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# Cycloaddition reactions of unsaturated sulfones

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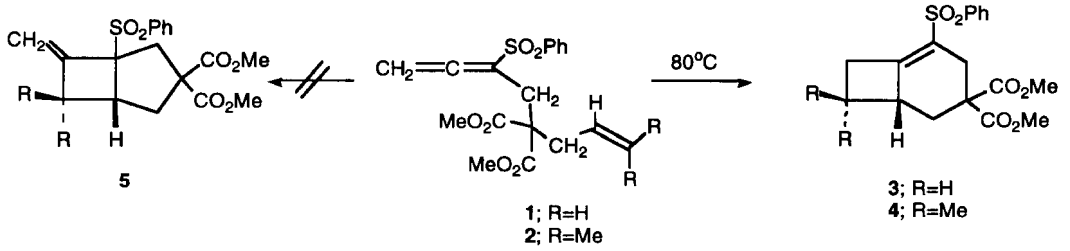
***Abstract**: The reaction of a series of allyl-substituted bis(phenylsulfonyl)-methanes or dimethyl malonates with 2,3-bis(phenylsulfonyl)-1,3-butadiene in the presence of base afforded alkenyl-substituted allenes in good yield. The reaction proceeds by initial attack of the soft carbanion onto the terminal position of the diene and subsequent $PhSO_2^-$ elimination to give the phenylsulfonyl substituted allene. The thermal reactions of these phenylsulfonyl allenes gave [2+2]-cycloadducts. Only the $C_1$-$C_2$ double bond of the allene participates in the [2+2]-cycloaddition. Stepwise bonding prefers to occur in a 1,6-exo manner rather than in a 1,7-endo fashion. The formation of all products can be rationalized by a mechanism which includes an initial carbon-carbon bond formation involving the central allene carbon to give a diradical intermediate. The product distribution is then determined by the substitution pattern of the alkene and the fate of the diradical intermediate.*

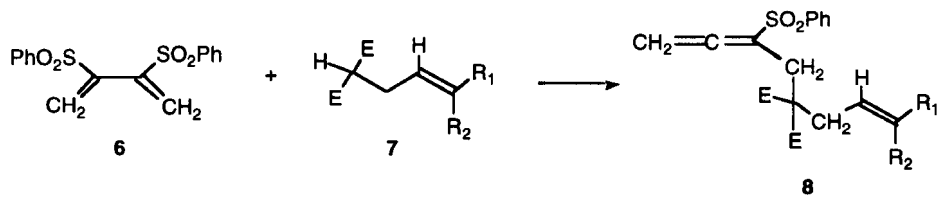
[2+2]-Cycloaddition reactions between allenes and ethylene derivatives have frequently been employed for the preparation of methylene cyclobutane derivatives.[1] Many of these reactions proceed by way of photochemical initiation, in which case the mechanistic pathway involves stepwise ring closure *via* diionic or diradical intermediates.[2] Not only is there considerable regiochemical regularity in the [2+2]-photoaddition, but the products are also easily transformed into useful ring systems by one of several general methods[3] making this a very synthetically useful reaction. While well represented in the literature, these photochemical protocols are not the sole choice for allenic [2+2]-cycloadditions. Certain examples involve Lewis acid catalysis, where ionic intermediates are clearly involved.[4,5] Still others proceed under strictly thermal conditions.[6,7] The mechanistic details associated with these [2+2]-reactions constitute a topic of much study and debate.[8] Substitution on the allene not only enhances its reactivity but also allows for the formation of a mixture of regioisomers. In most cases it has not been unequivocally established whether the cyclizations are concerted or stepwise in nature. A concerted reaction would require an *antarafacial-suprafacial* orbital interaction and result in a stereospecific cyclization. On the other hand, a stepwise mechanism would proceed by an initial rate-determining carbon-carbon bond formation, most likely involving the central carbon of the allene, due to allyl stabilization in the resulting diradical, followed by a subsequent radical coupling. This latter step has been termed the *"product-determining step"*[9] since there are two possible sites for secondary ring closure. If this process is rapid enough, the entire cyclization will occur with stereospecificity. Thus, the distinction between a concerted and stepwise mechanism is not necessarily apparent in product distribution. Furthermore, molecular orbital calculations indicate that the two mechanisms are comparable energetically.[10] Intramolecular [2+2]-cycloaddition of allenes has also been studied, and this process constitutes a particularly versatile method for the stereocontrolled synthesis of a variety of functionalized polycyclic compounds.[11]

In connection with our efforts toward the development of new methodologies using sulfonyl substituted allenes,[12] we uncovered a highly chemo- and stereospecific intramolecular [2+2]-cycloaddition of phenylsulfonyl allenes **1** and **2**.[13] The only products formed in both cases corresponded to the [2+2]-cycloadducts **3** and **4** in 90 and 85% yield, respectively. It is particularly interesting to note that only the $C_1$-$C_2$ double bond of the allene




participates in the cycloaddition. This result is quite interesting since phenylsulfonyl substituted allenes react with various 4π-systems in a highly chemoselective fashion undergoing cycloaddition across the more activated $C_2$-$C_3$ π-bond.[14] Our ongoing interest in the generality and synthetic utility of intramolecular cycloaddition reactions inspired us to take a more detailed look at the scope and mechanistic details of this process.

Our general interest in this area originates from a study of the reaction of 2,3-*bis*(phenylsulfonyl)-1,3-butadiene (**6**) with soft carbanions. Treatment of **6** with a series of allyl-substituted *bis*(phenylsulfonyl)methanes (**7**) afforded allenes **8** in 60-80% yield. The reaction proceeds by initial conjugate addition onto one of the vinyl sulfone groups to give a phenylsulfonyl-stabilized allyl anion which collapses with phenylsulfinate ejection to form the allene. Thus, through the use of *bis*(phenylsulfonyl)alkenes, themselves conveniently prepared by the reaction of *bis*(phenylsulfonyl)methane with the corresponding alkyl halide, allenes **8** were easily generated.

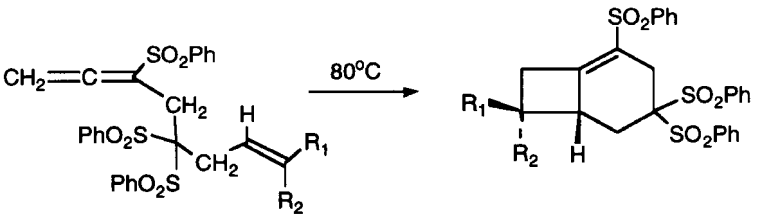



The thermal reactions of these allenes were performed by heating the reactants in benzene. The only products formed in all cases (*ca* 80-98% yield) corresponded to the 2+2-cycloadducts **9** which were fully characterized by their $^1H$ and $^{13}C$-NMR spectra. In the case of **8c**, the stereochemistry of the cycloadduct (**9c**) was unequivocally established by X-ray crystallographic analysis.

Several trends are evident upon inspection of these results. First of all, if the reaction had proceeded *via* the concerted pathway, the regioselectivity would be quite surprising, inasmuch as the observed products are the result of a formal [2+2]-cycloaddition across the non-activated π-system of the allene. According to MNDO calculations, the largest and second largest LUMO coefficients reside on the $sp^2$ carbons *beta* and *alpha* to the sulfonyl group, respectively. Indeed, this activated π-bond has been shown to engage in [4+2]-cycloadditions with very high chemoselectivity.[14] We believe that the periselectivity observed is related to stereoelectronic factors. The primary spatial requirement for [2+2]-cycloaddition is that the distance between the $C_2$ carbon of the allene and the olefinic π-bond should be sufficiently close that effective overlap of the π-systems can occur. The initial rate-determining carbon-carbon bond formation occurs between the central allene carbon and the proximal alkene carbon atom. The regioselectivity on the alkene system is due to less

clear-cut parameters. Evidently, it is easier for stepwise bonding to occur in a 1,6-*exo* manner (leading to diradical **10**) than in a 1,7-*endo* fashion. When one compares this type of ring closure with analogous radical cyclizations, the observed *6-exo trig* process on the proximal alkene carbon follows the empirically derived rule which disfavors the *7-endo trig* alternative involving the distal alkene carbon.

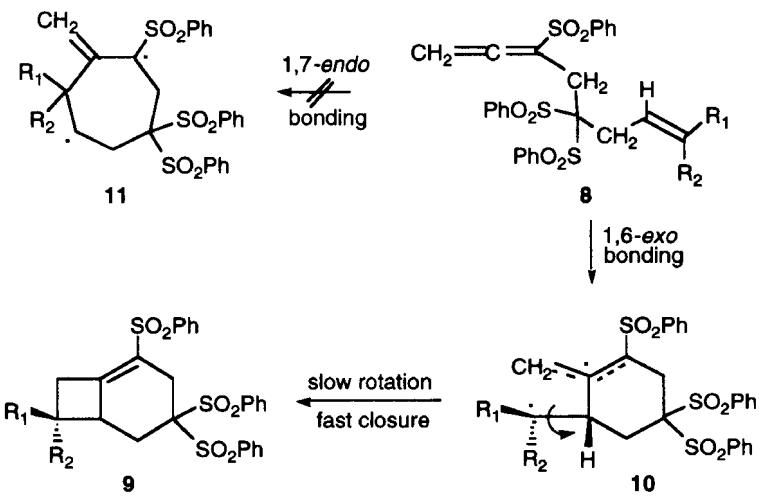
Substitution on the alkene portion also affects the rate of the reaction, presumably by influencing the stability of that portion of the resulting diradical. Thus, cyclization of the dimethyl derivative **8b** (*via* the tertiary radical **10b**) is complete in 45 min, whereas the unsubstituted analog **8a** (giving rise to the primary radical intermediate **10a**) requires 22 h for completion. The rates of the two monomethyl variants **8c** and **8d** (secondary radical intermediates **10c** and **10d**) fall between the other two values (*i.e.*, 7 h), as expected.




**8a**; $R_1$=$R_2$=H
**8b**; $R_1$=$R_2$=Me
**8c**; $R_1$=Me; $R_2$=H
**8d**; $R_1$=H, $R_2$=Me

**9a**; $R_1$=$R_2$=H
**9b**; $R_1$=$R_2$=Me
**9c**; $R_1$=Me; $R_2$=H
**9d**; $R_1$=H, $R_2$=Me

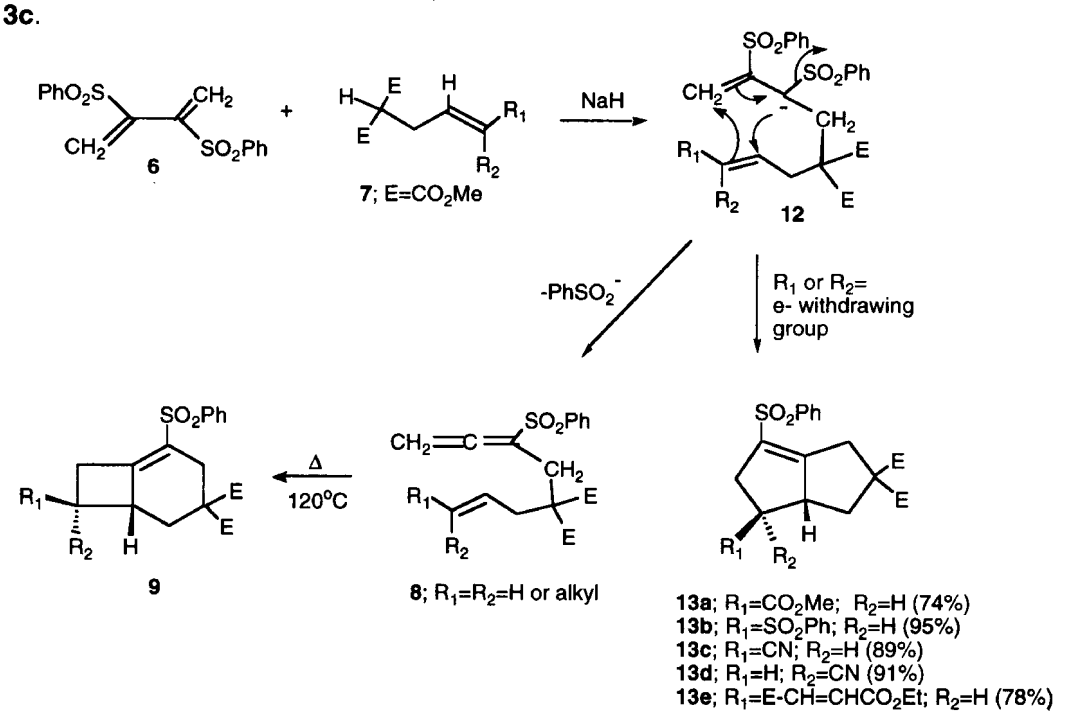
Another aspect of the cycloaddition worth noting is the complete stereospecificity of the process. Heating a sample of allene **8c** in benzene for 7 h produced cycloadduct **9c** as the exclusive product. Thermolysis of **8d**, on the other hand, gave rise to diastereomer **9d** in 90% yield with no detectable signs of **9c**. Since the allene adduct **10** contains two orthogonally twisted π-bonds, the initially formed allyl radical is also orthogonally twisted. Considering the lack of significant stabilization of the nonallylic part of the diradical intermediate, it might be expected to cyclize rapidly, thereby accounting for the high stereoselectivity observed. In fact, rotation of the allylic radical site might well be subject to considerable barriers. The regioselectivity encountered may also be due to efficient radical stabilization by the $PhSO_2$ group, which, unlike $RCO_2$, is free from anisotropic constraints of π-overlap.



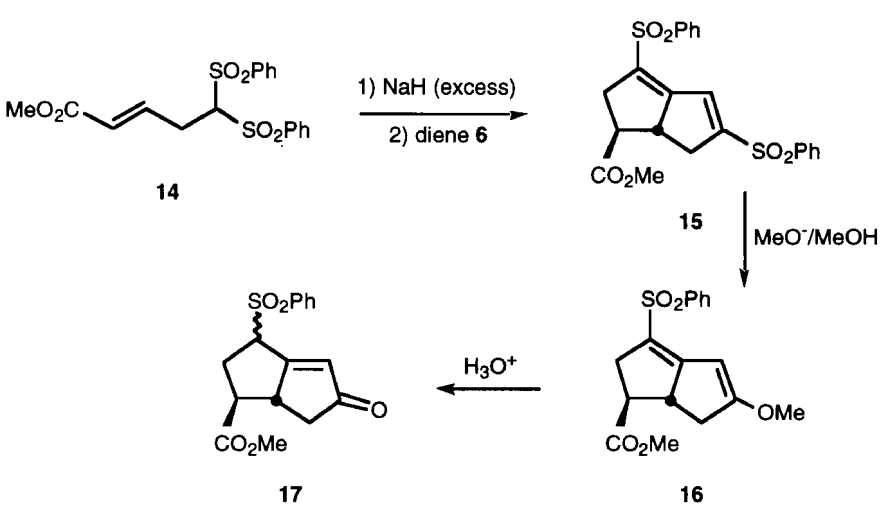

**11** **8** **9** **10**

When an electron-withdrawing substituent was situated on the double bond, an entirely different transformation occurred.[15] Thus, treatment of **7a** with NaH in THF at 0°C, followed by the addition of diene **6** afforded bicyclo[3.3.0]octene **13a** in 74% yield. When

these conditions were applied to the other alkenes investigated, the corresponding bicyclic compounds were obtained in high yield. Another aspect of the cycloaddition worth noting is the complete stereospecificity of the process. For example, subjecting isomerically pure *E*-alkenes **7a-7c** and **7e** to the tandem cyclization process produced only the *trans*-cycloadducts. Likewise, *Z*-nitrile **7d** afforded *cis*-adduct **13d** with no detectable signs of **13c**.




Tandem or cascade processes occupy a central role in molecular construction, and new methods which lead to synthetically versatile arrays are particularly valuable.[16] The considerable importance of cyclopentanoid natural products has led to the development of a great number of new strategies for their construction. While most of the cyclization methodologies typically involve the construction of a single carbon-carbon bond,[17] interest in new cyclopentannulation sequences by multiple bond constructions has intensified since these processes generate complex molecular frameworks in a single operation.[18] The functional tolerance and stereochemical control displayed by the above process makes it extremely useful for the synthesis of natural products containing fused *bis*-cyclopentanes.[19] An interesting application of the method involves the preparation of bicyclo[3.3.0]octenone **17**. *Bis*(sulfone) **14** was prepared and studied as a tandem Michael substrate. The phenyl-



sulfonyl groups permit ready activation of $C_5$ as a Michael donor and then, following cyclization, allow for the removal of the cumbersome functionality. Indeed, the reaction of **14** with excess NaH using diene **6** afforded **15** in 58% yield. This compound is derived by elimination of phenylsulfinate from the initially formed cycloadduct. Further treatment of **15** with sodium methoxide in MeOH gave enol ether **16** which, on aqueous hydrolysis, produced the synthetically useful bicyclo[3.3.0]octenone **17** as a 2:1-mixture of diastereomers.

The results from the above examples show that phenylsulfonyl-substituted allenes undergo clean intramolecular [2+2]- and [3+2]-cycloadditions. In the case of the [2+2]-cycloaddition reaction, the products can be rationalized by a mechanism which proceeds *via* an initial carbon-carbon bond formation involving the central allene carbon to produce a diradical intermediate. The product distribution is then determined by the regioselectivity of the alkene and the fate of the diradical intermediate. These internal [2+2]-cycloadditions proceed in high yield and provide highly functionalized ring systems. Our studies also demonstrate the potential of using the tandem Michael addition-[3+2]-anionic cyclization sequence of unsaturated sulfones for the formation of five-membered rings. The overall reaction involves a series of three sequential conjugate additions followed by phenylsulfinate ion ejection. The tandem cyclization sequence takes advantage of the usual role of the sulfonyl group as a carbanion stabilizer and also illustrates its utility as a leaving group under extremely mild conditions.[20]

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