HETEROAROMATIC-FUSED 3-SULFOLENES

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Abstract —This review deals with our recent works[1] on the preparation of heteroaromatic-fused 3-sulfolenes (**5**) and their chemistry, especially Diels-Alder reactions with several dienophiles under thermal or high pressure conditions. Related chemistry of the positional isomers (**6**) is also reviewed.

CONTENTS

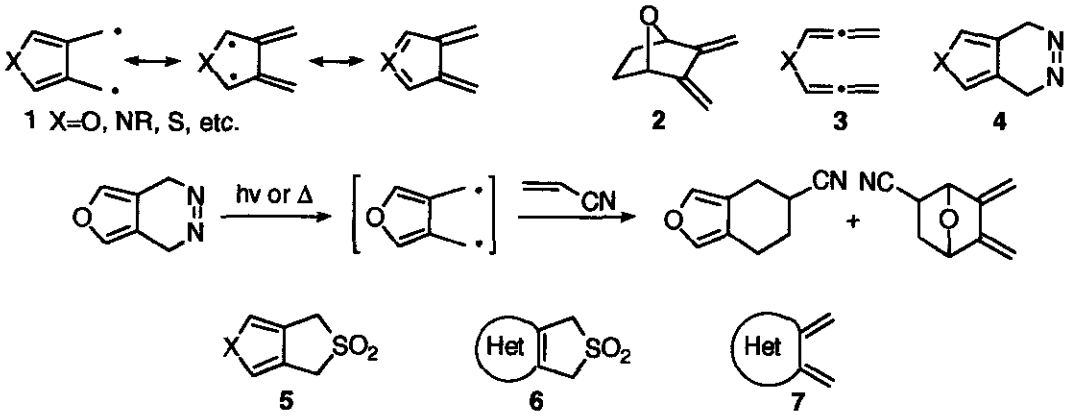
1. Introduction

The 3,4-dimethylene-heteroaromatics (**1**) are π-conjugated non-Kekulé molecules for which full-valence structures can be written only by expansion of heteroatom octet, and aroused theoretical interest. They were postulated many years ago as transient intermediates in the pyrolysis of 2,3-dimethylene-7-oxabicyclo[2.2.1]heptane (**2**)[2] and the intramolecular allene dimerization of the diallenyl compounds (**3**).[3] Berson *et al.* discovered that the low-temperature photolysis of the diazenes (**4**) generates the 3,4-dimethylene-heteroaromatics (**1**) (X=O, S) which are detected with uv and nmr spectra,[4] and reported the reaction of **1** with alkenes.[5] For example, 3,4-dimethylene-furan reacts with acrylonitrile on either the furan and the dimethylene moiety to give the two types of cycloadducts. This result is synthetically interesting, because the obtained cycloadducts further

Dedicated to Professor Alan R. Katritzky on the occasion of his 65th birthday.

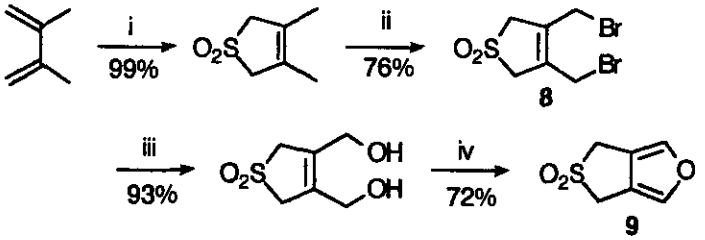
could react with different dienophiles to offer a rapid elaboration of variously substituted multicyclic compounds. Unfortunately neither the diazenes (**4**) nor the diallenyl compounds (**3**) are stable and allow functionalization. Also the pyrolysis of **2** is too hazardous (600-800 °C). Since 3-sulfolenes were known to be masked dienes and easily functionalized by deprotonation / substitution reaction, heteroaromatic-fused 3-sulfolenes (**5**) seemed to be ideal precursors to (**1**). In the course of our studies on the chemistry of 3-sulfolenes as useful synthetic building blocks,[6] we planned to prepare (**5**) (X=O, NR, S, etc.) in order to study their reactivities and synthetic applications.

The aim of this review is to summarize our recent works on the preparation of heteroaromatic-fused 3-sulfolenes (**5**) and their chemistry, especially inter- and intramolecular Diels-Alder reactions. Related chemistry of the positional isomers (**6**), which are excellent precursors of heteroaromatic *o*-quinodimethanes (**7**),[7] is also briefly reviewed.



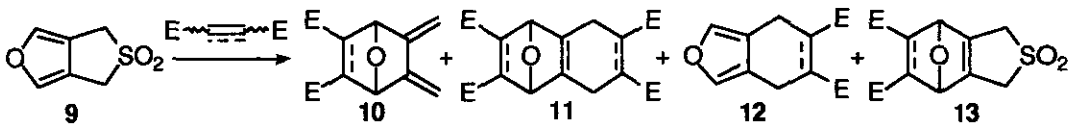
2. Preparation and Diels-Alder reaction of furan-fused 3-sulfolene (9)

Previously unknown 4*H*,6*H*-thieno[3,4-*c*]furan 5,5-dioxide (furan-fused sulfolene) (**9**) was synthesized as shown in Scheme 1.[8] The dibromide (**8**) was obtained by brominating the cycloadduct of 2,3-dimethyl-1,3-butadiene and sulfur dioxide, by following the literature method[9] with some modifications,[8,10] and hydrolyzed with silver trifluoroacetate in water to afford the diol in 93% yield. On treatment with pyridinium chlorochromate (PCC) in the presence of trifluoroacetic acid,



Scheme 1 *Reagents and conditions* : i, SO_2, hydroquinone, MeOH, 25 °C; ii, NBS, CH_2Cl_2, reflux; iii, CF_3CO_2Ag, H_2O; iv, PCC, CF_3CO_2H, acetone-CH_2Cl_2.

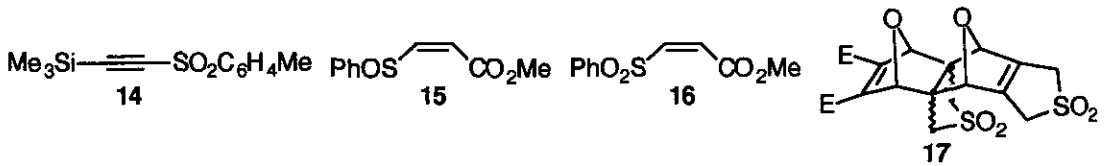
Table 1 Diels-Alder reactions of furan-fused sulfolene (**9**) with dienophiles[a]



9 **10** **11** **12** **13**

Entry	Dienophile	Reaction conditions	Time (h)	Products (yield, %)[b] 10	11	12	13
1	DMAD	150 °C	1	**10a** (45)	**11a** (47)		
2	DMAD	120 °C	1	**10a** (62)	**11a** (29)		
3	DMAD	25 °C	168	**10a** (54)	**11a** (39)		
4	dimethyl fumarate	150 °C	2	**10b** (61)	**11b** (26)		
5	dimethyl fumarate	120 °C	4	**10b** (78)	**11b** (11)		
6	dimethyl maleate	150 °C	3	**10c** (*exo* 10) (*endo* 53)		**12c** (10)	
7	dimethyl maleate	120 °C	12	**10c** (*exo* 10) (*endo* 51)	**11c** (*exo* 18) (*endo* 11)		
8	*N*-phenylmaleimide	150 °C	3	**10d** (*exo* 46)		**12d** (26)	
9	*N*-phenylmaleimide	120 °C	1		**11d** (*exo* 72)		
10	maleic anhydride	25 °C	72				**13e** (*exo* 62)
11	DMAD	12 kbar[c,d]	48				
12	DMAD	4 kbar[c]	24	**10a** (97)	**11a** (3)		
13	**14**	4 kbar[c]	24	**10f** (73)			
14	dimethyl fumarate	12 kbar[c]	48	**10b** (37)			**13b** (41)
15	dimethyl maleate	12 kbar[c]	48				**13c** (*endo* 81)
16	**15**	12 kbar[c]	48	**10g** (*exo* 5)			**13g** (*endo* 79)
17	**16**	12 kbar[c]	48	**10h** (*exo* 7)			**13h** (*endo* 80)

a) The reaction was performed by using 3 equivalents of dienophiles in benzene (sealed tube) unless otherwise noted. b) Isolated yields. c) The reaction was performed in CH_2Cl_2 at room temperature. d) **17** was obtained in 32% yield.



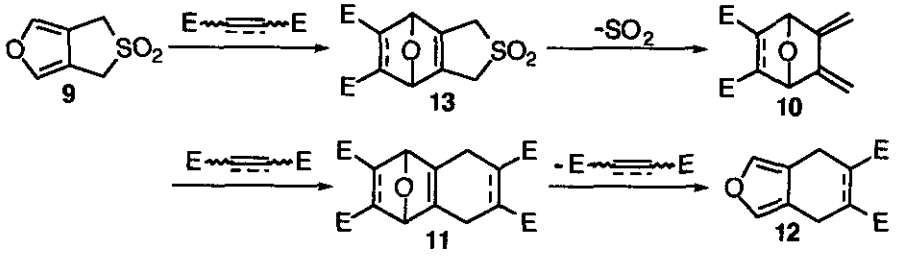
14 **15** **16** **17**

furan-fused sulfolene (**9**) was obtained in 72% yield.

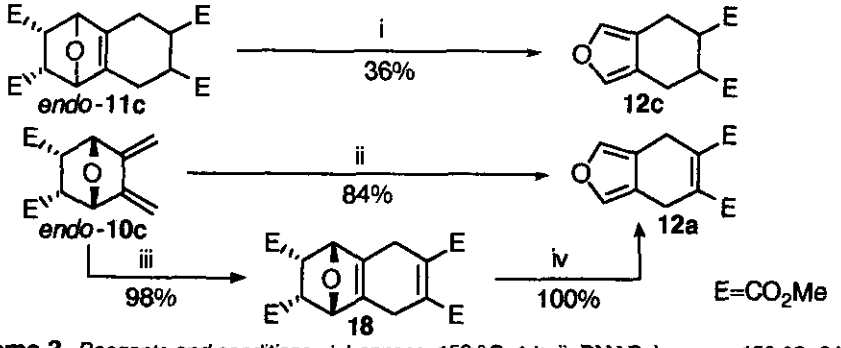
Diels-Alder reactions of furan-fused sulfolene (**9**) with several dienophiles are summarized in Table 1.[8] *Heating* **9** *with dimethyl* acetylenedicarboxylate (DMAD, 3 equiv.) at 150 °C in a sealed tube for 1 h produced two types of cycloadducts, 5,6-dimethylene-7-oxanorbornene (**10a**) (45%) and the 1:2 adduct (**11a**) (47%) (Entry 1). Even at room temperature, the same products were obtained (Entry 3). Essentially the same type of reaction was observed with dimethyl fumarate (*Entries* 4, 5). *With dimethyl maleate and N-phenylmaleimide, thermolysis at* 150 °C gave a new type of products (**12c**) and (**12d**) respectively in addition to **10** (Entries 6, 8). It was found that when **9** was treated with maleic anhydride at room temperature, *exo*-**13e** was obtained as a single

isomer (62%) (Entry 10). Thus, **9** reacts with various dienophiles to give four types of cycloadducts (**10-13**), depending on the dienophiles and the reaction conditions. Taking into account the isolation of **13e**, the above results can be explained by the mechanism in Scheme 2. That is, desulfonylation of initially formed sulfolenes (**13**) affords dimethylene compounds (**10**), which react with another dienophile to give the 1:2 adducts (**11**). The formation of tetrahydroisobenzofurans (**12**) can be understood as a retro Diels-Alder reaction of **11** owing to the restoration of aromatic character and the reduction of steric strain.[11] Indeed, **12c** was obtained when *endo*-**11c** was kept at 150 °C for 1 h. Also *endo*-**10c** reacted with DMAD at 150 °C to afford **12a** (84%), which was alternatively obtained from thermal reaction of the mixed 1:2 adduct (**18**) in a quantitative yield (Scheme 3).

Diels-Alder reactions of **9** under high pressure conditions (4-12 kbar) were next studied (Table 1).[12] Each reaction was performed by using 3 equiv. of dienophiles in CH_2Cl_2 at room temperature. The cycloaddition of **9** with DMAD at 12 kbar resulted in the isolation of only a 1:1 adduct (**17**) of **13a** and **9**. This was prevented by conducting the reaction at 4 kbar to give **10a** in 97% yield (Entry 12). Under the same condition, **9** reacted with *p*-tolyl 2-trimethylsilylethynyl sulfone (**14**) to give **10f** exclusively. At 12 kbar, the reaction of **9** with dimethyl fumarate yielded **10b** together with **13b**, which spontaneously underwent desulfonylation to afford **10b** at atmospheric pressure. With dimethyl maleate, the reaction afforded *endo*-**13c** as a single isomer in 81% yield (Entry 15). Isolated *endo*-**13c** underwent desulfonylation to give **10c** in a quantitative yield at 120 °C (sealed

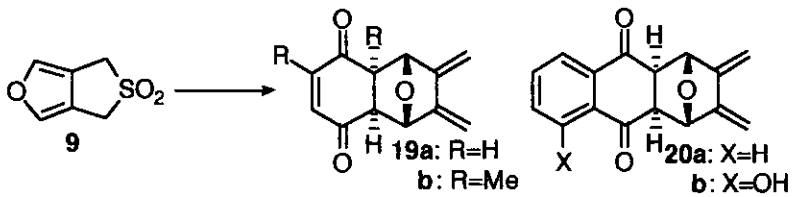


Scheme 2 Reaction mechanism



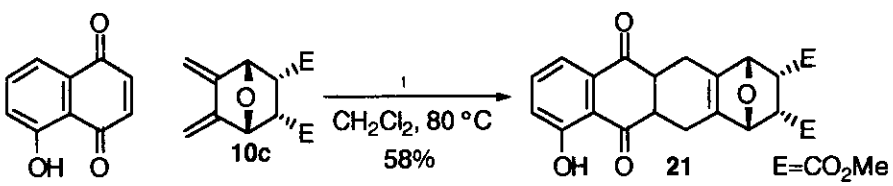
Scheme 3 *Reagents and conditions* : i, benzene, 150 °C, 1 h; ii, DMAD, benzene,150 °C, 3 h; iii, DMAD, CH_2Cl_2,12 kbar, 28 °C, 48 h; iv, benzene, 150 °C, 1 h.

Table 2 Diels-Alder reaction of furan-fused sulfolene (**9**) with quinones



Entry	Quinone	Solvent	Temp.[a] (°C)	Products (yields,[b] %)	Recovery of **9** (%)
1	1,4-benzoquinone	benzene	120	**19a** (*exo* 78)	22
2	2,6-dimethylbenzoquinone	benzene	120	**19b** (*exo* 2)	88
3	1,4-naphthoquinone	benzene	120	**20a** (*exo* 50)	47
4	1,4-naphthoquinone	benzene	150	**20a** (*exo* 58)[c]	
5	1,4-naphthoquinone	toluene	150	**20a** (*exo* 21,*endo* 4)[d]	
6	1,4-naphthoquinone	CH_2Cl_2	150	**20a** (*exo* 31)	13
7	1,4-naphthoquinone	$CHCl_3$	150	**20a** (*exo* 24)	2
8	juglone	benzene	120	**20b** (*exo* 60)	13

a) In a sealed tube. b) Isolated yields. c) The 1:2 adduct (**11**) was obtained (4%). d) The fused furan (**12**) was obtained (12%).



tube, benzene, 0.5 h). Essentially the same reactions were observed with **15** and **16** (Entries 16, 17). Thus high pressure reaction makes it possible to circumvent tandem Diels-Alder reactions and obtain selectively **13** or **10**, depending on whether alkenes or alkynes have been employed as dienophiles.

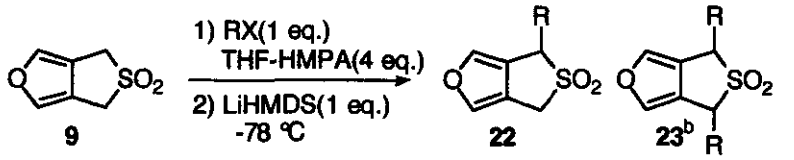
The current interest in brief construction of clinically important polycyclic quinones such as anthracyclines,[13] pradimicin A (anti HIV),[14] and their analogues prompted us to examine the reaction of furan-fused sulfolene (**9**) with several quinones (Table 2).[15] Heating of **9** at 120 °C in a sealed tube in the presence of 2 equivalents of 1,4-benzoquinone gave the dimethylene compound *exo*-**19a** as a single product in 78% yield (Entry 1). Treatment of **9** with 1,4-naphthoquinone at 150 °C gave **20a** in 58% yield together with a small amount of the 1:2 adduct **11** (Entry 4). In examining of solvent effects in this reaction, we found benzene to be the most favorable one (Entries 4-7). It is significant that the configuration of all the products is *exo*,[16] probably due to the steric repulsion between the dienophiles and the sulfonyl group of **9** in *endo*-transition states. Further, the reaction of **10c** with juglone (5-hydroxy-1,4-naphthoquinone) gave a 58% yield of the tetracyclic quinone (**21**). This approach to tetracyclic quinones may well have fruitful application in constructing the important polycyclic quinones.

The above results show the sulfolene moiety of **9** not only has the role of a precursor of *s-cis*-butadiene but also enhances the reactivity of the furan ring in Diels-Alder reaction, and thus introduces the use of **9** as a source of important intermediates in the synthesis of natural products.

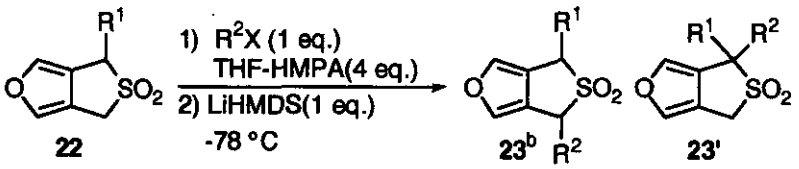
3. Chemical modification of furan-fused sulfolene (9) and their Diels-Alder reactions

In order to demonstrate the applicability of **9** as a synthetic building block, we investigated the chemical modifications of **9** at the position α to the SO_2 group and submitted the resulting products

Table 3 Alkylation of furan-fused sulfolene (**9**)



Entry	RX	Method[a]	**22** (%)	**23** (%)	**9** (%)
1	MeI	A	26	—	49
2	BuI	A'	20	21	7
3	BuI	B	58	21	21
4	BuI	C	36	36	28
5	iPrI	B	67	10	21
6	CH_2=$CHCH_2Cl$	B	44	21	36
7	$PhCH_2Cl$	B	40	27	32
8	MeI	B	28	44	28
9	CH_2=$CH(CH_2)_3Br$	B	59	16	21
10	CH_2=$CH(CH_2)_4Br$	B	58	18	24
11	EtO_2CCN	B'	89	—	—



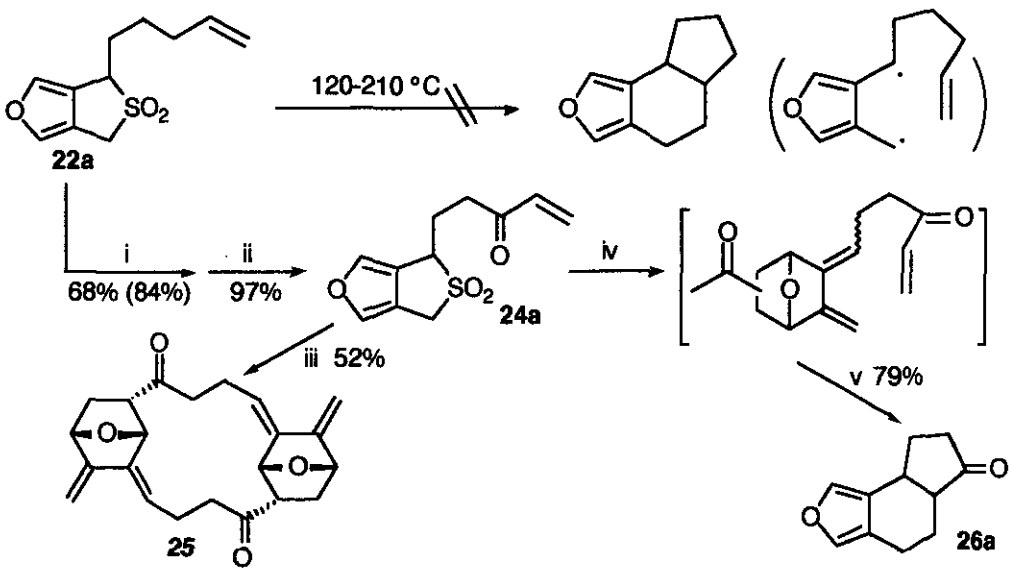
Entry	R^1	R^2X	Method[a]	**23** (%)	**22** (%)
12	Bu	BuI	D	68	18
13	Bu	MeI	B	77	23
14	$(CH_2)_3CH$=CH_2	MeI	B	97	—
15	$(CH_2)_3CH$=CH_2	$PhCH_2Cl$	B	56	22
16	CO_2Et	CH_2=$CH(CH_2)_4Br$	B	86 (**23'**)	3

a) A : RX was added after lithiation (-78 °C, 30 min). A' : (-78 °C, 1 min). B : The carbanion was generated in the presence of RX at -78 °C. B' : B except that 2 eq. of LiHMDS was used. C : The carbanion was generated in the presence of RX at -105 °C. D : B except that 9, 2 eq. of RX, and 2 eq. of LiHMDS were used. b) *cis-trans* mixture (1:1 to 1:5).

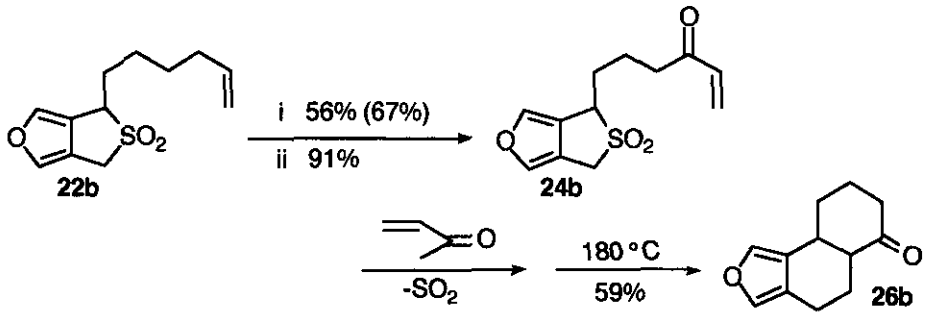
to Diels-Alder reactions.

The alkylation studies of **9** are summarized in Table 3.[10,17] Although the carbanion from **9** was labile even at -78 °C (Entries 1, 2), **9** was successfully alkylated by generating the anion in the presence of alkyl halides (Entries 3-11). PrⁱI has a higher selectivity for monoalkylation, on the other hand, the more reactive allyl, benzyl, and methyl halides have lower selectivities. When ethyl cyanoformate (Mander's reagent)[18] was used as an alkylating reagent, 2 equiv. of LiHMDS was needed to get the best result (Entry 11). The dialkylation of **9** with BuI (2 equiv.) and LiHMDS (2 equiv.) was performed effectively to give 4,6-dibutyl derivatives (**23**) (R=Bu) in 68% yield (Entry 12). Similarly, the alkylation of monoalkyl derivatives (**22**) with different alkylating reagents gave **23** in good yields (Entries 13-15). All dialkyl derivatives (**23**) were *cis-trans* mixture in ratios of 1:1 to 1:5. Alkylation of **22** (R=CO_2Et) with 6-bromo-1-hexene after treatment with LiHMDS (1 equiv.) gave a 4,4-disubstituted compound (**23'**) (86%) (Entry 16), a result which means that regioselective dialkylation of **9** is possible. That is, 4,6-dialkyl derivatives (**23**) are selectively obtained from **22** (R^1=alkyl), on the other hand, 4,4-dialkyl derivatives (**23'**) are obtained from **22** (R^1=CO_2Et) since the ethoxycarbonyl group can be easily transformed to several kinds of functional groups, including alkyl.

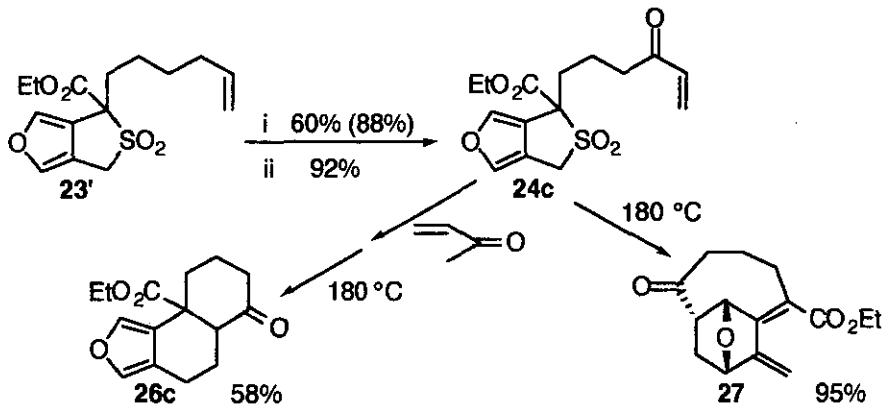
After establishing alkylation procedure, we next turned our attention to the intramolecular Diels-Alder reactions. Unexpectedly, **22a** decomposed when heated (120-210 °C) rather than generating a 3,4-dimethylenefuran intermediate (Scheme 4). In order to activate the alkene unit, **22a** was oxidized to the enone(**24a**). When **24a** was heated at 120 °C, a bimolecular Diels-Alder reaction followed by desulfonylation occurred to give the dimer (**25**). However, when **24a** was heated after protection of the furan with methyl vinyl ketone, an intermolecular Diels-Alder reaction



Scheme 4 *Reagents and conditions* : i, SeO_2 *t*-BuOOH; ii, Me_2SO, $(COCl)_2$, Et_3N; iii, 120 °C, benzene; iv, methyl vinyl ketone, 25 °C; v, 180 °C, toluene; (Yield based on consumed **22a** in parentheses).



Scheme 5 *Reagents and conditions* : i, SeO_2, *t*-BuOOH; ii, Me_2SO, $(COCl)_2$, Et_3N; (Yield based on consumed **22b** in parentheses).



Scheme 6 *Reagents and conditions* : i, SeO_2, *t*-BuOOH; ii, Me_2SO, $(COCl)_2$, Et_3N; (Yield based on consumed **23'** in parentheses).

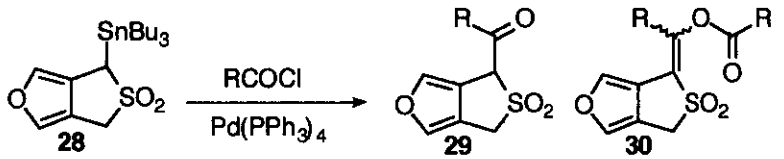
with methyl vinyl ketone,[19] followed by desulfonylation, an intramolecular Diels-Alder reaction, and a retro Diels-Alder reaction occurred sequentially to give the tricyclic fused furans (**26a**) (*cis-trans* mixture; 3.2:1) in 79% yield (Scheme 4). By the same method, the tricyclic furans (**26b**) (*cis-trans* mixture; 2.1:1) were synthesized from **22b** in good yield (Scheme 5). Compound (**23'**) was obtained by two steps (77%) or one step dialkylation (67%) of **9** and oxidized to the enone (**24c**), which was heated after treating with methyl vinyl ketone to give the tricyclic furan (**26c**) as a single isomer. Heating the enone (**24c**) directly gave **27** in 95% yield by an intramolecular Diels-Alder reaction on the furan moiety and following cheletropic elimination of SO_2 (Scheme 6).

Further we planned to prepare some 4-substituted derivatives by cross coupling reactions.[20] The stannane (**28**) was obtained in 53% yield from **9** by metalation with LiHMDS (1.0 eq.) in THF at -105 °C for 10 min, followed by trapping with tributyltin chloride. Acylation of **28** with acyl chlorides in the presence of $Pd(PPh_3)_4$ catalyst (2.5 mol%) gave 4-acyl derivatives (**29**) in up to 51% yield along with the double acylation products (**30**). These results were rather disappointing. Further, typical electrophiles, aryl halides and vinyl halides, could not undergo the coupling reaction with **28**. The reaction of the anion generated from **9** (LiHMDS, THF, -105 °C) with benzoyl chloride

gave only **30** (11%) and **9** (23%). Finally aldol reaction followed by oxidation was found to give 4-acyl derivatives in satisfactory yields. When a solution of **9** in THF-HMPA (4 equiv.) was successively treated with LiHMDS (1.0 equiv.) for 10 min, then 1.5 equiv. of aldehyde, the aldol products (**32**) were obtained in good yields (diastereoisomer ratio 1.3 - 3.2:1, separable) (Table 5). The oxidation of **32** was performed by Jones reagent to give 4-acyl derivatives (**29**).

Diels-Alder reactions of 4-acyl derivatives were studied. When a benzene solution of **29a** was heated at 120 °C with DMAD (3 equiv.) in a sealed tube, the Diels-Alder reaction followed by desulfonylation occurred to afford mono-adducts, (**33a**) and (**34a**), as an inseparable mixture in 79% yield (5.4:1) (Table 6). The stereochemistry of the dienes has been determined *via* NOE experiments. To our surprise, the more sterically congested (*E*)-isomer (**33a**) was formed predominantly. The cyclohexylcarbonyl compound (**29b**) and ester (**22c**) also gave the (*E*)-isomer

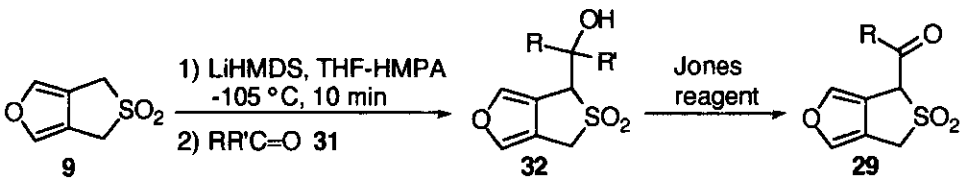
Table 4 Cross coupling reactions of 4-stannylfuran sulfolene (**28**) with acid chlorides



28 **29** **30**

Entry	R	Solvent	Time(h)	Temp.	**29** (%)	**30** (%)	**9** (%)
1	Ph	THF	20	25 °C	0	-	100
2	Ph	HMPA	3	0 °C	51	-	14
3	*p*-O_2N-Ph	HMPA	0.5	0 °C	-	33	14
4	*p*-MeO-Ph	HMPA	3	25 °C	36	-	25
5	*p*-Cl-Ph	HMPA	3	25 °C	37	-	22
6	CH_3	HMPA	2	0 °C	38	5	15

Table 5 Aldol reactions of furan-fused sulfolene (**9**) followed by oxidation

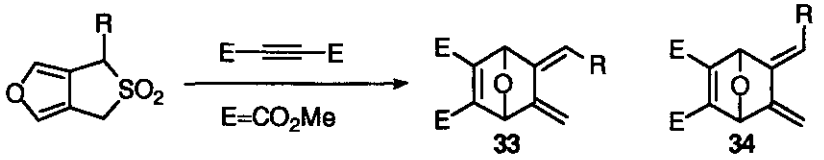


9 **32** **29**

Entry	**31**	Product	Yield of **32**	**9**	Product	Yield of **29**
1	PhCHO	**32a**	62% (1.3:1)[c]	17%	**29a**	72%
2	c-HexCHO[a]	**32b**	71% (3.2:1)	12%	**29b**	80%
3[b]	c-HexCHO[a]	**32b**	44% (2.0:1)	46%		
4	EtCHO	**32c**	63% (1.7:1)	33%		
5	Me_2CHCH_2CHO	**32d**	55% (1.8:1)	36%		
6	Me_2CO	**32e**	63%	23%		

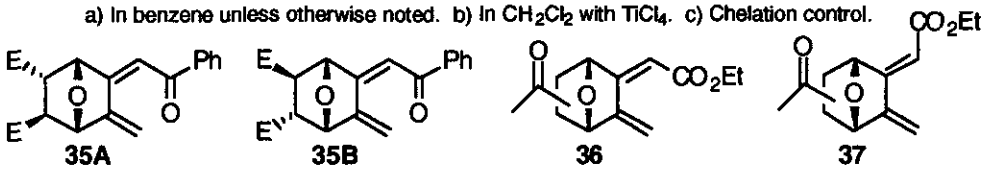
a) c-Hex = cyclohexyl. b) LiHMDS was added to **9** in THF-HMPA (4 eq.) in the presence of **31** at -78 °C.
c) Diastereoisomer ratio.

Table 6 Diels-Alder reactions of 4-substituted furan-fused sulfolenes[a]



R		Dienophile	Temp. (°C)	Time (h)	Products, Yields
PhCO	**29a**	EC≡CE	120	6	**33a**, **34a** 79% (5.4:1)
PhCO	**29a**	(*E*)-ECH=CHE	100	20	**35A**, **35B** 47% (1.4:1)
c-HexCO	**29b**	EC≡CE	130	3	**33b**, **34b** 95% (4.7:1)
EtO_2C	**22c**	EC≡CE	120	4	**33c** 67%, **34c** 20%
EtO_2C	**22c**	$AcCH=CH_2$	110	10	**36** 83%, **37** 11%
EtO_2C	**22c**	$AcCH=CH_2$[b]	-78	3	**36** 12%, **37** 78%[c]
Bu	**22d**	EC≡CE	80	2.5	**33d**, **34d** 54% (1:2.0)

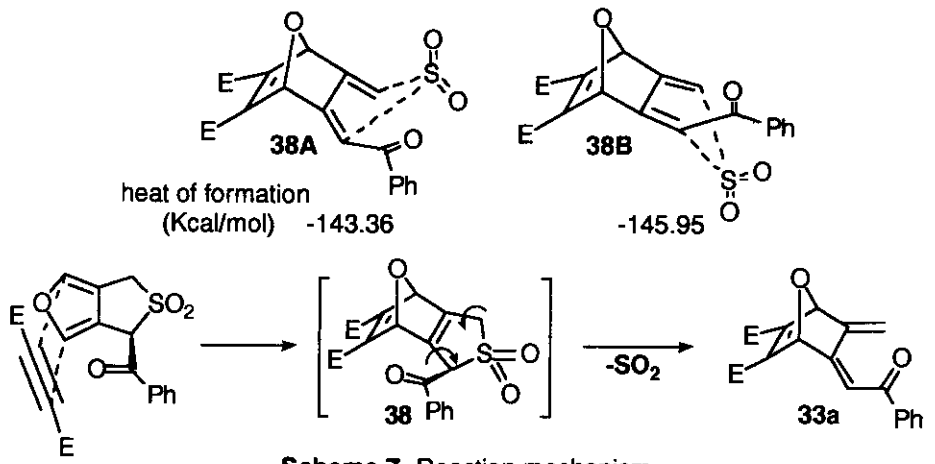
a) In benzene unless otherwise noted. b) In CH_2Cl_2 with $TiCl_4$. c) Chelation control.



(**33b**) and (**33c**) as a main product, respectively. The predominant formation of (*E*)-isomers rather than the (*Z*)-isomers, is novel. The butyl derivative (**22d**) reacted with DMAD to afford mainly the (*Z*)-isomer (**34d**) (**33d**:**34d**=1:2.0, 54%) along with the 1:2 adducts (two isomers in 1:0.9 ratio, 16%). These differences probably arise from the reactivities of the product dienes (**33a**) and (**33d**). The more reactive **33d** reacts with both SO_2 and the dienophile to give the more stable product (**34d**) and the 1:2 adducts under the reaction conditions. The reaction of **29a** with dimethyl fumarate gave only the (*E*)-isomers (**35A**) and (**35B**) (1.4:1). Neither (*Z*)-isomer nor the 1:2 adduct was observed. The ester (**22c**) reacts with methyl vinyl ketone at 110°C in a sealed tube to give (*E*)-isomers (**36**) in 83% yield along with (*Z*)-isomers (11%).

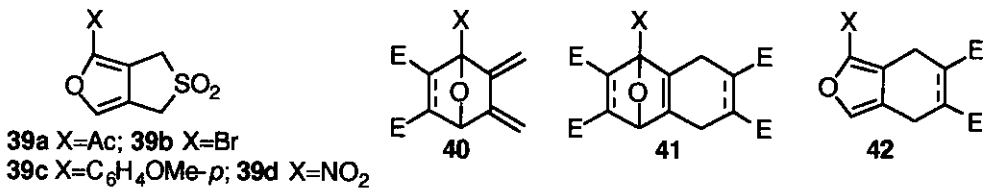
MNDO-PM3 calculations showed that the main product (**33a**) is actually less stable than the (*Z*)-diene (**34a**) by 1.2 kcal mol^{-1} as we expected. We focused our attention on the mechanism of desulfonylation of the intermediate sulfolene. Sulfur dioxide was placed over and under the diene plane of **33a** and the energies were recalculated. The structure (**38B**) is more stable than **38A** by 2.6 kcal mol^{-1}. This means that SO_2 is eliminated under the diene plane of **33a**. Also it is reasonable that the Diels-Alder reaction occurs from the less hindered face of furan to give **38** (Scheme 7). All the experimental results can be reasonably explained by the above mechanism.

Next we studied the chemical modification of the furan moiety in **9**.[21] Acetylation of **9** was performed with acetic *p*-toluenesulfonate in acetonitrile to give **39a** in 80% yield. The best yield (35%) of 1-bromo derivative (**39b**) was obtained on treating **9** with a Br_2-dioxane complex in dioxane at 50 °C. $Pd(PPh_3)_4$ catalyzed cross coupling reaction of **39b** with *p*-methoxyphenyl-(trimethyl)tin smoothly proceeded at 105 °C to afford 1-methoxyphenyl derivative (**39c**) in 57%

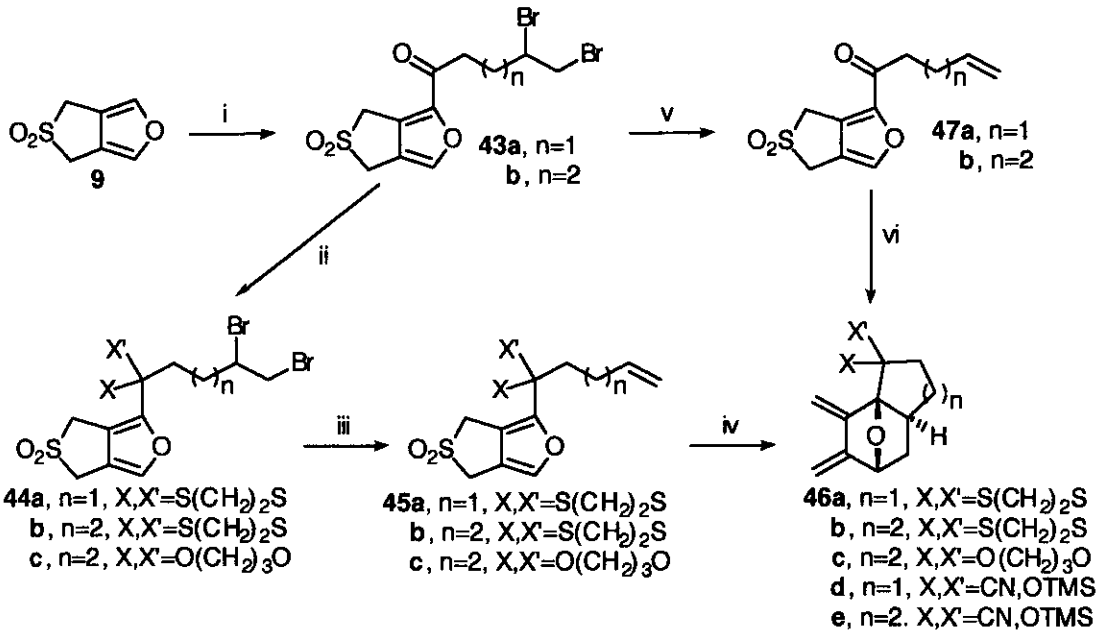


Scheme 7 Reaction mechanism

yield. Using nitronium triflate from nitronium tetrafluoroborate and silver triflate, **9** was nitrated to afford **39d** (37%). Diels-Alder reactions of the 1-substituted derivatives (**39a-d**) thus obtained with DMAD, dimethyl fumarate, and maleate were studied to give **40-42** depending on the dienophiles except **39d**, which mainly decomposed. These results were similar to those of non-substituted **9**. Considering the low reactivity of 2-acetylfuran, it is noteworthy that the acetyl derivative (**39a**) reacts with DMAD to give the cycloadducts in a high total yield (**40** (14%), **41** (57%) and **42** (16%)).



Further, treatment of **9** with 4,5-dibromopentanoyl chloride in the presence of $AlCl_3$ gave **43a** in 85% yield (Scheme 8).[22] The carbonyl group was protected by 1,2-ethanedithiol since it decreases the reactivity of furan as a diene.[23] The thioketal (**44a**) thus obtained (87%) was reduced by zinc to afford olefin (**45a**), a precursor for the intramolecular Diels-Alder reaction in 80% yield. In the same way, **45b** was obtained by using 5,6-dibromohexanoyl chloride through **43b** and **44b** in a similar yield. The protection of **43b** by 1,3-propanediol and the following Zn reduction gave **45c**. The cyclization was smoothly proceeded in refluxing xylene: heating **45** in xylene under reflux for 2 h stereoselectively gave the *exo*-adducts (**46a-46c**) in good yields (**46a**, 74%; **46b**, 70%; **46c**, 74% yield). The cycloadducts (**46d** and **46e**) were produced from the keto olefins (**47**), obtained from **43** by Zn treatment (**47a**, 80%; **47b**, 76% yield), through sequential protection and cyclization. Thus, **47** was heated under reflux in benzene with trimethylsilyl cyanide (TMSCN)[24] in the presence of catalytic amount of potassium cyanide (KCN) and 18-crown-6 to



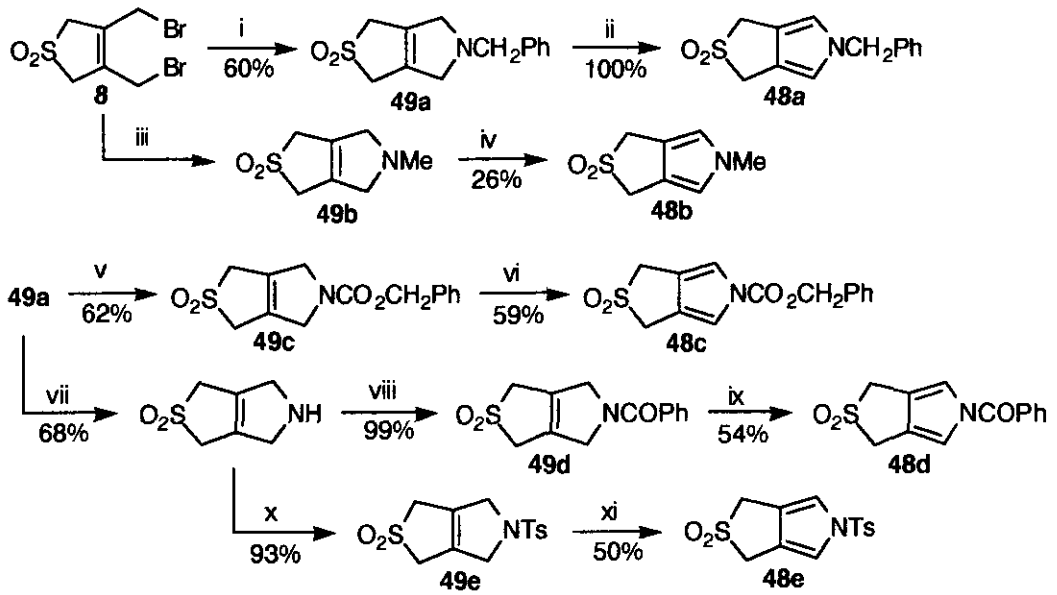
Scheme 8 *Reagents and conditions* : i, 4,5-dibromopentanoyl chloride or 5,6-dibromohexanoyl chloride, $AlCl_3$ in CH_2Cl_2 , 25 °C.; ii, 1,2-ethanedithiol or 1,3-propanediol / *p*-TsOH, reflux in benzene, 24 h; iii, Zn in THF-phosphate buffer, 25 °C, 1 h; iv, reflux in xylene, 2 h; v, TMSCN, KCN, 18-crown-6, reflux in benzene, 24 h.

afford the adducts (**46d**, 63%, **46e**, 59% yield). This procedure exclusively gave the *exo*-adducts again, but a mixture of isomers on the cyanohydrin part (3:1 for **46d**, and 3:2 for **46e**). The cyclization took place after carbonyl protection by TMSCN since heating **47** alone (reflux in xylene for 2 days) gave no adduct. In this case, attempted use of thioketal or ketal protective group (1,2-ethanedithiol or 1,3-propanediol / *p*- TsOH, reflux in benzene for 24 h) instead of cyanohydrin resulted in a complex mixture.

The above results concerning chemical functionalizations of **9** on both the sulfolene and the furan moieties and the following inter- and intramolecular Diels-Alder reactions demonstrate the versatility of **9** as a synthetic building block.

4. Preparation and Diels-Alder reaction of pyrrole-fused sulfolenes (48)

Some *N*-aryl derivatives of pyrrole-fused sulfolene (**48**) have been known for a long time as oxidation products of the corresponding pyrrolinesulfolenes.[25] However, there were no report about their reactivities. We planned to establish the general method of preparing a series of pyrrole-fused 3-sulfolenes, the 3,5-dihydro-1*H*-thieno[3,4-*c*]pyrrole 2,2-dioxides (**48**) containing a variety of *N*-substituents.[26] Compounds (**48**) can be efficiently synthesized, as summarized in Scheme 9, *via* the oxidation of the corresponding pyrrolinesulfolenes (**49**). The pyrrolinesulfolenes (**49a**) and (**49c**) were prepared from the dibromide (**8**) by a modification of standard procedures.[27]

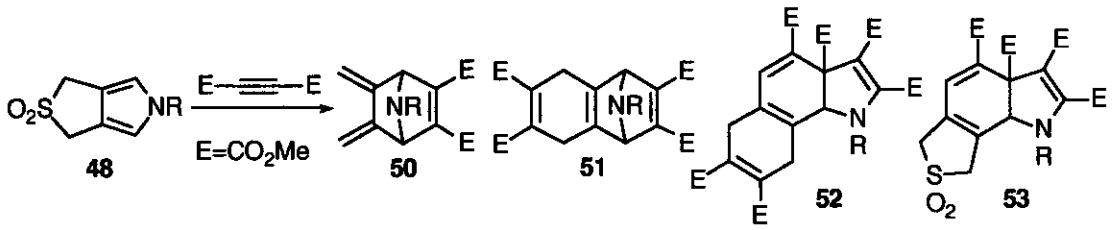


Scheme 9 *Reagents and conditions* : i, $PhCH_2NH_2$, MeCN; ii, DDQ, dioxane; iii, $MeNH_2$, MeCN; iv, DDQ, C_6H_6; v, $ClCO_2CH_2Ph$, C_6H_6; vi, chemical manganese dioxide, C_6H_6; vii, $ClCO_2CHClMe$ in $ClCH_2CH_2Cl$, then MeOH, 50 °C; viii, $PhCOCl$, K_2CO_3, $CHCl_3$; ix, *p*-$MeC_6H_4SO_2Cl$, pyridine.

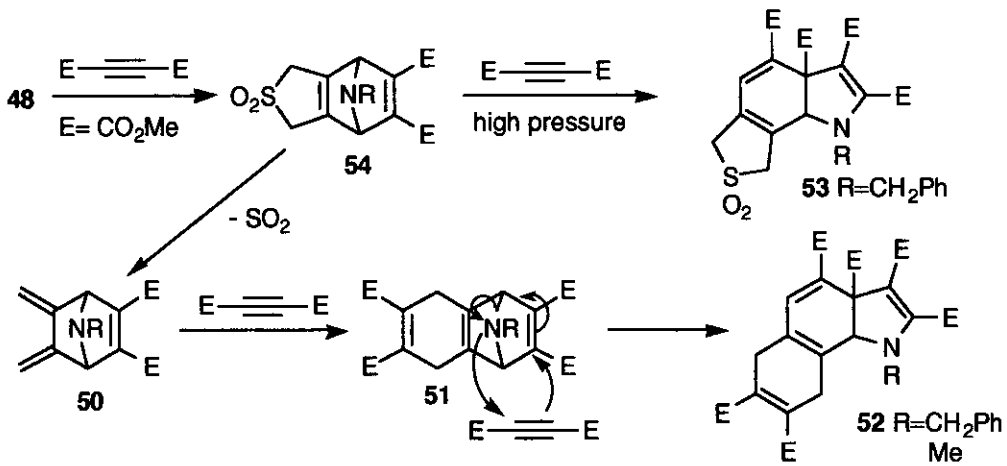
The *N*-benzylpyrrolinesulfolene (**49a**) was treated with α-chloroethyl chloroformate followed by warming to 50 °C in MeOH[28] to give the unsubstituted pyrrolinesulfolene, which was reacted with benzoyl or *p*-toluenesulfonyl chloride in the presence of base to give **49d** or **49e** in a high yield. The oxidation of **49a** was performed by treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in dioxane to give **48a** in a quantitative yield. The *N*-methylpyrrolesulfolene (**48b**) was prepared from **8** and methylamine followed by DDQ oxidation. The pyrrolinsulfolenes (**49c-49e**) having electron withdrawing substituents on the nitrogen were oxidized with not DDQ but 'chemical manganese dioxide'[29] (CMD-U[30]) (30 equiv.) in benzene at room temperature for 4-5 days to give the corresponding pyrrolesulfolenes (**48c-48e**) in good yields with some recovery of starting materials (22-41%).

The results of Diels-Alder reaction of the pyrrole-fused sulfolenes (**48**) thus obtained with DMAD are shown in Table 7. When a solution of **48a** (R=CH_2Ph) in benzene was heated with DMAD (3 equiv.) at 100 °C in a sealed tube for 4 h, 7-aza-5,6-dimethylenenorbornene (**50**) (R=CH_2Ph) and 1a,3a,6,9-tetrahydrobenz[g]indole (**52**) (R=CH_2Ph) were obtained in 28 and 47% yields, respectively, along with the 1:2 adduct (**51**) (R=CH_2Ph, trace) and the starting pyrrolesulfolene (15%) (Entry 1). All attempts to get **50** selectively by decreasing the quantity of DMAD and / or lowering the reaction temperature were unsuccessful. Reaction of 4 equiv. of DMAD with **48a** at 140 °C for 16 h gave **52** in 97% yield. Compound (**52**) was also obtained at 4 kbar. At 12 kbar, thedihydroindolosulfolene (**53**) was obtained. The reaction of the *N*-methylpyrrolesulfolene (**48b**) with DMAD (3 equiv.) gave **52** (R=Me) in 73% yield. Compounds (**48c-48e**), which have electron-

Table 7 Diels-Alder reaction of pyrrole-fused sulfolenes (**48**) with DMAD



Entry	R		DMAD (eq.)	Solvent	Temp. (°C)	Time (h)	Pressure (kbar)	Yield (%) 50	51	52	53	48
1	CH_2Ph	**48a**	3	benzene	100	4		28	0.1	47		15
2		**48a**	4	benzene	140	16				97		
3		**48a**	3	CH_2Cl_2	25	48	4			62		
4		**48a**	3	CH_2Cl_2	25	48	12				38	
5	Me	**48b**	3	benzene	150	2				73		
6	CO_2CH_2Ph	**48c**	3	benzene	150	13			85			
7		**48c**	3	CH_2Cl_2	25	48	12		52			16
8	COPh	**48d**	3	benzene	170	7			99			
9	Ts	**48e**	3	benzene	170	14			97			



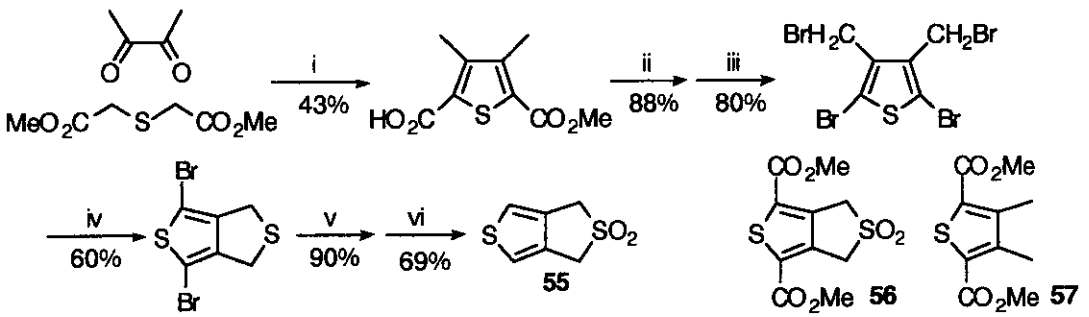
Scheme 10

withdrawing substituents on the nitrogen, react with DMAD to give only the 1:2 adduct **51** in high yields. These results can be reasonably explained by the mechanism in Scheme 10. The Diels-Alder reaction occurs on the pyrrole moiety to give **54**, which are instantaneously desulfonylated to give compounds (**50**). Compounds (**50**) react with another DMAD molecule to give **51**. If the substituent on the nitrogen is electron donating, **51** react further with DMAD to give **52** *via* a sequential Michael-Michael reaction.[31] Under high-pressure conditions, **54** react with DMAD without desulfonylation to give **53**. The reaction of isolated **50** (R=CH_2Ph) with DMAD (3 equiv.) to give **52** (91%) supports this mechanism.

Diels-Alder reactions of **48** with the alkene dienophiles are under investigation and will be reported somewhere in due time.[32]

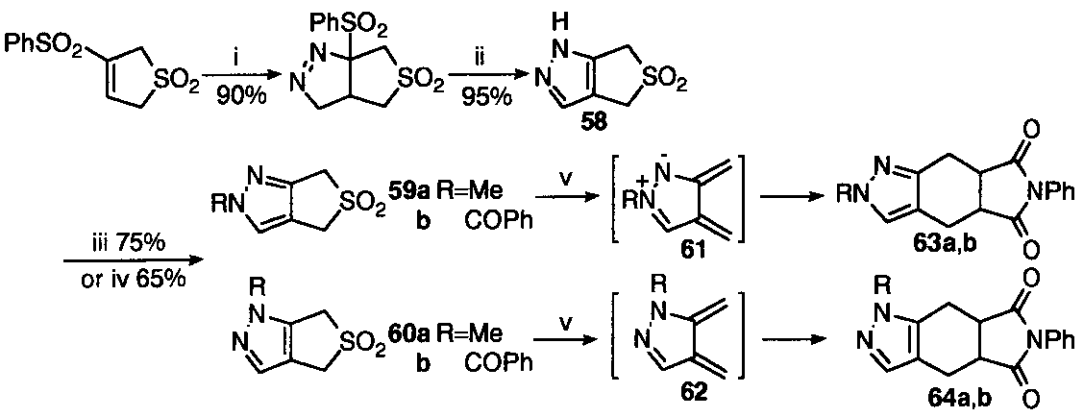
5. Other heteroaromatic-fused 3-sulfolenes

The preparation of thiophene-fused sulfolene (**55**) was reported by Wynberg *et al.* in 1969 (Scheme 11).[33,34] However, they did not mention about its chemical reactivities. Only the pyrolysis of the derivative (**56**) at 350 °C was performed to give **57**, which indicated that sulfur dioxide had been expelled.[35]



Scheme 11 *Reagents and conditions* : i, NaH, DMSO; ii, NaOH, H_2O then Br_2; iii, NBS, dibenzoyl peroxide; iv, Na_2S, MeOH; v, H_2O_2, AcOH; vi, Zn, AcOH.

Storr *et al.* obtained an inseparable mixture of the pyrazole-fused sulfolene (**59**) and its positional isomer (**60**) (R=Me, 3:1; R=COPh, 1:1) by alkylation of pyrazolo-sulfolene (**58**).[36,37] On heating at 200 °C in the presence of *N*-phenylmaleimide, the mixture of **59** and **60** gave two adducts (**63**) and (**64**) in the ratio 3:1 (R=Me, 56%) or 10:1 (R=COPh, 45%). Although this is consistent with loss of SO_2 from **59** to give **61** which is intercepted by the *N*-phenylmaleimide, it is possible that an

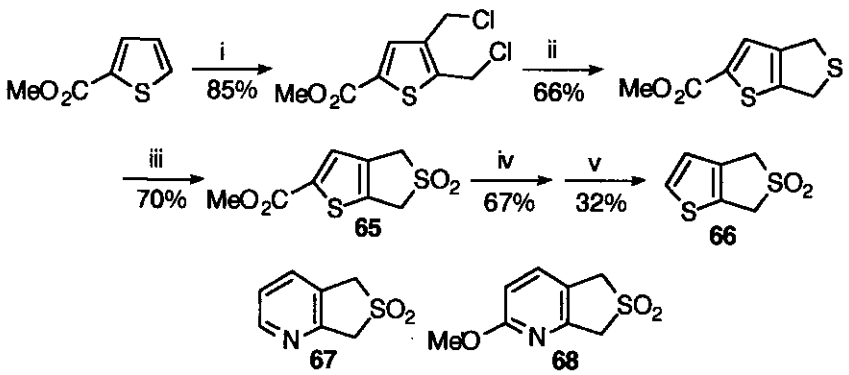


Scheme 12 *Reagents and conditions* : i, CH_2N_2, ether; ii, KOH, MeOH; iii, Me_2SO_4, NaOMe, MeOH; iv, PhCOCl, pyridine; v, *N*-phenylmaleimide, 200 °C.

appreciable portion of the products arise *via* **62** followed by isomerization of **64** to **63**. Chou *et al.* reported the pyrazole sulfolene(**59c**)(R=Ph) remained intact upon heating at 180 °C for more than 90 min, whereas the extrusion from **60c** (R=Ph) proceeded smoothly (within 30 min) at 180 °C.[49]

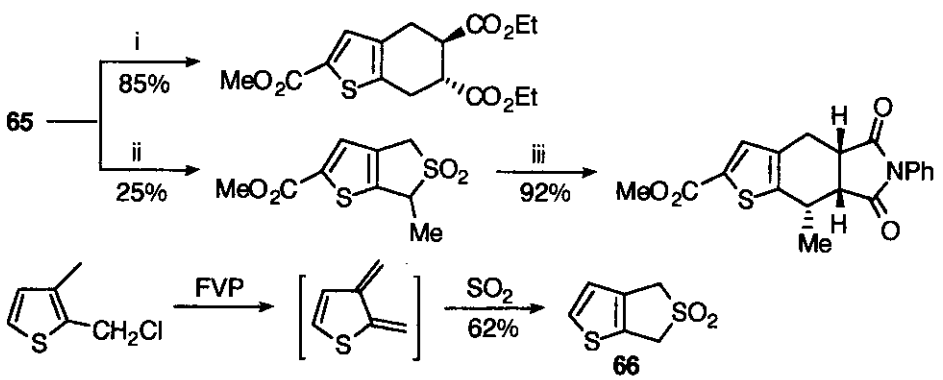
6. Chemistry of the positional isomers (6)

The thieno-sulfolene (**66**)[34] and its derivative (**65**)[38] were first prepared by Wynberg *et al.* in 1960's (Scheme 13). Also the pyridino-sulfolenes (**67**)[39] and (**68**)[40] were prepared *via* a similar route. However, there were no reports about their reactions and synthetic applications.



Scheme 13 *Reagents and conditions* : i, $ClCH_2OCH_3$, $ZnCl_2$; ii, Na_2S, MeOH; iii, H_2O_2, AcOH; iv, KOH, H_2O then Br_2; v, Pd/C, MeOH.

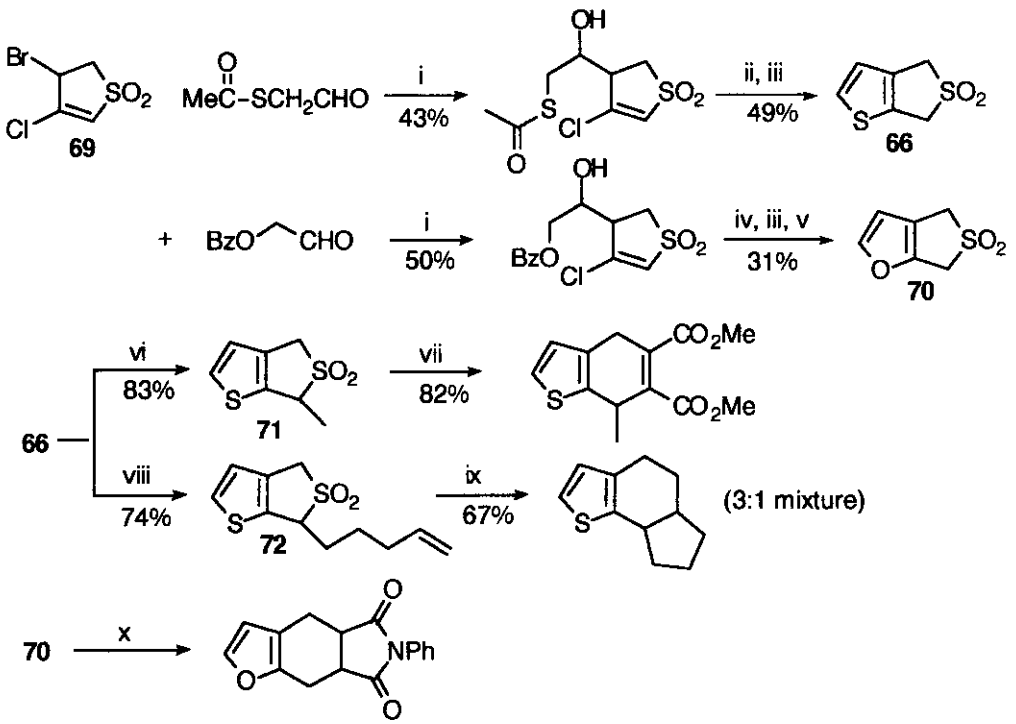
Recently Storr *et al.* heated **65** and **66** in sulfolane at 200 °C in the presence of a range of dienophiles to get Diels-Alder adducts in high yields (Scheme 14).[41,37] The cycloaddition of sulfur dioxide to the thiophene *o*-quinodimethane is also a very efficient reaction even when co-condensation with reactive dienophiles failed to produce Diels - Alder adducts. Thus thieno-



Scheme 14 *Reagents and conditions* : i, diethyl fumarate, sulfolane, 200 °C; ii, LDA, MeI,THF, -75 °C; iii, *N*-phenylmaleimide, sulfolane, 200 °C.

sulfolene (**66**) was alternatively prepared by flash pyrolysis of 2-chloromethyl-3-methylthiophene followed by co-condensation with sulfur dioxide in 62% yield. Furthermore, they performed methylation of **65** using LDA and methyl iodide to get a single isomer, which reacted with *N*-phenylmaleimide to give an *endo*-adduct in 92% yield.

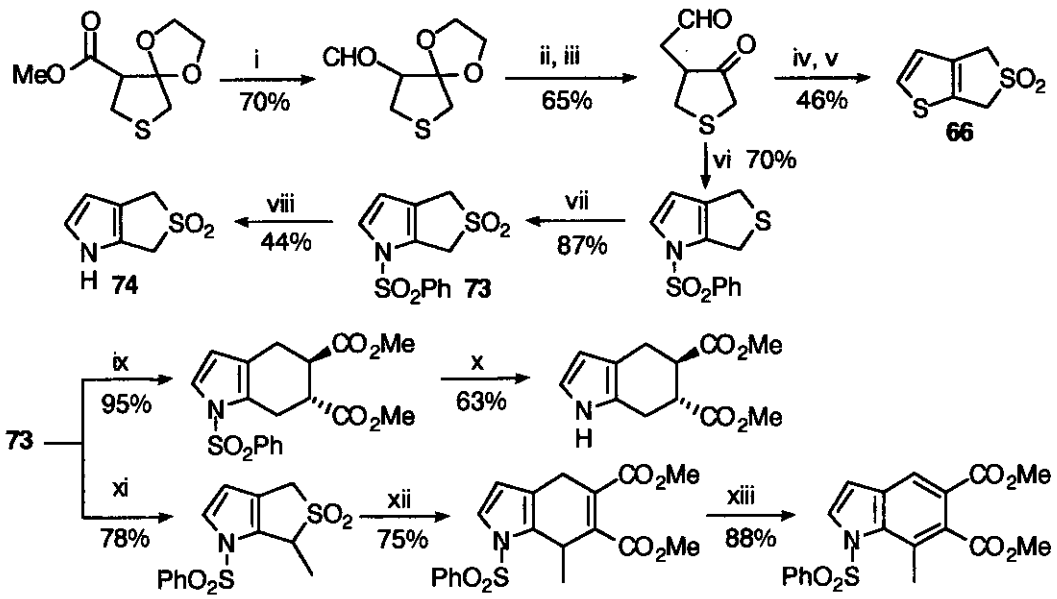
Chou *et al.* reported the third approach to the thieno-sulfolene (**66**) (Scheme 15). A sequence of ultrasound-promoted zincation of **69**, condensation with an aldehyde, cyclization, and dehydration produced not only **66**[42] but also furo-sulfolene (**70**).[43] Treatment of **66** with BuLi in THF followed by alkyl iodides produced **71** (88%) or **72** (74%) regioselectively, both of which were heated to give inter- or intramolecular Diels-Alder adducts. The furo-sulfolene (**70**) reacts with *N*-phenylmaleimide at 160 °C to yield the cycloadduct.



Scheme15 *Reagents and conditions* : i, Zn, ultrasound, BF_3•Et_2O; ii, KCN, $NaHCO_3$; iii, $MeSO_2Cl$, Et_3N, CH_2Cl_2; iv, KCN, MeOH; v, NaOH, MeOH; vi, BuLi, -105 °C then MeI, -78 °C; vii, DMAD, 200 °C; viii, BuLi, HMPA then pent-4-enyl iodide; ix, 200 °C; x, *N*-phenylmaleimide, 160 °C, 3 h.

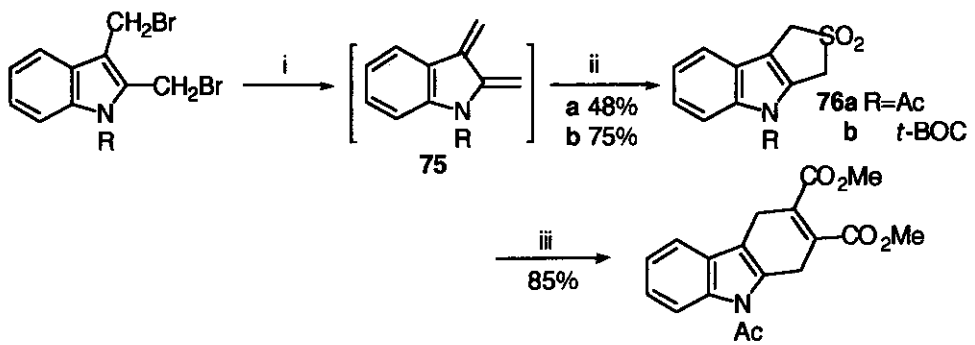
Chou *et al.* prepared pyrrolo-sulfolenes (**73**) and (**74**) by the route shown in Scheme 16, which was also a new route for the thieno-sulfolene (**66**).[44] Deprotonation / methylation of **73** takes place highly regioselectively, and the product sulfolene reacts with dimethyl acetylenedicarboxylate at 200 °C to give the functionalized indole after aromatization.

Indolo-sulfolenes (**76**) can be easily prepared by passing gaseous SO_2 through a solution of indole-2,3-quinodimethanes (**75**), which are generated upon treatment of 2,3-bis(bromomethyl)



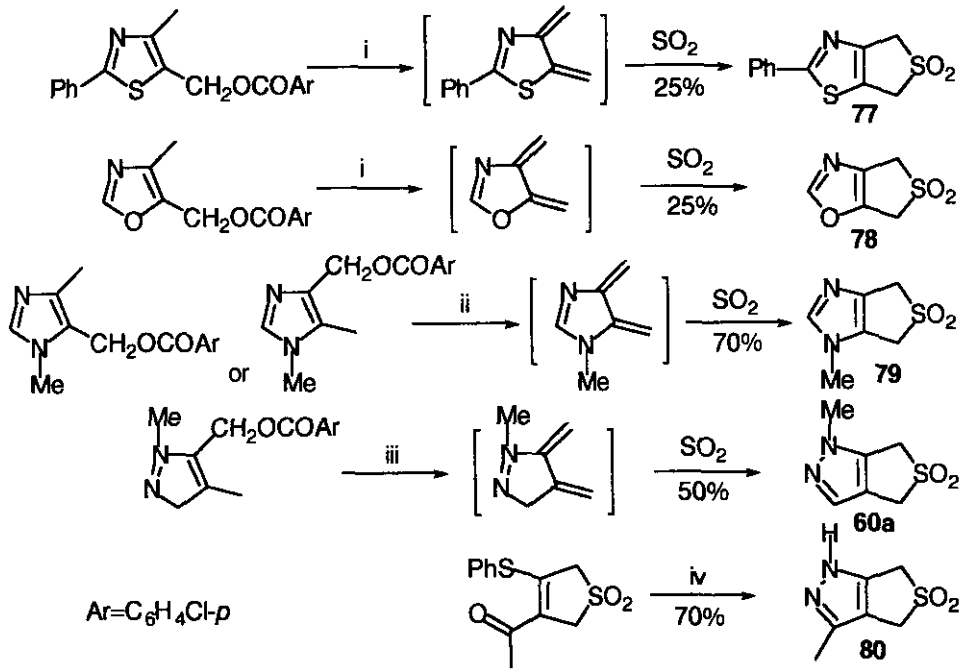
Scheme 16 *Reagents and conditions* : i, DIBAL-H, CH_2Cl_2, -78 °C; ii, $Ph_3PCH_2(OMe)Cl$, LDA, THF, 0 °C; iii, 20% H_2SO_4, Et_2O; iv, Lawesson's reagent, toluene, reflux; v, $MeCO_3H$, room temp.; vi, $PhSO_2NH_2$, *p*-TsOH, toluene, reflux; vii, *m*CPBA, CH_2Cl_2, 25 °C; viii, LiOMe, MeOH-THF, 25 °C; ix, dimethyl fumarate, toluene, 160 °C; x, Na-Hg; xi, LiHMDS, MeI, THF-HMPA, -105 °C; xii, DMAD, toluene, 200 °C; xiii, DDQ, toluene, reflux.

indoles with sodium iodide (Scheme 17).[45] These indolo-sulfolenes upon heating at 80-110 °C undergo cheletropic elimination of SO_2 to regenerate **75** which can be trapped with dienophiles to give the corresponding adducts.



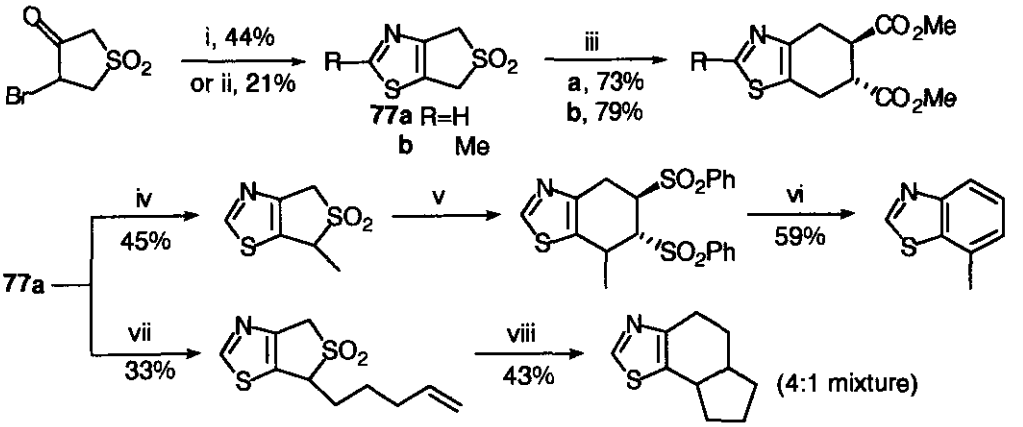
Scheme 17 *Reagents and conditions* : i, NaI, acetone, -30 °C; ii, SO_2; iii, DMAD, 80-110 °C.

Thiazolo-sulfolene (**77**), oxazolo-sulfolene (**78**), 1-methylimidazolo-sulfolene (**79**),[46] and 1-methylpyrazolo-sulfolene (**60a**)[36,37] were obtained by flash pyrolysis of the corresponding *p*-chlorobenzoate esters, followed by co-condensation with SO_2. 3-Methylpyrazolo-sulfolene (**80**) was prepared from the acetylsulfolene and hydrazine by Storr *et al.*[37]



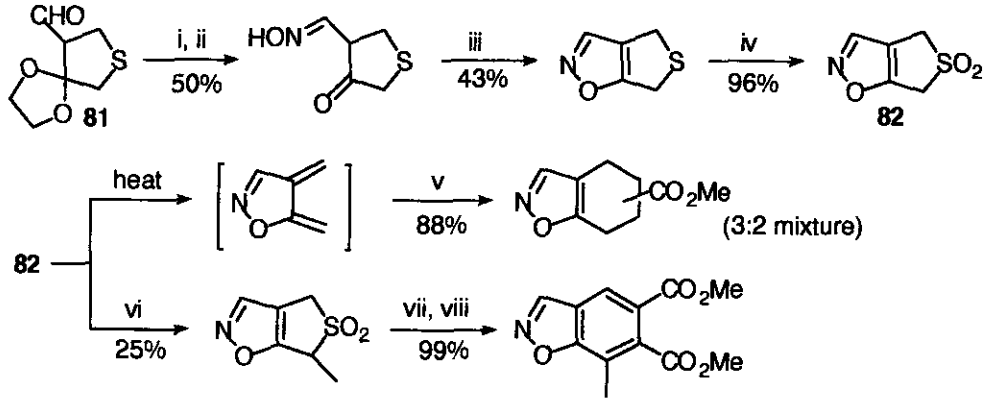
Scheme 18 *Reagents and conditions* : i, 700 °C, 10^{-2} torr; ii, 650 °C, 10^{-4} torr; iii, 750 °C, 10^{-4}torr; iv, hydrazine hydrate, EtOH, reflux.

The alternative route to the thiazolo-sulfolenes (**77**) and their inter- and intramolecular Diels-Alder reactions were reported by Chou *et al.* and the results demonstrated the strategy of using thiazolo-sulfolene as an equivalent of thiazole *o*-quinodimethane is more advantageous than the flash pyrolysis strategy for synthetic purpose (Scheme 19).[47]

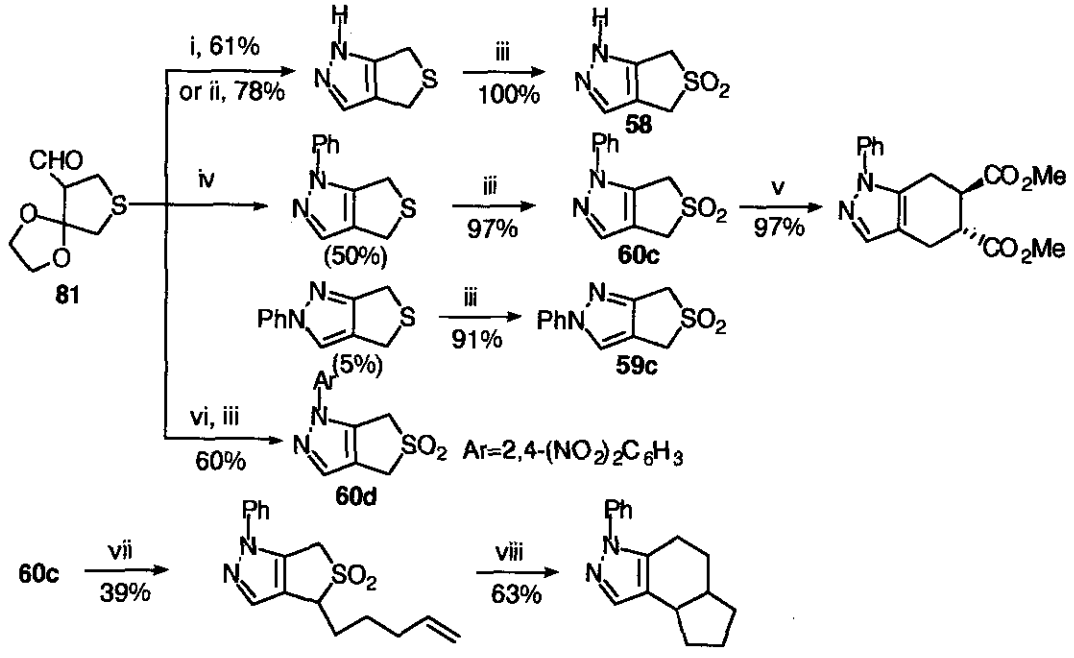


Scheme 19 *Reagents and conditions* : i, formamide, P_2S_5, dioxane, reflux; ii, thioacetamide, dioxane, reflux; iii, dimethyl fumarate, 180-190 °C; iv, BuLi, HMPA, -78 °C then MeI; v, *trans*-1,2-bis(phenylsulfonyl)ethylene, 180 -190 °C; vi, 5N NaOH, MeOH; vii, BuLi, HMPA, -78 °C then 5-iodo-1-pentene; viii, toluene, 180-190 °C.

Furthermore, Chou *et al.* synthesized the isoxazolo-sulfolene (**82**) from the readily available starting material (**81**) (Scheme 20).[48] Heating **82** in the presence of a suitable dienophile readily produced the [4+2] cycloadduct. The alkylation reaction of **82** is also regioselective and no other regioisomers are obtained.



Scheme 20 *Reagents and conditions* : i, 20% H_2SO_4, 25 °C; ii, NH_2OH•HCl; iii, polyphosphoric acid; iv, *m*CPBA, CH_2Cl_2; v, methyl acrylate, 160 °C, $CHCl_3$; vi, LiHMDS, HMPA, THF, then MeI (5 eq.), -78 °C; vii, DMAD (1.2 eq.), toluene, 180 °C; viii, DDQ, 140 °C.



Scheme 21 *Reagents and conditions* : i,hydrazine hydrate (10 eq.), dioxane-5% HCl (3:1) then 10% H_2SO_4; ii, *t*BocNHNH$_2$ (1.1 eq.), TsOH, THF then 20% H_2SO_4; iii, *m*CPBA; iv, PhNHNH$_2$ (1.1 eq.), TsOH, THF then 30% H_2SO_4-THF (1:1); v, dimethyl fumarate, 180 °C; vi, 2,4-dinitrophenylhydrazine, TsOH, THF then conc. H_2SO_4 - 95% EtOH (1:5); vii, LiHMDS (1.2 eq.), HMPA then 5-bromo-1-pentene, -105 °C; viii, toluene, 180 °C.

A new route to pyrazolo-sulfolenes (**60**) was reported by Chou *et al.* (Scheme 21).[49] The reaction of **81** with the corresponding hydrazine give **58**, **60c**, and **60d**. Alkylation of **60c**, followed by intra-molecular Diels-Alder reaction gave the tricyclic pyrazole.

7. Conclusions

Heteroaromatic-fused 3-sulfolenes (**5**), especially the furan-fused sulfolene (**9**) and the pyrrole-fused sulfolenes (**48**) turned out to be useful masked bis-dienes which could sequentially react with a variety of dienophiles. Also the results obtained from the furan-fused sulfolene (**9**) indicate that the heteroaromatic-fused sulfolenes can be easily functionalized on both the heteroaromatic and the sulfolene moieties. Therefore, inter- and intramolecular Diels-Alder reactions, coupled with chemical modification on the both moieties should produce various types of functionalized polycyclic compounds.

The positional isomers (**6**) seem to be the most ideal precursors of the heteroaromatic *o*-quinodimethanes. Since several routes to them are now established and the functionalizations on both the heteroaromatic and the sulfolene moieties should be possible, derivatives of them would become available.

The combination of the cheletropic elimination of SO_2 and inter- and intramolecular Diels-Alder reactions is undoubtedly of synthetic importance especially for the construction of polycyclic molecules.

Efforts to further expand the scope and utility of the heteroaromatic-fused sulfolenes (**5**) are presently under active investigation in our laboratory.

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