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TANDEM [3+2]-CYCLOADDITION [2,3]-SIGMATROPIC REARRANGEMENT REACTION OF ALLENYL SULFOXIDES WITH NITRONES

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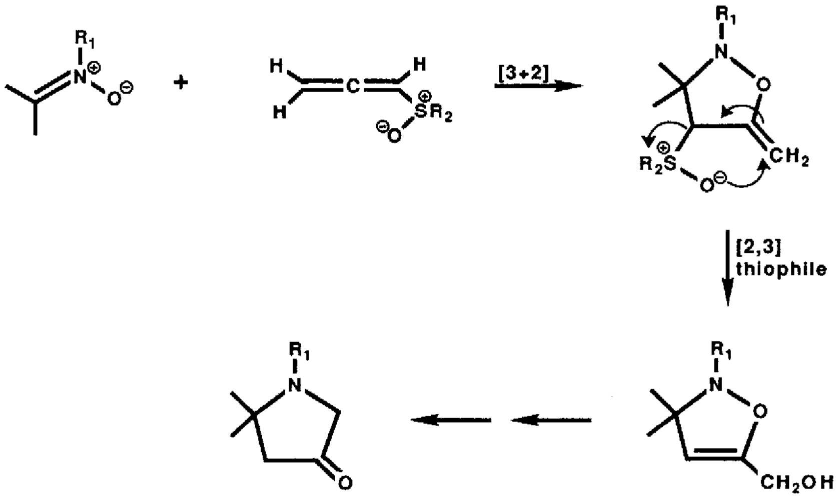
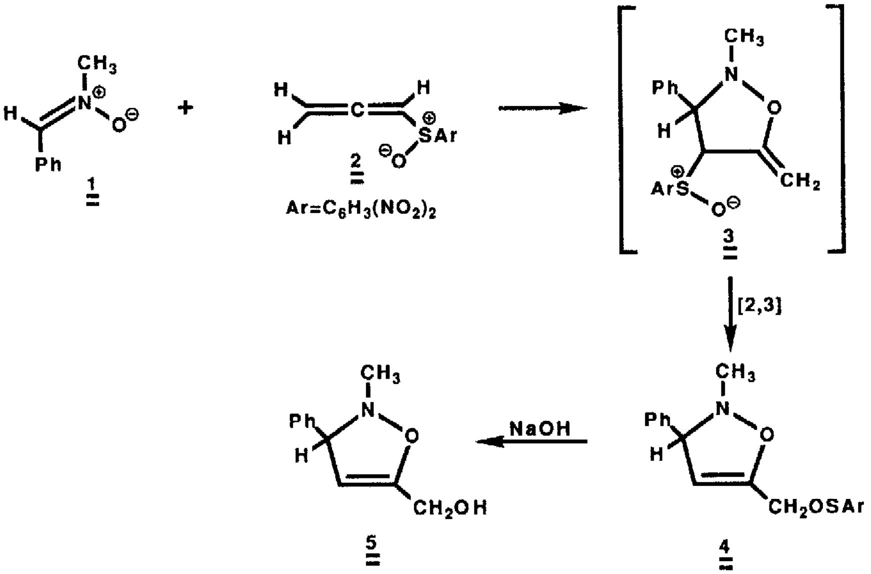
Abstract: The cycloaddition reaction of 2,4-dinitrophenylsulfinylpropadiene with several nitrones has been investigated. The initial 3+2-cycloadduct readily undergoes a subsequent 2,3-sigmatropic rearrangement.

A wide range of natural products containing the five-membered pyrrolidine ring continue to be isolated and to challenge the imagination of synthetic chemists.[1] New strategies for the construction of this heterocyclic ring are constantly being developed.[2-5] Dipolar cycloaddition of nitrones with alkenes represents an efficient method for the simultaneous introduction of a nitrogen substituent and creation of a carbon-carbon bond, and this strategy has been extensively exploited for the synthesis of alkaloids possessing the pyrrolidine ring.[6] As part of an ongoing program in the area of heterocyclic chemistry, we have been investigating the 1,3-dipolar cycloaddition chemistry of nitrones with allenes followed by their thermal rearrangement as a method for pyrrolidine synthesis.[7-9] If the [3+2]-cycloaddition of nitrones could be achieved with allenyl sulfoxides, then the resulting 5-methylene isoxazolidine might undergo a [2,3]-sigmatropic rearrangement and this would be followed by cleavage of the isoxazolidine ring and eventual cyclization. We record here some successful examples of this tandem [3+2]-cycloaddition-[2,3]-sigmatropic rearrangement protocol.

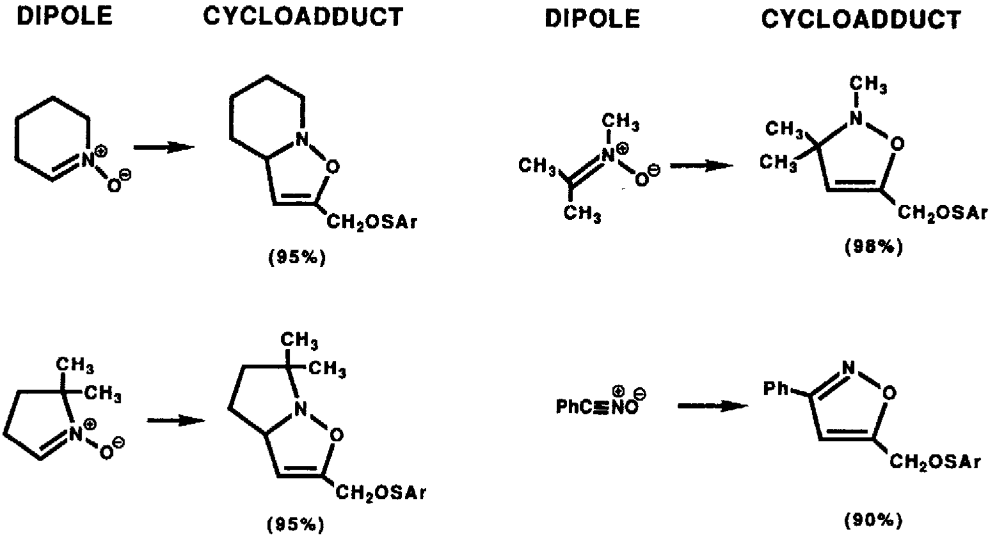


Allenes are an intriguing group of dipolarophiles since they contain two positions for attack.[10] All attempts to obtain a cycloadduct from the reaction of a wide assortment of nitrones with phenylsulfinylpropadiene failed, even at elevated temperatures or under high pressures (6-12 kbar). This result stands in marked contrast to the dipolar cycloaddition of nitrones with phenyl-sulfonyl allene which readily reacts at room temperature.[11] The difference in reactivity is probably a consequence of a large HOMO-LUMO gap with the phenylsulfinyl allene. Based on FMO theory,[12] introduction of electron withdrawing groups on the aromatic ring should cause a lowering of the LUMO energy level and facilitate the cycloaddition. This indeed proved to be the case. The reaction of 2,4-dinitrophenylsulfinylpropadiene with N-methyl-C-phenylnitrone in benzene at 40°C for 8 h gave the rearranged sulfenate ester **4** in 95% yield [NMR ($CDCl_3$, 300 MHz) δ 2.91 (s, 3H), 4.52 (d, 1H, J=13.0 Hz), 4.58 (d, 1H, J=13.0 Hz), 4.75 (d, 1H, J=2.0 Hz), 5.21 (d, 1H, J=2.0 Hz), 7.25 (m, 5H), 8.05 (d, 1H, J=9.0 Hz), 8.42 (dd, 1H, J=9.0 and 2.0 Hz) and 9.07 (d, 1H, J=2.0 Hz)]. The mechanism for the formation of cycloadduct **4** involves an initial dipolar cycloaddition of the nitrone across the more activated allene pi bond followed by a 2,3-sigmatropic rearrangement.



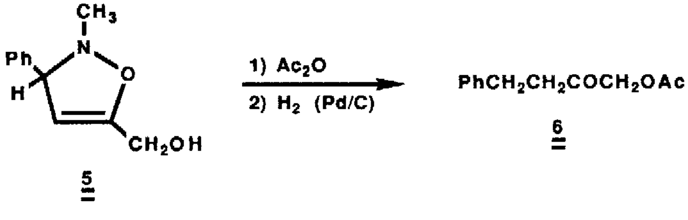
The dinitrophenylsulfinyl substituted allene was found to react smoothly with a variety of other nitrones to give sulfenate esters as outlined in Table I. In all cases, the yield of the isolated cycloadduct is excellent. The allylic sulfenates were readily converted to the corresponding alcohols either by treatment with trimethyl phosphite or by stirring with a 10% sodium hydroxide solution. We also studied the cycloaddition reaction of allene **2** with phenyl nitrile oxide. In this case the isoxazole ring was formed in 90% yield. It should be noted that dinitrophenylsulfinyl allene corresponds to a formal "equivalent" of propargyl alcohol which itself is too unreactive to undergo 1,3-dipolar cycloaddition with nitrones or nitrile oxides.

TABLE I



The preparation and chemistry of allylic sulfoxides and sulfenates have been elegantly elucidated in studies by Mislow,[13] Evans[14] and Braverman.[15] The sulfoxide is usually thermodynamically favored in the [2,3]-sigmatropic equilibrium, although the presence of low concentrations of sulfenate can be demonstrated by suitable trapping experiments. Numerous synthetic applications of these rearrangements have been reported.[16] The preferential formation of the sulfenate ester in the above cases can be attributed to the presence of the strongly withdrawing nitro substituents which presumably destabilizes the sulfoxide functionality as a consequence of an inductive effect. Previous work in the literature has shown that the sulfenate-sulfoxide equilibrium is quite sensitive to both structure and solvent effects.[13,17]

The N,O-heterocycles of the isoxazole series have proven to be particularly useful reagents for the synthesis of many nitrogen-containing natural products. The key feature of this approach involves the reductive cleavage of the heterocyclic ring to a γ-amino alcohol, which is further manipulated into other functional groups.[18-20] The Δ^4-isoxazoline ring present in structure **5** contains two potentially reducible functionalities: the C=C double bond and the N-O single bond. We have found that treatment of **5** with acetic anhydride followed by catalytic reduction over



palladium afforded 1-acetoxy-4-phenyl-2-butanone (**6**) in high yield. In this case, the initially reduced product readily eliminates methyl amine and the resulting enone is further reduced to the saturated ketone.[21]

Studies of the reduction reaction with other systems and its application toward the synthesis of the pyrrolidinone ring are in progress and will be reported on at a later date.

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21. Further work dealing with the hydrogenation of the N-substituted cycloadducts is in progress and will be reported on at a later date.

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