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DIPOLAR CYCLOADDITION REACTION OF (PHENYLSULFONYL)PROPADIENE WITH NITRONES AND ALKYLATION STUDIES OF THE CYCLOADDUCTS

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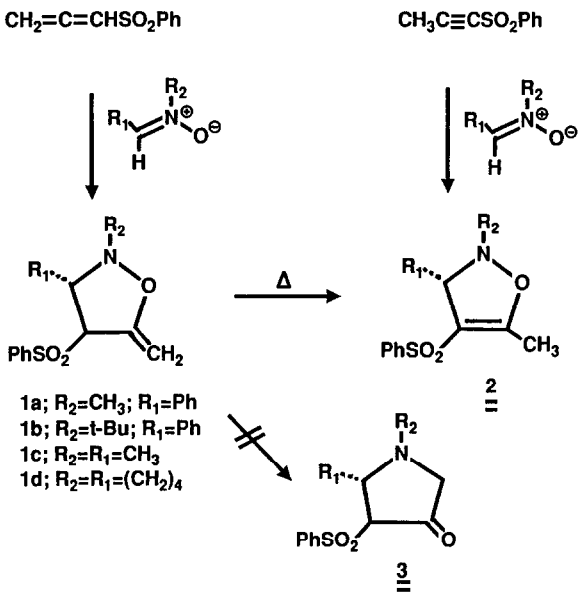
Abstract: Dipolar cycloaddition of nitrones with (phenylsulfonyl)propadiene give 4-sulfonyl substituted isoxazolidines whose reactions with base and several electrophiles have been studied.

The ability of allenes to undergo bimolecular cycloaddition reactions with a variety of unsaturated pi-systems has provided the synthetic chemist with a convenient route for the construction of complex ring systems.[1-5] While the Diels-Alder reaction of allenes with dienes has been studied in some detail,[6-8] the use of allenes in 1,3-dipolar cycloadditions has been severely limited as a consequence of their unreactive nature as dipolarophiles.[9-12] As part of our ongoing interest in the synthetic applications of nitrone cycloaddition chemistry,[13] we have investigated the utility of (phenylsulfonyl)-propadiene as a synthetic equivalent of allene.[14] The phenylsulfonyl group can be readily removed by various methods[15] after the cycloaddition and thus the dipolar cycloadduct formed should be of some use in organic synthesis.

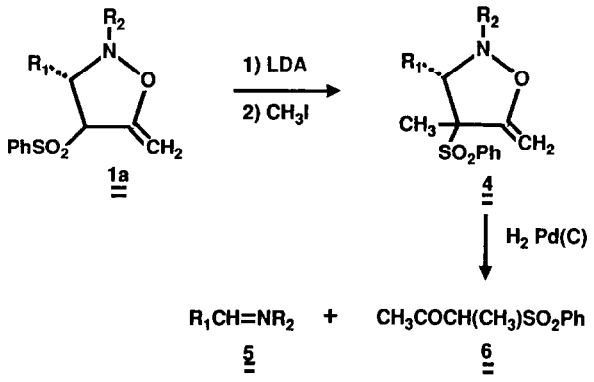
Based on FMO theory, allenes possessing electron withdrawing substituents are expected to undergo dipolar cycloaddition across the activated π-bond. MNDO calculations of (methylsulfonyl)propadiene indicate that the introduction of a sulfonyl group causes a significant lowering of the LUMO energy level compared with allene (ΔE=1.3 eV) and the largest LUMO coefficient resides on the central carbon and the next on the position bearing the sulfonyl group. This suggests that the reaction of nitrones with (phenylsulfonyl)propadiene will proceed in a highly regioselective fashion.

Stirring a solution of C-phenyl-N-methylnitrone and (phenylsulfonyl)propadiene in benzene at 40^{o}C for 6 hr gave cycloadduct 1a in 98% yield, mp 88-89^{o}C, NMR ($CDCl_3$,360 MHz) δ 2.40 (s, 3H), 4.23 (d, 1H, J=7.4 Hz), 4.37 (t, 1H, J=1.8 Hz), 4.48 (dt, 1H, J=7.4 and 1.8 Hz), 4.71 (t, 1H, J=1.8 Hz), 6.74 (t, 1H, J=7.4 Hz), 6.85 (t, 1H, J=7.5 Hz), 6.96 (m, 1H), 7.12 (m, 1H) and 7.30 (d, 1H, J=7.4 Hz). The isolation of cycloadduct 1a is of some interest since related 5-exo-methylene substituted isoxazolidines have only been reported as transient

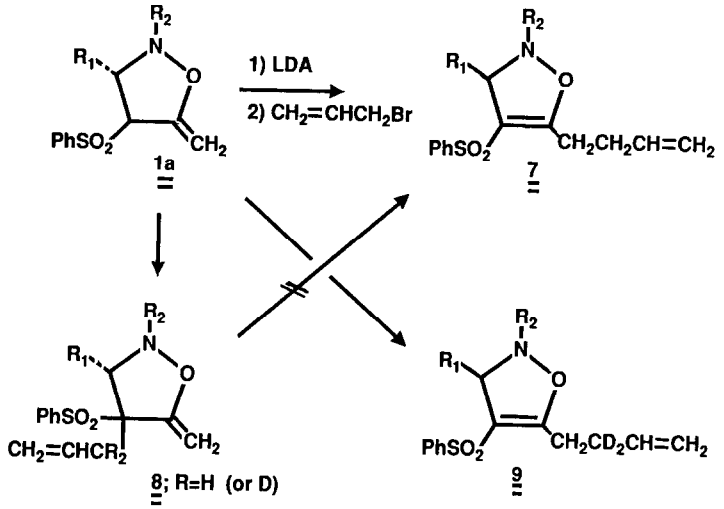


species which rapidly rearrange to 3-pyrrolidinones.[9,11] We have studied the thermolysis of 1 at 80°C and find that it reacts via a 1,3-hydrogen shift to give 2 rather than by N-O bond scission. Structure 2 was assigned on the basis of its spectroscopic data and by comparison with an independently synthesized sample prepared by the reaction of the nitrone with 1-(phenylsulfonyl)propyne.[16] Similar results were obtained with related nitrones (i.e. 1b-1d).

Considerable interest has recently been focused on the chemical transformations of allyl sulfones.[15] The key step of these transformations is the generation of allyl sulfonyl carbanions and their reactions with electrophilic compounds, leading to the formation of new C-C bonds. The RSO_2 functionality is subsequently removed from the product via reduction, elimination, or substitution, affording the target molecule. The reaction of lithiated allylic sulfones with alkyl halides is a well documented, synthetically useful process leading to α-alkylation.[17] Thus, the formation of 4 from the reaction of 1a with LDA followed by methyl iodide treatment came as no surprise. Hydrogenation of this material resulted in cleavage of the N-O bond followed by a retro-aldol type reaction to give imine 5 and acetylsulfone 6.



In order to obtain further information about the behavior of allyl sulfonyl carbanions of this kind, we investigated the reaction of 1a with allyl bromide. The only product formed from this reaction corresponded to the γ-allylated product 7. This result is a bit



surprising since, in most cases, allyl sulfonyl anions undergo exclusive α-alkylation.[15,17] Two fundamentally different mechanisms can explain the formation of compound 7. One route involves γ-alkylation, possibly owing to the steric environment about the α-site. The alternate path involves α-alkylation to give structure 8 (R=H) as a transient intermediate which rapidly undergoes a subsequent Cope rearrangement to the observed product. In order to distinguish between these two possibilities, we have investigated the reaction of 1a with LDA and 3-bromo-3,3-d_2-1-propene. The only product isolated from this reaction was structure 9 where the deuterium atoms were located at the β-position of the side chain. No

detectable quantities of the Cope product could be found since there was no incorporation of deuterium into the olefinic manifold. Evidently, the sulfone reaction proceeds via selective γ-alkylation, undoubtedly a consequence of steric hindrance to attack at the α-site. With a small electrophile such as methyl iodide, α-alkylation does occur. As the bulk of the electrophile increases, γ-alkylation becomes the dominant path. In fact, we have found that the reaction of 1a with a series of electrophiles (i.e. ethyl iodide, trimethylsilyl chloride, ethylene oxide, benzaldehyde, acetyl chloride, etc.) produced only the γ-alkylation product in high yield.

The base induced alkylations of related cycloadducts derived from activated allenes and their application toward alkaloid synthesis will be reported at a later date.

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