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Synthesis and applications of sulpholenes

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Abstract

The synthesis and applications of sulpholenes are discussed.

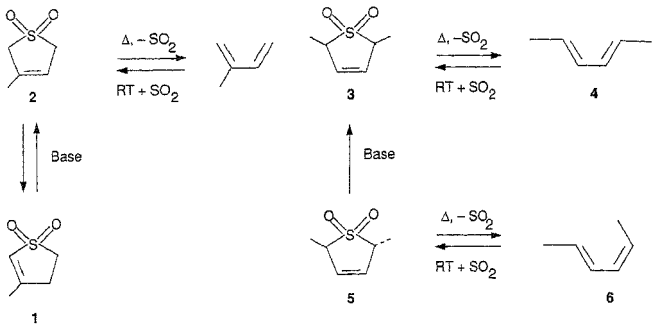
Key words : Substituted sulpholenes, synthetic applications.

Conjugated dienes are versatile building blocks in the synthesis of organic natural products, especially as a component of the Diels–Alder reaction in the synthesis of 6-membered cyclic compounds. In addition, conjugated dienes are often encountered in the insect sex pheromones and other natural products as well. Recently, a number of new methods for the stereoselective synthesis of conjugated dienes have been developed utilising either organometallic species[1] or the thermal ring opening of cyclobutenes[2] and sulpholenes[3].

The $C_{2,5}$- or $C_{2,3}$- dihydrothiophene-1, 1-oxide (3- or 2-sulpholene, respectively) serves as masked 1,3-butadienes, since the interconversion between 2-sulpholenes (**1**), 3-sulpholenes (**2**) and the corresponding butadienes requires only mild reaction conditions. The reaction of 1,3-butadienes with liquid sulphur dioxide at room temperature normally gives 3-sulpholene in good yield. The thermal extrusion of SO_2 from 3-sulpholene takes place at 100–120°C to afford the corresponding dienes (Scheme 1). Most importantly, these SO_2 addition and extrusion reactions are stereospecific *via* a concerted suprafacial disrotatory process. Thus, the thermal extrusion from *cis*-2, 5-disubstituted-3-sulpholene (**3**) leads to *trans-trans*-1,3,-butadiene (**4**) whereas the *trans*-isomer of sulpholene (**5**) leads to *cis-trans*-isomer of diene (**6**). For 3-sulpholenes bearing functional groups which are sensitive to heat the stereoselective removal of SO_2 from them can be achieved by treatment with either $LiAlH_4$ at room temperature[4] or ultrasonically dispersed potassium at 0°C in the presence of a proton source[5].

Thus, the general stability of 3-sulpholenes in acidic and neutral conditions, the ease of removal of SO_2 and the stereospecificity of the extrusion reaction make them excellent precursors to the corresponding 1,3-butadienes.

The intent of this paper is to cover recent work in the area of synthetic utility of sulpholenes and their applications in the total synthesis of natural products.



SCHEME 1.

The desired substituted sulpholenes can be obtained through the synthesis of 2,5-dihydrothiophenes followed by oxidation with *m*-chloroperbenzoic acid (mcpba) or any other reagent. Alternatively, the alkylations of sulpholenes or bromo-sulpholenes leads to the desired substituted derivatives.

1. 2,5-Dihydrothiophenes

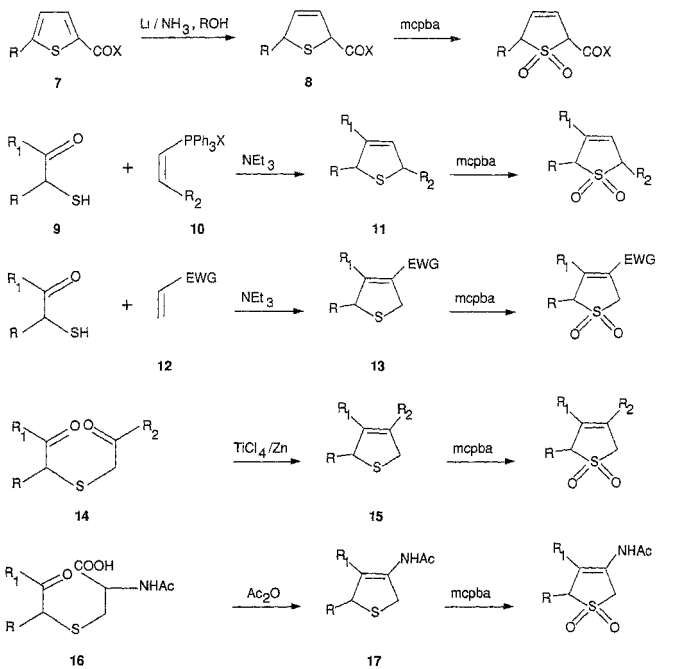
Synthetic approaches of 2,3- and 2,5-dihydrothiophenes have been reviewed in 1982[6]. Therefore, only salient features of prominent routes are discussed below (Scheme 2).

The thiophenes having electron-withdrawing group at C_2 position (**7**) undergo clean Birch reduction to the corresponding dihydro derivatives (**8**). An alternate strategy involving the addition of α-mercaptyl–carbonyl compound (**9**) to a vinyl phosphonium salt (**10**) followed by an intramolecular Wittig reaction leads to the construction of 2,5-dihydrothiophene skeleton (**11**). Using similar strategy involving Michael–Aldol reactions between the compound **9** and α, β-unsaturated carbonyl compound (**12**, EWG=COOEt, $COCH_3$ or CN) leads to dihydrothiophene (**13**). Alternatively, low-valent titanium-induced intramolecular reductive carbonyl coupling reaction of di-β-carbonyl-sulphide (**14**) has been successfully employed in the synthesis of highly substituted 2,5-dihydrothiophene (**15**). The intramolecular reaction of sulphide **16** obtained from N-acetylcysteine has been employed in the synthesis of 3-acetylamino-2,5-dihydrothiophene (**17**).

The dihydrothiophenes **8**, **11**, **13**, **15** and **17** have been oxidized with mcpba to the corresponding 3-sulfolenes which on subsequent thermolysis yield the respective dienes.

2. Alkylations of 3-sulpholenes: Substitution at C_2 and C_5 positions

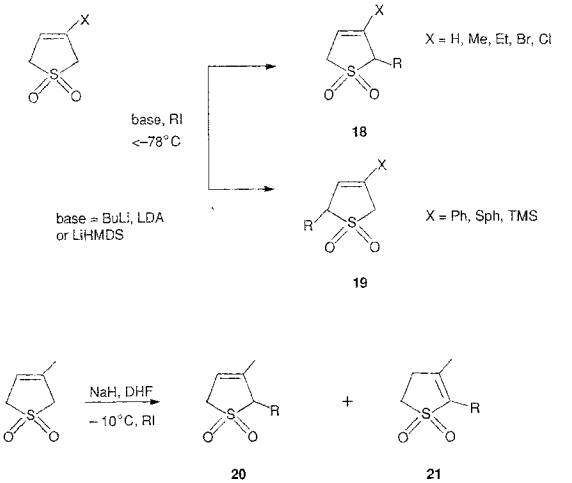
The C_2 and C_5 positions of 3-sulpholenes are activated by the electron-withdrawing sulphone functionality and hence 3,4-double bond are good sites for deprotonation and carbanion formation which on treatment with electrophile yield substituted sulpholenes. The controlled regioselective alkylations of C_3-unsymmetrically substituted sulpholenes can be achieved



SCHEME 2.

depending on the nature of the substituent present at C_3 position to yield either 2-substituted (**18**) or 5-substituted (**19**) derivatives (Scheme 3)[6,7].

The problem in the manipulation of 3-sulpholenes is their tendency to undergo ring opening on treatment with basic reagents at ~ –20°C (Scheme 4)[8]. This problem of anionic cycloreversion can be circumvented by placing strong electrophile (alkyl iodide or bromide) in the reaction mixture during the generation of sulpholenyl anion with BuLi, LDA or LiHMDS at < –78°C because in this condition the ring opening reactions of 3-sulpholene anions are slower than their substitution reactions with electrophiles. The sulpholenyl anion generated with BuLi remains stable at least for 15 minutes at –105°C. However, the use of heterogeneous base system, namely, NaH/DMF at –10°C has also been employed for alkylation

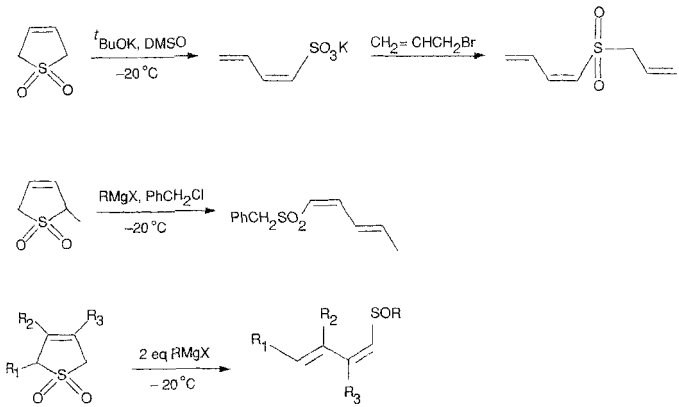


SCHEME 3.

of 3-sulpholenes[9] which yielded 2-alkyl-3-sulpholene (**20**) along with 2-alkyl-2-sulpholene (**21**).

The deprotonation/alkylation reactions of 2,3-benzothiophene-S,S-dioxide (**22**) can be achieved more comfortably in the presence of NaH, KH or BuLi at -78°C or higher temperature (Scheme 5). In this case, the potential anionic cycloreversion of the α-anion is circumvented since the aromaticity of the benzene ring would be destroyed. The alkyl derivatives (**23**) are excellent precursors to substituted orthoquinodimethanes (**24**)[10]. Alternate method of avoiding anionic cycloreversion of the 3-sulpholene-α-anion is to protect the $C_{3,4}$- double bond before the deprotonation/alkylation stage. Thus, alkylation of 4,4-dioxa-4-thia-tricyclo [5.2.1.$0^{2,6}$]-8-decene (**25**)[11] is straight forward to obtain stereospecific alkyl derivative (**26**) by the attack of electrophile from exoface which on vacuum pyrolysis under fairly severe conditions (~650°C) releases SO_2, cyclopentadiene and the desired acyclic diene (**27**). The extrusion of SO_2 followed by Cope rearrangement of five-membered ring sulphones fused to cyclobutane ring can be achieved to yield 1,5-dienes[12]. Thus, the epoxide (**29**) on thermolysis gives 1,5-diene (**30**).

The deprotonation/alkylation reaction of 3-sulpholene can be extended to hydroxyalkylation by treating the anion with a ketone or aldehyde. The intermediate alcohols (**31**) of these reactions can be further dehydrated and thermolyzed to give substituted 1,3,5-hexatrienes (**32**, Scheme 6)[13]. The conjugated carbonyl adds to sulpholene anion in 1,4 fashion to give γ-carbonyl derivatives.



SCHEME 4.

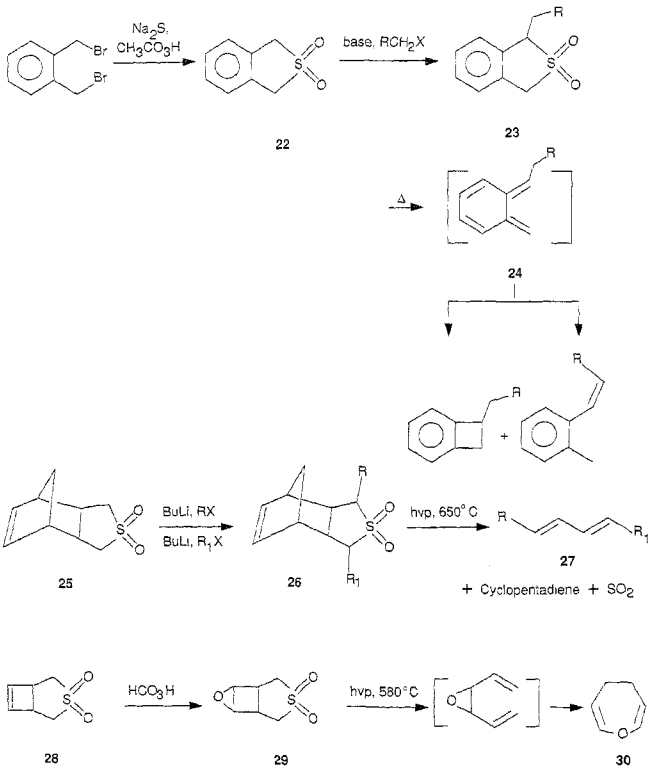
The reactions of sulpholene anion with acyl chloride[8], trimethyl silyl chloride[14], tributyltin-chloride[15], etc., have been achieved to obtain the corresponding substituted sulpholenes **33**, **34**, **35**, respectively (Scheme 6). Further, coupling of sulpholene **35** with vinyliodide in the presence of Pd $(PPh_3)_4$ gives 2-vinyl-sulpholene which on facile thermolysis yields the conjugated triene **36**. Using similar approach vinylallenes (**38**) can be prepared from sulpholene **37**[16].

3. Other substitutions of sulpholenes

An alternate method for achieving regioselective hydroxyalkylation of sulpholenes involves allylzincation in the presence of ultrasound with 4-bromo-2-sulpholene (**39**, Scheme 7). Complementary regiocontrol appears possible by changing the metal used to magnesium. Thus, 4-hydroxy-alkyl-2-sulpholene (**40**) and isomeric 2-hydroxy-alkyl-3-sulpholene (**41**) have been synthesised[17].

3-Bromosulpholene undergoes nucleophilic displacement at C_3, on treatment with various sulphur[18], nitrogen and carbon nucleophiles[19], allowing facile access to 3-substituted compounds **42**, **43**.

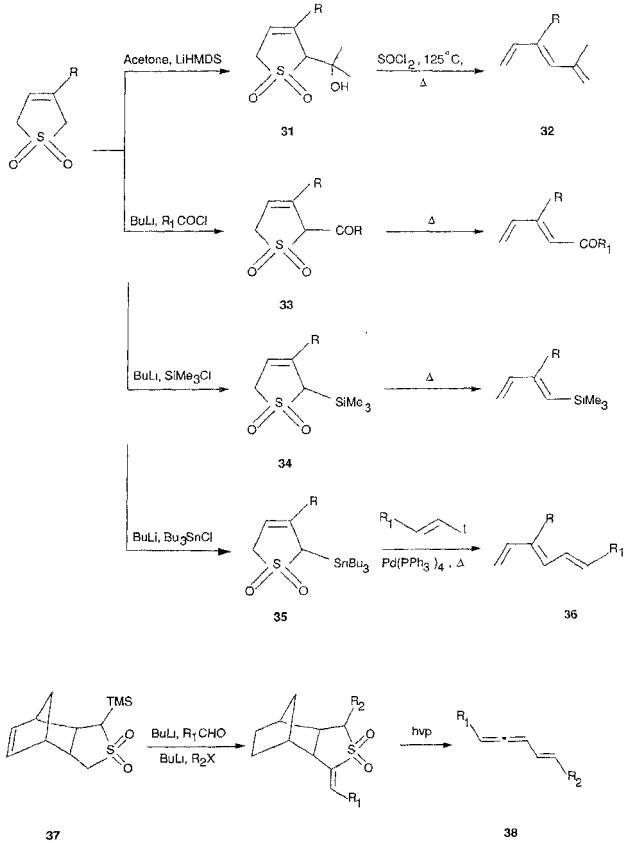
The addition of phenylsulphenyl chloride to 3-sulpholene yields 3-chloro-4-phenylthiosulpholane (**44**) which upon treatment with Et_3N gives the substituted 3-sulpholene (**45**)[20a–d]. These derivatives undergo Friedel–Crafts acylation to give 3-phenyl-thio-4-acyl-1-3-sulpholene (**46**)[20e]. The addition of *p*-octyl-phenylsulphenyl chloride followed by further manipulations afford sulpholene having surfactant side chain which has been used for the study of micellar Diels–Alder reaction[21]. Alternatively, the treatments of 3-sulpholene with phenylselenyl chloride followed by NEt_3 give 3-phenyl-selenyl-3-sulpholene[22].



SCHEME 5.

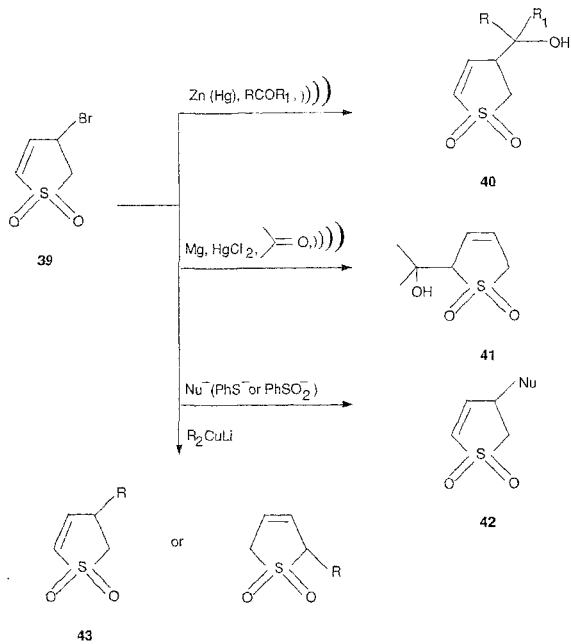
3-Nitro-3-sulfolene (**48**) is obtained from 3-sulpholene by treatment with N_2O_4[23]. The direct coupling of 3-sulpholene with iodoarenes takes place readily in the presence of palladium catalyst[24] leading to 3-aryl-3-sulpholene (**49**, Scheme 8).

Allylic bromination of 3-methyl-3-sulpholene with NBS proceeds smoothly to afford 3-bromomethyl-3-sulpholene (**50**)[25] which on nucleophilic displacement of bromine gives substituted derivatives **51**[26] (Scheme 9).



SCHEME 6.

In addition to nucleophilic substitution the bromomethylated sulpholene (**50**) can also be converted into an organozinc species by treatment with Zn/Ag which reacts with nitriles to give mainly 3-acyl-4-methyl-3-sulpholenes **52**[27].

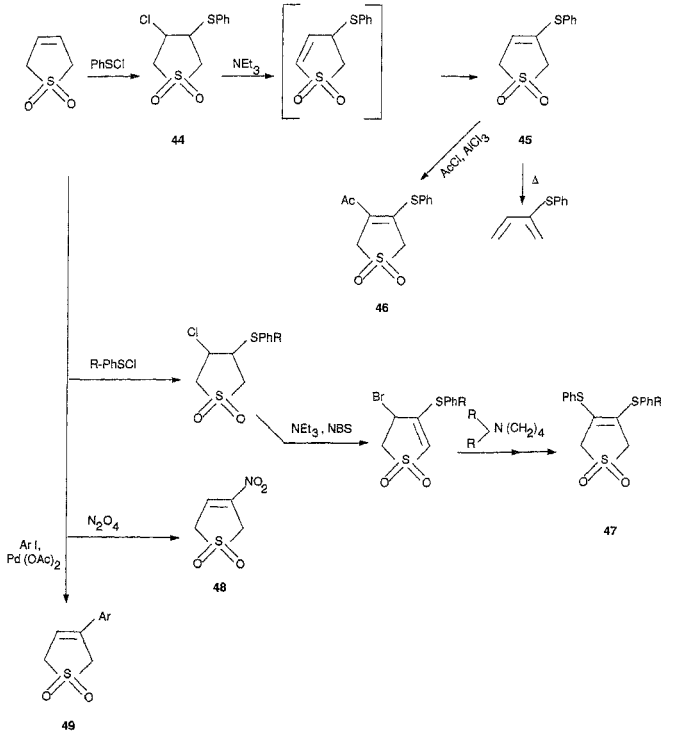


SCHEME 7.

4. Application of substituted sulpholenes in the synthesis of natural products

The substitution reactions of 3-sulpholene benzo-3-sulpholene (**22**) and tricyclosulpholene (**25**) have been extensively used for the synthesis of natural products.

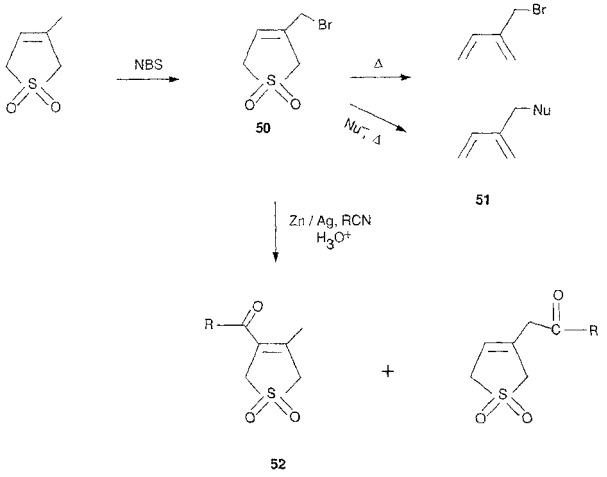
A number of insect pheromones[28] and some other natural products containing substituted 1,3-diene functionalities such as red bollworm moth pheromone (**53**), codling moth pheromone (**54**), light-brown apple moth pheromone (**55**), precursor of hypotensive triazene WS-1228A (**56**), insecticidal pellitorine (**57**), pipercide (**58**), bean beetle pheromone (**59**) have been synthesised *via* deprotonation/alkylation of sulpholene **22** in 4–5 steps (Schemes 10, 11). The more efficient synthesis of the pheromones **53**, **54** and cabbage webworm pheromone **60** have been achieved through direct deprotonation alkylation reactions of 3-sulpholene[29]. Similar strategy of alkylation of 3-methyl-3-sulpholene leads to the synthesis of natural products β-ocimene (**61**), α-farnesene (**62**)[30], α-sinensal (**63**, n=2)[31], E-tagetone (**64**)[13].



SCHEME 8.

The exomethylene sulpholene (**65**) reacts with nucleophile at C_6 allowing the synthesis of ipsenol (**66**) (Scheme 12)[32]. Allylzincation of 4-bromo-2-sulpholene (**39**) provides an efficient route to α-myrcene (**67**)[3a].

Alternatively, SO_2 extrusion reactions of sulpholenes provide dienes having further applications in inter- and intra-molecular (IMDA) Diels–Alder reactions. Several decalin systems of bioactive natural products (**70**)[33,34] such as blood-pressure lowering forskolin, insecticidal neem compounds, antifeedant warburganal and antibacterial isozonarol, etc., have been synthesised through regioselective alkylation of 3-methyl-3-sulpholene followed by



SCHEME 9.

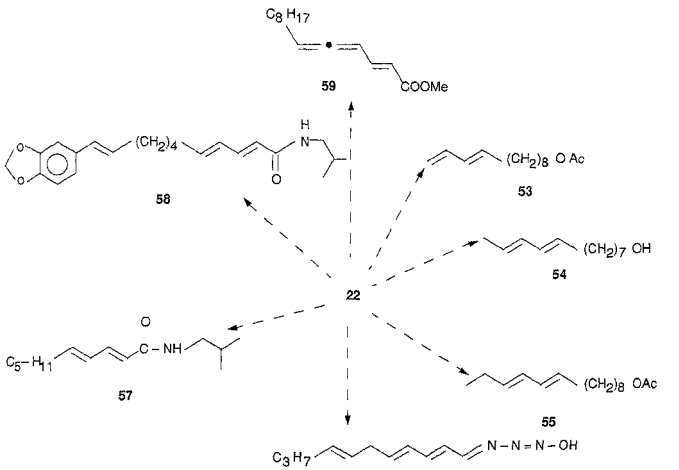
Diels–Alder reaction with 2-formyl-4, 4-dimethyl-cyclohexadienone (**68**) with properly substituted 3-methyl-3-sulpholenes (**69**) (Scheme 13).

Using strategy of sulpholene alkylation followed by IMDA the sesquiterpenes of eudesmane family[35,3a] such as selina-4, 7 (11)-diene (**71**), α-selinene (**72**) and α-eudesmol (**73**), and alkaloids elaeokanine A (**74**)[36,37] and lupinine (**75**)[38] along with epilupinine (**76**) have been synthesised (Schemes 14,15). This strategy has also been utilized in the synthesis of aspidospermine (**77**)[39]. Starting from *m*-cyano-benzo-sulpholene (**78**) the synthesis of estradiol (**79**) has been achieved[40].

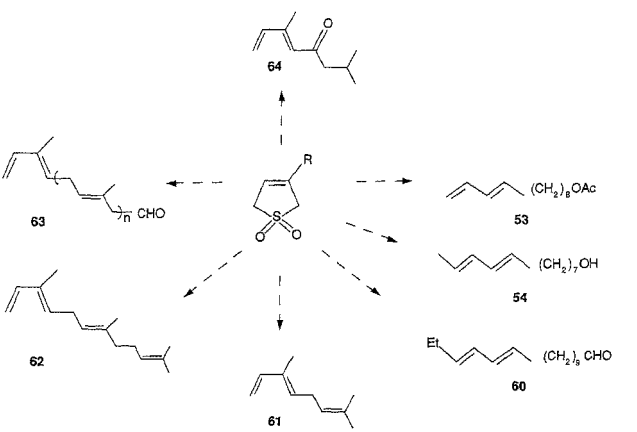
An elegant synthesis of quassinoids[41a] is achieved through the condensation of 2-(3-methyl-3-sulpholen-2-yl)-acetaldehyde(**80**) with carvone. Further alkylation followed by IMDA of the corresponding triene yields tricyclic derivative (**81**) which has been further elaborated to tetracyclic quassinoid skeleton (**82**) (Scheme 16). This strategy has also been employed in the synthesis of decalin system (**83**)[41b].

5. Bi- and tricyclic sulpholenes

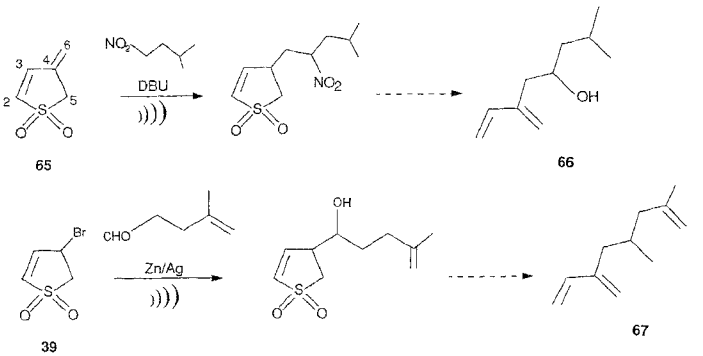
Several bicyclic skeletons with fused sulpholenes have been synthesised (Schemes 17, 18). From 3,4-bis bromomethyl-3-sulpholene (**84**) the tricyclic sulpholene **85**[42], bicyclic pyrrole **86**[43a] and bicyclic thiophene **87**[43b] derivatives have been synthesised. Low band-gap-



SCHEME 10.



SCHEME 11.



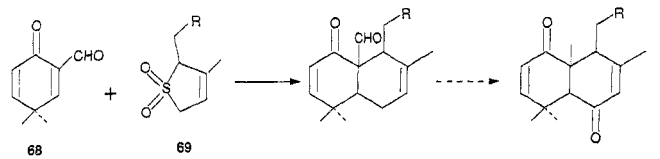
SCHEME 12.

conducting polymers have been obtained by thermolysis of alkylidene derivative (**88**) of thiophene **87**. The reaction of 3-chloro-4-bromo-2-sulpholene (**89**) with β-acetoxy-thio-acetaldehyde followed by cyclization affords the isomeric thiophene (**90**)[44]. The 2+2 cycloaddition of 3-sulpholene with maleimide yields tricyclic derivative **91**[45], whereas the 2+3 cycloaddition of diazomethane to 3-phenylsuphonyl-3-sulpholene, followed by elimination in basic condition affords the pyrazole derivative **92**[46]. The tetrahydrofurano-sulpholene (**93**) has been obtained from 4-hydroxy-2-sulpholene through radical-mediated condensation with ethyl-vinyl-ether[47]. An elegant synthesis of pyrimidino-sulpholene (**95**) has been achieved from 3-oxo-4-carboethoxy-tetrahydrothiophene (**94**)[48].

The dialkylations of 3-alkyl-3-sulpholene with α-ω-dihalo-alkanes afford bicyclic sulpholenes **96**, **97**, **98**[49]. Similarly, using O-dibromomethylbenzene for alkylation, the tricyclic skeleton **99** is obtained. The bicyclic sulpholenes **100** and **101** are obtained through Diels–Alder reaction of 3-alkoxy-2-sulpholene with Danishefsky diene[50] and acid-catalysed cyclisation of sulpholene derived from ocimene, respectively. The sulpholene **101** on pyrolysis affords pyronene (**102**)[51].

6. Conclusions

Substituted 3- and 2-sulpholenes can be obtained through either oxidation of dihydrothiophenes or reactions of preformed sulpholenes. By properly controlling the reaction conditions sulpholenes can be regioselectively deprotonated and substituted with electrophiles. Thus, alkyl-, aralkyl-, hydroxy-alkyl-, trimethylsilyl-, tributylstannyl-substituted sulpholenes are obtained. Sulpholenes are stable in Heck-arylation, Fridel–Crafts acylation and acid-catalysed cyclisation conditions. The phenylthio- and phenylseleno derivatives of sulpholenes are obtained by treatment, respectively, with phenylsulphenyl chloride or phenylselenyl chloride



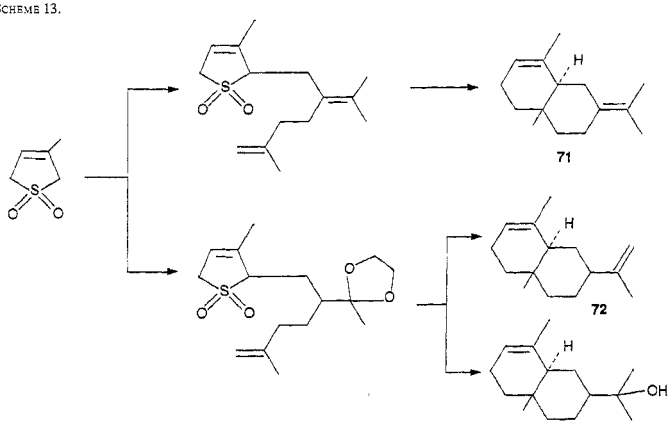
R = OMe, –SPh, Ph, –Ph(OMe$_2$, 2', 5')

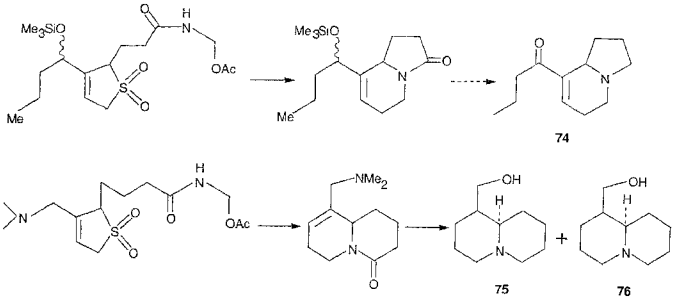
–CH_2OMe, –CH_2CH(O,O), –CH_2–C(Me)(O,O),

–CH_2–C(Me)(–CH=CH_2)(OCH_2OCH_3)

–CH_2–C(Me)=CH–CH_2OCH_3

SCHEME 13.





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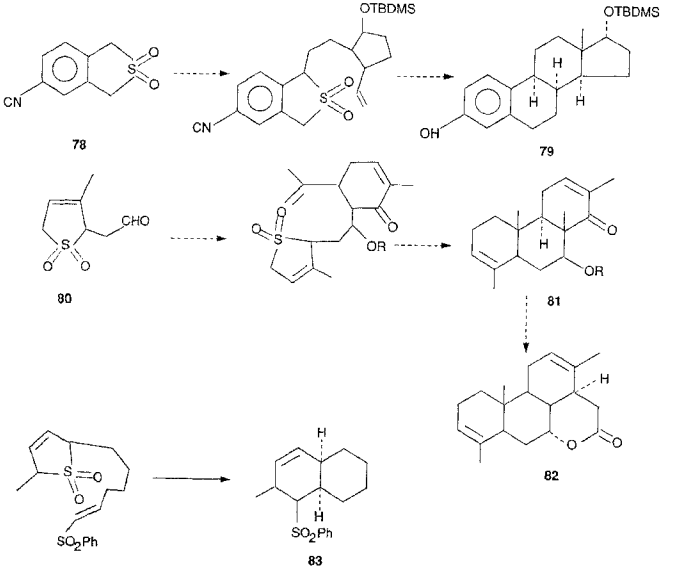

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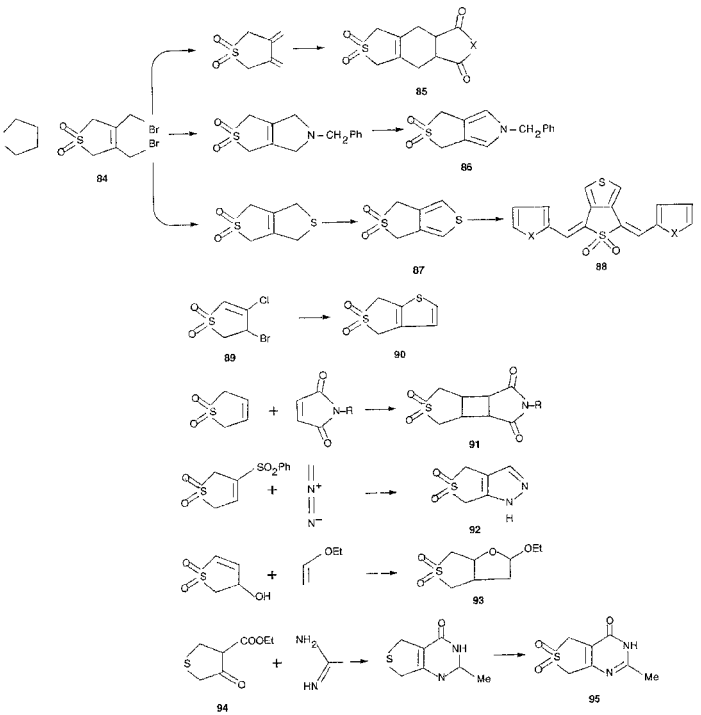


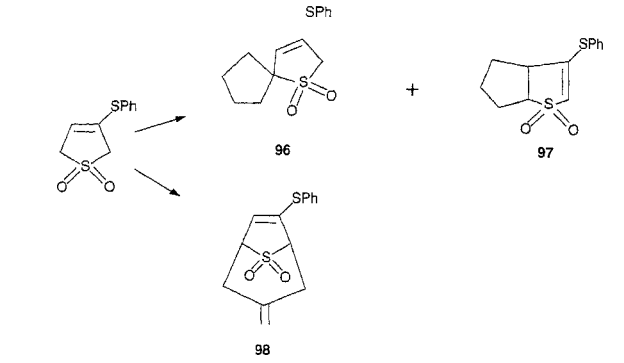
SCHEME 17.

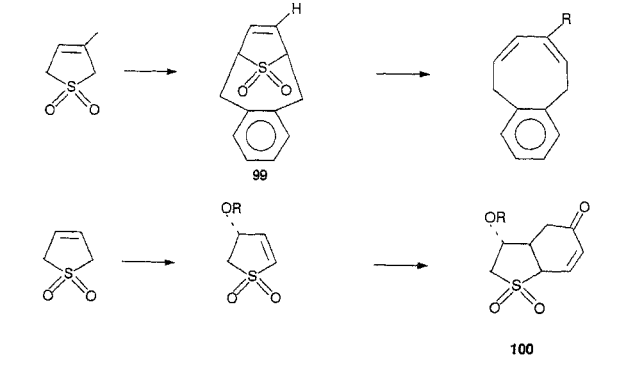
followed by base. The nucleophilic displacement of 4-bromo-2-sulpholenes or 3-bromomethyl-3-sulpholenes affords a wide variety of stable precursors of substituted dienes.

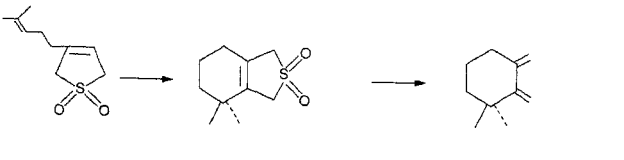
The facile stereospecific SO_2 extrusion from sulpholenes assures very high purity of the geometrical isomers of the 1,3-dienes which have further application in the Diels–Alder reaction. This strategy has been used in the synthesis of a variety of natural products and hetero- and carbocyclic dienes.

Acknowledgement

The author thanks Mr T. Subramanian for assistance in literature search.







SCHEME 18.

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