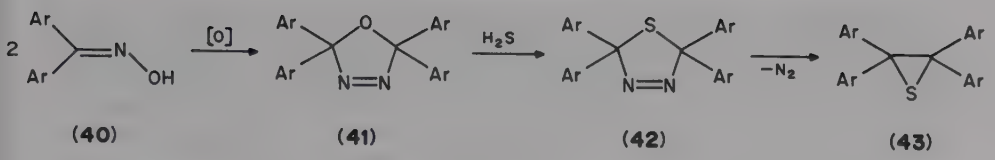
Finally, conrotatory ring closure of **36** has been clearly demonstrated by stereochemical studies[126]. While steric hindrance seems to be the most important factor in the formation of *cis*- or *trans*-thiazolidines **35** from thiones and diazo compounds, the reverse geometry has been observed for the thiirane (Scheme 17). This feature has been utilized for simple syntheses of very hindered thiiranes, which give the corresponding olefin by desulfurization[126,137–144]. An example of this strategy applied to the synthesis of the tetracyclopropyl ethylene derivative **39** is shown in Scheme 19[145].



(39)

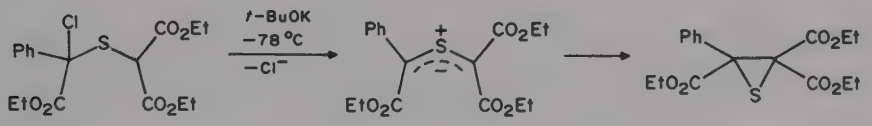
SCHEME 19

The synthesis of thiiranes from the reaction of thiones and diazo compounds in most of the cases gives very good results. Thioketones, halo-substituted thioketones[146], thiocarbonates[134,147–149], thioesters and dithioesters[150] have been successfully used. The versatility of the method is enhanced by the fact that the synthesis of **35** can be achieved by other routes[135,136] avoiding the use of diazo compounds and the often unpleasant smelling thioketones. For instance, **35** can be prepared by hydrogen sulfide treatment of the corresponding oxygen heterocycle (Scheme 20). Oxidation of the oxime **40** gives rise to the oxadiazolidine **41**, which by hydrogen sulfide is transformed into the unstable thio derivative **42**. Spontaneous nitrogen elimination from **42** allows the isolation of the thiirane **43**[135].



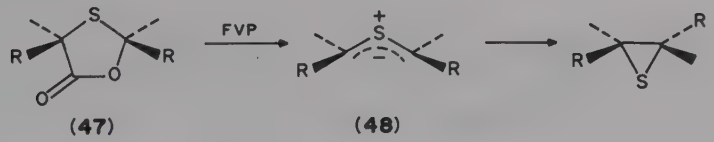
SCHEME 20

The equilibrium between thiocarbonyl ylides and episulfides has been used for the preparation of the latter. This equilibrium is strongly influenced by the electron-withdrawing character of the substituents[151–153], so that in the case of ylide **44** (Scheme 21) the 'push–pull' equilibrium between **44** and **45** is quantitatively shifted toward the episulfide **45**, which can thus be simply prepared by basic treatment of the sulfide **46**[154].



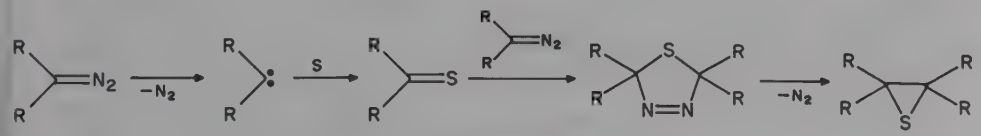
SCHEME 21

In a different approach carbon dioxide extrusion from 1,3-oxathiolan-5-ones of type **47** in flash vacuum pyrolysis (FVP) conditions leads to the thiiranes with inversion of configuration (Scheme 22)[152,153].



SCHEME 22

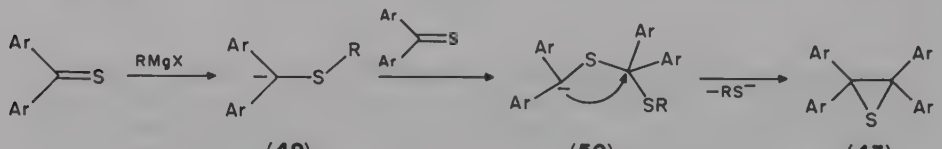
While the intermediacy of carbenoid species can be reasonably ruled out in the reaction of diazo compounds with thiones, such reactive species have been proposed in the synthesis of episulfides from diazo compounds and elemental sulfur[155–157] (Scheme 23). This reaction, which is accelerated by UV irradiation, may involve the formation of a carbene by nitrogen extrusion from the diazo compound, followed by the reaction of the carbene with sulfur to give the corresponding thione, and the subsequent formation of a 1,3,4-thiadiazolidine which decomposes to a thiirane.



SCHEME 23

Another general method for the preparation of thiiranes starting from thiocarbonyl compounds is their reaction with nucleophiles[3,7,8,14–19]. Both carbophilic and thiophilic attack of the nucleophile on the thione may lead to the synthesis of episulfides. Organometallic reagents are among the most common nucleophiles used for this purpose.

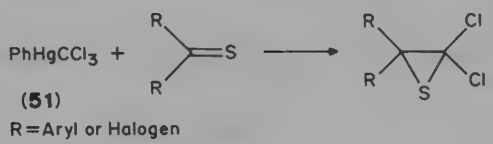
Aryl substituted episulfides of type **43** can be conveniently prepared by reaction of the corresponding diaryl thioketone with a Grignard reagent[158,159] (Scheme 24). It is interesting to note that the substitution of the three-membered ring formed depends only upon the substitution of the thioketone, and the organomagnesium reagent is important only for determining the yield of the reaction. The mechanism outlined in Scheme 24 involves the thiophilic attack of the organometallic reagent on the thione with formation of the anion **49**, which in turn may interact with another molecule of thione affording the new carbanion **50**, which gives the thiirane derivative by intramolecular nucleophilic substitution.



SCHEME 24

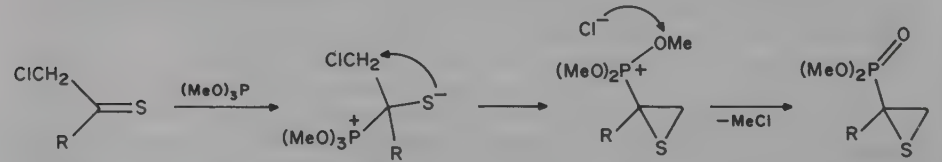
Modifications of this method are the reactions of thiones with metallic magnesium, with magnesium iodide[160] or with a sodium acetylide[161]. However, in all these cases the yields are lower than those obtained using Grignard reagents.

Polyhalogenated thiiranes can be easily prepared from an organomercurial species of type **51** with thioketones[162,163] (Scheme 25). **51** is reported to be effective for the synthesis of thiiranes by reaction with elemental sulfur[162,163].



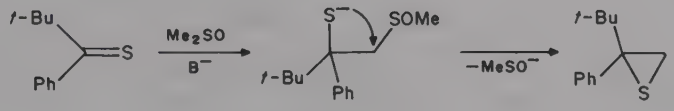
SCHEME 25

Other nucleophiles, such as trimethyl phosphite, also react with thioketones of type **52** (Scheme 26) leading to phospho-substituted thiiranes **53** through the formation of thiophosphonium salt **54**. The latter, by internal nucleophilic displacement of chloride, gives the substituted phosphonium salt **55**, Arbuzov reaction of which affords the phospho-substituted thiirane **53**[164].



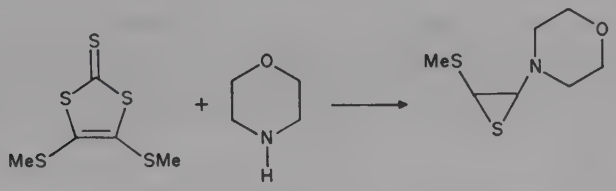
SCHEME 26

A similar mechanism seems to be operative also in the formation of disubstituted thiiranes from the reaction of a non enolizable thione like *t*-butyl phenyl thioketone and dimethyl sulfoxide under basic conditions[165] (Scheme 27).



SCHEME 27

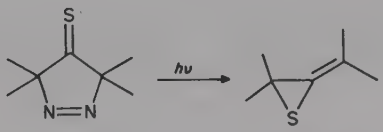
Finally, a moderate yield of the hetero-substituted thiirane **56** has been obtained by reaction of morpholine with 1,3-dithiole-2-thione **57**[166] (Scheme 28).



(57) **(56)**

SCHEME 28

Thiones have been also used for the synthesis of vinyl substituted episulfides. For example, the episulfide **58** was obtained in 36% yield by irradiation of the diazothione **59**[167] (Scheme 29).



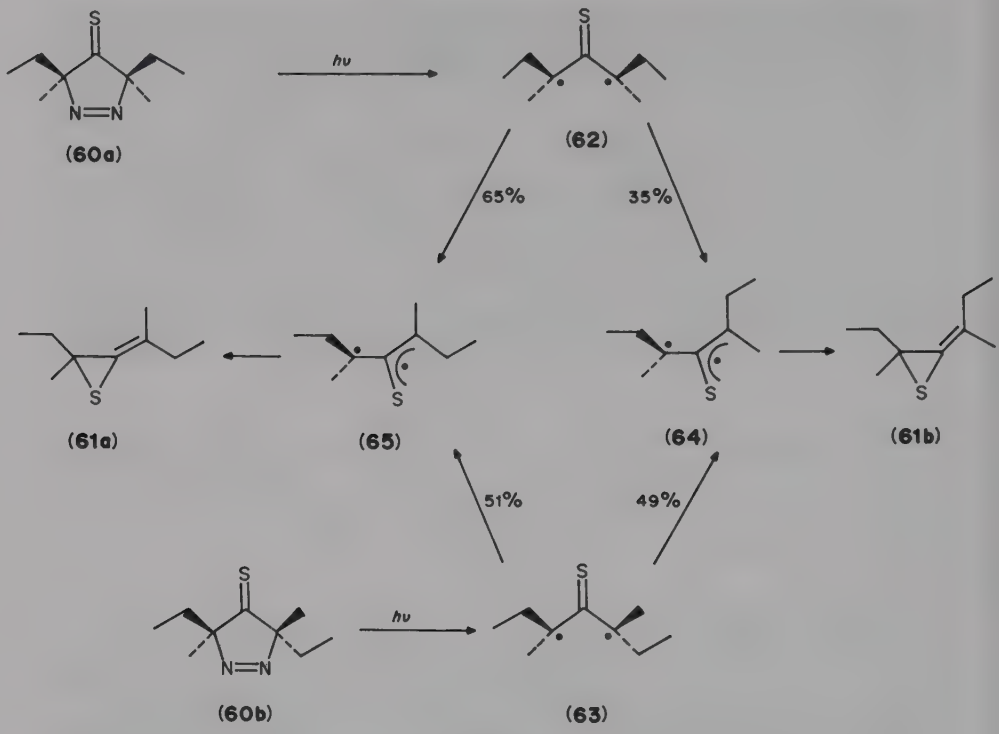
(59) **(58)**

SCHEME 29

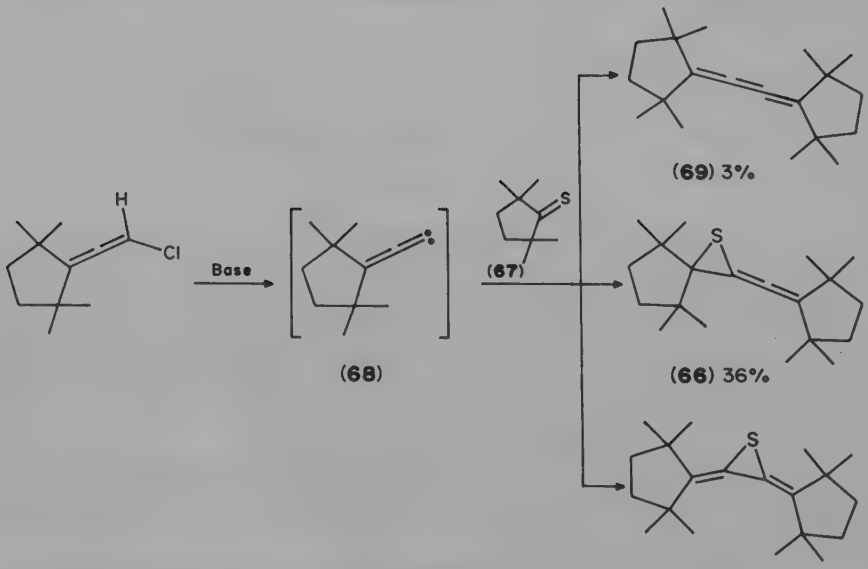
A detailed study of the reaction of diazothiones **60a** and **60b** led to the reaction mechanism shown in Scheme 30[168]. Irradiation of *cis* and *trans* diazo derivatives **60a** and **60b** leads to the quantitative elimination of nitrogen with the formation of equimolar amounts of *Z* and *E* episulfides **61a** and **61b** starting from *trans* diazo thione **60b**, while a 65:35 mixture of *Z*:*E* **61** was obtained from the *cis* diazo thione **60a**.

The initial formation of two different diradical species **62** and **63**, respectively, from *cis* and *trans* **60** has been suggested. These species rearrange to the delocalized diradicals **64** and **65**, which collapse to *E* and *Z* thiirane **61**. The ratio of formation of **64** and **65** reflects the ratio of the *E* and *Z* episulfides **61**.

The 1,2,3-butatriene-1-episulfide **66** has been obtained from the thioketone **67** and the carbene **68**[169] (Scheme 31).

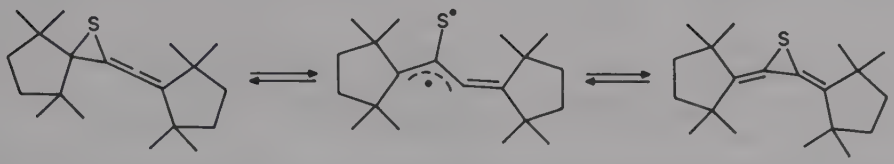


SCHEME 30



SCHEME 31

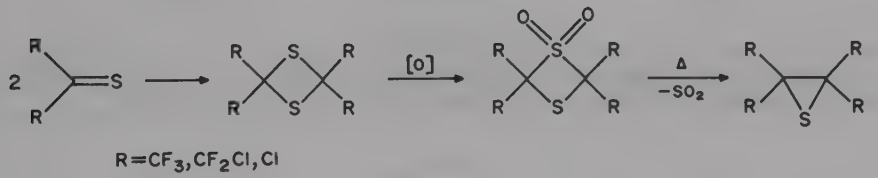
Small amounts of the triene **69** and of the episulfide **70** were also observed. While the formation of **69** is simply rationalized by desulfurization of thiiranes **66** and/or **70**, the formation of 1,2,3-butatriene-2-episulfide **70** has been explained by a thermal rearrangement of **66** through the diradical species **71**[169] (Scheme 32).



(66) **(71)** **(70)**

SCHEME 32

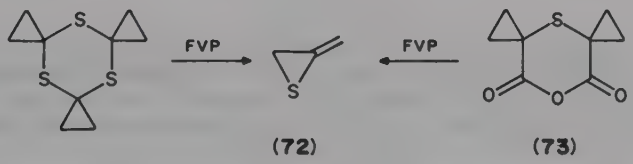
Dimers and trimers of thiocarbonyl compounds have been also used for the synthesis of thiiranes. Halogen substituted thioketones easily generate the corresponding dimers, which have been transformed into polyhalogenated episulfides by oxidation to 1,3-thiolane-1,1-dioxides. Thermal sulfur dioxide extrusion gave the thiirane derivatives[133,170,171] (Scheme 33).



R=CF_3, CF_2Cl, Cl

SCHEME 33

Finally, the trimer of cyclopropyl thioketone can be converted into methylidene episulfide (**72**) by thermolysis at low pressure[172] (Scheme 34). The episulfide **72**, which is stable only in cold dilute solution, can also be prepared from the thio-substituted cyclic anhydride **73**[147].



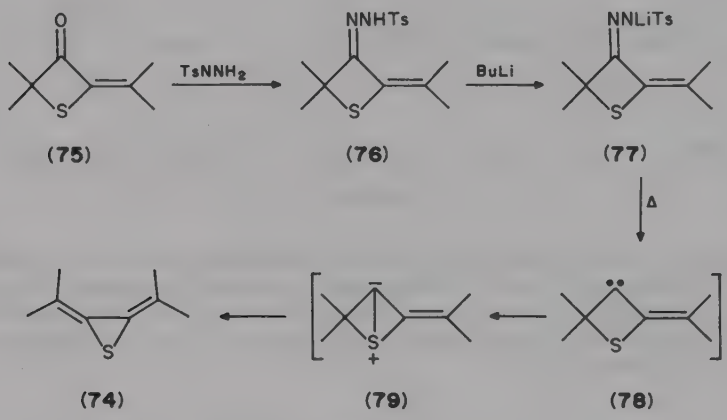
(72) **(73)**

SCHEME 34

4. Thiiranes from heterocycles

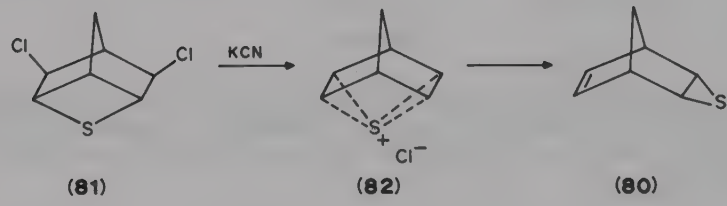
Some of the thiirane syntheses starting from heterocyclic compounds have been already described in other sections of this chapter, but a few different strategies using four- or five-membered ring heterocycles deserve to be also mentioned[5].

a. Thiiranes from four-membered heterocycles. The thiirane **74** can be synthesized by treatment of the thietanone **75** with tosylhydrazine and subsequent deprotonation of the tosylhydrazone **76** with butyllithium to give **77**. Thermolysis of **77** generates the carbene **78**, which evolves to the bicyclic ylide **79**. Rearrangement of the ylide **79** gives the thiirane **74**[173,174] (Scheme 35).



SCHEME 35

The bicyclic thiirane **80** can be obtained from the reaction of the dichlorothietane derivative **81** with potassium cyanide[175] (Scheme 36).



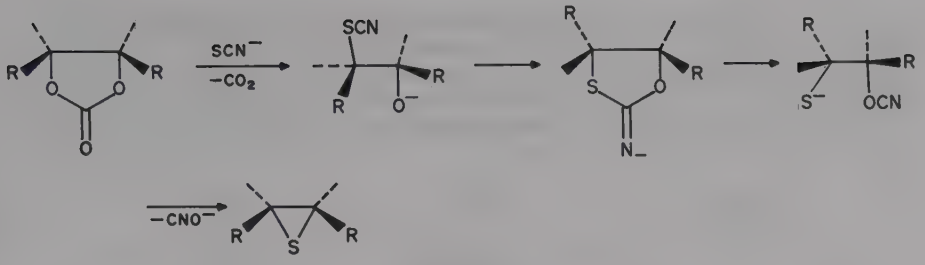
SCHEME 36

The intervention of the nonclassical cation **82** as intermediate in this reaction seems very reasonable. The latter gives the bicyclic thiirane **80**, which is not easily prepared following conventional routes. Other examples of syntheses of bicyclic episulfides with the intervention of nonclassical cations are reviewed in other sections of this chapter.

b. Thiiranes from five-membered heterocycles. Although 1,3,4-thiadiazolidines and oxazolidines are the most common synthons used, other approaches for the preparation of thiiranes involving five-membered ring heterocycles have been reported.

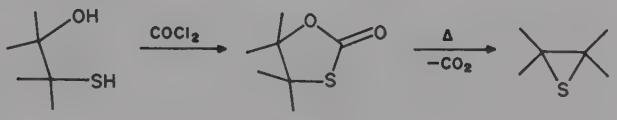
Cyclic carbonates can be easily converted into thiiranes in the presence of thiocyanate ions[176,177] (Scheme 37).

The proposed mechanism is very similar to that described for the reaction of thiocyanate ions with epoxides (see Scheme 1), and involves a double Walden inversion, so that retention of configuration from the carbonate to the episulfide is observed[6,8,176–178]. On the other hand mono-, di- and trithio carbonates are transformed into thiiranes simply by



SCHEME 37

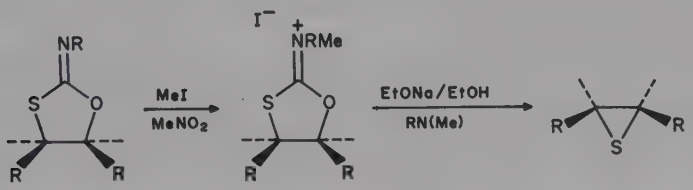
heating[179,180]. Due to the easy synthesis and the high stability of monothio carbonates **83**, these compounds have been largely used as useful thiirane precursors[179] (Scheme 38).



(83)

SCHEME 38

Reaction of 2-amino-1,3-oxathiolanes (**84**) with methyl iodide in nitromethane followed by sodium ethoxide treatment of the methyliminium salts **85** generates the thiirane derivatives **86**[181] (Scheme 39).



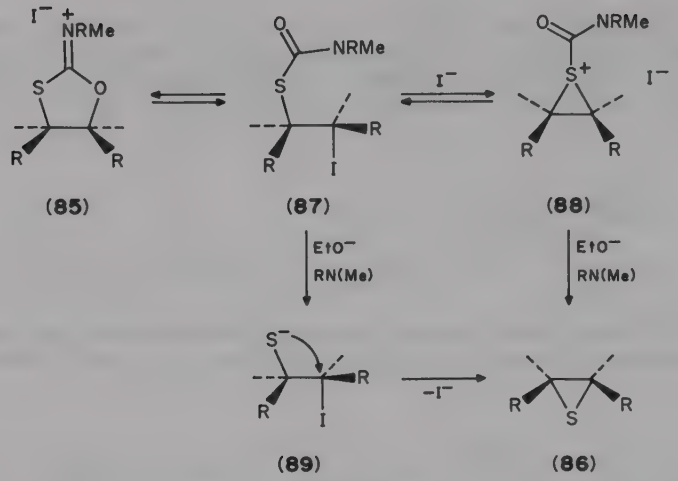
(84) **(85)** **(86)**

SCHEME 39

The mechanism of this reaction (Scheme 40) seems to involve the initial formation of the iodo thiocarbamate **87** by iodide attack on the oxygen substituted carbon of iminium salt **85**. In turn **87** affords the thiirane **86** through the episulfonium iodide **88** or through the iodo thiolate **89**. Both these mechanisms are in agreement with the global retention of configuration observed in this reaction[181].

5. Thiiranes from acyclic compounds

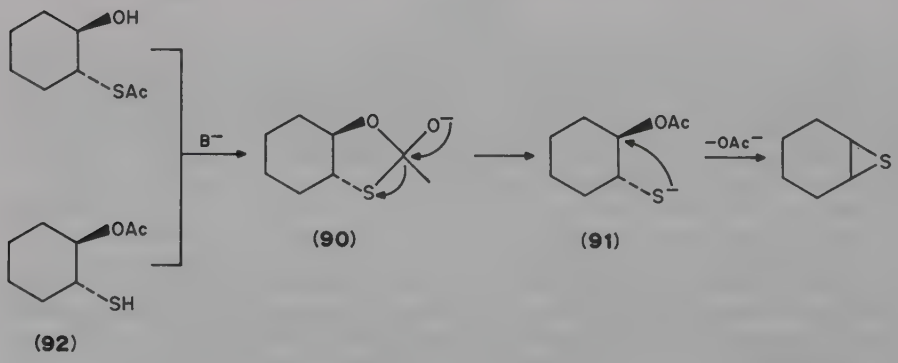
The most common strategy for the preparation of episulfides from acyclic compounds involves the formation of a thiol or a thiolate ion bearing a suitable leaving group in the β-position. In such systems intramolecular nucleophilic substitution leads to the formation of thiiranes[3,6–8,14–19]. In this section the most important examples of this synthetic approach will be discussed.



SCHEME 40

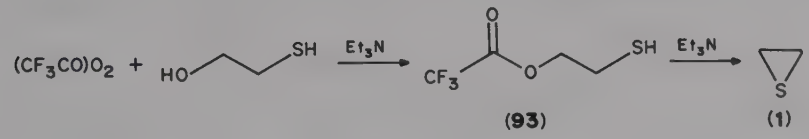
a. Oxygen as leaving group. Even though the direct conversion of β-hydroxy thiols into thiiranes has been reported in a special case[182], this reaction does not usually occur. One or both of the thiol and hydroxy groups have to be activated in order to obtain the episulfide. Among the substituted β-hydroxy thio derivatives *S*-acetyl[105,183], *O*-acetyl[105,183], *S,O*-diacetyl[105,183–185], *O*-carbamates[105], *O*-carbonates[105], *O*-tosylates[105] or *O*-mesylates[105] have been successfully employed for the preparation of thiiranes. Usually, these reactions are performed by heating the substrate in basic media and distilling off continuously the formed episulfide in order to avoid thermal decomposition and base-catalyzed polymerization.

The formation of thiirane derivatives from the reaction of *S*-acetyl β-hydroxythiols suggests that, in this reaction, the first step is the base-catalyzed formation of the cyclic intermediate **90** (Scheme 41), which rearranges to the thiolate **91**. The latter gives the thiirane derivative by intramolecular nucleophilic acetate displacement. The intervention of **90** in the synthesis of thiiranes from the *O*-acetyl thiol **92** has also been suggested.



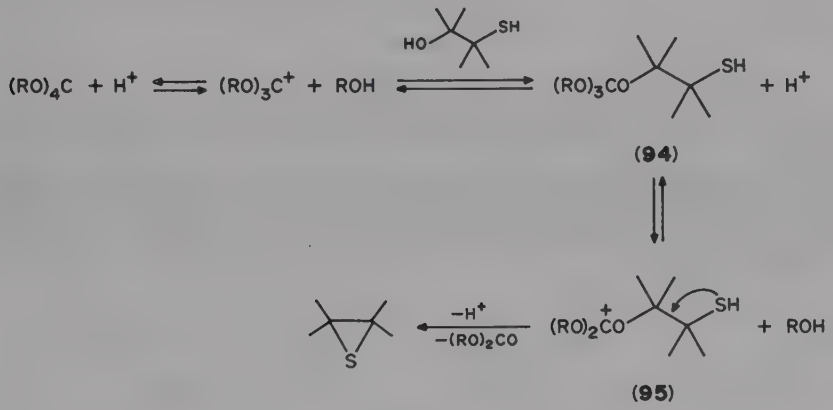
SCHEME 41

This method suffers from the easy decomposition of the episulfides in the reaction medium, especially when a very low molecular weight thiirane has to be prepared. An easy modification which minimizes the risk of decomposition and polymerization for the preparation of thiirane itself starts from 2-mercaptoethanol, when the formation of the trifluoroacetate **93** and the use of diglyme as solvent allowed the isolation of **1** in good yields[186] (Scheme 42).



SCHEME 42

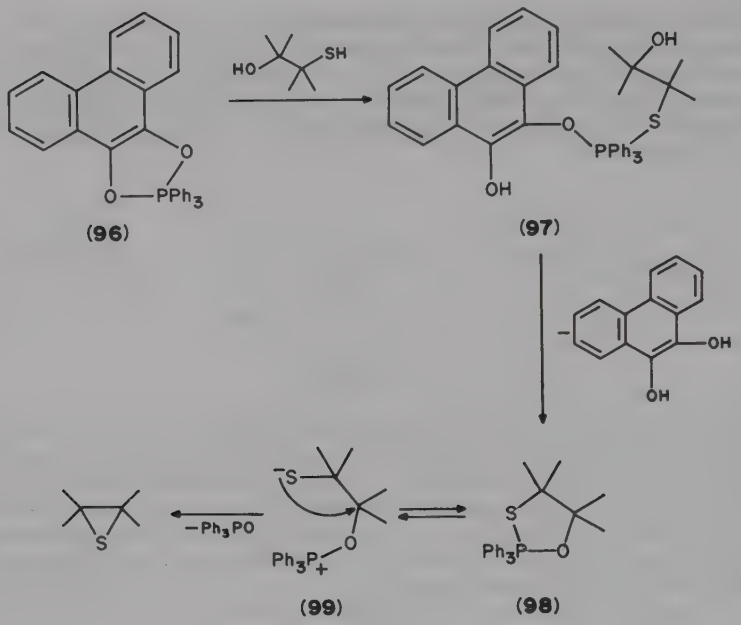
Episulfides have also been prepared by acid-catalyzed reaction of a 2-mercapto alcohol with tetraalkyl carbonates[187] (Scheme 43). The use of apolar solvents such as chloroform or dichloromethane, and acid catalysts like *p*-toluenesulfonic acid, trichloroacetic acid or boron trifluoride etherate gives quantitative yields of the thiirane derivative. The mechanism involves formation of the mixed orthocarbonate **94** which, in the acid medium, yields the carbocation **95**. Attack of the mercapto group of **95** at the activated β-position leads to the formation of the thiirane derivative.



SCHEME 43

Organophosphorus compounds have also been used for the transformation of hydroxy thiols into the corresponding thiiranes[188,189]. Among the various phosphorus compounds tested, 2,2,2-triphenyl-4,5-(2′,2″-biphenylene)-1,3,2-dioxaphospholene (TDP) (**96**) has been found to be very effective in transforming 1,2-mercaptoalcohols into thiiranes[188] (Scheme 44). The proposed mechanism involves the formation of the penta-substituted phosphorous intermediate **97**, which in turn gives the cyclic derivative **98** that is in equilibrium with the phosphonium salt **99**. Nucleophilic attack of the thiolate ion at the β-position generates the episulfide with elimination of triphenylphosphine oxide.

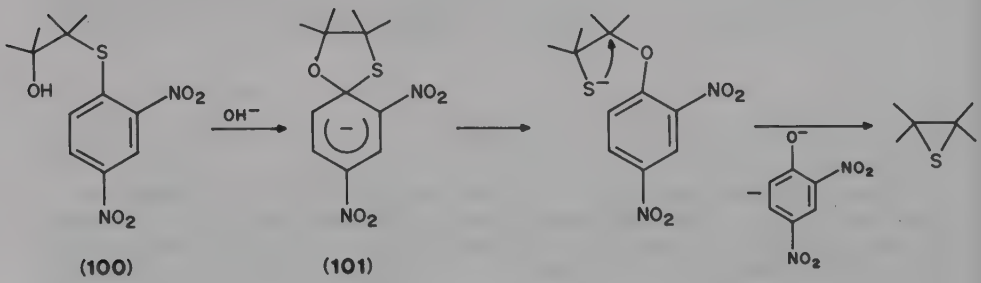
TDP **96** is able to convert suitable mercaptoalcohols into the corresponding sulfur-containing rings. A general mechanism for this reaction is shown in the section dedicated to the synthesis of thiolanes and thianes.



SCHEME 44

Thiiranes can also be synthesized from 2-hydroxyalkyl halides and thiourea[190]. This reaction is quite similar to the already described synthesis of episulfides from epoxides and thiourea.

Other species which are able to give episulfides are hydroxy derivatives of type **100**[191] (Scheme 45). Alkaline hydrolysis of **100** affords the corresponding thiirane probably through the formation of Meisenheimer intermediates **101** followed by elimination of 2,4-dinitrophenoxy ion.

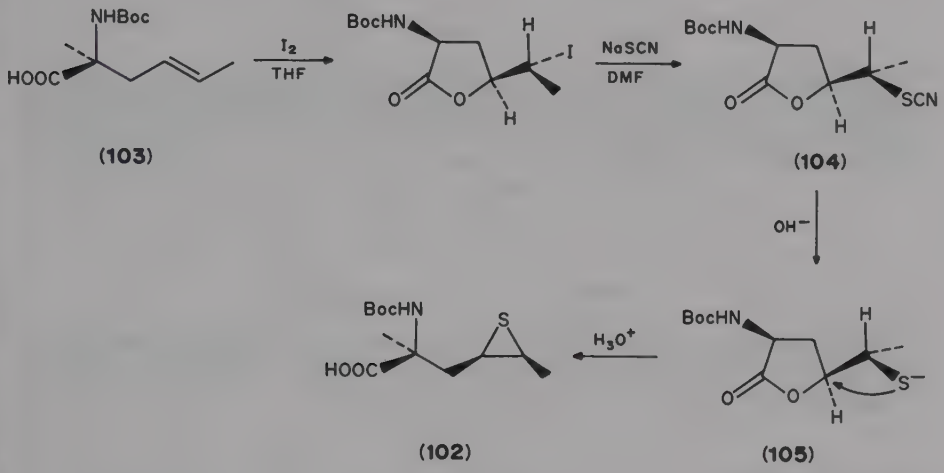


SCHEME 45

β-O-substituted alkyl thiocyanates can be considered precursors of thiirane derivatives. In fact alkaline hydrolysis of these species generates a thiolate ion suitable for ring closure to thiirane derivatives[56,192–195]. This reaction is very sensitive to the nature of the *O*-substituted leaving group. Usually mesyloxy or benzyloxy derivatives are the reagents

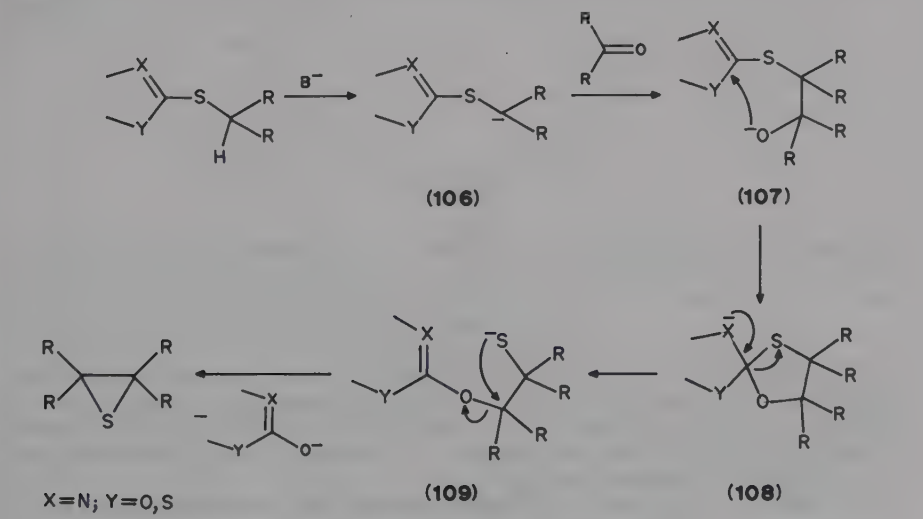
of choice, and were used in the synthesis of sugars[196,197] or steroids[195,198,199] containing thiirane rings.

Recently, this approach has been used for the preparation of both stereoisomers of **102**, an episulfide analogue of L-methionine[200] (Scheme 46). The complete reaction scheme involves iodolactonization of the crotyl glicyne derivative **103** followed by nucleophilic displacement of iodide by thiocyanate to give **104**. Alkaline hydrolysis of **104** generates the thiolate ion **105**, in which thiolate ion attack occurs with opening of the lactone ring to give the episulfide **102**.



SCHEME 46

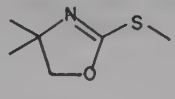
Aldehydes and ketones with suitable sulfur-stabilized carbanions also yield thiirane rings[201–206]. The general mechanism proposed for this reaction is described in Scheme 47.



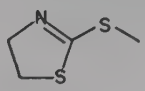
SCHEME 47

Attack of the carbanion **106** on carbonyl derivatives gives the oxyanion **107**, which generates the oxathiolane **108**. Rearrangement of **108** gives the thiolate ion **109** that easily forms the thiirane derivative.

The most common thio-substituted carbanion precursors are the oxazoline **110**[202,207,208] and the thiazoline **111**[209].

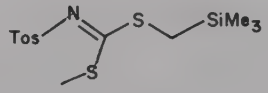


(110)

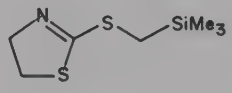


(111)

From these the carbanion is usually obtained by means of strong bases such as LDA or butyllithium. A recent paper describes the use of methylthiotrimethylsilyl derivatives like **112** or **113** as carbanion sources[210].

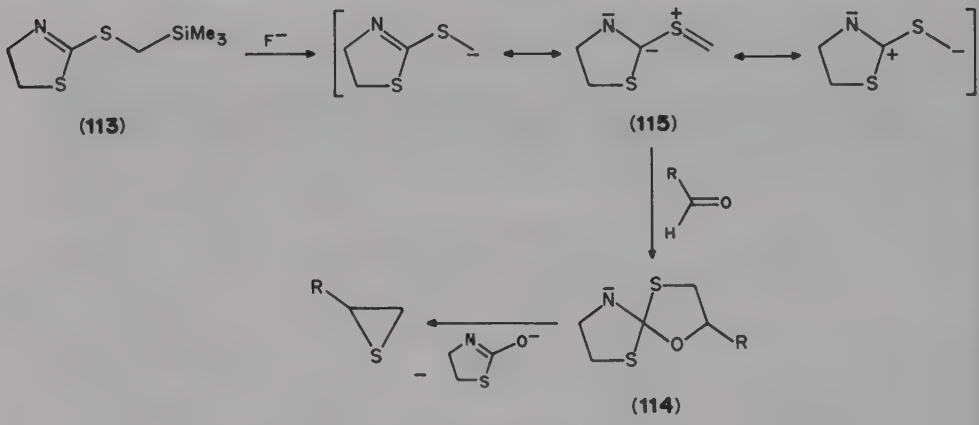


(112)



(113)

The anion is obtained by fluoride ion treatment of either **112** or **113** (Scheme 48), and the formation of the oxathiolane intermediate **114** is suggested to occur via a 1,3-dipolar cycloaddition of the anion **115** to the carbonyl compound.

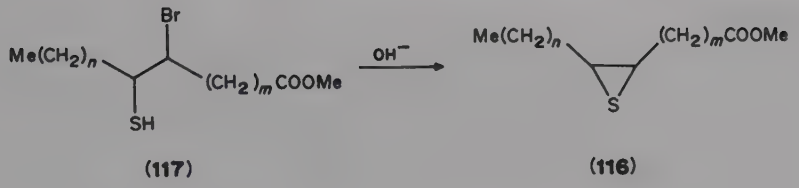


(113) (115) (114)

SCHEME 48

b. Halogen as leaving group. β-Halomercaptans are unstable compounds which yield thiiranes by simple alkaline hydrolysis. Due to their instability they are usually not isolated, but directly transformed into episulfides. The simplest synthesis of β-chloro mercaptans is by hydrochloric acid treatment of 2-mercaptoalcohols. Thiiranes are then obtained by smooth alkaline hydrolysis[211–214].

The preparation of fatty acid episulfide derivatives of type **116** starting from the bromo thio esters **117**[215–217] has been also reported (Scheme 49).

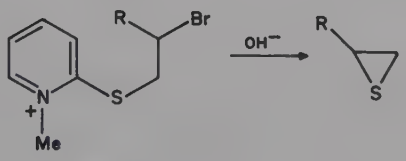


(117) (116)

$n=m=7$; $n=10, m=4$

SCHEME 49

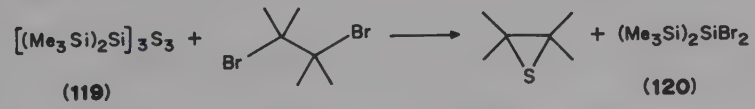
As described above, alkaline hydrolysis of β-halothiocyanates also gives thiiranes[180,197,218,219] (see Scheme 14). This method was used in 1920 for the first preparation of thiirane (**1**)[220]. An efficient synthesis of thiiranes which can be used also for the preparation of larger sulfur-containing rings is the alkaline hydrolysis of pyridinium salts **118**[221] (Scheme 50).



(118)

SCHEME 50

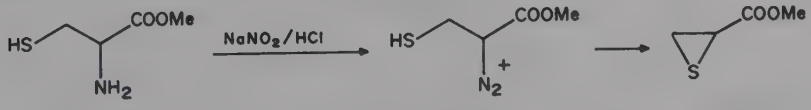
The direct conversion of dihalo derivatives with an appropriate sulfide ion source is a strategy often employed for the preparation of medium-size cyclic sulfides, but it cannot be usually used for thiiranes since extensive polymerization occurs[220]. However, the silyl trisulfide **119** has been successfully used as sulfide ion carrier in reactions with 1,2-dibromo derivatives. The reaction gives the corresponding episulfide and the bromosilane **120**[222] (Scheme 51).



(119) (120)

SCHEME 51

c. Nitrogen as leaving group. It is possible to use 2-mercaptoamines as episulfide precursors. The cysteine derivative **121** when treated with sodium nitrite in acid conditions generates the corresponding diazonium salt **122**, which decomposes to give the carbomethoxy-substituted thiirane **123**[223] (Scheme 52).



(121) (122) (123)

SCHEME 52

D. Reactivity

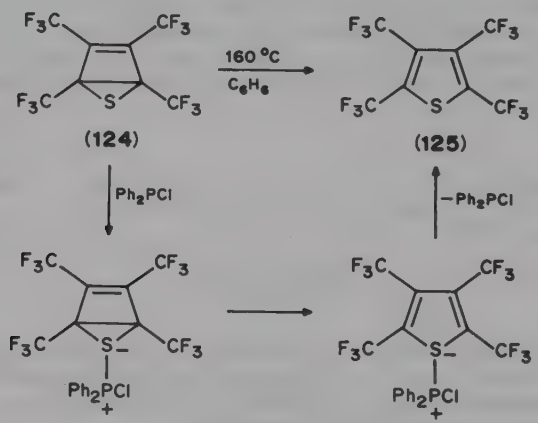
Thiiranes can easily react with a wide number of reagents, which generally induce opening of the ring. The ring-opened species can further give fragmentation, isomerization or desulfurization, or can react with other species affording the final products.

The reactivity of thiiranes is very close to that of oxiranes, however structural properties and physical parameters of the two classes differentiate their behavior. Thus the lower reactivity of cyclic sulfides compared to that of oxiranes towards electrophilic reagents can be adequately explained, considering the electron density at the heteroatom and the polarity of the carbon–heteroatom bond which are smaller in thiiranes, than in oxiranes.

Although no detailed studies on the reactivity of thiiranes, compared with that of oxiranes towards nucleophiles, have been reported, the former can be considered quite similar or a little higher than that of the latter. Reactions which involve ring opening are generally easier with thiiranes than with oxiranes. For instance, the thermal desulfurization of cyclic sulfides is faster than deoxygenation of oxiranes. In this case the lower ring strain in thiiranes is overruled by the lower bond energy of the C—S bond with respect to that of C=O bonds.

1. Isomerization

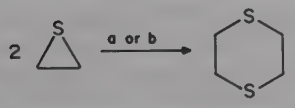
The reaction of potassium thiocyanate with substituted thiiranes in DMF or in water–ethanol is a common and efficient method for the *cis–trans* isomerization of three-membered cyclic sulfides. Yields depend upon the nature of the starting sulfides and can vary between 14% and 65%[80,224,225]. In the case of the 'Dewar thiophene' **124**, the isomerization to the corresponding thiophene **125** occurs with triphenylphosphine or diphenylphosphine chloride[226], or thermally at 160 °C (Scheme 53).



SCHEME 53

2. Dimerization

The dimerizaion of thiirane (**1**), which affords the dithiane **126**, requires quite drastic reaction conditions[227,228] (Scheme 54).



(1) (126)

(a) Al_2O_3, 220 °C (94%)
(b) Pt, $PdCl_2$/CO, 60 atm

SCHEME 54

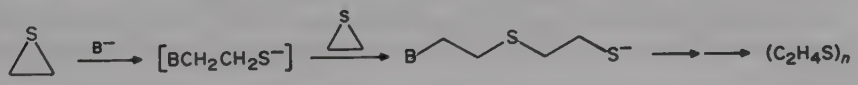
The thermal treatment of propene sulfide in the presence of *p*-toluenesulfonic acid similarly allows synthesis of the 2,5-dimethyl-1,4-dithiane[229].

3. Polymerization

The polymerization of thiiranes is the subject of many publications, monographs and patents. The mechanism and kinetics of anionic polymerization of episulfides[230], stereoselective and asymmetric selective polymerizations[231–234] and the use of the episulfides in polymer synthesis[235] have received particular attention.

Thiiranes undergo easy polymerization, even in the absence of initiators. Even when stored at room temperature, they gradually form a powder of polymerized products, which are insoluble in commonly used solvents[236]. This is why ethylene sulfide (1) was synthesized as monomer only eighty years later than the first publication on the isolation of its polymer. The early attempts, consisting of the treatment of ethylene bromide with potassium sulfide or sodium sulfide, gave only polymerized products[237–239]. The amorphous polymer obtained has been isolated and characterized either as a modification which depolymerizes and which is converted to dithiane upon heating, or as a modification which does not depolymerize. It has been demonstrated that the polymer which gives the dithiane is obtained from the reaction with sodium sulfide, and contains some halogen combined organically[237].

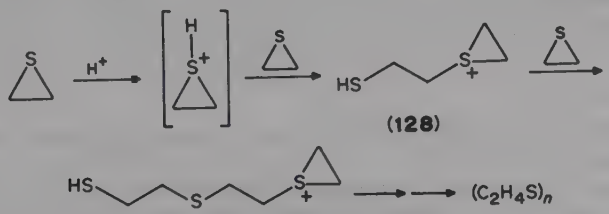
Thiirane polymerization is generally accomplished under base or acid catalysis, the former being the faster. This is due to the high nucleophilicity of the thiolate ion **127** formed during the base-catalyzed polymerization of the thiirane ring (Scheme 55).



(127)

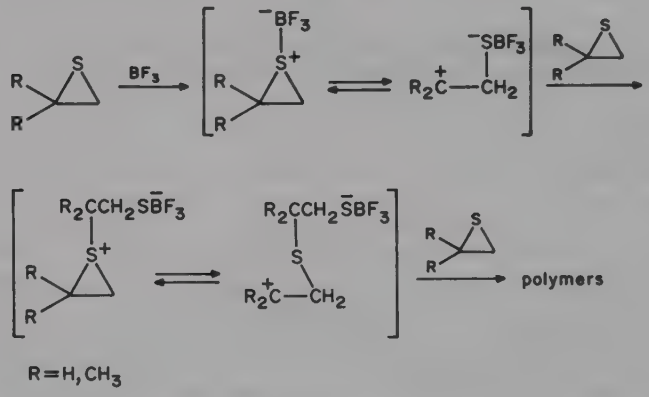
SCHEME 55

Scheme 56 shows the accepted mechanism for the acid-catalyzed polymerization of thiirane.



SCHEME 56

The nucleophilic ring-opening of the thiirane by the thiolate intermediate **127** (Scheme 55) is easier than the breaking of the C—S bond of the thiiranium intermediate **128** by the thiirane sulfur in the acid-catalyzed polymerization (Scheme 56), which makes the former process faster and more efficient. Good basic initiators of the polymerization are ammonia, pyridine, piperidine, primary amines, hydrazine, sodium hydroxide and ethylenediamine. The polymers obtained have molecular weights below 1000[90,240]. Initiation by Lewis acids has been also used. Thus catalysis by boron trifluoride produces a polymer according to Scheme 57[241].



SCHEME 57

Methyl and ethyl thiiranes show a low tendency to polymerize and can be stored for several months at room temperature[242]. No polymerization was observed even in the presence of acetic, hydrochloric or nitric acid[197], and the use of alkali or ammonia produces only slow polymerization to viscous products. However, low molecular weight polymers can be prepared using Lewis acid catalysts such as titanium tetrachloride and aluminum trichloride. The best results can be obtained with anionic catalysts, such as $NaNH_2$, KOH and Na, which gave high molecular weight polymers[243].

Styrene sulfide polymers are generally amorphous and soluble in organic solvents[244]; they are formed in the presence of catalytic amounts of aluminum trialkyls or heavy-metal mercaptides.

Radical polymerization has been observed for highly fluorinated thiiranes, when irradiation or peroxides are the initiators used[245].

Many copolymers of thiiranes have been also prepared[78,150,246–249]; they exhibit important technological properties and are used as lubricating oils[250], elastomers[251] or highly thermostable polymers[252]. Recent interest in polyalkylene sulfides especially concerns stereoselective polymerizations of thiiranes and much effort has been devoted to the synthesis of polythiiranes containing predesigned chiral centers[232–234,246].

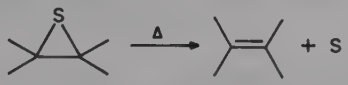
4. Desulfurization

Desulfurization to give olefins remains an important strategy for the preparation of hindered alkenes[150,247].

Several reagents are effective in realizing this reaction. Among these we will consider trivalent organophosphorous derivatives, organolithium compounds, Grignard reagents and methyl iodide.

Thermal fragmentation of thiiranes also yields olefins. In this case elemental sulfur is formed during the reaction.

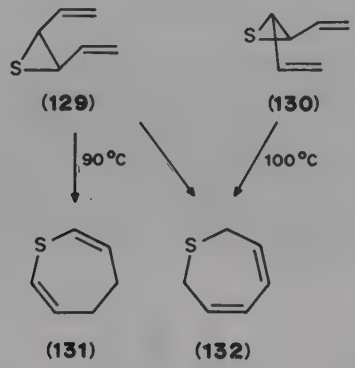
a. Thermal desulfurization. Many thiiranes undergo thermal desulfurization[248] (Scheme 58).



SCHEME 58

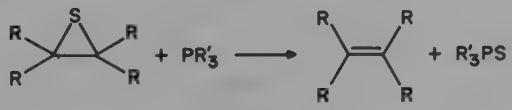
When thiiranes are substituted with more than one aromatic ring or with electron-withdrawing groups, extrusion of sulfur is particularly easy[78,249]. The mechanism of sulfur extrusion has been investigated in the thermal decomposition of 2,2-dichloro-3-[9-fluorenyl]episulfide in decalin, toluene and *p*-xylene[250,251]. At low concentrations of the episulfide a first-order process occurs, while at high concentrations a bimolecular pathway becomes more important. In the former, cleavage of the C—S bond at the carbon bearing the two chlorine atoms is not favored because of their electron-withdrawing effect, while the positive charge on the carbon of the fluorene skeleton is stabilized by resonance.

In the pyrolysis of *cis*- and *trans*-divinylthiiranes **129** and **130**[252], the two stereoisomers undergo only partial loss of sulfur to form nonstereospecifically a mixture of *cis*- and *trans*-1,3,5-hexatriene, while the prevalent reaction is a rearrangement which gives both **131** and **132** from the *cis*-isomer **129** and only **132** from the *trans*-isomer **130**[252] (Scheme 59).



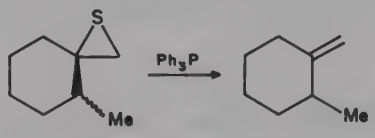
SCHEME 59

b. Desulfurization by organophosphorous compounds. Desulfurization of thiiranes can be quantitatively accomplished with trialkyl-[67,79] and triarylphosphines[79,253,254] at room temperature or with trialkylphosphites[70,79,196,253,255] on moderate heating (Scheme 60). Thus it is possible to obtain olefins even from aliphatic thiiranes which, on heating, tend to polymerize or dimerize.



SCHEME 60

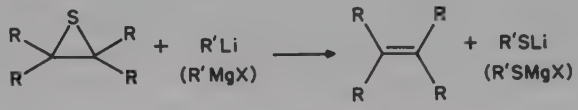
The mechanistic interpretation of the reaction suggests a nucleophilic attack on sulfur by phosphorus to give the phosphine sulfide and the olefin in one step without formation of charge-separated intermediates[256]. An interesting example of this desulfurization is given by the diastereomeric mixture of thiiranes **133** which, upon heating with triphenylphosphine, gives the chiral olefin **134** whose absolute configuration was not determined[202] (Scheme 61).



(133) **(134)** $[\alpha]_{576} = -0.45°$(c 11, hexane)

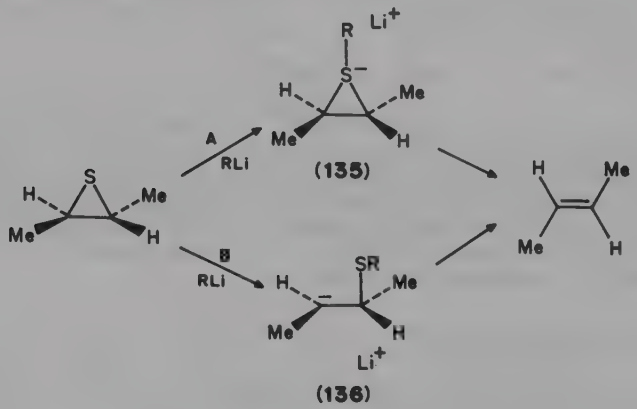
SCHEME 61

c. Desulfurization by organometallic compounds. Organometallic compounds, in particular organolithium and Grignard reagents, desulfurize thiiranes to give olefins and metal thiolates (Scheme 62).



SCHEME 62

The stereochemistry of the desulfurization by organolithium compounds has been throughly investigated. The reaction is highly stereoselective: for example, *trans*-2,3-dimethylthiirane and butyllithium react to give *trans*-but-2-ene, while *cis*-2,3-dimethylthiirane gives mainly *cis*-but-2-ene. Based on these results two mechanisms have been proposed[257] (Scheme 63). The first mechanism (path A) involves the formation of a thiirane anion (**135**) which collapses to the products. The second mechanism (path B) proposes as intermediate a carbanion **136** which decomposes to products at a rate faster than carbon–carbon bond rotation.

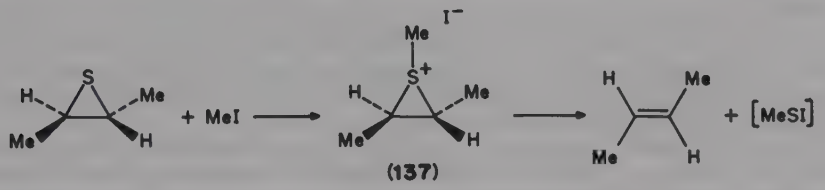


SCHEME 63

Further studies have been made in order to distinguish between the two mechanisms[14], in particular as to the stereochemistry of the olefins obtained by decomposition of the *erythro*- and *threo*-carbanions generated from the corresponding *erythro*- and *threo*-2-bromo-3-ethylthiobutanes. Since both carbanions gave mixtures of *cis*- and *trans*-olefins, path A (Scheme 63) is probably followed in this desulfurization reaction.

Lithium aluminum hydride is reported to give quantitative desulfurization of thiiranes, but only for a restricted number of derivatives[193, 258].

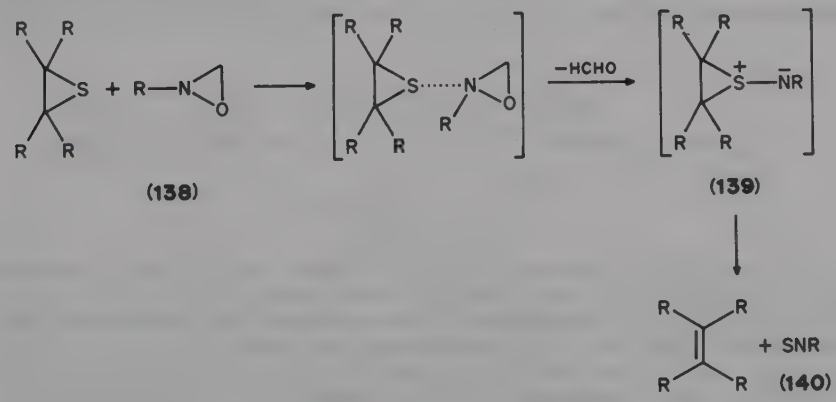
d. Desulfurization by methyl iodide. Stereospecific desulfurization of 2,3-dimethylthiiranes and other 2,3-dialkylthiiranes occurs with methyl iodide on heating[259] or using catalytic amounts of iodine at room temperature[91]. The stereospecificity of the reaction points to the formation of a methyl thiiranium intermediate **137**, in which an iodide ion attacks at sulfur to give the alkene and the unstable methyl sulfenyl iodide (Scheme 64).



SCHEME 64

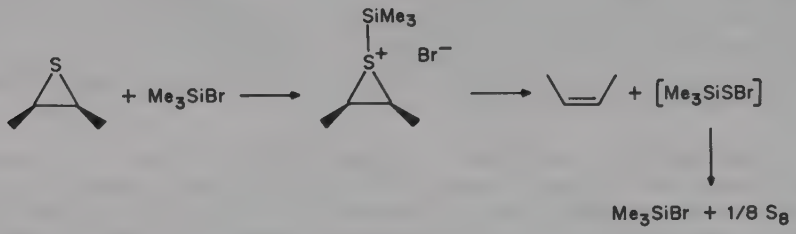
e. Desulfurization by other reagents. Among the many other methods reported to obtain desulfurization of thiiranes[3,8], some interesting ones have been recently published. Raney nickel (ethanol, −40 °C) or lithium (ethylamine, −15 °C), for example, react with polysubstituted thiiranes to give, after desulfurization, the corresponding alkenes. However, monosubstituted thiiranes with Raney nickel, and α,β-disubstituted thiiranes with lithium, are reduced to the corresponding alkanes[260].

Oxaziridine derivatives **138** also desulfurize thiiranes[261,262] (Scheme 65). During the reaction the ylide **139** is formed. The olefin and the thionitrosoalkane **140** are obtained as final products after fragmentation of **139**. From a mixture of *cis*- and *trans*-thiiranes, the stereospecific formation of the corresponding olefins has been observed and the stereochemical course of the reaction seems to be completely independent of the structure of the oxaziridine[262].



SCHEME 65

The action of trimethylsilyl iodide and bromide towards thiiranes as catalytic and stereospecific desulfurizating agents has been recently investigated[117] (Scheme 66).



SCHEME 66

Alkyl- and aryl-substituted thiiranes with trimethylsilyl halide form the thiiranium derivative **29** which, at the reaction temperature, decomposes to give the trimethylsilyl halide, elemental sulfur and the alkene. The decomposition of the initially formed sulfenyl bromide **28** makes the process catalytic while the formation of the thiiranium salt **29** explains the observed stereochemical control of the reaction.

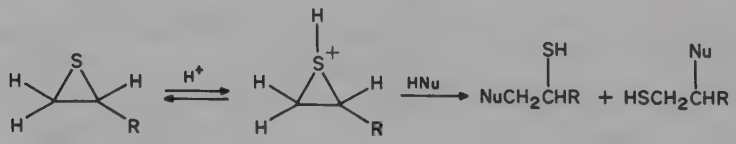
Sodium thiophenoxide has been successfully used as desulfurizating agent as well[263]. Initially the reaction is rapid but, as the eliminated sulfur interacts with the starting materials, it causes a decrease in the reaction rate. Based on structure–rate relationships, a mechanism for this reaction has been proposed.

5. Electrophilic ring opening

Since the thiirane ring can be seen as a donor–acceptor dipole system, electron-donor or electron-acceptor interactions between the cyclic sulfide and the reactants are both possible.

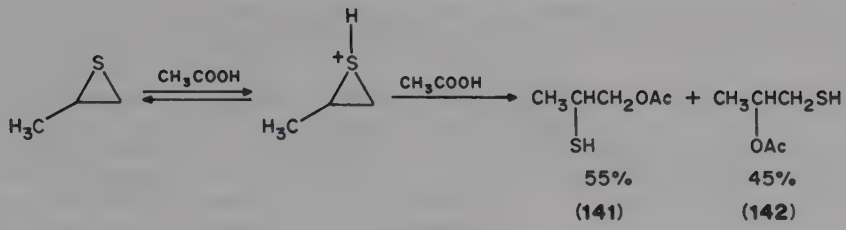
Electrophilic ring opening of episulfides has been widely studied, but its mechanism is still controversial. The attack at the sulfur atom of the thiirane ring by electrophiles gives cyclic sulfonium salts which can be in equilibrium with ring-opened cations. However, the cyclic intermediates are usually more stable than the ring-opened ones.

a. Reaction with acids. The reactions of thiiranes with hydrogen halides, carboxylic acids, alcohols, thiols, etc. is a quite common process often requiring acid catalysis and gives ring-opened products via a S_N2 or S_N1 mechanism (Scheme 67).



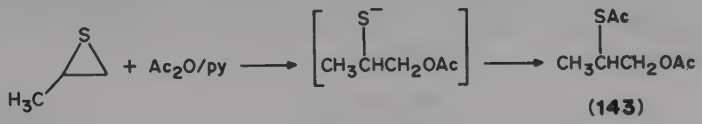
SCHEME 67

In these conditions oligomerization or polymerization can also occur if the sulfydryl group of the ring-opened product attacks another molecule of the thiirane. Acetic acid, for example, induces slow polymerization of thiirane, whereas no polymerization occurs with methyl- and ethyl-thiirane[218]. The solvolysis of methylthiirane in hot acetic acid gives both the acetates **141** and **142**[264] (Scheme 68). The acetate **141** is the major reaction product. This can be interpreted in terms of a more pronounced S_N2 character of the ring-opening step since steric factors are determinant in these reactions.



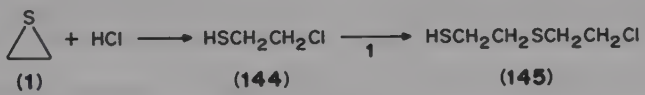
SCHEME 68

With acetic anhydride and pyridine, methylthiirane gives the acetate **143** with the ring fission mainly occurring at the primary carbon[265] (Scheme 69).



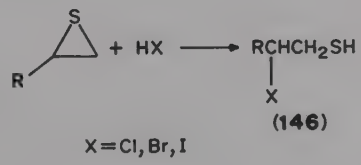
SCHEME 69

Hydrogen halides react with episulfides to yield the corresponding β-halothiols. Dilute hydrochloric acid leads to polymers while the reaction of thiirane (**1**) with concentrated hydrochloric acid yields both the monomeric and dimeric adducts **144** and **145**[266] (Scheme 70). If gaseous hydrogen chloride in ethereal solution is used, only **144** is obtained.



SCHEME 70

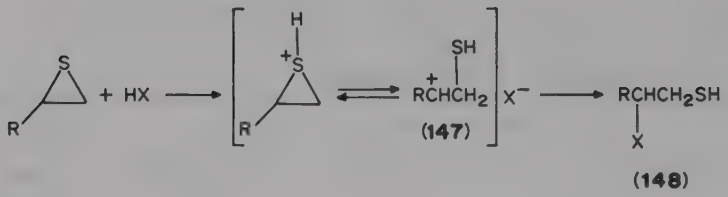
It has been reported that the ring opening of unsymmetrically substituted thiiranes by hydrogen halides occurs with halide attack mainly at the secondary carbon atom giving **146**[72] (Scheme 71).



SCHEME 71

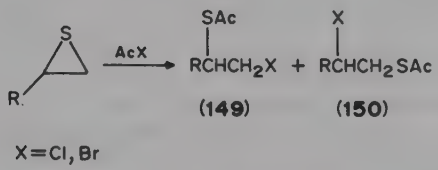
This result has been explained by a reaction mechanism in which the formation of the ring-opened intermediate **147** is nearly complete in the transition state leading to **148** (Scheme 72).

With Lewis acids, the most important reaction of thiiranes is polymerization[267]; polymerization of optically active thiiranes yields optically active polymers[268].



SCHEME 72

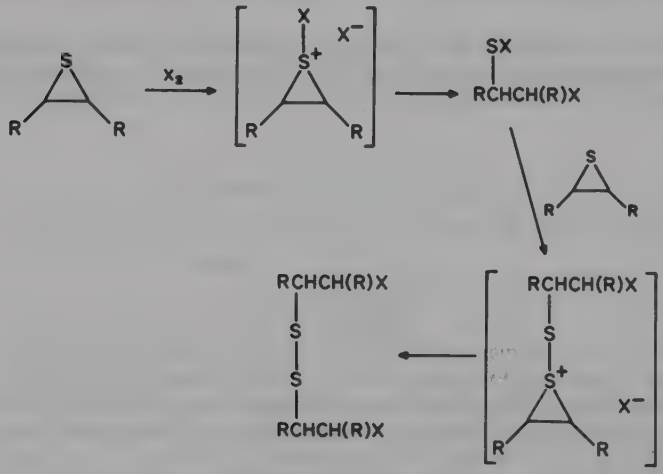
b. Reaction with acyl halides. Early papers[72,80] report that a variety of acyl halides react with methylthiirane to give 2-haloalkyl thioesters[269]. However, the reactions of methylthiirane, 2,2-dimethylthiirane and chloromethylthiirane with acetyl chloride or bromide have been found to give ring opening at both the carbon–sulfur bonds, yielding anti-Markovnikov and Markovnikov-like products **149** and **150**, respectively[269] (Scheme 73).



SCHEME 73

These results can also be explained assuming a thiiranium ion intermediate in which the site of attack is chosen by the nucleophile, depending on steric and polar factors[270].

c. Reaction with halogens. The reaction of thiiranes with halogens is generally quantitative and fast, so that thiiranes can be titrated with bromine solutions. The halogens react

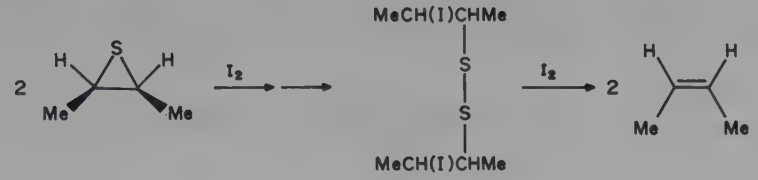


SCHEME 74

by initial formation of a halosulfonium salt which undergoes ring opening, generating a sulfenyl halide which further reacts with another thiirane molecule to give halo-substituted disulfides (Scheme 74).

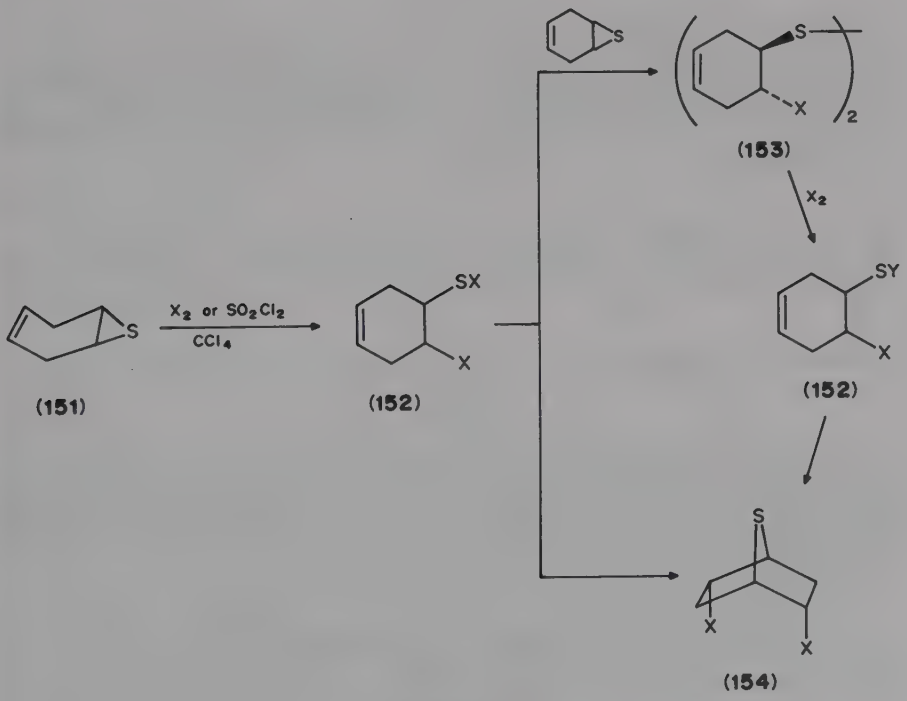
In the case of asymmetric thiiranes, the ring opening by halogens usually gives mixtures of isomeric disulfides[59,269]. However, when methylthiirane reacts with a solution of chlorine or bromine only Markovnikov ring-opened products have been isolated.

Iodine can also be used for desulfurization. The diiododisulfides, which are formed at room temperature, decompose with desulfurization on further treatment with warm iodine solutions[64] (Scheme 75).



SCHEME 75

Rearrangements have been observed during halogenation with chlorine, bromine, iodine or sulfuryl chloride if a carbon–carbon double bond is located near the thiirane ring[271] (Scheme 76)

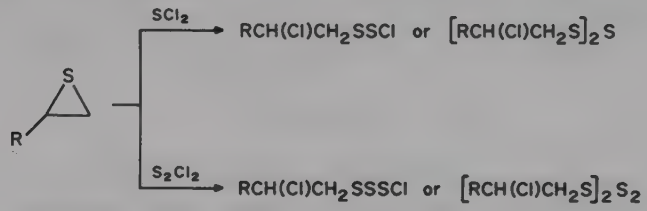


SCHEME 76

Halogenolysis of **151** leads to electrophilic ring opening with formation of the sulfenyl halide **152**. The latter can further react with **151** to give the disulfide **153**. If an excess of chlorine or bromine is present, the disulfide is cleaved to regenerate **152**, which undergoes intramolecular addition of sulfenyl halide to the double bond to give **154**.

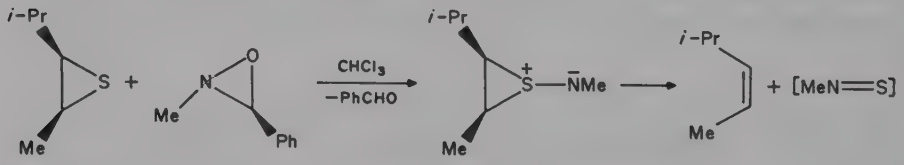
Treatment of thiiranes with halogens under vigorous conditions always gives polymers as side products[5].

d. Reaction with compounds bearing electrophilic sulfur, nitrogen or phosphorus. The addition of sulfur, nitrogen or phosphorus electrophiles to thiiranes follows a pathway similar to that discussed for the reaction with halogens[3,5]. Thus sulfur dichloride and sulfur monochloride both react to give the corresponding monomeric and dimeric products[272]. As shown in Scheme 77, Markovnikov ring opening occurs generally.



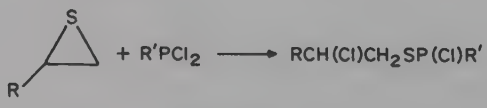
SCHEME 77

Reactions of thiiranes with electrophilic nitrogen are not very common. Attempts to react 2,3-di-*t*-butylthiirane with chloramine-T or *p*-toluenesulfonyl azide were without success[273]. However *cis*- or *trans*-2-methyl-3-phenyloxaziridine (**155**) reacts with thiiranes via electrophilic attack of nitrogen at sulfur with formation of the intermediate **157**. This reactive species undergoes desulfurization to give the alkene which retains the same stereochemistry like the thiirane **156** (Scheme 78).



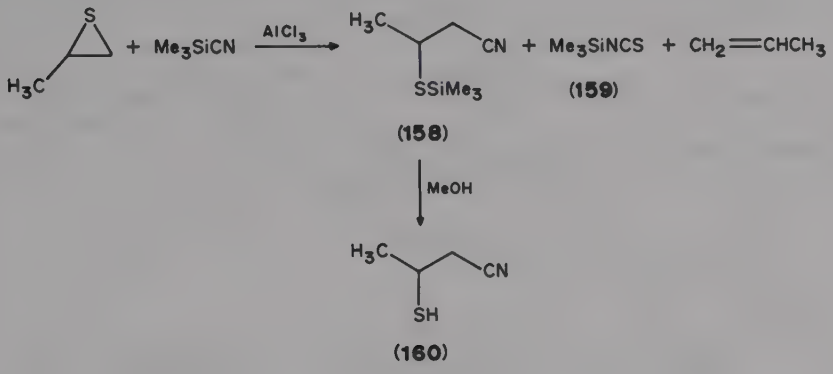
SCHEME 78

Organic and inorganic phosphorus(III) halides are reported to react with thiiranes to yield 2-haloethyl thiophosphines[5] (Scheme 79). The reaction is quite general and requires low temperature; higher temperature, in fact, can lead to desulfurization of the episulfide (see Scheme 60).



SCHEME 79

e. Reaction with organometallics. Thiiranes react with organometallics to give ring-opened derivatives. An example of regioselective opening of the thiirane ring is represented by the reaction of methylthiirane with trimethylsilyl cyanide under aluminum trichloride catalysis[274] (Scheme 80). 2-Trimethylsilylthiopropionitrile (**158**) was obtained as major product, but trimethylsilylisothiocyanide (**159**) and propene were also formed. Fractional distillation allowed isolation and characterization of **158** and **159**. Methanolysis of **158** produced the functionalized secondary thiol **160**.



SCHEME 80

A similar behavior has been reported for the reaction of thiiranes with other organosilicon compounds as well[274]. The reaction of thiiranes with trimethylsilyl bromide and iodide give stereoselective desulfurization[117] (see Scheme 66).

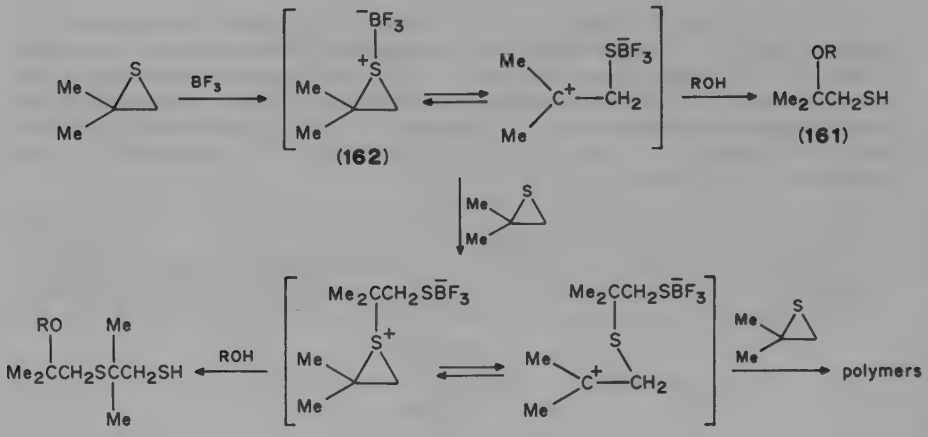
6. Nucleophilic ring opening

The reactivity of thiiranes towards nucleophilic species is very similar to that of oxiranes[3]. However, polymerization is always a side reaction when thiiranes react with nucleophiles and proper reaction conditions must be chosen to avoid the formation of undesired products.

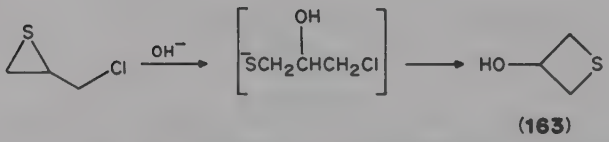
a. Reaction with oxygen nucleophiles. Generally, oxygen nucleophiles attack the ring carbons of thiiranes. In few cases attack at sulfur with subsequent desulfurization was observed[5].

Primary alcohols react with thiiranes, in the presence of boron trifluoride as catalyst, to yield β-alkoxymercaptans[275]. The reaction of 2,2-dimethylthiirane with alcohols is reported in Scheme 81. The alkoxymercaptan **161** is obtained, but higher boiling materials are also formed. In fact, the thiiranium species **162**, which is formed by the complexation of boron trifluoride on the thiirane sulfur, can react either with a molecule of the alcohol to give **161**, or with another molecule of thiirane to give higher molecular weight products.

In basic media the reaction between thiiranes and alcohols or phenols generally gives only polymeric materials[57,243]. However, the alkaline hydrolysis of chloromethylthiirane gives good yields of the thietane **163** (Scheme 82) as a single product, which suggests that the Markovnikov ring opening of the thiirane system is the preferred pattern of the reaction and that polymerization is inhibited by the intramolecular cyclization of the intermediate thiolate ion.

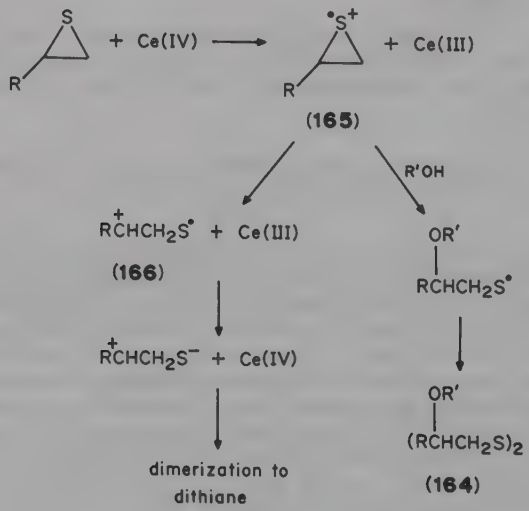


SCHEME 81



SCHEME 82

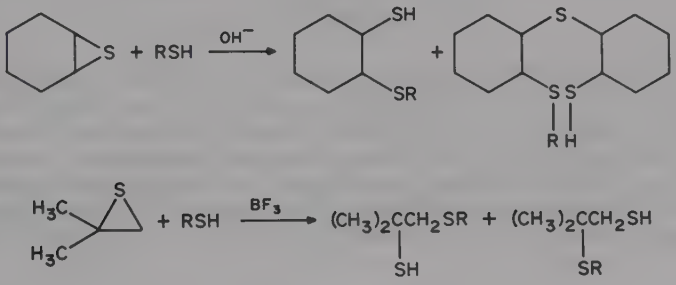
Cerium(IV) salts are suitable reagents for the ring opening of thiiranes by alcohols[276]. The main reaction products are the disulfide **164** and a dithiane derivative (Scheme 83).



SCHEME 83

Cyclohexene sulfide, styrene sulfide and propene sulfide were converted to the corresponding disulfides of type **164** by different alcohols using equimolar amounts of various cerium(IV) salts, with ceric sulfate, because of its low solubility in alcohols, the reaction is slower and requires higher temperatures. Catalytic amounts of cerium(IV) in refluxing carbon tetrachloride can also react with cyclohexene sulfide, styrene sulfide and propene sulfide. However, in these conditions the corresponding dithianes are the only products formed. The mechanism of these reactions is not certain, but the presence of radical cations **165** and **166** as intermediates leading to the two different products has been suggested[276]. This hypothesis is also supported by the considerable decrease in the reaction rate observed when radical trapping agents or oxygen atmosphere were used.

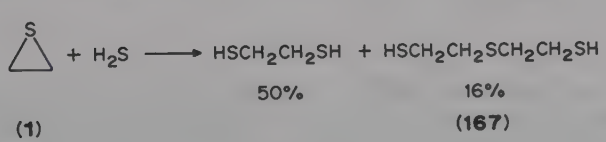
b. Reaction with sulfur nucleophiles. Thiols, like alcohols, react with thiiranes only under acid or base catalysis (Scheme 84).



SCHEME 84

In both cases the yield of the products is generally low (20–50%); moreover, the ring opening of the three-membered ring is not regiospecific[277].

Hydrogen sulfide also reacts with thiirane (**1**) at 50 °C to form 1,2-ethanedithiol and the dithiolsulfide **167** which is generated by reaction of the ethanedithiol with **1**[54] (Scheme 85).

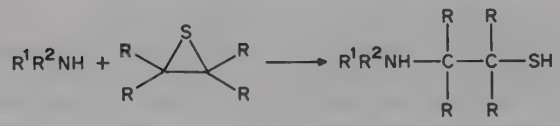


SCHME 85

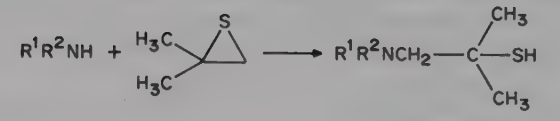
Interestingly, trithioglycerol can be obtained from the reaction of chloromethylthiirane with potassium hydrogen sulfide, but the formation of large amounts of polymers seriously lowers the yield[54].

c. Reaction with amines. The reactions of thiiranes with amines are the most extensively studied subject of the reactivity of these cyclic compounds[3,5]. Primary and secondary aliphatic amines react in mild conditions with thiiranes to give 2-mercaptoethylamine derivatives in good yields (Scheme 86).

Substituted thiiranes are attacked preferentially at the less hindered carbon. The exclusive formation of the aminothiol **168** is reported in the reaction of 2,2-dimethylthiirane with secondary amines[275] (Scheme 87).



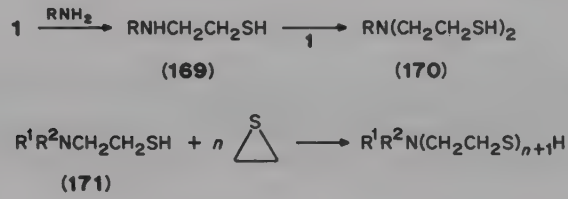
SCHEME 86



(168)

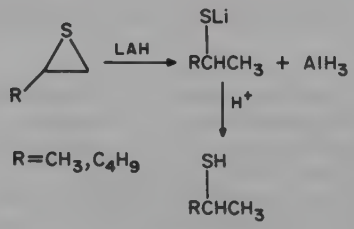
SCHEME 87

Highly hindered or weakly basic amines react slowly with thiiranes and give poor yields of the addition products. Aromatic amines are, generally, less reactive than the aliphatic ones and high temperature is required to obtain resonable yields of aminothiols. The most significant side reactions occurring during amination of thiiranes are further reaction of the aminothiol initially formed with the thiirane derivative and polymerization (Scheme 88). Oligomerization and polymerization observed during these reactions are likely initiated by the thiol groups of **169**, **170** or **171** as well as by other nucleophilic species[242].



SCHEME 88

d. Reductive nucleophilic ring opening. Thiiranes react with LAH undergoing a reductive ring cleavage; lithium mercaptides which, in acid media, are transformed into the corresponding thiols are the products obtained. As shown in Scheme 89, unsymmetrically substituted thiiranes are reduced regioselectively to secondary thiols[269]. Side products formed during the reduction are polymers and sulfur-containing unidentified compounds[85].

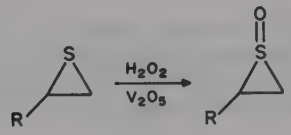


SCHEME 89

As previously discussed (see Section II.D.4.c), LAH can also induce reductive desulfurization of thiiranes.

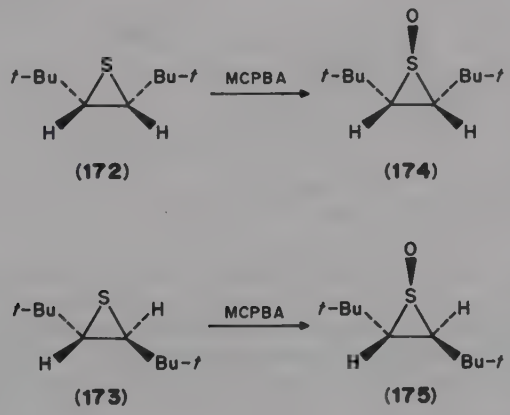
7. Oxidation

Oxidation of thiiranes generally does not afford the cyclic sulfoxides or sulfones because of easy ring opening of the oxidized species[59]. Anyway, it has been possible, in some cases, to transform thiiranes into the corresponding sulfoxides by using hydrogen peroxide and catalytic amounts of vanadium pentoxide[279] (Scheme 90).



SCHEME 90

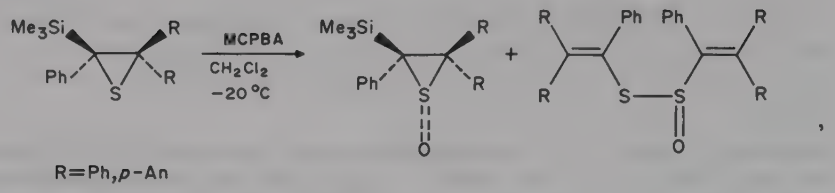
Cis- and *trans*-2,3-di-*t*-butylthiiranes **172** and **173** are more inert to ring opening because of the presence of the two *t*-butyl groups, and they can be oxidized to the corresponding sulfoxides by *m*-chloroperbenzoic acid[273] (Scheme 91).



SCHEME 91

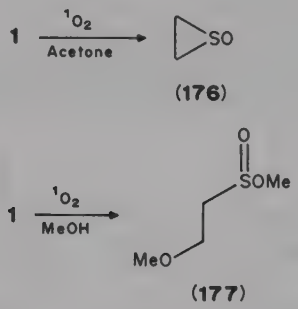
It is worth of mention that only the stereoisomer **174** is formed from the *cis*-thiirane **172**, as could be anticipated on the basis of attack from the less shielded side. The sulfoxide **175** is thermally unstable and eliminates sulfur monoxide when heated above 50 °C. Attempts to further oxidize the sulfoxides **174** and **175** to the corresponding sulfones failed: the *cis*-isomer does not react, probably because of steric hindrance, while **175** decomposes to unidentified products[273].

Examples of oxidation of silylated thiiranes with peroxyacids have been recently reported[280]. The reaction allows the isolation of the cyclic sulfoxides together with some ring-opened products (Scheme 92).



SCHEME 92

Singlet oxygen also reacts with thiiranes, however it is not possible to outline a general reaction scheme, since the products obtained depend on solvent, substrate and concentration[281]. Aryl-substituted thiiranes are unreactive, while alkyl thiiranes react even at low temperature. Scheme 93 shows the products formed during the photooxidation of thiirane (**1**) in different solvents.



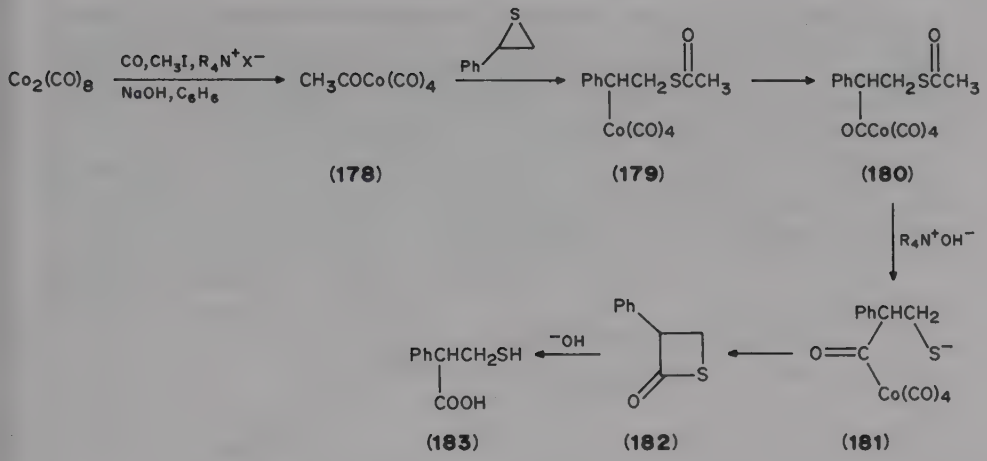
SCHEME 93

In weakly nucleophilic solvents such as acetone or acetonitrile, thiirane gave as the only product detected by NMR and GC the thiirane oxide **176**, while in methanol, at low concentration, the only product observed was the methyl-2-methoxyethanesulfinate **177**. High concentration of the episulfide gave polymeric materials. It is important to emphasize that if the reaction is carried out under nitrogen and in the absence of a sensitizer, no reaction occurs, and that singlet oxygen quencher, such as 1,4-diazabicyclooctane (DABCO), inhibits the oxygenation.

8. Carbonylation

Recently, the use of cobalt and palladium complexes in homogeneous or phase-transfer catalyzed carbonylation of thiiranes to acids, esters and lactones has been reported[282] (Scheme 94).

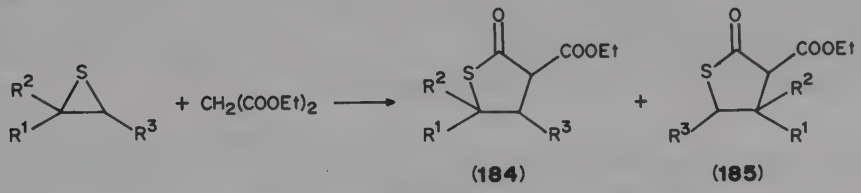
The acylcobalt carbonyl **178**, formed *in situ*, reacts with thiiranes to give the thioester complex **179**. The insertion of carbon monoxide affords **180**. Hydrogenolysis of the latter is rapid, so that **181** is the preferred intermediate, the intramolecular cyclization of which gives the thiopropiolactone **182**, and subsequent base-induced hydrolysis gives the mercapto acid **183**.



SCHEME 94

9. Reaction with diethyl malonate

Thiiranes react with diethyl malonate under base catalysis yielding thiolane derivatives **184** and **185** (Scheme 95).



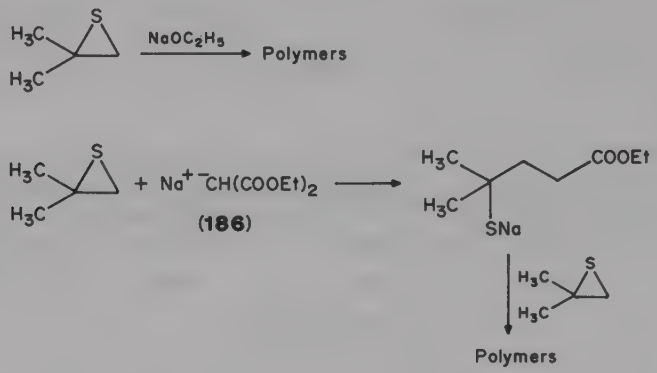
SCHEME 95

The reaction in the presence of sodium ethoxide shows high selectivity. In Table 5 are summarized the results with various thiiranes and the percentages of the different regioisomers obtained in each case[283]. Alkyl substituted thiiranes react selectively to give the

TABLE 5. Percentages of regioisomers formed in the reaction of substituted thiiranes and diethyl malonate

			Yield (%)	
R^1	R^2	R^3	**184**	**185**
CH_3	H	H	48	—
CH_3	CH_3	H	65	—
n-C_4H_9	H	H	59	—
n-C_6H_{13}	H	H	58	
C_6H_5	H	H	18	45

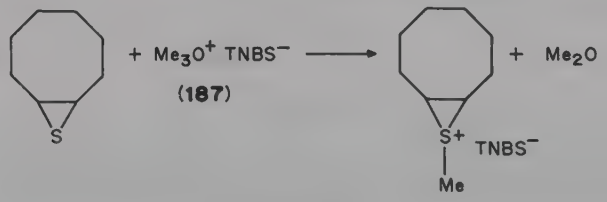
product formed by attack of the carbanion generated from the malonate ester, at the less hindered carbon of the thiirane ring. This selectivity has been also found for reactions of thiiranes with other stabilized carbanions. The yields of the thiolane derivatives are not very high and polymeric material is also formed, due to polymerization of the thiirane derivatives initiated by sodium ethoxide and/or by **186** (Scheme 96).



SCHEME 96

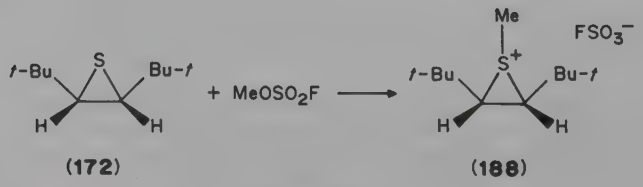
10. Formation of stable thiiranium salts

Thiiranes with strong alkylating agents may give stable thiiranium salts. Thus, treatment of cyclooctene episulfide with trimethyloxonium 2,4,6-trinitrobenzenesulfonate (**187**) gives the corresponding 1-methylthiiranium salt[284] (Scheme 97). The structure of the cyclooctene episulfide forces the attack on the oxonium salt at the sulfur atom from the less hindered side of the molecule, generating a single stereoisomer.



SCHEME 97

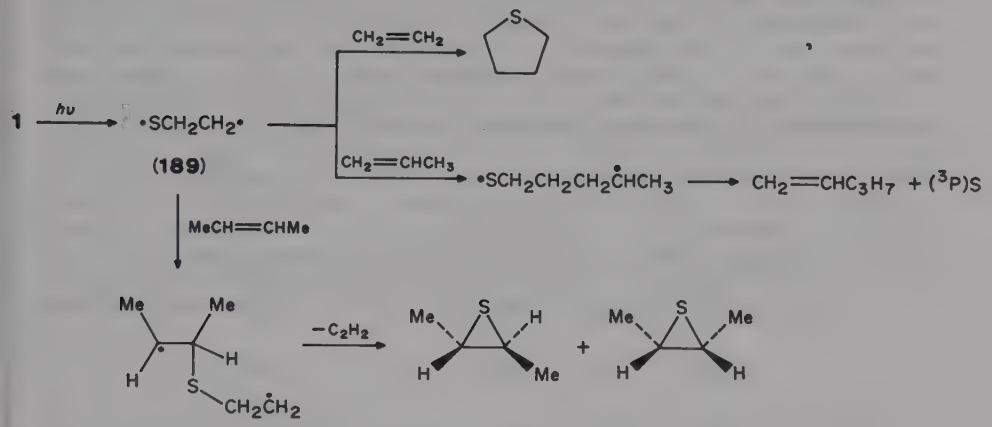
Steric effects are relevant even in the alkylation of *cis*- and *trans*-2,3-di-*t*-butylthiiranes **172** and **173** with methyl fluorosulfonate[273]. At room temperature only the *cis*-isomer **172** reacts giving **188** as single product (Scheme 98).



SCHEME 98

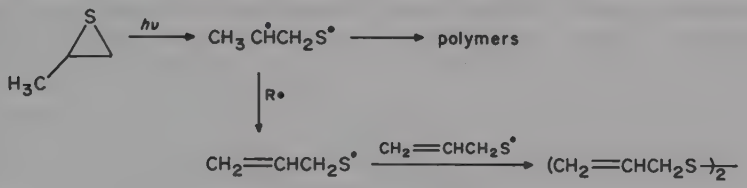
11. Photochemistry

When photolyzed, thiiranes undergo easy sulfur extrusion with formation of the corresponding olefins. Side products of the reaction are small amounts of hydrogen sulfide and acetylene derivatives that have been suggested to arise from a molecular fragmentation of the excited singlet state of the thiiranes. Photolysis of thiirane (**1**) in the presence of alkenes generates products, which depend upon the nature of the added olefin[286,287]. The first step of the reaction is the formation of the diradical **189** (Scheme 99), which has a lifetime long enough to be trapped by ethylene to give tetrahydrothiophene. Addition of propylene to **189** gives 1-pentene in a good yield, while addition of *cis*-2-butene gives a mixture of *cis*- and *trans*-2,3-dimethylthiiranes.



SCHEME 99

Ultraviolet irradiation of methylthiirane does not cause desulfurization, but formation of polymeric material and small quantities of allyl disulfide[288] (Scheme 100).



SCHEME 100

III. THIETANES

A. Structure and Spectroscopic Properties

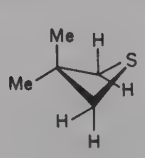
Thietanes are common and important sulfur-containing compounds[289–292], many of them have been synthesized[2] and their structural features studied[293,294].

Evidence of the puckered structure of the thietane ring has been reported[295]; the calculated energy barrier to planarity (0.78 kcal mol^{-1}) indicates that at room temperature only one-quarter of the population occupies vibrational levels above it [296,297]. The data

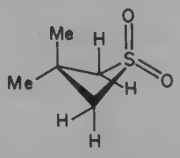
calculated for ring inversion show that the barrier is greater than that calculated for oxetane but less than that for cyclobutane. Dihedral angles and bond lengths have been reported[293,294] as well. Important data concerning the conformation of thietanes are derived from dipole moments[298,299], microwave[300], UV[301,302], IR[303–305] and low-frequency Raman[306,307] spectroscopy.

The proton NMR spectrum of the parent compound has been analyzed as an A_4B_2 system[308]. The configuration and conformation of several 3-substituted thianes and spiro derivatives have been clarified by carbon NMR measurements and the chemical shifts of some of these products have been tabulated[293].

The proton NMR spectra of 3,3-disubstituted thietanes, their 1-oxides and 1,1-dioxides represent a rich source of information[309]. The ring protons and methyl groups in 3,3-dimethylthietane (**190**) and its dioxide **191** are chemically equivalent, so that a planar ring conformation or a rapid equilibrium of folded conformers can be assumed. On the other hand, for 3,3-dimethylthietane-1-oxide (**192**) a puckered conformation is necessary to explain the chemical nonequivalence of the methyl groups and of the ring protons found in the NMR spectrum. Moreover, the puckering is revealed by the coupling constant values between the methyl groups and the ring protons[309].



(190)



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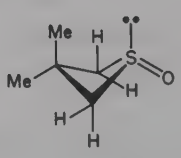


(192)

For the sulfinyl group of **192** an equatorial orientation has been proposed[310] on the basis of the absence of strong deshielding of methyl groups relative to those found in **190** and of the comparison of the chemical shifts of equatorial and axial protons in **192** and **190**.

The deshielding of ring protons or methyl groups, equatorial at C-3 with respect to an axial lone electron pair on sulfur in thietanium ions[311,312] and in thietane-1-oxide[311–313], which are conformationally stable species, has been widely studied in order to gain structural information on these ring systems. An axial lone pair usually causes a greater shielding effect to the syn–axial proton at C-3 than an axial S=O bond. This is not a general rule, since a reverse effect has been found in *cis*-4-acetoxythietane-1-oxide[313].

Equatorial methyl groups or protons at C-2 in a four-membered cyclic sulfur compound are also influenced by the presence of an axial lone electron pair: in thietanes and thietane-1,1-dioxides they are more shielded than methyl groups in axial position. A reverse situation exists for thietane-1-oxides[311–313] and thietanium salts[311,312]. Detailed NMR analysis of 2,4-,2,2- and 3,4-disubstituted thietanes as well as of polysubstituted thietanes have been accurately reviewed[298,313,314].

The nonplanar conformation of the thietane ring occurs also in the radical cation species[315–317], e.g. in the 1,2-dithietane radical cation. A barrier to ring flipping higher than 5 kcal mol^{-1} has been found in the case of the 3,4-dimethyldithietane radical cation[315–317].

The mass spectra of thietanes generally show intense molecular ion peaks. Retro 2+2 cycloaddition to give a thiocarbonyl species is the main fragmentation path occurring in thietanes, thiolactones and iminothietanes, while loss of sulfur oxides occurs in thietane-*S*-oxides. Thietane-*S*-dioxides give ring opening. Loss of an α-hydrogen atom occurs during fragmentation of thietes and benzothietes[316].

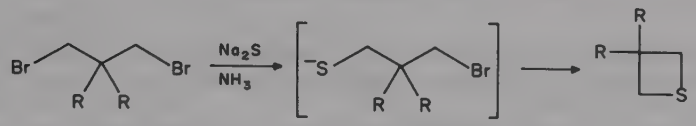
Protonation of thietanes has been accomplished in superacid media[318] and in aqueous sulfuric acid[319]. In the latter case, the pK_B of the thietane has been compared to the pK_B values of other cyclic sulfides. Thietane is less basic than thiolane but more basic than thiane. Moreover, the basicity of the sulfur atom in cyclic sulfides does not change appreciably compared to acyclic sulfide sulfur atoms[319,320].

B. Synthesis

Methods for the synthesis of four-membered ring sulfides are relatively few and only rarely have general applicability. The most important ones have been already reviewed[293,294,321–327]. In this section we shall consider the synthesis of thietanes from acyclic precursors, with formation of one or two ring-bonds, and from other heterocycles with transformation of the original ring system.

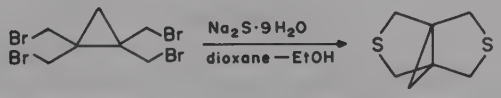
1. Thietanes from acyclic precursors

The oldest and most widely used method for the preparation of thietanes consists in the treatment of 1,3-dihalopropanes with sodium or potassium sulfide[328]. The reaction involves the intermediacy of 3-halopropanethiolates which usually are not isolated (Scheme 101). Various solvents, including ammonia, and different reaction conditions have been employed[329–332]. Yields vary between 10% and 70% but are only rarely higher than 50%, because polymeric material and elimination products are often formed [333,334]. The yields of 3,3-disubstituted thietanes are generally higher than those of the less-substituted ones, since in the former case elimination reactions are not possible.



SCHEME 101

When the formation of a five-membered ring is also possible, thiolane derivatives are preferentially obtained[335] as happens in the reaction of **193** with sodium sulfide (Scheme 102). Although the spirothietane **194** could be formed, only the propellane **195** has been isolated.

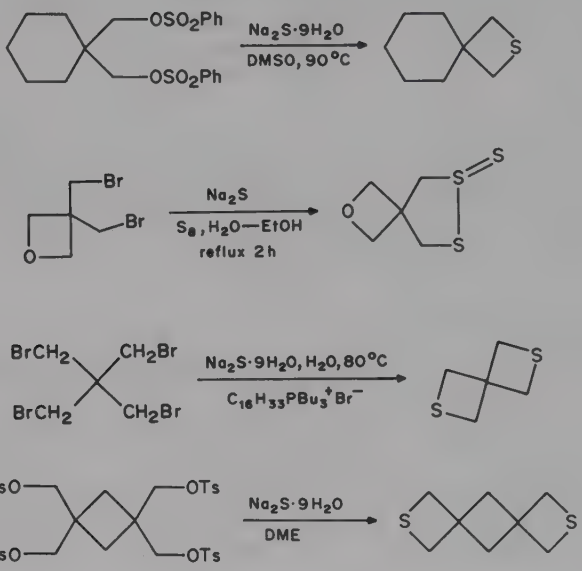


(193) **(195)**

(194)

SCHEME 102

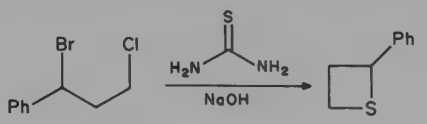
Spirothietanes have been similarly synthesized in good yields[331,332,336,337] (Scheme 103).



SCHEME 103

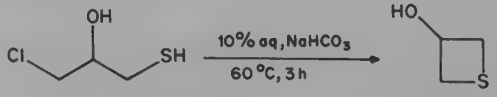
Phase-transfer catalysis has been used for the synthesis of thietanes from 1,3-dihaloalkanes and sodium sulfide[34], when the yields from primary alkyl halides are generally excellent.

Another source of nucleophilic sulfur is thiourea. Under basic conditions it reacts with 1,3-dihalo derivatives to give four-membered ring sulfides[338,339] (Scheme 104). In this case 3-halopropanethiolates are the intermediates for the ring closure.



SCHEME 104

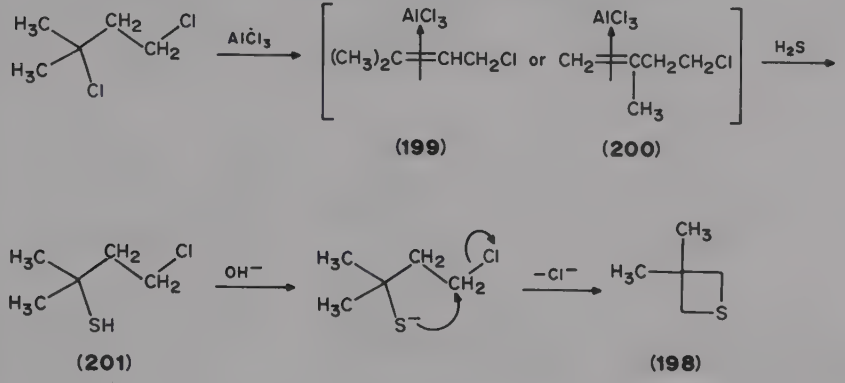
1,3-Halothiols can obviously be used as starting materials for the synthesis of thietanes. Thus 2-hydroxy-3-chloropropanethiol **196** undergoes ring closure to the thietane **197** in particularly mild conditions[89] (Scheme 105).



(196) **(197)**

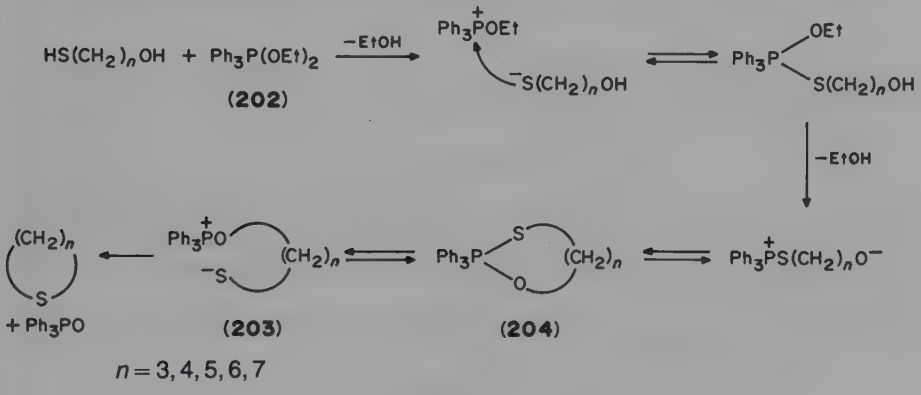
SCHEME 105

A modification of the synthesis of thietanes from 1,3-dihalo derivatives and sodium sulfide has been proposed[340] (Scheme 106). The reaction of 1,3-dichloro-3-methylbutane with aluminum chloride and hydrogen sulfide gives 2,2-dimethylthietane **198**. The formation of an orange alkyl chloride/alkene complex of type **199** or **200** has been proposed as the first intermediate. Addition of hydrogen sulfide generates a tertiary thiol **201** which, in turn, undergoes nucleophilic substitution to give **198**.



SCHEME 106

Simple thietanes have been synthesized from 1,3-mercaptoalcohols in the presence of diethoxytriphenylphosphorane[341] (Scheme 107).

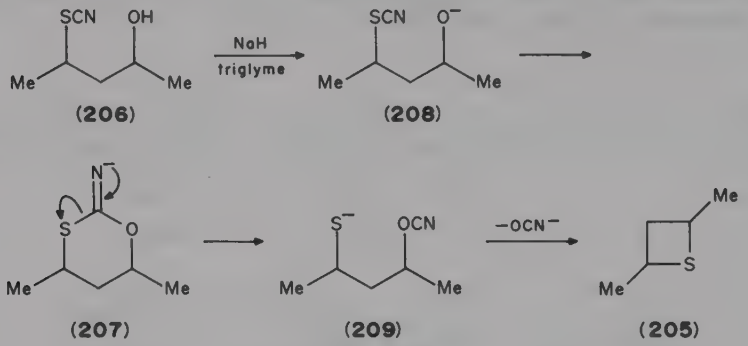


SCHEME 107

The 1,3-mercaptoalcohol with the phosphorane **202** gives the betaine **203** via the 1,3,2-oxathiophospholane **204**. Elimination of triphenylphosphine oxide and ring closure affords the thietane, in yields depending on the reaction temperature. Excellent yields (90%) have been reported for the synthesis of 2,2-dimethylthietane running the reaction at −25 °C. This reaction can also be applied to other mercaptoalcohols, thus providing a general synthetic pathway to cyclic sulfides of various size.

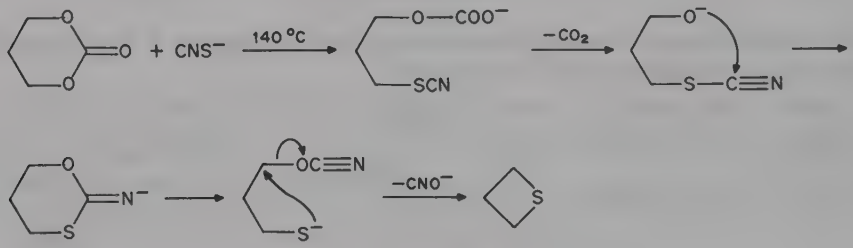
Thietanes can also be prepared using an alcohol containing a masked thiol group which becomes unmasked during the reaction[342,343], as shown in Scheme 108 for the synthesis of

2,4-dimethylthietane (**205**) from the hydroxythiocyanate **206**. The oxathiane derivative **207**, formed from **208** by hydroxide ion attack at the cyano group, has been proposed as intermediate. Subsequent rearrangement of **207** to the thiolate ion **209** and ring closure gives **205**.



SCHEME 108

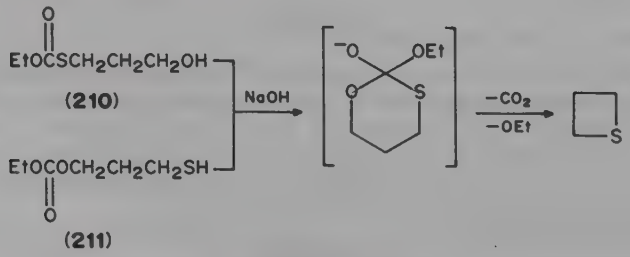
Species similar to **206**, **207** and **208** have been already invoked[176] in an early study on the reaction of potassium thiocyanate with 1,3-dioxane-2-one which provides thietane (Scheme 109).



SCHEME 109

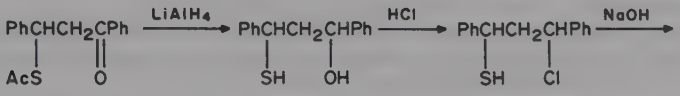
The above method, which can also be used for the synthesis of other cyclic sulfides, is warmly recommended to prepare four-membered ring sulfides because it is simple and starting materials are readily available. Stereochemical studies regarding this reaction have been reported as well[338].

Thietane has been also synthesized from the S-ester **210** or the O-ester **211** of 3-mercapto-1-propanol (Scheme 110).

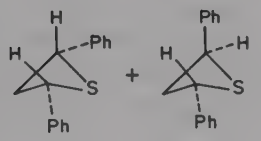


SCHEME 110

Reduction of the ketone **212** with LAH in THF has been reported[313] to afford the hydroxythiol **213** in excellent yield. Treatment of **213** with concentrated hydrochloric acid gives the corresponding chlorothiol **214**, which is then transformed into a mixture of *cis*- and *trans*-2,4-diphenylthietane, **215** and **216**, by treatment with aqueous sodium hydroxide (Scheme 111)



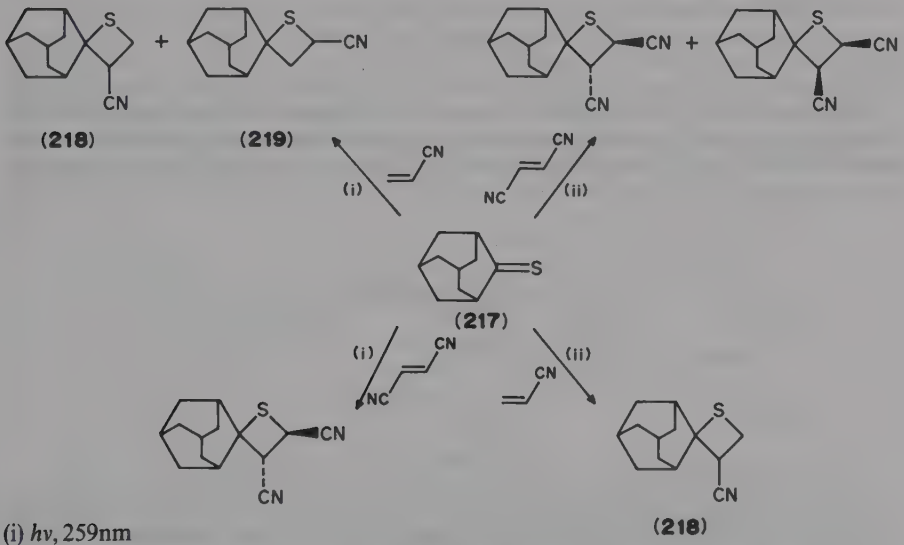
(212) **(213)** **(214)**



(215) **(216)**

SCHEME 111

Photochemical cycloadditions represent a very useful and versatile approach to the synthesis of four-membered rings. 2+2 Cycloaddition reactions of thioketones, thioketenes, isothiocyanates, sulfenes and iminosulfenes with alkenes, allenes, ketenes, ketenimines and alkynes give thiolane derivatives[294,344,345]. Photocycloaddition of thiocarbonyl compounds to alkenes and allenes has been studied in detail. It should be

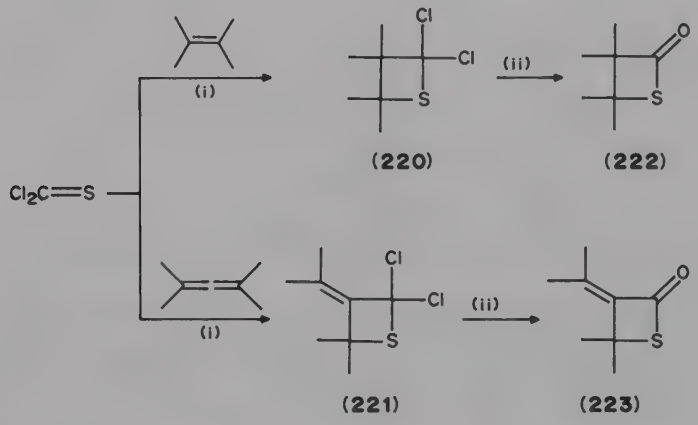


(i) *hv*, 259nm
(ii) *hv*, 500nm

SCHEME 112

considered that thietanes are photolabile compounds and irradiation at short wavelengths gives partial loss of product. Moreover, the wavelengths used for irradiation can determine the stereo- and regiochemical outcome of the reaction[293,294,346–348]. At short wavelength (259 nm) the thione **217** reacts with acrylonitrile to give a mixture of the two spiro thietanes **218** and **219**, while only the regioisomer **218** is obtained when a longer wavelength is used. On the contrary, the reaction of **217** with *trans*-dicyanoethylene is highly stereoselective at short wavelength[347,348] (Scheme 112).

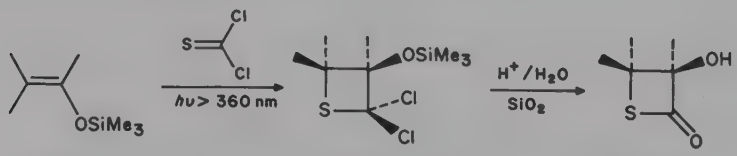
Dichlorothiophosgene undergoes photocycloaddition with olefins and allenes[349] and gives the thietanes **220** and **221**, respectively. These derivatives can be further transformed into the thiolactones **222** and **223** (Scheme 113).



(i) $h\nu > 455$ nm
(ii) SiO_2, C_6H_6–H_2O

SCHEME 113

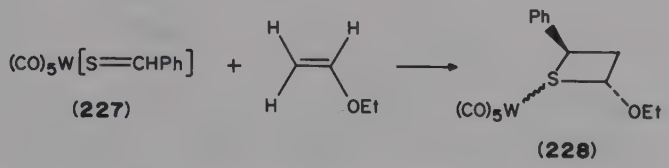
Photochemical 2 + 2 cycloaddition between thiophosgene and 3-methyl-2-trimethylsiloxy-2-butene (**224**) followed by acid-catalyzed hydrolysis and desilylation of the cycloadduct **225** is a recent example of synthesis of hydroxythiolactone **226** in a two-step, one-pot reaction[350] (Scheme 114).



SCHEME 114

Stable thiocarbonyl compounds are widely used for the synthesis of thietanes. Unstable thioaldehydes cannot be usually used in these syntheses. However, recently a thermal 2 + 2 cycloaddition of vinyl ethers to a metal-coordinated thioaldehyde has been reported[351],

using the stable pentacarbonyl tungsten complex **227**. Using **227** as the source of thiobenzaldehyde, the reaction with vinyl ethers proceeds regiospecifically and stereoselectively to give the thietane complex **228** (Scheme 115).

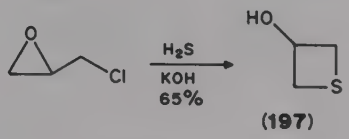


SCHEME 115

2. Thietanes from cyclic precursors

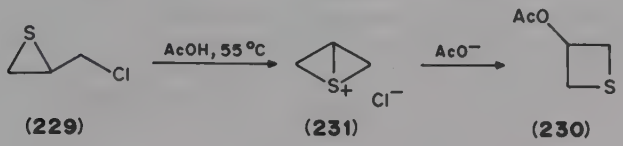
Transformations of other heterocycles into thietanes have been reviewed[293,294,321].

3-Hydroxythietane has been prepared from epichlorohydrin in satisfactory yields[53,54] (Scheme 116).



SCHEME 116

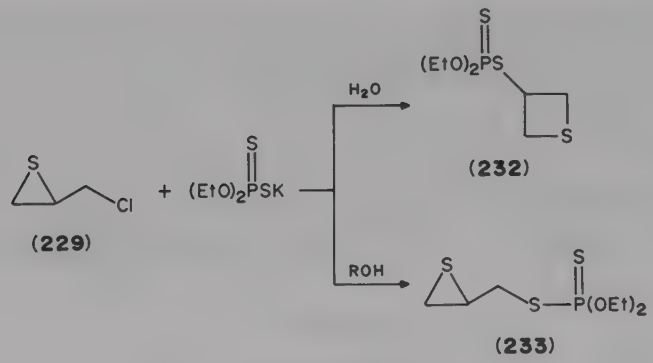
The chlorothiirane **229** and its derivatives are other useful precursors for the synthesis of thietanes. They react with oxygen or sulfur nucleophiles to give 3-substituted thietanes. The reaction of **229** with acetate ion in acetic acid gives the 3-acetoxythietane **230.** The proposed mechanism of this reaction[352, 353] is reported in Scheme 117. The key intermediate is the sulfonium ion **231** which, under attack by the acetate ion, gives **230**. Solvent and salt presence seem to be important, since the reaction does not occur in the absence of acetate ion[352].



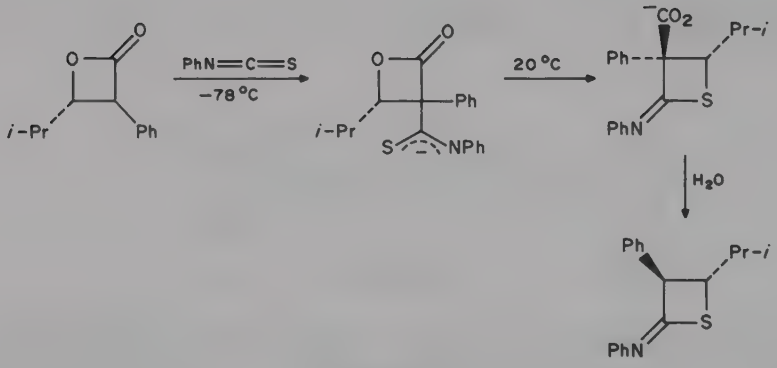
SCHEME 117

A special solvent effect has been found in the reaction of chlorothiirane **229** with the potassium salt of dithiophosphoric acid, which in water gives the thietane **232**, while in ethanol or in propanol it gives the thiirane **233** as the main product[354] (Scheme 118).

Transformations of non-sulfur-containing four-membered heterocycles into thiiranes are quite rare. An example[355] is shown in Scheme 119.

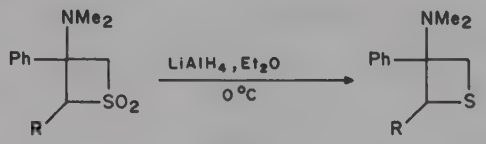


SCHEME 118



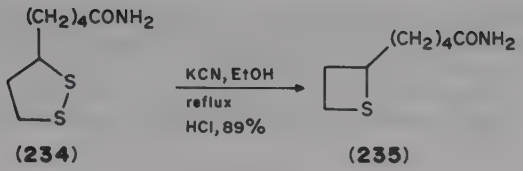
SCHEME 119

Since thietane sulfones can be prepared by cycloaddition of sulfenes to enamines[356–359], their reduction to thietanes by LAH is a useful method for the synthesis of 3-amino substituted thietanes[289,360,361] (Scheme 120).



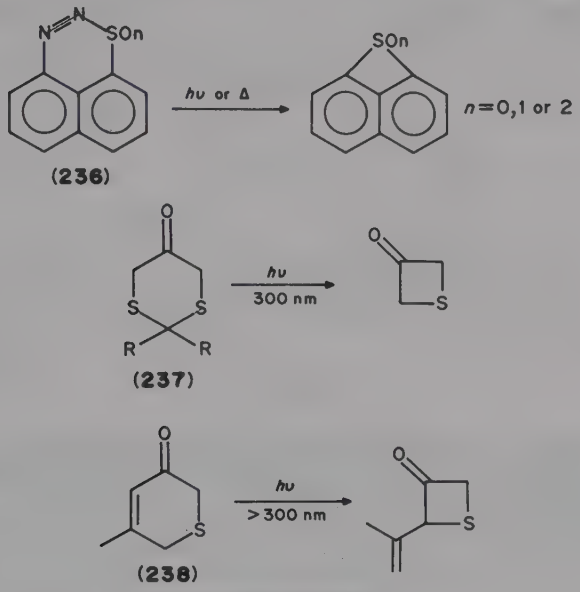
SCHEME 120

Sulfur extrusion from the naturally occurring 1,2-dithiolane **234** with potassium cyanide gives the thietane **235**[362] (Scheme 121). This methodology can be extended to a variety of 1,2-dithiolanes, which undergo similar desulfurization with ring contraction by treatment with tris(diethylamino)phosphine[363].



SCHEME 121

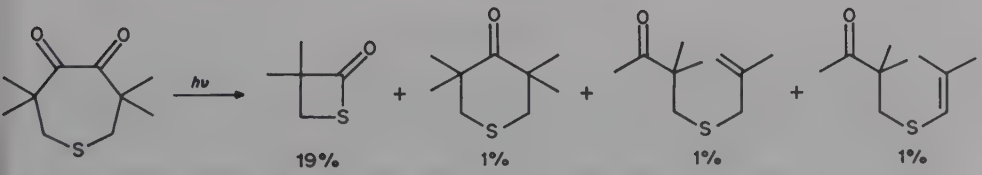
Methods of formation of thietanes from six-membered heterocycles include the photochemical or thermal loss of nitrogen from **236**[364,365], the photochemical fragmentation of **237**[366,367] and the photochemical rearrangement of **238**[366,367] (Scheme 122).



SCHEME 122

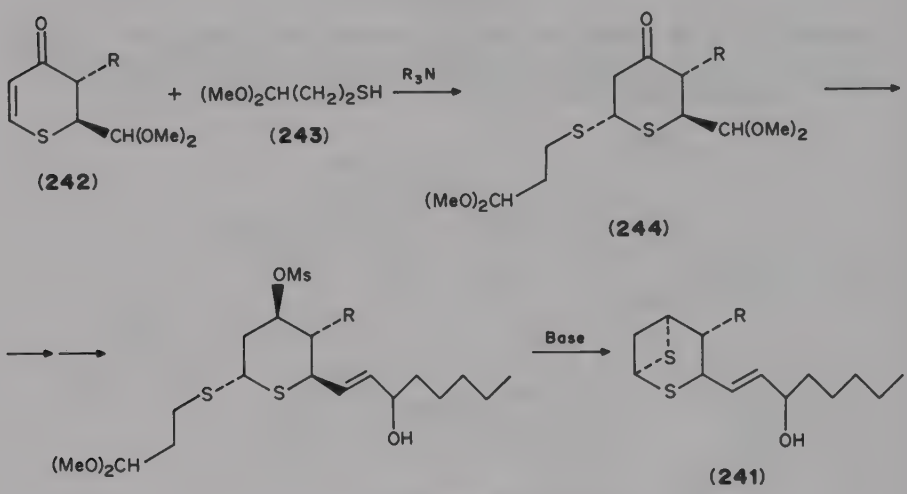
Ring opening of cyclic carbonates by thiocyanate ions seems the most versatile method to obtain a four-membered ring from six-membered heterocycles[176,338] (see Scheme 109).

It has been possible to obtain the four-membered cyclic thioester **239** even from the seven-membered heterocyclic precursor **240**[368] (Scheme 123). Irradiation of 3,3,6,6-tetramethyl 1-thiacycloheptan-4,5-dione (**240**) gives four different products with the thiolactone **239** being the predominant species.



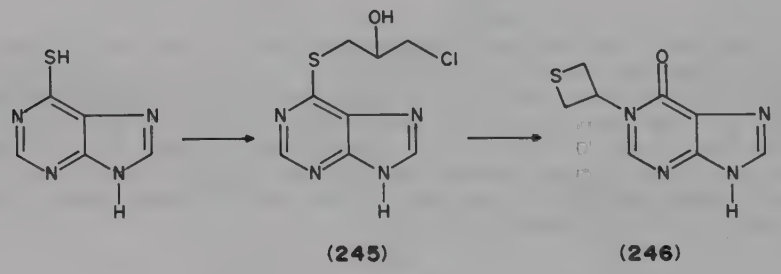
SCHEME 123

The examples reported in Scheme 124 deserve particular attention for their biological interest. Thus in the synthesis of **241**, the very potent sulfur analogue of thromboxane A2 from prostaglandin E_2 (PGE_2) methyl ester **242**[369,370], the first step is the addition of the thiol **243** to the thiane derivative **242** to give **244**. The construction of the 2,6-dithiabicyclo[3.1.1]heptane skeleton of **241** has been achieved from **244** by base-catalyzed ring closure.



SCHEME 124

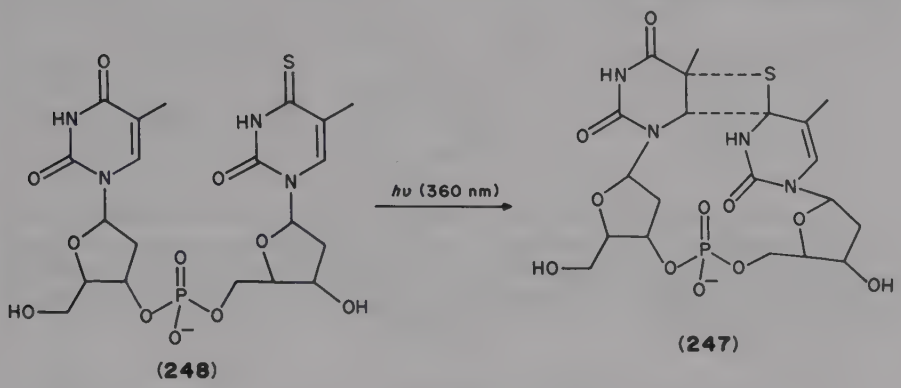
Another example concerns the unusual rearrangement of **245**, which is easily obtained from 6-mercaptopurine[371] (Scheme 125). Treatment of **245** with sodium hydrogen carbonate gives the purine substituted thietane **246**.



SCHEME 125

Finally, the thietane **247** has been synthesized from **248** by internal photochemical cycloaddition (Scheme 126). The formation of **248** has been taken as the model for processes of DNA damage. It is known[372] that the (6–4)pyrimidine–pyrimidone photoproducts represent one of the major photolesions revealed at pyrimidine sequences in DNA caused by the UV portion of sunlight. The mechanism of this damage is still obscure, but it has been supposed to proceed via an unstable intermediate which might have an

oxetane, azetidine or thietane structure[373]. The photochemical synthesis of **247** from **248** seems to support the intervention in this process of a thietane derivative.



(248) **(247)**

SCHEME 126

C. Reactivity

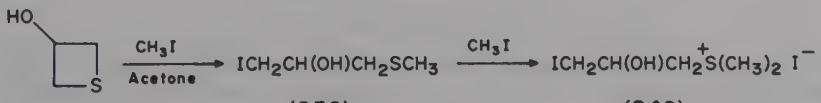
This section includes different types of reactions which involve thietane ring-opening (including expansion or contraction of the ring), or functionalization without ring-opening.

1. Protonation

Protonation of four-membered rings in classical media did not give easily understandable results. In fact the reaction of thietanes with aqueous acids gave unidentified polymers[319,374,375]. Sulfur dioxide and polymeric species were obtained in sulfuric acid[376]. Ring opening in acid media was obtained for monothioacetals such as α-alkoxythietanes[377]. However, when thietane was dissolved in FSO_3H–SbF_5–SO_2 solution at −60 °C, the protonated species was detected by NMR[378]; unfortunately, even in these conditions polymerization is easy so that special precautions must be used to avoid this side reaction.

2. Reaction with alkyl halides and halogens

The reaction of thietanes with alkyl or acyl halides has been throughly studied[293]. Alkylation at sulfur is usually followed by ring opening.

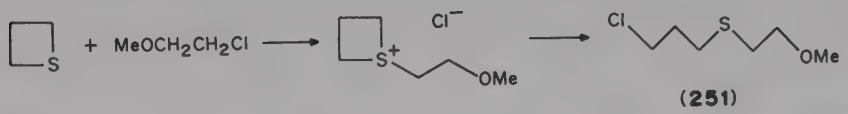


(197) **(250)** **(249)**

SCHEME 127

Scheme 127 shows the reaction of **197** with methyl iodide. The final product is a sulfonium ion **249**, which results from further alkylation of the methyl sulfide **250**[89,379].

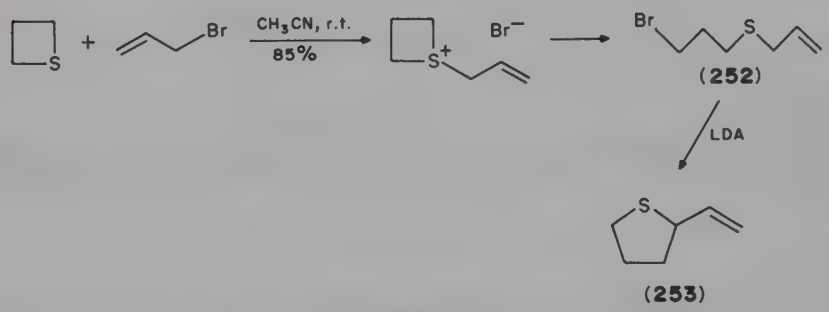
1-Chloro-2-methoxyethane reacts with thietane to give the sulfide **251**[375] (Scheme 128). Similarly, benzoyl chloride (or bromide) reacts with thietane to give the acyclic *S*-(3-chloropropyl)thiobenzoate[83].



(251)

SCHEME 128

Electrophilic attack at the sulfur atom of thietane by allyl bromide (or chloride) gives the allyl sulfide **252** (Scheme 129). The latter is a useful intermediate in the synthesis of larger sulfur-containing cyclic compounds[382], e.g. it undergoes cyclization to vinylthiolane **253** by treatment with LDA. The thiolane so obtained can be used for the synthesis of sulfurated macrocycles[383].



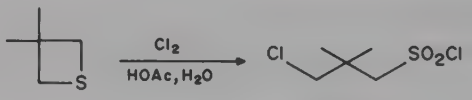
(252)

(253)

SCHEME 129

On alkylation of thietanes with trimethyloxonium fluoroborate, ring opening is prevented and stable methylsulfonium salts can be isolated[311,384].

Reactions of thietane with chlorine[294,385,386], bromine[387] and sulfuryl chloride[388] are facile and yield ring-opened products. For example, the reaction of 3,3-dimethylthietane with chlorine in acetic acid gave the sulfonyl chloride **254**[386] (Scheme 130).



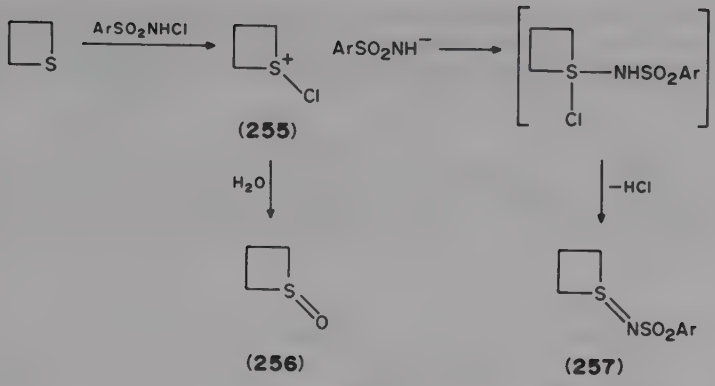
(254)

SCHEME 130

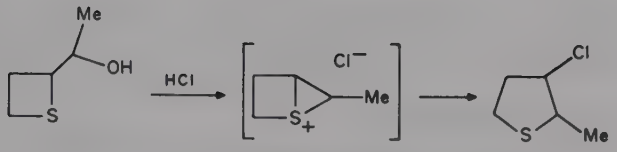
Other halogen electrophiles, such as chloramine-T, react with thietane, yielding the chlorosulfonium ion **255** which can give either the sulfoxide **256** or the sulfinimine **257**[389] (Scheme 131).

3. Ring expansion and contraction

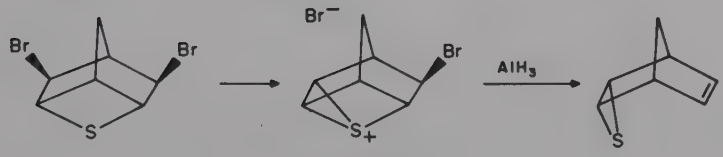
The sulfur atom of thietanes can interact intramolecularly with carbocations leading to ring expansion or contraction as shown in Schemes 132 and 133 [390–392].



SCHEME 131

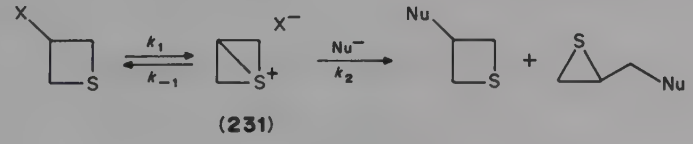


SCHEME 132



SCHEME 133

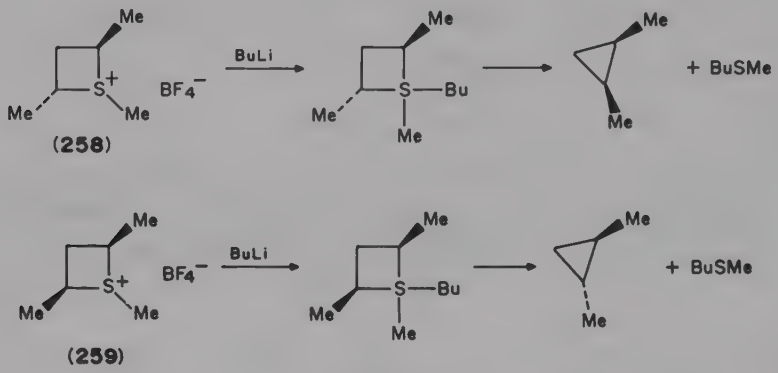
When a good leaving group is present at the 3-position of the thietane ring, intermediates like **231** can be formed[393] (Scheme 134). In this case ring contraction is less important and substitution occurs preferentially. This reaction has been studied kinetically and different hypotheses on the structure of the intermediate **231** have also been reported.



SCHEME 134

The two isomeric 1,2,4-trimethylthietanium tetrafluoroborates **258** and **259** react with butyllithium giving desulfurization and ring contraction to cyclopropane derivatives

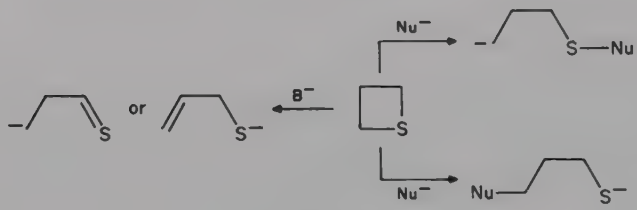
(Scheme 135). The reaction is stereospecific, so that **259** gives *trans*-1,2-dimethylcyclopropane and **258** produces the *cis*-isomer[394,395]. Three reaction mechanisms have been proposed. All of them assume the initial formation of a tetracoordinated sulfur species.



SCHEME 135

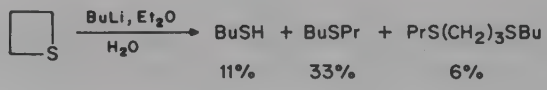
4. Reaction with nucleophiles and bases

Nucleophiles and bases react with thietanes as exemplified in Scheme 136.



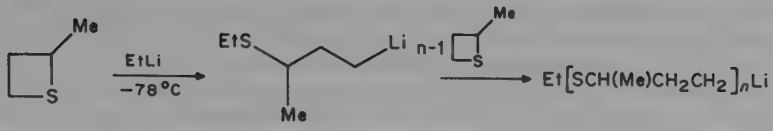
SCHEME 136

While nucleophiles can attack either the sulfur atom or the carbon atom α to the sulfur, bases always effect a C-2 deprotonation of the ring. In both cases open-chain species are obtained. Butyllithium[82,377], ethyllithium[377,396], phenyllithium[82] and phenylmagnesium bromide[377,396] give the ring-opened products after initial attack of the nucleophile at sulfur (Scheme 137).



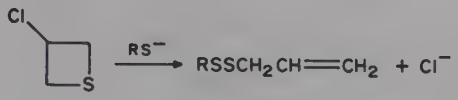
SCHEME 137

Ethyllithium reacts with 2-methylthietane giving rise to polymerization products[396] (Scheme 138). Even in this case an initial nucleophilic attack of the organolithium at sulfur has been invoked.



SCHEME 138

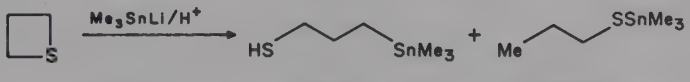
3-Chlorothietane undergoes attack at sulfur by sulfur nucleophiles like thiolate ions to give allyl disulfides **260**[397] (Scheme 139).



(260)

SCHEME 139

The reaction of trimethylstannyllithium with thietane gives **261** and **262**[398] (Scheme 140). The two products likely arise from attack of the trimethyltin anion at the C-2 ring carbon and at the heteroatom, respectively. The sulfide **262** and the thiol **261** are then formed by quenching of the corresponding lithium salts.



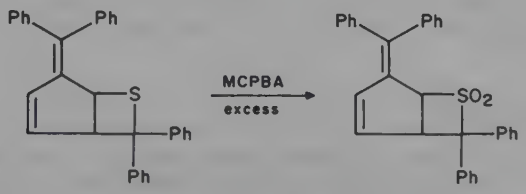
(261) **(262)**

SCHEME 140

5. Oxidation

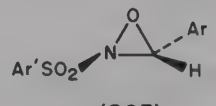
Oxidation at sulfur of thietanes can be readily and successfully realized by treatment with a wide number of oxidizing agents[193,194,321]. Peroxy acids, *t*-butyl hypochlorite, chromium trioxide-pyridine, monoxygenase enzyme from Aspergillus niger, oxaziridines, singlet oxygen and 1-chlorotriazole can all be used affording oxidized derivatives in good yields. Hydrogen peroxide is generally used in acetic acid but also in formic acid, ethanol and water[309,312,379,399–401]. The optimization of sulfoxide formation is possible by avoiding excess of hydrogen peroxide and working at low temperatures in the presence of WO_3[402,403]. Peroxy acids give sulfoxide under mild conditions with high yields, but excess of the oxidizing agent can further oxidize the sulfoxides to sulfones.

An example of remarkable selectivity of thietane oxidation with *m*-chloroperbenzoic acid to the corresponding thietane dioxide without oxidizing other functionalities present in the molecule is reported in Scheme 141.

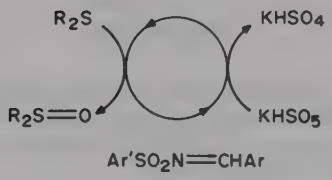


SCHEME 141

Aprotic and neutral oxidizing reagents, successfully used with organic sulfur compounds including thietanes, are the *N*-sulfonyloxaziridines **263**[404]. These reagents selectively and in high yield oxidize thietane to the corresponding sulfoxide[404]. Another oxidation of sulfides to sulfoxides occur by potassium peroxymonosulfate (Oxone) in the presence of catalytic amounts of sulfonylimine **264**[405] (Scheme 142). However, the oxidation of thietane by this method gives only the corresponding sulfone[405]. It has been suggested that the polar sulfoxide, formed by *N*-sulfonyloxaziridine oxidation of thietane, undergoes further oxidation by the peroxymonosulfate anion (Scheme 143).

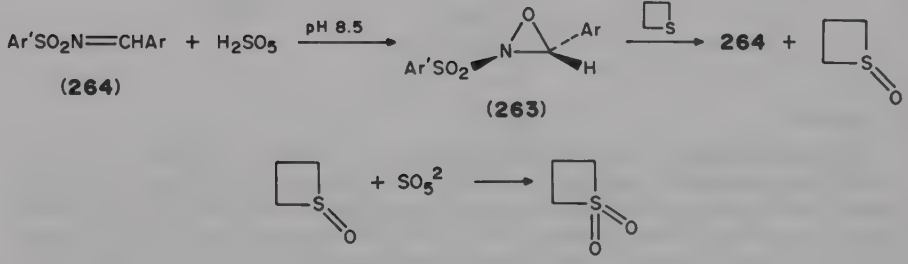


(263)



(264)

SCHEME 142



SCHEME 143

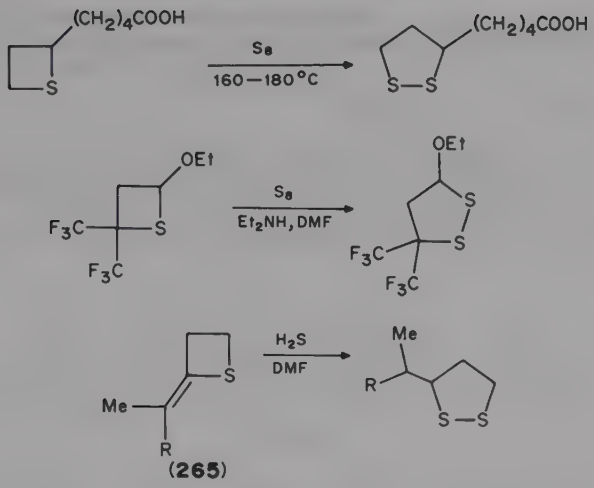
6. *Sulfur insertion*

Particular cases of ring expansions are represented by the insertion of sulfur into the thietane structure[377,406,407] (Scheme 144). In all cases 1,2-dithiolanes are obtained.

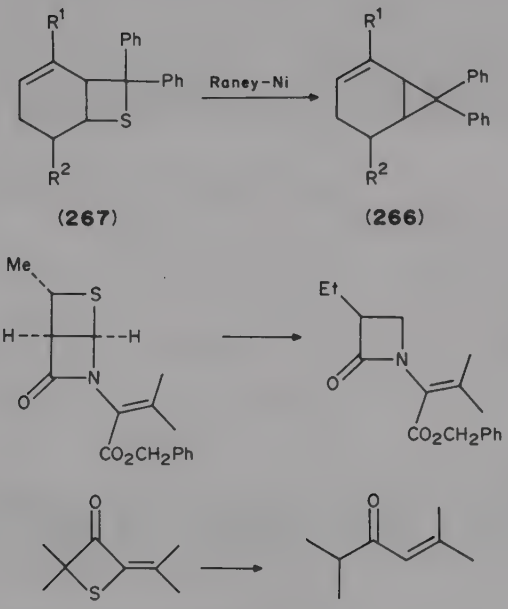
Thermal insertion of sulfur is the most general way to obtain dithiolane derivatives. If an exocyclic carbon–carbon double bond is present at the 2-position of the four-membered ring as in **265**, 3-substituted-1,2-dithiolanes are obtained in good yield by reaction with hydrogen sulfide[406,407].

7. *Desulfurization reaction*

Desulfurization of thietanes is generally accomplished by Raney nickel in ethanol or methanol. This popular method produces ring contraction or open-chain products in variable yields[330,408–412] (Scheme 145).



SCHEME 144



SCHEME 145

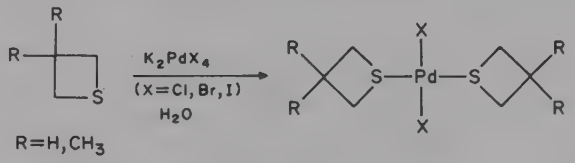
The formation of the cyclopropane derivative **266** from **267** seems to be linked to the presence of at least one phenyl or two alkyl groups at the 2-position of the thietane derivative.

Alternatives to Raney nickel desulfurization of thietanes are reducing agents like potassium-graphite[413] or sodium dithionite[414]. Molybdenum also removes sulfur from

thietane to give cyclopropanes and alkenes[415]. Alkyllithium reagents can also desulfurize thietanium salts to cyclopropane derivatives (see Scheme 135).

8. Reaction with metal ions and complexes

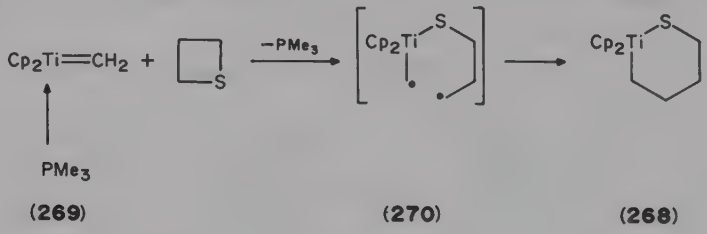
Thietanes give stable complexes with many metal ions. In particular, mercuric complexes are generally used for the characterization of thietanes. They are solid compounds easily prepared from mercuric chloride[259], bromide[337] or acetate[376]. Palladium and platinum complexes of thietanes have been prepared as well[416–418] (Scheme 146).



SCHEME 146

The analysis of the NMR spectra of these species, at variable temperature, has been used to determine the barrier to pyramidal inversion at the sulfur atom and to underline its dependence upon ring size[416]. Complexes of thietanes show a high pyramidal sulfur inversion barrier. Complexes of thiolane and thiane derivatives show inversion energies comparable with those of complexes of linear sulfides and complexes of thiiranes are conformationally stable up to temperatures where decomposition occurs.

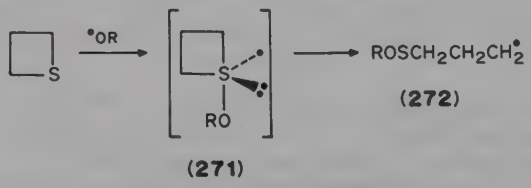
Among the reactions of thietanes with organometallics, a recent publication deals with the unexpected product **268**, obtained when the complex **269** reacts with the thietane ring, suggested to occur via the very reactive diradical **270**[419] (Scheme 147).



SCHEME 147

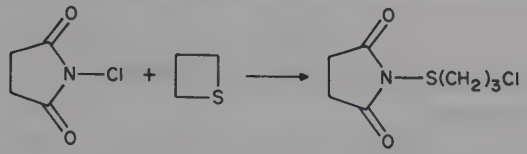
9. Reaction with radicals

Alkoxy or trimethylsilyloxy radicals attack the sulfur atom of thietane with formation of alkyl radicals[420] (Scheme 148). ESR spectroscopic data suggest the formation of the tricoordinate species **271** as an intermediate in the formation of **272**.



SCHEME 148

When *N*-chlorosuccinimide reacts with thietane at room temperature, the attack of a nitrogen-centered radical at sulfur generates the sulfenamide **273**[385] (Scheme 149). However, according to the reaction conditions, an ionic mechanism can also be operative.



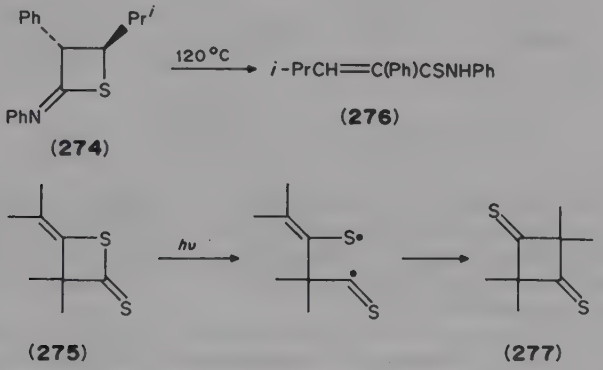
(273)

SCHEME 149

Irradiation of thietanes generates very reactive diradical intermediates which undergo a variety of transformations, so that the photochemical reactivity of thietanes is of very little importance from the synthetic point of view[421–425].

10. Rearrangements

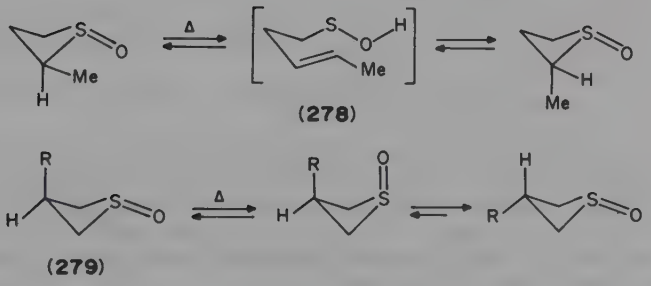
2-Iminothietane **274** and 2-thionothietane **275** undergo thermal or photochemical rearrangements[426,427] (Scheme 150), when the former gives the alkene derivative **276**, while the particular structure of the latter allows the formation of the cyclobutane derivative **277**.



(274) **(276)**

(275) **(277)**

SCHEME 150



(278)

(279)

SCHEME 151

A reversible thermal isomerization can occur with alkyl-substituted thietane 1-oxides[428] (Scheme 151). The isomerization seems to proceed via the sulfenic acid **278**. In the case of thietane *S*-oxide **279** the same isomerization has been rationalized via pyramidal inversion at sulfur[310].

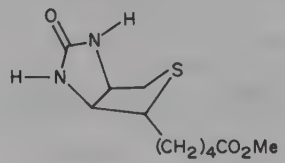
IV. THIOLANES AND THIANES

A. Conformational Analysis

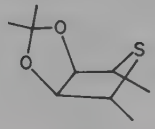
Conformation of five- and six-membered ring sulfides has been investigated in recent years by means of X-ray analysis, NMR or microwave spectroscopy. In several cases data obtained have been compared with the results of empirical, semiempirical and *ab initio* calculations. In some instances mass spectrometry and chromatography have also been studied and related to the geometry of each species. Most of these subjects have been reviewed[341,429–437].

Calculated bond lengths and angles obtained by molecular mechanics calculations (Westheimer–Hendrickson method)[438] of thiolane itself (**280**) are in agreement with values obtained by X-ray analysis. Moreover, a C_2 molecular symmetry resulted from the diffractometric study. On the other hand, NMR and X-ray analysis of biotin (**281**) and the related thiolan **282** showed an envelope conformation assumed by the five-membered ring[439].

(280)



(281)



(282)

Generally, alkyl substituents in position 2 and 5 of thiolane prefer an equatorial orientation. A similar trend has been reported for 2-alkyl-substituted thiolanes, thiane *S*-oxides and *S*-tosylsulfinylimines[440]. Many other examples of such preference in alkyl or aryl substituted thiolanes have been documented[341,437]. The same preference has also been found for thiane derivatives[341,435,437].

Substitution of a carbon atom by sulfur in a five- or six-membered saturated carbocyclic ring causes only minor changes in the conformation of the ring. Nevertheless, the carbon–sulfur bond in five- or six-membered ring heterocycles is longer than the carbon–carbon bond in the corresponding cycloalkanes (1.80 Å vs 1.54 Å), and the C—S—C angle in thiolanes and thianes (about 100°)[341] is smaller than the C—C—C angle in carbocylic species of the same size. The variation of the dipole moment due to the introduction of the heteroatom and the large sulfur van der Waals radius have minor influences on the conformation[435,437].

X-ray analysis of several thiane derivatives showed a chair conformation similar to that of the corresponding carbocyclic systems[441–447].

The variations due to the introduction of the sulfur atom have been well investigated by NMR[435]. Complete line-shape analysis of NMR spectra showed that the barrier for ring inversion of thiane is smaller than that of cyclohexane and tetrahydropyran (ΔG^* 9.4 kcal mol^{-1} for thiane, 10.3 kcal mol^{-1} for pyran and cyclohexane)[448–450]. This difference probably arises from the smaller torsional barrier which exists around a carbon–sulfur bond compared to a carbon–carbon bond.

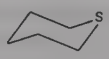
As far as the ring shape is concerned, thiane is distinctly more puckered than cyclo-

hexane[451]. The evaluation of ring shape can be easily accomplished by measuring the *R* parameter, which represents the ratio of coupling constants between vicinal protons and which is directly related to the dihedral angle HC—CH[451]. Undistorted geometry should have *R* values between 1.9 and 2.2, which correspond to a dihedral angle of 56–58°. Data obtained for the thiane ring are reported in Table 6.

Another interesting and widely studied feature of these systems is the preferential axial or equatorial orientation showed by thianes bearing a substituent at sulfur. The results are summarized in Table 7.

The preference for axial or equatorial orientation of the group linked to sulfur is often due to steric or electrostatic interactions with the substituents in positions 3 and 5. However, the relatively long carbon–sulfur bond minimizes these interactions so that in solution the two conformations are almost equally populated [for thiane *S*-oxide (**284**) eq:ax = 32:68; for thiane *S*-imine (**286**) eq:ax = 55:45; for thiane *S*-tosylimine (**287**) eq:ex =

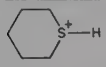
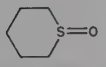
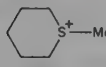
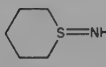
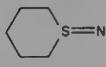
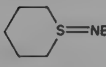
TABLE 6. Measured *J* and calculated *R* and dihedral angle (φ) values for the two segments of thiane ring



Segment	^3J *trans* (Hz)	^3J *cis* (Hz)	R^a	φ
α–β	8.15	2.96	2.65	61°
β–γ	8.47	3.28	2.58	60°

$^aR = {}^3J\ trans/{}^3J\ cis$.

TABLE 7. Preferred orientation calculated for sulfur-substituted thiane derivatives

Substrate	Solvent	Preference
 (**283**)	FSO_3H/SO_2	axial[449]
 (**284**)	CH_2Cl_2	axial[448]
 (**285**)	CH_2Cl_2/SO_2	equatorial[450]
 (**286**)	$CH_2Cl_2/CHClF_2$	equatorial[452,453]
 (**287**)	$CHClF_2$	axial[452,453]
 (**288**)	$CHClF_2$	axial[452,453]

40:60; for thiane *S*-benzylimine (**288**) eq:ax = 45:55]. The orientation of the substituent at sulfur and the relative abundance of the two isomers have been measured by means of ^{1}H and ^{1}C NMR spectroscopy using both chemical shifts and coupling constants values.

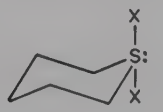
In the case of the protonated thiane **283** Olah and coworkers were able to assign the orientation of the sulfur–hydrogen bond by directly measuring the ^3J coupling constant through sulfur[318]. In all other cases the differences between proton and carbon chemical shifts in the two isomers have been successfully used to assign their geometry[454–457]. It should be noted that to obtain an exact interpretation of NMR data, it is necessary to consider that while carbon–carbon and carbon–sulfoxide sulfur bonds have the same magnetic anisotropy sign, the carbon–sulfur bond behaves in an opposite manner.

For substituents in position 2 or 6 of thianes, the preference for equatorial or axial orientation depends strictly on the nature of the substituent itself. Alkyl or aryl groups prefer an equatorial arrangement[435,439,458], polar groups such as alkoxy or alkylthio prefer an axial orientation probably because of the anomeric effect[459–462].

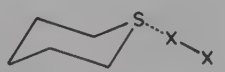
Electronegative substituents such as chlorine, bromine or acetoxy in position 3 of thianes show a greater preference for equatorial orientation, while they prefer axial orientation when in position 4[463,464].

Recently, the conformation of saturated six-membered heterocycles, including thiane, has been described numerically by means of puckered coordinates deriving from endocyclic torsion angles[465].

Structure and ionic character of halogen–thiane adducts have been investigated by means of NMR spectroscopy and conductance measurements[451]. Two structures are possible for the 1:1 adducts: a sulfurane species **289** with a bipyramidal trigonal arrangement or a molecular complex **290** with a tetrahedral arrangement at sulfur. For the adducts of bromine and iodine with thiane, NMR data did not show any distortion of the six-membered ring so that a bipyramidal trigonal structure **289** can be reasonably ruled out. The ionic character measured by conductance showed a greater charge separation for the bromine than for the iodine adduct.



(289)

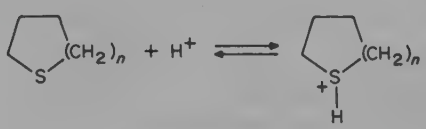


(290)

B. Basicity

The relative basicity of cyclic sulfides has been indirectly measured evaluating the stability of the corresponding iodine adducts[466,467], or by measuring the relative strength of the hydrogen bond between cyclic sulfides and phenol[468].

A direct evaluation of pK_{BH^+} deriving from the equilibrium shown in Scheme 152 has been obtained in sulfuric acid[319].



SCHEME 152

The concentrations of the different species in solution have been measured by means of ^{1}H NMR spectroscopy. No influence of ring size on the basicity was observed (pK_{BH^+}

measured values for thiolane and thiane are −6.84 and −6.74, respectively). On the other hand, a very similar behavior of thiolane and thiane in superacid medium has been reported by Olah and coworkers[318].

C. Synthesis

Several methods for the synthesis of five- and six-membered cyclic sulfides are available and many reviews dealing with this matter have been published[321,429–434,469].

Due to the small ring strain in thiolane and thiane derivatives, many of the methods used for the preparation of open-chain sulfides can be applied successfully to the synthesis of five- and six-membered ring sulfides.

The most important methods regarding reactive sulfur centers will be considered specifically. The synthetic approaches which do not involve a sulfur functionality in the reaction will be considered only in special cases.

Among the cyclization techniques used are the following: (1) intramolecular nucleophilic displacement of a suitable leaving group by a thiolate ion; (2) intramolecular addition of a sulfur-centered radical to a carbon–carbon multiple bond; (3) electrophilic addition of sulfur functionalities to multiple bonds; (4) Diels–Alder reactions where a sulfur–carbon double bond is involved as diene or dienophile (in this case an unsaturated six-membered ring is obtained); (5) partial desulfurization of a cyclic disulfide; (6) Michael-type reactions of thiols or thiolate ions.

1. Intramolecular nucleophilic displacement

Nucleophilic sodium sulfide displacement of two appropriate leaving groups in suitable positions in the same molecule has been most often exploited for the preparation of a wide range of thiolane and thiane derivatives[321,429–434,469].

Halide ions, tosylates or mesylates have been used as leaving groups. Solvents of choice are usually water or alcohols, even though examples where DMSO, DMF, acetonitrile or acetone were used have been reported[429–434]. Often reaction conditions are quite drastic in order to increase to solubility of the reagents. The syntheses of sulfides **291**[470], **282**[471], **292** and **293**[472], and **294**[473] are shown in Scheme 153. Using the same methodology, labelled compounds[474,475] and thiapropellane systems like **295**[476] have also been prepared (Scheme 154).

Alternative approaches have been used in order to avoid the problems linked to the low solubility of sodium sulfide in organic solvents and the drastic reaction conditions often necessary to complete the reaction.

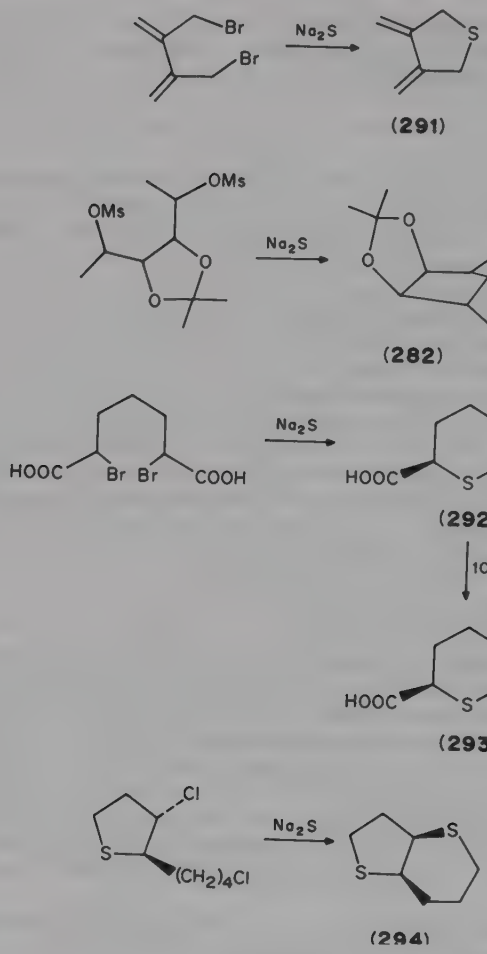
Thus the reaction of a suitable pyridinium salt of type **296** under alkaline conditions leads to the formation of cyclic sulfides (Scheme 155)[477].

Similarly, benzoxazole **297** was used as sulfur carrier. Using this reaction, functionalized benzyl bromide **298** has been successfully converted into cyclic sulfides **299** and **300** (Scheme 156[478]).

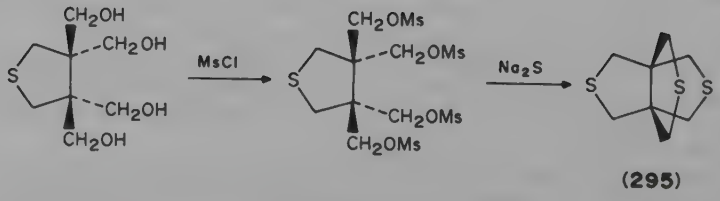
Regarding the preparation of a suitable source of sulfide anion soluble in apolar solvents, Gladysz and coworkers[479] gave one of the first answers by reacting molecular sulfur with lithium triethylboronhydride as shown in Scheme 157.

The lithium sulfide generated *in situ* reacts with alkyl, benzyl and acyl chlorides affording the corresponding sulfides, as shown in Scheme 158 for the reaction of the dibromo compound **301**. The ring closure to the thiane derivative **302** occurs in mild conditions and in satisfactory yield[479].

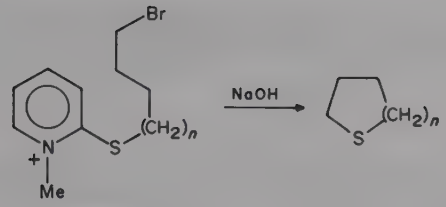
Bis(tributylstannyl) sulfide (**303**) is an efficient sulfide ion carrier in that it is able to react with benzyl or vinyl bromides in the presence of sodium iodide as catalyst to give the corresponding sulfides[480]. Using this method **302** was quantitatively prepared from **301**.



SCHEME 153

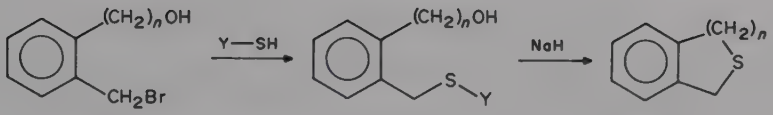


SCHEME 154

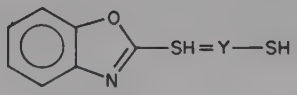


(296)

SCHEME 155



(298) (299) $n=1$ (300) $n=2$

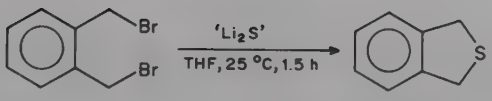


(297)

SCHEME 156

$$1/8\ S_8 + 2LiEt_3BH \xrightarrow[25\ ^\circ C]{THF} \text{'}Li_2S\text{'} + 2\,Et_3B + H_2$$

SCHEME 157

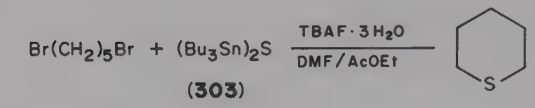


63%

(301) (302)

SCHEME 158

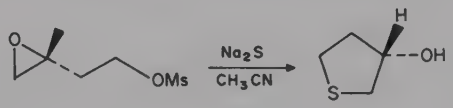
Recently, Harpp and coworkers developed the fluoro or cyano demetallation of group 14 sulfides to give active sulfide ions[481,482]. In these reactions the release of sulfide ion from species such as **303** or the corresponding bis(trimethylsilyl) sulfide occurs under even milder conditions. Thus bis(tributyltin) sulfide (**303**), when destannylated using tetrabutylammonium fluoride (TBAF), is able to quantitatively convert 1,5-dibromopentane into thiane[482] (Scheme 159).



(303)

SCHEME 159

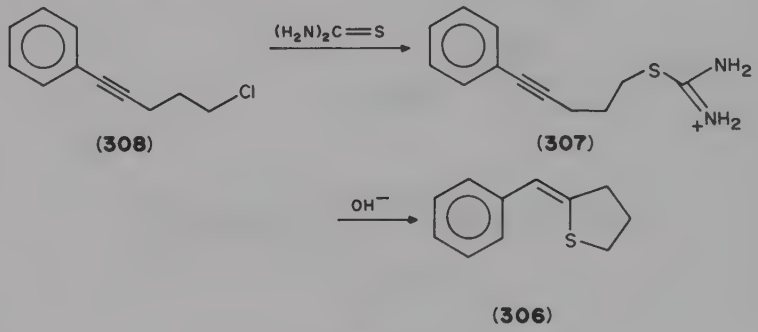
The ring opening of oxiranes by sulfide ions, followed by intramolecular nucleophilic displacement, gives thianes or thiolanes. Thus, reaction of oxiranes with alkali metal sulfides (Na_2S or K_2S) has been very often used for the preparation of hydroxy substituted thiane and/or thiolane derivatives[483–485], as e.g. in the synthesis of thiolane **304** from the oxirane **305**[486] (Scheme 160).



(305) (304)

SCHEME 160

Nucleophilic attack of a thiolate ion at a carbon–carbon triple bond has been exploited for the preparation of the exocyclic unsaturated thiolane **306**[487]. The thiolate anion was generated by alkaline hydrolysis of the thiouronium salt **307** easily prepared from the chloride **308** and thiourea (Scheme 161).

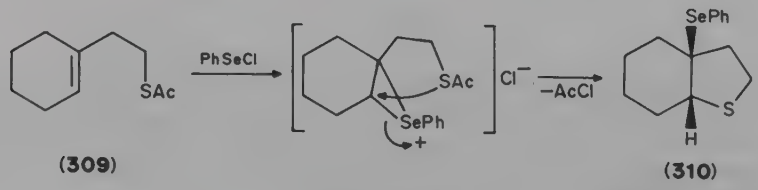


(308) (307)

(306)

SCHEME 161

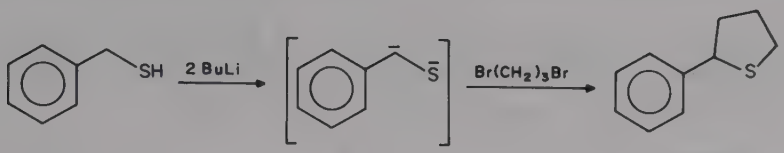
Often, five- or six-membered ring sulfides have been obtained by nucleophilic attack of a suitable sulfur-containing group on an activated double bond[488]. For example, the thioacetate **309** yields the bicyclic thiolane **310** by phenylselenyl chloride activation of the double bond[418] (Scheme 162).



(309) (310)

SCHEME 162

Finally, the preparation of the dianion **311** from benzylthiol and butyllithium and its reaction with 1,3-dibromopropane has been used for the preparation of 2-phenylthiolane (**312**)[163] (Scheme 163).

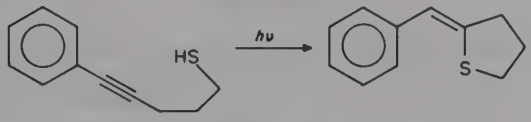


(**311**) (**312**)

SCHEME 163

2. Intramolecular radical cyclization

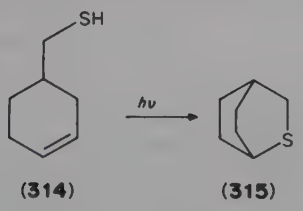
Another classical method for the preparation of cyclic sulfides is the intramolecular cyclization of a sulfur-centered radical[321,429–434,469]. Irradiation of an unsaturated thiol is a widely used technique to obtain cyclic species. Thus the thiolane derivative **306** can also be prepared by irradiation of the unsaturated thiol **313**[490] (Scheme 164).



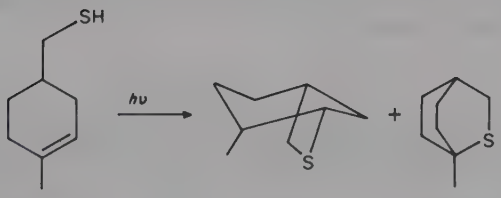
(**313**) (**306**)

SCHEME 164

Often, the substitution at the double bond influences the nature of the products[491]. For example, irradiation of thiol **314** yields only the [2.2.2] bicyclic sulfide **315** while a methyl substituent at the double bond as in **316** leads to the formation of a 3:1 mixture of **317** and **318** deriving from ring closure at both olefinic carbons[491] (Scheme 165).



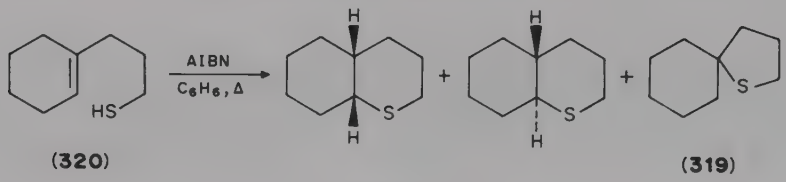
(**314**) (**315**)



(**316**) (**317**) (**318**)

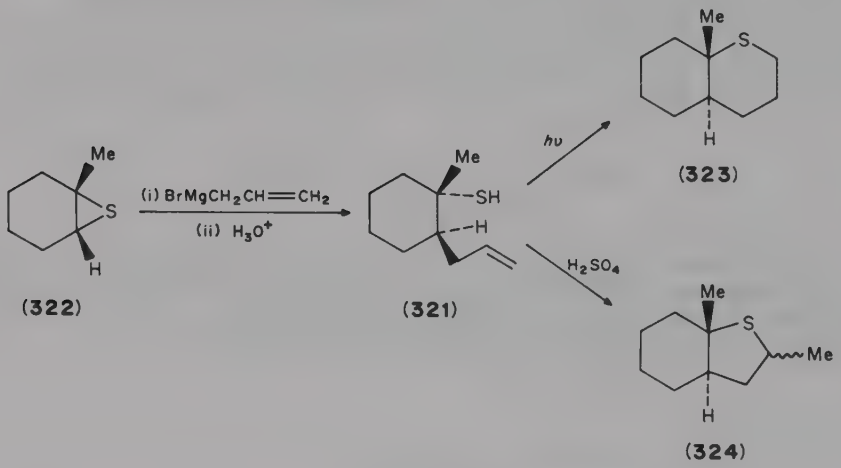
SCHEME 165

Unsaturated thiols can also be cyclized using radical initiators such as AIBN[492]. A mixture of *cis*- and *trans*-1-thiodecalin together with the spiro thiolane **319** were obtained by AIBN-catalyzed cyclization of the thiol **320** (Scheme 166).



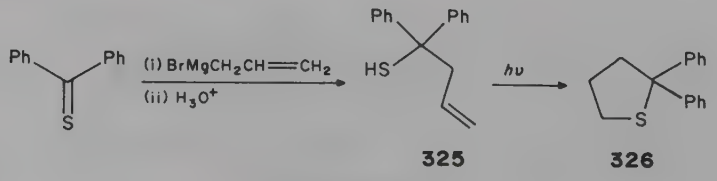
SCHEME 166

Unsaturated thiols can be simply prepared by allylmagnesium bromide ring opening of episulfides. In the example reported in Scheme 167, the thiol **321**, generated from thiirane **322**, can cyclize to give two different products depending on the reaction conditions[493]. The radical cyclization gives the thiane derivative **323**, while acid-catalyzed ring closure leads to the bicyclic thiolane **324**.



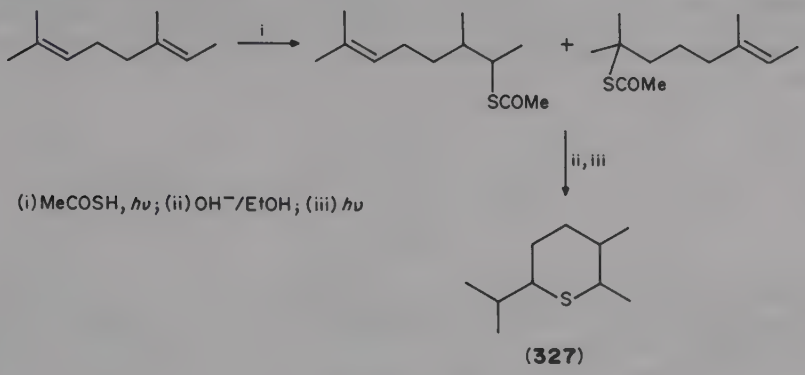
SCHEME 167

Carbophilic attack of allylmagnesium bromide on thiocarbonyl compounds is an alternative route to unsaturated thiols (Scheme 168)[494]. The homoallylic thiol **325** obtained by allylmagnesium bromide addition to diphenylthioketone was photochemically cyclized to the thiolane derivative **326**.



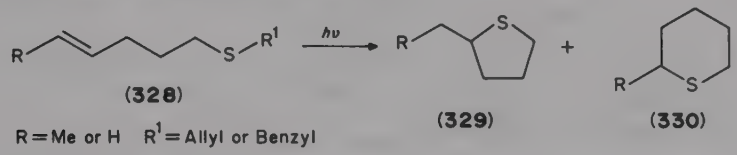
SCHEME 168

Thioacetic acid has also been successfully used in the preparation of cyclic sulfides. The method involves a photocatalyzed double addition to nonconjugated dienes as shown in Scheme 169 for the synthesis of the thiaterpene **327**[495]. Here, thioacetic acid is a synthetic equivalent of a diradical sulfur atom.



SCHEME 169

Sulfur radical species can also be generated by irradiation of sulfides of type **328** where the R^1 group is an allyl or a benzyl residue[496], when mixtures of substituted thiolanes **329** and thianes **330** were obtained[496] (Scheme 170).

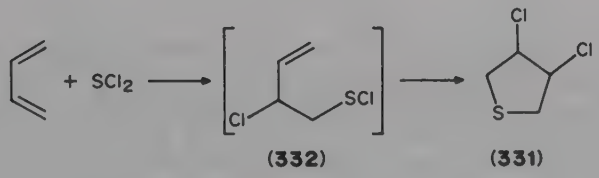


SCHEME 170

3. Electrophilic intramolecular addition

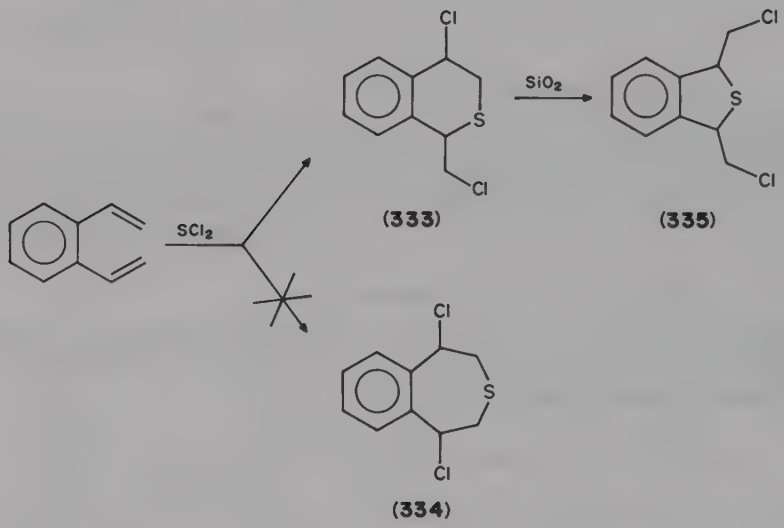
Intramolecular addition of electrophilic sulfur functionalities to carbon–carbon multiple bonds is another fruitful method for the synthesis of thiolanes and thianes.

Sulfur dichloride is the simplest molecule containing an electrophilic sulfur atom, and its addition to open-chain or cyclic dienes offers the possibility to synthesize dichloro-substituted cyclic or bicyclic derivatives. This reaction was discovered long ago[497] but is still used. For example, butadiene with sulfur dichloride affords 3,4-dichlorothiolane (**331**)[498] (Scheme 171).



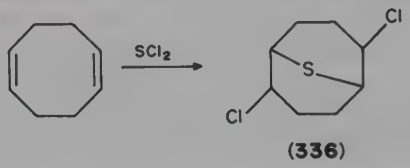
SCHEME 171

The reaction occurs by addition of the sulfur dichloride to one of the two double bonds of the butadiene to give the homoallyl sulfenyl chloride **332**, which undergoes fast intramolecular electrophilic addition to the second double bond to give the thiolane **331**. In some instances this reaction showed interesting regioselectivity[499]. For example, 1,2-divinylbenzene with sulfur dichloride gives selectively the thiane derivative **333** while no trace of the thiepane **334**, which could also be formed, was detected. The thiane derivative **333** can be further converted into the thiolane **335** by treatment with silica[499] (Scheme 172).



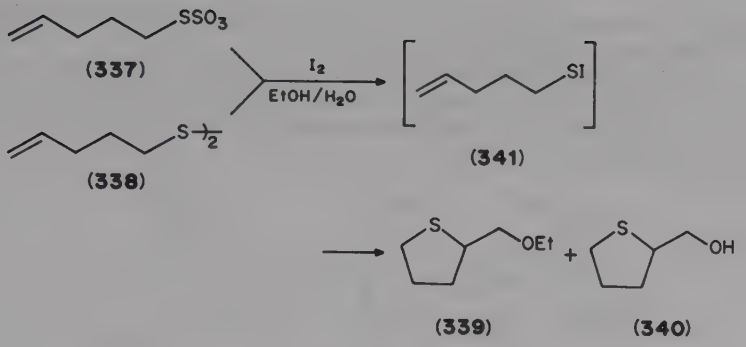
SCHEME 172

Sulfur dichloride with cyclic dienes give biclic sulfides whose size depends on the nature of the diene. For example, the [3.3.1] bicyclic sulfide **336** is obtained when sulfur dichloride reacts with 1,5-cyclooctadiene[500,501] (Scheme 173).



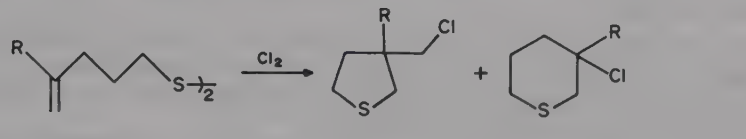
SCHEME 173

Generation of an electrophilic sulfur can also be achieved by halogen cleavage of the sulfur–sulfur bond of disulfides or thiosulfates. If an unsaturated center is present in a suitable position, a substituted cyclic sulfide is formed[502–504]. For example, thiolsulfate **337** or disulfide **338** reacts with iodine in refluxing ethanol–water mixture to give 2-ethoxymethylthiolane (**339**) as the main product together with minute amounts of alcohol **340**[505] (Scheme 174). In both cases the sulfenyl iodide **341** is the probable intermediate of the reaction.



SCHEME 174

The generation of a sulfenyl chloride from an unsaturated disulfide can be exploited as well. It has been demonstrated that chlorinolysis of the sulfur–sulfur bond occurs faster than chlorine addition to the double bond[502,506]. In the case of chlorinolysis of disulfides **342**, both thiolanes **343** and thianes **344** are formed in ratios which depend on the reaction conditions and the nature of the substituents[503] (Scheme 175).



(342) **(343)** **(344)**

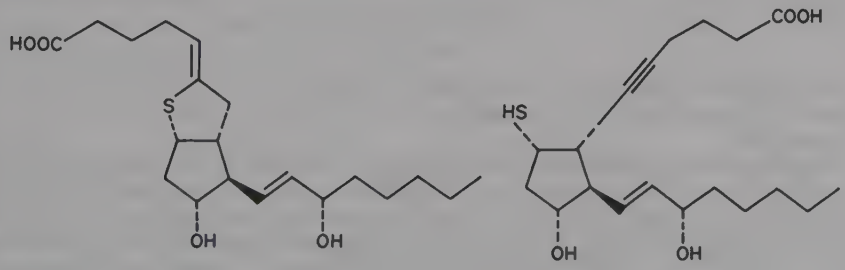
(342a),(343a),(344a) : R=H
(342b),(343b),(344b) : R=Me

Kinetic distribution
343a:**344a** = 80:20
343b:**344b** = 95:5

Thermodynamic distribution
343a:**344a** = 18:82
343b:**344b** = 4:96

SCHEME 175

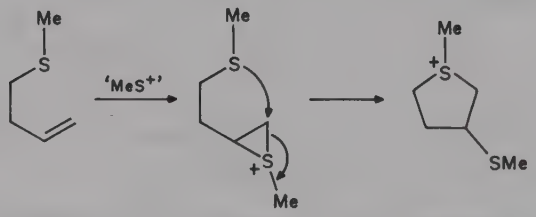
At −30 °C the reaction of the unsubstituted disulfide **342a** gives as major product the thiolane **343a**. The two cyclic sulfides on thermal equilibration give a mixture in which the thiane derivative **344a** predominates. A similar behavior is shown by the methyl-substituted disulfide **342b**.



(345) **(346)**

Using a similar approach the 6,9-thiaprostacyclin **345** has been prepared from the thiol **346**[507] or from the corresponding disulfide[508].

A related strategy was used for the synthesis of the sulfonium salt **347**. Addition of dimethyl(methylthio)sulfonium tetrafluoroborate, a methylthio cation source, to the unsaturated sulfide **348** generates the thiiranium ion **349**, which in turn yields the stable five-membered ring **347**[509] (Scheme 176).



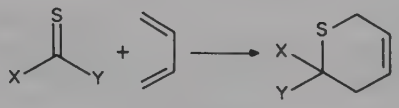
(348) **(349)** **(347)**

SCHEME 176

4. Diels–Alder reaction

4 + 2 Cycloaddition of thiocarbonyl compounds with 1,3-dienes probably represents the most versatile method for the preparation of unsaturated thiane derivatives[510]. A wide range of substituents and a variety of dienes can effectively be used and a very large number of 2,6-dihydrothiopyranes have been prepared[321,511–519].

Thioketones and thioaldehydes are most frequently used in these cycloadditions even though many other thiocarbonyl derivatives have been synthesized in order to obtain particular substituted dihydrothiopyranes[519] (Scheme 177).

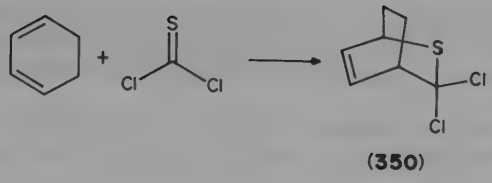


X = Alkyl, Aryl or H, Y = RCO, RO_2C, Ph_2PO, CN.
X = Alkyl or Aryl, Y = SR, SO_2Ar, SiR_3.
X = RS, Y = CN
X = R_2N, Y = CN
X = Y = Cl, RCO, RO_2C

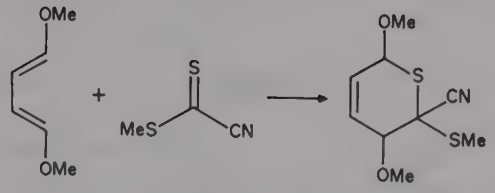
SCHEME 177

For example, the reaction of thiophosgene or cyanodithioformate with suitable dienes affords functionalized dihydrothiopyran systems such as **350**[520] or **351**[521,522] (Scheme 178).

These reactions usually follow the reactivity rules of typical 4 + 2 cycloadditions. With unsymmetrical dienes the predominant regioisomer usually derives from an advanced formation in the transition state of the sulfur–carbon bond compared to the new carbon–carbon bond[321]. Some examples are reported in Scheme 179 where the reactions of 1-acetoxy[523–525], 1-alkyl[526] and 2-ethoxy-substituted[527] dienes with thiocarbonyl compounds are shown.

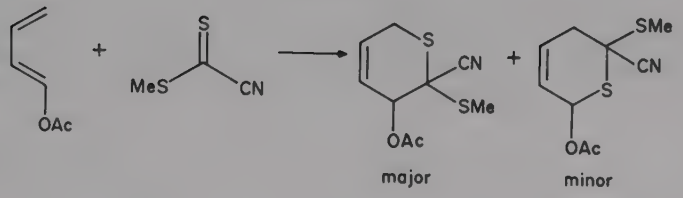


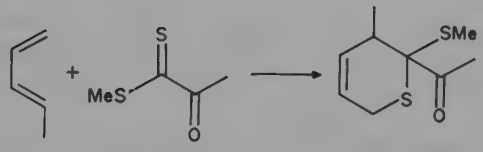
(350)

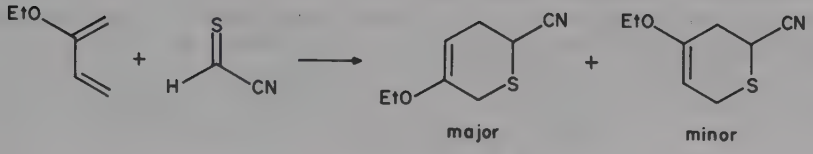


(351)

SCHEME 178

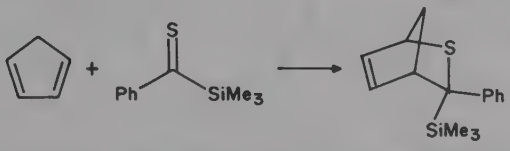






SCHEME 179

When a cyclic diene reacts with an unsymmetrical thiocarbonyl compound, the *endo* cycloadduct is obtained as the major isomer. Thioacylsilanes are very selective dienophiles from this point of view: thus thione **352** reacts with cyclopentadiene giving rise to the *endo* isomer **353** as the sole product[528] (Scheme 180).

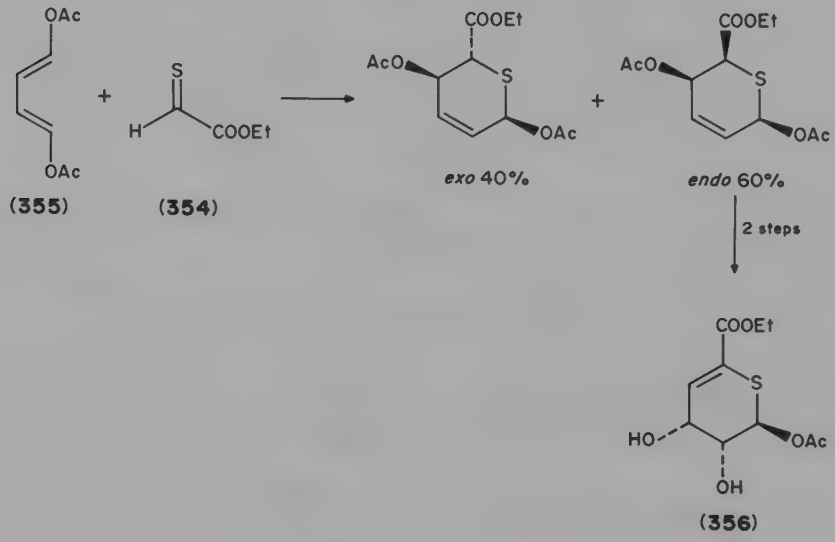


(352) (353)

SCHEME 180

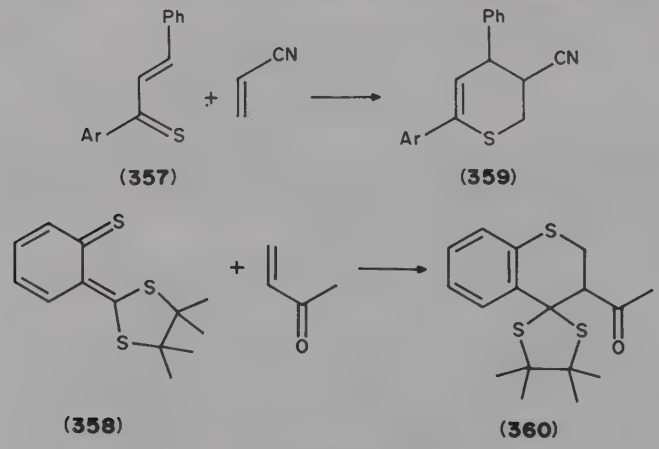
However, it has been recently reported that in some instances the formation of the *exo* isomer as major product in the Diels–Alder reaction of a thione with a cyclic diene can be simply achieved by the appropriate choice of the method utilized for the synthesis of the thiocarbonyl compound[259].

The cycloaddition of the thioaldehyde **354** with the diene **355** was the key step for the synthesis of the thiashikimic acid derivative **356**, a product of potential pharmacological interest[530] (Scheme 181).



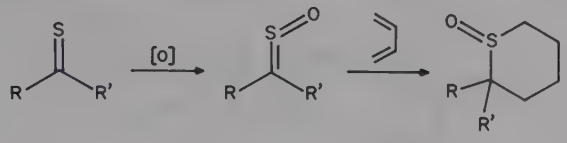
SCHEME 181

The presence of conjugated double bonds in thiones **357** or **358** makes these good dienic systems suitable for cyclization even with electron-poor alkenes[531–537], and enabled one to synthesize 5,6-dihydrothiopyran derivatives **359** or **360** (Scheme 182).



SCHEME 182

The versatility of the Diels–Alder reactions is even more enhanced by the possibility to convert the thiones into the corresponding *S*-oxides, which open an easy way for the synthesis of cyclic unsaturated thiane *S*-oxides[538] (Scheme 183).

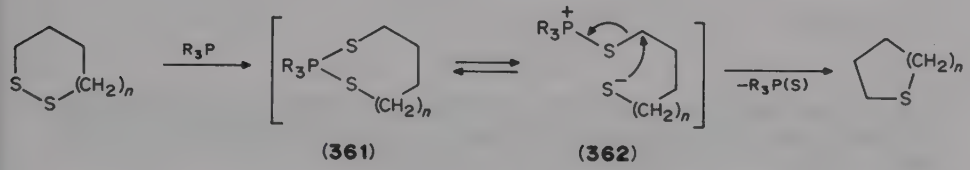


SCHEME 183

5. *Desulfurization of cyclic disulfides*

Some cyclic sulfides have been prepared by partial desulfurization of the corresponding cyclic disulfides. Bases such as sodium hydroxide have been used [539], but trivalent phosphorus compounds such as phosphines[540,541], phosphites[542] and amino-substituted phosphorus derivatives[363,543,544] are mostly exploited for sulfur extrusion.

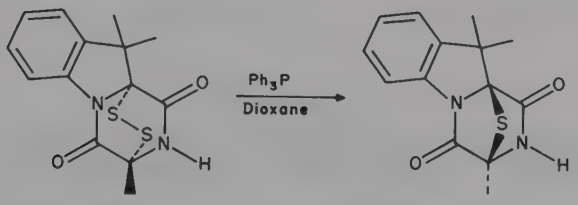
The mechanism seems to involve insertion of phosphorus into the sulfur–sulfur bond to give the cyclic intermediate **361**, which is in equilibrium with the phosphonium thiolate **362**. Intramolecular displacement of a phosphine sulfide derivative by the thiolate ion of **362** leads to the formation of the cyclic sulfide[189] (Scheme 184).



(361) **(362)**

SCHEME 184

Several studies on this reaction have been carried out in order to clarify its stereochemistry[543,545–547]. In one case it has been demonstrated by X-ray analysis that sulfur extrusion occurs with inversion of configuration at both carbon atoms linked to sulfur[545]. Thus when the piperazine derivative **363** reacts with triphenylphosphine, the cyclic sulfide **364** shows an inverted configuration at both carbons (Scheme 185).

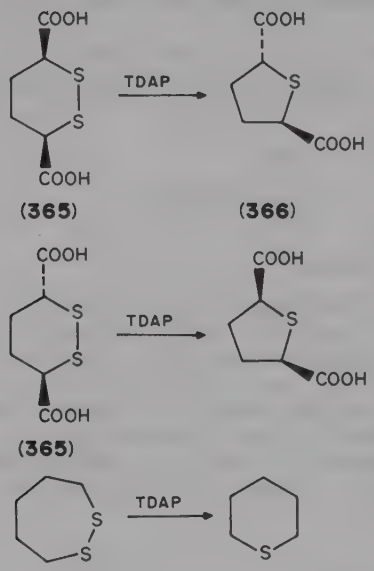


(363) **(364)**

SCHEME 185

Among the various trivalent phosphorus compounds, tris(diethylamino) phosphine (TDAP) is very effective. For example, treatment of the 1,2-dithiane **365** with TDAP at room temperature gives quantitatively the thiolane **366**[544]. Many other examples of

DTAP desulfurization of cyclic disulfides have been published by Harpp and co-workers[543] (Scheme 186).

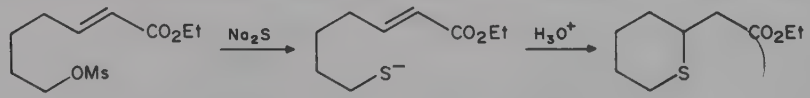


SCHEME 186

The reaction of suitable mercaptoalcohols with diethoxytriphenylphosphorane (DTPP) is a general and useful method for the synthesis of cyclic sulfides with three- to seven-membered rings[189]. Yields are very sensitive to the ring size as well as to the substitution pattern of the mercaptoalcohol chain (see Scheme 107).

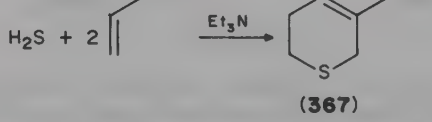
6. *Michael addition*

Michael addition of a thiol or thiolate to an activated double bond is an efficient method for the synthesis of thiolane and thiane derivatives[548–550]. The thiolate ion can be generated *in situ* by sodium sulfide nucleophilic displacement as described in Scheme 187.



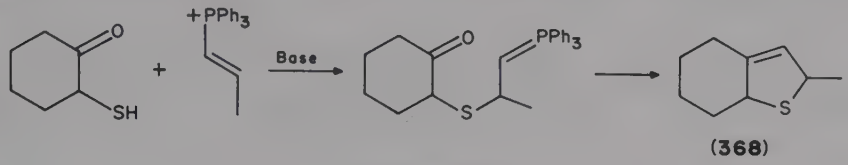
SCHEME 187

Hydrogen sulfide can be also used as Michael donor[550,551], when it reacts with two equivalents of propenal affording the unsaturated thiane **367** (Scheme 188).



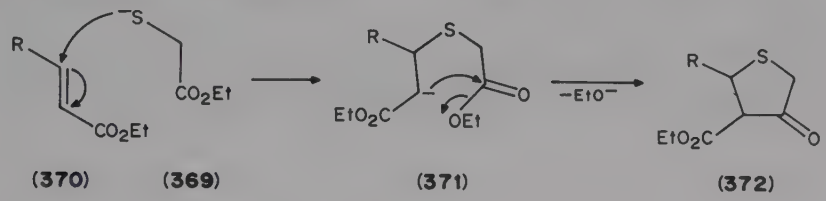
SCHEME 188

Vinyl phosphonates and vinylphosphonium salts have been successfully used as Michael acceptors in these reactions[552,553]. The bicyclic thiolane derivative **368** has been prepared in a one-pot procedure[554–556] using a sequence of Michael addition and Wittig reaction (Scheme 189).



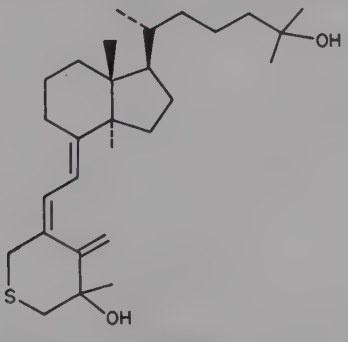
SCHEME 189

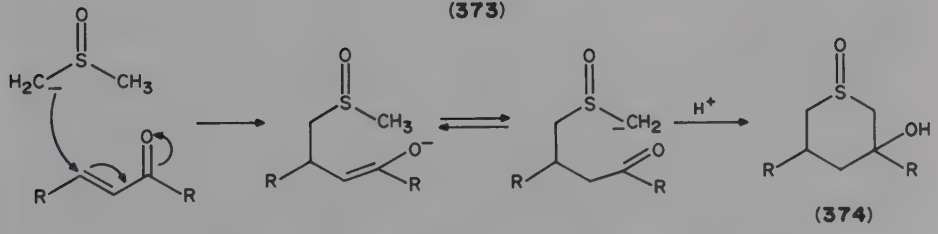
The reaction of the carboethoxythiolate **369**, used as Michael donor, with activated olefinic compounds like **370** leads to the formation of the anion **371**, which easily undergoes Dieckmann condensation affording precursors of thiaprostaglandin ring units such as **372**[549, 557–559] (Scheme 190).



SCHEME 190

Recently, using the reagent **369**, a sulfur analogue of dihydroxy vitamin D_3, **373**, which showed an activity very similar to the natural product, has been synthesized[560].

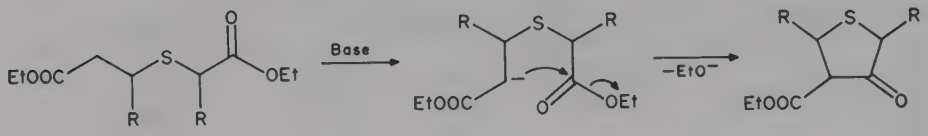




SCHEME 191

In a similar reaction the anion obtained from DMSO reacts with α,β-unsaturated ketones giving rise to 3-hydroxythiane-*S*-oxide derivatives of type **374**[561] (Scheme 191).

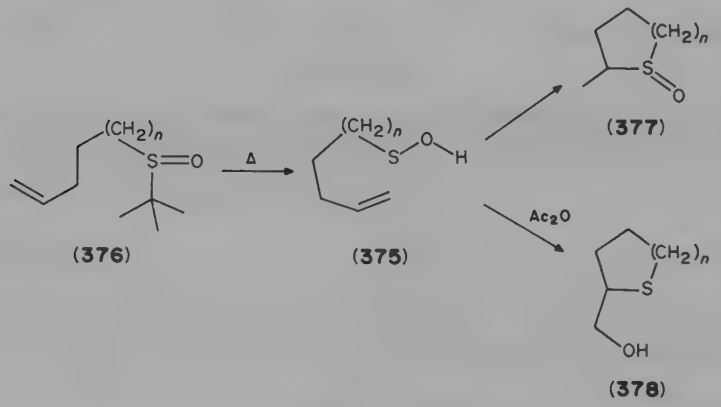
Various cyclic sulfides bearing a carbonyl function in the ring have also been prepared by Dieckmann-type cyclizations[562–564] (Scheme 192).



SCHEME 192

7. Miscellaneous methods

An interesting method for the synthesis of thiolan and thiane-*S*-oxide derivatives is the cyclization of an unsaturated sulfenic acid[428,565–568] (Scheme 193). The unstable sulfenic acid **375** can be easily generated by thermolysis of the *t*-butyl sulfoxide **376**. Cyclization of **375** in the 'RSO + H' fashion affords the cyclic *S*-oxide **377** or in the 'RS + OH' fashion gives rise to the 3-hydroxymethyl-substituted cyclic sulfide **378**. The latter cyclization mode is strongly favored by carrying out the reaction in the presence of acetic anhydride.



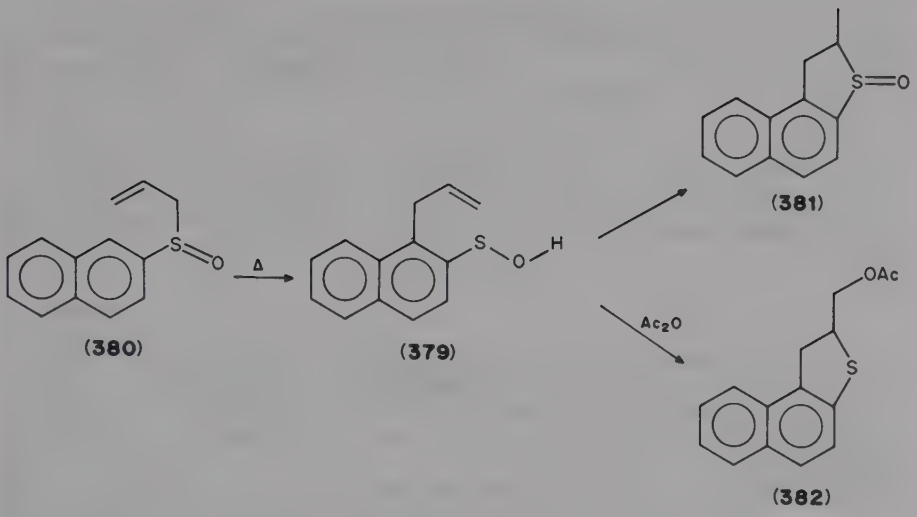
SCHEME 193

Similarly, the sulfenic acid **379**, generated from the sulfoxide **380**, thermally cyclizes to **381**, while in the presence of acetic anhydride the cyclization gives the sulfide **382**[569] (Scheme 194).

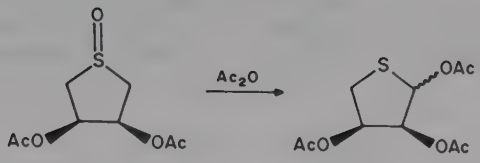
Cyclic sulfoxides can be easily converted into the corresponding sulfides by selective reducing agents[570] and also by the Pummerer reaction[571]. The latter method has been successfully used for the preparation of thiosugar derivatives[572] (Scheme 195).

Other syntheses of thiolane derivatives starting from a preconstructed cyclic system involve the reduction[573,574] or oxidation[575] of thiophene derivatives.

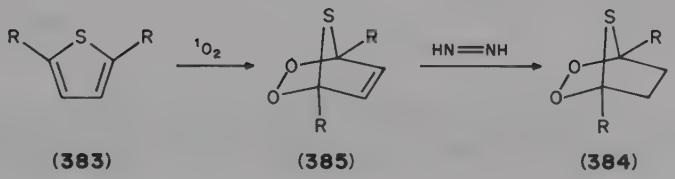
The transformation of alkyl-substituted thiophene derivatives **383** into the bicyclic peroxides **384** has been achieved by singlet oxygen oxidation followed by reduction with diimine of the initially formed peroxide **385**[575] (Scheme 196).



SCHEME 194



SCHEME 195

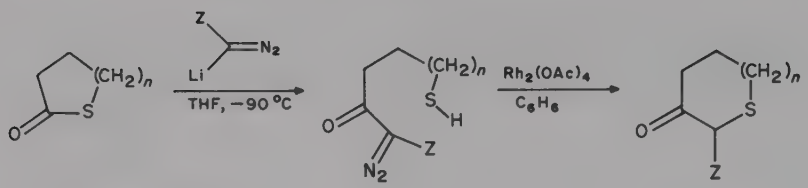


SCHEME 196

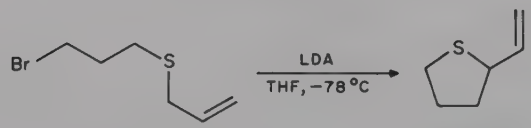
Among other methods for the preparation of cyclic five- and six-membered sulfides are the reactions of hydrogen sulfide with 1,5-diketones[576] or with tetrahydro-4*H*-pyrans[577,578], which are useful for the synthesis of 2,6-disubstituted thianes.

Recently, ring enlargement of thiolactones into 3-oxo cyclic sulfides has been obtained by ring opening of thiolactones with lithium diazo derivatives, followed by rhodium-catalyzed cyclization[579] (Scheme 197).

2-Vinyl-substituted thiolanes and thianes are the precursors of the corresponding sulfonium salts which, in turn, are used in a very elegant ring-enlargement reaction leading to medium- or large-size cyclic sulfides[580]. The synthesis of 2-vinylthiolane (**386**) has been achieved by treatment of 3-bromopropyl vinyl sulfide (**387**) with LDA in THF at $-70\,^{\circ}C$[581] (Scheme 198).

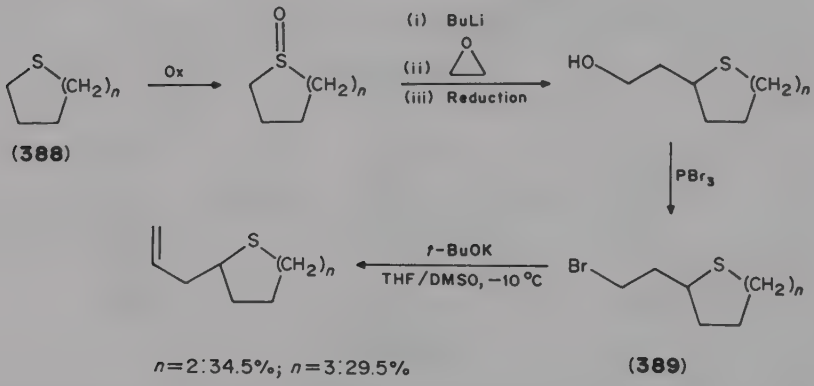


SCHEME 197



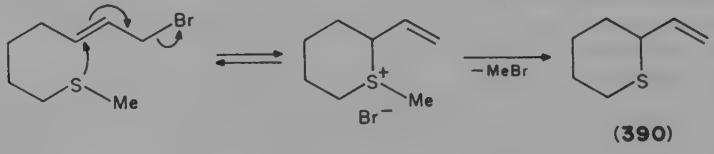
SCHEME 198

An alternative method for the synthesis of 2-vinyl-substituted cyclic sulfides from unsubstituted precursors is also available[581] (Scheme 199). The transformation of **388** into the corresponding *S*-oxide is necessary to obtain an easier deprotonation at the carbon α to sulfur. The critical step of this sequence is the dehydrobromination of **389**, which requires very controlled reaction conditions in order to obtain reasonable yields of the vinyl sulfides.



SCHEME 199

2-Vinylthiane (**390**) has been prepared as shown in Scheme 200[582].



SCHEME 200

A classical synthesis of 2-vinyl-substituted cyclic sulfides is the reaction of vinylmagnesium bromide with the corresponding 2-chloro-substituted derivative. However, these reactions usually give low yields of products[582,583].

D. Reactivity

In this section the reactivity of thiolane and thiane derivatives will be discussed, dealing with oxidation at the sulfur atom, halogenation of the ring, sulfur participation in reactions where the reactive center is far from the heteroatom and with some aspects of the reactivity of cyclic sulfonium ylides.

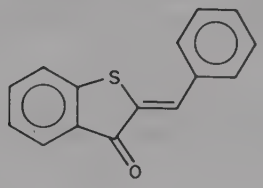
1. Oxidation

Oxidation of thiolane and thiane derivatives to the corresponding sulfoxides or sulfones is possible using a large variety of oxidizing agents[321,429–434,584].

Selective oxidation of thiolanes and thianes to *S*-oxides, avoiding formation of *S*, *S*-dioxides, was achieved with 1-chlorobenzotriazole[585]. Ando and coworkers reported that, in the singlet oxygen oxidation of ring sulfides, only thiolane afforded oxidized products arising from a carbon–sulfur bond breaking, while only *S*-oxidized products were isolated from thietane, thiane and thiepane ring systems[586].

Hydrogen peroxide oxidation of three- to six-membered ring sulfides in ethanol–water mixtures[399] showed that the ring size has almost no influence on the reaction rate, although small rings are oxidized slightly faster than thiolane and thiane.

Unsaturated cyclic sulfides are oxidized preferentially at sulfur by almost all the oxidizing agents. However, using **391** the oxidation with sodium hypochlorite occurs at sulfur or at the double bond, depending on the pH[587].



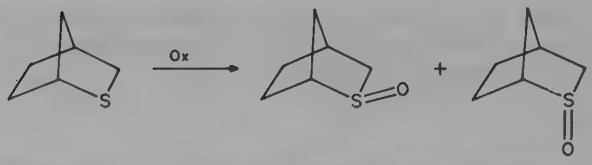
(391)

Oxidation of cyclic sulfide with peroxy reagents proceeds preferentially at the less hindered side of the sulfur atom, while when using *t*-butyl hypochlorite the more hindered sulfoxide is obtained[588]. However, several exceptions to this rule have been reported[439,589].

The oxidation of the bicyclic sulfide **392** with ozone or *t*-butyl hypochlorite is shown in Scheme 201[590]. The more stable *exo*-sulfoxide **393** is the major isomer obtained using ozone, while the *endo* isomer **394** becomes predominant using *t*-butyl hypochlorite.

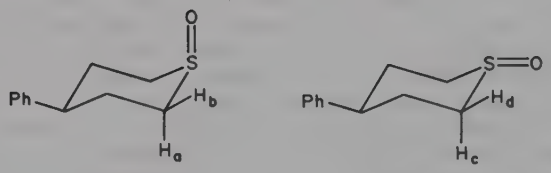
The different chemical behavior of axial or equatorial and *endo* or *exo* sulfoxides has been thoroughly investigated. Usually, spectroscopic data allow the assignment of the geometry of the two isomers[591,592]. For example, the ^{13}C NMR chemical shifts of *cis*- and *trans*-4-*t*-butylthiane-*S*-oxide[593] showed that, in the more stable *cis*-isomer (oxygen axial), C_2 and C_3 are more shielded by 7.5 and 5.3 ppm compared to the corresponding carbons in the *trans*-isomer (oxygen equatorial). This behavior was explained by an electronic effect for C_2 and a steric effect for C_3.

Exchange rates of axial or equatorial protons α to the sulfoxide sulfur in rigid molecules have been studied. For **395** and **396** proton exchange was stereoselective in D_2O



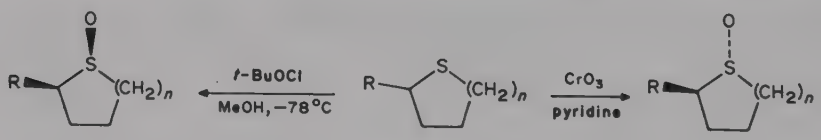
SCHEME 201

or MeOD, but not in *t*-BuOD/DMSO. The measured acidity order was $H_a > H_b > H_c > H_d$[594].



(395) (396)

The oxidation of 2-alkyl substituted thiolane and thiane derivatives **397** has been investigated[439]. Using *t*-butyl hypochlorite, in methanol at low temperature, the *cis*-isomers (oxygen axial) were obtained predominantly, while using chromic anhydride in pyridine afforded the *trans*-isomers (oxygen equatorial) as major product (Scheme 202).

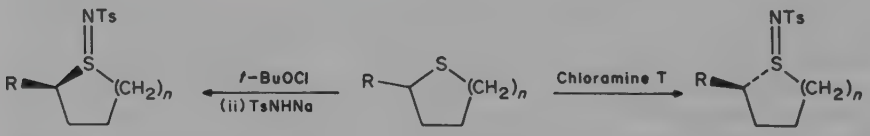


(397)

n=1,2; R=Me, Et, *i*-Pr, *t*-Bu

SCHEME 202

Cis-*S*-tosylsulfinylimines were prepared by a two-step procedure, which includes the reaction of the sulfide with *t*-butyl hypochlorite and further treatment with the sodium salt of *N*-tosylimine. The corresponding *trans* derivatives were directly synthesized from the sulfides by reaction with chloramine T (Scheme 203).



n=1,2; R=Me, Et, *i*-Pr, *t*-Bu

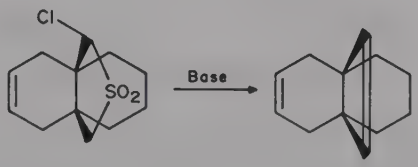
SCHEME 203

Structural assignments of the *N*-tosylsulfinylimines have been obtained by ^{13}C NMR and X-ray diffractometric analysis. In thiane systems the alkyl groups R are in the equatorial position, while the polar NTs group prefers an axial orientation[435]. Chair conformation does not change significantly with variation of alkyl groups. ^{13}C NMR chemical shifts are very useful in these structure determinations, since the carbons in the 3 and 5 positions of the *cis*-isomer are more shielded than the corresponding carbon atoms in *trans*-*N*-tosylsulfinylimines.

In thiolane *N*-tosyl derivatives the effects responsible for ^{13}C NMR chemical shift variation are smaller than in six-membered ring analogues. X-ray diffractometric analysis showed that they both may have half-chair or envelope conformations with the polar NTs group preferring axial orientation and alkyl substituents at the 2 position being in the equatorial position.

Oxidized cyclic sulfides undergo easy sulfur dioxide extrusion. One of the most used methods is the Ramberg–Bäcklund reaction of α-chlorosulfones, leading to the formation of a new carbon–carbon double bond[595–603].

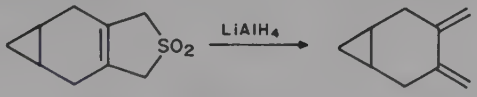
Oxidation and subsequent chlorination of cyclic sulfides as well as the inverted sequence are two easy ways for the synthesis of α-chlorosulfones. The Ramberg–Bäcklund reaction can also be used to prepare highly strained cyclic olefins such as the tricyclic system **398**[604] (Scheme 204).



(398)

SCHEME 204

Sulfur dioxide extrusion from cyclic sulfones occurs also by action of BuLi and $LiAlH_4$[605], as shown for the preparation of the diene **399** from **400**[606] (Scheme 205).

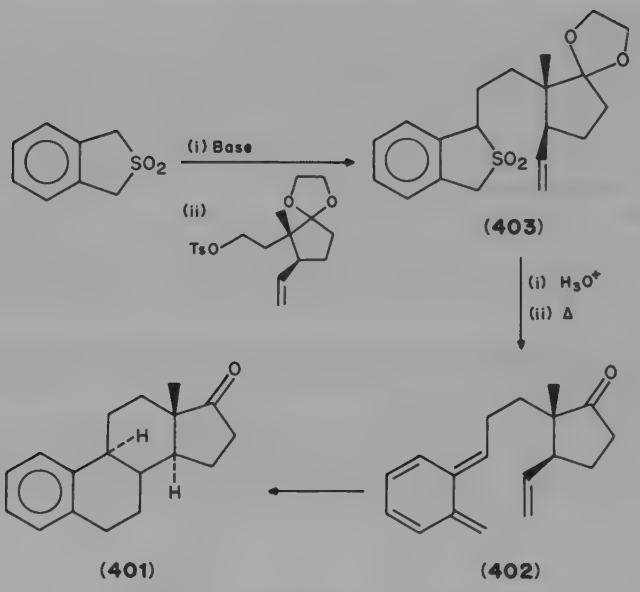


(400) **(399)**

SCHEME 205

One of the most interesting synthetic applications of 2,5-dihydrothiophene derivatives is the oxidation to the corresponding *S*-oxides or *S*,*S*-dioxides (3-sulfolenes), which thermally decompose in a concerted *retro*-cycloaddition reaction giving rise to 1,3-dienes[606–615]. 3-Sulfolene derivatives can also be prepared by addition of sulfur dioxide to 1,3-dienes, so that 3-sulfolenes can be used as masked 1,3-dienes.

Even though the reactivity of cyclic sulfones is not strictly the subject of this chapter, it seems noteworthy to point out the utility of benzosulfolene systems as synthetic precursors of *o*-quinodimethane derivatives[616]. These have been successfully employed for the synthesis of complex, naturally occurring compounds like the steroid **401** prepared in 85% overall yield[617] (Scheme 206). The key step of the synthesis is the formation of the *o*-quinodimethane **402** by thermal sulfur dioxide extrusion from **403**.

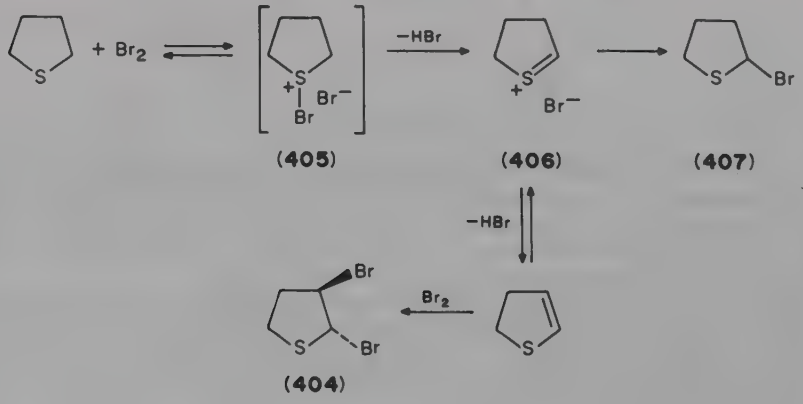


SCHEME 206

2. Halogenation

Halogenation of thiolane and thiane rings has been carefully investigated from mechanistic and synthetic points of view. 1:1 Thiane–bromine and thiane–iodine adducts have been shown to exist as molecular complexes with an undistorted ring and a tetrahedral arrangement around the sulfur atom. These species are effective halogenating agents[451,618].

Addition of one equivalent of bromine to two equivalents of thiolane in dichloromethane at 10 °C affords a 1:1 mixture of starting material and 2,3-dibromothiolane **404** (Scheme 207)[619,620]. This result has been rationalized assuming the initial formation of the

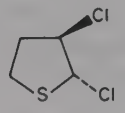


SCHEME 207

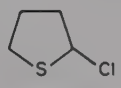
molecular complex **405** followed by hydrogen bromide elimination to give the sulfonium salt **406**. In principle this salt might generate both 2-bromothiolane (**407**) and the dibromo derivative **404**.

The proposed mechanism fits the finding that when the solvent is more polar, the nucleophilicity of the bromide ion is less, so that the amount of dibrominated species **404** increases. On the other hand, addition of hydrogen bromide to the reaction mixture disfavors the formation of **406** and the amount of **407** increases.

A similar mechanism has been reported for the chlorination of thiolane[388,583,619–621]. The distribution of *trans*-2,3-dichlorothiolane (**408**) and of 2-chlorothiolane (**409**), both obtained in chlorination of thiolane with *N*-chlorosuccinimide, has been studied as a function of the solvent[622]. The formation of the dichloro derivative **408** increases with increasing solvent polarity and becomes dominant in dichloromethane or tetrahydrofuran. The ratio **408**:**409** has been measured transforming both the chlorosulfides into the corresponding 2-methoxyethers because of the instability of **409**, which easily undergoes elimination of hydrogen chloride. It has been stressed[622] that the stability of **408** arises from the *trans* arrangement of the chlorine atoms which avoids the easy *trans* elimination of hydrogen chloride.

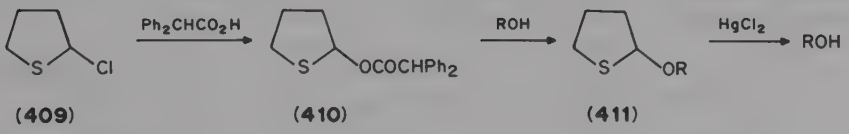


(408)



(409)

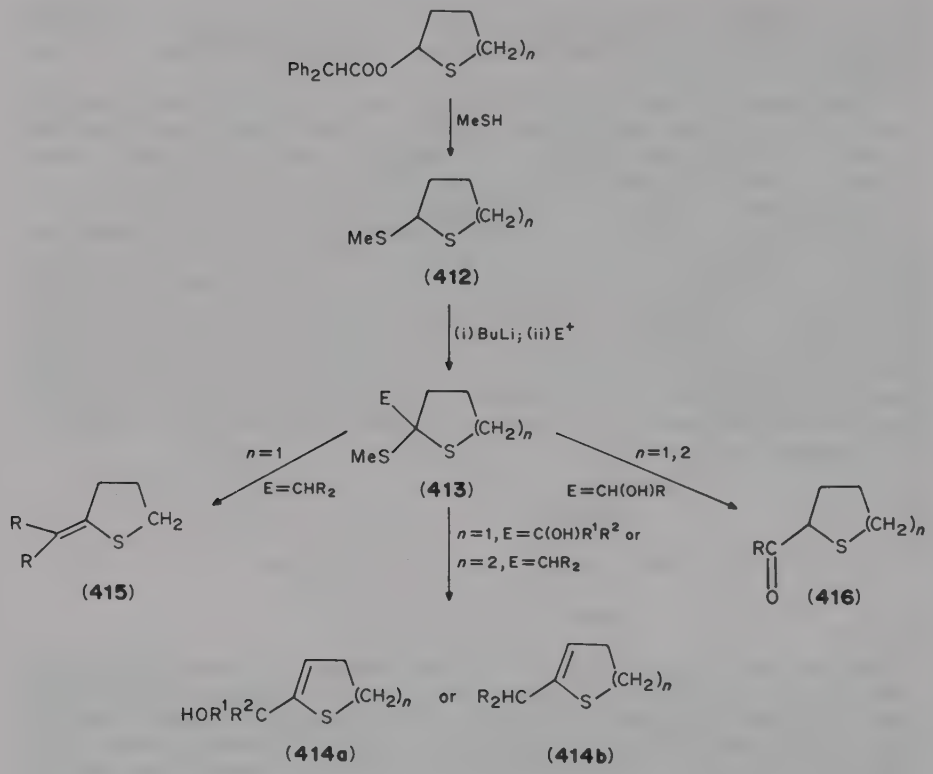
409 is also useful as an alcohol protecting group. The easiest preparation of the unstable **409** uses sulfuryl chloride as chlorinating agent and carbon tetrachloride as solvent, in the presence of triethylamine, when 2-chlorothiolane was obtained in 75% yield[623]. However, 2-chlorothiolane cannot be used directly since its reaction with alcohols affords only low yields of the expected 2-alkoxytetrahydrothiophene derivatives. However, the reaction of **409** with diphenylacetic acid gives rise to the formation of the corresponding reactive 2-acetoxy ester **410** (Scheme 208), which affords very good yields of the 2-alkoxy derivatives **411**, from which the alcoholic functionality can be quantitatively restored by reaction with mercuric chloride[623].



(409) **(410)** **(411)**

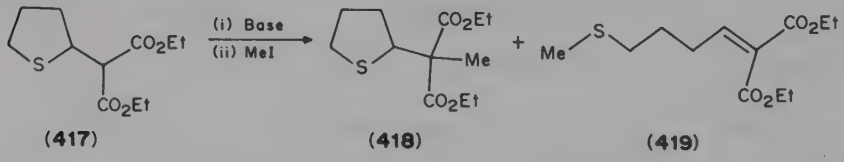
SCHEME 208

Other functionalized cyclic sulfides, such as 2-methoxy-5-thiacyclohexene[624] or 2,3-dihydrothiophene[625], have been used as alcohol protecting groups, although the method of Scheme 208 seems to be the most versatile one. The diphenylacetate **410** has also other interesting synthetic applications. It can be simply converted into the thioacetal **412** which, in turn, can be deprotonated and reacted with different electrophiles to give thioketals **413**[626] (Scheme 209). Compounds **413** undergo spontaneous or acid-catalyzed loss of methylthiol, affording 2,3-unsaturated cyclic systems **414**, 2-vinylidène-substituted cyclic sulfides **415** or 2-acyl-substituted derivatives **416**, depending on the ring size and the nature of the electrophile used (Scheme 209).



SCHEME 209

Attack of various nucleophiles on 2-chlorothiolane **409** yields a wide range of 2-substituted thiolane derivatives[627]. Among these, the diester **417**, on deprotonation and subsequent reaction with methyl iodide, afforded the expected substitution product **418** together with the open-chain derivative **419**[628] (Scheme 210).



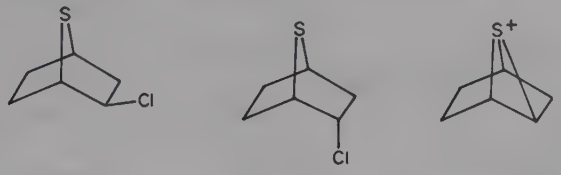
SCHEME 210

3. Sulfur participation

Due to the ability of sulfur to stabilize positive charges, its presence in a ring may influence those reactions which develop a charged intermediate in one of the ring positions. This role played in nucleophilic displacements has been investigated as a function of the relative positions of the sulfur and of the leaving group[629–631].

Sulfur participation may play a dramatic role in solvolyses. For example, the solvolysis

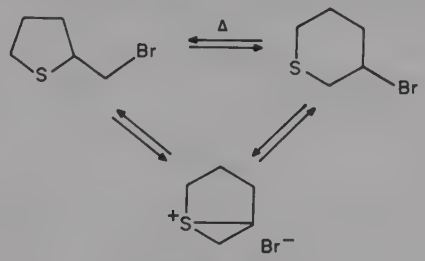
of *exo*-2-chloro-7-thia[2.2.1]cycloheptane (**420**) in acetic acid is at least 5×10^9 times slower than the rate of the *endo* isomer **421**, since in the former the geometry does not allow an easy formation of the ion **422**, which is responsible for the fast solvolysis of **421**[632].



(420) **(421)** **(422)**

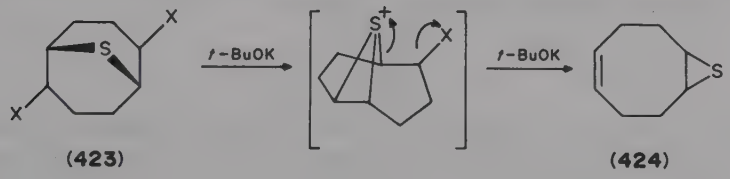
Similarly, in the solvolysis of *p*-nitrobenzoyl substituted thiolanes and thianes, when a further substitution on the reactive center increases the stability of the charged intermediate, the role played by sulfur becomes less important[633].

In some reactions sulfur participation can cause peculiar results. For example, 3-bromothiane and 2-bromomethyl thiolane are thermally equilibrated through a bicyclic sulfonium salt (Scheme 211)[634].



SCHEME 211

Sulfur participation has been also suggested in the base-catalyzed hydrolysis of the bicyclic sulfide **423**, which surprisingly affords the thiirane **424**. The formation of the bicyclic episulfide has been rationalized by assuming the formation of a sulfonium ion, which generates **424** by halide elimination and carbon–sulfur bond breaking (Scheme 212)[635].



(423) **(424)**

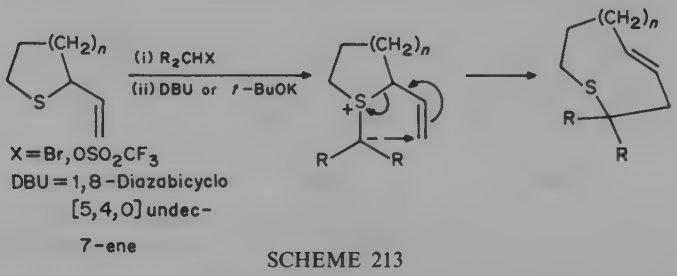
SCHEME 212

The ability of thiolanes as carbonium ion trapping agents to give thiolanium salts is well documented[636,637]. Moreover, it has been demonstrated that racemization of partially resolved thiolanium perchlorates occurs via pyramidal inversion at sulfur and not by sulfur–carbon bond breaking[638,639].

4. Reactivity of cyclic sulfonium ylides

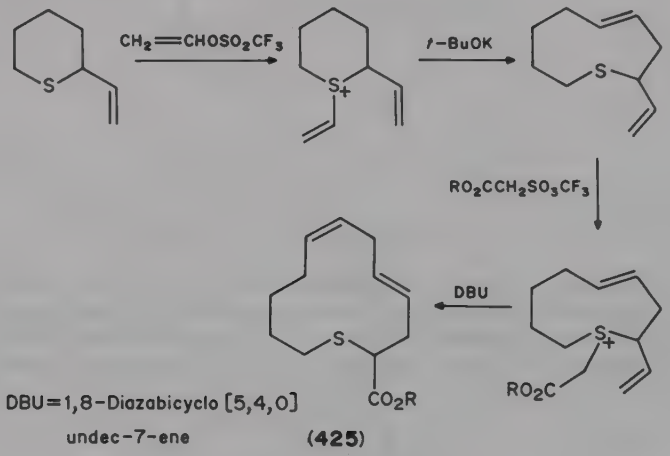
2,3-Sigmatropic rearrangement occurring on stabilized and unstabilized 2-vinyl-substituted cyclic sulfonium ylides derived from thiolanes and thianes is one of the most

important synthetic application of these systems[321,580–582,640]. The product of this reaction, when starting from 2-vinyl-substituted thiolanes, thianes or thiepanes is an unsaturated cyclic sulfide with three carbon atoms more in the ring (Scheme 213).



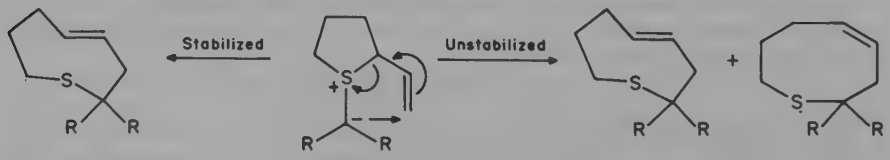
SCHEME 213

When the alkylation is carried out using a vinyl bromide or a vinyl triflate, the reaction scheme can be repeated thus affording a cyclic sulfide containing in the ring six carbon atoms more than the starting material. This is shown in Scheme 214 for the transformation of 2-vinylthiane into the twelve-membered ring sulfide **425**[382,383,582].



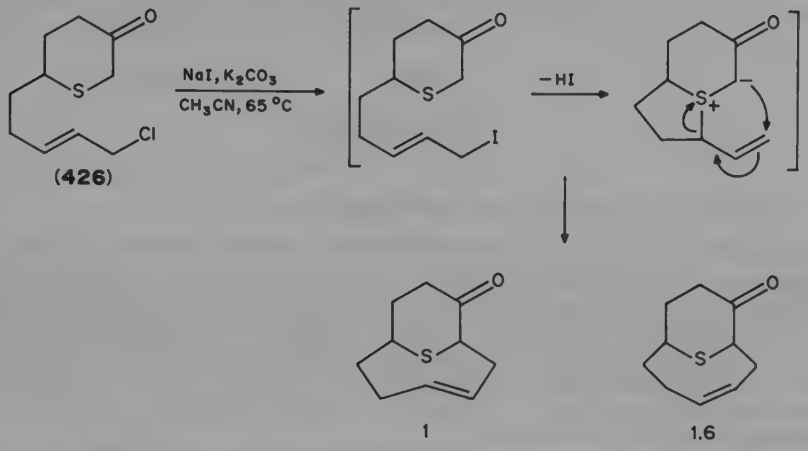
SCHEME 214

Fava and coworkers studied the stereochemistry of the ring enlargement[640]. In the rearrangement involving 2-vinylthiolanium ylides, the formation of the *Z* eight-membered cyclic olefin is strongly favored for stabilized ylides. In the case of unstabilized ylides a mixture of *E* and *Z* unsaturated sulfides is obtained (Scheme 215). The geometry of final cyclic thia-alkene seems strictly related to the geometry of the sulfonium ylide.



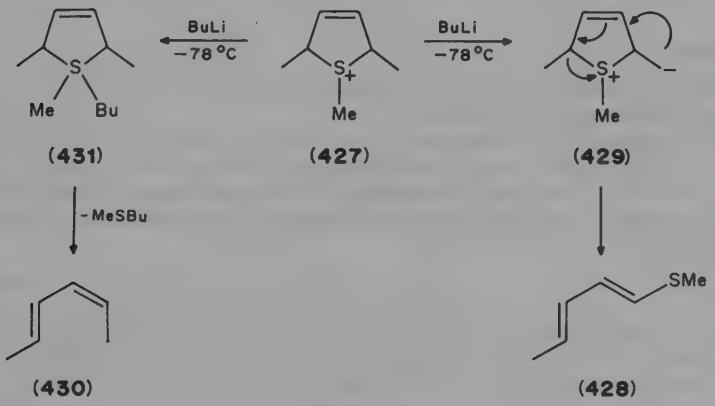
SCHEME 215

Quite interestingly, the rearrangement can also occur with systems where the sulfur ylide and the 2-vinyl group are generated by reaction of a remote allyl iodide group as described in Scheme 216[641]. In this case, starting from the substituted 3-oxothiane **426** a mixture of *E* and Z bicyclic unsaturated sulfides is obtained.



SCHEME 216

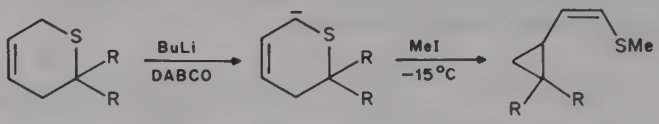
Cyclic sulfonium ylides show other interesting reactivities. For example, when the methylsulfonium salt **427** reacts with BuLi, two different reaction products can be isolated. The methylthio-1,3-diene **428**, which arises from an electrocyclic rearrangement of ylide **429**, was the major product obtained while the diene **430**, deriving from methyl butyl sulfide extrusion from the sulfurane **431**, was formed as minor product (Scheme 217)[498].



SCHEME 217

A quite interesting synthesis of cyclopropane systems of type **432** was achieved by reaction of the sulfur-stabilized carbanion **433** with methyl iodide[642] (Scheme 218). The exact mechanism of this transformation was not clarified; however, the substitution

pattern seems important since the reaction occurs only when at least one of the R groups is phenyl.



(433) (432)

SCHEME 218

E. Natural Products Containing Thiolane or Thiane Rings

Biotin **281** is probably the most important natural product containing a thiolane ring. Several approaches have been published dealing with the preparation of the racemic or enantiopure form of this compound. In some cases natural amino acids such as L-(+)-cysteine were used as starting materials[643,644], in other cases sugar derivatives such as D-glucose[645], glucosamine[646] or mannose[647] were employed. Many other syntheses of biotin deal with synthetic starting materials such thiophene[648] or dihydrothiophene[649] derivatives and many others[650–653]. A critical comparison of different methods of biotin synthesis is available in the literature[654].

Many other naturally occurring compounds containing thiolane or thiane ring units have been isolated from plants[655–657], sponges[658] or obtained by degradation of other sulfur-containing natural products[659].

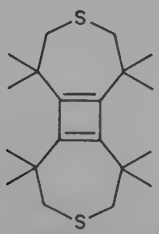
V. THIEPANES

Thiepane is, according to the Hantzsch–Widman method, the name of the parent seven-membered ring sulfide. It can be also named thiacycloheptane.

A. Structure

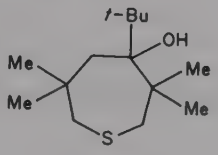
Structure investigations of the parent thiepane are very few, but exhaustive studies have been reported for some of its derivatives.

X-ray diffractometric analyses of tetrahydrothiepin derivatives have been published[660–665]. In particular, the preferred chair conformation of **434** in the solid state has been revealed[664,665]. A flat boat form is the preferred conformation of thiepines as well as thiepine *S*-oxides, as has been deduced by theoretical calculations, X-ray analysis and NMR spectra[664].



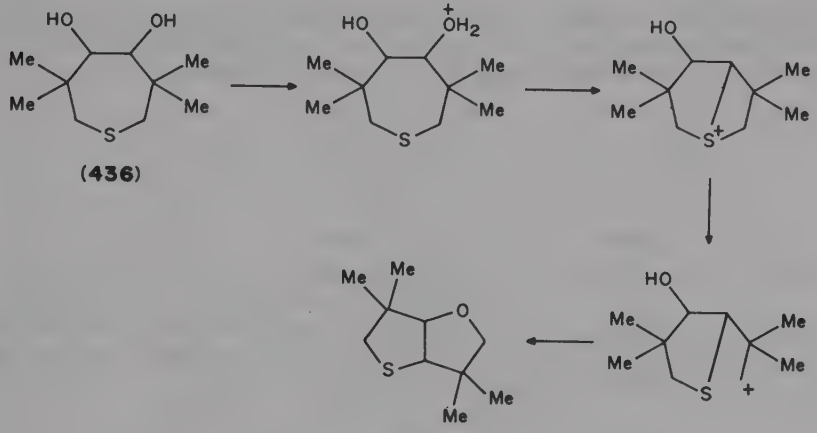
(434)

IR spectroscopy has been largely used to obtain structural information[664,666–669]. According to IR data, 3-thiepanone and 4-thiepanone present an intramolecular interaction between the sulfur atom and the carbonyl group. Analogously, 4-thiepanol shows an important interaction between the hydroxy group and the sulfur atom. This transannular hydrogen bond is particularly effective in the 4-*t*-butyl derivative **435**, where the adoption of an equatorial position by the *t*-butyl group forces the hydroxy group into an axial orientation suitable for hydrogen-bond formation.

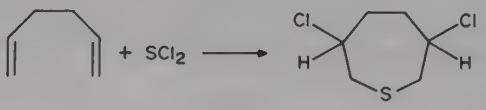


(435)

Another example of transannular interaction concerning the sulfur atom in a thiepane ring can be found in the acid-catalyzed rearrangement of the diol **436** to the bicyclic thiolane **437** (Scheme 219). It is noteworthy that in this case transannular interactions occur, although normally this requires at least an eight-membered ring system.

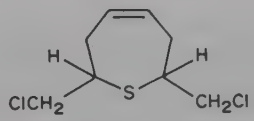

HO
OH
Me
Me
Me
Me
S
HO
+
OH2
HO
S+
O
Me
Me
Me
Me

Another thiepane synthesis with the formation of two bonds is the reaction of 1,5-hexadiene with sulfur dichloride[660,673] (Scheme 221). Unfortunately, the purification of the product is not easy, thus sensibly reducing the synthetic utility of this reaction.



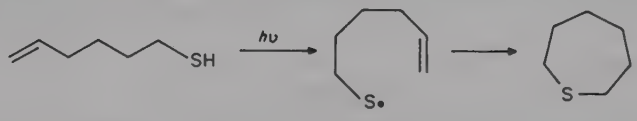
SCHEME 221

Sulfur dichloride reacts similarly with 1,4,7-octatriene, affording the thiepane **438**, albeit in low yield[674].



(438)

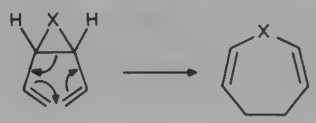
Thiepane can also be produced by formation of one bond. Photolysis of an unsaturated thiol like **439**, generates the thiyl radical **440**, which undergoes intramolecular radical addition to the double bond leading to the cyclic sulfide[675] (Scheme 222).



(439) **(440)**

SCHEME 222

Some useful thiepane syntheses use heterocyclic compounds as starting materials. *Cis*-1,2-divinylthiirane **441**[676] and its corresponding 1,1-dioxide **442**[677] rearrange thermally to yield **443** and **444**, respectively (Scheme 223).

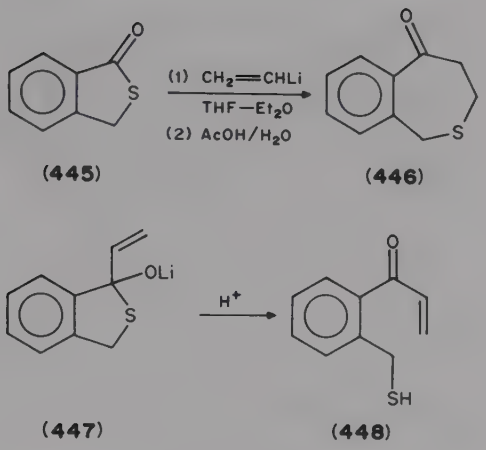


(441) X=S **(443)** X=S

(442) X=SO_2 **(444)** X=SO_2

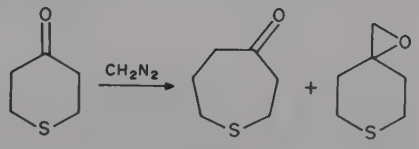
SCHEME 223

Another interesting reaction is the ring expansion of the thiolactone **445** (Scheme 224). The latter reacts with vinyllithium, and subsequently with acetic acid, to give the thiepanone **446**[678]. The reaction proceeds via the initial attack of the vinyllithium on the carbonyl group of **445** to give the tetrahedral adduct **447**, which in acid medium rearranges to the vinyl ketone **448** and in turn undergoes cyclization to **446**. This method has been successfully used also to prepare eight-membered ring sulfides from 2-thiochromanones.



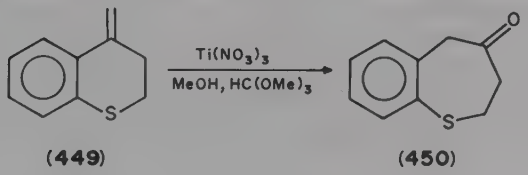
SCHEME 224

Ring expansion from six- to seven-membered cyclic sulfides can be achieved in several ways[664]. Thiepane-4-one has been prepared from the reaction of thiane-4-one with diazomethane[679] (Scheme 225).



SCHEME 225

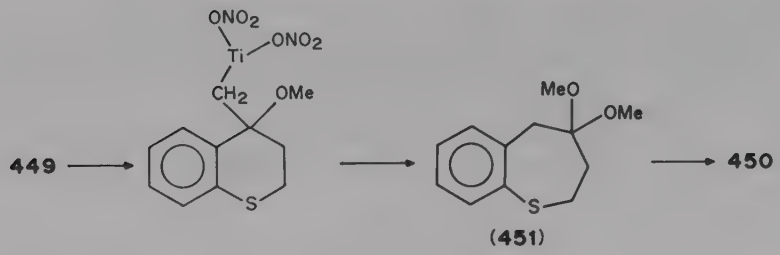
Using thallium nitrate and methyl orthoformate, the thiane derivative **449** can be transformed into the thiepanone **450**[680] (Scheme 226).



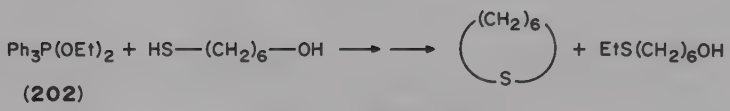
SCHEME 226

The first step of the reaction is the oxythallation of the double bond, followed by the selective insertion of the methylene carbon to give the ketal **451**, which on hydrolysis yields the thiepanone **450** (Scheme 227). The reaction is instantaneous and easily monitored by precipitation of thallium(I) nitrate.

Ring expansion from six- to seven-membered rings has been reviewed[664]. As reported for thietanes, diethoxytriphenylphosphorane (DTPP) can convert mercaptoalcohols to cyclic sulfides. This method gives good results for the synthesis of cyclic sulfides from four- to six-membered rings, but when applied to the synthesis of thiepanes gives poor results[189,681]. In fact, 6-mercapto-1-hexanol reacts with **202** to give 6-ethylthio-1-hexanol as the major product (Scheme 228).



SCHEME 227



SCHEME 228

The low yield of thiepane in this reaction can be rationalized considering the energetic restrictions existing for the cyclization of the betaine of type **203** to thiepane (see Scheme 107).

C. Reactivity

Thiepane is quite stable and can be purified by distillation at atmospheric pressure. However, at higher temperature (400 °C) and in the presence of aluminum silicate catalyst, thermal decomposition occurs which gives hydrogen sulfide as principal product[682].

The reactivity of thiepanes mostly involves sulfur as the site for chemical transformations and it is similar to that of other dialkyl thioethers.

Oxidations of seven-membered ring sulfides are common and important reactions. The products, sulfoxides and sulfones are very stable species. Thiepane-1-oxide is the only product in the reaction of equimolar amounts of peracids with thiepane[399], while excess of the oxidant generates thiepane 1,1-dioxide[683].

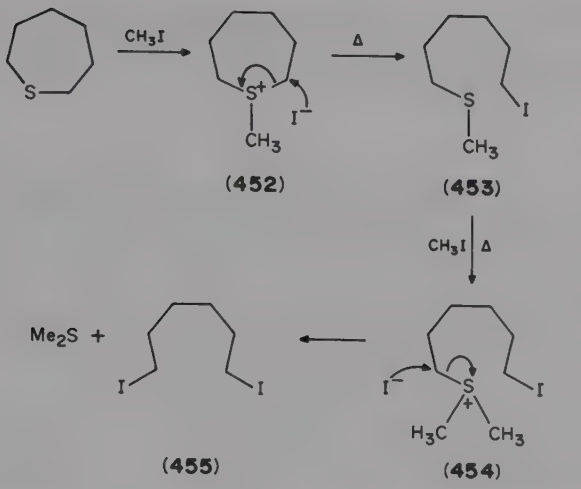
Singlet oxygen oxidation of sulfides has been widely studied[684] and the different behavior of five-, six- or seven-membered ring sulfides has been reported[586]. Singlet oxygen oxidation of thiepane using *meso*-tetraphenylporphyrin (TPP) as sensitizer gives mixtures of the corresponding sulfoxides and sulfones[586].

Autoxidation of thiepanes has been observed at high temperatures and under oxygen pressure[685].

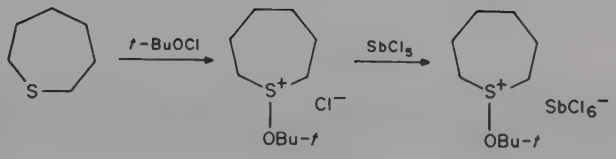
As with other sulfides electrophilic attack by alkyl halides on thiepanes gives sulfonium salts[660,664]. The sulfonium iodide **452** is readily formed by reaction of methyl iodide with thiepane[671,686] (Scheme 229). However, in the presence of excess of the alkyl halide and at high temperature the iodide ion attacks the ring carbon α to the sulfonium sulfur leading to the iodosulfide **453**, which is further methylated to give the dimethylsulfonium iodide **454**, from which the di-iodo derivative **455** is then obtained.

The stable *t*-butoxysulfonium salt **456** has been prepared by reaction of thiepane with *t*-butyl hypochlorite followed by addition of antimony pentachloride[687] (Scheme 230).

Thiepanes react reversibly and quantitatively with mercuric dichloride to form 1:1 complexes. This reaction, followed by the regeneration of thiepanes, can be used as an efficient method for the purification of this class of compounds[399].

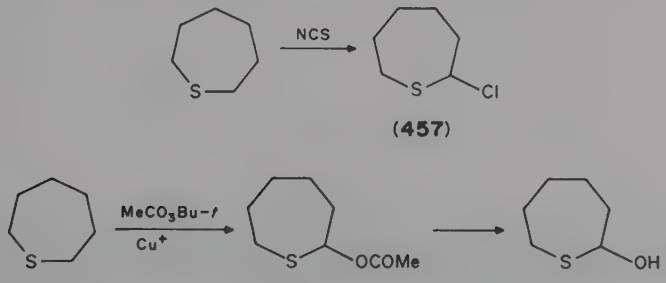


SCHEME 229



SCHEME 230

Thiepanes undergo substitution at the α position by a radical mechanism initiated by several reagents. Two examples of this reactivity are reported in Scheme 231. A radical pathway is generally accepted for the α-chlorination of thiepane by *N*-chlorosuccinimide (NCS)[583]. The chlorosulfide **457** has not been isolated but was characterized by its NMR spectra. 2-Acetoxythiepane is formed in good yield by reaction of thiepane with *t*-butyl peracetate in the presence of a copper(I) salt as catalyst[670,688]. Hydrolysis of 2-acetoxythiepane gave the 2-hydroxythiepane in excellent yield[670].



SCHEME 231

VI. THIOCANES

Thiocane is the name of the eight-membered ring sulfide (Hantzsch–Widman method). It can also be named thiacyclooctane.

A. Synthesis

Thiocane can be prepared from 1,7-dibromoheptane with sodium sulfide at high dilution[686,689]. It has been found that a 0.2 molar solution of the dibromide in ethanol in the presence of an excess of sodium sulfide gives the best yield (47%) of thiocane. The low solubility, and hence the low concentration, of the sodium sulfide in ethanol might explain this unexpected result[690].

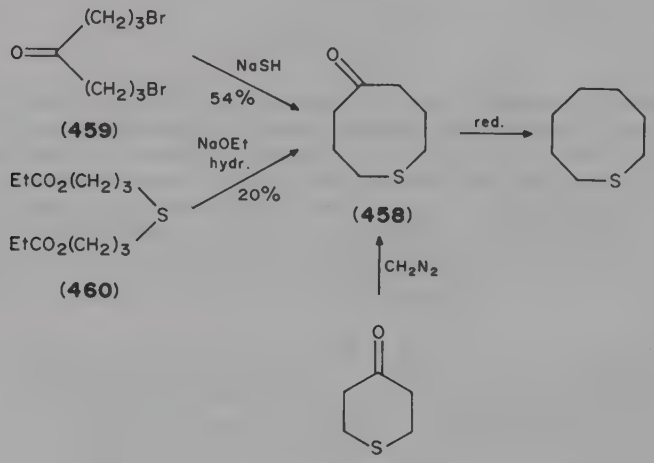
The reactive lithium sulfide has been used for the synthesis of thiocane from 1,7-dibromoheptane[480]. Other medium-sized thiacycloalkanes are also accessible using a solution prepared *in situ* from bis(trimethylsilyl)sulfide and methyllithium[480] (Scheme 232). The yields of cyclic sulfides are comparable to those obtained using the high dilution technique[689], but some open-chain sulfides are always present. The monomer-to-dimer ratio depends upon the size of the ring. The best results were obtained for thiepane and thiocane, while for larger-ring sulfides the yields are not really satisfactory.

$$(Me_3Si)_2S + 2MeLi + Br(CH_2)_nBr \xrightarrow[\text{refl. 6h}]{\text{THF}} (CH_2)_nS + Br(CH_2)_nS(CH_2)_nBr + 2Me_4Si + 2LiBr$$

$n = 6, 7, 8, 9, 10, 12$

SCHEME 232

Thiocane can also be prepared by Wolf–Kishner reduction of 5-thiocanone **458**[691], which is easily prepared starting from the dihaloketone **459**, or from the diester **460** or using the ring expansion reaction of thiolane-4-one (Scheme 233).

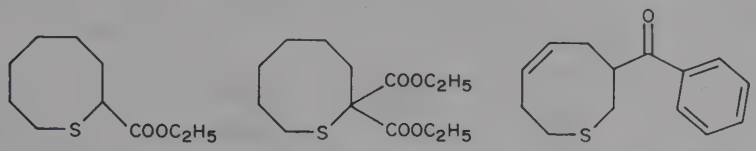


SCHEME 233

2,3-Sigmatropic rearrangement of stabilized sulfonium ylides[382,560,692,693] is an elegant method to build eight-membered cyclic sulfides.

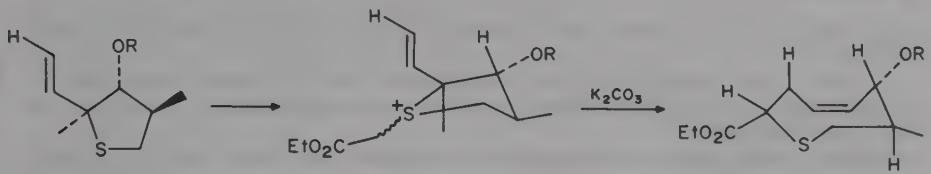
Functionalized thiocanes can also be prepared using this method. The eight-membered

ring sulfides **461**, **462** and **463** have been synthesized by 2,3-sigmatropic rearrangement of the corresponding ylides in 80%, 54% and 74% yield, respectively.



(461) **(462)** **(463)**

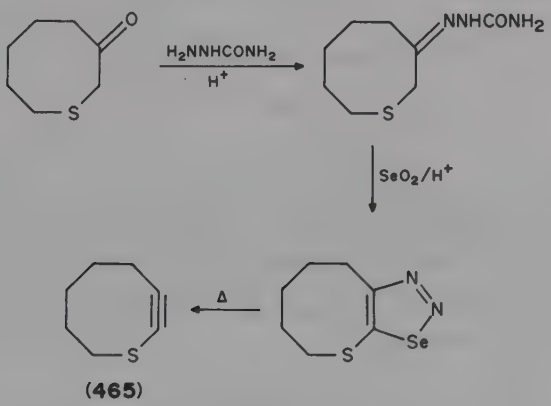
Another successful application of this synthetic route has been realized by Vedejs and coworkers for the synthesis of **464**[694] (Scheme 234).



(464)

SCHEME 234

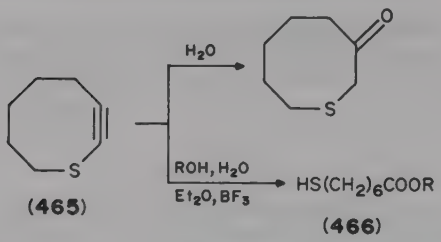
The synthesis of the 1-thia-2-cyclooctyne (**465**) has been recently reported[695]. This strained thiocane derivative has been prepared from the thiocane-3-one by the selenadiazole method as reported in Scheme 235.



(465)

SCHEME 235

The thiacyclooctyne **465** with its strained triple bond is a very reactive species. It adds water under neutral conditions leading to thiocan-3-one and gives ring opening to **466** with alcohol–water mixtures in the presence of boron trifluoride (Scheme 236). It also undergoes cycloadditions with several species.



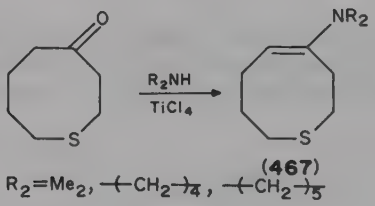
SCHEME 236

B. Reactivity

The reactivity of thiocane and its derivatives is practically identical to that of open-chain sulfides.

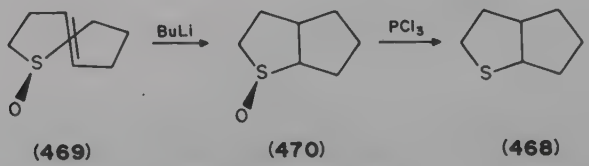
Thiocane reacts with alkyl iodides to give sulfonium salts and with oxidizing agents to give the corresponding oxidized derivatives. The thiocane 1,1-dioxide has a particular but not unpleasant odor[686].

Thiocane-5-one gives the corresponding ketosulfone by oxidation[666] and enamines **467** by reaction with secondary amines in the presence of titanium tetrachloride[696] (Scheme 237). The structure of the enamines **467** has been studied and clarified by NMR techniques[696].



SCHEME 237

A transannular cyclization gives the bicyclic sulfide **468** on the reaction of the cyclic eight-membered (*E*)-homoallylic sulfoxide **469** with butyllithium[697,698] (Scheme 238). Treating the sulfoxide **469** with butyllithium in a 2:1 molar ratio, the bicyclic sulfoxide **470** is formed as the single product. Reduction of **470** with phosphorous trichloride gives the *cis*-2-thiabicyclo[3.3.0]octane (**468**). It is important to note that this transannular cyclization occurs readily with 8-, 9- and 10-membered *E*-homoallylic cyclic sulfoxides but does not occur with their *Z* counterparts[697].



SCHEME 238

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Index compiled by P. Raven

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Updates from the Chemistry of Functional Groups
Edited by Saul Patai and Zvi Rappoport

SYNTHESES OF SULPHONES, SULPHOXIDES AND CYCLIC SULPHIDES

In *The Chemistry of the Functional Groups* series several volumes contained chapters on the syntheses of sulphides, sulphoxides and sulphones. The present volume updates three chapters which appeared in 1988 in the volume *The Chemistry of Sulphones and Sulphoxides* (those written by Professors K. Schank, M. Mikołajczyk and coworkers and U. Zoller) and both the original chapters and their updates are presented.

In addition a new chapter on 'Cyclic Sulphides' by Professor G. Capozzi and coworkers, which has not been included in any of the main volumes of the series, but which is very relevant to the subject matter of this Update volume is also published here.

ISBN 0-471-93970-6

9 780471 939702

JOHN WILEY & SONS
Chichester · New York · Brisbane · Toronto · Singapore