

Chapter 9

Reactions of Organosulfur Compounds and Other Chalcogenides

CHEMICAL SELECTIVITY OF ORGANIC CHALCOGENIDES

Group VIA in the Periodic Table contains such important elements as oxygen and sulfur. The divalent oxygen is a hard base, the others are soft.

Acetals are very labile toward aqueous acids, whereas the thioacetals are remarkably stable because of the softness of the sulfur atoms.

Hydrolytic cleavage of the latter class of compounds almost invariably involves coordination with soft or borderline acceptors such as Hg(II) , Tl(III) , Ag(I) , Cu(II) , R⁺ , Hal⁺, and NH₂⁺.

Secondary isotope effects and NMR evidence clearly show that a C—O bond scission occurs during the acid hydrolysis of oxathiolanes.

Protontransfer rates for acidic alcohols are several orders of magnitude higher than those for the corresponding thiols.

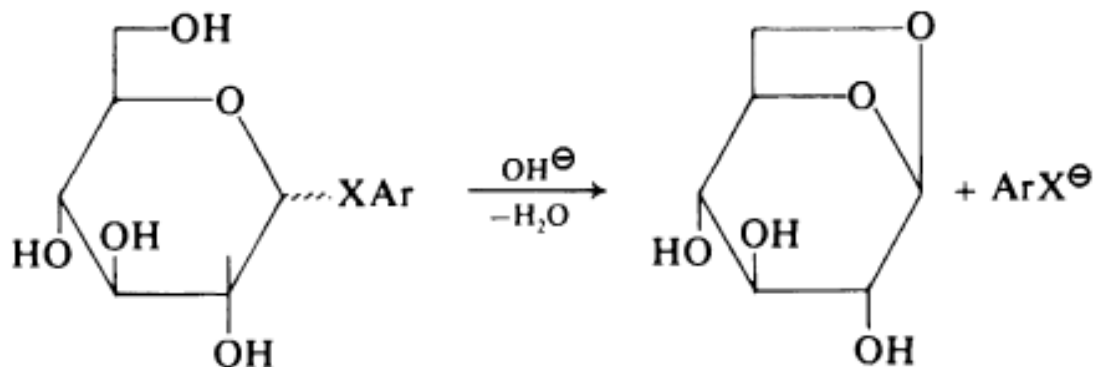
The S—C=O linkage is susceptible to attack by hard bases . The inherent reactivity is caused by the soft-hard union.

Heavy metal ion-assisted aminolysis of thioesters is also known.



The ease of anhydro sugar formation from alkali treatment of the chalcogen isolog decreases in the order $X = \text{Se} \gg \text{S} > \text{O}$.

The major factor governing the glucoside stability toward alkali is considered by this author to be symbiosis at the anomeric center. Thus, the ionization of ArX^- is easier when X is softer, as the destabilization of the glucoside is thereby removed.

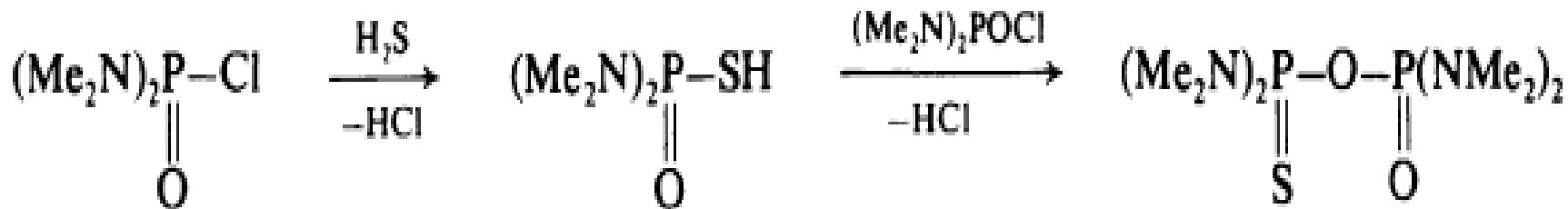


When submitted to acid hydrolysis these compounds show the reverse order of reactivities: $X = O \gg S > Se$. It is reasonable to assume that under such conditions protonation at X occurs prior to ionization and ring closure. Of course, the harder atom X protonates better.

Ambident chalcogenides generally react according to the HSAB principle. For example, arylsulfenate anions yield methyl sulfoxides on exposure to MeI, and they give methyl arylsulfenates with the harder methylating agents Me_2SO_4 and $MeOSO_2F$.

Phosphorothioate ions are also O,S-ambident. Their reactions with alkyl halides and sulfenyl chlorides occur at the sulfur.

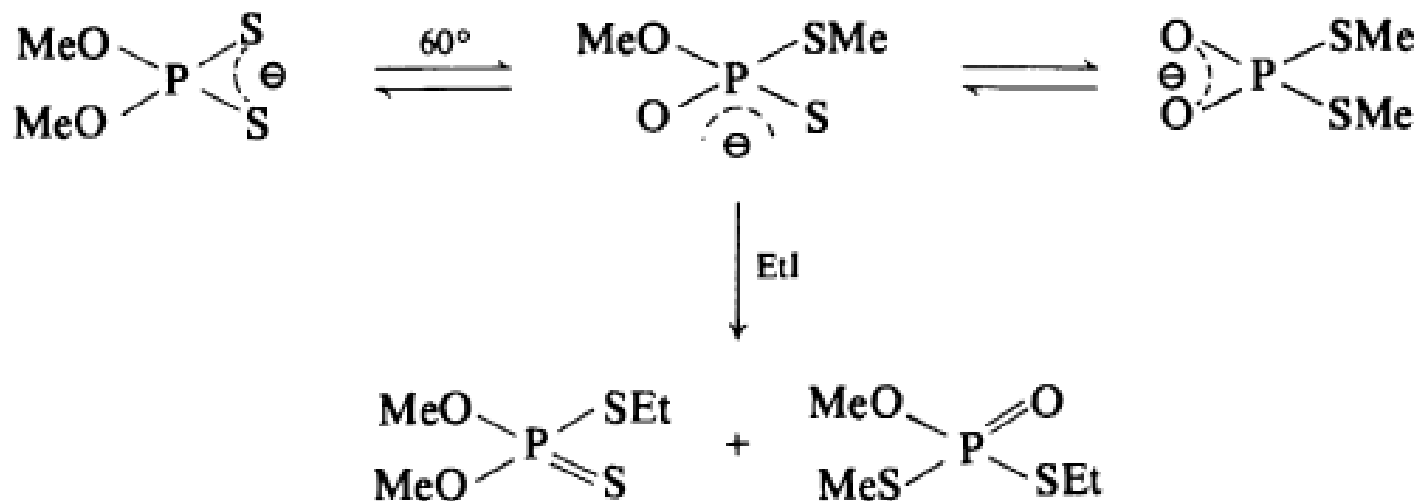
Treatment of *N,N, N',N'*-tetramethylphosphorodiamidic chloride with hydrogen sulfide gives a mixed anhydride indicating that the intermediary phosphorothioate is phosphorylated at the hard oxygen.



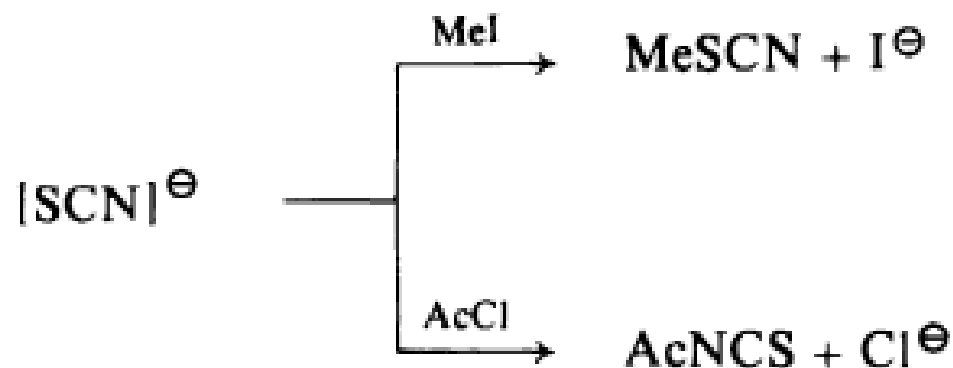
Sodium *O,O*-dimethylphosphorodithioate is gradually transformed into the *O,S*-isomer and then into the *S,S*-isomer on warming .

The isomerization improves the unfavorable bonding situation between the hard P and the soft S atoms.

When the equilibrium mixture is allowed to react with ethyl iodide, only *S*-ethylation is observed.



Regiospecific alkylation and acylation of the ambident thiocyanate ion are known to occur at sulfur and nitrogen, respectively.



Mercuric thiocyanate reacts with primary alkyl halides to give alkyl thiocyanates.

However, alkyl isothiocyanates become the major products when the reactions are carried out with secondary or tertiary alkyl halides in nonplanar solvents.

These latter processes are likely to involve ion-pair intermediates in which the harder carbocations bond with the nitrogen end of the complexed thiocyanate counterions.

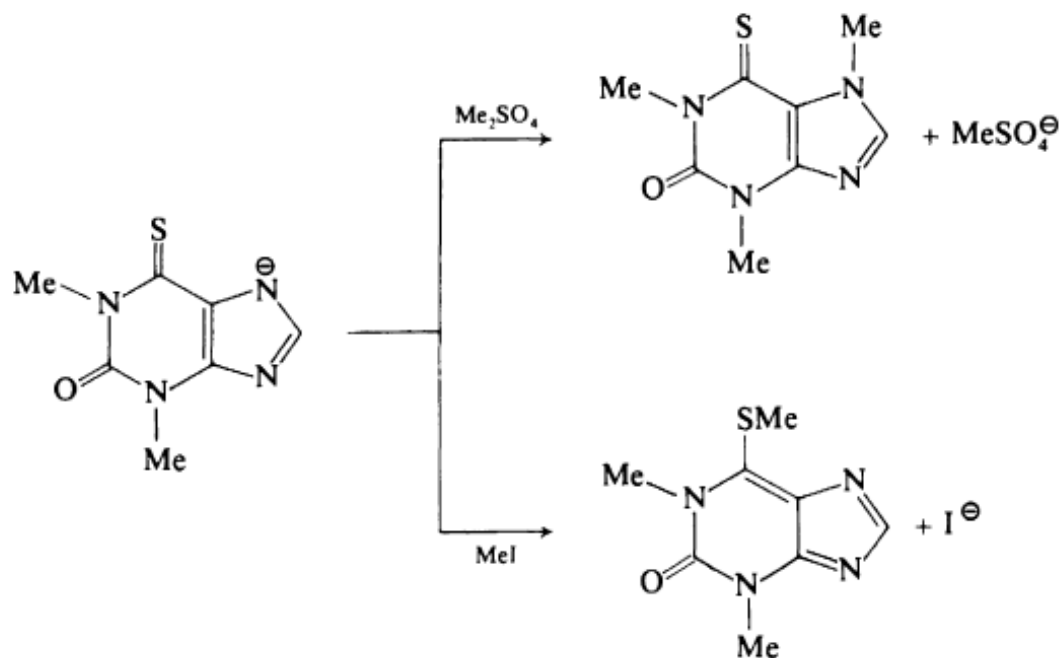


The deamination of 4-chlorobenzhydramine in the presence of thiocyanate ion gives the thiocyanate and isothiocyanate ($k_S : k_N$ 3.8), in addition to solvolytic products.

The displacement of alkyl halides by NaSCN in acetonitrile at 50° has also been studied .

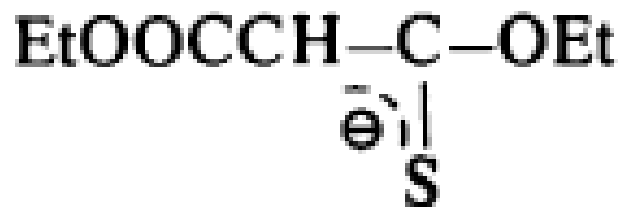
The $k_S : k_N$ ratios (*i*-PrI, 85; 4-MeOC₆H₄CH₂Br, 206-240; PhCH₂Cl, 420-436; PhCH₂Br, 835-850; PhCH₂I, 1300) vary according to the trend predicted by the HS AB principle.

Following the same pattern, the harder and softer methylating agents, Me_2SO_4 and MeI , react selectively on N and S termini of thiopurines .

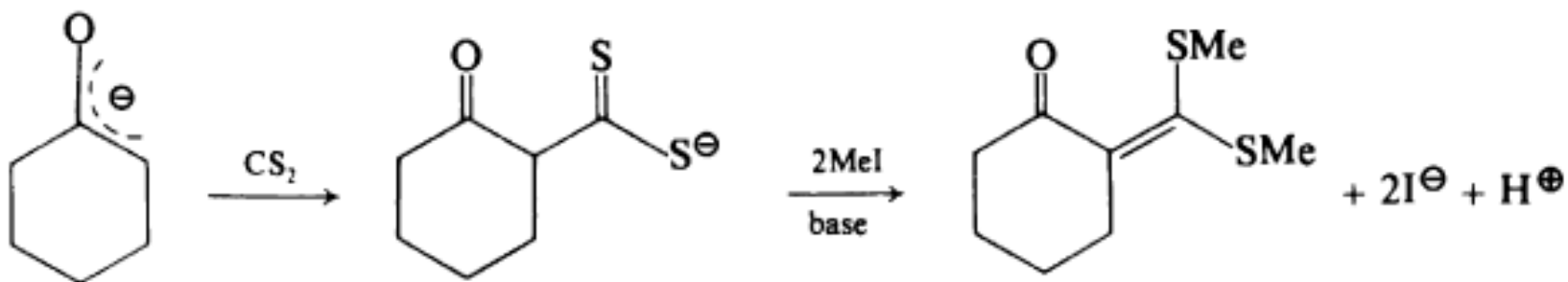


Ethyl 3-acyl-2-thioxo-1,3-oxazolidine-4-carboxylates are acylated and phosphorylated at N and alkylated at S.

The various reactions of benzothiazole-2-thiolate ion has been analyzed using the oxibase scale. Because sulfur is softer than carbon, the rate ratio of 1.7 for the ethylation of the monothiomalonate anion favoring sulfur is most reasonable.

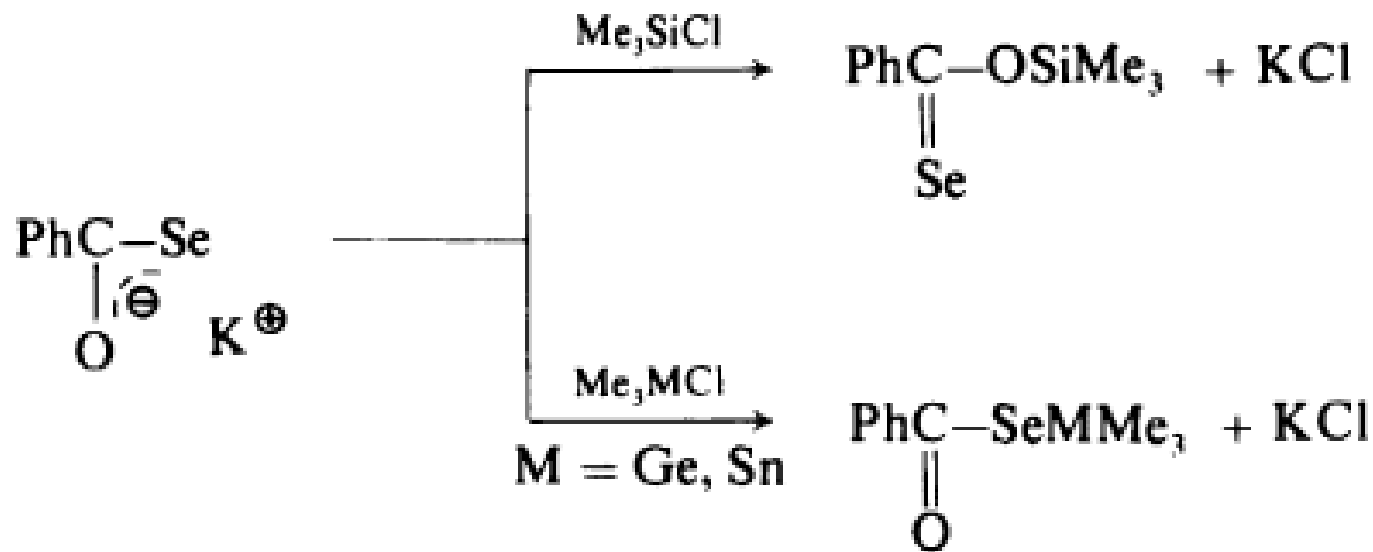


The treatment of a ketone enolate with carbon disulfide followed by quenching with methyl iodide affords α -di(methylthio)methylene ketones.

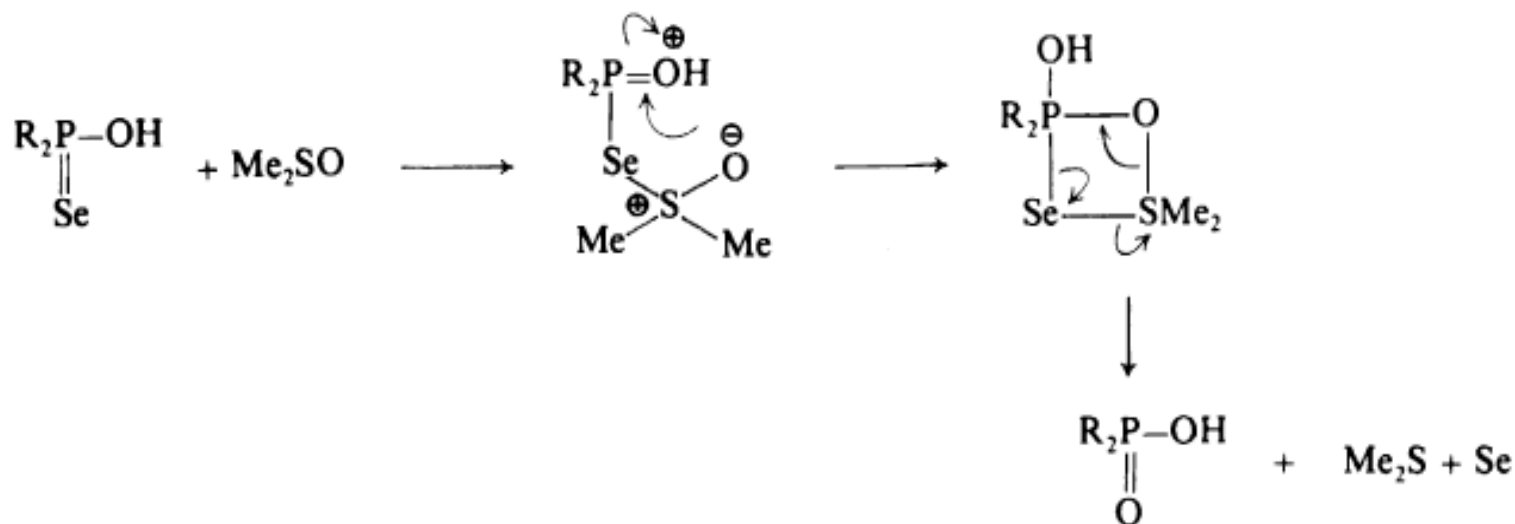


The disparity of O and Se bases is illustrated in the esterification of potassium selenobenzoate. Thus, the O-trimethylsilyl esters are produced on reaction with Me_3SiCl , although compounds containing $\text{C}=\text{Se}$ bonds are very unstable.

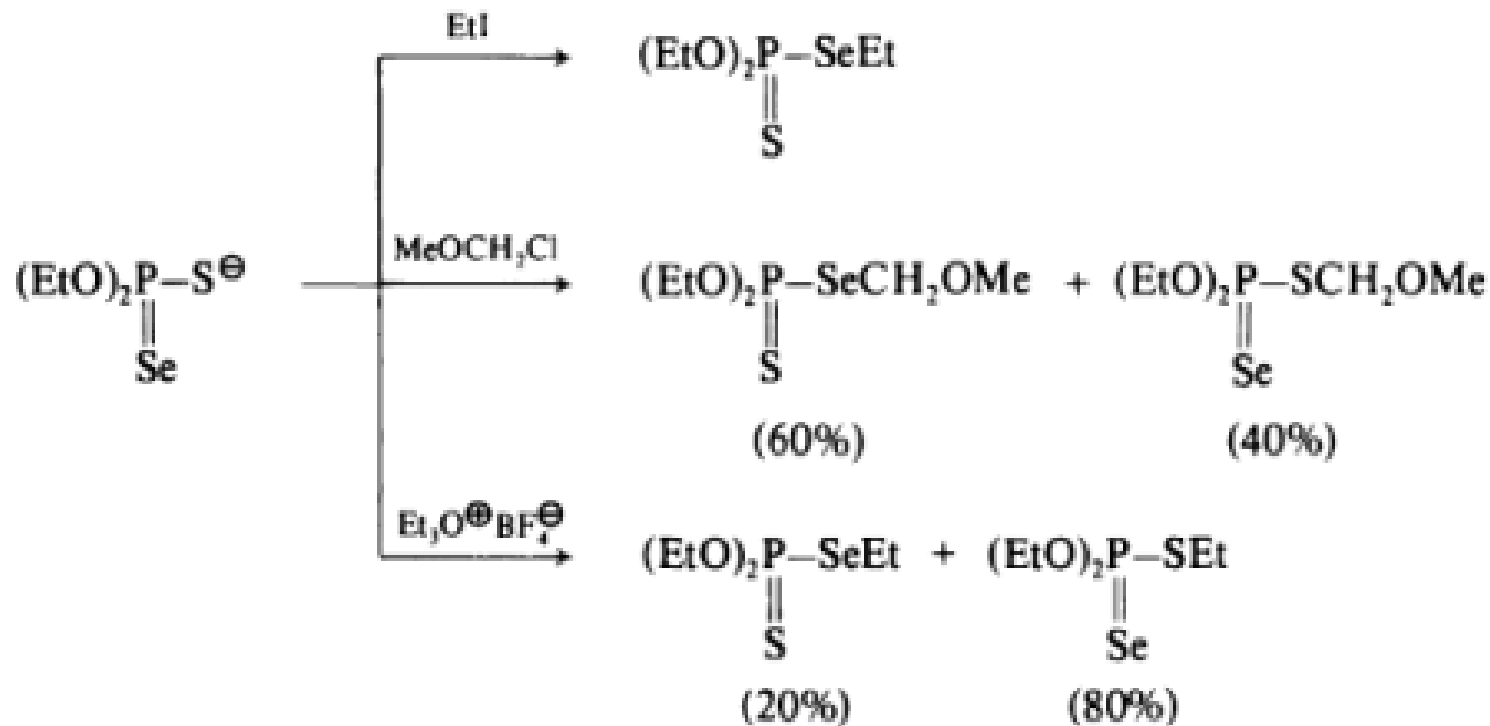
On the other hand, the salt reacts with trimethylmetal chlorides of more polarizable elements to furnish the seleno esters. The trimethylsilyl ester is sensitive to moisture owing to the presence of a hard Si center. The stannoselenyl and germanoselenyl esters are quite stable toward hard bases.



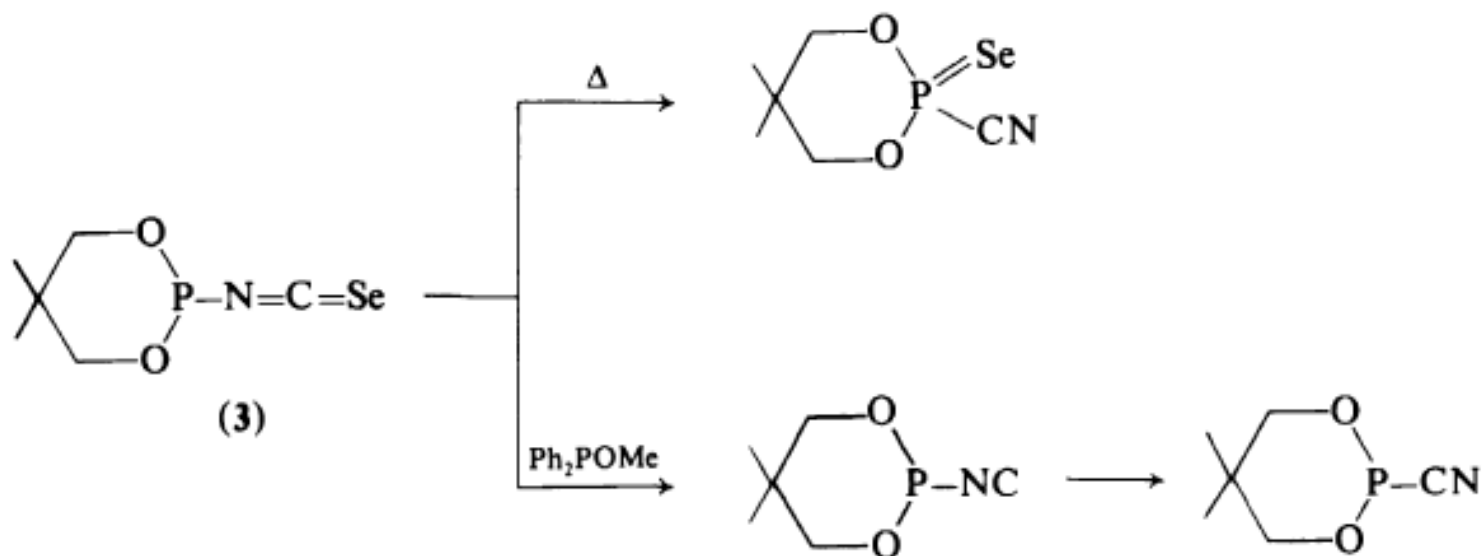
The deselenonation of phosphinoselenoic acids by dimethyl sulfoxide (DMSO) proceeds exothermically, whereas the corresponding reaction with phosphinothioic acids requires heating at 100°. The reactivity of the P=X bond is proportional to the softness disparity of the two adjoining atoms.



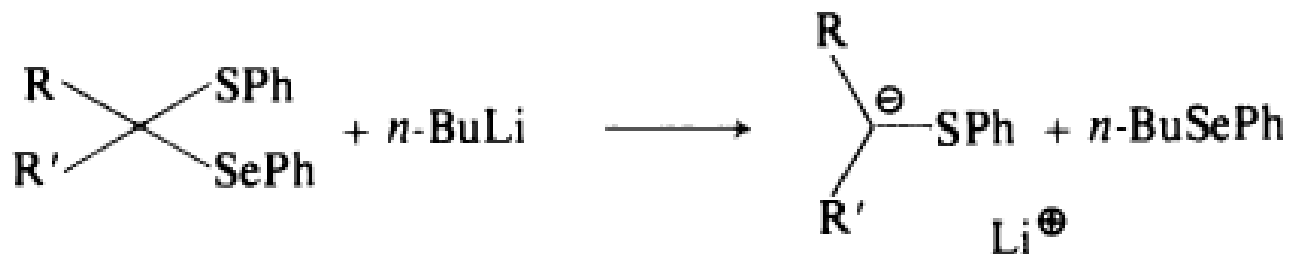
The competitive alkylation and acylation confirm the anticipated relative softness of S and Se.



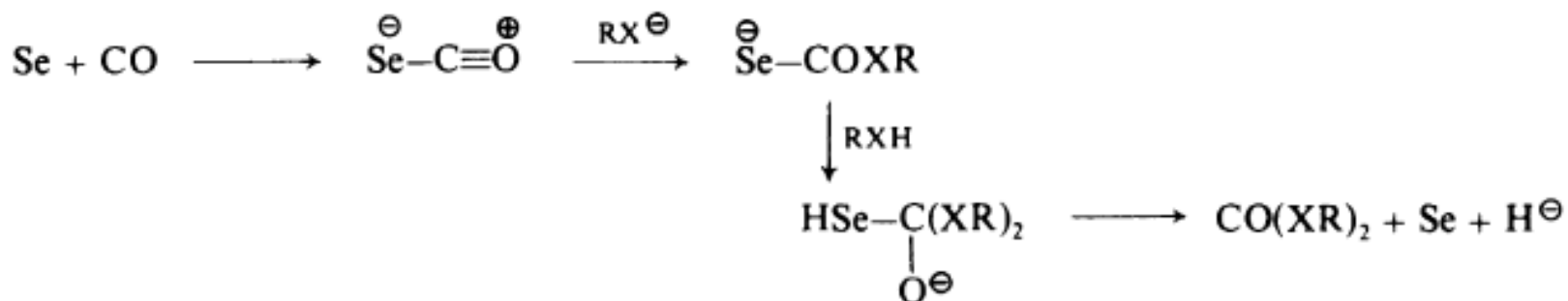
Selenium compounds are typical soft acceptors.



The soft Se atoms of diselenoacetals and selenothioacetals are the sites of attack by organometallic reagents.



The Se-mediated reactions of alcohols and amines with carbon monoxide furnish further evidence for the very soft-acceptor characteristic of elemental selenium. Trapping of the soft carbon monoxide by Se is crucial to the processes.



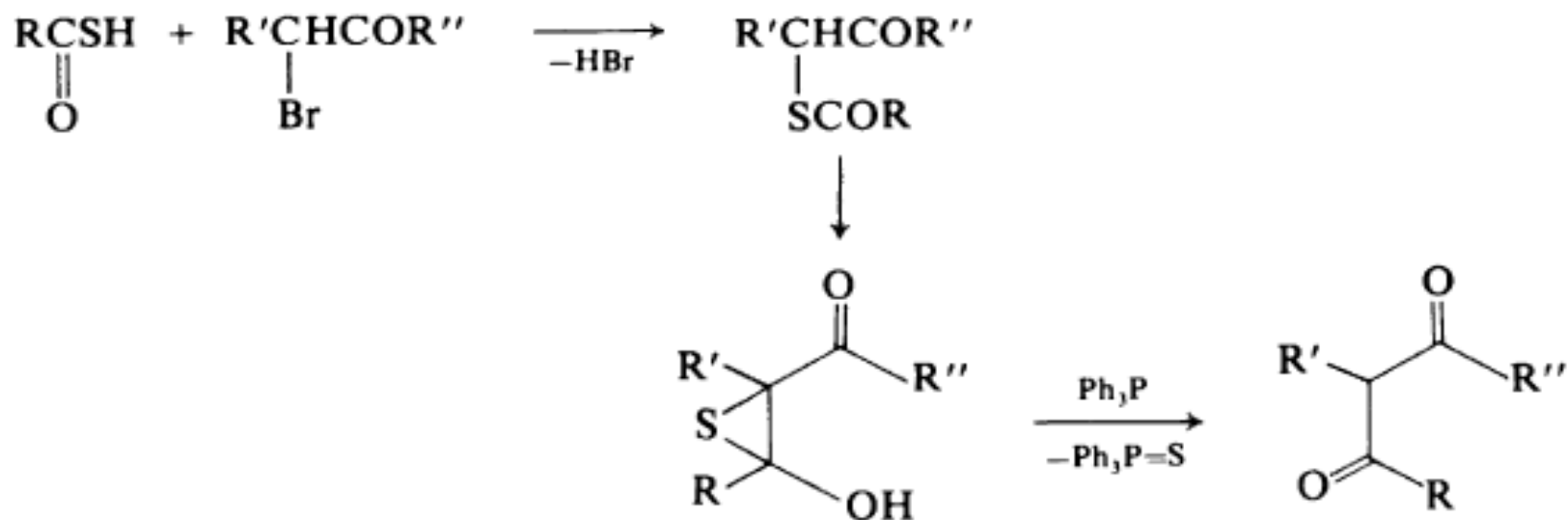
DIVALENT SULFUR COMPOUNDS AS SOFT DONORS

Divalent sulfur compounds are highly nucleophilic. However, the activated halogens of α -haloketones are not displaced by thiols or thiolates, owing to the fact that the reagents are soft and the substrates are hardened. Instead, the substrates are reduced.

Only under forcing conditions does Me_2S react with α -bromo- γ -butyrolactone to give α -methylthio- γ -butyrolactone, presumably via a biphilic mechanism.

In the absence of a proton source the carbanion-bromosulfonium ion pair intermediate resulting from attack on bromine by the sulfur atom can only collapse via C—S bond formation and elimination of methyl bromide.

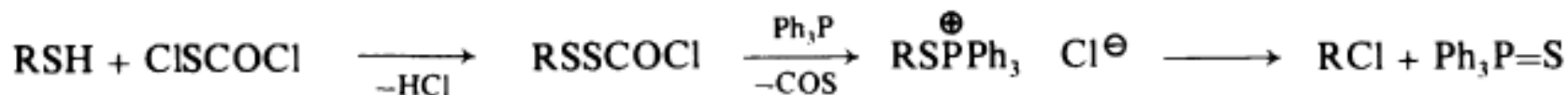
The conversion of 2-chloro-1,3-diketones to 2-alkylthio-1,3-diketones and the first step of a 1,3-diketone synthesis shown below consist of a biphilic process.



The α -(alkylthio)ketones are dehydrogenated by phenylsulfenyl chloride. In this case chlorine transfer between the sulfur atoms of the reactants could be the initial and crucial step. There is little evidence asserting either a biphilic course or direct displacement at S during reaction of thiols with sulfenyl chlorides and acylsulfenyl chlorides. Both are soft interactions.



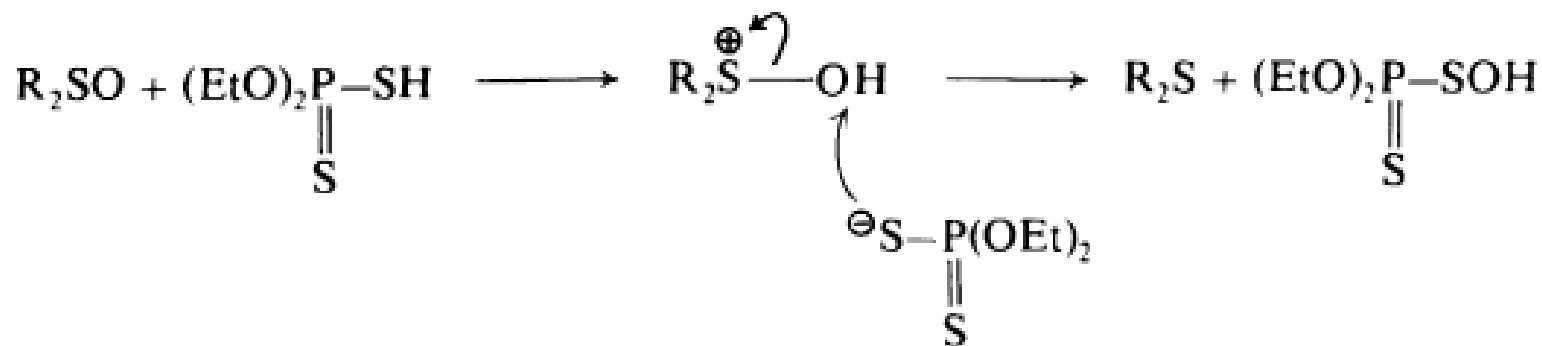
The direct conversion of thiols into chlorides has been effected by a soft base-induced fragmentation of the acyl chloride (4). The formation of (4) from thiols also involves a specific soft-soft interaction.



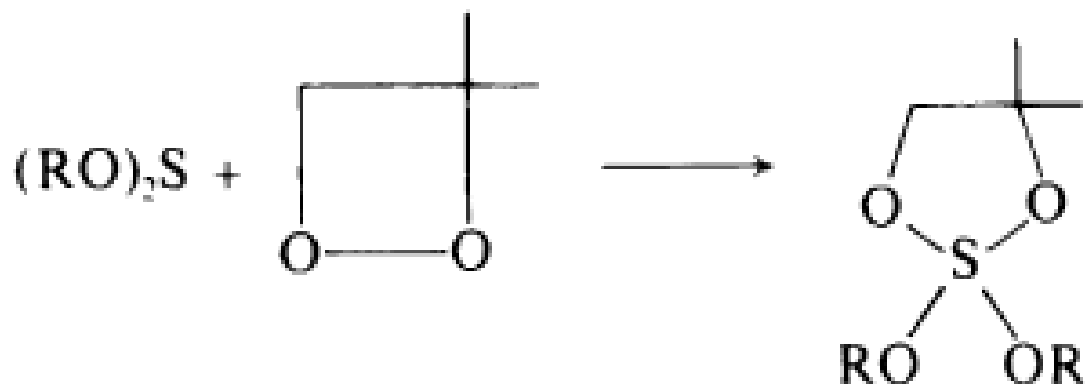
The rate of ionic decomposition of diacyl peroxides by sulfides are $(4\text{-O}_2\text{NC}_6\text{H}_4\text{CO})_2\text{O}_2 > (\text{PhCO})_2\text{O}_2 > \text{Ac}_2\text{O}_2$. The fact that the softer sulfides are more effective is consistent with an initial displacement at the peroxy center by the S bases.

Dimethyl sulfide is a convenient reagent for cleaving ozonides to the carbonyl compounds.

The semipolar $\text{S} \rightarrow \text{O}$, $\text{S} \rightarrow \text{N}$, $\text{N} \rightarrow \text{O}$, and $\text{N} \rightarrow \text{N}$ bonds are severed by phosphorothiolothionic acids which utilize their sulfur atoms as nucleophiles.



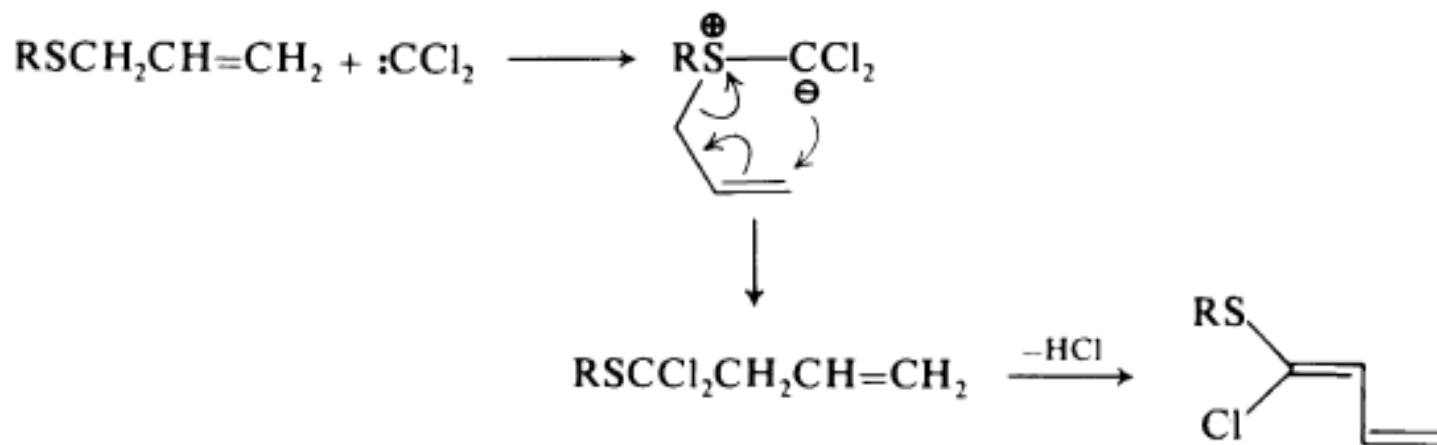
The insertion to the O-O bond of dioxetanes by dialkoxysulfides constitutes a novel access to tetralkoxysulfuranes.



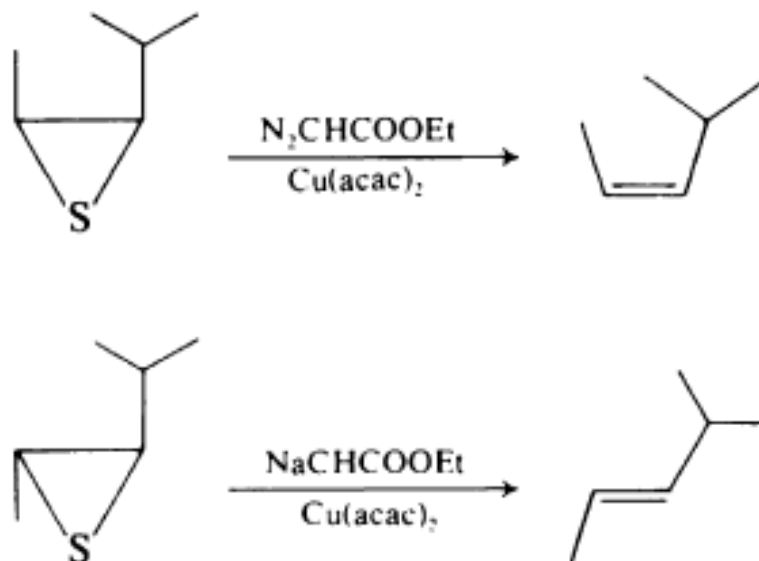
The ease of intercepting carbenes by divalent sulfur compounds attests to the soft nature of the S atom.

The inhibition of dichlorocarbene addition to cyclohexene by sulfides further demonstrates that sulfides are softer than olefins.

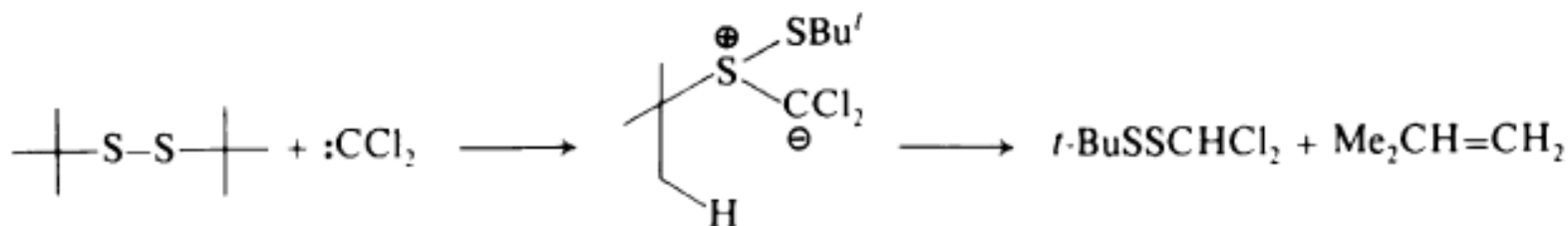
Dichlorocarbene inserts into allyl sulfides via the Stevens rearrangement of the ylide intermediates. Internal competition for a carbene is always won by sulfur atom over olefins, even though attack on sulfur would give rise to strained molecules.



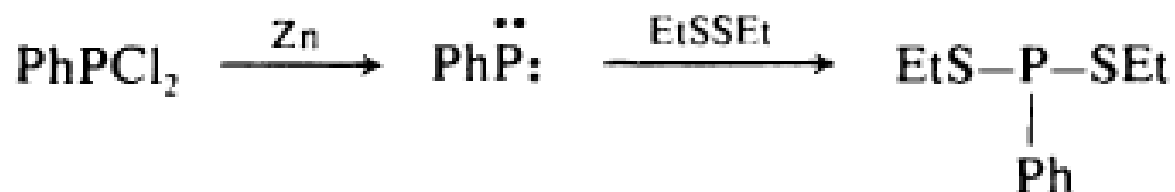
The stereospecific desulfurization of thiiranes may be effected by carbenes. Epoxides are deoxygenated with much lower efficiency.



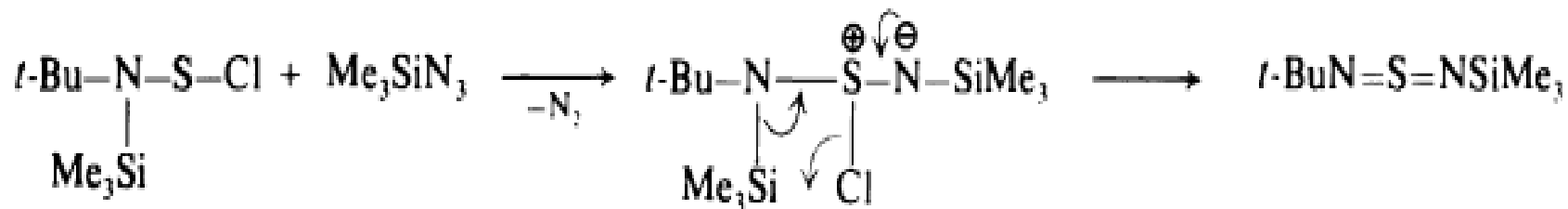
Disulfides are also very reactive toward carbenes. The elimination of isobutene has been observed when di-*tert*-butyl disulfide is treated with $:\text{CCl}_2$.



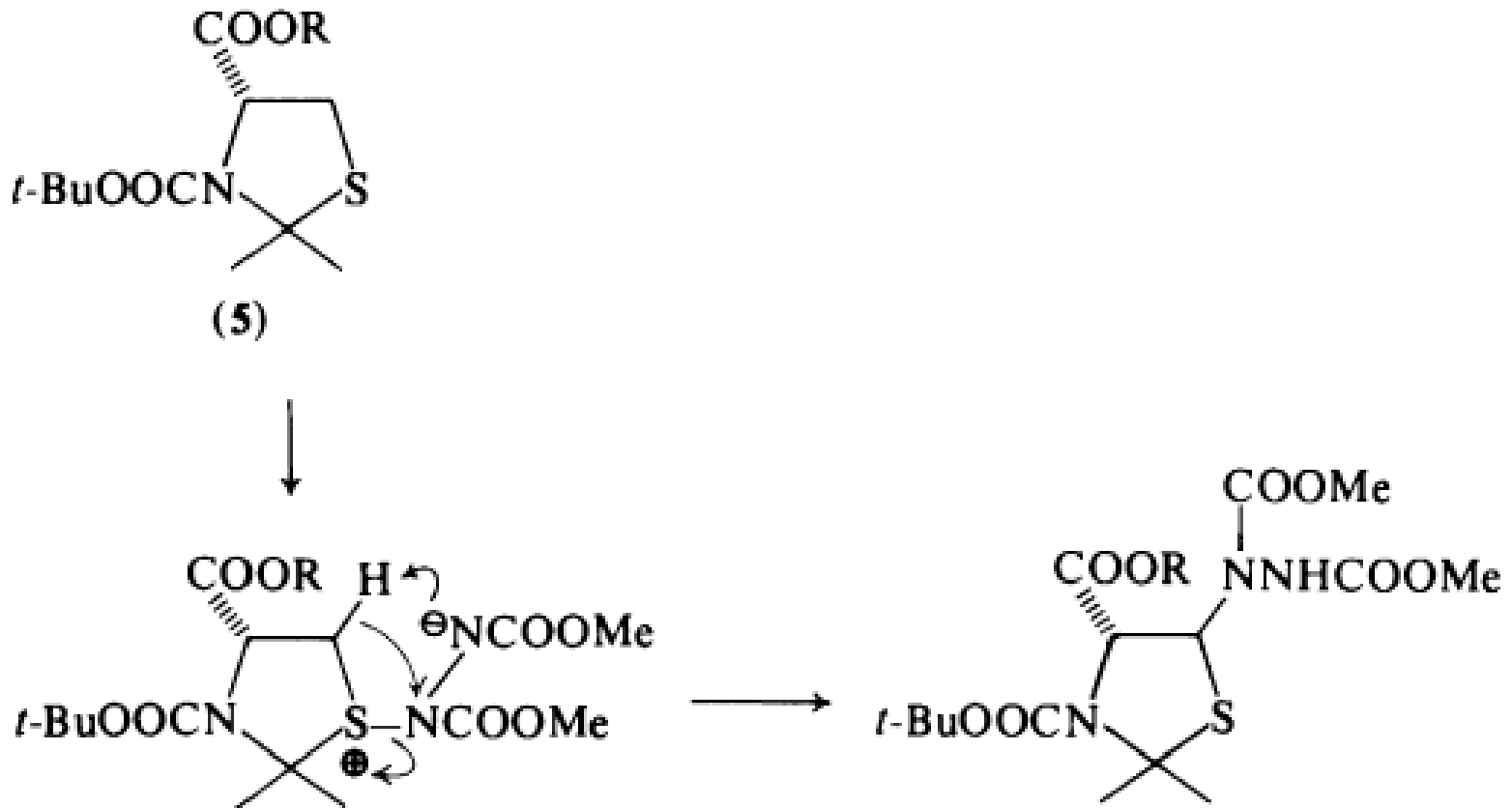
Diethyl disulfide is inserted by phenylphosphene, apparently involving a bifilic reaction.



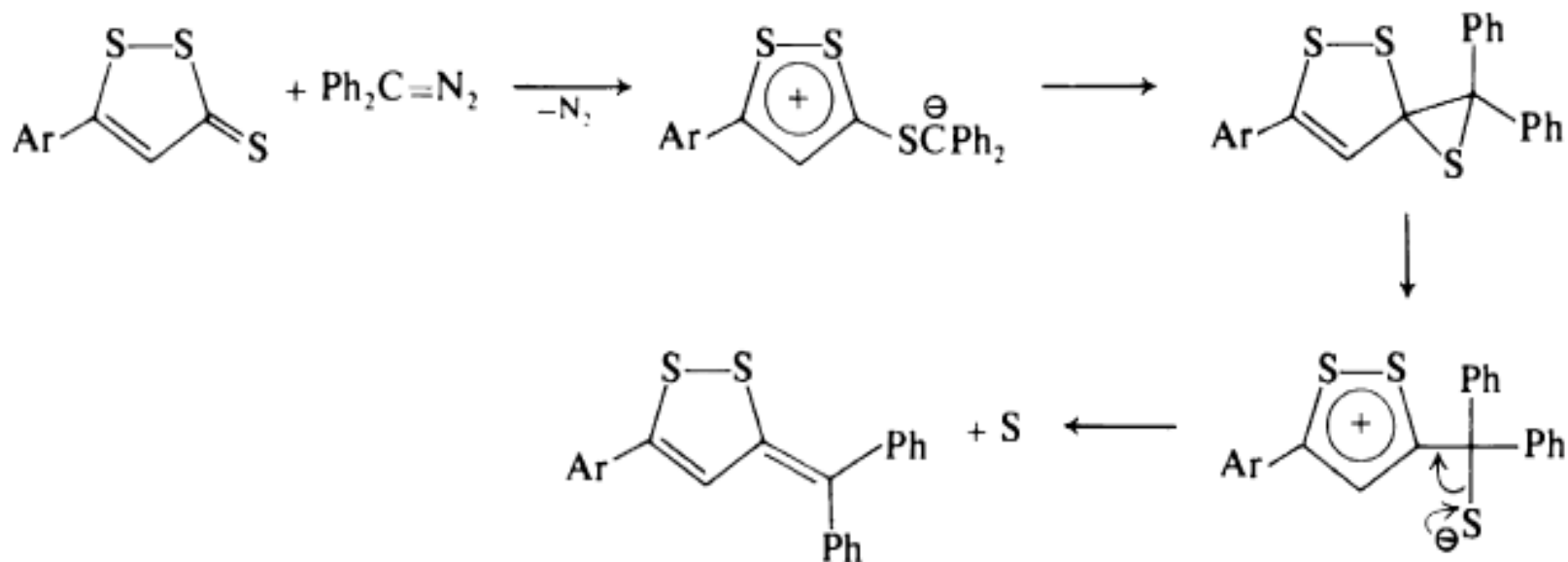
The mechanism of sulfo(IV)diimide formation during the reaction of an aminosulfonyl chloride with trimethylsilyl azide can be depicted by nitrene interception and the subsequent elimination of chlorotrimethylsilane from the adduct.



In the total synthesis of the antibiotic cephalosporin C, Woodward *et al.* introduced a nitrogen function to the methylene group alpha to a sulfur atom in (5) by heating with dimethyl azodicarboxylate. It has been adduced that the unusual process involves an initial addition of the sulfur atom across the azo linkage in a typical soft-soft interaction.



The decomposition of diazo compounds in the presence of 1,2-dithiole-3-thiones leads to 3-methylene-1,2-dithiole derivatives



The reactivity of the thiocarbonyl group toward alkyl halides has been evaluated by the CNDO method .

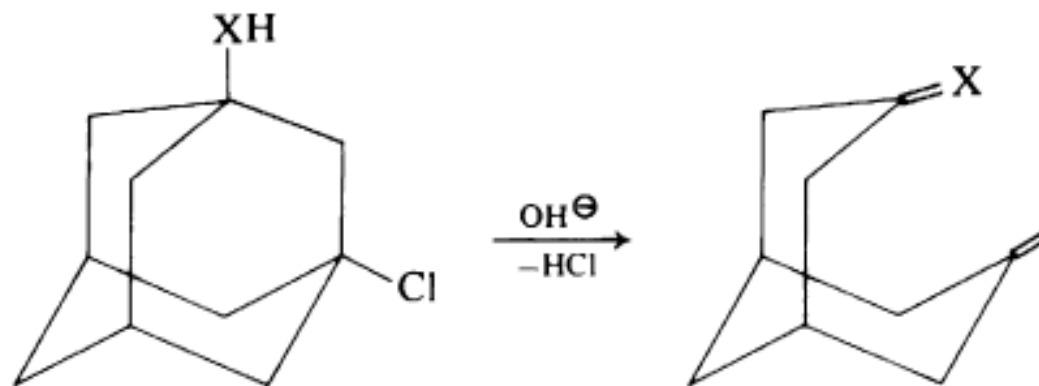
A much higher energy transition state for the displacement of fluoride ion than of chloride ion is indicated.

The demarcation is in keeping with the significantly different softness of the two halogens.

Davis *et al.* have determined the oxibase parameter (H/E) of some thioanions: CS_3^{2-} : 4.27; EtOCS_2^- : 1.43; EtSCS_2^- : 1.42; MeCS_2^- : 1.97; NCS^- : 0.55.

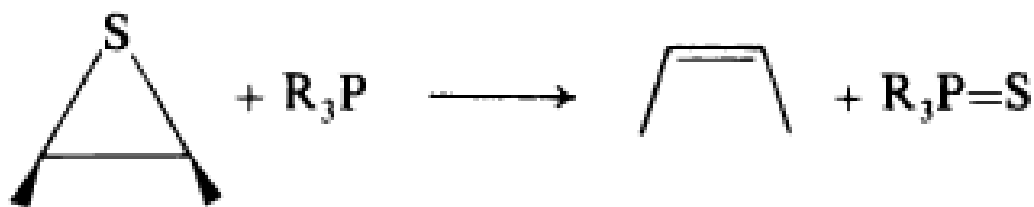
Thus, comparison can be made of their softness and nucleophilicity.

3-Chloroadamantan-1-ol undergoes fragmentative dehydrochlorination more than 15 times faster than the corresponding thiol. The larger fragmentative effect of the former is due to the greater tendency to form a C=O bond rather than the C=S bond.

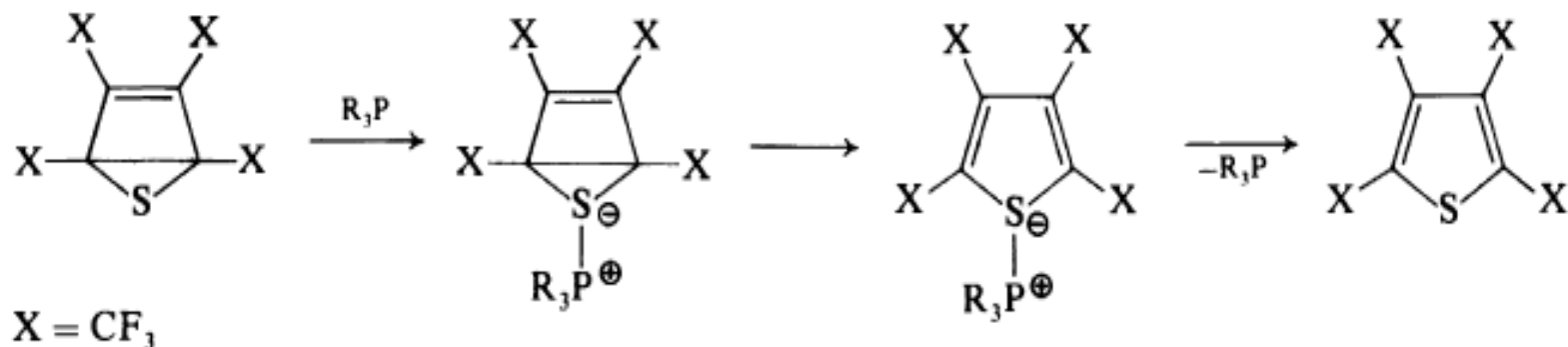


DIVALENT SULFUR COMPOUNDS AS SOFT ACCEPTORS

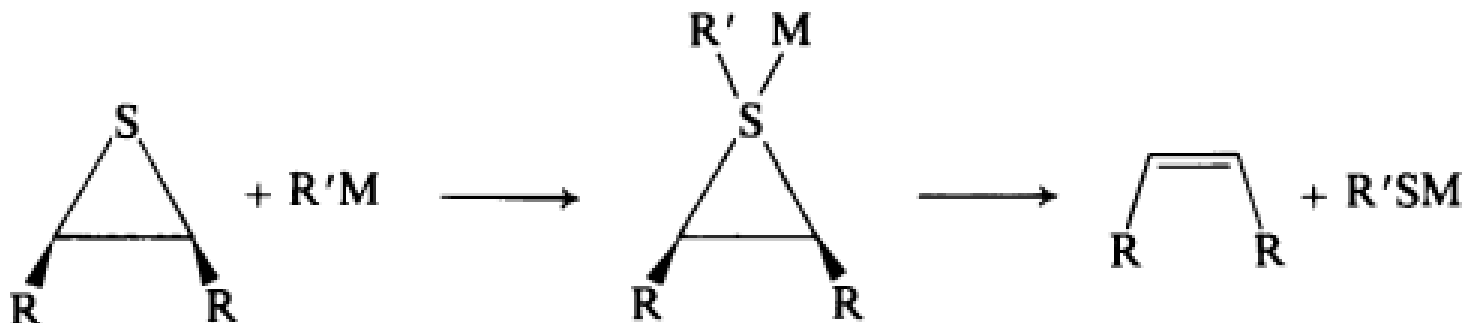
The soft donor property of S atom is manifested in sulfur extrusion from thiiranes by carbenes and other soft Lewis acids such as iodine, and iodomethane; thiiranes assume the role of acceptors when reacting with phosphines. Oxiranes, on the contrary, do not react with phosphines except under drastic conditions whereby a mixture of isomeric alkenes are produced.



Dewar thiophenes are thiiranes fused to cyclobutene rings. While the reversion of the tetrakis(trifluoromethyl) derivative to the normal thiophene structure requires a high temperature ($\tau_{1/2}$ [160°, C₆H₆] 5.1 h), the transformation can be achieved at room temperature by phosphines such as Ph₃P.



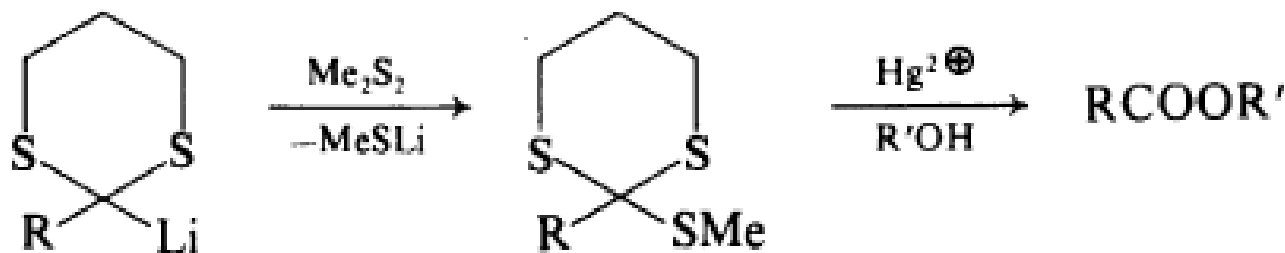
Organolithium reagents elicit fragmentation of thiiranes. 2-butene epoxides undergo stereospecific desulfuration. Lithium aluminum hydride may also be used



Disulfides are good soft acceptors. They are reduced to thiols by hydroselenide ion.

The utilization of dimethyl disulfide as an indirect oxidant during conversion of aldehyde to acid derivatives via the dithiane synthesis has been reported.

The alkylation of the lithiodithiane derived from cinnamaldehyde occurs exclusively at the heterocyclic carbon. This may be indicative of symbiotic stabilization of the transition state and the product.



Divalent Sulfur Compounds as Soft Acceptors

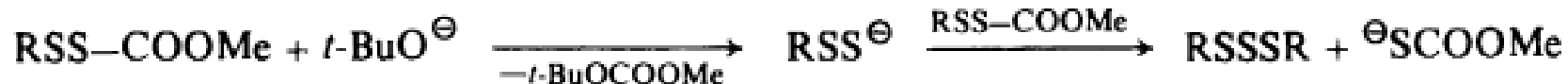
The S-S linkage of sulfenyl thiocyanates, thiosulfates, and Bunte salts are also susceptible to cleavage by soft bases.

The displacement on the trithionate ion $\text{S}(\text{SO}_3)_2^{2-}$ takes place at the central divalent sulfur via a transition state resembling that of the $\text{S}_{\text{N}}2$ reaction.

The increasing effectiveness of the bases $\text{CN}^- < \text{Ph}_3\text{P} < \text{PhS}^- < \text{EtS}^-$ has been established.

Mixed disulfides can be synthesized by the reaction of alkyldithioformic esters with thiols through a soft-soft interaction.

However, attempts to extend the reaction to prepare sulfenate esters using alkoxides as nucleophiles led to dialkyl trisulfides instead.

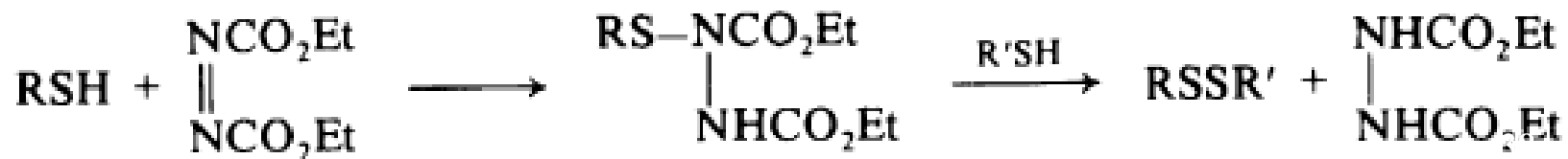


A synthesis of primary amines has been developed by exploiting the activating and protective ability of PhS groups and their ready removal from amino nitrogen (102a) with soft bases.

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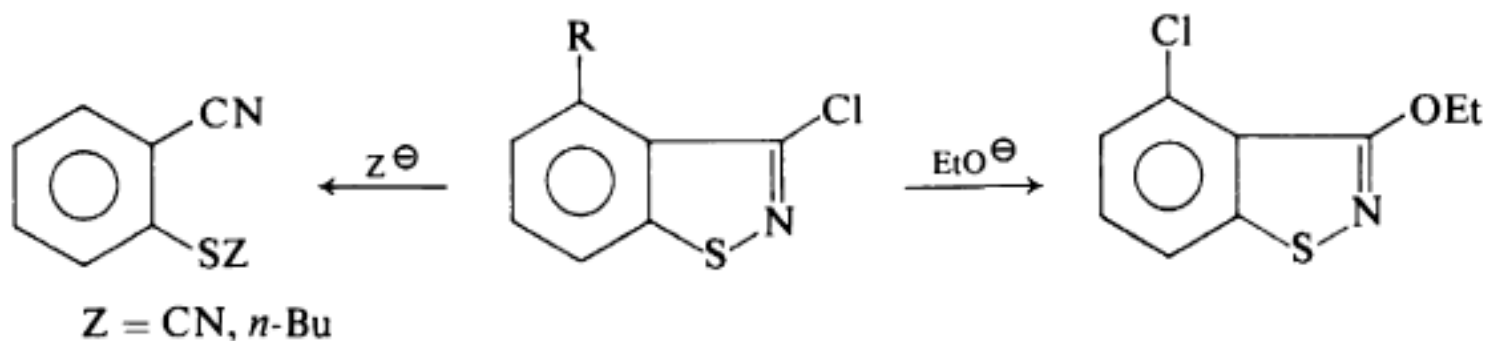


Mixed disulfides are obtained from a sequential treatment of azodiformate esters with two different thiols.

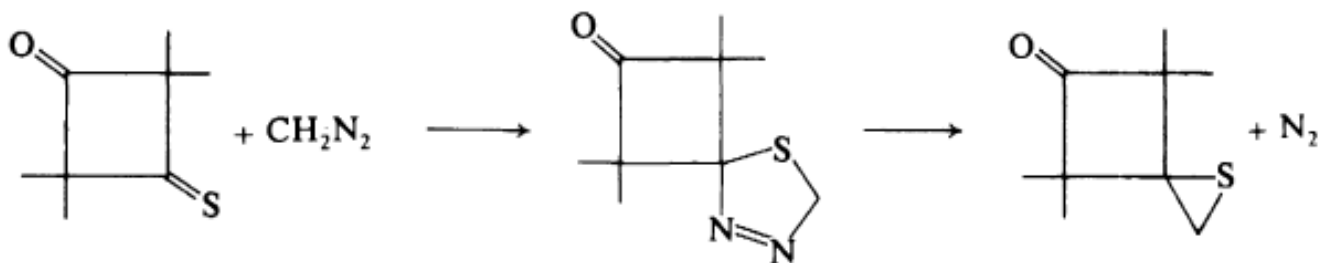


3-Chloro-1,2-benzisothiazoles undergo normal substitution at C-3 with ethoxide ion and amines .

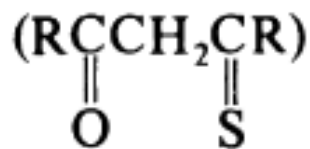
The soft bases attack at S causing rupture of the heterocycle.



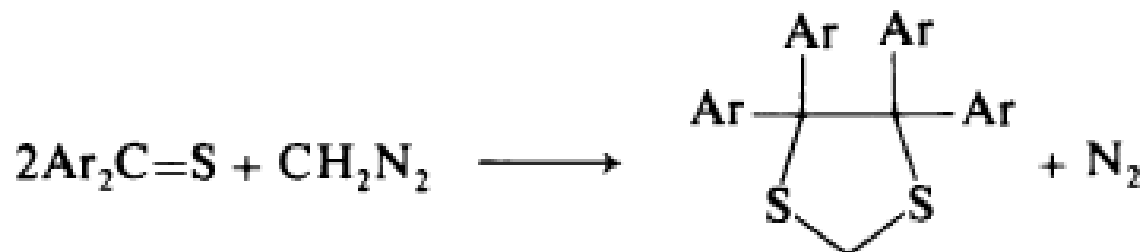
Since the thione group is much softer than a ketone, diazomethane adds to a thione selectively in the presence of a carbonyl.



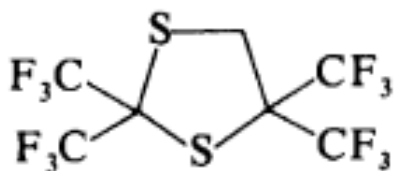
The thione group of β -ketothiones is more reactive toward (soft) bases.



When they react with diazomethane, aromatic thiones are dimerized with incorporation of a methylene group.

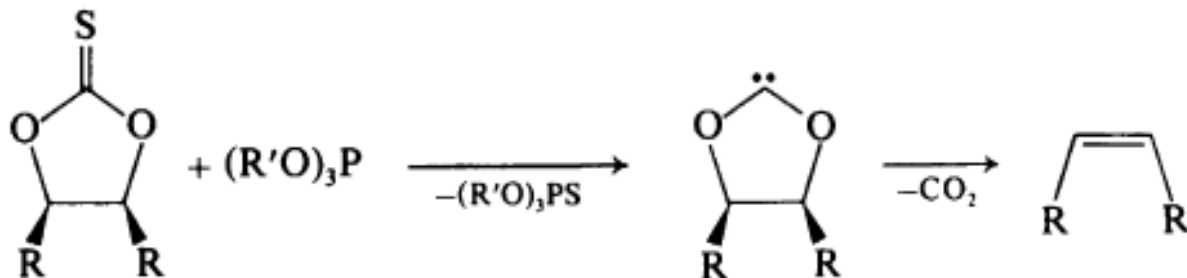


Hexafluorothioacetone participates in a similar process, but the product has an unsymmetrical structure.



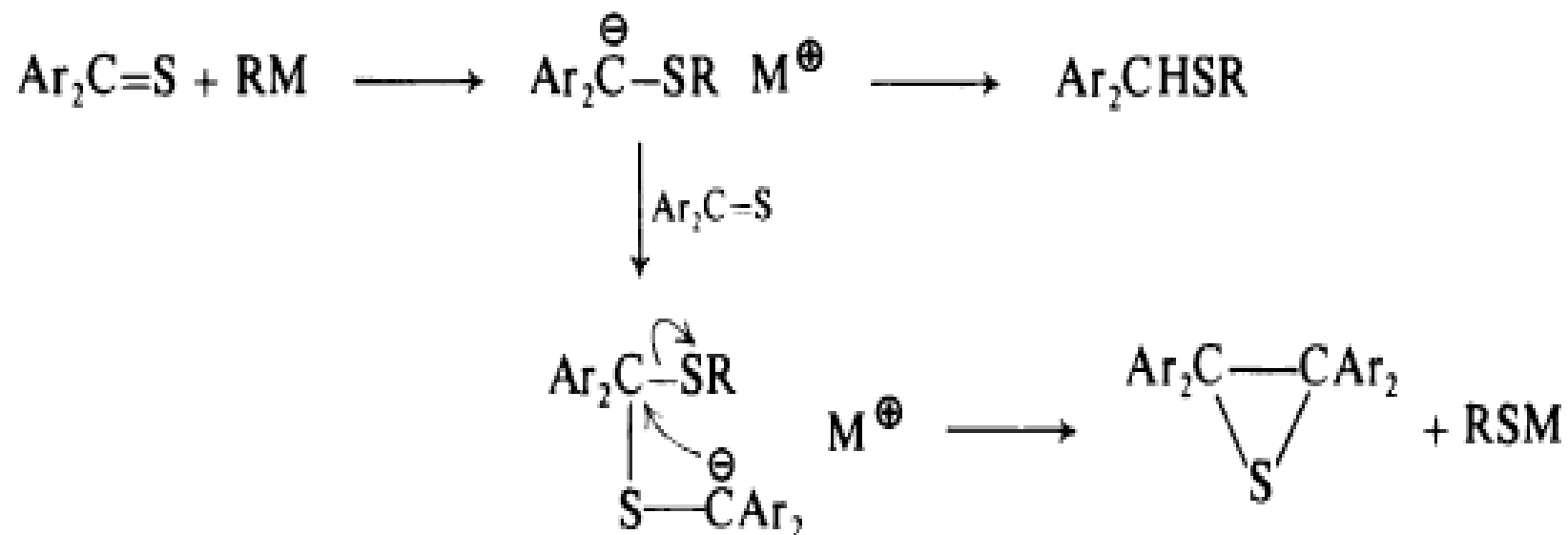
Phosphites can abstract the sulfur from the thione group to generate a carbene.

Corey-Winter olefin synthesis:



Chemistry of the Sulfinyl Group

Organometallic agents attack the thionic S leading to a reductive alkylation.

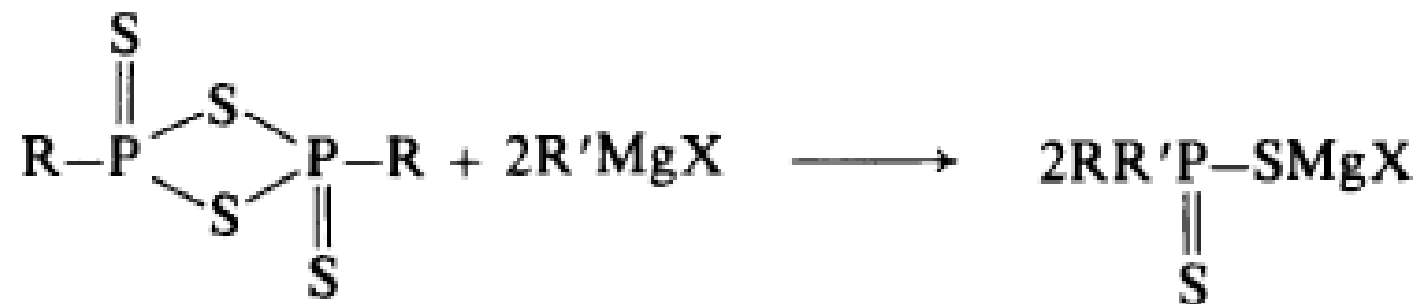


The extent of the reaction can be correlated with the softness of the organometallic reagents.

Thus, the softer MeMgI gives 55% of the adduct with thiobenzophenone, whereas only a 23% yield of the same product is obtained from the corresponding MeMgBr reagent.

The harder MeMgBr reacts to the carbonyl
of the thione moiety as well. The dependence of the yield of thiophilic product on the softness of the Grignard reagents is also observed during their reaction with dithiocarboxylic esters.

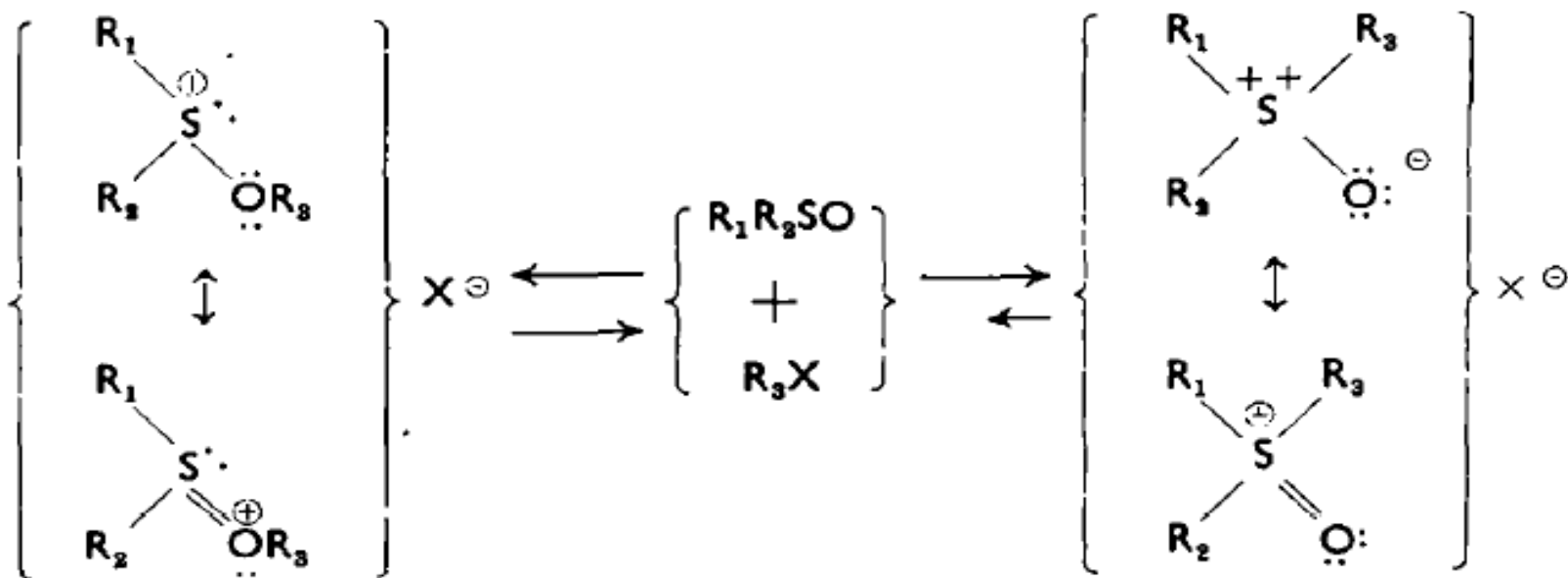
Perthiophosphonic anhydrides furnish dithiophosphinic acids on treatment with Grignard reagents.



CHEMISTRY OF THE SULFINYL GROUP

Sulfoxides are ambident bases which can be alkylated at either S or O.

Dimethyl sulfoxide gives $\text{Me}_2\text{S}^+\text{OMe} \text{BsO}^-$ and $\text{Me}_3\text{S}^+\text{O} \text{I}^-$ from reaction with methyl brosylate and methyl iodide, respectively.



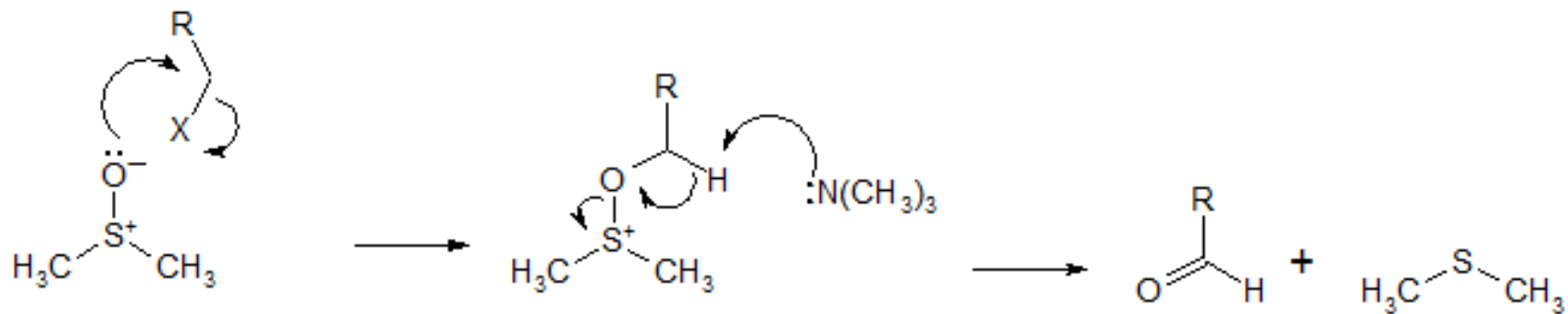
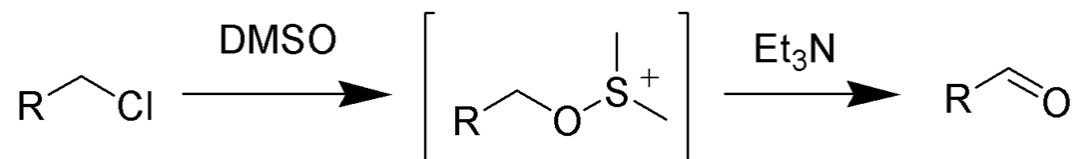
Alkyl halides are oxidized to carbonyl compounds by dimethyl sulfoxide (DMSO) at elevated temperatures.

The drastic conditions can be obviated by introducing silver ion into the mixture.

Alternatively, the halides may be converted to the corresponding tosylates which are more susceptible to attack by DMSO.

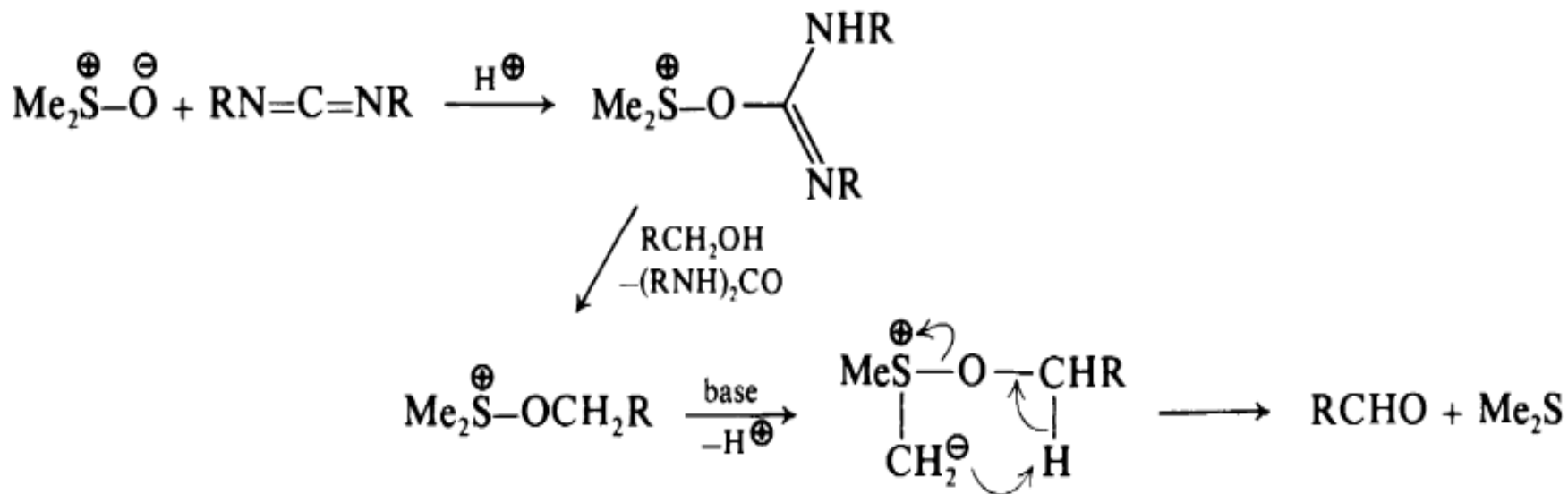
α -Bromoketones and esters yield the dicarbonyl compounds on standing with DMSO.

Kornblum oxidation:

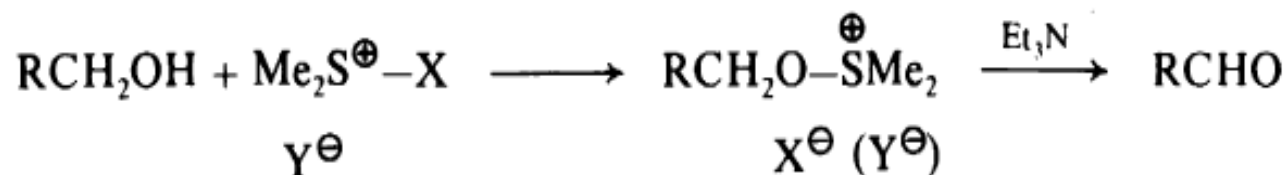
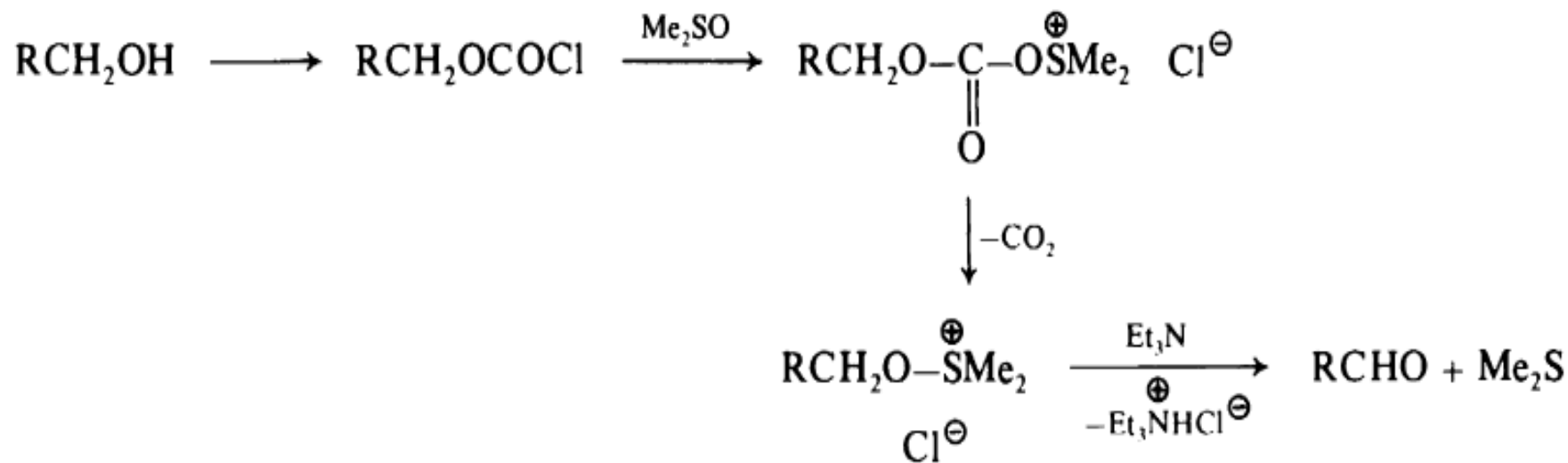


Moffatt oxidation:

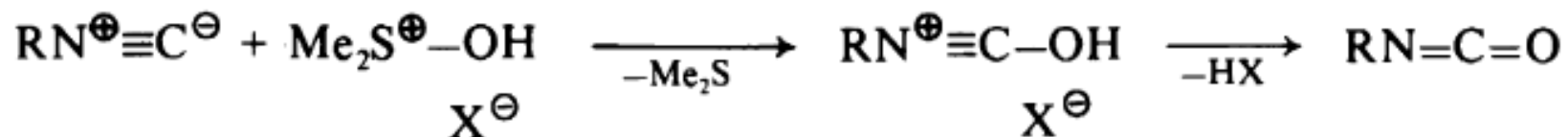
The Moffatt oxidation and its numerous modifications involve activation of DMSO by removing the excess negative charge on O, thus rendering the S atom very hard (as sulfonium center) and receptive to hard bases such as alcohols.



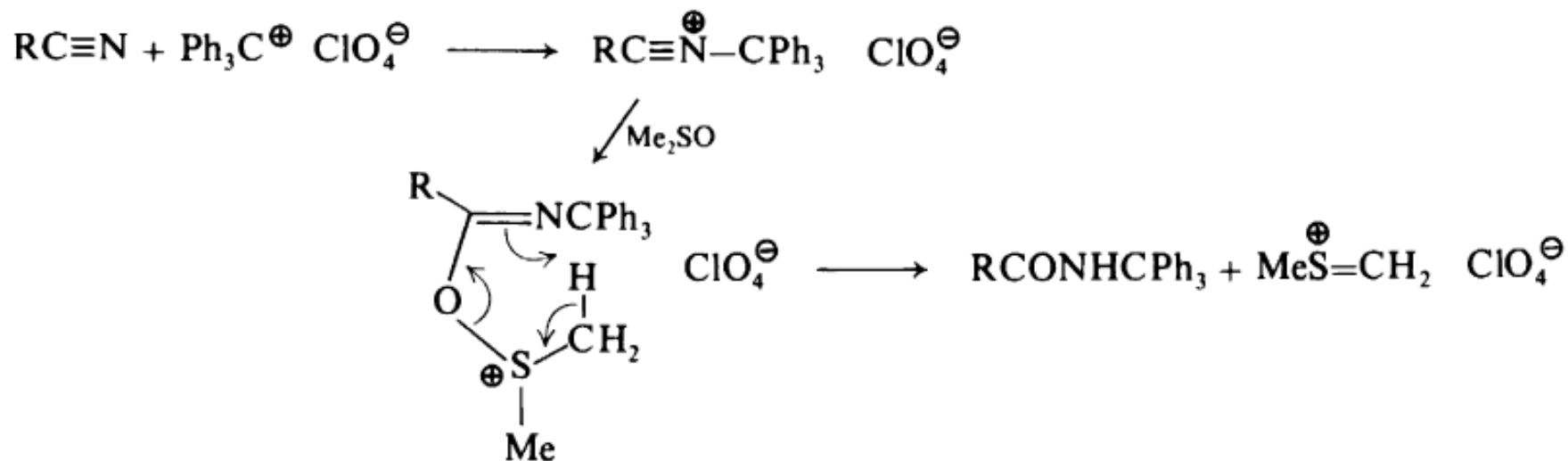
Barton *et al* achieved the alcohol oxidation by converting the substrates into the chloroformate esters which are capable of acylating DMSO. Subsequently, Corey and Kim reported a much less laborious method utilizing halosulfonium salts derived from dimethyl sulfide. The reaction of these highly electrophilic species with alcohols produces the same dimethylsulfoxonium intermediates.



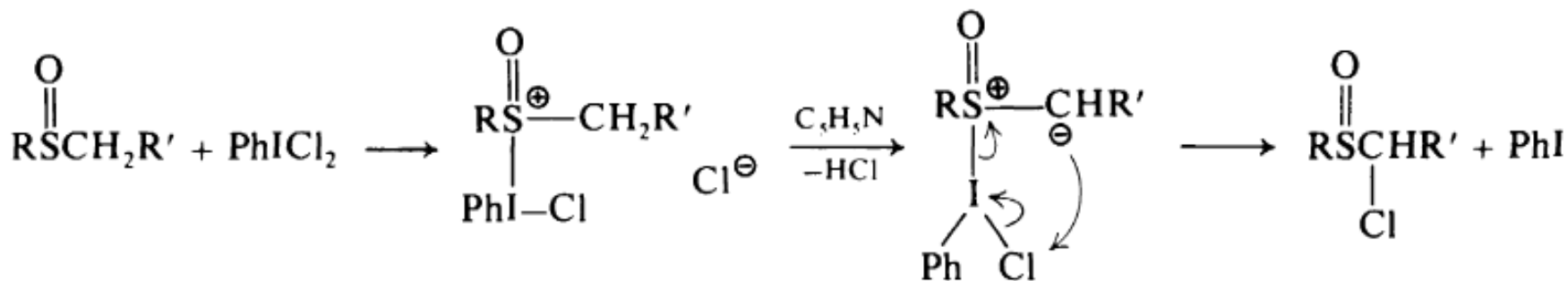
Sulfoxonium salts react with hard bases at sulfur and with soft nucleophiles at the oxygen end. Although the acid-catalyzed oxidation of isonitriles to isocyanates has been formulated as involving an *a* addition of H⁺ and DMSO at the carbon atom of the isonitrile, the alternative mechanism shown below appears more viable in the HS AB context.



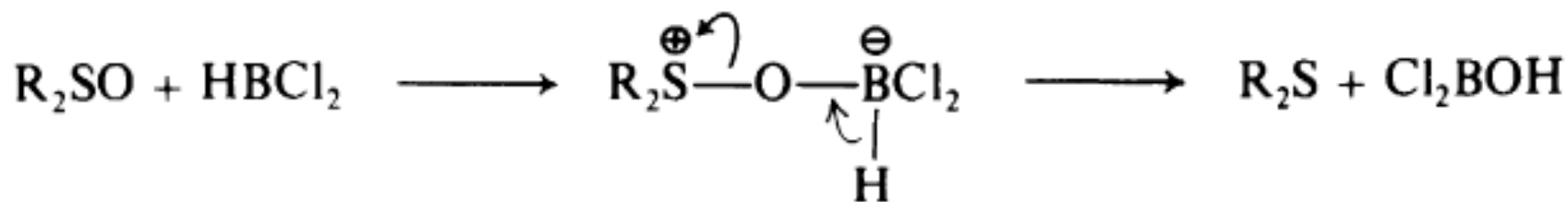
The alkylative hydration of nitriles is a quite different matter. The role of DMSO is that of a hard base for neutralizing a very hard nitrilium carbon. The synthesis of N-tritylamides is representative.



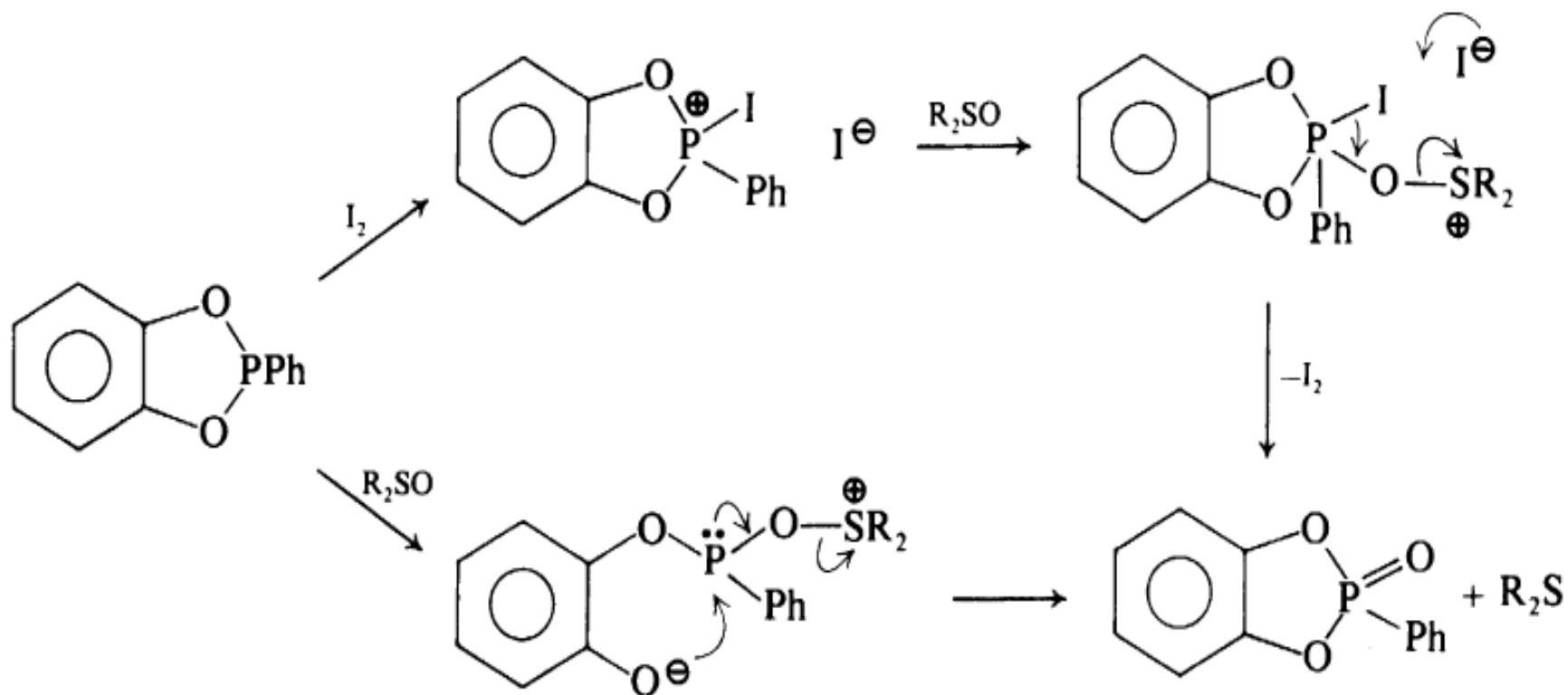
Sulfoxides may be α -chlorinated by iodobenzene dichloride. Steps involving S-I bond formation, deprotonation, and internal chlorine transfer are postulated to account for the overall process. The iodine atom in the reagent plays the dual roles of an anchoring group as well as of an activator toward ylide generation.



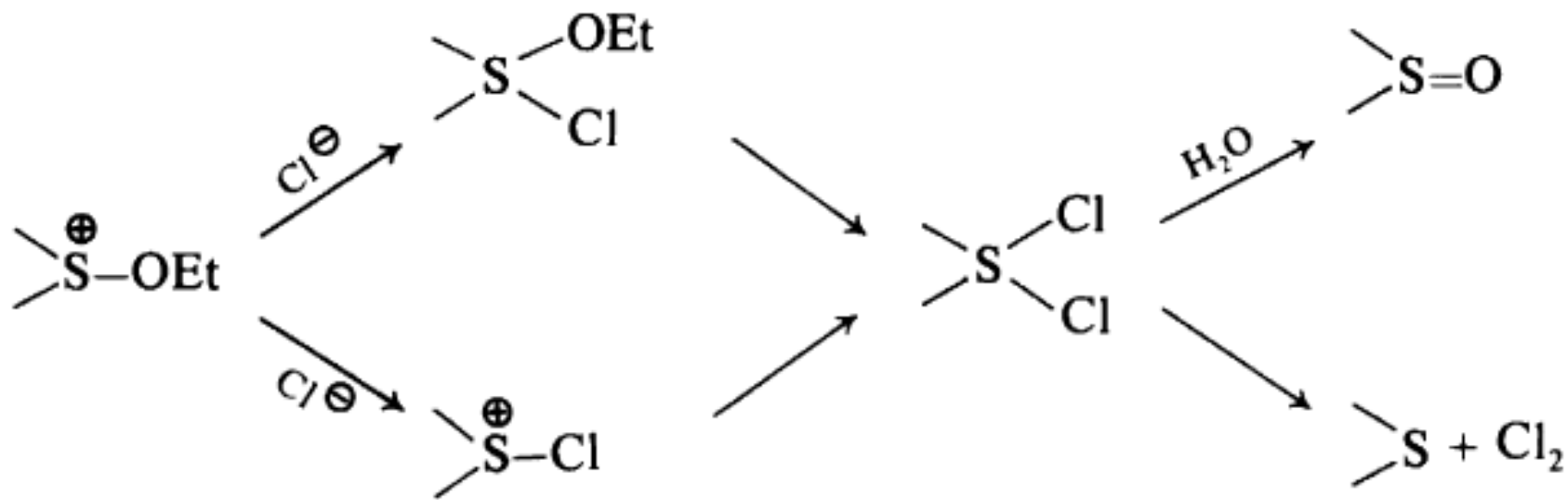
A sulfoxide deoxygenation method consists of treatment with dichloroborane. The substitution of two hydrogen atoms of borane by chlorine appears to impart the boron with a hardness compatible with the sulfoxide oxygen.



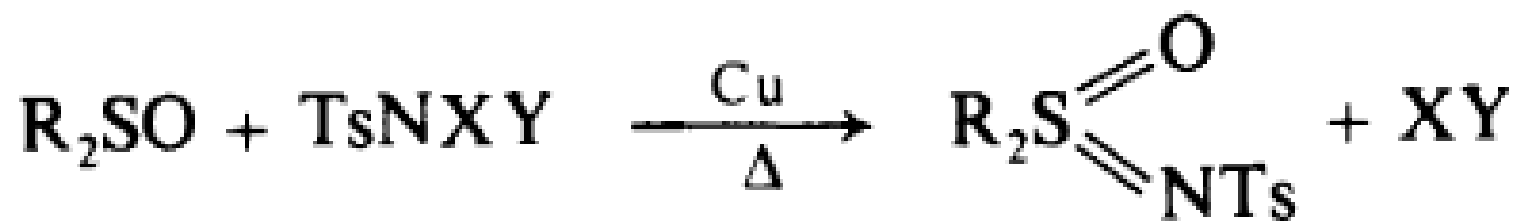
Another procedure for the deoxygenation calls for the use of phenyl Phenylenedioxyphosphine. However, the mechanism presented by the authors does not explain the acceleration effect of iodine and the fact that aliphatic sulfoxides react faster than their aromatic counterparts. The alternative pathways below agree better with experimental observations.



Alkoxysulfonium salts are cleaved by bromide and iodide ions to sulfoxides with retained configurations indicating a S_N2 displacement at alkoxy carbon by the soft nucleophiles. The use of equimolar chloride ion leads to a mixture of sulfides and partially racemized sulfoxides. The intervention of sulfurane intermediates has been postulated for the reaction.

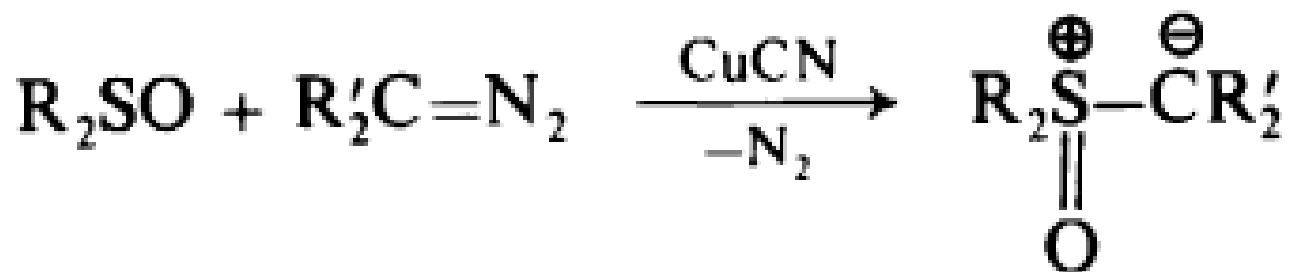


Copper-catalyzed decomposition of tosyl azide or chloramine T in the presence of DMSO leads to *N*-tosylsulfoximines. The configuration of sulfur is retained. Thus, the nitrenoid intermediates are trapped by the softer sulfur of the sulfoxides.



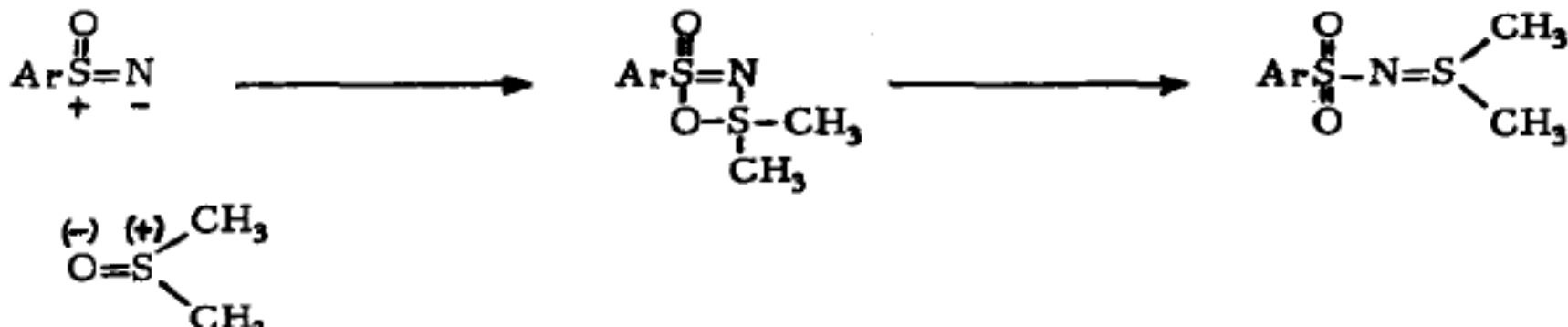
Heating arenesulfinyl azides in DMSO affords arenesulfonyl sulfilimines. The results are consistent with nitrene trapping followed by rearrangement.

Carbenes are also intercepted by sulfoxides. For example, diazo compounds give sulfinyl ylides during their decomposition by cuprous cyanide in the presence of a sulfoxide.



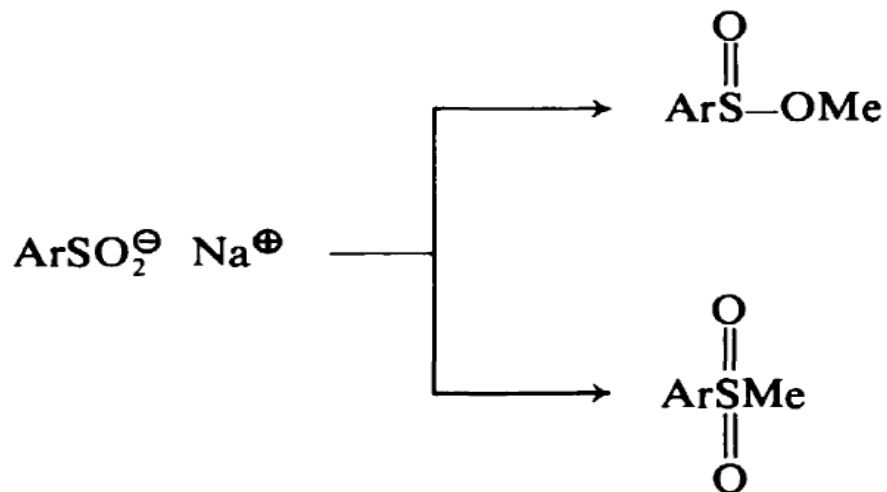
Sulfinamides are chlorinated at the soft sulfur atom by 1-chlorobenzotriazole to yield sulfonimidoyl chlorides.

Carbenes are also intercepted by sulfoxides

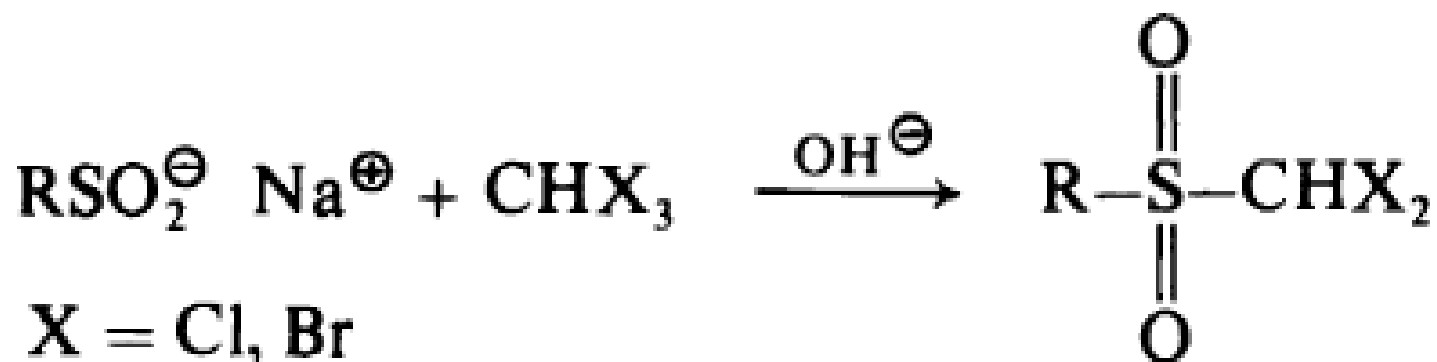


REACTIONS OF HIGHER VALENT SULFUR DERIVATIVES

The sulfonyl group (sulfinate) is an ambident nucleophile which shows a discriminative mode of action toward different kinds of electrophiles. The methylation of sodium p-toluenesulfinate affords predominantly a sulfonate ester when the leaving group is hard; it gives methyl p-tolylsulfone when reacting with soft reagents.



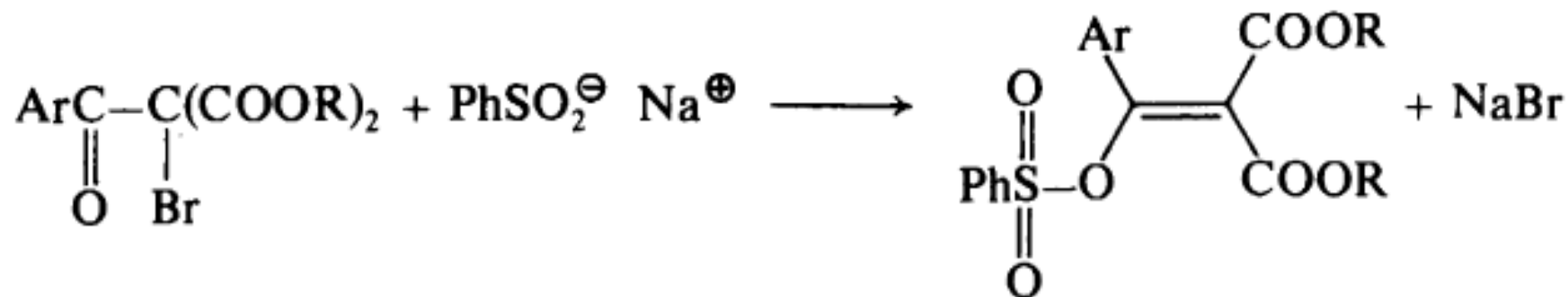
The alkylation of sulfinate anion by haloforms is possible only in the presence of aqueous alkali. Dihalocarbenes must be the true electrophiles. The exclusive formation of sulfones by this route provides support for the HSAB principle.



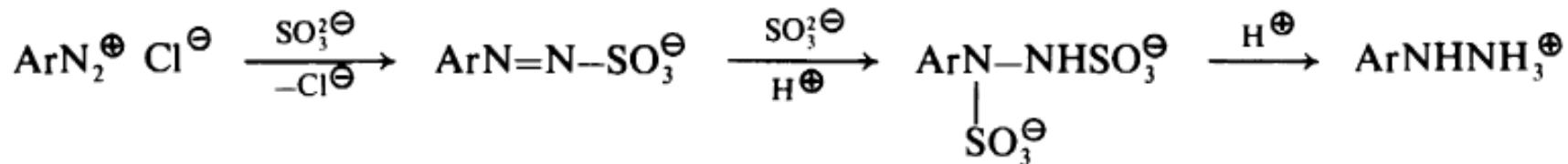
p-Toluenesulfinate anion adds to α,β - and β,β -dichloroacrylonitriles in the Michael fashion using the sulfur as the attacking point. This is characteristic of a soft-soft interaction.

Perkov reaction:

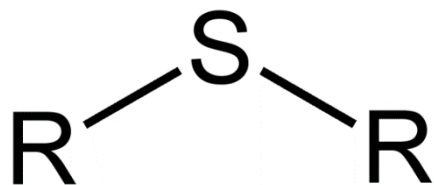
A sulfur equivalent of the Perkov reaction has been reported. Whether the sulfinate ion attacks on the halogen (biphilic) or directly on the carbonyl oxygen remains to be clarified.



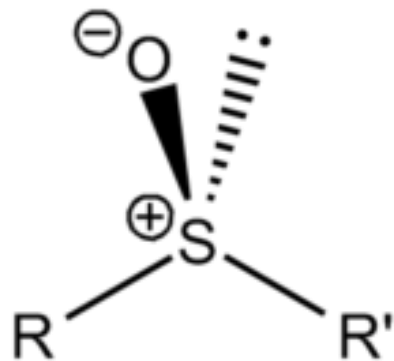
During the reduction of aromatic diazonium salts to arylhydrazines, a successive addition of the soft sulfite anion to the two nitrogen atoms is most likely involved. The nitrogen acceptors are soft.



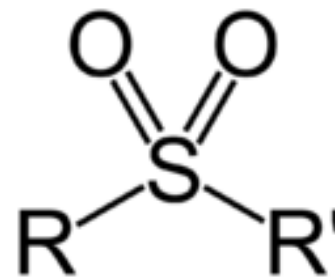
Kice and co-workers have investigated systematically the electrophilic behavior of sulfur atoms in the various oxidation states. As anticipated, it is found that the hardness increases in the order sulfenyl < sulfinyl < sulfonyl.



sulfenyl

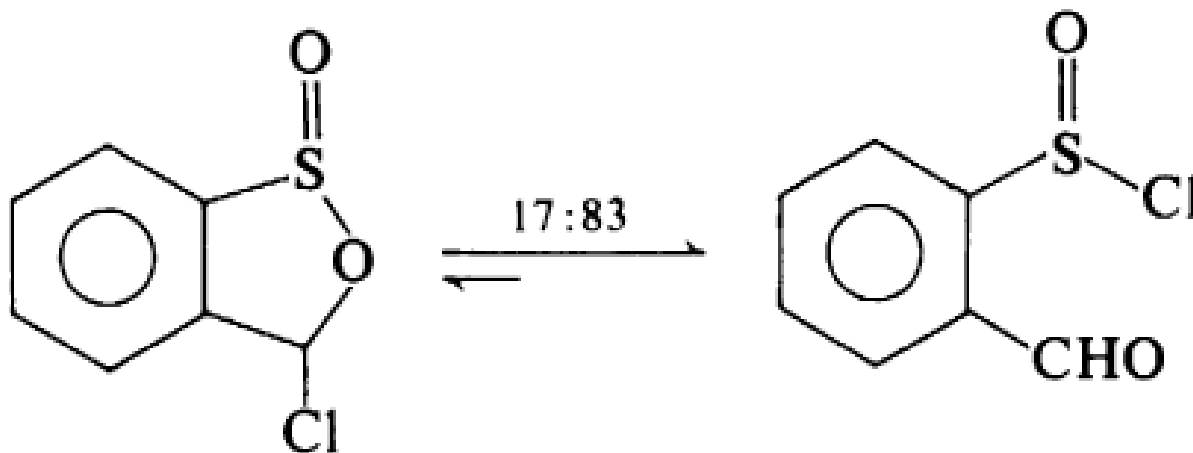


sulfinyl



sulfonyl

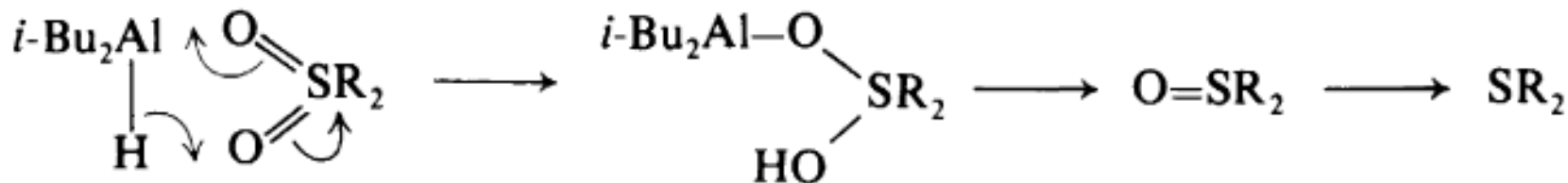
Since sulfinyl S is quite soft, the borderline chloride is a better bonding partner than the alkoxy oxygen.



Chemical reduction of the sulfonyl group is not easy because most reducing agents are soft.

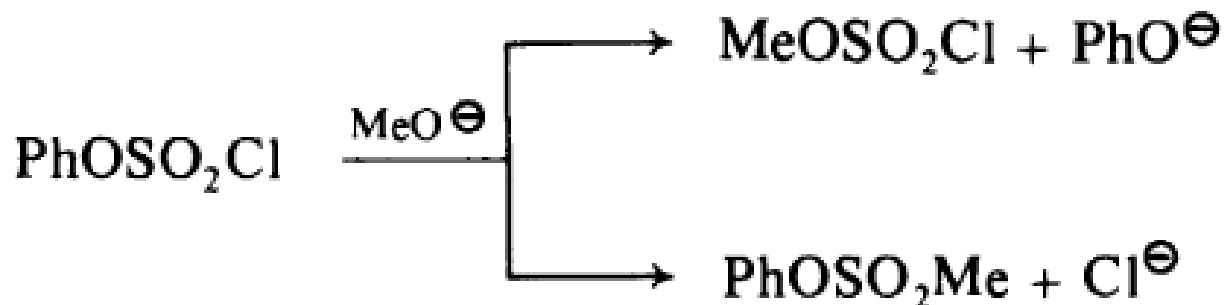
The low yield conversion of sulfones to sulfides by LiAlH_4 is improved by using $i\text{-Bu}_2\text{AlH}$.

The latter reagent is harder and its uncharged Al atom permits interaction with the hard oxygen atoms of the sulfonyl group. Sodium diethylaluminum hydride is ineffective as it is even softer than LiAlH_4 .

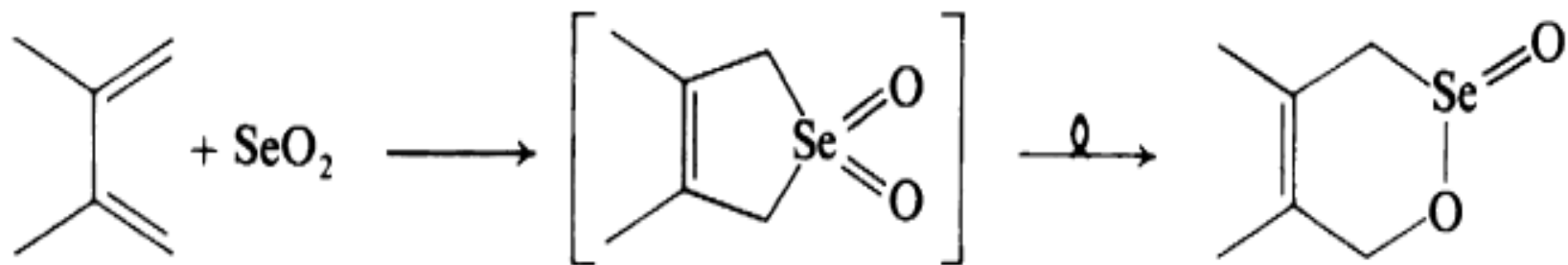


The release of Cl^- and PhO^- from phenyl chlorosulfate is effected by treatment with methoxide ion.

The observed temperature dependence indicates that the O-S bond fission has a much higher enthalpy of activation than that leading to S-Cl cleavage, as symbiosis would suggest.



The cheletropic reaction between conjugated dienes and sulfur dioxide yields cyclic sulfones. However, the isolated adducts of selenium dioxide and dienes possess the selenalactone structures. The only apparent explanation for the different stabilities of the cheletropic products is that selenium is softer and tends to avoid a higher oxidation state.



Sharpless and Lauer have presented evidence in favor of allylselenenic acids as intermediates during oxidation of alkenes by selenium dioxide. Sulfur dioxide does not undergo this type of reaction with simple alkenes.

