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Intramolecular [3+2]-Cycloaddition of Nitrones with Allenes and Alkynes

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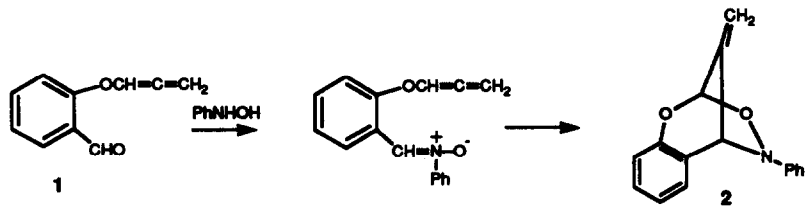
Abstract: *The intramolecular dipolar cycloaddition reactions of allenyl and alkynyl nitrones proceed smoothly to give high yields of cycloadducts.*

The 1,3-dipolar cycloaddition of a nitrone with an olefin is an extremely powerful, yet mild, means of producing carbon-carbon bonds as well as carbon-oxygen and carbon-nitrogen bonds.[1-6] The power of this reaction for ring construction is now well appreciated and has been employed by numerous groups in the total synthesis of alkaloids and other nitrogen-containing natural products.[7] Intramolecular nitrone cycloadditions have also been of considerable synthetic and mechanistic interest,[8] especially since the resulting isoxazolidine ring can serve as a precursor to 1,3-amino alcohols.[9] 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.[10] Allenes are an intriguing group of dipolarophiles since they contain two positions for attack.[11] The use of allenes in 1,3-dipolar cycloaddition chemistry has, however, been severely limited as a consequence of their unreactive nature as dipolarophiles. One way to overcome this problem is to incorporate an electron-withdrawing substituent onto the π-bond. MNDO calculations indicate that the introduction of an electron-withdrawing group causes a significant lowering of the LUMO energy level compared with allene, and the largest LUMO coefficient resides on the position bearing the substituent group.[12] This suggests that the reaction of nitrones with electron-deficient allenes will proceed in a highly regioselective fashion with cycloaddition occurring across the more activated C_1-C_2 π-bond. This proved to be the case in the reaction of various nitrones with allenes possessing cyano, carbomethoxy, or phenylsulfonyl substituents.[13]

As intramolecular cycloadditions exhibit enhanced reactivity and stereoselectivity over their bimolecular counterparts,[8] we reasoned that dipolar cycloaddition of a nitrone with an unactivated allene might also take place intramolecularly. In order to probe this possibility, we examined the reaction of o-(1,2-propadienyloxy)benzaldehyde (1) with phenylhydroxylamine. This reaction proceeded at room temperature in ethanol to give dioxaazabicyclo[3.2.1]octene **2** in 84% yield [mp 77-78°C; NMR ($CDCl_3$, 300 MHz) δ 4.86 (s, 1H), 5.18 (s, 1H), 5.42 (s, 1H), 6.14 (s, 1H), and 6.96-7.40 (m, 9H)]. The formation of **2** can readily be accounted for in terms of initial formation of a N-phenyl nitrone followed by intramolecular cycloaddition across the C_1-C_2 π-bond of the allene. The

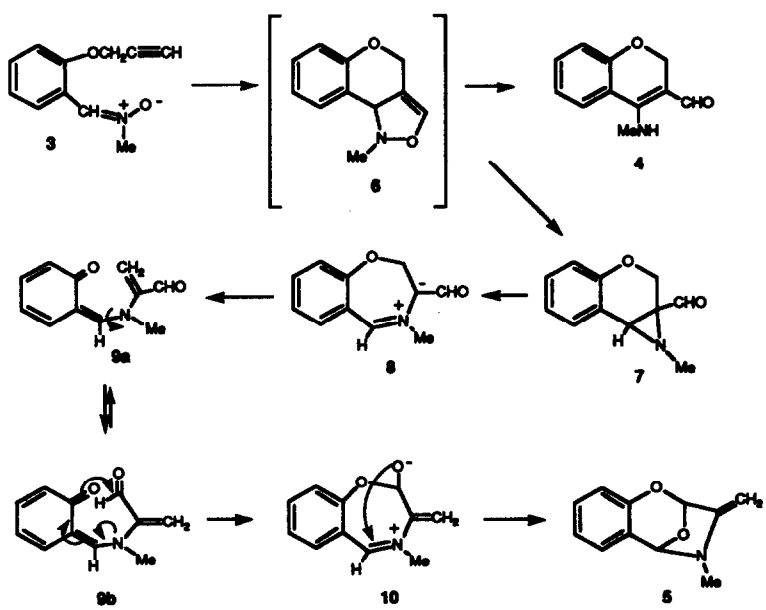


1 2

regiochemistry of the intramolecular nitrone dipolar cycloaddition reaction is complicated by an interplay of factors such as alkene polarity, ring strain, and other nonbonded interactions.[14] In general, the intramolecular situation can be assessed as a competition between the bridged and fused modes of cycloaddition. In the above case, only the bridged bicyclic system **2** is formed. This is consistent with its transition state possessing both better orbital overlap and fewer nonbonded interactions.

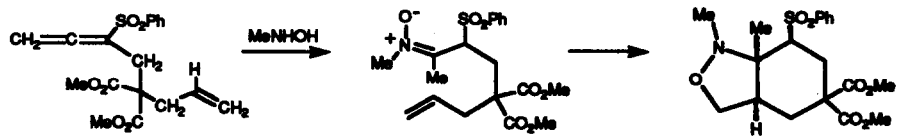
As a comparison, we also investigated the intramolecular dipolar-cycloaddition of the related acetylenic nitrone **3**. Heating a sample of **3** in benzene at 95°C for 4.5 h afforded a 1:5 mixture of compounds **4** and **5**. The structure of **5** was assigned on the basis of its characteristic spectral data.[15] A reasonable mechanism to rationalize the reaction is outlined in Scheme I. The first step involves an initial dipolar cycloaddition across the acetylenic bond to give the expected 4-isoxazoline **6** as a transient intermediate.[16] The next step proceeds by thermal cleavage of the weak O-N linkage and this is followed by ring closure to give aziridine **7**.[17] Subsequent C-C bond cleavage

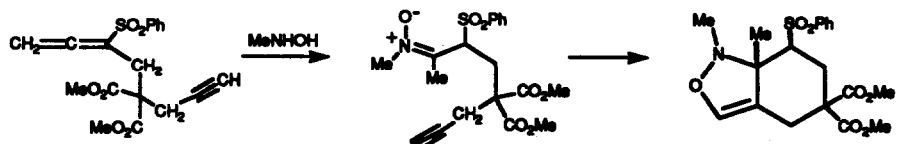
Scheme I



generates azomethine ylide 8[18,19] which readily collapses to *ortho*-quinone methide 9. This transient species is ultimately converted to 5 by the series of reactions outlined in Scheme I. In addition to producing aziridine 7, the diradical derived from 4-isoxazoline 6 can also undergo a hydrogen shift to afford aldehyde 4. Good analogy exists for most of the transformations depicted in the Scheme.[16-20]

Recently, a number of groups have studied the reaction of an oxime with an activated π-bond as a method for the preparation of a variety of substituted nitrones.[21] The reaction generally requires the presence of a Michael acceptor olefin in order to produce the nitrone. Once formed, the nitrone has been observed to undergo both inter- and intramolecular dipolar cycloaddition. The intramolecular version of the oxime cyclization has been employed in a number of natural product syntheses.[22] As part of our ongoing interest in the synthetic applications of nitrone-allene cycloaddition chemistry, we also examined the reaction of the phenylsulfonyl activated allene 11[23] with methylhydroxylamine. We reasoned that the initially formed nitrone 12 would undergo dipolar-cycloaddition to the neighboring π-system. Indeed, stirring a sample of 11 with MeNHOH at 25°C afforded 12 which cyclized to isoxazolidine 13 in 80% yield on heating in benzene for 4 h. A similar reaction occurred with the acetylenic system 14 producing 4-isoxazoline 16 in 89% overall yield.





The general nature of these observations and their application to the synthesis of various heterocyclic compounds are the object of ongoing investigations.

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