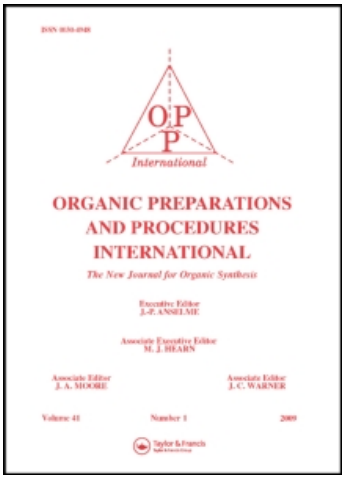

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USE OF SUBSTITUTED 3-SULFOLENES AS PRECURSORS FOR 1,3-BUTADIENES

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USE OF SUBSTITUTED 3-SULFOLENES AS PRECURSORS FOR 1,3-BUTADIENES

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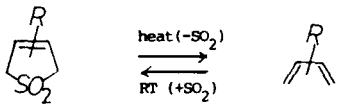
INTRODUCTION

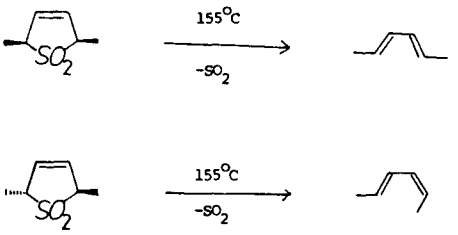
1,3-Butadienes are important synthons that have been utilized extensively in organic synthesis. However, they are in general sensitive to heat, light and acidic conditions. 3-Sulfolenes, on the other hand, may serve as masked 1,3-butadienes because they are stable to acidic conditions and moderately elevated temperatures, and the interconversion between 3-sulfolenes and their corresponding 1,3-butadienes requires only mild reaction conditions.

Reaction of 1,3-butadienes with liquid sulfur dioxide at room temperature normally gives the 3-sulfolenes in good yields. Thermal extrusion of sulfur dioxide from 3-sulfolenes takes place at about 100-130°C to afford the dienes cleanly (eq 1)[1]. The rates of SO_2 addition and extrusion vary with the substituents on the diene.[2] Practically, SO_2 extrusion from 3-sulfolenes can be achieved by refluxing in xylene, or by heating at 130°C in low-boiling solvents in a sealed tube for a few hours, or by thermolysis at a higher temperature for a short period of time.



(eq 1)

Most importantly, these SO_2 addition and extrusion reactions have been shown to be stereospecific via a concerted, disrotatory process.[3] For example, *cis*-2,5-dimethyl-3-sulfolene gives, upon thermolysis, *E,E*-2,4-hexadiene while *trans*-2,5-dimethyl-3-sulfolene gives *E,Z*-2,4-hexadiene (eq 2).[3a,b]



(eq 2)

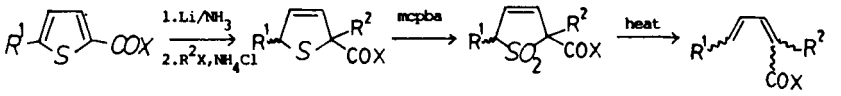
For 3-sulfolenes bearing functional groups which are sensitive to heat, stereospecific removal of SO_2 from them can be achieved alternatively by $LiAlH_4$ treatment at room temperature.[4] 2,5-Disubstituted and 2,2,5-trisubstituted 3-sulfolenes can also be treated with ultrasonically dispersed potassium at 0°C for one minute to produce the dienes stereospecifically.[5]

The general stability of 3-sulfolenes, the ease of removal of SO_2, and the stereospecificity of the extrusion reaction make them excellent precursors to the corresponding 1,3-butadienes. Several methods have been reported for the preparation of substituted 3-sulfolenes. It is the intent of this review to cover different approaches to the synthesis of substituted 3-sulfolenes and their applications in organic synthesis. Since the discussion is focused on the preparation of 1,3-dienes by way of 3-sulfolenes, those reactions involving the formation of 3-sulfolenes from SO_2 addition to the corresponding dienes will not be included.

I. PREPARATION OF 3-SULFOLENES FROM DIHYDROTHIOPHENES

Oxidation of 2,5-dihydrothiophenes to the corresponding 1,1-dioxides, the 3-sulfolenes, can be achieved with *meta*-chloroperbenzoic acid (mcpba) or other oxidants. Therefore, if a substituted 2,5-dihydrothiophene is accessible, the corresponding 3-sulfolene should be prepared without difficulty. Synthetic approaches to 2,3- and 2,5-dihydrothiophenes have been reviewed in 1982.[6] Therefore, only the more recent work and some representative examples in this area will be discussed here.

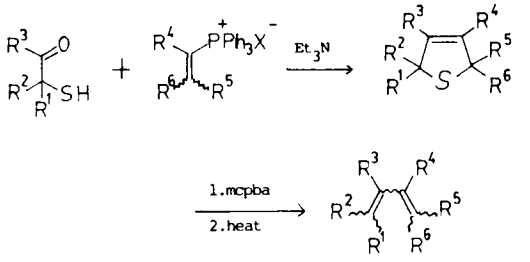
Conceptually, direct 1,4-reduction of thiophenes might be envisioned as a route to 2,5-dihydrothiophenes, which may then be oxidized to 3-sulfolenes. However, these reductions are generally not synthetically useful unless an acid derivative or a ketone is attached to the 2-position of a thiophene. In this case, metal reductions can be controlled so that 1,4-reduction becomes the predominant reaction.[7] A number of substituted 2,4-dienoates and alkyl dienyl ketones have been successfully prepared via Birch reduction and subsequent oxidation (eq 3).[7c]



(eq 3)

An elegant strategy for the preparation of substituted 2,5-dihydrothiophenes and their 1,1-dioxides has been developed by McIntosh.[8] This strategy (eq 4) involves the use of the Michael addition of an α-mercaptocarbonyl compound to a

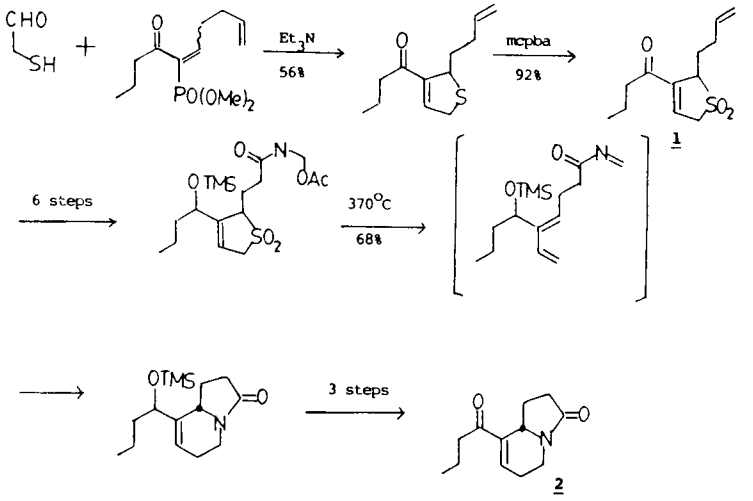
vinyl phosphonium salt followed by an intramolecular Wittig reaction for the construction of the dihydrothiophene skeleton. The dihydrothiophenes can then be oxidized and thermolyzed to give 1,3-dienes substituted at all possible positions.

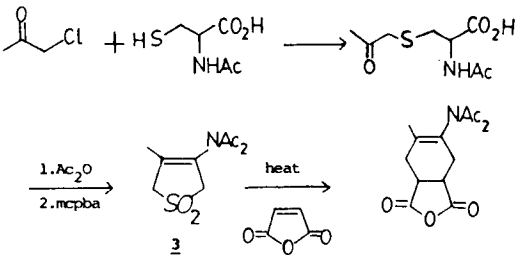


(eq 4)

Utilization of the intramolecular Wittig reaction in the construction of a substituted 3-sulfolene **1** was reported by Weinreb in the synthesis of elaeokanine A **2** (Scheme I).[9] An intramolecular hetero Diels-Alder reaction is the key step.

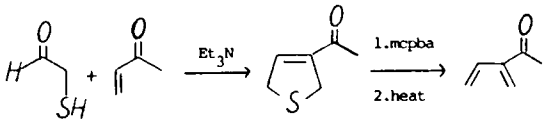
Scheme I





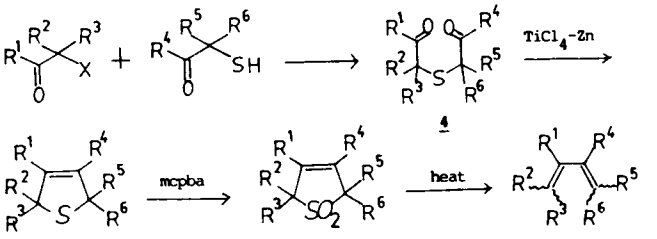
(eq 5)

Using a similar strategy, Belleau[10] prepared 2-acetyl-1,3-butadiene by an intramolecular condensation reaction (eq 6) and studied the chemical reactivity of this unstable compound.



(eq 6)

Low-valent titanium induced intramolecular reductive carbonyl coupling reactions of di-β-carbonyl sulfides **4** yield symmetrically or unsymmetrically substituted 2,5-dihydrothiophenes. Subsequent oxidation and thermolysis afford the highly substituted 1,3-dienes (eq 7).[11]



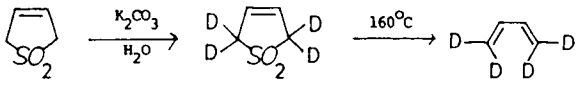
(eq 7)

II. PREPARATION OF 3-SULFOLENES *via* α-SUBSTITUTION

Since 3-sulfolene is cheap and commercially available, it has been used to synthesize 2-substituted 3-sulfolenes. The

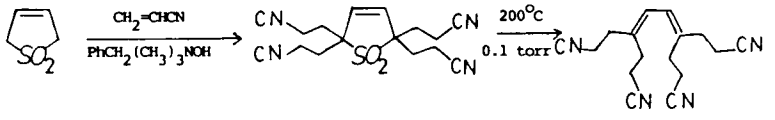
2-position of a 3-sulfolene is activated by the electron-withdrawing sulfone functionality and the C_3,C_4-double bond and hence is a good site for deprotonation and carbanion formation. Treatment of these carbanions with electrophiles should afford 2-substituted 3-sulfolenes.

Deuterium exchange at the α- and α'-position of 3-sulfolene occurs very fast under basic conditions to give tetradeuterated 3-sulfolene[12] which can be thermolyzed to 1,1,4,4-tetradeutero-1,3-butadiene (eq 8).[12a]



(eq 8)

On the other hand, the reaction of 3-sulfolene with acrylonitrile in the presence of a catalytic amount of an ammonium hydroxide gives tetrakis(cyanoethyl)-3-sulfolene which can be thermolyzed to the corresponding tetrasubstituted 1,3-diene **5** (eq 9).[13]



(eq 9)

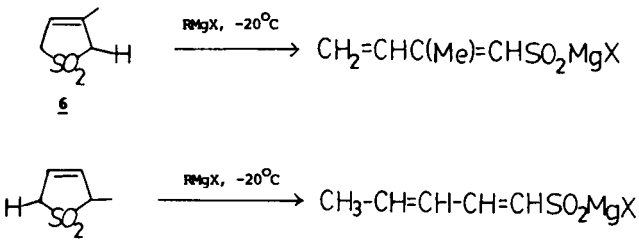
5

Despite these results, earlier attempts for the deprotonation and substitution of 3-sulfolenes with a strong base, such as BuLi,[14] LDA,[15] a Grignard reagent,[16] potassium *t*-butoxide[17] or sodium amide[18] failed to give the desired 2-substitued 3-sulfolenes. The major reason for this failure is the anionic cycloreversion process of the 2-carbanions leading to the thermodynamically more stable butadienyl

sulfinate (eq 10). Studies of the structures of the butadienyl sulfinates revealed that the double bond bearing the sulfinate group is in the *Z*-form.[19]

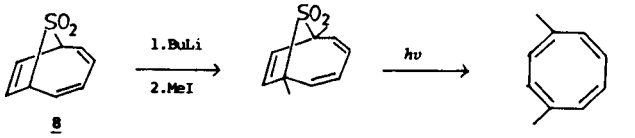
(eq 10)

Although the introduction of a 2-substituent in 3-sulfolene failed, the regioselectivity of deprotonation of unsymmetrically substituted 3-sulfolenes can be studied by examining the sulfinate products. It has been found that deprotonation occurs selectively at the 2-position of 3-methyl 3-sulfolene **6** and that deprotonation of 2-methyl-3-sulfolene **7** occurs selectively at the 5-position (eq 11).[20]



(eq 11)

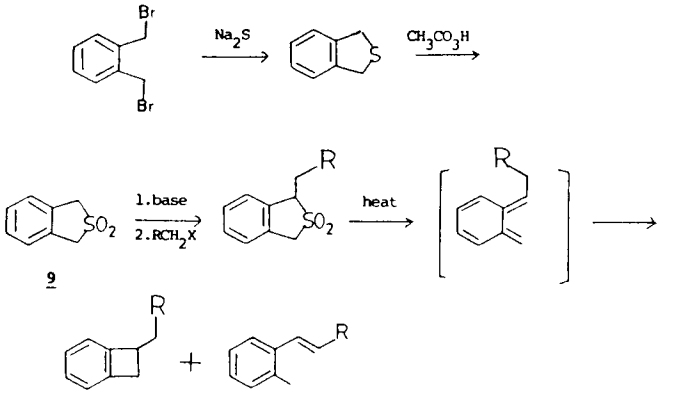
A successful example of deprotonation of **8** with BuLi and subsequent alkylation with MeI was reported in 1974 (eq 12).[21]



(eq 12)

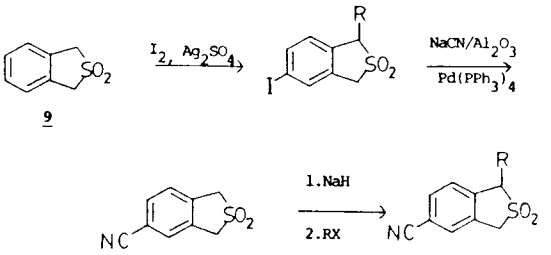
In a benzosulfolene molecule, the potential anionic cycloreversion of the α-anion is circumvented since the aromaticity of the benzene ring would be destroyed. Thus, deprotonation/alkylation reactions of benzo-3-sulfolene **9**,

readily prepared in two steps from bis(bromomethyl)benzene,[22] have been successful. The deprotonation can be achieved with NaH,[23] KH,[24] or BuLi[25] at -78°C or higher temperatures. The intermediate anion can be alkylated or dialkylated to give precursors to substituted orthoquinodimethanes (eq 13).



(eq 13)

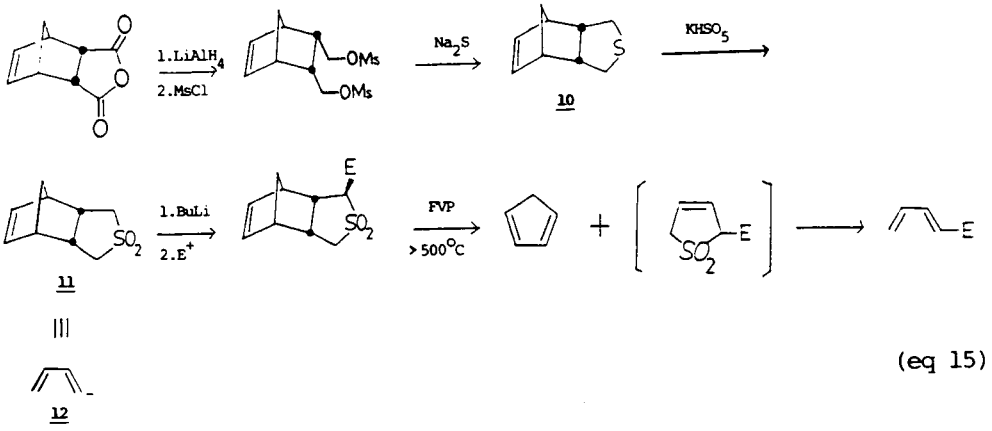
A cyano substituent on the benzene ring of benzo-3-sulfolene has a dominating effect on the regioselectivity of the reaction presumably through an electronic effect (eq 14).[26] Applications of this strategy in the synthesis of natural products will be discussed in Section V.



(eq 14)

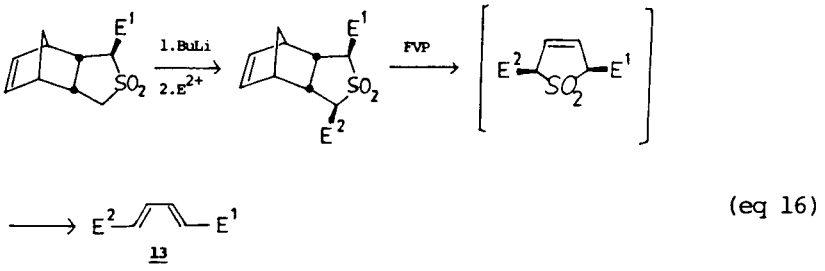
One possible way to avoid anionic cycloreversion of the 3-sulfolene α-anion is to mask the C_3-C_4 double bond during the deprotonation/alkylation stage. Using this idea, Bloch was able to deprotonate 4,4-dioxo-4-thiatricyclo[5.2.1.$0^{2,6}$]-8-decene **11** (a latent 3-sulfolene whose double bond is masked as

a cyclopentadiene adduct) with a strong base and further treated the anion with electrophiles including alkyl halides and carbonyl compounds.[27] The retro Diels-Alder reaction to remove the cyclopentadiene from these substituted products is achievable by flash pyrolysis at temperatures above 500°C. Since the intermediate 3-sulfolenes do not survive at such high temperatures, the substituted 1,3-dienes are obtained directly upon pyrolysis (eq 15). Thus, compound **11** can be regarded as a butadienyl 1-anion equivalent **12**.



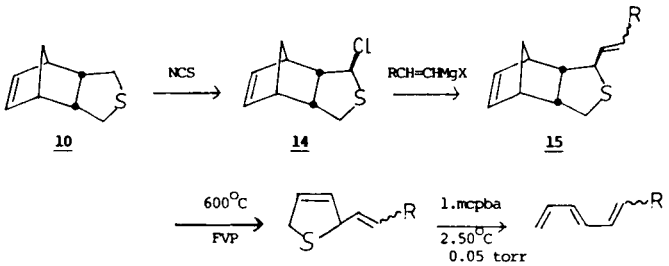
(eq 15)

In disubstitution reactions of the tricyclic sulfone **11**, the second deprotonation/substitution takes place at the α'-position regioselectively and at the *exo* face stereoselectively so that the two substituents are in a *cis*-form. Upon flash vacuum pyrolysis, *E*,*E*-1,3-dienes **13** are obtained (eq 16).[28]



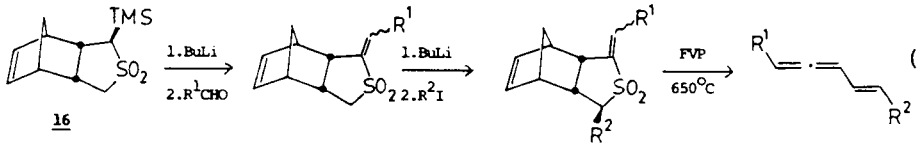
(eq 16)

The tricyclic sulfide **10**, can be chlorinated at the α-position with NCS and the intermediate chloride **14** can be substituted with many nucleophiles, for example, vinyl Grignard reagents. Thermolytic removal of cyclopentadiene followed by oxidation and medium-temperature thermolysis produces a 1-substituted 1,3,5-hexatriene.[29] If the tricyclic sulfides **15** are oxidized to sulfones before pyrolysis, the thermally unstable trienes can not be obtained cleanly (eq 17).



(eq 17)

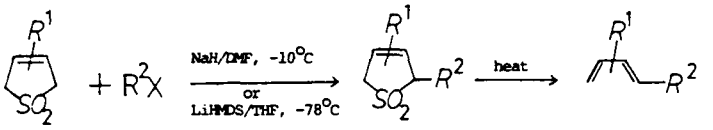
By a similar process, vinyl allenes can be prepared by deprotonation of a trimethylsilylated derivative **16** followed by treatment with an aldehyde and finally pyrolysis (eq 18).[30]



(eq 18)

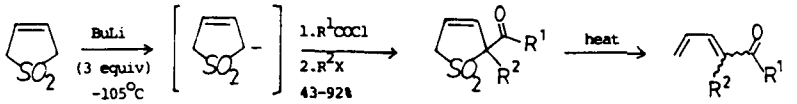
More recently, direct deprotonation/alkylation reactions have been found to be successful on unmasked 3-sulfolenes under carefully controlled conditions. The problem of anionic cycloreversion can be circumvented by placing electrophiles in the reaction mixture during the generation of the sulfolenyl anion because the ring-opening reactions of 3-sulfolene anions are slower than their substitution reactions with

electrophiles. Two practical conditions for the α-substitution of 3-sulfolenes using this strategy have been successful. One involves the use of a heterogeneous base system, NaH/DMF at -10°C,[31] where substituted 2-sulfolenes are routinely produced as side products due to a base-induced double bond isomerization. The other involves the use of a homogeneous base system, LiHMDS/HMPA/THF at -78°C, where double bond isomerizations are normally not observed (eq 19).[32] A serious limitation of these two processes is that electrophiles bearing acidic protons may compete with sulfolene for the base so that the reaction may become very complex. For example, the reaction of 3-sulfolene with acetyl chloride under the LiHMDS/HMPA condition gave only a complex mixture.



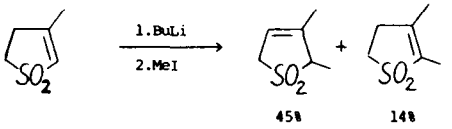
(eq 19)

It has been found that to lower the reaction temperature for deprotonation is another way to avoid anionic cycloreversion of the 3-sulfolenyl 2-anion. Thus, when 3-sulfolene is treated with n-BuLi at -105°C, the carbanion can be generated smoothly and remains stable for at least 15 min. Thus at this temperature, electrophiles bearing an acidic proton, for example, acyl chlorides, can be introduced without difficulty giving products which are precursors of the corresponding acylated dienes (eq 20).[33]



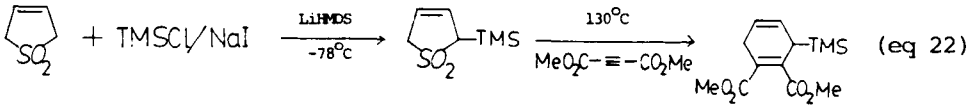
(eq 20)

2-Sulfolenes may also be deprotonated and methylated by this process to afford substituted 2- and 3-sulfolenes (eq 21).[34]



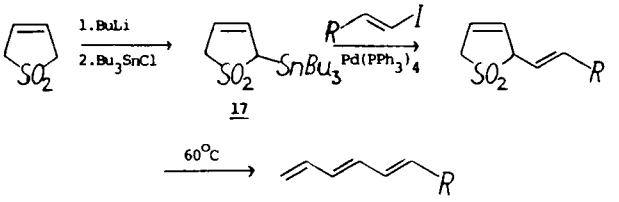
(eq 21)

Besides alkyl and acyl groups, the trimethylsilyl group can also be introduced into a 3-sulfolene *via* deprotonation/ substitution process.[35] Thermolysis of these silylated sulfolenes in the presence of a proper dienophile gives, without the isolation of the 1,3-dienes, the [4+2] cycloadducts (eq 22).



(eq 22)

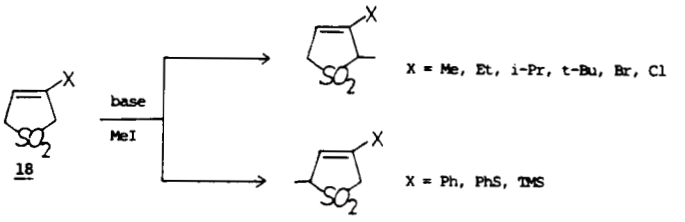
2-Tributyltin substituted 3-sulfolene **17** has been successfully prepared by a similar process.[36] Compound **17** may be couple with vinyl iodides in the presence of a catalytic amount of $Pd(PPh_3)_4$ to give, after thermolysis, substituted 1,3,5-hexatrienes (eq 23).



(eq 23)

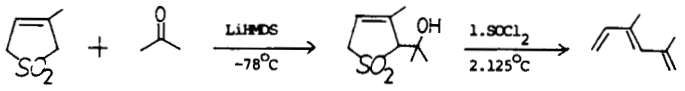
C_3-Unsymmetrically substituted 3-sulfolenes are normally deprotonated and alkylated with very high regioselectivity.

The deprotonation/alkylation reaction of **18** (X = Me, Et, i-Pr, t-Bu, Br, or Cl) using either BuLi, at -105°C or LiHMDS, at -78°C takes place exclusively at the 2-position. Whereas for other substituents (**18**, X = Ph, PhS, TMS) the reaction takes place exclusively at 5-position (eq 24). Apparently, the regioselectivity is influenced more by electronic effects than by steric effects.[37] Because of the high regioselectivity, 3-methyl-3-sulfolene **18** (X = Me) serves as a synthetic equivalent of the isoprenyl 1-anion.



(eq 24)

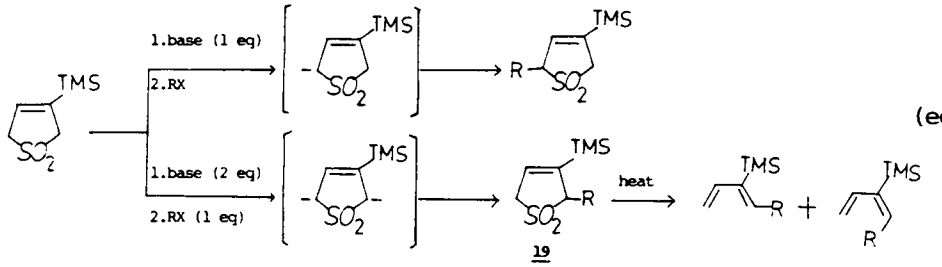
The deprotonation/alkylation reaction of 3-sulfolenes can be extended to hydroxyalkylation by treating the sulfolenyl α-anion with a ketone or an aldehyde. The intermediate alcohols of these reactions can further be dehydrated and thermolyzed to give substituted 1,3,5-hexatrienes (eq 25).[38]



(eq 25)

Normally, the deprotonation/alkylation reaction of 3-(trimethylsilyl)-3-sulfolene occurs at the 5-position. However, the regioselectivity can be reversed by proper modification of the reaction conditions. Generation of the sulfolenyl α,α'-dianion followed by alkylation at the more reactive site produces 2-substituted derivatives. Thermolysis

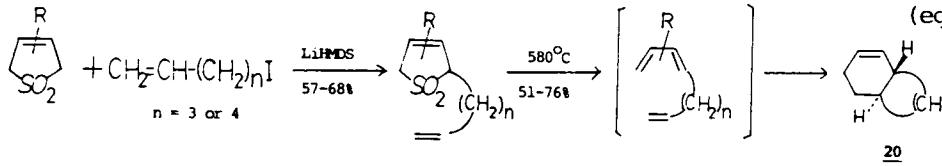
of a 3-(trimethylsilyl)-2-alkyl-3-sulfolene **19** gives a mixture of *E,E* and *E,Z* isomers of the corresponding 1,3-dienes (eq 26).[39]



(eq 26)

19

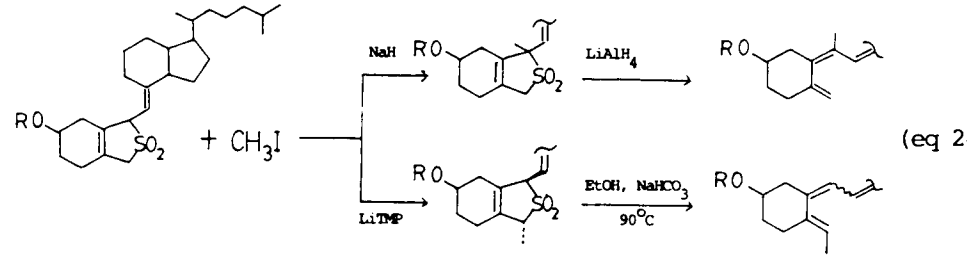
Alkylation of a substituted 3-sulfolene with an alkenyl iodide affords a precursor suitable for an intramolecular Diels-Alder reaction. Subsequent high temperature thermolysis of the alkenylated 3-sulfolene gives the bicyclic system **20** (eq 27). Hydroindens and hydronaphthalenes are efficiently prepared by this reaction sequence.[40]



(eq 27)

20

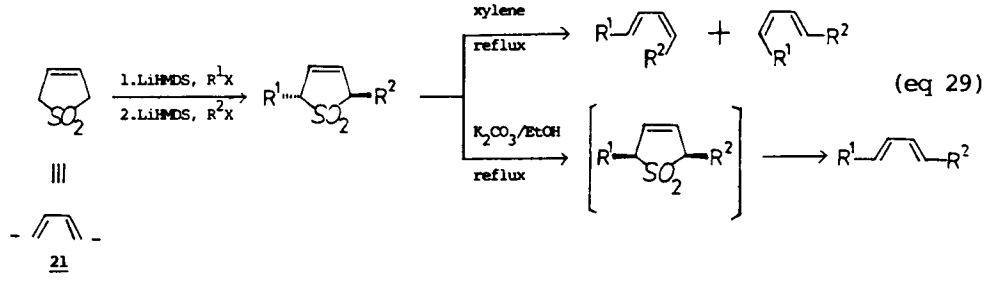
By using different bases, 2-substituted 3-sulfolenes may in some cases be deprotonated and alkylated at different positions. Thus, the SO_2 adduct of vitamin D can be selectively alkylated at the more substituted α-position by



(eq 28)

using NaH as the base, or at the less substituted α-position by using LiTMP as the base.[41] These alkylated compounds are thermolyzed to give the corresponding vitamin D derivatives (eq 28).

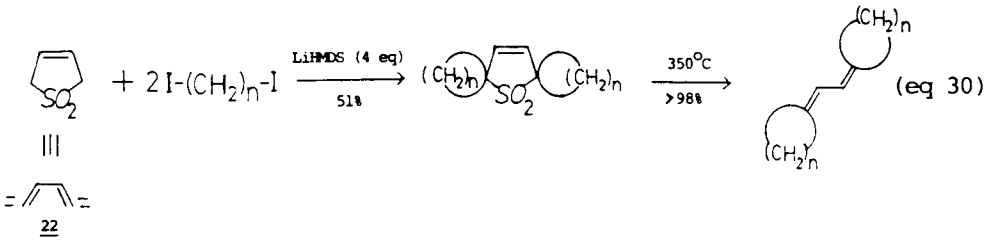
Sequential dialkylation of 3-sulfolene gives 2,5-dialkylated derivatives regioselectively. In this regard, 3-sulfolene serves as a butadienyl 1,4-dianion equivalent 21. The stereochemistry of the two alkyl groups are primarily *trans*, probably because the second alkylation is kinetically controlled. Direct thermolysis of the dialkylated products yields mainly *E*,*Z*-dienes.[32a] On the other hand, thermolysis of the *trans*-dialkylated 3-sulfolenes in the presence of carbonate yields selectively the *E*,*E*-dienes.[32b] Presumably, the *trans*-isomers are converted into the *cis*-isomers rapidly under these conditions and the *cis*-isomers are thermolyzed more easily than the *trans*-isomers (eq 29).



(eq 29)

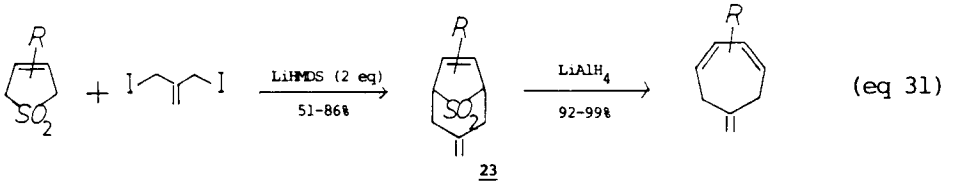
21

One-pot multialkylation reactions of 3-sulfolene have been reported. For example, 3-sulfolene can be transformed into a dispirosulfone by treatment with 4 moles of LiHMDS and 2 moles of an α,ω-diiodoalkane (eq 30). These dispirosulfones are thermolyzed to the corresponding bis(cycloalkylidene)-ethanes. Thus, 3-sulfolene serves also as butadienyl 1,1,4,4-tetraanion equivalent 22.[42]



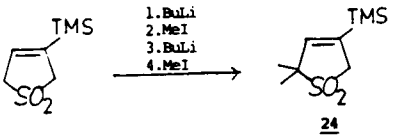
22

Attempted dialkylative cyclization of 3-sulfolene with α,ω-diiodopropane or diiodobutane to give bridged bicyclic sulfolenes failed. However, 2-alkylidene 1,3-dihalopropane works as a good cyclizative dialkylating reagent.[43] Bridged bicyclic sulfolenes **23** can be obtained by treatment of 3-sulfolenes with 1 mole of 2-alkylidene 1,3-diiodopropane and two moles of LiHMDS. Treatment of **23** with $LiAlH_4$ leads to the seven-membered carbocyclic dienes (eq 31). Thermolytic removal of SO_2 results in the formation of double bond isomers due to a facile 1,5-hydrogen shift.

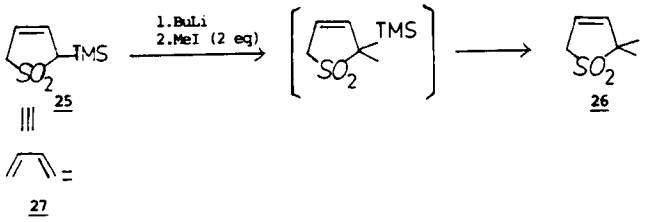


23

Although dialkylation of 3-sulfolene takes place sequentially at the 2- and 5-positions, a trimethylsilyl substituent has a dramatic influence on the regioselectivity of the second alkylation. 3-(Trimethylsilyl)-3-sulfolene is methylated twice at the 5-position to give the 5,5-dimethyl derivative **24** (eq 32).[39] Treatment of 2-(trimethylsilyl)-3-sulfolene **25** with one mole of base and two moles of alkylating agent gives 2,2-dialkyl-3-sulfolene **26** (eq 33).[44] These examples demonstrate the use of silylated 3-sulfolenes as butadienyl 1,1-dianion equivalents **27**.



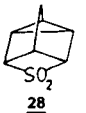
24 (eq 32)



25 26 (eq 33)

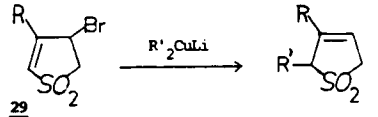
27

The deprotonation/substitution reactions is successful for unstrained 3-sulfolene systems, however, attempted deprotonation/alkylation reactions of strained sulfolene systems **23** or **28** resulted in the recovery of the starting materials.[45]

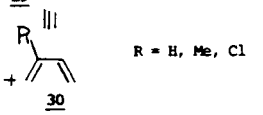


28

A completely different approach to the preparation of 2-substituted 3-sulfolenes involves the allylic nucleophilic substitution of 4-brominated 2-sulfolenes with alkyl or aryl cuprates (eq 34). In this approach, the 4-bromo-2-sulfolenes **29** react as butadienyl cation equivalents **30**.[46] The regioselectivity of nucleophilic substitution of **29** is effected by the substituents and the nature of the organocuprate reagents. In some cases, direct substitution reactions may occur.

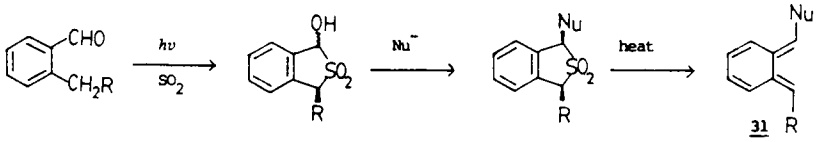


29 (eq 34)



30

If a benzosulfolene contains a leaving group at the α-position, direct nucleophilic substitution at C-2 takes place.[47] Substituted orthoquinodimethanes **31** are prepared by this process (eq 35).

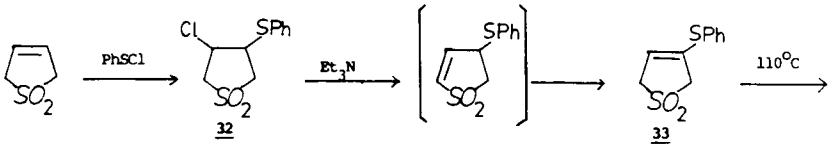


(eq 35)

III. PREPARATION OF 3-SULFOLENES *via* β-POSITION FUNCTIONALIZATION

The deprotonation/alkylation reaction provides an entry to 2-substituted 3-sulfolenes which serve as precursors to 1-substituted 1,3-dienes. On the other hand, 3-substituted 3-sulfolenes, the precursors to 2-substituted 1,3-dienes, can be prepared by an addition/elimination process.

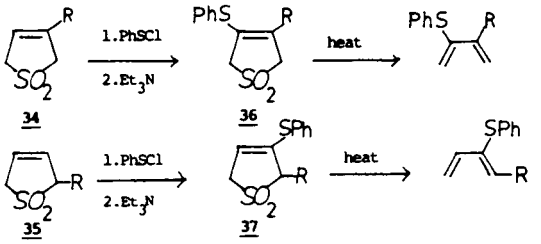
The addition of phenylsulfinyl chloride to 3-sulfolene yields 3-chloro-4-phenylthiosulfolane **32** which upon treatment with Et_3N gives the substituted 3-sulfolene **33**. Thermolysis of this compound gives 2-phenylsulfenyl-1,3-butadiene, a reactive diene for Diels-Alder reaction (eq 36).[48] It has been found that the two-step process can be accomplished in one-pot by a sequential treatment with phenylsulfinyl chloride and Et_3N.[49]



(eq 36)

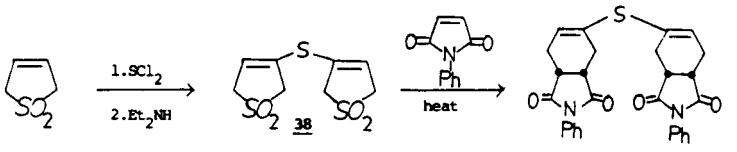
2- Or 3-substituted 3-sulfolenes **34** and **35** can be treated

similarly to give the corresponding 3-arylthio-3-sulfolenes **36** and **37**, respectively (eq 37).[50]



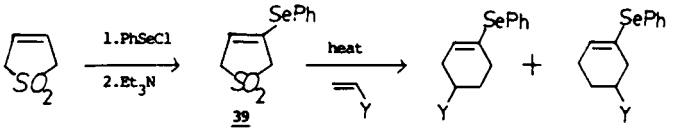
(eq 37)

Based on the same strategy, a sulfur-bridged disulfolene **38** was prepared by reacting 3-sulfolene with sulfur dichloride.[51] The bis-diene product is a potential intermediate to sulfur-bridged polyimides (eq 38).



(eq 38)

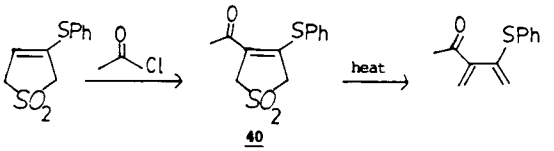
Treatment of 3-sulfolene sequentially with phenylselenyl chloride and triethylamine gives 3-(phenylselenyl)-3-sulfolene **39**. 2-(Phenylselenyl)-1,3-butadiene obtained by its thermolysis shows moderate regioselectivity in the Diels-Alder reactions with unsymmetric dienophiles (eq 39).[52]



(eq 39)

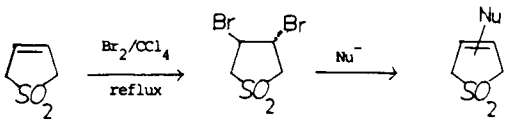
Owing to the electron-withdrawing effect of the sulfone functionality, the nucleophilicity of the double bond of a 3-sulfolene is low. Attempted Friedel-Craft acylation reactions of 3-sulfolene or 3-(trimethylsilyl)-3-sulfolene

were unsuccessful. However, if a phenylthio group is attached to the 3-sulfolene, the acetylation reaction proceeds smoothly giving 3-(phenylthio)-4-acetyl-3-sulfolene **40**. The Diels-Alder reaction and the regioselectivity of the corresponding diene have been examined (eq 40).[53]



40 (eq 40)

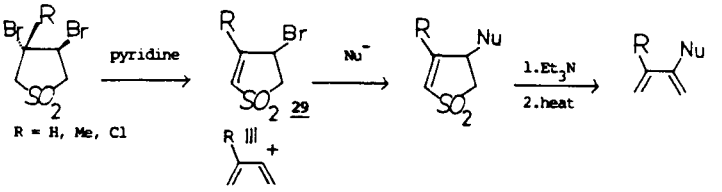
Addition reactions of bromine to 3-sulfolenes are in general achieved at high temperatures such as reflux in $CHCl_3$ or in CCl_4. The resulting dibromosulfolanes are versatile intermediates in the synthesis of 3-heterosubstituted 3-sulfolenes (eq 41).[54]



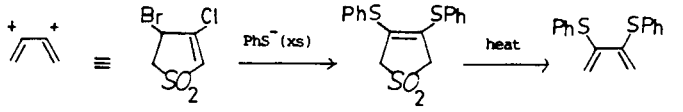
(eq 41)

On the other hand, dibromosulfolanes can be partially debrominated to give 4-bromo-2-sulfolenes **29**.[55] When these compounds are treated with nucleophiles, different reactions may take place.[46,56] The mode of reaction depends on the nature of the nucleophile and the original substituent on the bromosulfolene. Alkylcuprate nucleophiles normally result in allylic substitution (eq 34), whereas arylcuprate and heteroatom nucleophiles normally give direct substitution products which can be treated with a base or an excess of the nucleophile to give the corresponding 3-sulfolenes. This process provides an efficient route to the preparation of

2,3-dihetero substituted 1,3-dienes (eq 42, 43).[57]

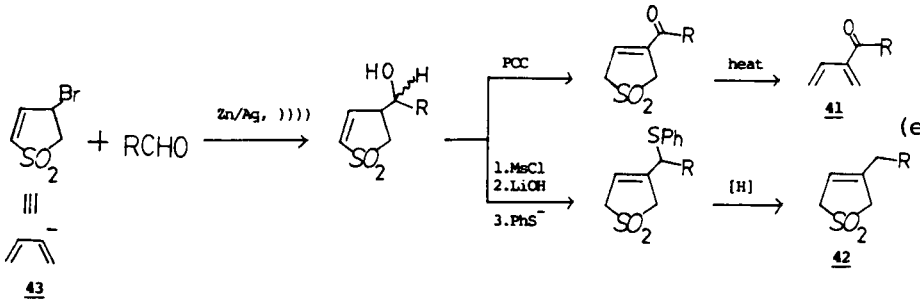


(eq 42)



(eq 43)

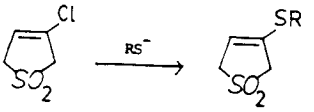
Not only can nucleophiles be introduced into the 2- or 4-positions of 4-bromo-2-sulfolene, but electrophiles may also be introduced. Ultrasonically promoted allylzincation of 4-bromo-2-sulfolene in the presence of an aldehyde or a ketone gives the 4-hydroxyalkylated 2-sulfolene.[45,58] These intermediates can be converted into acylated or alkylated 3-sulfolenes via chemical manipulation and ultimately give the 2-substituted 1,3-dienes **41** and **42** (eq 44). Therefore, 4-bromo-2-sulfolene serves also as a 1,3-butadienyl 2-anion equivalent **43**.



(eq 44)

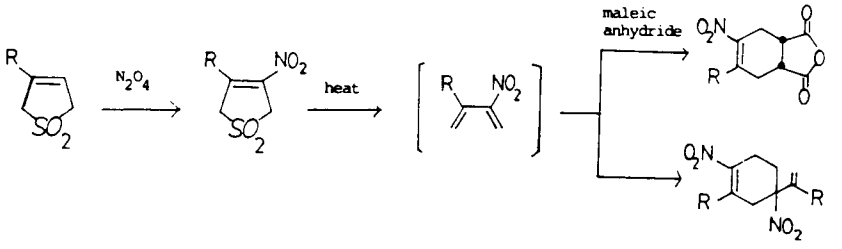
Chloroprene sulfone has been reported to react with sulfur nucleophiles to give alkylthio or arylthio substituted 3-sulfolenes (eq 45).[59] However, double bond isomerization of these products to 3-thiolated 2-sulfolenes is a serious side

reaction.[45]



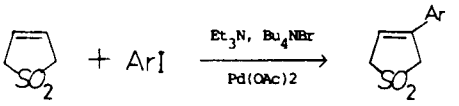
(eq 45)

3-Nitro-3-sulfolenes can be prepared from 3-sulfolenes by treatment with N_2O_4. Thermolysis of these nitrosulfolenes gives the corresponding nitro-1,3-dienes which may be reacted directly with electron-deficient dienophiles to give [4+2] cycloadducts (eq 46). Thus, the isolation of the unstable nitrodiene is avoided.[60]



(eq 46)

Recently, direct coupling of 3-sulfolene with iodoarenes have been found to take place readily in the presence of palladium catalyst (eq 47).[61] These 3-aryl-3-sulfolenes are precursors of 2-aryl-1,3-butadienes.

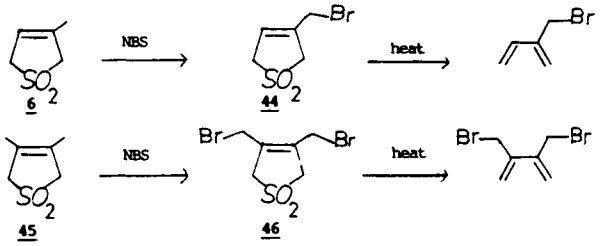


(eq 47)

IV. PREPARATION OF 3-SULFOLENES *via* BRANCHED-CHAIN MODIFICATION

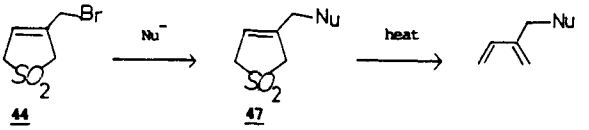
A variety of functionalized 1,3-dienes can be obtained indirectly from substituted 3-sulfolenes by branched chain

modifications. For example, allylic bromination of isoprenyl sulfone **6** followed by thermolysis gives 2-(bromomethyl)-1,3-butadiene *via* the intermediate sulfone **44**.[62] Similarly, 3,4-dimethyl-3-sulfolene **45** can be brominated and thermolyzed to give 2,3-bis(bromomethyl)-1,3-butadiene *via* the intermediate sulfone **46** (eq 48).[63]



(eq 48)

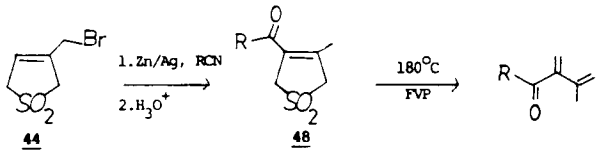
The bromomethylated 3-sulfolenes **44** and **46** can also serve as precursors to other substituted dienes. The bromine atom on **44** can be replaced with a halide or phenylsulfide by direct nucleophilic substitution (eq 49).[64] The product from the reaction of 3-bromomethyl-3-sulfolene with KCN was originally incorrectly assigned to be 3-methyl-4-cyano-3-sulfolene[64b] but was later proved to be 3-(cyanomethyl)-3-sulfolene (**47**, Nu = CN), the direct substitution product.[64c]



(eq 49)

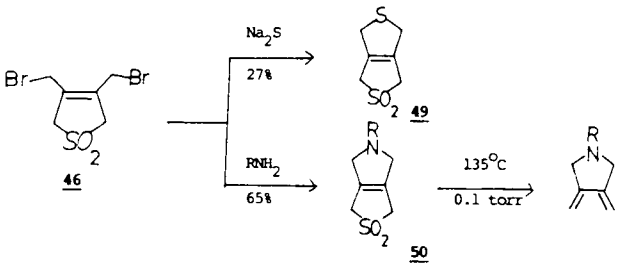
In addition to nucleophilic substitution, the bromomethylated sulfolene **44** can be converted into an organozinc species by treatment with Zn/Ag. Generation of this organozinc reagent in the presence of nitriles gives mainly the 3-acylated 4-methyl-3-sulfolenes **48** which are precursors

of 2-acylated 1,3-dienes (eq 50).[65]



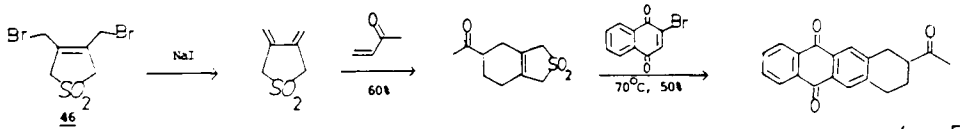
44 48 (eq 50)

3,4-Bis(bromomethyl)-3-sulfolene **46** can undergo a double nucleophilic substitution with sodium sulfide or a primary amine to give bicyclic sulfolenes **49** and **50** which are precursors of the *ortho*-bismethylene heterocycles (eq 51).[66] The relative basicity versus nucleophilicity of these nucleophiles affects the success of these double substitution reactions. Strong nucleophiles with low basicity work well, whereas weak nucleophiles give no reaction, and nucleophiles with high basicity cause elimination and polymerization reactions.[67]



46 49 50 (eq 51)

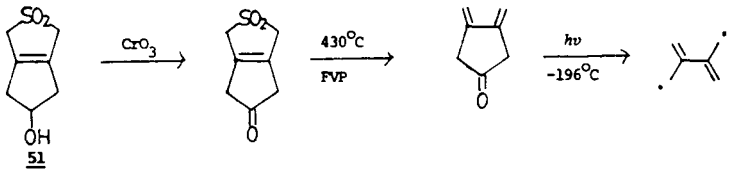
Treatment of 3,4-bis(bromomethyl)-3-sulfolene **46** with sodium iodide gives 3,4-bismethylenesulfolane. Although attempted thermolysis of this compound does not yield the desired 2,2'-bisallyl diradical species,[68] it serves as an



46 (eq 52)

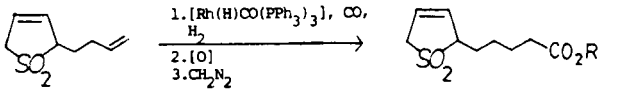
equivalent to the diradical *via* a sequential cycloaddition reaction (eq 52).[69]

The carbocyclic ring of a cyclopentenol-fused 3-sulfolene **51** can be modified by a sequence of oxidation, thermolysis, and photolysis to generate the 2,2'-bisallyl diradical (eq 53).[70]



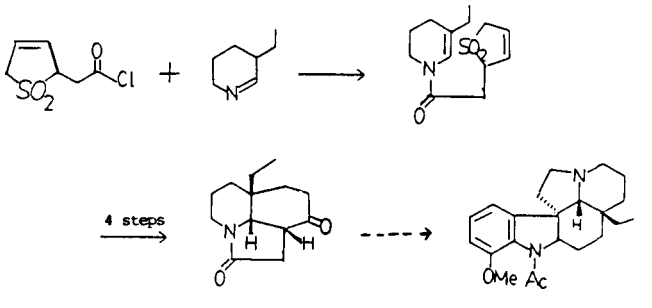
(eq 53)

A 3-sulfolene bearing a terminal olefinic substituent can be treated under catalytic carbonylation conditions without touching the sulfolene functionality so that the precursor of a terminal dienyl ester is smoothly prepared (eq 54).[71]



(eq 54)

Hexa-3,5-dienoic acid chloride masked as a 3-sulfolene can, after chemical transformations, produce a precursor for the intramolecular Diels-Alder reaction in the construction of polycyclic compounds.[72] This strategy has been utilized in a



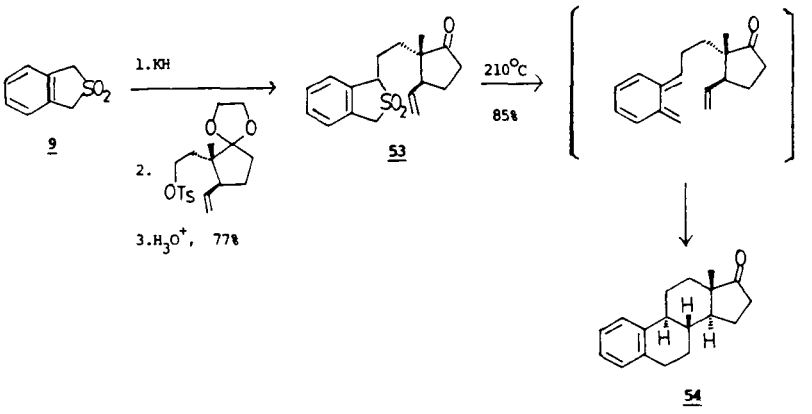
52

(eq 55)

formal synthesis of aspidospermine **52** and the total synthesis of other natural products (eq 55).

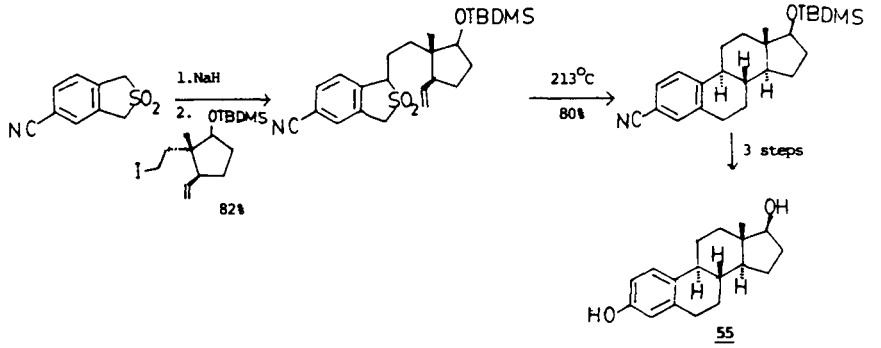
V. APPLICATION OF SUBSTITUTION REACTIONS OF 3-SULFOLENES IN THE SYNTHESIS OF NATURAL PRODUCTS

The substitution reactions of 3-sulfolenes and benzo-3-sulfolenes have been widely employed in the total synthesis of natural products. Nicolaou[24] utilized benzo-3-sulfolene **9** to obtain **53** and subsequently used the intramolecular Diels-Alder reaction as the key step in the total synthesis of estra-1,3,5(10)-trien-17-one **54** (eq 56).



(eq 56)

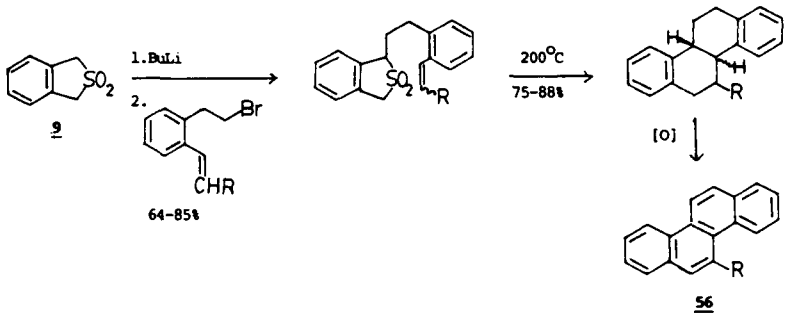
The same strategy was also used by Oppolzer[26] in the synthesis of optically active (+)-estradiol **55** where m-cyanobenzo-3-sulfolene was used as the starting material.



(eq 57)

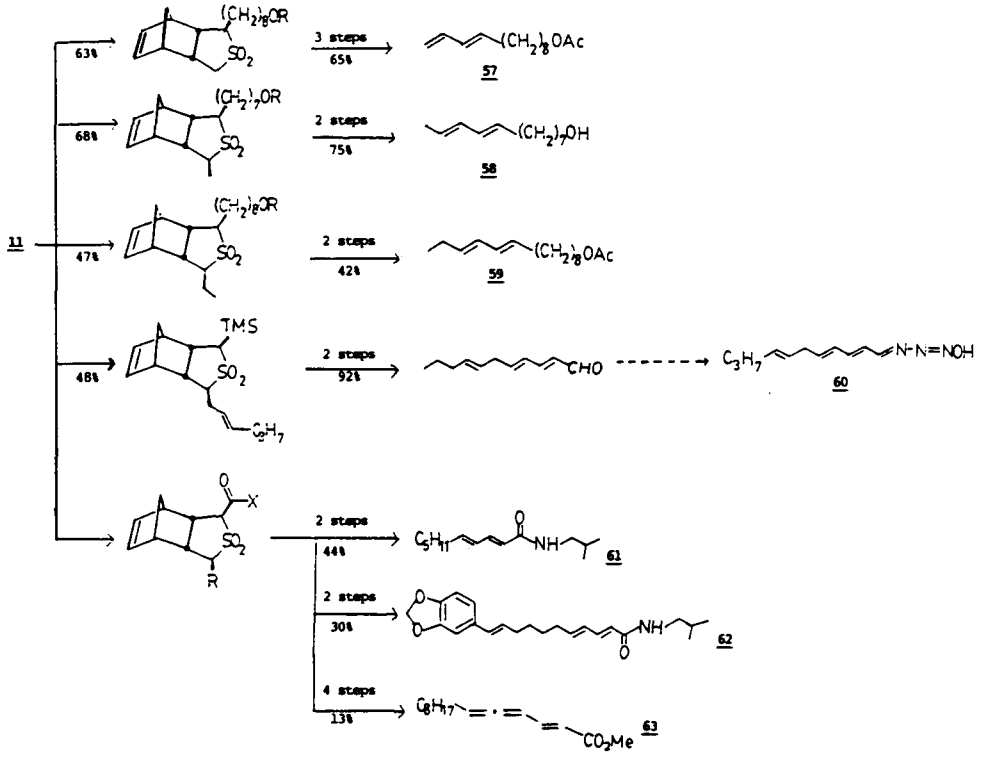
The regioselective deprotonation/alkylation and the stereoselective intramolecular Diels-Alder reaction ensures the success of the total synthesis (eq 57).

Polycyclic aromatic hydrocarbons such as 5-substituted chrysenes **56** were prepared efficiently via benzosulfolene alkylation and intramolecular [4+2] cycloaddition (eq 58).[73]



(eq 58)

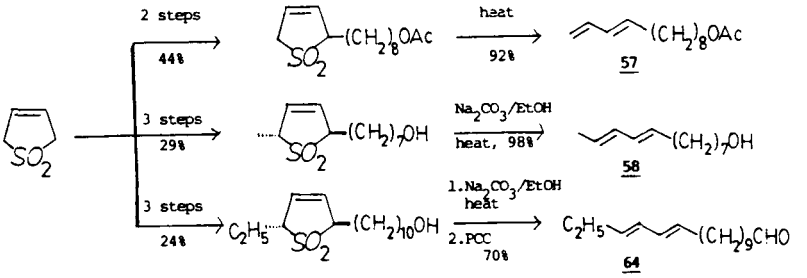
Scheme II



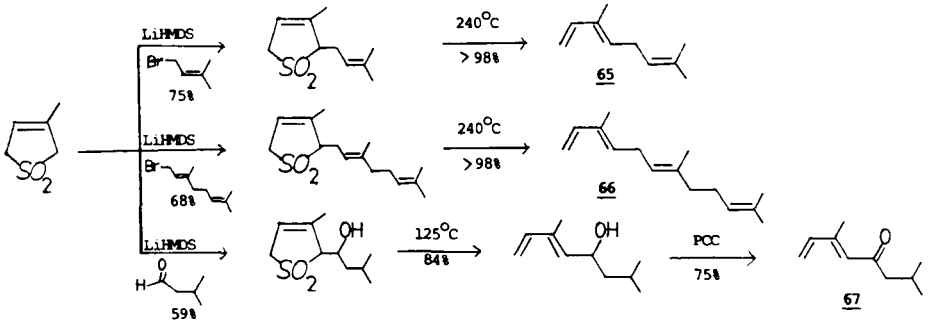
A number of insect pheromones[27,28] and some other natural products[74] containing substituted 1,3-diene functionalities such as red bollworm moth pheromone **57**, codling moth pheromone **58**, light-brown apple moth pheromone **59**, WS-1228A **60**, pellitorine **61**, pipercide **62**, and bean beetle pheromone **63** have been conveniently prepared via deprotonation/alkylation reactions of sulfone **11** (Scheme II).

The direct deprotonation/alkylation reaction of 3-sulfolene provides an even more efficient route to the insect pheromones **57**, **58**, and cabbage webworm pheromone **64** (Scheme III).[75]

Scheme III



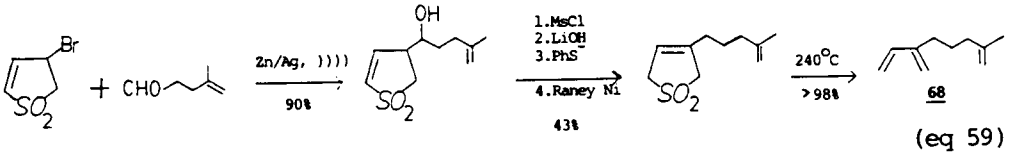
Scheme IV



3-Methyl-3-sulfolene, an isoprenyl anion equivalent, has been utilized in the synthesis of some open-chain terpenoid

natural products including β-ocimene **65**, α-farnesene **66**,[76] and (*E*)-tagetone **67**[38] using the same strategy (Scheme IV).

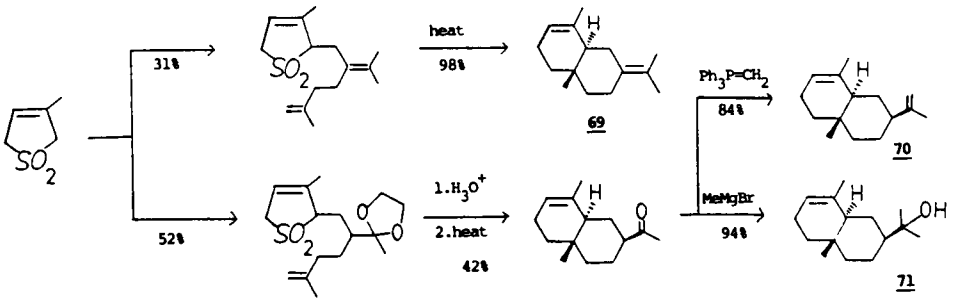
Substitution at the 3-position of 3-sulfolene by way of allylzincation of 4-bromo-2-sulfolene provides a good route to α-myrcene **68** which contains a 2-substituted 1,3-butadiene moiety (eq 59).[45]



(eq 59)

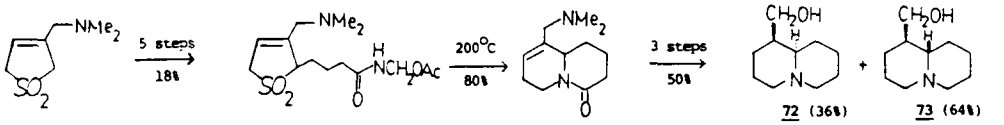
Since the introduction of a long chain terminal alkenyl group onto 3-sulfolenes is known to produce intermediates for the construction of bicyclic and multicyclic hydrocarbons *via* intramolecular Diels-Alder reaction, deprotonation/alkylation reactions of 3-sulfolenes with a properly chosen alkenyl halide should be useful in the total synthesis of bicyclic natural products. According to this strategy, sesquiterpenes of eudesmane family such as selina-4,7(11)-diene **69**,[77] α-selinene **70**, and α-eudesmol **71**[45] have been synthesized efficiently (Scheme V).

Scheme V



Quinolizidine alkaloids lupinine 72 and *epi*-lupinine 73

were synthesized from a substituted 3-sulfolene by way of deprotonation/alkylation and a subsequent intramolecular hetero Diels-Alder reaction (eq 60).[78]



(eq 60)

VI. CONCLUSION

By properly controlling the reaction conditions, 3-sulfolenes can be regioselectively deprotonated and substituted at either the 2- or 5-position with electrophiles to give alkylated, acylated, hydroxyalkylated or silylated 3-sulfolenes. In this manner, 3-sulfolenes are synthetic equivalents to 1,3-butadienyl 1-anions. Regioselective sequential 2,5-dialkylation, 2,2,5-trialkylation, and 2,2,5,5-tetraalkylation reactions provide entries to the preparation of 1,4-disubstituted, 1,1,4-trisubstituted and 1,1,4,4-tetrasubstituted 1,3-dienes. Therefore, 3-sulfolene serves as synthetic equivalents to 1,3-dienyl 1,4-dianion, 1,1,4-trianion, and 1,1,4,4-tetraanion equivalents. The geminal dialkylation of 2-(trimethylsilyl)-3-sulfolene yields 2,2-dialkyl-3-sulfolenes which are precursors of 1,1-disubstituted 1,3-butadiene. This demonstrates that, by proper modifications, 3-sulfolene can also serve as a 1,3-butadiene 1,1-dianion equivalent. The allylzincation of 4-bromo-2-sulfolene in the presence of aldehydes followed by PCC oxidation of the 4-hydroxyalkylated 2-sulfolenes allows the formation of 3-acylated 3-sulfolenes, whereas a sequence

of elimination, Michael addition, desulfuration of the 4-hydroxyalkylated 2-sulfolenes allows the formation of 3-alkylated 3-sulfolenes. Hence, 4-bromo-2-sulfolene serves as a 1,3-butadienyl 2-anion equivalent. On the other hand, nucleophilic substitution reactions of 4-bromo-2-sulfolenes lead to 2- or 4-substituted 3-sulfolenes, so that 4-bromo-2-sulfolenes serve as butadienyl cation equivalents. Since 4-brominated 2-sulfolenes are readily available from 3-sulfolenes by a bromine addition-partial dehydrobromination process, by proper combinations of the deprotonation/ substitution reactions of 3-sulfolenes and the nucleophilic substitution of 4-brominated 2-sulfolenes, one would be able to prepare a wide variety of stable precursors of substituted 1,3-dienes. Unfortunately, good procedures to attach an oxygen or nitrogen functionality to a 3-sulfolene by substitution reactions are lacking. This is a limitation of this strategy.

The major advantages of preparation of substituted 1,3-dienes by way of their masked form in sulfolenes are: (1) the 3-sulfolenes may be used directly as the dienes under thermolytic conditions especially in Diels-Alder reactions, so that isolation of the unstable dienes is unnecessary; (2) the relative stability of the sulfolenes makes them easier to purify and to store than the corresponding 1,3-dienes; (3) the stereospecificity of the SO_2 extrusion from sulfolenes assures very high purity of the configurational isomer of the 1,3-dienes; (4) modification of the substituents of a sulfolene is convenient so that various substituted 1,3-dienes may be prepared readily. This strategy should be very useful in organic synthesis.

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