CYCLOADDUCTS DERIVED FROM SULFENES OR KETENES AND TROPONE OR ANALOGS OF TROPONE

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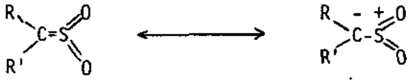
Abstract - Tropone and analogs of tropone (i.e., iminotropones or 8-azaheptafulvenes, and thiotropone) react with sulfenes as well as ketenes forming cycloadducts, wherein a new five-membered ring has been generated. The cycloadducts in turn undergo interesting conversions via a cycloheptatriene-norcaradiene-ring opening sequence.

Sulfenes[1-4] and ketenes[5] have long been recognized as participants in a variety of cycloaddition reactions. Both species undergo, what have been termed [2 + 2], [4 + 2] and [8 + 2] cycloadditions. This review will focus on the cycloaddition reactions of sulfenes and ketenes with three systems that exhibit significant dipolar character, i.e., tropone, iminotropones and thiotropone, and subsequent ring-opening reaction of those cycloadducts.

1. Sulfenes

Sulfenes are reactive intermediates, conveniently generated in situ by treatment of the corresponding sulfonyl chloride with triethylamine in an inert solvent. The regioselectivity of sulfenes with polarized π electron systems has been attributed to the canonical form 2.[6] Consistent with the sulfonyl group exhibiting electrophilic character and the carbon unit nucleophilic character is the formation of the corresponding sulfonic acid derivatives by reaction with active hydrogen-containing compounds.



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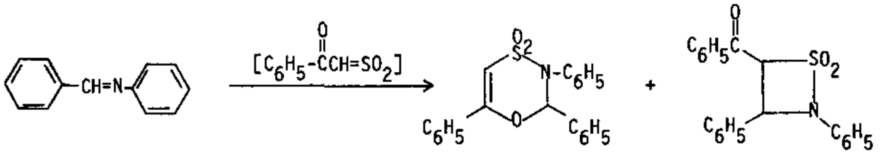
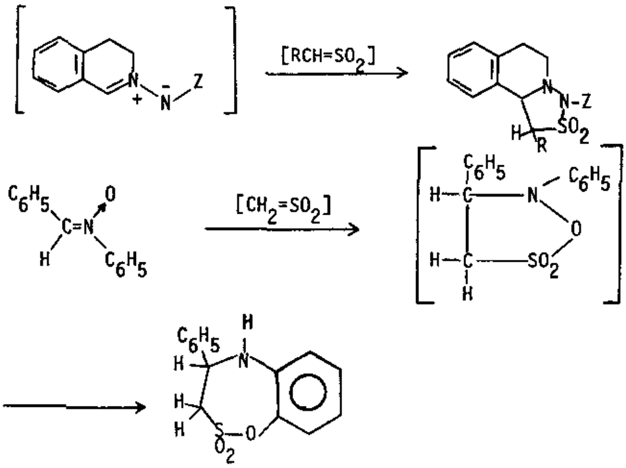
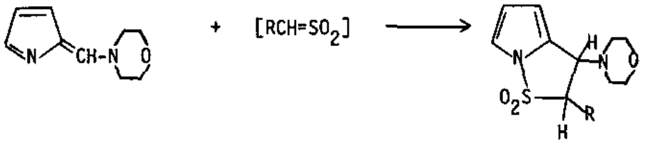
By reaction of sulfenes with enamines,[7-9] ketene acetals,[10-11] ketene aminals,[12] as well as ynamines,[13,14] variously substituted thietane 1,1-dioxides and thiete 1,1-dioxides have been prepared. Another 1,2-dipolar system, from which four-membered cyclic adducts have been observed with sulfenes, is the carbonyl unit (in the form of several perhalogenated aldehydes and ketones)[15,16] and the imino grouping as in Schiff bases.[17,18] Conjugated systems can result in the formation of six as well as four-membered ring adducts, e.g., α-ketosulfenes react with Schiff bases to give [4 + 2] cycloadducts and/or the [2 + 2] cycloadducts.[19,20]



Perhaps more relevant to the principal substrates of this review, tropone and its analogs, are the 1,3-dipolar systems, azomethine imines[21] and diarylnitrones.[22,23] Examples of the behavior of these reactants under sulfene-generating conditions are diagramed below.



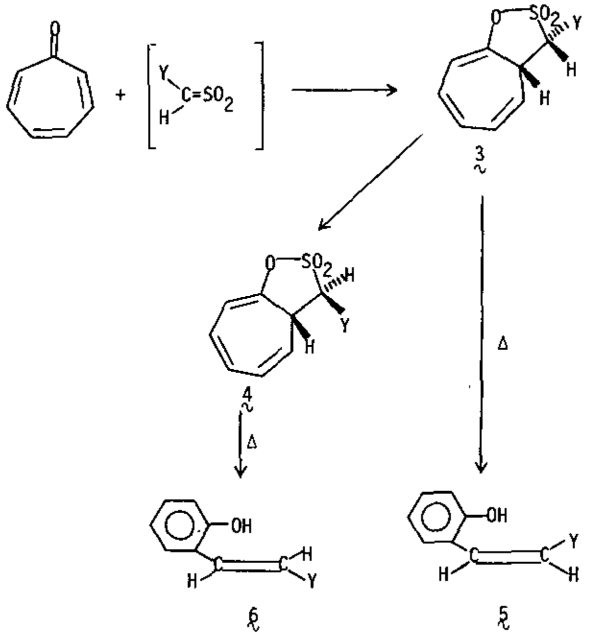
A particularly relevant example, is the [6 + 2] cycloaddition of sulfene and of phenylsulfene with a 6-amino-1-azafulvene derivative.[24] The product of this reaction is a unique γ-sultam.



(R=H, C_6H_5)

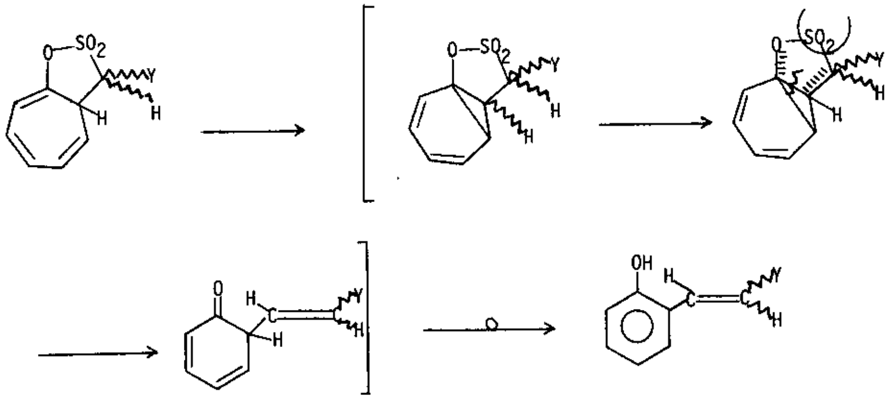
As might be anticipated from the dipolar character of tropone, iminotropones and thiotropone, they too form cycloadducts with sulfenes. Not only are the initial γ-sultones, γ-sultams and γ-thiosultones interesting; but, in many instances, they serve as precursors to other heteroatom systems.

Generation of monosubstituted sulfenes in the presence of tropone,[25] results in the formation of γ-sultones, 3.[26,27]

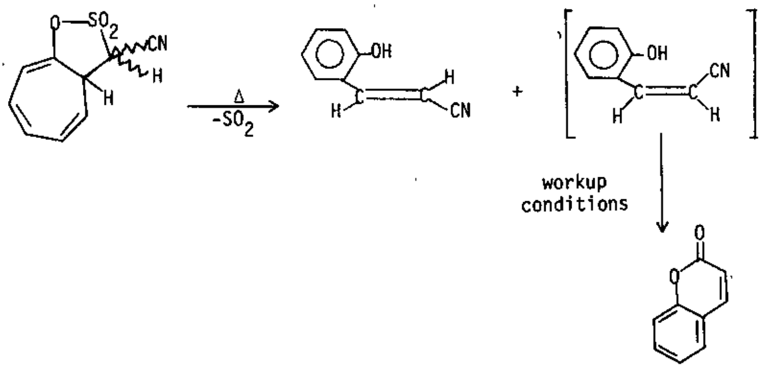


The anion-stabilizing capability of the sulfene substituent has a marked effect in determining if the cycloadduct isolated will have cis or trans geometry. When the substituent, Y, is aryl, cycloadduct 3 is obtained. The cis geometry can be rationalized as coming about via the endo approach of the substituted sulfene, and involving a concerted [8 + 2] process or a zwitterionic intermediate with preferred collapse to the cyclic sultone. However, when Y is capable of significant anion stabilization ($-COC_6H_5$, $-SO_2CH_3$, $-CO_2CH_2CH_3$) the trans cycloadduct 4 is obtained. Presumably the cis cycloadduct is formed initially; but, due to the availability of base in the reaction medium and the inherent acidity of the α-sulfonyl proton, post isomerization occurs. Where structure 3 is actually isolated, isomerization to 4 can be accomplished by treatment with strong base at low temperature followed by protonation.

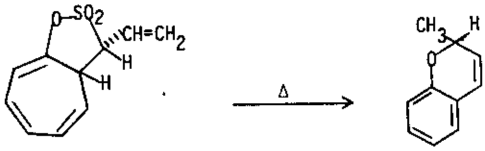
Upon heating, the γ-sultones lose sulfur dioxide to produce the corresponding *o*-hydroxystilbene or ω-substituted *o*-hydroxystyrene. This extrusion-rearrangement process proceeds stereospecifically with cis-*o*-hydroxystyrene (stilbene) 5 being obtained from 3 and trans-*o*-hydroxystyrene (stilbene) 6 from 4. Presumably the initial cycloadduct undergoes closure of the cycloheptatriene moiety to the norcaradiene tautomer, followed by a retro Diels-Alder type process.



The thermolysis of an equilibrium mixture of γ-sultones (3 and 4, Y=CN) led to the expected trans-*o*-hydroxy-β-cyanostyrene and coumarin, arising through the cis-cyanostyrene.

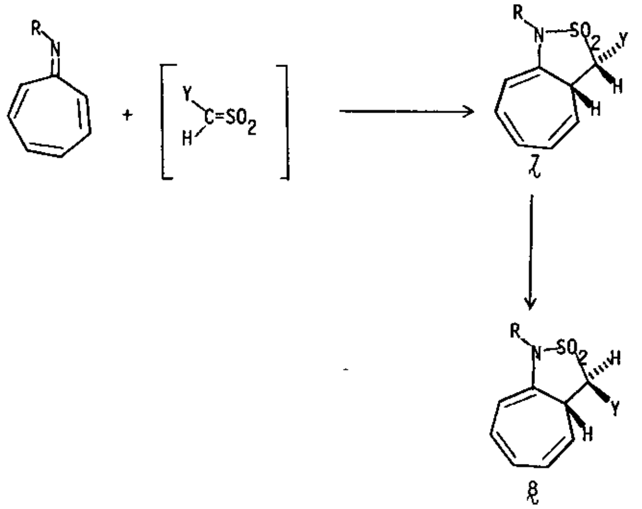


In a similar type of system, cis-γ-sultone (3, Y= $CH=CH_2$) gave 2-methyl-2H-1-benzopyran on heating in aqueous dioxane.



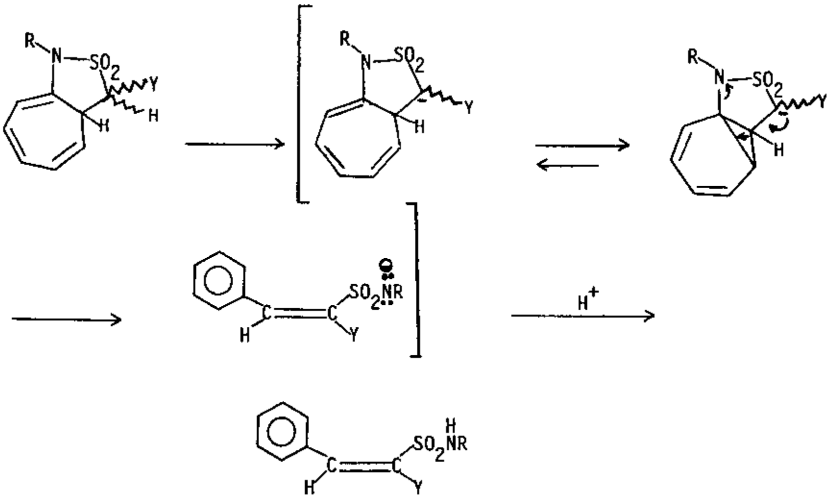
Attempts to obtain tropone cycloadducts from simple sulfene and alkylsulfenes failed. Instead, sulfene dimerizes to mesylsulfene prior to adduction with the substrate.

Iminotropones exhibit greater reactivity than tropone does towards sulfene cycloadditions, inasmuch as simple sulfene and alkylsulfenes form cycloadducts. Alkyl-[28,29] as well as aryl-azaheptafulvenes[30-32] are reactive substrates resulting in γ-sultams, 7. The initial cycloadduct bears cis (endo) stereochemistry when the sulfene substituent is alkyl or aryl (structure 7).



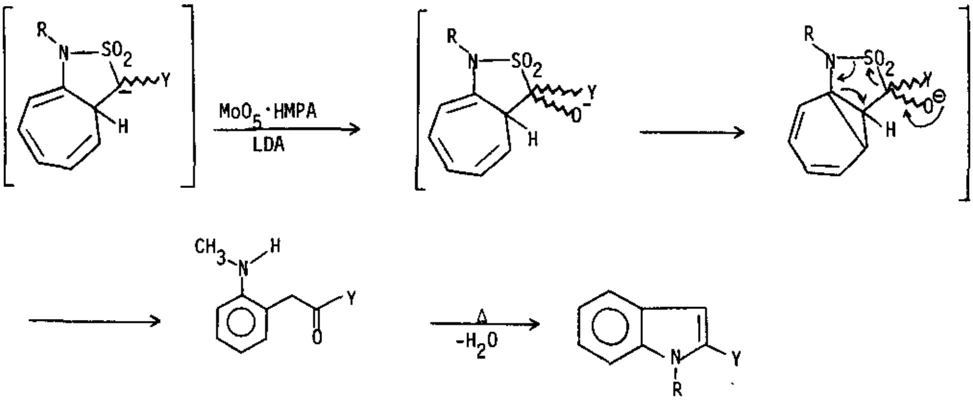
Isomerization of cis-γ-sultam, 7, to the trans-γ-sultam, 8, can be accomplished under basic conditions. However, when the sulfene substitutent is a strong anion-stabilizing unit, presumed post isomerization of 7 leads to the isolation of 8.

In contrast to the γ-sultones, the γ-sultams do not undergo the retro Diels-Alder reaction (loss of SO_2). However, both cis and trans-γ-sultams do undergo an interesting rearrangement under basic conditions.[29,32] Treatment with butyllithium or with LDA at low temperature followed by warming or heating yields (Z)-α-substituted styrenesulfonamides.



The rearrangement presumably involves the norcaradiene tautomer and was observed when Y was aryl or alkyl, but not when it was hydrogen, mesyl or carboethoxyl. A like rearrangement took place with the phenylsulfene-tropone adduct to yield trans-1,2-diphenylethenesulfonic acid.[29]

Still another interesting conversion of the γ-sultams and γ-sultones constitutes a novel synthesis of 1,2-disubstituted indoles and 2-arylbenzofurans, respectively,[33] and involves a low temperature oxidation of the corresponding γ-sultam or γ-sultone anions using $MoO_5\cdot HMPA$ reagent.[34-36] The reaction is unique in that oxidation, rearrangement and *ring closure to the indole or benzofuran* occurs in one pot with good yields. The system accommodates a variety of substituents.



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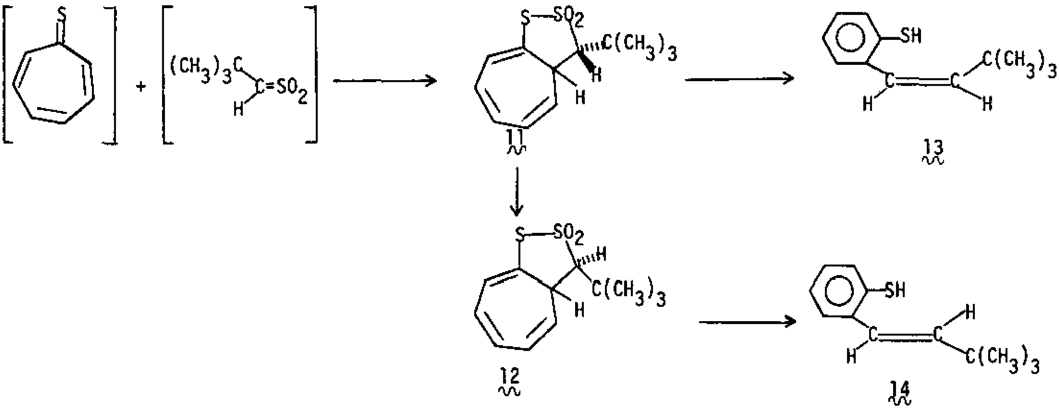
The intermediacy of 9 ($Y=CH_3$ and $R=CH_3$) was supported by the nmr and ir data on the oil isolated under non-acidic, low temperature conditions.

Although thiotropone has not received the attention that tropone and iminotropone have, cycloaddition with t-butylsulfene results in the cis-γ-thiosultone (11).[37] Isomerization to the trans-γ-thiosultone (12) is accomplished with lithium diisopropylamide at -78°C.



Both the cis and trans $\underline{\gamma}$-thiosultone undergo loss of SO_2 to give the cis-*o*-mercapto-$\underline{\beta}$-t-butylstyrene (**13**) and the trans-*o*-mercapto-$\underline{\beta}$-t-butylstyrene(**14**), respectively. Interestingly, the γ-thiosultones undergo loss of SO_2 under much less drastic conditions (65°C, 1 hour) than do the $\underline{\gamma}$-sultones (110°, 12 hours).

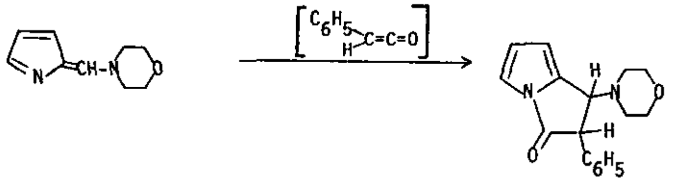
2. Ketenes

Ketenes as reactive intermediates usually are generated in situ by inducing an appropriate precursor to rearrange or to eliminate the ketene moeity under photolytic, thermal or basic conditions.[5] The most extensively investigated cycloaddition reaction involving ketenes is the [2 + 2] process leading to four-membered rings. For example, dichloroketene[38] and diphenylketene[39] readily undergo [2 + 2] cycloadditions with cyclic and acyclic vinyl ethers to form the corresponding substituted cyclobutanones.

The reaction between cyclopentadiene and dichloroketene gives the expected [2 + 2] cycloadduct (which on treatment with aqueous acetate rearranges to tropolone in good yield).[40-43] Furthermore, the stereochemistry of the reaction of mono-and disubstituted ketenes with cyclopentadiene has been been extensively investigated.[44] The results are in accord with a Woodward-Hoffmann thermally-allowed $[\pi_2{}^s + \pi_2{}^a]$ cycloaddition involving the orthogonal approach of the ketene to the olefin.[45]

Additional substrates employed for cycloadditions with ketenes have included ynamines,[46,47] acetylenic ethers[48-50], carbonyl compounds,[51-52] Schiff bases,[53-56] and nitrones.[57]

Perhaps the system which bears closest analogy to the focus of this review, is the cycloaddition between 6-amino-1-azafulvene and phenylketene.[24]



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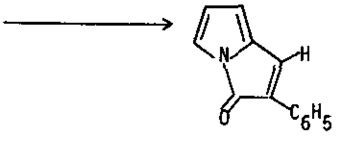

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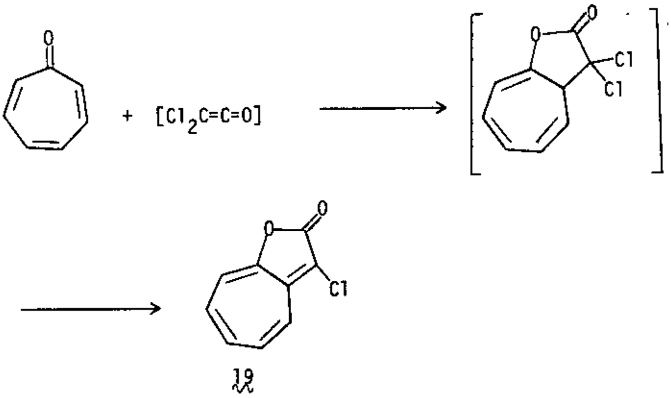
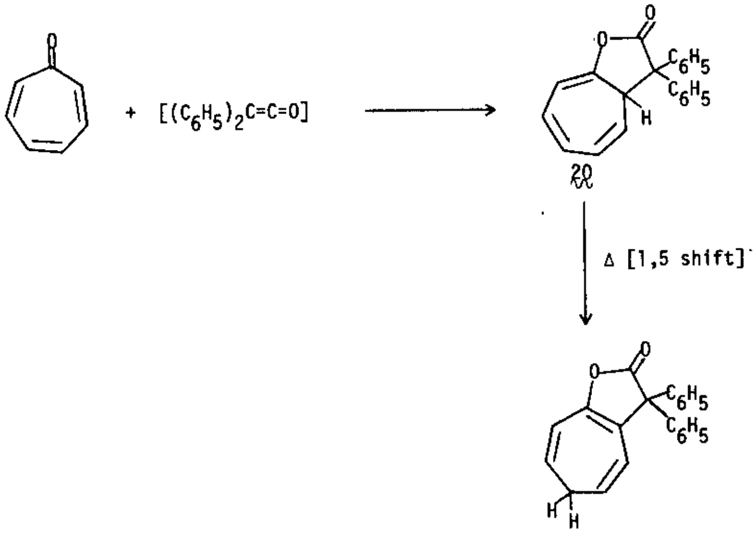
The resulting $\underline{\gamma}$-lactam, **17**, can be made to eliminate morpholine to give **18**.

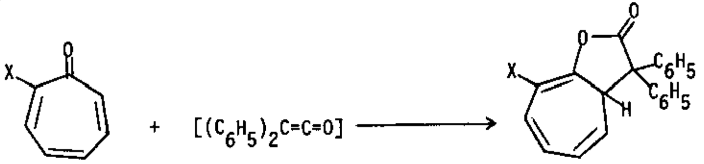
Dichloroketene undergoes cycloaddition with tropone to give the heptafulvene (**19**) but only in 19% yield.[58] The [8 + 2] cycloadduct is formed first, followed by elimination of HCl.



Similarly, diphenylketene undergoes cycloaddition with tropone generating the [8 + 2] cycloadduct (**20**) in good yield.[59] However, on heating, the γ-lactone undergoes a [1,5] sigmatropic shift.

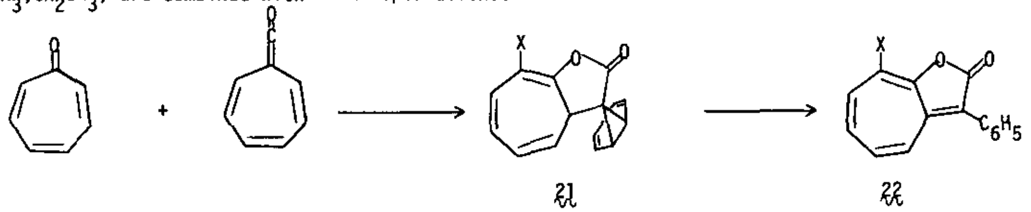


Substitution at the number 2 carbon of the tropone nucleus has a significant effect on the yield of [8 + 2] cycloadduct, when reacting with diphenylketene. The regioselective outcome is what might be anticipated, cycloaddition occurs only at the unsubstituted carbon.[60]



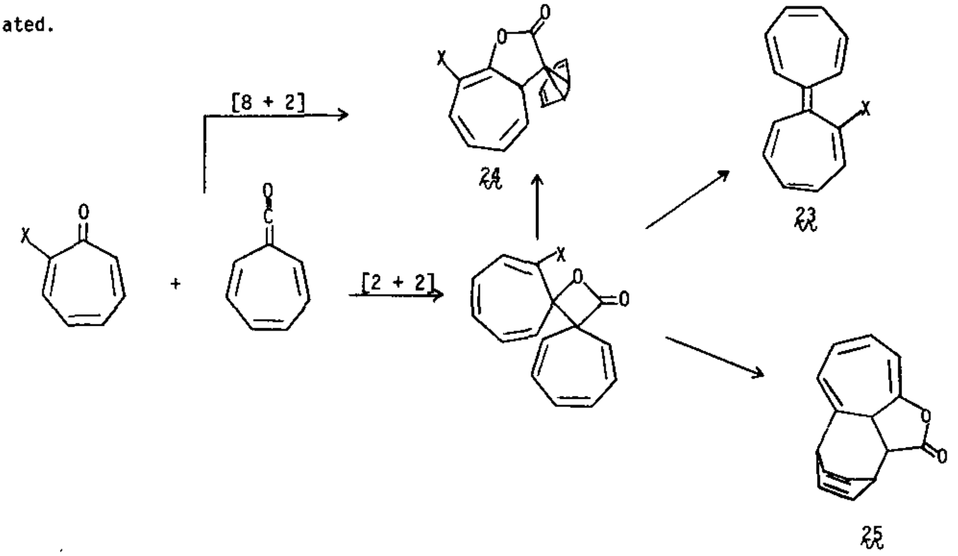
X=OCH_3, 50%; X=$N(CH_3)_2$, 7.8%
X=Cl, 82%

8-Oxoheptafulvene proved to be a very interesting ketene unit in cycloadditions with tropone. Only one product (21) is obtained when tropone, 2-halotropones (X=Cl, Br), or 2-alkyltropones X=CH_3,CH_2CH_3) are combined with 8-oxoheptafulvene.[61,62]



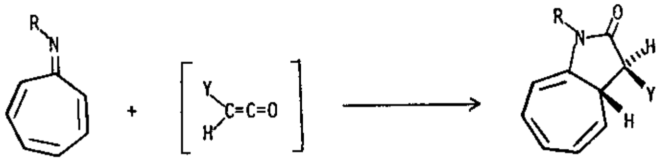
When the γ-lactone (21) is refluxed in xylene, the norcaradiene unit aromatizes and undergoes dehydrogenation to γ-lactone, 22.

However, when 2-methoxy-and 2-dimethylaminotropone[62-64] were allowed to react with 8-oxoheptafulvene, the results suggest that more than a simple [8 + 2] cycloaddition may be involved in product formation. With 2-methoxytropone adducts 23 (11.4%), 24 (13.3%) and 25 (28%) are isolated.

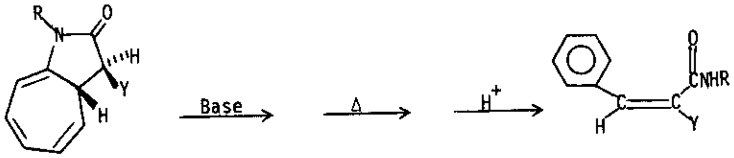


The 2-methoxyheptafulvene arises from a [2 + 2] cycloaddition followed by decarboxylation. The γ-lactone (24) could be accounted for by either a [2 + 2] cycloaddition followed by a valence bond isomerization or a simple [8 + 2] cycloaddition. The cyclohexa-1,4-diene (25) was proposed to arise via an initial [2 + 2] process, a [1,7] oxygen migration, a [3,3] sigmatropic shift and finally elimination of methanol. The 2-dimethylaminotropone system produced like products in similar yields.

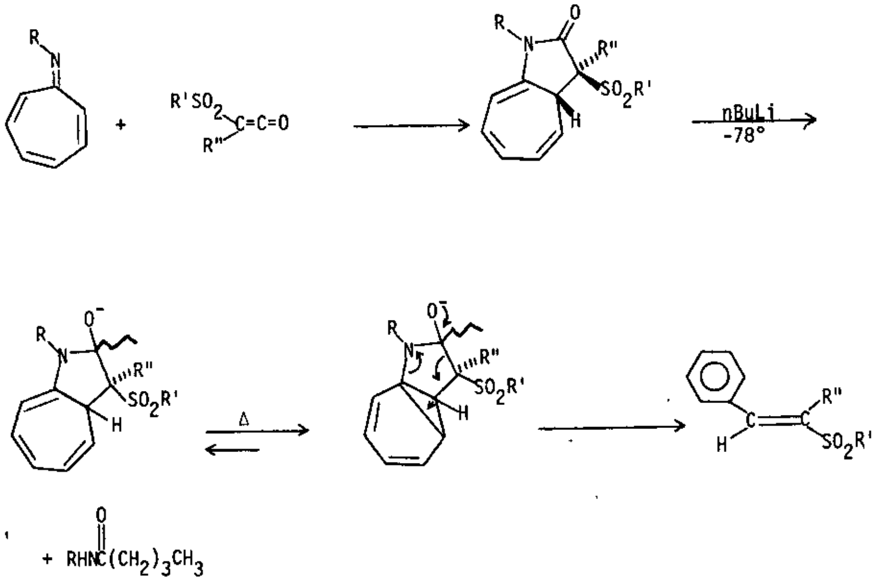
Iminotropones likewise cycloadd ketenes in an [8 + 2] fashion. Monosubstituted alkyl-and arylketenes yield 1:1 cycloadducts when generated in the presence of 8-alkyl-and-8-aryl-azaheptafulvenes.[65] The initial cycloadducts bear trans (exo) stereochemistry. These $\underline{\gamma}$-lactams



on treatment with one equivalent of lithium diisopropylamide followed by heating are converted into (Z)-$\underline{\alpha}$-substituted cinnamamides.[66]

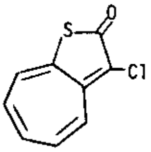


As would be expected disubstituted ketenes[65] also undergo [8 + 2] cycloaddition with iminotropones. Of some synthetic value are the cycloadducts from iminotropones and disubstituted ketenes bearing at least one sulfonyl unit. The cycloaddition is stereospecific as indicated in the equation below.[67]



Furthermore, treatment of the [8 + 2] cycloadduct with an alkyllithium reagent at low temperature gives exclusively the (E)-vinylic sulfone.

In the area of ketene cycloadditions, thiotropone has received only limited attention. Reaction with dichloroketene and diphenylketene gave the [8 + 2] adducts (26 and 27) in good yield (80%),[68] while reaction with 8-oxoheptafulvene gave the γ-thiolactone (28) in 15% yield.[64]



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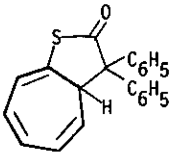

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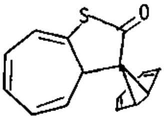

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It is our hope that this review concerning the cycloaddition reactions of sulfenes and ketenes with tropone and tropone analogs will be helpful and stimulating for further work in this interesting area of chemistry.

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