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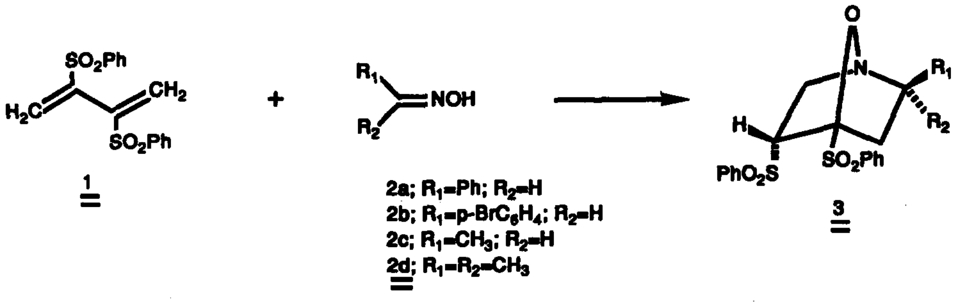
INTRAMOLECULAR CYCLOADDITION REACTIONS OF OXIMES WITH VINYL SULFONES

Albert Padwa and Bryan H. Norman*
Department of Chemistry, Emory University
Atlanta, GA 30322 U.S.A.

Abstract: The reaction of oximes with vinyl sulfones containing a π-bond produce cycloadducts which are derived from an intramolecular dipolar cycloaddition of a transient nitrone.

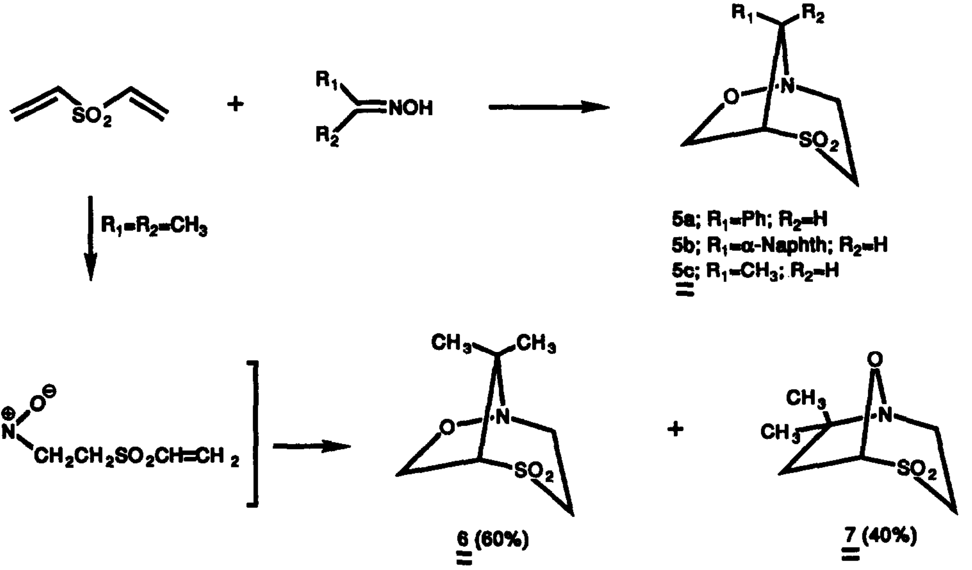
In recent years the 4+2-cycloaddition reaction of imino dienophiles has emerged as a powerful method for preparing highly functionalized nitrogen heterocycles.[1-3] Oximino dienophiles such as oximes or oxime ethers are of considerable interest because of their potential value in natural product synthesis.[4,5] It seemed to us that the Diels-Alder reaction of oximes might be facilitated by using a highly activated 4π-component such as 2,3-diphenylsulfonyl-1,3-butadiene.[6] The synthetic utility of **1** in inverse electron demand Diels-Alder reactions with various imino dienophiles has been ignored to date. We report here on a novel intramolecular dipolar-cycloadditon reaction which occurs upon treating **1** with several oximes. We also show that molecular mechanics calculations have excellent predictive value regarding product formation and stereochemistry.

We have studied the reaction of aldehyde and ketone oximes with **1** in methylene chloride at 25°C for 12 h and observe the exclusive formation of a single product (90-95% yield) in all four cases examined. The structure of the cycloadduct follows from its spectroscopic properties.[7]



The mechanism by which cycloadduct **3** is formed is of considerable interest. Two fundamentally different pathways seem possible. One path (A) involves a Diels-Alder reaction to give a transient 4+2-cycloadduct which undergoes a further conjugate addition of the hydroxylamine across the neighboring vinyl sulfone. The second possibility (path B) involves conjugate addition of the oxime onto **1** to give a transient nitrone (i.e. **4**) which then undergoes a subsequent intramolecular dipolar-cycloaddition reaction. If mechanism A were correct, treatment of 1 with oxime ethers should also result in 4+2-cycloaddition. This is not the case as only recovered starting materials were obtained even under forcing conditions.[8]

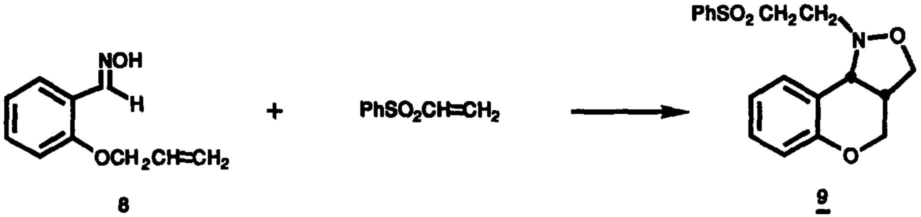
Additional support for path B was obtained by studying the reaction of several oximes with divinyl sulfone. The aldehydic oximes afforded cycloadduct 5 as the sole product in 90-95% yield. A significant loss of regioselectivity was observed, however, in the reaction of acetone oxime which produced a 3:2 mixture of cycloadducts 6 and 7 in 95% overall yield. A related intramolecular



5a; R_1=Ph; R_2=H
5b; R_1=α-Naphth; R_2=H
5c; R_1=CH_3; R_2=H

6 (60%)

7 (40%)



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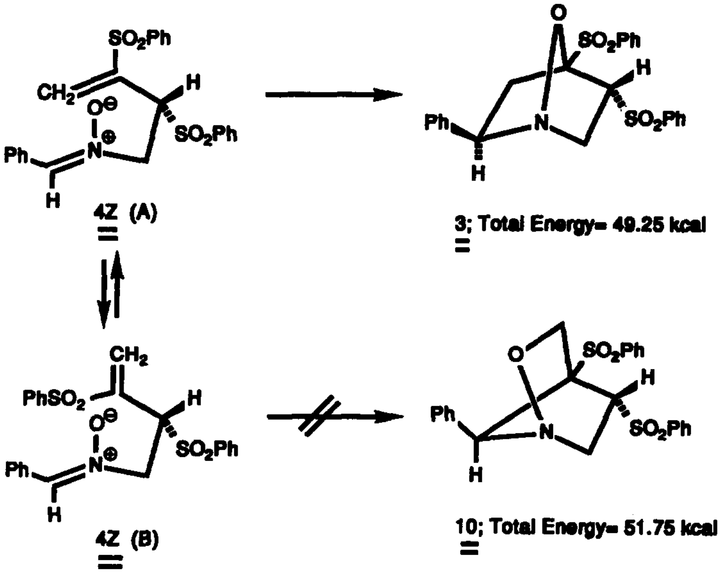
nitrone cycloaddition reaction also occurred upon heating oxime 8 with phenyl vinyl sulfone in toluene at 110°C for 12 h. In this case a 90% yield of cycloadduct 9 was obtained. It should be pointed out that Grigg and coworkers have very recently encountered analogous results with some related systems.[9]

The complete stereoselective cycloaddition of nitrone 4 to bicyclic 3 is consistent with some earlier regiochemical observations.[10] Examination of molecular models reveals the incompatibility of a two carbon bridge linking the dipole and dipolarophile with an exo transition state because of severe angle strain. Accordingly, the stereochemistry of the cycloaddition is best explained in terms of an exclusive reaction of the Z-nitrone 4Z via the easily attainable endo orientation of the reactive groups.[11]



4Z (A)

3; Total Energy= 49.25 kcal

4Z (B)

10; Total Energy= 51.75 kcal

Recently available parameters for transition state oxygen permit MMX calculations on transition state energies for the two possible orientations (A and B).[12] These calculations reveal that both ground and transition state energies are significantly lower (2.5 kcal/mole) for the formation of **3** than for **10** for which ring closure was was not observed. The MMX calculations also nicely rationalize the exclusive formation of cycloadduct **5** from the reaction of aldehyde oximes with divinyl sulfone and account for a mixture of isomers when acetone oxime was used. This can be attributed to a 2.6 kcal difference between the two regioisomeric transition states for the aldehyde oximes but only a 0.6 kcal difference with acetone oxime. This is a subtle effect which is not immediately obvious on inspection of molecular models but for which MMX calculations serve well to predict regiochemistry in such intramolecular dipolar-cycloadditions.

Other aspects of the reaction of oximes with vinyl sulfones and their application to natural product synthesis will appear in forthcoming papers.

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Notes and References

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2. S. M. Weinreb **Acc. Chem. Res.** *18*, **16** (1985).
3. F. Bohlmann, D. Habeck, E. Poetsch and D. Schumann **Chem. Ber.** *100*, **2742** (1967).

4. W. Oppolzer, E. Francotte and K. Battig **Helv. Chim. Acta.** *64*, **478** (1981).
5. Simple oximino compounds are normally unreactive but do cycloadd intramolecularly.[1]
6. W. H. Okamura and S. Jeganathan **Tetrahedron Lett.** *4673* (1982).
7. The stereochemistry of cycloadduct **3a** was assigned on the basis of its spectral properties, NMR ($CDCl_3$, 300 MHz) δ 2.23 (ddd, 1H, J=12.8, 5.3 and 2.2 Hz), 3.70-3.85 (m, 3H), 4.34 (dd, 1H, J=7.9 and 5.3 Hz), 4.53 (ddd, 1H, J=10.2, 4.6 and 2.2 Hz), 6.80 (d, 2H, J=7.5 Hz) and 7.15-8.0 (m, 13H). The stereochemical assignment of the phenylsulfonyl group at C_5 as endo is based on the fact that the 5-exo hydrogen at δ 4.53 exhibits a long range W-coupling (J=2.2 Hz) with the hydrogen at δ 2.23. This hydrogen (i.e. δ 2.23), in turn, is coupled by 5.3 Hz with the hydrogen at C_2 thereby fixing the geometry of the C_2-phenyl group as exo.
8. Butadiene **1** has been found to undergo 4+2-cycloaddition with a variety of aldehyde imines. Details of this reaction will be reported in a future publication.
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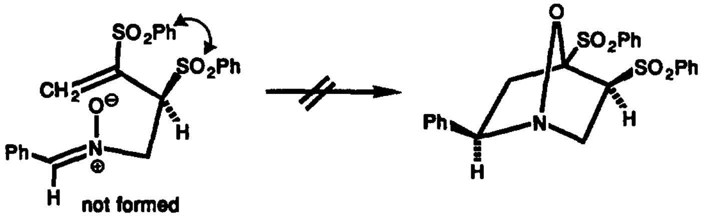
10. W. C. Lumma **J. Am. Chem. Soc.** *91*, **2820** (1969); J. J. Tufariello and E. J. Trybulski **J. Chem. Soc. Chem. Commun.** *720* (1973); J. B. Bapat, D. St. C. Black, R. F. C. Brown and C. Ichlov **Aust. J. Chem.** *25*, **2445** (1972); W. Oppolzer, S. Siles, R. L. Snowden, B. H. Bakker and M. Petrzilka **Tetrahedron** *41*, **3497** (1985).
11. Steric interaction between the two diphenylsulfonyl groups is probably responsible for the formation of a single diastereomer from the conjugate addition reaction of oximes with butadiene **1**.



12. MMX88 Calculations were performed on a Vax11/785 using Model 2.9. The relative energy differences of the transition states were estimated by calculating transition state total energy. The program is parameterized for transition state carbon (C\$,C#,C*) as well as transition state oxygen (O#). Transition-state bond orders of 0.3 were entered which gave transition state bond lengths and torsional angles very similar to those obtained from the more rigorous calculations.

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