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REDUCTION OF SULFOXIDES TO THIOETHERS*

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* For oxidation of thioethers to sulfoxides see review by M. Madesclaire, *Tetrahedron* **42**, 5459 (1986).
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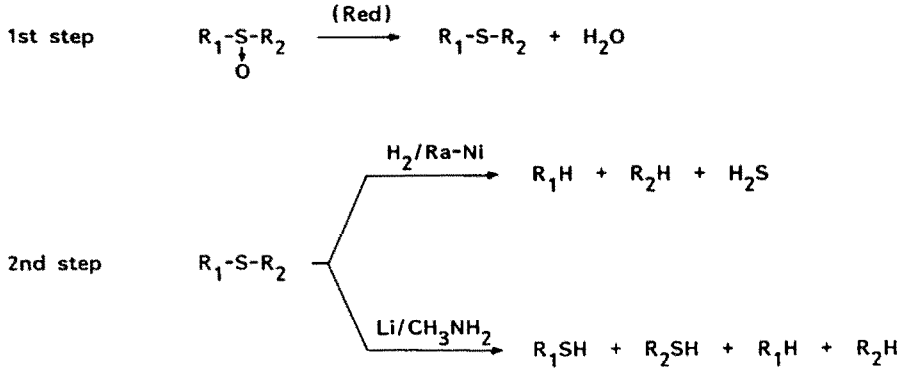
1. INTRODUCTION

The enduring interest that chemists have always taken in the reduction, or deoxygenation, of sulfoxides to thioethers has produced an abundant and regular literature, from the pioneering work of Michaelis *et al.*[1,2] to the most recent use of highly novel reducing systems. This reaction has gained further importance with the use of sulfoxides as chirons in asymmetrical synthesis.

The chiral sulfinyl group, after stereoselective induction, is eliminated in two steps; reduction to thioether, and then removal of sulfur either by catalytic hydrogenation (H_2/Ra-Ni)[3] or other chemical means (e.g. Na or Li/NH_3 or $R\text{-}NH_2$)[3] (Scheme 1).



Scheme 1.

For this purpose, sulfoxides have a double advantage over sulfones: not only can they be chiral, but unlike sulfones, their S—O bond is readily cleaved.

We present here an exhaustive literature review of the various methods for reducing sulfoxides to thioethers. This updates the review of Drabowicz *et al.*[4] published in 1977, as it includes methods of microbiological or enzymatic reduction, and those involving novel reagents. The most important reactions are presented diagrammatically and whenever possible the reaction mechanism and the scope of the method are briefly mentioned. The reactions of the Pummerer[5] or Kornblum[6,7] type, and all the reactions using dimethyl sulfoxide as oxidizer are not dealt with specifically here. Finally, the classification we propose is necessarily arbitrary in places since certain complex reducing agents and those associated with co-reagents are difficult to classify.

2. REDUCTION OF SULFOXIDES WITH HALIDE IONS

2.1. *Hydrogen halides*

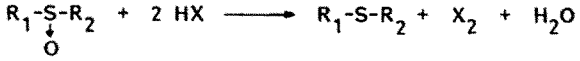
Among the earliest methods for reducing sulfoxides were those using hydrogen halides.[10–16] The general reaction with HX is shown in Scheme 2.

The reduction occurs via a halosulfonium ion [reaction (2)], subsequently reduced to a thioether by a second halide ion [reaction (3)] (Scheme 3).[17]

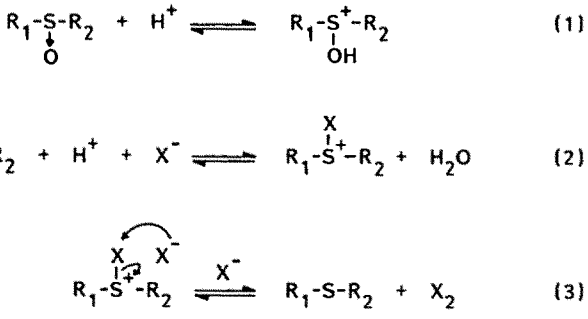
This reaction is actually more complex than this. The halosulfonium ion can also undergo cleavage of the C—S bond to form a carbonium ion [reaction (4)], or a Pummerer type rearrangement [reaction (5)] (Scheme 4).

The fate of the halosulfonium ion depends on the reaction medium, on the halide ion and on the nature of groups R_1 and R_2.

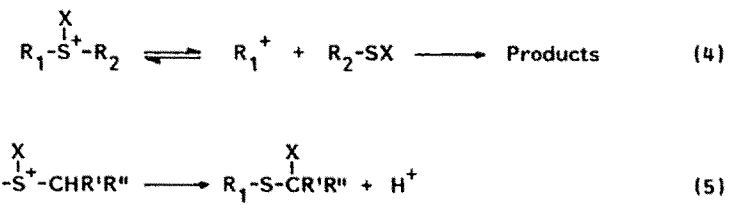
Considerable work has been done on the comparative kinetics of this reaction carried out with HI, HBr and HCl.[17–26] The best acid for the deoxygenation of sulfoxides proves to be hydriodic acid, which does not give rise to any side reactions and which achieves almost stoichiometric reduction. Indeed, the reaction with HI can be used for quantitative assay of sulfoxides. Hydro-



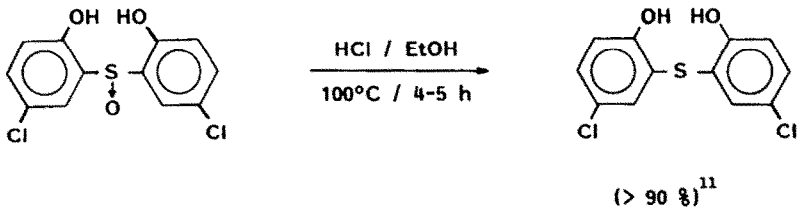
Scheme 2.



Scheme 3.



Scheme 4.



Scheme 5.

bromic and especially hydrochloric acid, however, often shift the equilibrium of reaction (3) towards the left, resulting in acid-catalysed racemization of the sulfoxide.[17-32]

2.1.1. *Hydrogen chloride.* In 1909 Smythe[10] described the reduction of dibenzyl sulfoxide to dibenzyl sulfide using HCl in various solvents, though the yield was low (<30%), due to numerous side reactions. On the other hand, Gazdar and Smiles[11] in 1910 reported the deoxygenation of diaryl sulfoxides to their corresponding thioethers with high yields, by simple heating in a sealed tube in the presence of HCl in ethanol (Scheme 5). These authors found that the reduction of certain sulfoxides was accompanied by the formation of chlorinated thioethers through reductive chlorination.

At about the same time, Hilditch[14] observed that certain aliphatic sulfoxides such as diisoamyl sulfoxide were rapidly decomposed by hydrochloric acid at ambient temperature.

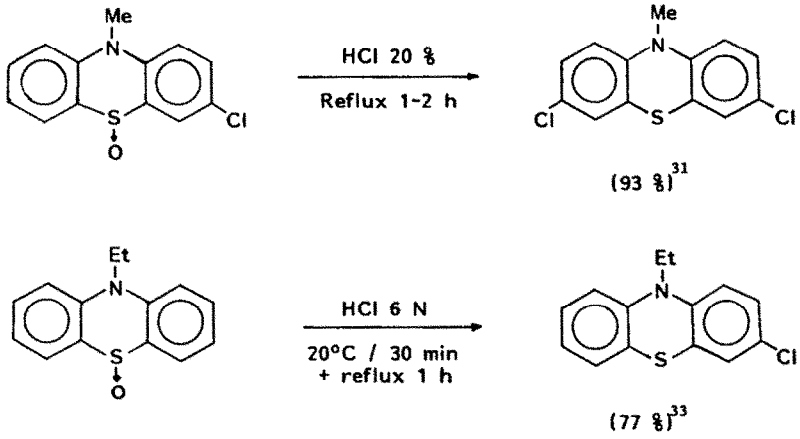
Following on from the work of Page and Smiles,[12] a number of papers describe the deoxygenation of nitrated,[15] chloro[33,34] and/or *N*-alkylated[12,33,35] derivatives of phenothiazine *S*-oxide with HCl. This method of reduction of phenothiazine sulfoxides gives excellent yields but is generally accompanied by chlorination (Scheme 6).

Similarly, Fries and Vogt[13] and Shine and Dais,[36] found that thianthrene *S*-monoxide gave, in concentrated HCl at ambient temperature, a mixture of thianthrene and 2-chlorothianthrene by reductive chlorination. The latter[36] reported obtaining pure thianthrene in low yield by working in an inert atmosphere. A large proportion of the starting sulfoxide was recovered unchanged (Scheme 7).

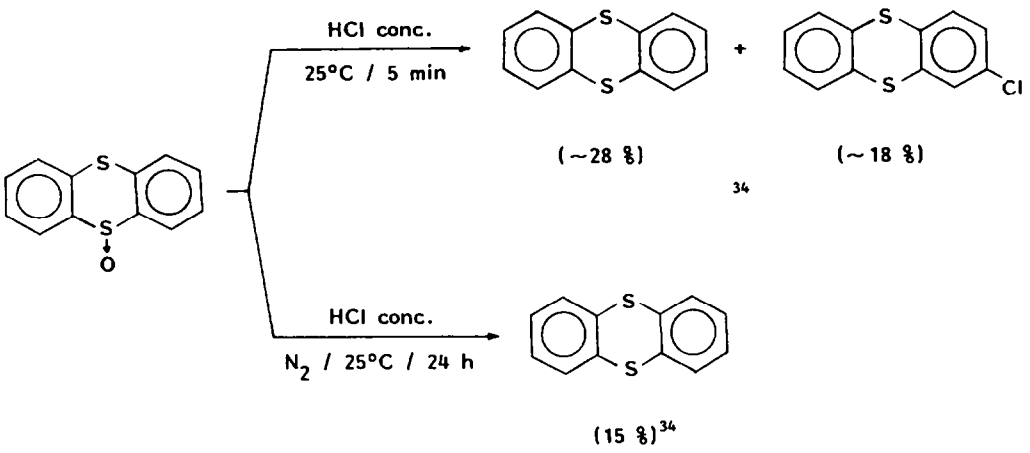
Castrillón and Szmant[37] reduced thiaxanthone *S*-oxide and its hydrazone, without chlorination, using concentrated HCl in dioxane at ambient temperature (Scheme 8).

More recently, Chasar *et al.*[38] investigated the problem of unwanted reductive chlorination of aromatic sulfoxides in a study of the action of anhydrous HCl in chloroform on a series of variously substituted diaryl sulfoxides. They showed that the reductive chlorination occurs via an electrophilic species since it is favored by the presence of ring substituents that activate electrophilic attack.

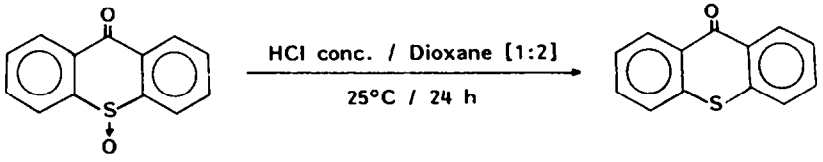
Conversely, simple reduction of diaryl sulfoxides is facilitated by the presence of deactivating groups. In addition, the presence of phenol in the reaction mixture markedly increases the reduction yield (Scheme 9).



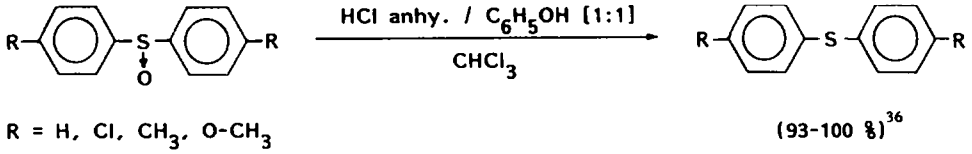
Scheme 6.

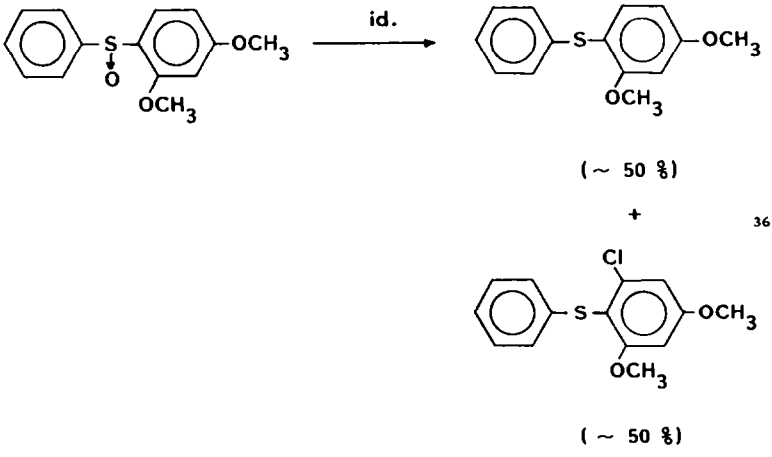


Scheme 7.



Scheme 8.





Scheme 9.

2.1.2. *Hydrogen bromide and bromine in acid media.* Little work has been reported on the reduction of sulfoxides using HBr. The earliest work is that of Fries and Vogt[39] who in 1911 reduced thianthrene 5,10-dioxide to thianthrene by heating in the presence of HBr.

Much later, Gilman *et al.*[35,40] used a 32% solution of hydrobromic acid to reduce 10-ethyl phenothiazine sulfoxide and thianthrene mono and dioxide yielding bromo-derivatives of phenothiazine and thianthrene (Scheme 10). These authors found that the presence of a sulfonyl group deactivates the aromatic rings with regard to electrophilic attack, enabling reduction to take place without bromination (Scheme 10).

An isolated example is the reduction of 4-methoxy phenyl methyl sulfoxide to its thioether by heating with HBr in dioxane.[24]

Some relatively early work[40-42] described the reductive bromination of aryl sulfoxides with bromine in various solvents. The deoxygenation of the sulfinyl group is due to HBr formed by the ring halogenation.

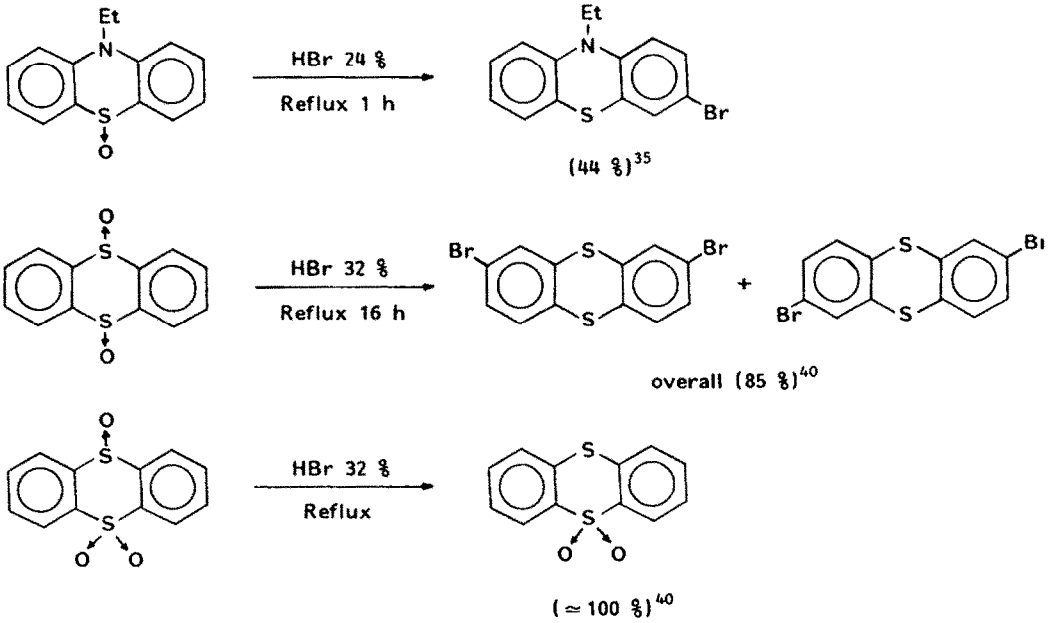
Japanese workers[43] have reported a novel catalytic reduction of dimethyl sulfoxide (DMSO) and other dialkyl and arylalkyl sulfoxides with Br_2/HBr. This method cannot be applied to diphenyl sulfoxide since a hydrogen bound to a carbon α to the SO group is compulsory. The reaction starts by the ready bromination of the sulfoxide. The α-bromosulfoxide thus formed then reacts with a second molecule of sulfoxide to give a thioether, oxidation products and HBr which then deoxygenates the sulfoxide (Scheme 11).

2.1.3. *Hydrogen iodide and iodine in acid media.* Hydroiodic acid readily deoxygenates sulfoxide, often quantitatively, unlike HCl and HBr (Scheme 12).

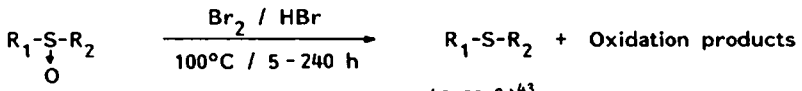
The earliest results for HI were those of Zincke and Baeumer[16] who reduced substituted diaryl sulfoxides by heating with HI (Scheme 13).

Subsequently, this reaction was widely used by many workers and was applied to a great variety of sulfoxides.[17-26,35,44-68] Thus in 1936 Lavine, Toennies and Kolb[43-45] described the reduction of *l*-cystine disulfoxide[44,45] and *dl*-methionine sulfoxide[46] using iodides (NaI, KI) in acid media (HCl, $HClO_4$). Similarly, Karaulova and Gal'pern[48] reported the reduction of dialkyl and diaryl sulfoxides with good yields (51 to 96%) (Scheme 14). Gilman and Eisch,[35] who used HCl, HBr and HI to reduce 10-ethyl phenothiazine sulfoxide, observed no reductive halogenation with HI, whereas both HBr and particularly HCl gave halogenated side products (Scheme 14).

In view of the importance of this reaction, numerous studies have been undertaken of the mechanism,[17,19,22,26,52,58,62-64] kinetics and stereochemistry of acid-catalysed deoxygenation by



Scheme 10.

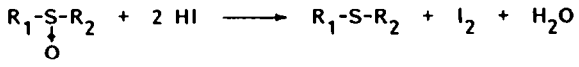


$R_1 = R_2 = CH_3,\ C_2H_5,\ n\text{-}C_4H_9,$

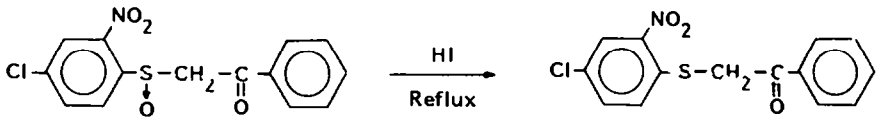
$R_1 = CH_3\ ;\ R_2 = C_6H_5$

$R_1R_2 = (\text{-}CH_2\text{-})_4$

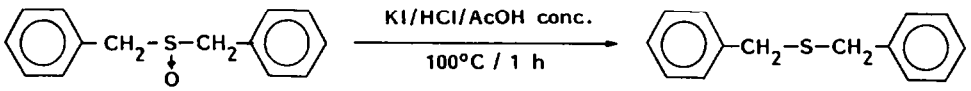
Scheme 11.

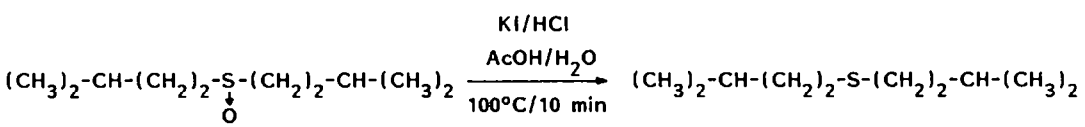


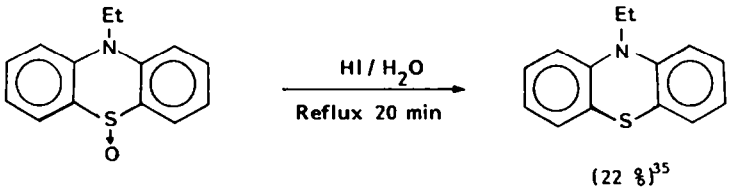
Scheme 12.



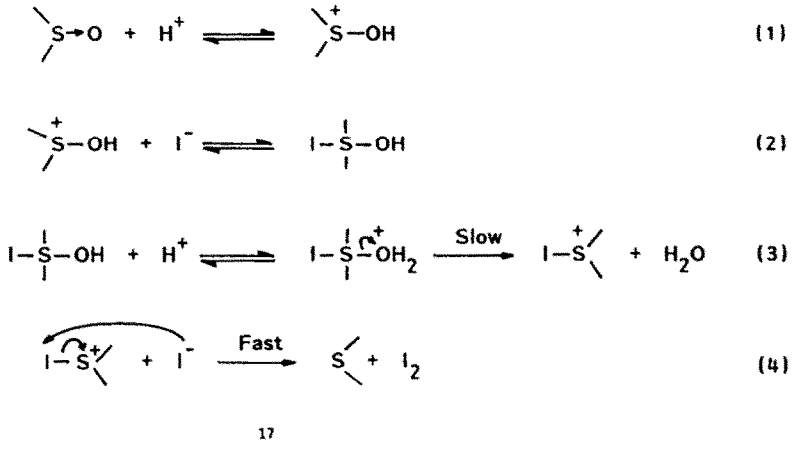
Scheme 13.







Scheme 14.



Scheme 15.

aqueous iodide of sulfoxides, particularly DMSO,[22,52,58] of arylalkyl sulfoxides[17,19,22,52,62] and of cyclic sulfoxides.[63,64]

Several mechanisms were proposed by Landini *et al.*,[22,52] Strecker and Andersen[62] and Tamagaki *et al.*[63] and reviewed by Modena[17] who considers the most probable and most widely-accepted mechanism to be that shown above (Scheme 15).

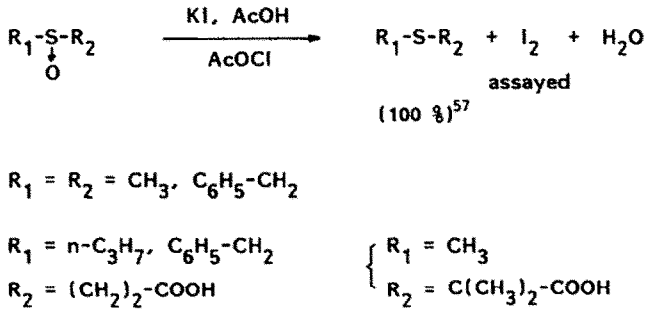
According to this author, the first iodide ion must intervene before the second proton, since a diprotonated species ($>\overset{+}{S}-\overset{+}{O}H_2$) would be highly unlikely. In addition, the formation of the iodosulfonium ion[17,62] is rate-determining. The second iodide that appears in the equation is thus not involved in the reaction kinetics. This has been confirmed in numerous kinetic studies showing the reaction to be first order in sulfoxide and first order in iodide[17,19,22,58,62] provided there is no neighboring-group participation.[25] The influence of protons H^+ on this reaction is more complex and depends on acid concentration.[19,22,58,62,63] Finally, the stereochemistry of the deoxygenation of the sulfinyl group by iodide in dilute acid is that of an S_N2 type attack at the sulfur atom.[52,63]

As the acid-catalysed reduction of sulfoxides by iodide is easy to perform and very often stoichiometric, it was proposed in 1937 by Larsson[47] as a method of assay of certain organosulfur compounds especially sulfoxides.

This quantitative method was subsequently further developed.[51,57] Allenmark[57] assayed a series of dialkyl and diaryl sulfoxides using potassium iodide in acetic acid in the presence of an acylating reagent (KI/AcOH or AcOX). In all cases the reaction went to completion in a few minutes (2 to 5 min) (Scheme 16).

Tamagaki *et al.*[63] and Curci *et al.*[64] studied the effect of ring size on the reduction of some cyclic sulfoxides. The rate of acid-catalysed reduction by iodide of a number of polycyclic aromatic sulfoxides was found to follow the order of their basicity: dibenzothiophene 1-oxide > phenoxathiin 1-oxide > thianthrene 1-oxide.[63]

For alicyclic sulfoxides,[63,64] the order of rates was 5- > 4- > DMSO > 7- > 6-membered ring



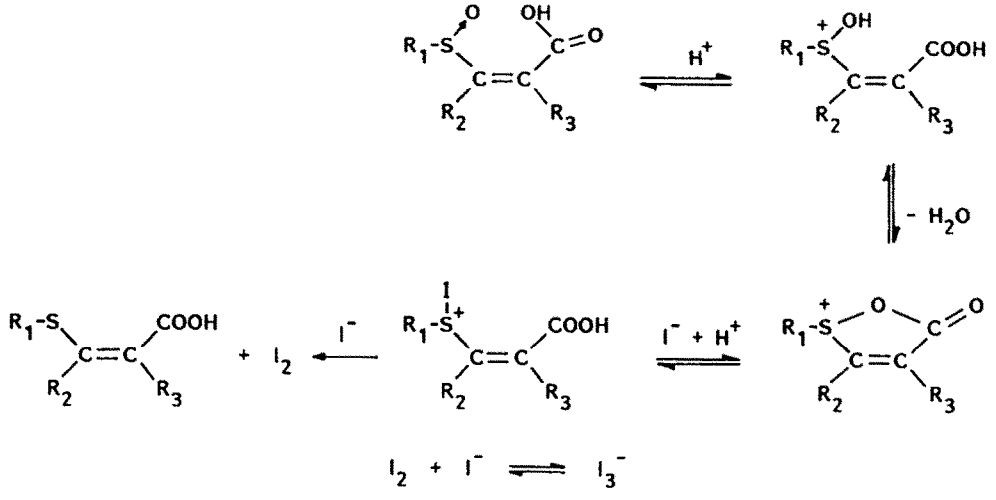
Scheme 16.

sulfoxides. The low reduction rate encountered with the six-membered ring sulfoxide may be due to the predominantly axial position (82%) of the sulfinyl group SO.[64]

Numerous other studies[18,20,21,25,50,54–56,60,61,65,67,68] underline the importance of steric effects on the reduction of dialkyl and arylalkyl sulfoxides bearing functional groups to thioethers using iodide ions in acid medium. Thus Allenmark *et al.*[18,50,54-56,60] found that the reduction of certain alkylsulfinyl carboxylic acids with iodide was much faster than that of DMSO. This was due to the participation of a neighboring group in the reduction and particularly the carboxyl group when favorably situated (Scheme 17). Anchimerically assisted sulfoxide reductions have also been described for alkylsulfinyl benzoic acids by Landini *et al.*,[18,61] for alkylsulfinyl alicyclic carboxylic acids and by other workers[65,67,68] for more complex cyclic sulfoxides.

The mechanism shown below is consistent with the results of Allenmark[18] and those of Landini *et al.*[25] According to these authors, the very marked increase in the rate of reduction (100 to 10^4-fold) is due to the formation of a cyclic acyloxysulfonium salt (Scheme 17).

Recently, Doi *et al.*[67,68] described the kinetics of a sulfoxide–thioether system studied as a possible model for biological redox reactions. The rate of reduction by HI of these mesocyclic sulfoxides was 10^6 times greater than that of DMSO. This difference was attributed to intramolecular catalysis by interaction across the ring of thioether or tertiary amine groups which stabilize the cationic sulfur by means of their lone electron pair. A moderate variation in pH (less than two pH units) shifts the redox equilibrium quantitatively in one or the other direction (Scheme 18).



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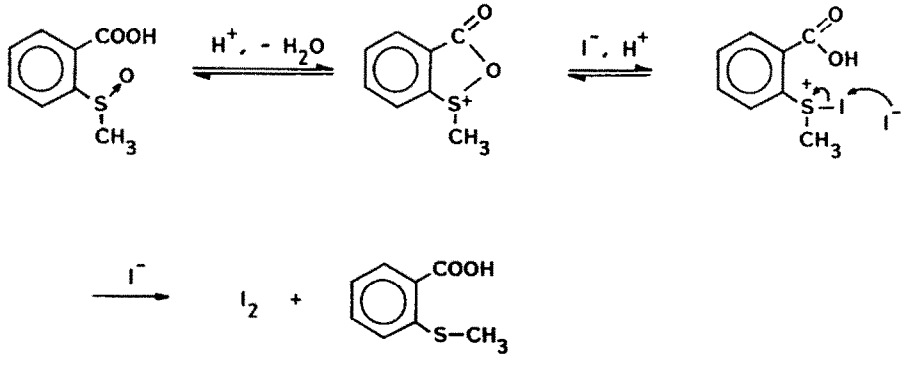

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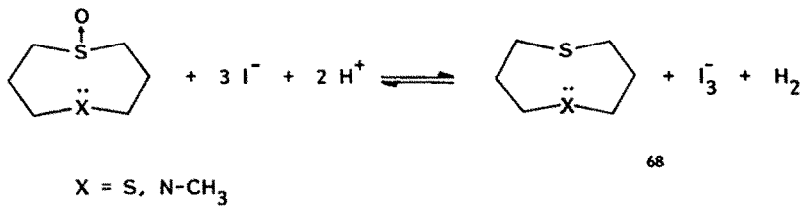
Scheme 17.



Scheme 18.

Finally, Chasar and Shockcor[66] achieved ready and efficient deoxygenation of some dialkyl and diaryl sulfoxides with KI/HCl in anhydrous medium. Yields of thioethers were excellent (86–100%), and no reductive chlorination occurred (Scheme 19).

2.1.4. *Hydrofluoric acid.* Very little work has been done on the deoxygenation of sulfoxides using hydrofluoric acid. Schmalz and Berger[33] in 1954 carried out a reduction of 10-methyl phenothiazine sulfoxide by heating under reflux in 48% HF solution for 4 h. The yield of phenothiazine obtained was not very high (47%)

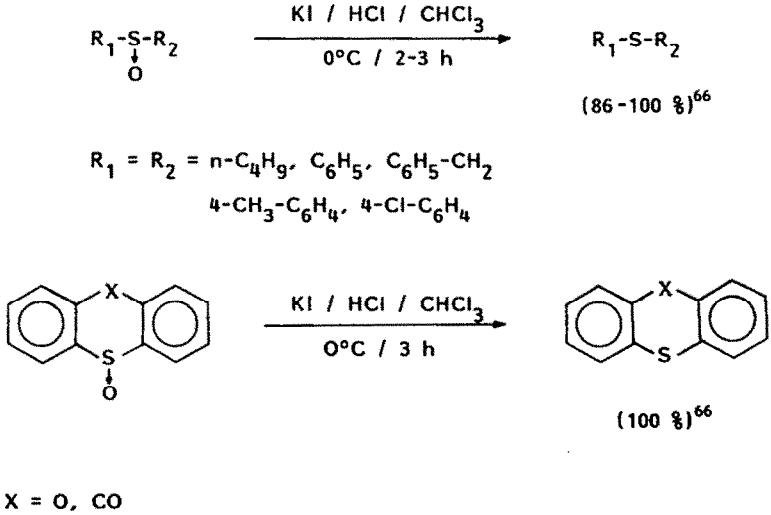
2.2. *Other halo-systems*

2.2.1. *Other iodo-systems.* Nojima *et al.*[69] successfully used an iodine–pyridine–sulfur dioxide system to reduce under specific conditions some diaryl, diphenyl and dibenzyl sulfoxides to thioethers. The yields were generally much higher with iodine (84–96%) than with bromine (19–95%).

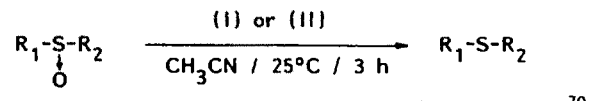
A similar technique was proposed by Olah *et al.*,[70] who achieved the reduction of dialkyl and diaryl sulfoxides to sulfides with the following two systems: $NaI/I_2/(CH_3)_3N$ or $(C_2H_5)_3N/SO_2(I)$ or NaI/pyridine/SO_3(II). In both cases, the reduction took place at ambient temperature in acetonitrile and the yields obtained were excellent with either system (78–91%) for the dialkyl sulfoxides. However, yields fell (<25%) with system (I) for the diaryl sulfoxides (Scheme 20). A reaction mechanism was proposed for each system.[70]

2.2.2. *Cyanuric chloride and fluoride.* Olah *et al.*[71] used cyanuric chloride and fluoride to deoxygenate dialkyl, arylalkyl and diaryl sulfoxides. For the diaryl sulfoxides the cleavage of the S—O bond occurred readily by heating with cyanuric chloride in dioxane or triethyl phosphate, which reduces reaction time. However, this reagent gives reductive chlorination with dialkyl and arylalkyl sulfoxides. In this case, cyanuric fluoride can be used; the relatively low nucleophilicity of the fluoride ion prevents any reductive halogenation (Scheme 21).

2.2.3. t-*Butyl bromide.* Reduction under specific conditions of various sulfoxides to thioethers using *t*-butyl bromide was reported by Italian workers[72] (Scheme 22). This reaction, which gives

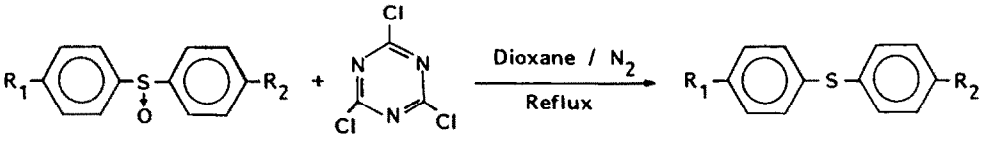


Scheme 19.

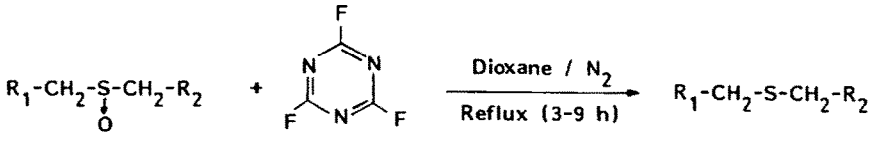


$R_1 = R_2 = n\text{-}C_3H_7,\ n\text{-}C_4H_9,\ C_6H_5\text{-}CH_2,\ C_6H_5,\ 4\text{-}CH_3\text{-}C_6H_4,\ 4\text{-}Cl\text{-}C_6H_4$

Scheme 20.



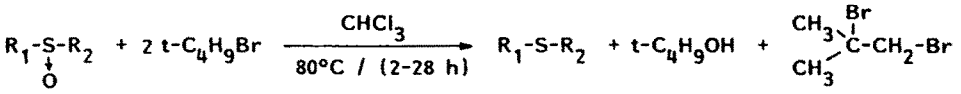
$R_1 = R_2 = H,\ CH_3,\ Cl$



$R_1 = R_2 = n\text{-}C_3H_7,\ n\text{-}C_4H_9,\ C_6H_5\text{-}CH_2$

$R_1R_2 = (\text{-}CH_2\text{-})_4$

Scheme 21.



$R_1 = R_2 = n\text{-}C_3H_7,\ n\text{-}C_4H_9,\ C_6H_5,\ C_6H_5\text{-}CH_2,\ 4\text{-}Cl\text{-}C_6H_4,\ 4\text{-}CH_3\text{-}C_6H_4$

$\begin{cases} R_1 = CH_3 \\ R_2 = C_6H_5 \end{cases}$

Scheme 22.

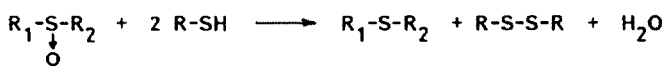
high yields (80–100%) involves classical attack of the *t*-butyl cation on the sulfinyl oxygen giving an intermediate alkoxysulfonium bromide.

3. REDUCTION OF SULFOXIDES WITH SULFUR COMPOUNDS

3.1. *Sulfhydryl compounds*

Sulfhydryl compounds (R—SH) have often found use in the deoxygenation of sulfoxides. The general reaction is shown below (Scheme 23).

3.1.1. *Thiols.* In 1909, Smythe[10] found that dibenzyl sulfoxide could be reduced to a thioether by heating with benzyl mercaptan. Later, Yiannios and Karabinos[73] reduced DMSO to dimethyl



Scheme 23.

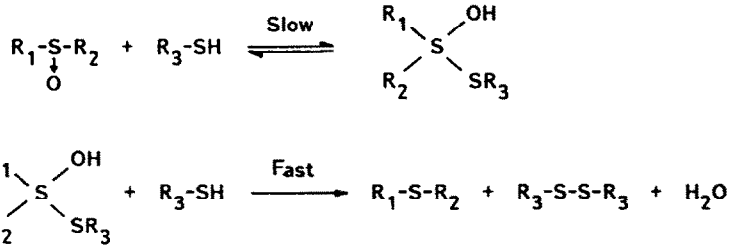
sulfide using various aryl thiols, arylalkyl thiols and alkyl thiols. Excess DMSO here acts as an oxidizer and as solvent. Yields were excellent.

Wallace and Mahon[74-78] report a detailed study of the spontaneous reaction of thiols and dithiols[75] with sulfoxides. These authors show that in the presence of excess sulfoxide or thiol, the reaction is pseudo-first order in thiol and sulfoxide,[76,77] and conclude that the redox reaction proceeds via the rate-determining formation of a thiol–sulfoxide addition product (Scheme 24).

Kinetic studies concerning mainly DMSO and thiolane 1-oxide show the reaction rate to be highly dependent on the acidity of the thiol, the order of reactivity being: Ar—SH > $ArCH_2$—SH > RSH (Scheme 25). In addition, the reaction is very sensitive to acid-base catalysis and in particular to catalysis by tri(*n*-butyl)amine which can increase the reaction rate by a factor of over 200.

The same authors[79] went on to study the reaction of trimethyl sulfoxonium iodide (ICH_3+DMSO) with some thiols (Scheme 26). The proposed mechanism is complex and brings into play the HI/I_2 system in the redox reaction.

The deoxygenation of methionine sulfoxide to methionine was readily achieved either by thréo-1,4-dithiol-2,3-butanediol (Cleland's reagent),[80] or by mercaptoacetic acid, or by 2-mercapto-ethanol.[81]



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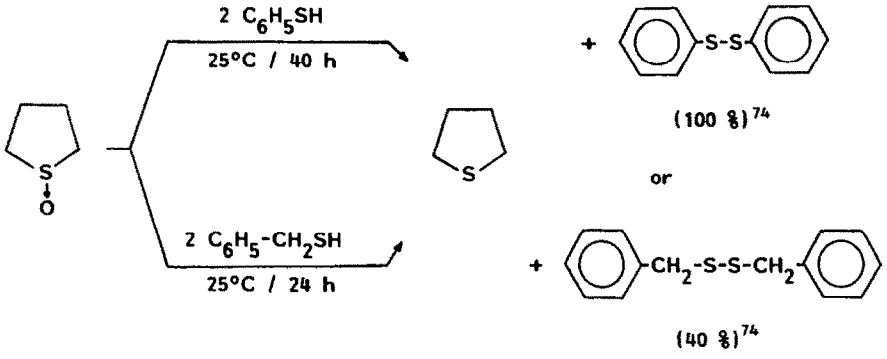
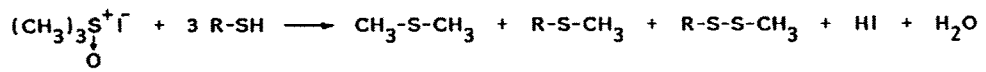
Scheme 24.



Scheme 25.



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R = C_6H_5, C_6H_5-CH_2, n-$C_{12}H_{25}$

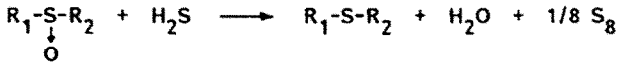
Scheme 26.

Finally, asymmetric reductions of racemic sulfoxides by optically active thiols such as L-cystein[82,83] and *N*-phthaloyl cystein[82] have been described.

3.1.2. *Hydrogen sulfide.* A single reference[84] deals with the reduction of alkyl sulfoxides and alicyclic sulfoxides (4- and 5-membered ring sulfoxides) with H_2S. The stoichiometry is shown below (Scheme 27).

3.1.3. *Thiol acids and carbodithioic acids.* Wallace and Weiss[78] used thiocarboxylic acids (R—COSH) to reduce sulfoxides. Only thiobenzoic acid (C_6H_5COSH) reduced DMSO and diisopropyl sulfoxide with good yields (75 and 88%). Mikolajczyk,[85] however, reduced DMSO and methyl phenyl sulfoxide with thiolacetic acid (CH_3COSH) after one week at ambient temperature (Scheme 28).

Carbodithioic acids (R—CS_2H) such as dithioacetic acid and dithiobenzoic acid are excellent reagents for gentle reduction of sulfoxides to sulfides, and also of *N*-tosylsulfilimines and sulfonium ylides. This method enabled Mikolajczyk and Para[86] and Oae *et al.*[87] to achieve quantitative reduction to thioethers of dialkyl, arylalkyl and diaryl sulfoxides (Scheme 29). They propose a mechanism.[87]



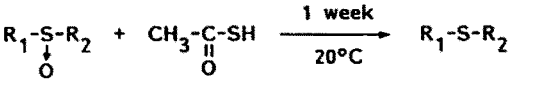
84

$R_1 = R_2 = CH_3,\ C_2H_5$

$R_1 = CH_3\ ;\ R_2 = C_2H_5$

$R_1R_2 = (-CH_2-)_3,\ (-CH_2-)_4$

Scheme 27.

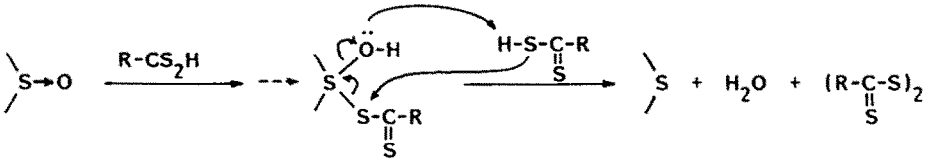


(≃ 70 %) [85]

$R_1 = R_2 = CH_3$

$R_1 = CH_3\ ;\ R_2 = C_6H_5$

Scheme 28.



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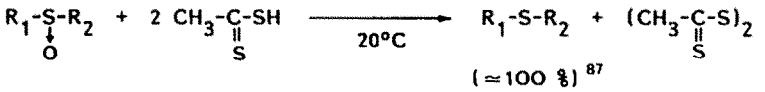
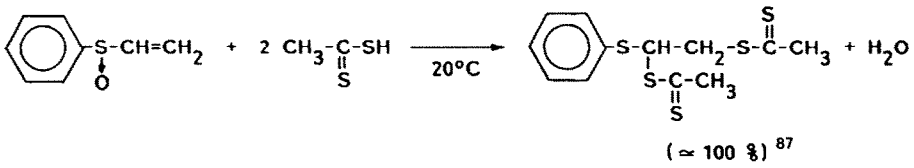


(≃100 %) [87]

$R_1 = R_2 = CH_3,\ C_6H_5$

$\begin{cases} R_1 = CH_3\ ;\ CH_3\ ;\ C_2H_5\ ;\ C_6H_5 \\ R_2 = C_2H_5\ ;\ C_6H_5\ ;\ C_6H_5\ ;\ C_6H_5\text{-}CH_2 \end{cases}$

Scheme 29.



Scheme 30.

With phenyl vinyl sulfoxide, dithioic acids give a Michael-type reduction–addition reaction (Scheme 30).

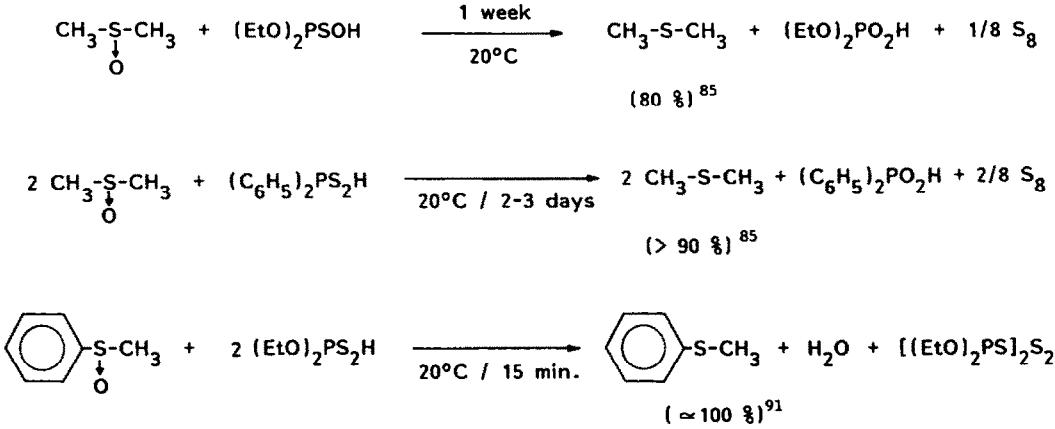
Under the same conditions, allyl phenyl sulfoxide is deoxygenated to its thioether, but other side products are formed including diphenyl sulfide and allyl alcohol.

3.1.4. *Thiophosphinic, thiophosphonic and thiophosphoric acids and selenium analogs.* Mikolajczyk alone[85,88] and with Para,[86,89] were the first to report the reduction of DMSO with thiophosphinic [R_2PS_2H], thiophosphonic [R,R'OPOSH] and thiophosphoric [$(RO)_2POSH$] acids. Yields and reaction rates were much higher with the dithio-acids than with the mono-thio acids (Scheme 31).

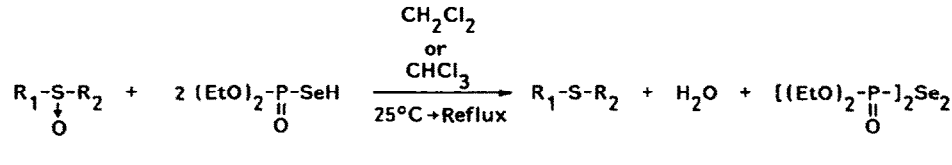
Oae *et al.*[90,91] used this method for the deoxygenation of dialkyl, arylalkyl and diaryl sulfoxides. The exothermic reaction is quantitative in a few hours at ambient temperature with the *O,O*-dialkyldithiophosphoric acids [$(RO)_2PS_2H$] (Scheme 31). The reduction by these acids of other compounds with semi-polar bonds such as sulfilimines, sulfonium ylides and pyridine *N*-oxide has also been reported.[91]

Mikolajczyk and Para[89] described the asymmetrical reduction of racemic sulfoxides by optically active thiophosphonic acids, particularly R(−)-*O*-ethyl ethylphosphonothioic acid [$(C_2H_5O)(C_2H_5)PSOH$].

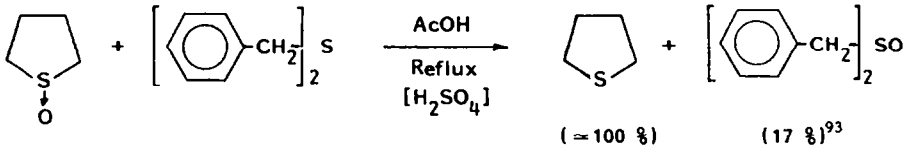
Finally, selenium analogs[88,92] of thiophosphoric acids [$(RO)_2POSeH$] have been used most successfully for the reduction of sulfoxides to their corresponding thioethers (Scheme 32).



Scheme 31.



Scheme 32.



Scheme 33.

3.2. *Organic sulfur compounds*

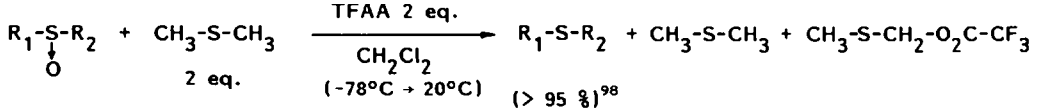
3.2.1. *Thioethers.* Sulfoxides are reduced by thioethers, which are themselves oxidized to sulfoxides,[95-97] by oxygen transfer.[93,94] In 1955, Bordwell and Pitt[93] observed a quantitative reduction of thiolane 1-oxide to thiolane by dibenzyl sulfide. The reaction is catalyzed by sulfuric acid in acetic acid (Scheme 33).

Tanikaga *et al.*[98] report the very rapid reduction by oxygen exchange of a large number of sulfoxides with dimethyl sulfide (DMS) and two equivalents of trifluoroacetic anhydride [$(CF_3CO)_2O$] (TFAA). The corresponding thioethers, via a sulfonium ion, are obtained in a few minutes with very good yields (>95%) (Scheme 34). Thionyl chloride ($SOCl_2$) and acetyl trifluoroacetate ($CF_3CO_2COCH_3$) can be used in place of TFAA, with similar results. This method is a particularly convenient means of reducing sulfoxides to sulfides.

Similarly, Tam *et al.*[99] used a mixture of dimethyl sulfide and hydrofluoric acid (DMS/HF; 3 : 1, v/v) to completely deoxygenate methionine sulfoxide to methionine in the course of peptide synthesis. For the same reduction, Shechter[100] obtained a comparable result with DMS–10.7 M HCl, while Okamoto *et al.*[101] used methyl phenyl sulfide with a mixture of trifluoromethane sulfonic acid and trifluoroacetic acid (CF_3SO_3H/CF_3COOH). Miotti *et al.*[30,102] and Ciuffarin *et al.*[103] studied the kinetics of the exchange of oxygen between arylalkyl sulfoxides and dialkyl and alicyclic sulfides in aqueous media; (H_2O/MeOH, 1 : 2, v/v, 4 M HCl;[30] H_2O/dioxane, 2 : 3, v/v; 4–6 M $HClO_4$ or H_2SO_4)[102] and in non-aqueous media (CH_3COOH or $C_6H_5NO_2$, CF_3—SO_3H)[103] (Scheme 35). Mechanisms are proposed; in general the oxygen transfer is favored by acid catalysis which provides an oxosulfonium ion which then undergoes a nucleophilic attack by sulfur.

3.2.2. *Sulfenyl, sulfinyl and sulfonyl chlorides.* Beside sulfides, certain sulfenyl, sulfinyl and sulfonyl organic compounds have been used to reduce sulfoxides by oxygen transfer. Boyle[104] observed a reductive chlorination of DMSO by 5-dimethyl aminonaphthalene-1-sulfonyl chloride. This rapid reaction takes place at room temperature by a Pummerer type mechanism via an oxosulfonium salt (Scheme 36).

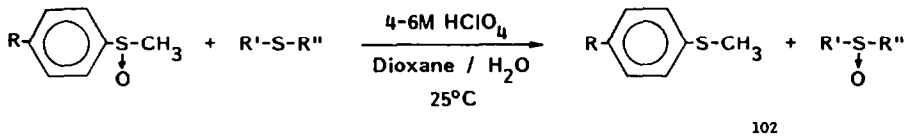
Later, Numata *et al.*[105] carried out the reduction of dialkyl, arylalkyl and diaryl sulfoxides both with methanesulfonyl chloride and with *p*-nitrobenzenesulfinyl chloride. The deoxygenation occurs under specified conditions giving high yields of thioethers (80–90%) (Scheme 37). These authors propose two mechanisms. Polycyclic sulfoxides such as thianthrene-1-oxide and phenoxathiin-1-oxide were also reduced with high yields by arenesulfinyl and arenesulfenyl chlorides[105] (Scheme 37). However, the latter reagent can only be used with sulfoxides bearing no proton α to the sulfinyl (SO). Sulfoxides with an α proton yield disulfides with 4-nitrobenzenesulfenyl chloride. This result was confirmed by Senning[106] using trichloromethane sulfenyl, sulfinyl and sulfonyl chlorides.



$R_1 = C_6H_5$; $R_2 = CH_3$, CH_3-$(CH_2)_5$, C_6H_5,
CH_2=CH-CH_2-O-$(CH_2)_2$, C_6H_5-S-$(CH_2)_2$

$R_1 = CH_3$; $R_2 = CH_3$-$(CH_2)_3$, CH_3-$(CH_2)_7$

Scheme 34.



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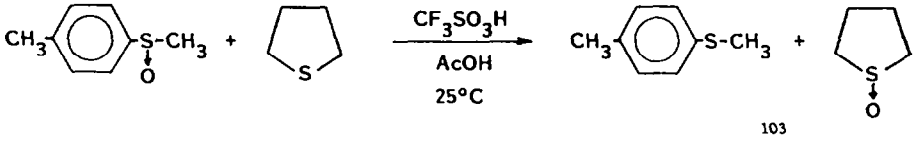
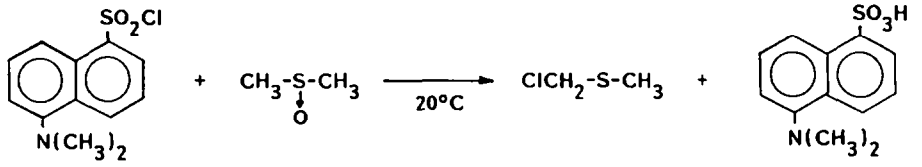
R = Cl, CH_3

R' = R" = CH_3, C_2H_5, n-C_3H_7, n-C_4H_9, i-C_3H_7



103

Scheme 35.



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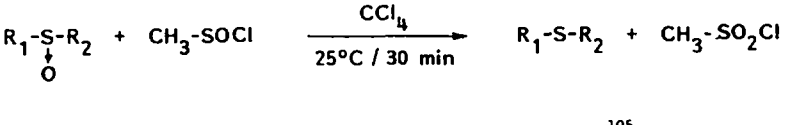
Scheme 36.

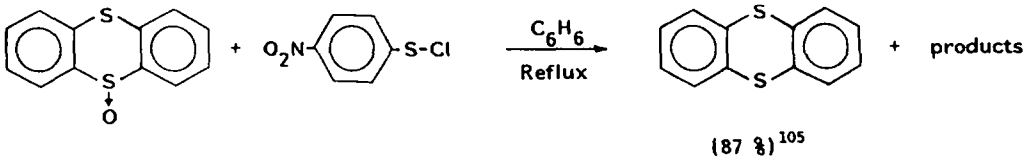


(80-90 %)[105]

$R_1 = R_2 = CH_3$, C_6H_5

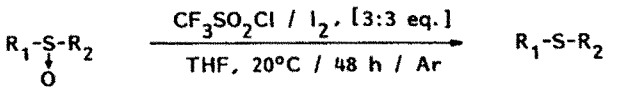
$R_1 = CH_3$; CH_3 ; C_2H_5

$R_2 = C_6H_5$; C_6H_5-CH_2 ; C_6H_5-CH_2



(87 %)[105]

Scheme 37.



$R_1 = R_2 = C_6H_5$, C_6H_5-CH_2, n-C_4H_9, n-C_6H_{13}

$R_1 = CH_3$; $R_2 = C_6H_5$

Scheme 38.

Sulfilimines and heteroatomic *N*-oxides are also efficiently reduced by treatment with sulfinyl chlorides.[105] More recently, Fukamiya *et al.*[107] reported easy reduction of various sulfoxides with trifluoromethanesulfonyl chloride and iodine at ambient temperature with high yields (52–96%) (Scheme 38).

3.2.3. *Disulfides.* Oae *et al.*[108] showed that diphenyl sulfoxide reacts vigorously with diphenyl disulfide at 250°C to give diphenyl sulfide, SO_2 and traces of benzenesulfonic acid (Scheme 39). A homolytic cleavage of the S—O bond is suggested by these authors.

Deoxygenation of thianthrene 1-oxide (unpublished work)[109] has also been carried out by heating with 4-nitrophenyl disulfide.

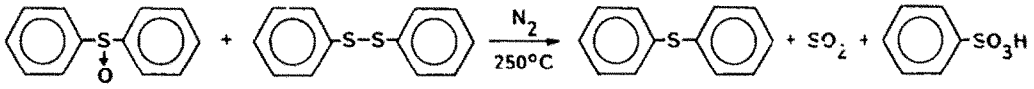
3.3. *Elemental sulfur*

Diphenyl sulfoxide[110–112] and di-*n*-butyl sulfoxide are quite rapidly reduced to their corresponding thioethers with elemental sulfur at high temperature (200–280°C) (Scheme 40). The reaction involves free radicals. On the other hand, dibenzyl sulfoxide does not give the expected sulfide under these conditions, but various products, predominantly stilbene.[111]

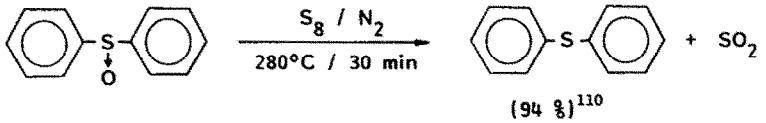
Gravilin *et al.*[112] simplified the reduction of diphenyl sulfoxide with sulfur by using thionyl chloride ($SOCl_2$) or sulfur dichloride (SCl_2) as catalysts at 110–120°C.

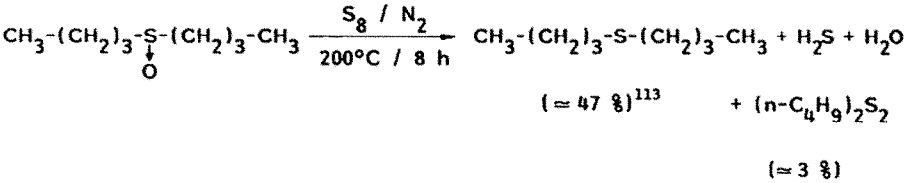
3.4. *Miscellaneous sulfur compounds*

3.4.1. *Thionyl chloride.* In 1894, Loth and Michaelis[2] reported the reductive chlorination of diphenyl sulfoxide by treatment with thionyl chloride ($SOCl_2$). Bordwell and Pitt[93] used thionyl chloride to prepare with high yields a series of α-chlorosulfides from sulfoxides (Scheme 41). The

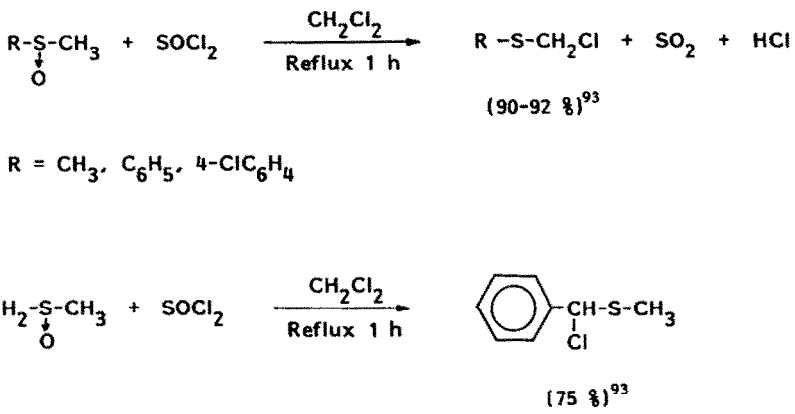


Scheme 39.





Scheme 40.



Scheme 41.

reaction probably proceeds by a mechanism analogous to a Pummerer rearrangement. Similarly, Volynskii *et al.*[114] showed that alkyl and aryl cyclohexyl and dicyclohexyl sulfoxides could be readily deoxygenated with thionyl chloride. Some chlorinated side products are also obtained.

Granoth[115] proposed using cyclohexane as a chlorine trap in the reduction of a series of diaryl sulfoxides with $SOCl_2$. A rapid deoxygenation ensues with high yields (85–92%) and no unwanted chlorinated products.

Finally, Grossert *et al.*[116] observed an oxygen transfer reaction between thiolane 1-oxide and $SOCl_2$. The thiolane, obtained with a low yield (25%) was contaminated with a small amount of 2-chlorothiolane (Scheme 42).

3.4.2. *Sulfites.* Micheel and Schmitz[117] in 1939 showed that an aqueous solution of sodium disulfite ($Na_2S_2O_5$) could efficiently cleave the S—O bond of *dl*-methionine sulfoxide and (+)α-ethyl-D-thioglucoside sulfoxide. By this method, Russell and Sabourin[118] carried out selective reduction of sulfoxides bearing functional groups, including β-ketosulfoxides, to their corresponding thioethers, with high yields (52 to 93%) (Scheme 43).

Johnson *et al.*[119] found fortuitously that an aqueous solution of sodium hydrogen sulfite ($NaHSO_3$) had reduced rapidly and quantitatively the *cis* isomer of a mixture of *cis*- and *trans*-2-methylthiolane sulfoxide (Scheme 44). This is thus a convenient method for preparing pure *trans*-2-methylthiolane sulfoxide.

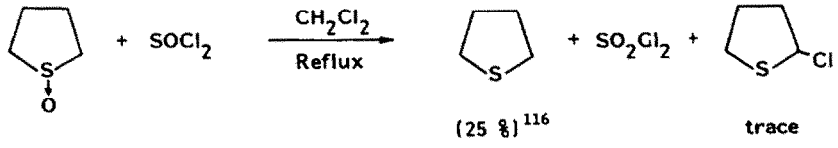
The generalization of this reduction to dialkyl and alicyclic sulfoxides gave middling results. Yields (18–52%) were in the order 7- > DMSO > 4- > 6-membered ring sulfoxides.

These authors also carried out reduction of sulfoxides to sulfides using aqueous sulfur dioxide (SO_2/H_2O). A recent patent[344] describes the reduction of various sulfoxides with $NaHSO_3/I_2$ or HI in acetic acid.

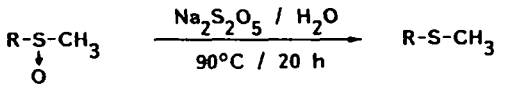
3.4.3. *Formamidinesulfinic acid.* Drabowicz and Mikolajczyk[120] report a simple and efficient reduction of dialkyl, arylalkyl and diaryl sulfoxides with formamidinesulfinic acid [$H_2NC(=NH)SO_2H$], catalysed by iodine (Scheme 45).

3.4.4. *Disilthianes.* Soysa and Weber[121] propose convenient deoxygenation of various sulfoxides with hexamethyl disilthiane [$(CH_3)_3Si]_2S$ or hexamethyl cyclotrisilthiane [—$Si(CH_3)_2$—]$_3S$ under mild conditions (20 to 60°C) in the presence of other functional groups (Scheme 46).

3.4.5. *Chlorosulfonyl isocyanate–sodium iodide.* Dialkyl, arylalkyl and diaryl sulfoxides were reduced to their corresponding thioethers with high yields (82 to 98%) by chlorosulfonyl isocyanate (O=C=N—SO_2Cl) (CSI)[122] in the presence of sodium iodide in molar ratio 1 : 3 : 8. The mechanism is assumed to involve a zwitterion sulfoxide-CSI addition species which is then attacked by I^-.



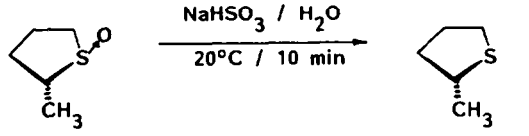
Scheme 42.



(52-93 %)[118]

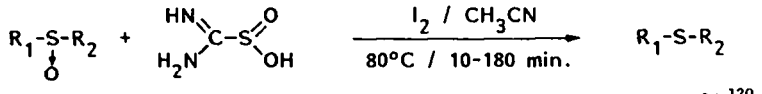
R = $C_6H_5COCH_2$, $C_6H_5CH(OH)CH_2$, $C_6H_5CH{=}CH$

Scheme 43.



(100 %)[119]

Scheme 44.



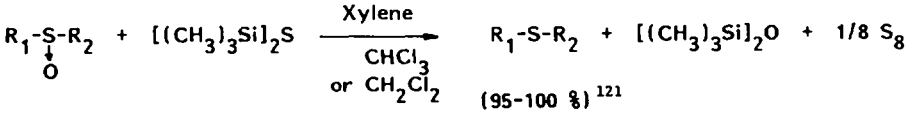
(89-95 %)[120]

1 eq. 2-3 eq.

$R_1 = R_2 = n\text{-}C_4H_9$, C_6H_5, $C_6H_5CH_2$

$R_1 = CH_3$; C_2H_5 ; $n\text{-}C_3H_7$; C_6H_5
$R_2 = C_6H_5$; C_6H_5 ; C_6H_5 ; $C_6H_5CH_2$

Scheme 45.



(95-100 %)[121]

$R_1 = R_2 = CH_3$, $n\text{-}C_4H_9$, C_6H_5

$R_1 = CH_3$; CH_2Cl ; CH_3 (65 % yield) ; C_6H_5 (55 % yield)
$R_2 = C_6H_5$; C_6H_5 ; $C_6H_5COCH_2$; glucidyl

Scheme 46.

$$R_1\text{-}CH_2\text{-}\underset{\underset{O}{\downarrow}}{S}\text{-}R_2 + F_3S\text{-}N(C_2H_5)_2 \xrightarrow[20°C]{ZnI_2} R_1\text{-}\underset{\underset{F}{|}}{CH}\text{-}S\text{-}R_2$$

(79-100 %)[123]

R_1 = H, $CH_3\text{-}(CH_2)_{14}$, $C_6H_5(CH_2)_2$, $(C_6H_5)_2NCH_2$, $C_2H_5O_2C(CH_2)_2$, $NC(CH_2)_2$

R_2 = C_6H_5, 4-$CH_3OC_6H_4$

Scheme 47.

3.4.6. *(Diethylamino)sulfur trifluoride.* Recently, McCarthy *et al.*[123] have reported the conversion of sulfoxides to α-fluorothioethers by (diethylamino)sulfur trifluoride $[(C_2H_5)_2NSF_3]$ (DAST) catalysed by ZnI_2 via Pummerer type rearrangement (Scheme 47).

This method gives high yields of sulfides (79–100%) with arylmethyl and arylalkyl sulfoxides without disturbing other functional group such as nitriles, tertiary amines and esters.

4. REDUCTION OF SULFOXIDES WITH PHOSPHORUS COMPOUNDS

By reason of their high affinity for oxygen, phosphorus derivatives are widely used to cleave the S—O bond of sulfoxides. In 1891, Michaelis and Godchaux[1] observed reductive chlorination of diphenyl sulfoxide with PCl_5.

4.1. *Trivalent phosphorus compounds*

4.1.1. *Phosphines.* In 1962, Ray *et al.*[124] used dimethyl sulfoxide and diphenyl sulfoxide to oxidize trivalent phosphorus compounds including triphenyl phosphine $[(C_6H_5)_3P]$; triphenyl phosphine oxide $[(C_6H_5)_3PO]$ and sulfide were formed (Scheme 48).

Szmant *et al.*,[125,126] Amonoo-Neizer *et al.*,[127] Olah *et al.*[128,129] and others[130,345] have reported extensive work on the deoxygenation of various sulfoxides with triphenyl and other phosphines, e.g. $[(alkyl)_3P]$,[127] $[(R_2N)_3P]$[127,129] under various operating conditions and with various co-reactants, e.g. CH_2Cl_2/N_2,[127] CCl_4,[125] CH_3COOH/BF_3,[126] I_2/NaI,[128,129] $[(C_2H_5)_2NCS_2]_2MoO_2$[345] (Scheme 49).

The rate of the reduction of sulfoxides by phosphines is closely linked to the nature of the phosphorus substituents; the following order was observed: $[(CH_3)_2N]_3P > (n\text{-}Bu)_3P > (C_6H_5)_3P$. The reaction is accelerated by acid catalysis, and the rate is greater the more basic the sulfoxide is. The accepted mechanism[127] for the deoxygenation of sulfoxides by phosphines that are good electron donors, involves nucleophilic attack by phosphorus (Scheme 49).

Amos[131] recently carried out the reduction of dialkyl, diaryl and arylvinyl sulfoxides with polystyryl diphenyl phosphine $[PS\text{-}P(C_6H_5)_2]$ with CCl_4 as co-reactant under specified conditions with high yields (81–99%).

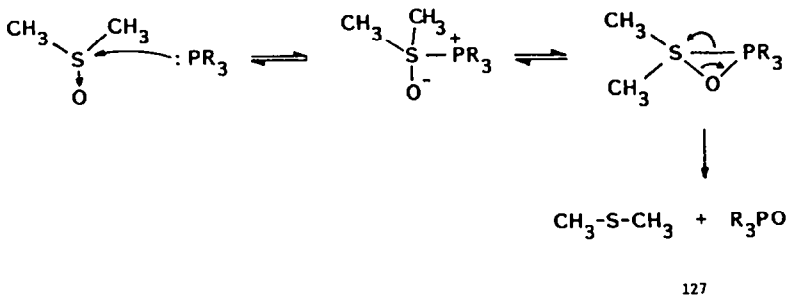
4.1.2. *Phosphites and cyclic phospholanes.* Amonoo-Neizer *et al.*[127] show that the rate of reduction of dimethyl sulfoxide by triphenyl phosphite $[(C_6H_5O)_3P]$ is very much faster than by triphenyl phosphine. Phosphites, which are good electron receivers, react by electrophilic attack by the phosphorus at the oxygen of the sulfinyl group (Scheme 50).

Oae *et al.*[132] also observed that methyl phenyl sulfoxide was quantitatively deoxygenated by triphenyl phosphite and methyl diphenyl phosphite by heating at 110°C (Scheme 51). However, with alkyl phosphite, the sulfoxide catalysed a Michaelis–Arbuzov type rearrangement to dialkyl

$$CH_3\text{-}\underset{\underset{O}{\downarrow}}{S}\text{-}CH_3 + (C_6H_5)_3P \longrightarrow CH_3\text{-}S\text{-}CH_3 + (C_6H_5)_3PO$$

124

Scheme 48.



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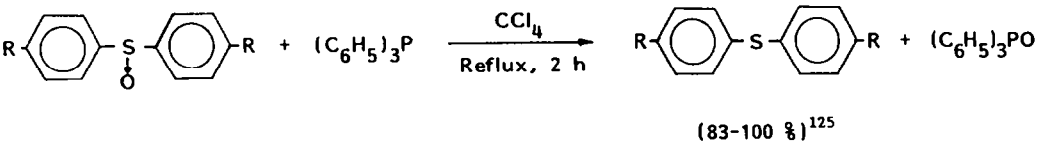
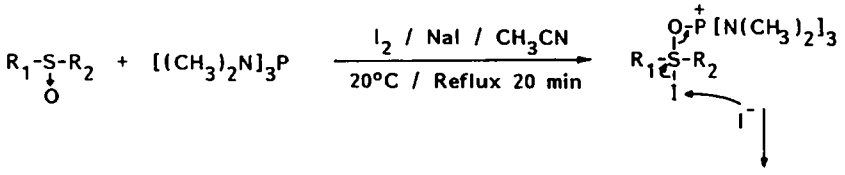


(83-100 %)[125]

R = CH_3, HO, CH_3O, O_2N, Br

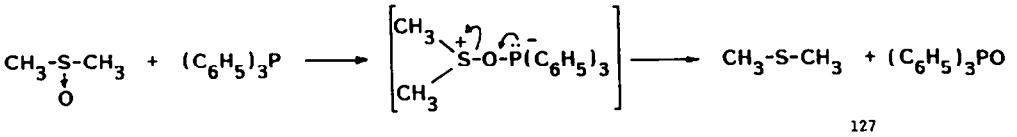


$R_1 = R_2$ = n-C_3H_7, n-C_4H_9, C_6H_5, C_6H_5-CH_2, 4-ClC_6H_4, 4-CH_3-C_6H_4

R_1R_2 = $(-CH_2-)_4$

(68-96 %)[129]

Scheme 49.



127

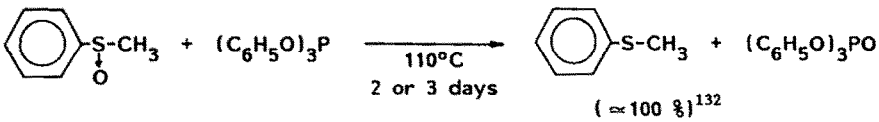
Scheme 50.

alkyl phosphonate [$(RO)_2P(O)R'$]. Dimethyl phenyl phosphite gave a mixture of phosphate, phosphonate and sulfide (Scheme 51).

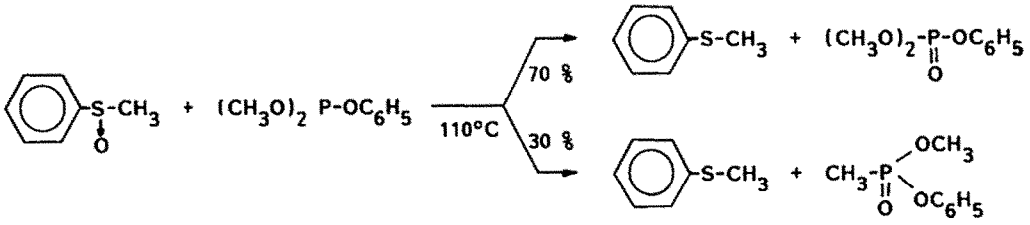
Dreux *et al.*[133] and Chasar and Pratt[134] report efficient reduction under mild conditions of numerous sulfoxides with cyclic phospholanes (Scheme 52).

The deoxygenation of sulfoxide is faster with 2-chloro-1,3,2-benzodioxaphosphole (15 to 60 min at ambient temperature) than with 2-phenoxy-1,3,2-benzodioxaphosphole (1–3 h under reflux in CCl_4). With the latter reagent, the reaction is markedly faster when iodine is added as a catalyst.

Finally, Sekine *et al.*[135] found tris(trimethylsilyl) phosphite [$[(CH_3)_3SiO]_3P$] to be more reactive than aminophosphines for the reduction of methyl phenyl sulfoxide to its thioether. The reaction mechanism remains somewhat uncertain (Scheme 53).



(≃100 %)[132]



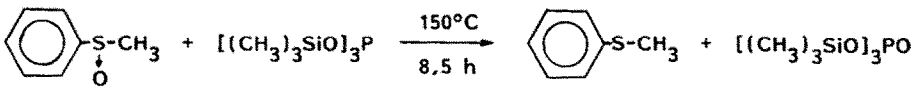
132

Scheme 51.

(87-95 %)[133]

X = O-C6H5[133], Cl[134] (72-100 %)[134]

Scheme 52.



(72 %)[135]

Scheme 53.

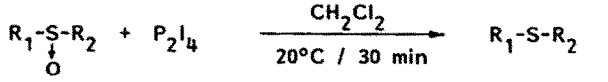
4.1.3. *Phosphorus(III) halides.*

4.1.3.1. *Phosphorus trichloride.* Dimethyl sulfoxide[127] and diaryl sulfoxides bearing various functional groups[136] were readily reduced by PCl_3 with high yields (90–98%). Kaiser *et al.*[137–139] and Spry[140,141] also used PCl_3 to deoxygenate cephalosporin *S*-oxides.

4.1.3.2. *Phosphorus tribromide.* The efficient reduction of penicillin *S*-oxides[142–144] and cephalosporin *S*-oxides[137,145] with PBr_3 in cold DMF has been reported.

4.1.3.3. *Phosphorus(III) iodides.* Denis and Krief[146] and Suziki *et al.*[147] showed that diphosphorus tetraiodide (P_2I_4) would readily reduce sulfoxides to thioethers without heating, with high yields (Scheme 54). Phosphorus tri-iodide[148] (PI_3) also gives excellent results.

4.1.4. *Hypophosphorous acid.* Günther[149] observed almost quantitative reduction of dimethyl sulfoxide to DMS when it was heated in a solution of hypophosphorous acid with a diselenide catalyst.

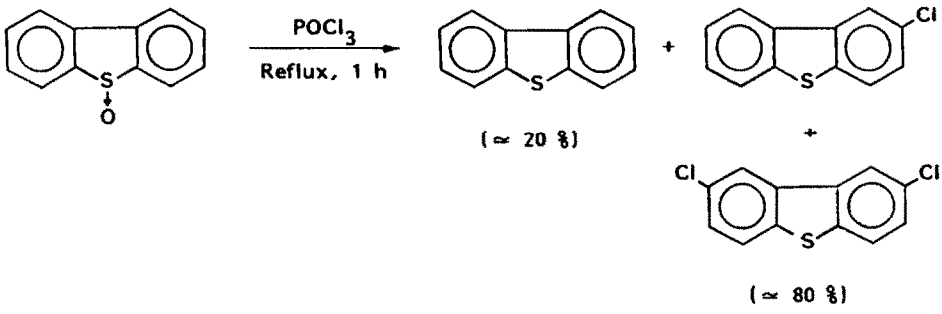


(78-82 %)[146]

$R_1 = R_2 = n\text{-}C_3H_7$

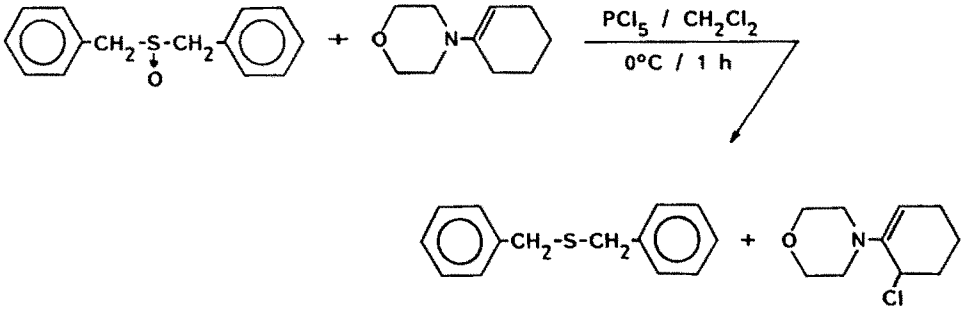
$R_1 = CH_3$; $R_2 = C_6H_5$

Scheme 54.



151

Scheme 55.



Scheme 56.

4.2. *Pentavalent phosphorus compounds*

4.2.1. *Phosphorus(V) halides.* In 1891, Michaelis and Godchaux[1] found that phosphorus pentachloride (PCl_5) would react with diphenyl sulfoxide to give 4-chlorophenyl methyl sulfide. This reductive chlorination with PCl_5 was also observed with bis(chloroalkyl) sulfoxides.[150]

Bird[151] studied the reductive chlorination of diaryl sulfoxides and some heterocyclic *S*-oxides (dibenzothiophene, thianthrene and phenoxathiin *S*-oxides) with phosphorus oxychloride ($POCl_3$) and thionyl chloride ($SOCl_2$). The reaction yielded a mixture of sulfides and mono- and dichloro sulfides, the latter predominating (Scheme 55).

Murphy,[152] in the course of a synthesis of cephalosporins, carried out an efficient deoxygenation of a cephalosporin *S*-oxide with PCl_5 and $POCl_3$ in pyridine at 45°C. In order to avoid chlorination with PCl_5 and $POCl_3$, several coreagents were used, such as dimethylaniline,[153] amisole,[153] NaI[154] *N,N*-dialkyl anilines[155] and enamines.[155] Pure sulfides were thereby obtained in high yields (Scheme 56).

NaI–$SOCl_2$ or $(COCl)_2$[154] and *N,N*-dimethyl aniline–$SOCl_2$, 1-piperidino-1-cyclohexane–$SiCl_4$ or $(CH_3O)_2SiCl_2$[155] gave results similar to PCl_5 for the reduction of the same dialkyl, arylalkyl and diaryl sulfoxides.

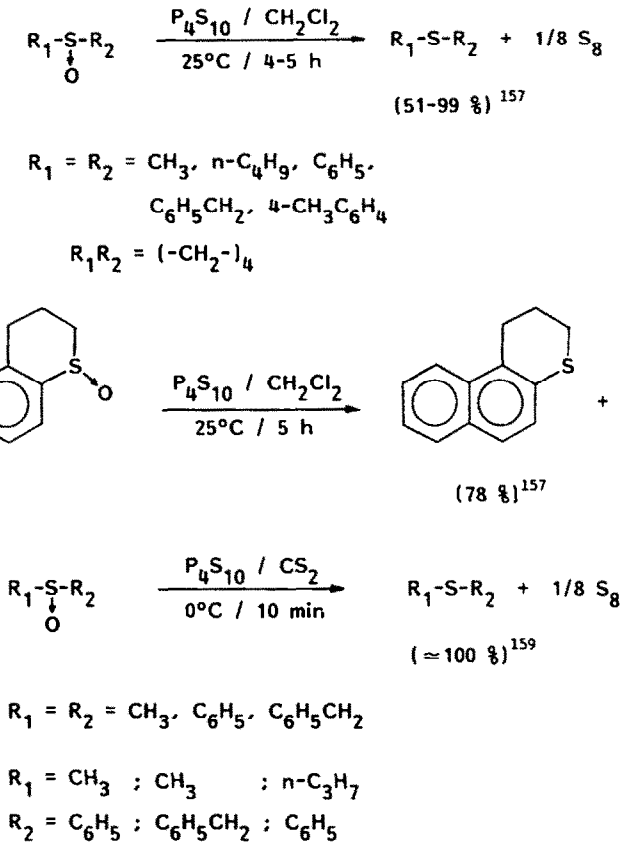
4.2.2. *Phosphorus sulfur compounds.*

4.2.2.1. *Phosphorus pentasulfide.* Micetich[156] proposed a convenient method for the deoxygenation of cephalosporin *S*-oxides with phosphorus pentasulfide (P_4S_{10})–pyridine in methylene chloride. The reduction with P_4S_{10} occurs via an intermediate thiosulfoxide which breaks down spontaneously into the sulfide (90% yield) and elemental sulfur.

Still *et al.*[157,158] and Baechler and Daley[159] subsequently reduced a large number of dialkyl, arylalkyl, diaryl, alicyclic[157,158] and heterocyclic[157,158,349] sulfoxides to their corresponding thioethers with P_4S_{10} under very mild conditions (Scheme 57).

4.2.2.2. *Thiophosphoryl and selenophosphoryl compounds.** Mikolajczyk and Luczak[160] report the

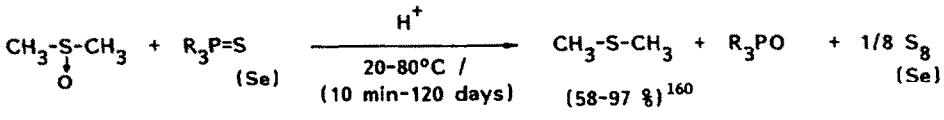
* Thio- and selenophosphoric acids and analogs are dealt with in part 3.1.4. (*cf* refs 85–92).



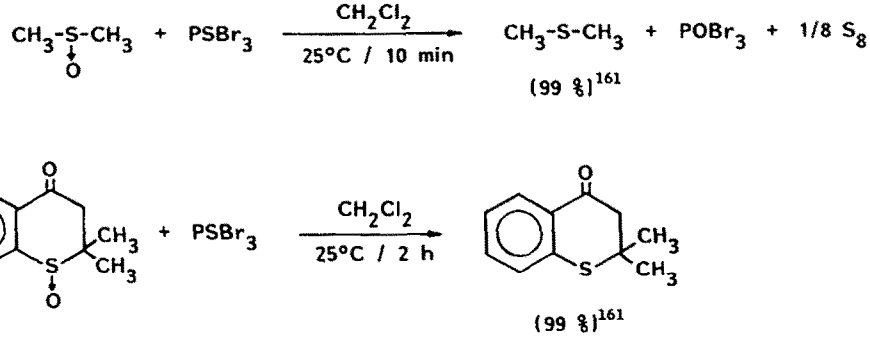
Scheme 57.

conversion of thio- or selenophosphoryl compounds into phosphoryl compounds in strongly acidic media by dimethyl sulfoxide, itself reduced to dimethyl sulfide (Scheme 58).

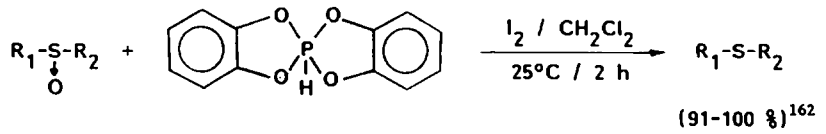
Still *et al.*[161] showed that thiophosphoryl bromide ($PSBr_3$) could be used to reduce various sulfoxides to thioethers under mild conditions (Scheme 59). The mechanism proposed involves a four-center transition state as with P_4S_{10}. The authors claim that $PSBr_3$ gives higher yields than



Scheme 58.



Scheme 59.



$R_1 = R_2 = CH_3$, n-C_4H_9, C_6H_5, 4-ClC_6H_4, $C_6H_5CH_2$, 4-$CH_3C_6H_4$

R_1R_2 = $(-CH_2-)_4$, phenothiazine

$R_1 = (C_2H_5O)_2POCH_2$; $R_2 = C_6H_5$

Scheme 60.

P_4S_{10}, and with shorter reaction times. $PSBr_3$ also reduces selenoxides to selenides with high yields. Attempts to reduce sulfoxides using thiophosphoryl chloride ($PSCl_3$) have failed so far.

4.2.2.3. *Spirophosphorane.* Savignac *et al.*[162] described almost quantitative deoxygenation of various sulfoxides by a spirophosphorane derivative of pyrocatechol catalyzed by I_2 (Scheme 60).

5. REDUCTION OF SULFOXIDES WITH SILICON COMPOUNDS

5.1. *Halosilanes*

Lappert and Smith[163] in 1961 reported reductive halogenation of dimethyl sulfoxide and diphenyl sulfoxide with silicon chloride ($SiCl_4$). More recently, other authors[155] have avoided the halogenation, which occurs after reduction, by using cyclic enamines to trap chloride ions.

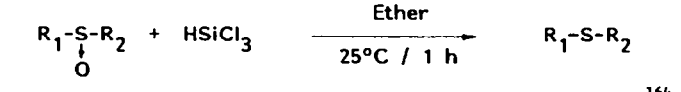
Chan *et al.*[164,165] reduced aryl sulfoxides with trichlorosilane ($HSiCl_3$) in ether with excellent yields. Under the same conditions, dibenzyl sulfoxide and alkyl sulfoxides were converted into mercaptals by Pummerer type rearrangement, and into sulfides (Scheme 61).

Olah *et al.*,[166] Numata *et al.*[167] and others[168,169] have reported successful deoxygenation of various sulfoxides with trimethylsilyl chloride [$(CH_3)_3SiCl$] along with various co-reactants such as NaI,[166] RSH,[167,170] Zn[168] and some weak bases[170] (Scheme 62).

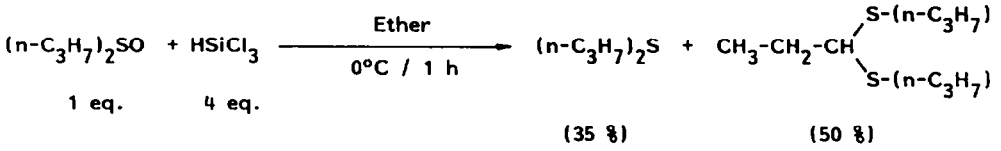
Miller and Hässig[169] obtained α-trimethylsilyl vinyl thioethers in one step from sulfoxides by treatment with excess lithium diisopropylamide (LDA) in THF in the presence of trimethylsilyl chloride.

Recent results[171] show that dialkyl, arylalkyl and dialkyl sulfoxides may be reduced to their corresponding sulfides in high yields (85–95%) with trichloromethyl silane–sodium iodide [CH_3SiCl_3/NaI] in acetonitrile at ambient temperature.

Other alkylhalosilane systems such as trimethylbromosilane [$(CH_3)_3SiBr$][172] or trimethyliodosilane [$(CH_3)_3SiI$][172] in CCl_4 and [$(CH_3)_3SiI/CCl_4$/pyridine] systems[173] provide gentle conditions



$R_1 = R_2 = C_6H_5$, 4-$CH_3C_6H_4$, 4-ClC_6H_4



Scheme 61.

$$R_1\text{-}\overset{\overset{\downarrow}{O}}{S}\text{-}R_2 + (CH_3)_3SiCl \xrightarrow[25°C\ /\ 10\text{-}20\ min]{NaI\ /\ CH_3CN} R_1\text{-}S\text{-}R_2$$

(78-96 %)[166]

$R_1 = R_2 = n\text{-}C_3H_7,\ n\text{-}C_4H_9,\ C_6H_5,\ C_6H_5CH_2,$
$4\text{-}ClC_6H_4,\ 4\text{-}CH_3C_6H_4$

$R_1R_2 = (-CH_2-)_4$

$$R_1\text{-}\overset{\overset{\downarrow}{O}}{S}\text{-}R_2 + (CH_3)_3SiCl + 2\ R\text{-}SH \xrightarrow[25°C\ /\ 5\text{-}15\ min]{Ether\ /\ Ar} R_1\text{-}S\text{-}R_2 + R\text{-}S\text{-}S\text{-}R + 1/2\ [(CH_3)_3Si]_2O$$

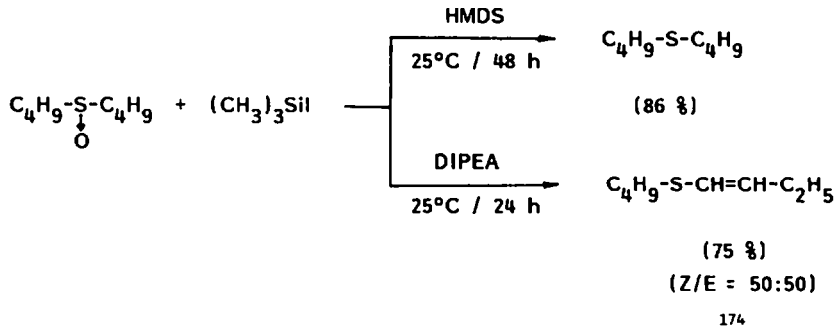
(70-100 %)[167]

$R = C_6H_5,\ n\text{-}C_4H_9$

$R_1 = R_2 = C_6H_5CH_2,\ n\text{-}C_4H_9$

$R_1 = CH_3\ ;\ C_2H_5\ ;\ CH_3$
$R_2 = C_6H_5\ ;\ C_6H_5\ ;\ n\text{-}C_4H_9$

Scheme 62.



Scheme 63.

for the deoxygenation of various sulfoxides to sulfides. Miller and McKean[174] carried out the reduction of dialkyl and arylalkyl sulfoxides with $[(CH_3)_3SiI]$ in the presence of sterically hindered amine bases, including hexamethyldisilazane (HMDS) and diisopropylethylamine (DIPEA).

Simple deoxygenation occurs with $[(CH_3)_3SiI/HMDS]$, whereas with $[(CH_3)_3SiI/DIPEA]$, vinyl sulfides are formed (Scheme 63). The authors consider HMDS to be too weak a base to deprotonate the substrate fast enough to form a double bond.

Lastly, Naumann *et al.*[175,176] have reported satisfactory reduction of diaryl sulfoxides with hexachlorodisilane (Si_2Cl_6) under mild conditions. However, with *p*-tolylsulfoxide, Si_2Cl_6 reacts to give a mixture of the corresponding sulfide and chloromethyl *p*-tolyl sulfide.

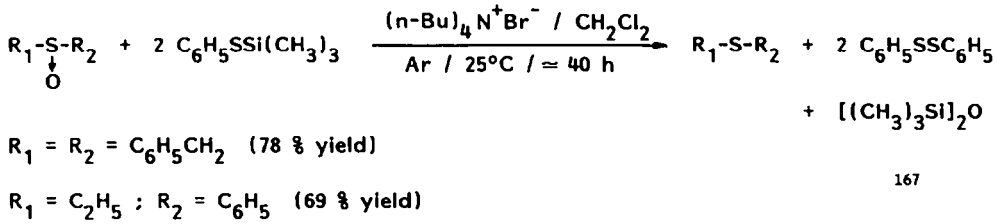
5.2. *Silanes*

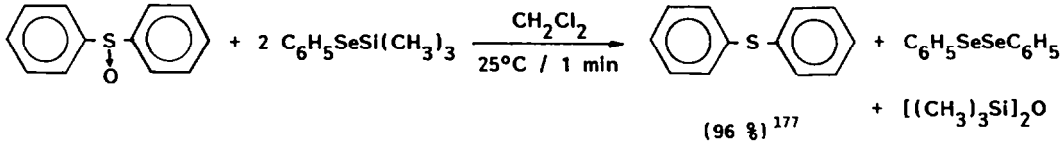
A number of sulfoxides have been efficiently reduced (80–87% yield) with phenyltrimethylsilane–iodine[172] $[C_6H_5Si(CH_3)_3/I_2]$ by heating at 120–130°C for 6–8 h.

Similarly, phenylthiotrimethylsilane[167] $[C_6H_5SSi(CH_3)_3]$ in the presence of a catalytic amount of tetrabutylammonium bromide $[(n\text{-}Bu)_4N^+Br^-]$, and phenylselenotrimethylsilane[177] $[C_6H_5\text{-}SeSi(CH_3)_3]$ allow sulfoxides to be gently reduced to their thioethers (Scheme 64).

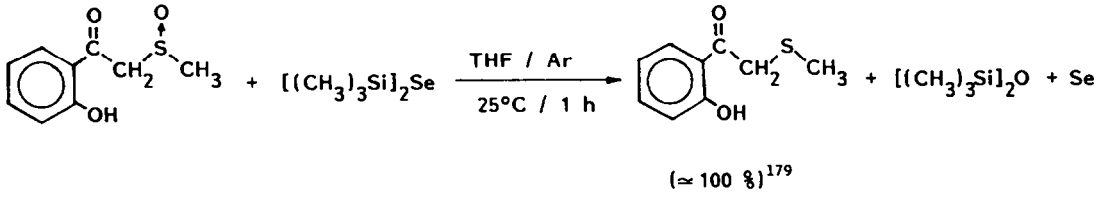
Dimethyl sulfoxide has been reduced quantitatively by various organylhydrosilanes[178] $[R_1R_2R_3SiH]$ in the presence of chloroplatinic acid $[H_2PtCl_6 \cdot xH_2O]$ in THF.

Detty and Seidler[179] report the reduction of sulfoxides to sulfides with high yields (80–100%) with various alkylchalcogenosilanes $[[(CH_3)_3Si]_2Y;\ (Y = S, Se, Te)]$, $[[(t\text{-}Bu)(CH_3)_2Si]_2Te]$. This





Scheme 64.



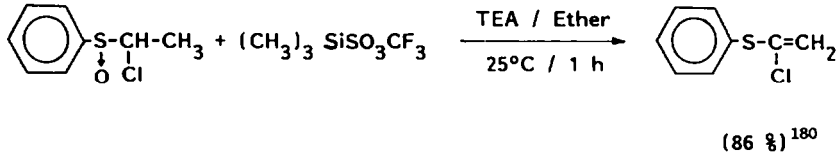
Scheme 65.

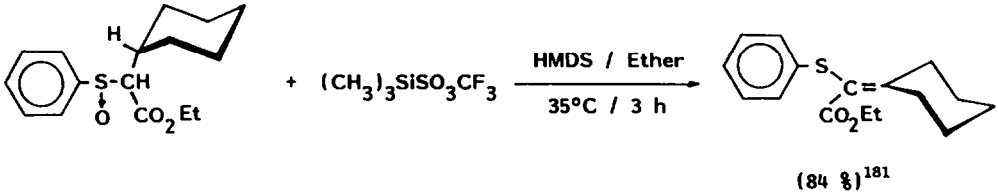
method enables selective cleavage of the S—O bond and leaves intact other functional groups (Scheme 65). (See also 3.4.4. and ref. 121.)

5.3. *Other silicon compounds*

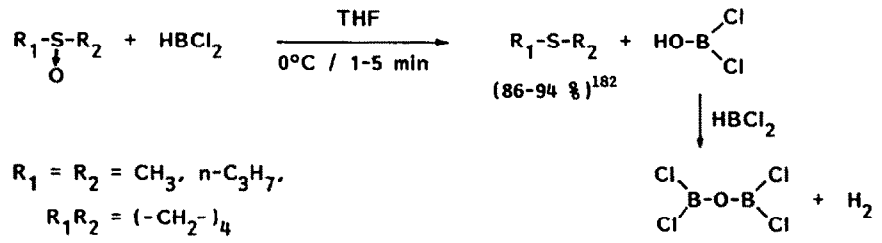
In a comparative study, silicon sulfide[159] (SiS_2) was used in parallel with P_4S_{10} to reduce various sulfoxides to sulfides. However, besides costing more and being more sensitive to moisture, it proved less reactive than P_4S_{10} and gave more unwanted side products.

Recently, Miller and Hässig[180] synthesized a series of α-halovinyl sulfides by a facile eliminative deoxygenation of α-halosulfoxides with trimethylsilyl triflate [$(CH_3)_3SiOSO_2CF_3$] in the presence of triethylamine (TEA). This same reagent converted α-cyano and α-carboalkoxy sulfoxides[181] into their corresponding vinyl sulfides in the presence of the weak base hexamethyldisilazane (HMDS) (Scheme 66). In this case, the presence of the electron-attracting cyano and carboalkoxy groups enables eliminative deoxygenation to occur.

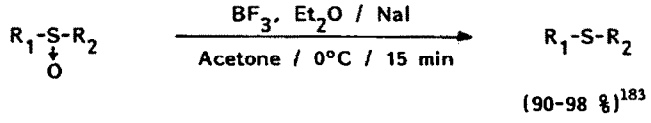




Scheme 66.



Scheme 67.



$R_1 = R_2 = CH_3,\ C_6H_5CH_2$

$R_1 = CH_3$; $n\text{-}C_4H_9$; C_6H_5

$R_2 = C_6H_5$; C_6H_5 ; $C_6H_5CH_2$

R_1R_2 = thianthrene

Scheme 68.

6. REDUCTION OF SULFOXIDES WITH BORON COMPOUNDS*

6.1. *Haloboron reagents*

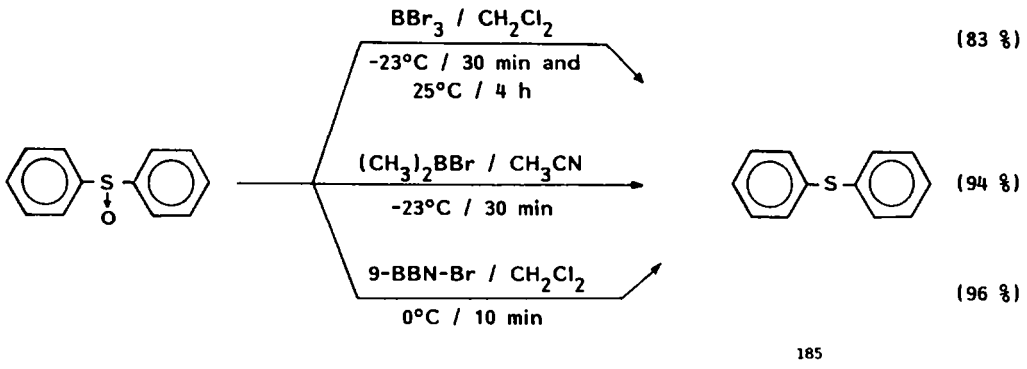
The use of boron derivatives to reduce sulfoxides to sulfides is relatively recent. The work of Lappert and Smith[163] in 1961 showed that boron trichloride in methylene chloride would react with sulfoxides, particularly DMSO, to give a stable chlorosulfide–boron oxychloride complex ($ClCH_2$—S—CH_3 · BOCl). Subsequently, Brown and Ravindran[182] carried out rapid (1–5 min) selective deoxygenation of some dialkyl and alicyclic sulfoxides with dichloroborane ($HBCl_2$) in THF (Scheme 67). This reagent also reduced diphenyl sulfoxide under very mild conditions with a high yield (90%), but much more slowly; the reaction took 24 h to reach completion.

Palumbo *et al.*[183] and Vankar and Rao[184] described an efficient conversion of various sulfoxides to their corresponding thioethers using boron trifluoride etherate–sodium iodide [$BF_3 \cdot Et_2O$/NaI]. The reaction takes place under mild conditions (0–25°C) and gives high yields (90–98%)[184] (Scheme 68).

Guindon *et al.*[185] studied the comparative reduction of dialkyl, arylalkyl, diaryl and heterocyclic sulfoxides with three boron bromide reagents; dimethylboron bromide [$(CH_3)_2BBr$], boron tribromide (BBr_3) and 9-borabicyclo [3.3.1.] nonyl bromide (9-BBN-Br). The deoxygenation of sulfoxides with these reagents is efficient and rapid at low temperature (−23°C–0°C) in various solvents, e.g. acetonitrile, dichloromethane, acetone, in the presence of propene which captures the bromine formed. However, BBr_3 reacted more slowly with the diaryl sulfoxides and gave lower yields of sulfides. Importantly, these authors observed no formation of any halogenated products or Pummerer-type products (Scheme 69).

Recently, Cha *et al.*[186] reported the deoxygenation of dialkyl and aromatic sulfoxides to their sulfides by thexylchloroborane–dimethyl sulfide [$(CH_3)_2CHC(CH_3)_2BHCl \cdot (CH_3)_2S$] (ThxBHCl–DMS) in CH_2Cl_2 at 0°C. This reagent is highly selective with respect to sulfoxides, which are rapidly reduced, and leaves intact other reducible groups such as epoxides, quinones, esters, amides, disulfides and sulfones (Scheme 70).

* Results concerning the reduction of sulfoxides to sulfides with sodium borohydride ($NaBH_4$) and other boron hydrides are given in 7.2. below (*cf* refs 225–232).



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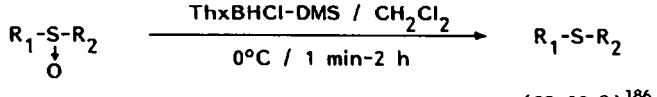
Scheme 69.



[186]

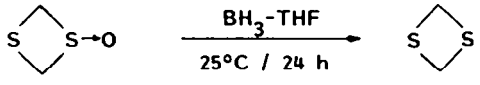
$R_1 = R_2 = CH_3,\ n\text{-}C_4H_9,\ C_6H_5,\ C_6H_5CH_2$

$R_1R_2 = (\text{-}CH_2\text{-})_4$

$R_1 = CH_3 \ ; \ C_2H_5 \ ; \ C_6H_5$

$R_2 = C_6H_5 \ ; \ C_6H_5 \ ; \ C_6H_5CH_2$

Scheme 70.



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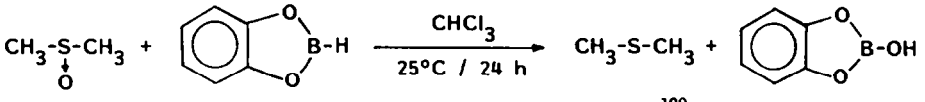
Scheme 71.



[190]

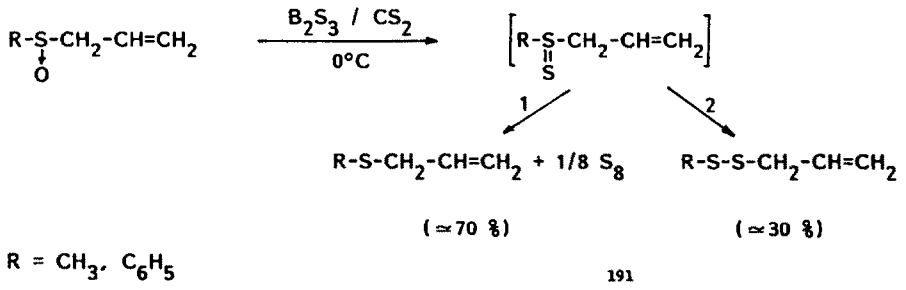
Scheme 72.

6.2. *Other boron reagents*

Block *et al.*[187] and more recently Cho and Yoon[188] used respectively borane–tetrahydrofuran ($BH_3 \cdot THF$) and various other systems; borane–triphenylborate (1 : 0.1) [$BH_3 \cdot (C_6H_5O)_3B$], borane–triethylborate (1 : 0.1) [$BH_3 \cdot (C_2H_5O)_3B$] and borane–boron trifluoride etherate (1 : 0.1) [$BH_3/BF_3 \cdot (C_2H_5)_2O$], to reduce 1,3-dithietane 1-oxide[187] (Scheme 71) and some dialkyl, arylalkyl and diaryl sulfoxides.[188]

Catecholborane (1,3,2-benzodioxaborole) is a versatile reducing agent which also readily reduces sulfoxides to thioethers[189,190] (Scheme 72).

Sulfoxides are also conveniently deoxygenated to sulfides via an intermediate thiosulfoxide by oxygen–sulfur exchange with boron sulfide (B_2S_3)[159,191] in CS_2 at 0°C. However, with allyl methyl and allyl phenyl sulfoxides the reduction leads to a mixture of sulfide and disulfide (about 30%)[191] (Scheme 73).



Scheme 73.

Clive and Menchen[192] successfully reduced a wide variety of sulfoxides under mild conditions using compounds with a selenium–boron bond, such as tris(phenylseleno)borane [$(C_6H_5Se)_3B$], tris(methylseleno)borane [$(CH_3Se)_3B$] and a cyclic selenoborane [C_4H_9—B<Se—Se>B—C_4H_9 (Se)]. The reaction is carried out in chloroform at low temperature (−30°C) and leaves other functional groups intact (ketones, carbon–carbon double bonds, lactams, amides) and gives high yields of thioethers (74–91%).

Lastly, Brown *et al.*[193–197 and refs] report deoxygenation of dimethyl sulfoxide with varying degrees of efficiency using various borane systems such as diborane-THF,[193,197] disiamylborane-THF,[194] thexylborane-DMS,[195,197] 9-borabicyclo[3.3.1.]nonane-THF[196] and thexylchloroborane-DMS.[197]

7. REDUCTION OF SULFOXIDES WITH METAL HYDRIDES

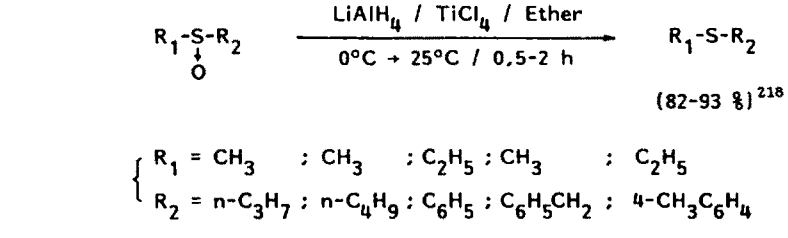
Many metal hydrides have found use for the deoxygenation of sulfoxides and also sulfones[198–207] to thioethers, and there is much published work on these reactions. It is also noteworthy that diisobuytylaluminium hydride (DIBAH)[208] and sodium borohydride–alumina ($NaBH_4/Al_2O_3$)[209,210] have been successfully used to convert sulfones to sulfoxides.

7.1. *Aluminium hydrides*

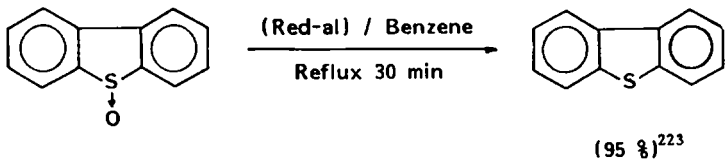
7.1.1. *Lithium aluminium hydride.* In 1950, Pitt[211] showed that sulfoxides could be reduced by $LiAlH_4$ by refluxing in ether. These results were at variance with those of Strating and Backer,[212] but were confirmed by Romo *et al.*,[213] Gal'pern *et al.*[48,214] and Russell *et al.*[118,215,216] These authors reduced respectively a benzylsulfinyl steroid, alkyl and diaryl sulfoxides and β-keto sulfoxides to corresponding sulfides and β-hydroxysulfides with $LiAlH_4$ by prolonged heating (about 24 h) in ether or THF with yields between 57 and 89%.

Brown *et al.*[217] in work on selective reduction of various functional groups with $LiAlH_4$ showed that dimethyl sulfoxide is slowly reduced by this reagent in THF at 0°C. Similarly, Anastassiou *et al.*[208] conveniently deoxygenated systems such as 9-thia[4.2.1.]nonabicyclic *S*-oxides with $LiAlH_4$. In work on improving the yield of the reduction of numerous sulfoxides to sulfides, and reducing the reaction time, Drabowicz and Mikolajczyk[218] found lithium aluminium hydride–titanium(IV) chloride ($LiAlH_4/TiCl_4$) in a 1 :1.2.3 molar ratio to be a highly efficient reagent (Scheme 74).

7.1.2. *Other aluminium hydrides.* Systematic studies of aluminium hydride systems as reducing agents for various representative functional groups were carried out by Brown *et al.*[219–221 and refs] The sulfoxide group was represented by DMSO.



Scheme 74.



Scheme 75.

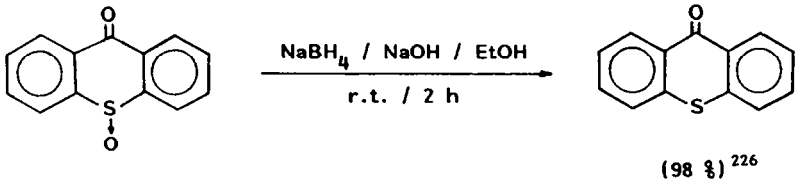
Of the aluminium hydrides, the most reactive for the reduction of DMSO to DMS was aluminium hydride (AlH_3),[220] which reacted much faster than $LiAlH_4$[217,220] or lithium trimethoxyaluminohydride [$LiAlH(OCH_3)_3$][219,220] in THF at 0°C. However, lithium tri-*t*-butoxyaluminohydride [$LiAlH(O\text{-}t\text{-}Bu)_3$][220,222] is inactive towards sulfoxides. Recently, Yoon and Gyoung[221] showed that thiolane-1-oxide was rapidly reduced by diisobutylaluminium hydride [$(i\text{-}Bu)_2AlH$] (DIBAH) in toluene at 0°C giving thiolane in 95% yield. Under the same conditions dimethyl sulfoxide was deoxygenated to only a small extent.

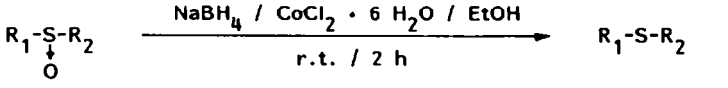
Of the various aluminium hydrides, one of the best reducing agents is sodium bis(2-methoxyethoxy)aluminium hydride (Red-al) [$Na[(CH_3OCH_2CH_2O)]_2AlH_2$] used by Ho and Wong[223] to reduce easily and in high yield ($\simeq$95%) a series of sulfoxides to their corresponding thioethers (Scheme 75).

Mikolajczyk and Drabowicz[224] achieved the asymmetric reduction of racemic sulfoxides with complexes of lithium aluminium hydride and optically active alcohols [$[LiAl(OR^*)_nH_{4-n}]$; R*OH = (+)quinidine, (−)ephedrine, (−)menthol, (−)quinine and (−)cinchonidine].

7.2. *Sodium borohydride*

Sodium borohydride ($NaBH_4$) alone does not react with sulfoxides, but associated with various co-reagents such as boron trifluoride etherate[225] [$BF_3 \cdot (C_2H_5)_2O$], sodium hydroxide,[226] cobalt chloride hexahydrate[227,228] ($CoCl_2 \cdot 6H_2O$), titanium(IV) chloride[229] ($TiCl_4$) (*cf* 8.1.2.), triphenylborate[230] [$(C_6H_5O)_3B$], it will readily reduce them to their sulfides, sometimes quantitatively (Scheme 76).

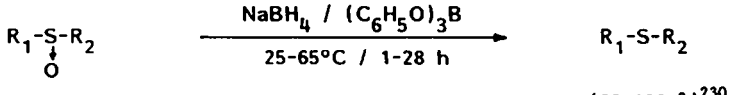




$R_1 = R_2 = n\text{-}C_4H_9,\ C_6H_5$

$R_1 = CH_3\ ;\ R_2 = C_6H_5$

R_1R_2 = thioxanthene

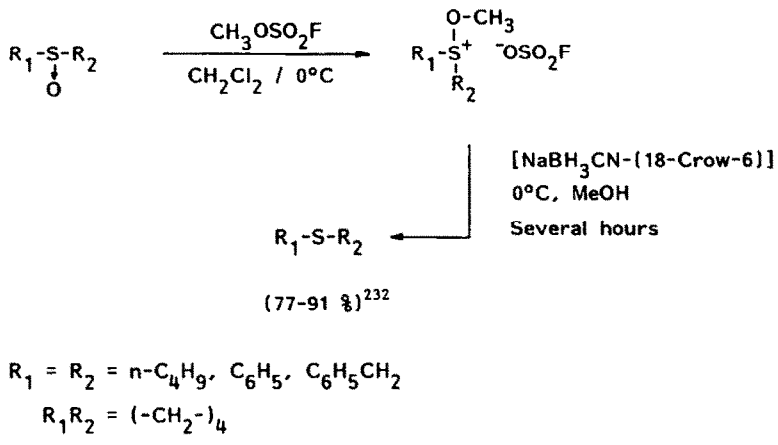


$R_1 = R_2 = C_2H_5,\ C_6H_5,\ C_6H_5CH_2$

$R_1R_2 = (\text{-}CH_2\text{-})_4$

$R_1 = C_6H_5\ ;\ R_2 = C_6H_5CH_2$

Scheme 76.



Scheme 77.

Johnson and Phillips[231] showed that $NaBH_4$ though inactive towards methyl phenyl sulfoxide, would reduce it efficiently to sulfide if it was first converted to alkoxysulfonium fluoroborate in an appropriate medium.

Similarly, Durst *et al.*[232] carried out selective deoxygenation under mild conditions of various sulfoxides as alkoxysulfonium fluorosulfonates using cyanohydridoborate crown ether [$NaBH_3CN$—(18-crown-6)] (Scheme 77).

7.3. *Other metal hydrides*

7.3.1. *Tri-*n*-butyltin hydride.* Kozuka *et al.*[233] describe the reduction to sulfide of diphenyl sulfoxide and thianthrene and phenoxanthiin *S*-oxides with tri-*n*-butyltin hydride [$(n\text{-}C_4H_9)_3SnH$] in the presence of an equimolar quantity of azobisisobutyronitrile (AIBN) as free-radical initiator in THF. Deoxygenation is quantitative for heterocyclic sulfoxides but it is inefficient for aryalkyl sulfoxides and dialkyl sulfoxides, as cleavage of the *S*-alkyl C bond occurs.

7.3.2. *Sodium and lithium hydrides.* Johnson and Phillips[234] obtained sulfides by reacting alkoxysulfonium fluoroborates obtained from sulfoxides with sodium hydride (NaH) and various alkoxides in THF. The reaction is almost quantitative for methyl phenyl sulfoxide and dimethyl sulfoxide.

Similarly, the reduction of dialkyl and diaryl sulfoxides to thioethers was performed successfully (60–90% yield) using lithium hydride–titanium(IV) chloride ($LiH/TiCl_4$) in a molar ratio 1 : 4 in THF (*cf* 8.1.2.).

8. REDUCTION OF SULFOXIDES WITH LOW-VALENT METAL IONS

Certain metal ions of low valency are highly selective reducing agents for sulfoxides.

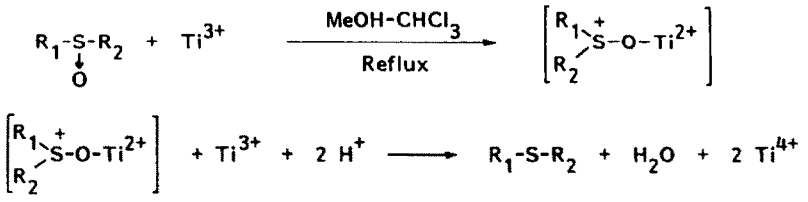
8.1. *Titanium chlorides*

8.1.1. *Titanium(III) chloride.* Barnard and Hargrave[236,237] and later Legault and Groves[238] used reduction with titanium(III) chloride ($TiCl_3$) to assay dialkyl arylalkyl and diaryl sulfoxides. This reagent was subsequently used by several authors[239–242] to deoxygenate various sulfoxides to their thioethers in high yield. Ho and Wong[241] have proposed a two-step mechanism for this reduction (Scheme 78).

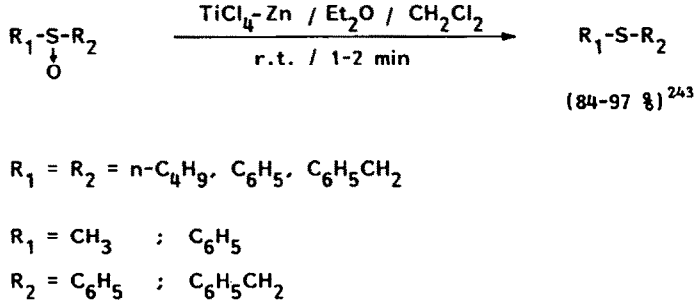
8.1.2. *Titanium(II) chloride.* Drabowicz and Mikolajczyk[243] have described an excellent method for reducing dialkyl, arylalkyl and diaryl sulfoxides to their sulfides with titanium(II) chloride ($TiCl_2$) prepared *in situ* from titanium(IV) chloride and zinc powder ($TiCl_4/Zn$). The reaction takes place under mild conditions, is rapid and gives excellent yields even with sulfoxides bearing a benzyl group (90–92%) which are generally difficult to reduce with other reagents (Scheme 79).

This method was used to synthesize a series of phenyl vinyl sulfides[244] from α-halosulfoxides by eliminative deoxygenation with [$TiCl_4/Zn$] in ether.

Kano *et al.*[229] and Dzhemilev *et al.*[236] have proposed the reduction of dialkyl, arylalkyl and



Scheme 78.



Scheme 79.

diaryl sulfoxides to sulfides with complexes of low valence titanium obtained *in situ* by reacting titanium(IV) chloride with respectively sodium borohydride ($TiCl_4/NaBH_4$)[229] and lithium hydride ($TiCl_4/LiH$)[235] (Scheme 80).

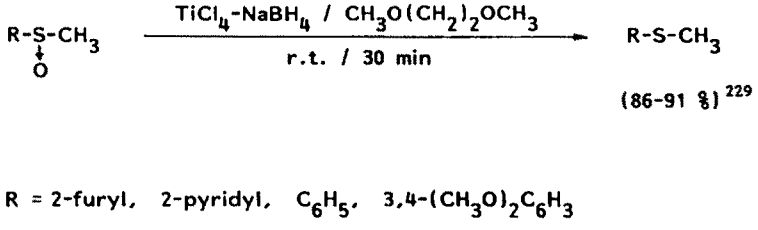
8.2. *Vanadium(II) chloride*

Vanadium(II) chloride in aqueous solution was used by Olah *et al.*[245] to reduce dialkyl and diaryl sulfoxides in THF. However, prolonged heating is required (8 h, 100°C), and though the yields of sulfides are high (74–88%), they remain slightly (about 5%) below those obtained with molybdenum(III) compounds which are more reactive towards sulfoxides.

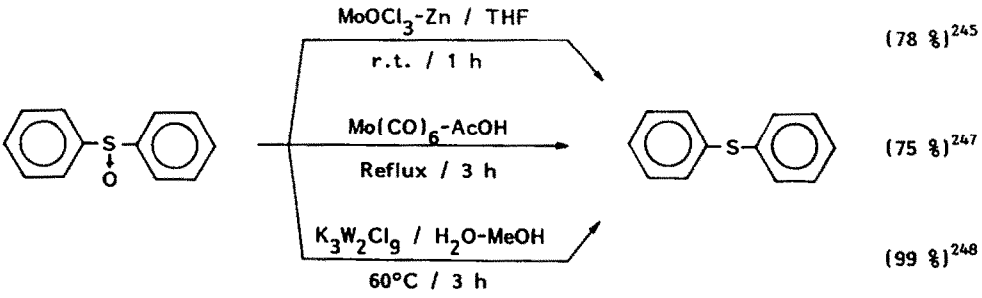
8.3. *Low-valent derivatives of chromium, molybdenum and tungsten*

8.3.1. *Chromium(II) chloride.* One reference[246] describes the use of chromium(II) chloride to deoxygenate diphenyl and dibenzyl sulfoxides by refluxing in methanol, but the yields of sulfides were low (20 and 24%).

8.3.2. *Various complex ions of molybdenum(II), -(III) and tungsten(III).* In a comparative study, Olah *et al.*[245] showed that low-valent molybdenum [Mo(III)] was a more efficient deoxidizing reagent than low-valent vanadium [V(II)] for conversion of sulfoxides to sulfides. The molybdenum(III) reagent is prepared *in situ* by treatment of molybdenyl chloride ($MoOCl_3$; from $MoCl_5$ and H_2O)



Scheme 80.



Scheme 81.

with powdered zinc in THF. Reduction of sulfoxides to sulfides goes to completion in 1 h at room temperature with high yields (78–91%) (Scheme 81).

To avoid having traces of zinc in the reducing reagent, Ho[247] proposes using molybdenum(II) carboxylates obtained easily by the reaction between carboxylic acids and molybdenum hexacarbonyl [$[Mo(Co)_6] \cdot AcOH$]. The reaction is complete after heating under reflux for 3 h in acetic acid under nitrogen (Scheme 81).

Nuzzo *et al.*[248] described a convenient, efficient and highly selective method that is applicable to a wide range of sulfoxides, using various low-valent Mo(II), Mo(III) and W(III) chlorides such as [$(NH_4)_4Mo_2Cl_8$—$NH_4Cl \cdot H_2O$], (K_3MoCl_6), (Cs_3MoCl_8H) and ($K_3W_2Cl_9$). The best yields of sulfides (88–100%) were obtained with the tungsten(III) reagent by heating at 60°C for 3 h in 10:1 water–methanol (Scheme 81).

8.4. *Tin(II) chloride*

Tin(II) chloride ($SnCl_2$), first used by Glynn,[249] like titanium(III),[236] to assay sulfoxides, was used to deoxygenate cephalosporin *S*-oxides[138] and various dialkyl arylalkyl and aromatic sulfoxides[250] with yields ranging from 62 to 93%.

9. REDUCTION OF SULFOXIDES WITH MISCELLANEOUS REAGENTS

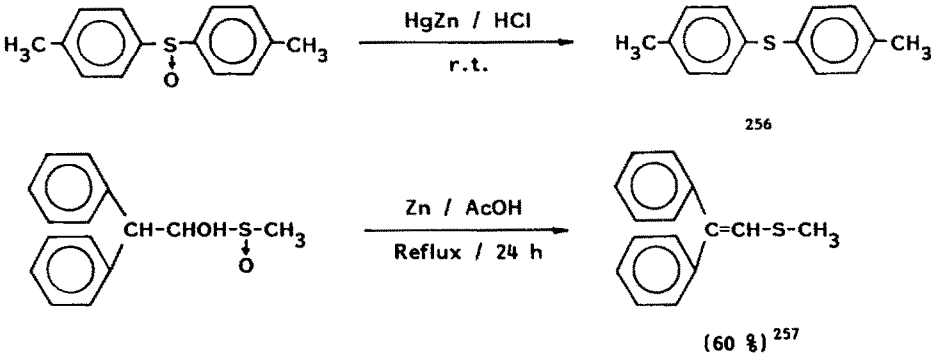
9.1. *Zinc in the presence of acids*

As early as 1910, Gazdar and Smiles[11] succeeded in reducing bis(2-hydroxy-5-methylphenyl) sulfoxide to its sulfide by refluxing with zinc powder in acetic acid.

This method later came to be widely used[138,150,251–259,348] to reduce a great variety of sulfoxides including haloalkyl sulfoxides,[150] diaryl sulfoxides,[253,254–256] phenylsulfinylnorbornenes,[255] α-hydroxysulfoxides,[257] cephalosporin *S*-oxides,[138,258] complex vinylsulfoxides[259] and disulfoxides[251,252] to their corresponding sulfides with yields between 60 and 95%.

Zinc amalgam in hydrochloric acid[253,256] and zinc and copper powders in acetic acid[255] have also been used for the same purpose.

Russell and Mikol[257] obtained vinylsulfides by reacting α-hydroxysulfoxides with zinc in boiling acetic acid (Scheme 82).



Scheme 82.

$$R_1\text{-}\underset{\underset{O}{\downarrow}}{S}\text{-}R_2 \xrightarrow[130\text{-}135^\circ C\ /\ 1\text{-}3\ h]{Fe(CO)_5\ /\ Solvent} R_1\text{-}S\text{-}R_2$$

(48-91 %)[260]

$R_1 = R_2 = n\text{-}C_3H_7,\ n\text{-}C_4H_9,\ n\text{-}C_6H_{13},\ C_6H_5,$
$4\text{-}CH_3C_6H_4,\ C_6H_5CH_2$

$R_1R_2 = (\text{-}CH_2\text{-})_4$

Scheme 83.

$$R_1\text{-}\underset{\underset{O}{\downarrow}}{S}\text{-}R_2 \xrightarrow[200^\circ C\ /\ 1\ mm\ Hg\ /\ 2\text{-}4\ h]{Reduced\ Iron} R_1\text{-}S\text{-}R_2$$

262

$R_1 = R_2 = C_6H_5$ (100 %)

$R_1 = R_2 = C_2H_5$ (65 %)

Scheme 84.

9.2. *Metal carbonyls and reduced iron*

Alper *et al.*[260,261] found that iron pentacarbonyl [$Fe(CO)_5$] could reduce various sulfoxides and disulfoxides to sulfides and disulfides much faster than molybdenum hexacarbonyl [$Mo(CO)_6$] in bis(2-methoxyethyl) ether or di-*n*-butyl ether with yields between 48 and 91% (Scheme 83).

Fujisawa *et al.*[262] showed that reduced iron at 200°C under reduced pressure was an excellent deoxygenating agent for sulfoxides and thiosulfonates, which it reduces respectively to sulfides and disulfides. This reduction is more efficient for diaryl sulfoxides than for dialkyl sulfoxides (Scheme 84).

9.3. *Aluminium iodide*

Recently, Babu and Bhatt[263] described the reduction of some dialkyl and diaryl sulfoxides to their corresponding sulfides with aluminium iodide (AlI_3) under mild conditions in acetonitrile, with good yields (68–84%).

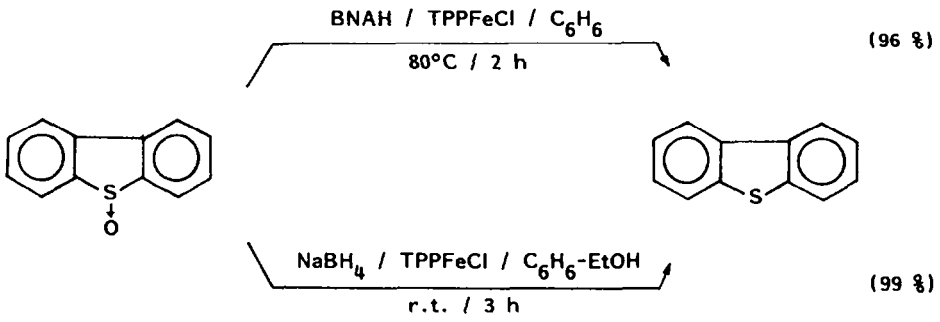
9.4. *Reduction catalyzed by metalloporphins*

Naga *et al.*[264] report the reduction of sulfoxides to sulfides by a one-electron transfer process by treatment with NAD(P)H model compounds such as 1-benzyl-1,4-dihydronicotinamide (BNAH) or sodium borohydride ($NaBH_4$) in the presence of catalytic amounts of metallo-*meso*-tetraphenylporphins (TPPMe) with Me = Fe(III), Co(II) and Cu(II) in the dark under argon. The catalytic effect of the metalloporphin in the reduction of sulfoxides with BNAH was found to follow the order TPPCu(II) < TPPCo(II) < $TPPFe(III)^+$. The reduction catalyzed by *meso*-tetraphenylporphinato iron(III) chloride (TPPFeCl) was more efficient with $NaBH_4$ than with BNAH (Scheme 85).

9.5. *Carbenes*

Oda *et al.*[265] were the first to report oxidation of dichlorocarbene and some other carbenes by heating with dimethyl sulfoxide which is reduced in the process to dimethyl sulfide. The mechanism proposed involves initial attack on the oxygen giving a 1,3-zwitterion (Scheme 86).

Subsequently, Soysa and Weber[266] and Dyer[267] reduced dialkyl, arylalkyl and diaryl sulfoxides to corresponding sulfides with dichlorocarbene generated by phase transfer catalysis (PTC/$:CCl_2$) with high yields (78–98%) except for dibenzyl sulfoxides and benzylphenyl sulfoxide (respectively



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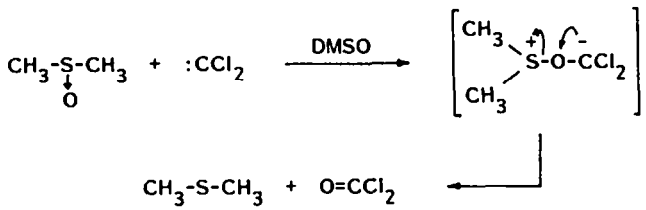
Scheme 85.



265

Scheme 86.

≃20 and 37% yield of sulfide). Moreover, this method is inefficient for the reduction of allyl sulfoxides.[267]

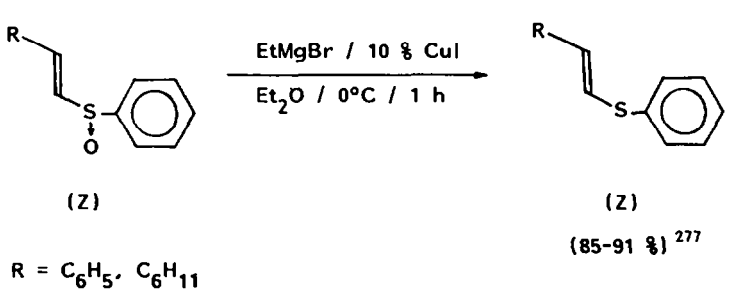
9.6. *Lithium*, n-*butyllithium and Grignard reagents*

9.6.1. *Lithium*. Recently,[268] dialkyl and arylalkyl sulfoxides were reduced to sulfides by lithium in dimethoxyethane (DME) at ambient temperature with yields between 62 and 78%. However, the reaction of benzyl sulfoxides with this reagent or with *n*-butyllithium is more complex and leads to a mixture of products containing 80% *trans*-stilbene.[268,269]

9.6.2. n-*Butyllithium*. One reference[270] describes the reduction of dibenzothiophene *S*-oxide with *n*-butyllithium at −10°C in ether. The yield of dibenzothiophene was low (≃11%) and the main product (55%) was 4-dibenzothiophene carboxylic acid.

9.6.3. *Grignard reagents*. Grignard reagents soon found use[271–273] for the reduction of dialkyl and diaryl sulfoxides, but the deoxygenation of dimethyl sulfoxide[271] and generally of α-methyl or α-methylene sulfoxides[275,276] with organomagnesium compounds is often accompanied by α-alkyl or α-arylation.

Posner and Tang[277] found that organometallic reagents, particularly ethylmagnesium bromide (EtMgBr), in the presence of 10% copper(I) iodide (CuI) could cleanly and efficiently reduce a wide variety of phenyl vinyl sulfoxides to their sulfides, under mild conditions and with good yields (60–93%) (Scheme 87).



Scheme 87.

(*Z*) and (*E*)-vinyl phenyl sulfoxides are deoxygenated with retention of the double-bond configuration in both cases.

9.7. *Hydroxylamine and hydrazine*

A recent patent[278] describes the reduction of various sulfoxides to sulfides with different salts of hydroxylamine and hydrazine by refluxing in ethanol in the presence of sodium carbonate (Scheme 88).

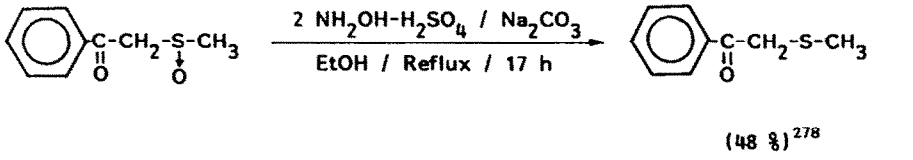
9.8. *Reduction using acyl reagents in the presence of co-reactants*

9.8.1. *Acid chlorides.* Many authors[57,93,137,279–282] have reported the activating effect of acid chlorides such as acetyl chloride[57,280–282] benzoyl chloride[93] and phenyl acetyl chloride[279] on the reduction of a wide range of sulfoxides either alone[282] or in the presence of co-reactants such as sulfides,[93] I^-,[57,137] Sn^{2+},[137,281] $S_2O_4^{2-}$.[137,280] The acyl reagent reacts with the sulfinyl oxygen to form a sulfonium salt which is more reactive than the sulfoxide itself towards reducing agents.

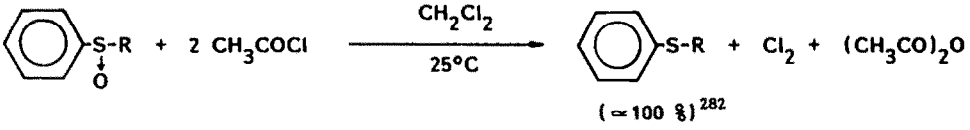
Numata and Oae[282] reduced, almost quantitatively, diaryl sulfoxides to their corresponding sulfides with acetyl chloride at ambient temperature in dichloromethane. The yields obtained with dialkyl sulfoxides were lower (≃70%) (Scheme 89).

Olah *et al.*[154] reported using oxalyl chloride with sodium iodide (ClCOCOCl/NaI) to efficiently and selectively deoxygenate alicyclic, dialkyl arylalkyl and diaryl sulfoxides and β-hydroxysulfoxides.[283] Excellent yields of sulfides were obtained (70–99%) (Scheme 90).

9.8.2. *Trifluoroacetic anhydride.* Drabowicz and Oae[284,285] and Tanikaga *et al.*[98] found the reduction of sulfoxides to sulfides using trifluoroacetic anhydride [$(CF_3CO)_2O$] and various co-reactants like NaI,[284] H_2S[285] and dimethyl sulfide[98] to be very fast and selective. The reaction takes place under very mild conditions (−60–0°C) in acetone or dichloromethane and gives very high yields (89–98%) (Scheme 91).

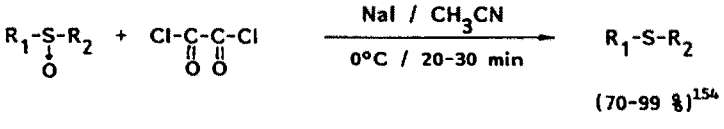


Scheme 88.



R = CH_3, C_2H_5, C_6H_5, $C_6H_5CH_2$

Scheme 89.



R_1 = R_2 = n-C_3H_7, i-C_3H_7, n-C_4H_9, C_6H_5, $C_6H_5CH_2$, 4-$CH_3C_6H_4$, 4-ClC_6H_4

R_1R_2 = $(-CH_2-)_4$ R_1 = C_6H_5 ; R_2 = C_2H_5

Scheme 90.

$$R_1\text{-}\underset{\underset{O}{\downarrow}}{S}\text{-}R_2 \xrightarrow[0°C\ /\ 1\ min]{(F_3C\text{-}CO)_2O\ /\ NaI\ /\ Acetone} R_1\text{-}S\text{-}R_2 + I_2 + 2\ F_3C\text{-}COONa$$

(90-98 %)[284]

$R_1 = R_2 = n\text{-}C_4H_9,\ C_6H_5,\ C_6H_5CH_2,\ 4\text{-}ClC_6H_4$

$\begin{cases} R_1 = CH_3 : C_2H_5 : t\text{-}C_4H_9 \\ R_2 = C_6H_5 : C_6H_5 : 4\text{-}CH_3C_6H_4 \end{cases}$

Scheme 91.

$$R_1\text{-}\underset{\underset{O}{\downarrow}}{S}\text{-}R_2 \xrightarrow[70°C\ /\ pH_2 = 10\ atm.\ /\ 3\text{-}8\ h]{H_2\ /\ CoO\text{-}MoO_3\ /\ Al_2O_3\ catalyst} R_1\text{-}S\text{-}R_2$$

(98-100 %)[288]

$R_1 = R_2 = C_2H_5,\ C_6H_5,\ C_6H_5CH_2$

$R_1 = CH_3 : R_2 = C_6H_5$

R_1R_2 = dibenzothiophene, 3-methylbenzo[b]thiophene
2- or 3-phenylbenzo[b]thiophene

Scheme 92.

9.9. *Reduction by catalytic hydrogenation*

James *et al.*[286] were the first to reduce under mild conditions dimethyl sulfoxide to dimethyl sulfide with molecular hydrogen using rhodium(III) complexes, e.g. ($RhCl_3 \cdot 3H_2O$) and [*cis*-$RhCl_3 \cdot (Et_2S)_3$] as catalysts.

Ogura *et al.*[287] used 5% palladium on carbon in ethanol under pressure to catalytically deoxygenate various sulfoxides with high yields (90–99%). The reduction is fairly selective, since it does not affect carbonyl groups and reduces olefines only to a very slight extent.

More recently, Geneste *et al.*[288] quantitatively reduced dialkyl, arylalkyl and diaryl sulfoxides and heterocyclic sulfoxides with molecular hydrogen in the presence of an industrial hydrodesulfurization catalyst of composition [$CoO \cdot MoO_3/Al_2O_3$] presulfurized with H_2S (Scheme 92).

10. REDUCTION OF SULFOXIDES BY OTHER METHODS

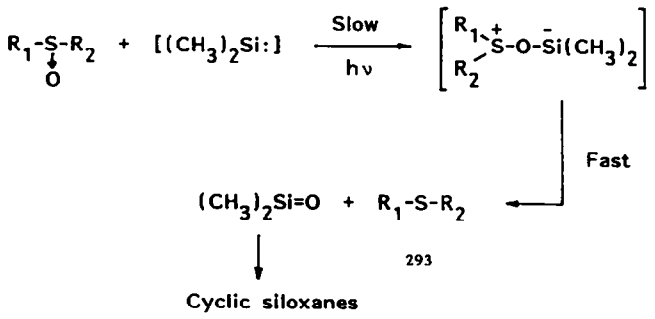
10.1. *Photochemical reduction*

In 1967, Kharasch and Khodair[289] observed that diphenyl sulfoxide gave a mixture of diphenyl sulfide (70%), biphenyl (53%) and a small amount of diphenyl disulfide by direct photolysis in benzene.

Later, Gurria and Posner[290] deoxygenated dibenzothiophene *S*-oxide and some arylalkyl and diaryl sulfoxides, obtaining the corresponding sulfides with excellent yields (85–95%) by direct photolysis or in the presence of sensitizers (acridine, chrysene, benzophenone) via an excited state of the triplet type. However, photolysis of dialkyl sulfoxides did not yield dialkyl sulfides but gave a mixture of products (aldehydes, disulfides, olefinic products).

Other work[291] reports the reduction of 2-sulfinyl benzaldehydes to corresponding sulfides by direct photolysis.

Soysa *et al.*[292] and Alnaimi and Weber[293] used dimethyl silylene [$(CH_3)_2Si$:] generated photochemically to reduce DMSO[292] or thiolane 1-oxide and dialkyl sulfoxides.[293] The more hindered the sulfoxides, the less efficient was the deoxygenation (Scheme 93).



$R_1 = R_2 = CH_3,\ C_2H_5,\ (CH_3)_2CH,\ (CH_3)_3C$

$R_1R_2 = (-CH_2-)_4$

Scheme 93.

10.2. *Reduction by electron pulse radiolysis*

Chaudhri *et al.*[294] studied the reduction of dimethyl sulfoxide to dimethyl sulfide by atomic hydrogen generated by pulse radiolysis of concentrated solutions of acids ($HClO_4$, H_2SO_4, HBF_4) via a radical cation intermediate $(CH_3)_2S^{+\cdot}$.

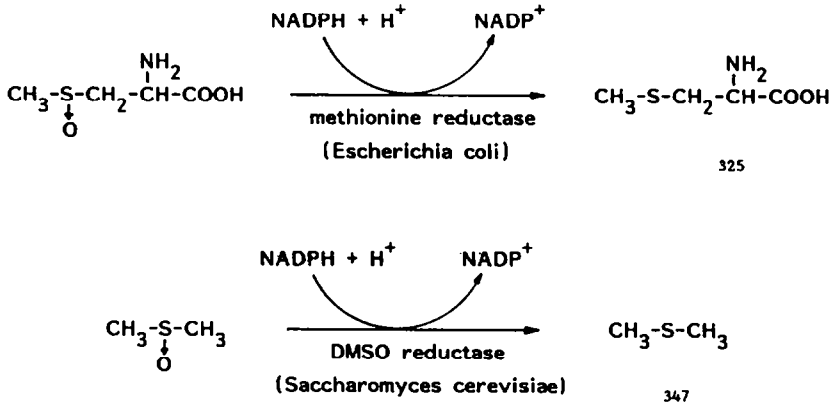
10.3. *Electrochemical reduction*

Some work has been reported on the determination of the redox potential of the reduction of dimethyl sulfoxide[295] and other sulfoxides[296] to their corresponding sulfides and their electrolytic reduction at various electrodes.[297,298]

10.4. *Enzymatic reduction*

Since 1950 considerable work has been done on the enzymatic reduction of DMSO,[299–311,346,347] of methionine sulfoxide,[312–326,347] of biotin sulfoxide[327–332] and of other sulfoxides[317,321,332] to their sulfides by enzyme systems present in yeasts,[308,309,311,315,316,327,328,346,347] in bacteria,[299,304–307,310,312,313,322–325,329,330] in mammals[300,302,320,321] and in plants[303,314,317,326,331] (Scheme 94).

In addition, metabolic studies have been carried out on the detoxification of drugs,[332–335] pesticides,[336–338] insecticides[339–341] and fungicides[342,343] bearing a sulfinyl group by enzymatic reduction to their sulfides in animal tissues,[332–335,338,341,343] in plants[336,342] and in the soil.[339,340]



Scheme 94.

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