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INTRAMOLECULAR DIELS-ALDER REACTIONS OF THE FURAN DIENE· SUBSTITUTENT AND SOLVENT EFFECTS

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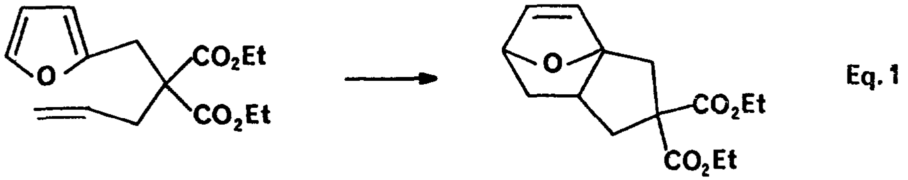
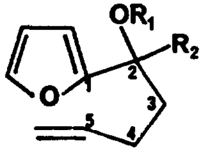
Abstract An internal Diels-Alder reaction, using furan as the diene component, formed a highly functionalized 5-membered carbocyclic ring in excellent yield. Solvent and substituent effects of this reaction were examined.

In connection with a project devoted to the synthesis of some natural products containing 5-membered carbocyclic rings we have been interested in developing a general method for the stereospecific synthesis of these ring systems. To this end we have explored the intramolecular Diels-Alder reaction of substituted furans, where the furan π systems serve as the diene, and the dienophile is connected by a 3-carbon chain. While several examples of intramolecular Diels-Alder reactions with furans have been described[1], only one example of this particular type has been reported (eq. 1)[1a]. In this case a 40% yield of product was achieved after refluxing the reactant in benzene for 5 days. In the same paper Parker et al. studied related Diels-Alder reactions in which the starting materials contained a heteroatom in the bridging chain. The conclusions reached in this paper and references therein are twofold 1. The yield of products[2] is dependent on the nature and position of substituents on the bridging chain (presumably these substituents influence the conformation), 2. Substituents in the β position of the dienophile retard the reaction while α substituents have a smaller effect. Mukaiyama[1gh] has recently devised a system where the bridging chain conformation is fixed by chelation with magnesium ion. In these examples, β substituted dienophiles, that are normally unreactive, have been induced to undergo intramolecular Diels-Alder reactions. In this letter we would like to report our results concerning solvent and substituent effects on related intramolecular Diels-Alder reactions wherein a 5-membered carbocyclic ring is formed.

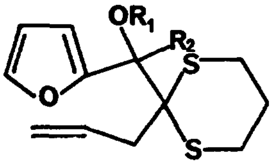


Eq. 1

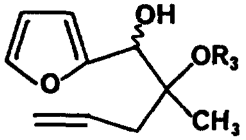
The compounds[3] that we have studied are depicted below. The reactions were carried out at 80°C in benzene for 3 days unless otherwise noted (the yields are indicated in parentheses). In general the compounds without substitution on carbon 3 (1-3) failed to undergo a Diels-Alder reaction even under forcing conditions. Compound 4, however, underwent cyclization to varying extents depending on the solvent (vide infra). Clearly the geminal substitution of carbon 3 was



1 $R_1 = R_2 = H$ (NR)
2 $R_1 = PhCH_2$, $R_2 = H$ (NR)
3 $R_1 = H_1$ $R_2 = CH_3$ (NR)



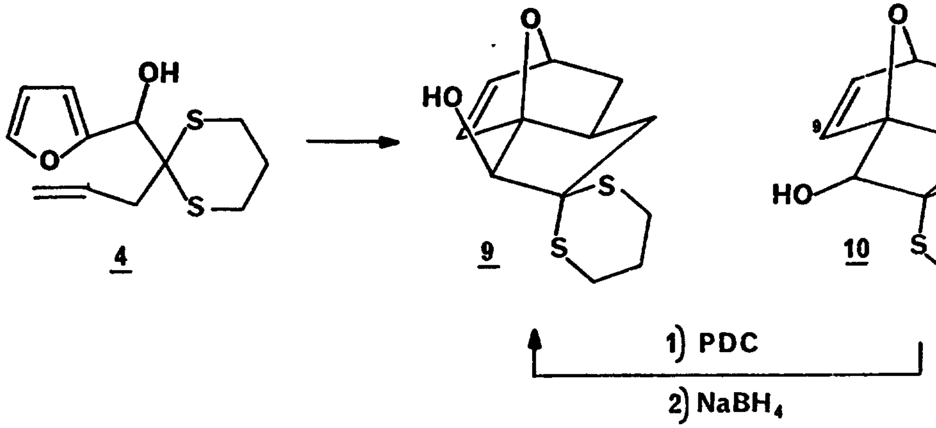
4 $R_1 = R_2 = H$ (63%)
5 $R_1 = OCOPh$, $R_2 = H$ (62% 2wks)
6 $R_1 = H$; $R_2 = CH_3$ (quant. 2d)



7 $R_3 = CH_2Ph$ (NR)
8 $R_3 = H$ (NR)

important (compare 1 and 4). In an effort to see if another substitutent at C-2 would further facilitate the reaction, 6 was prepared. Cyclization was quantitative (a 1/1 mixtures of epimers was obtained) in less than 2 days (as opposed to a 63% yield realized when 4 was cyclized at the same temperature for 3 days). Thus geminal substitution at C-2 does facilitate the Diels-Alder reaction but in itself is not sufficient for the reaction to proceed under the above conditions (cf. compound 3). To test whether the dithiane ring had some special significance (other than simple geminal substitution) 7 was prepared as a mixture of epimers. Only a trace of four isomeric Diels-Alder products could be isolated after 2 weeks. Preliminary NMR evidence showed that at least some of these isomers were produced after 12 hrs suggesting that equilibrium was reached fairly rapidly, but the starting material was favored to a great extent. The mixture of epimeric diols 8 was then prepared with the hope that at least one of the epimers might form a more stable Diels-Alder adduct due to internal hydrogen bonding of the vicinal alcohols in the product. This mixture proved completely unreactive. Thus it would appear that the rigidity imparted by the dithiane ring and/or the S-C-S bond angle contribute significantly to the success of the intramolecular Diels-Alder reaction of compounds 4 - 6.

Compound 4 forms two isomeric Diels-Alder products.[5] We have demonstrated that these isomers (9 mp 110-111°C and 10 mp 99-101°C) are epimeric at the hydroxyl bearing carbon by oxidation of 10 to the ketone with pyridinium dichromate followed by reduction with $NaBH_4$ to produce 9. The structures have tentatively been assigned as shown above. The C-4-C-5 bond is considered to be exo by analogy to similar compounds[1acg] and by consideration of orbital overlap in the endo and exo transition states of a Dreiding model of 4. The vinyl hydrogen at C-9 has a dramatically different chemical shift in both epimers (6.08 δ in 9 vs 6.68 δ in 10) as might be expected by the deshielding effect[6] of the proximal hydroxyl group in 10. When the Diels-Alder reaction of 4 was carried out in benzene at 80° a 1.2/1 ratio of 9 to 10 was produced. We hoped to influence this isomer ratio by protecting the hydroxyl group as the benzoate, 5. Cyclization of this compound proved to be somewhat sluggish. Thus after two weeks at 80°C in benzene, a 62% yield of a 1.7/1 mixture of epimers was realized (in this case the NMR spectra of the epimers were sufficiently similar to preclude an exact assignment). The role of the solvent was then explored since we expected that solvents that interfered with intramolecular



Eq. 2

H-bonding and/or were H-bonding themselves might favor the more exposed epimeric alcohol (this was presumed to be 10 by inspection of a model and from the results of the NaBH$_4$ reduction on the ketone). The results, tabulated below, show that the solvent had a modest effect on the isomer ratio. The ratios varied from 1.2 in benzene to 0.4-0.5 in ethanol, 1,2,dichlorethane and diisopropyl ether. These results are not readily explained by solvent polarity or the hydrogen bonding characteristics of the solvent.

A more striking effect is seen when one compares the overall percentage of products formed in different solvents. The yield of products doubles when the solvent is changed from water, acetonitrile or diisopropyl ether to ethylene glycol or a mixture of water and ethanol (5·2). It is interesting to note that increasing yields roughly parallel increasing solvent viscosity[7]

Table I Solvent Effects in the Internal Diels-Alder Reaction

Solvent (80°C, 3 days)	% yield (9 and 10)[a]	9:10[b]
water/ethanol (5 2)	93	0.9
ethylene glycol	89	0.8
neat[c]	75	0.8
methylcyclohexane	68	0.9
benzene[c]	63	1.2
ethanol	68	0.5
1,2-dichloroethane	51	0.5
diisopropyl ether	45	0.4
acetonitrile[c]	45	0.8
H_2O	45	0.5

a. Yields were determined by integration of an NMR spectrum, of the crude reaction mixture. In all cases only starting material and the two epimeric products were present.
b. Ratios were determined by integration on an NMR spectrum.
c. In these examples the results were shown to be kinetic by either subjecting the products to identical conditions and not achieving the same ratio or by allowing the reaction to proceed further.

with the exception of the reaction carried out in water which yields less product than might be expected. The result in water may possibly be attributed to the formation of micelles that, in this case, retard the Diels-Alder cyclization. Indeed it is curious that when either water or ethanol is used alone the yield of products is lower than when a mixture is used.

These results reveal that the rate of the intramolecular Diels-Alder reaction with a substituted furan as the diene component is dependent on the nature of substituents present on the bridging carbon chain as well as the solvent. With the proper choice of substituents excellent yields of highly functionalized 5-membered carbocyclic rings can be formed. Application of this reaction to the synthesis of some natural products is currently underway.

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REFERENCES

1. a. Kathlyn A. Parker and Mark R. Adamchuck, Tetrahedron Lett. 1689 (1978), b. H. H. Wasserman and A. R. Doumaux J. Amer. Chem. Soc. 84 4611 (1962), c. D. Bilovic, Z. Stojanac and V. Hahn, Tetrahedron Lett. 2071 (1964); d. Z. Klepo and K. Jacopcic, Croatica Chemica Acta, 47, 45 (1975), e. H. W. Gschwend, M. J. Hillman, B. Visis and R. K. Rodenbaugh, J. Org. Chem. 41, 104 (1976), f. G. H. Torosyan, S. L. Paravyan, R. S. Mkrtchyan, K. Ts. Tagmazyan, A. T. Babayan, Arm. Khim. Zh. 32 182 (1979), Chem Abst. 92 76234z, g. T. Mukaiyama, T. Tsuji and N. Iwasawa, Chem. Lett. 697 (1979), h. T. Mukaiyama and N. Iwasawa, Chem. Lett. 29 (1981).
2. No claim as to whether these yields are derived from incomplete reactions or are the equilibrium values was made.
3. All compounds displayed satisfactory spectral data.
4. The products of these reactions were mixtures of epimers at the oxygen bearing carbon(s).
5. Spectral data of 9: ^1H NMR (δ, D_6 benzene, 250 MHz) 6.08 (d J = 5.5 Hz, 1H) 5.82 (dd J = 1.5, 5.5 Hz, 1H), 4.87 (d J = 11.4 Hz, 1H) 4.60 (dd J = 4.4, 1.5 Hz, 1H) 3.23 (ddd J = 13.7, 12.0, 2.9, 1H) 3.13 (d J = 11.8 1H), 2.69 (ddd J = 11.3, 2.8, 14.3 Hz, 1H), 2.15 - 2.36 (m, 3H), 1.87 - 1.98 (m, 1H), 1.50 - 1.77 (m, 3H), 1.24 (ddd J = 11.5, 2.6, 4.4 Hz, 1H), 0.92 (dd J = 7.4, 11.4 Hz, 1H), ^{13}C NMR (δ $CDCl_3$ 22.5 MHz) 136.71 (d), 135.52 (d), 97.80 (s), 77.92 (d), 78.96 (d) 60.49 (s), 46.61 (t), 39.77 (d), 33.14 (t), 28.37 (t), 27.48 (t) 24.69 (t), IR ($CH_2Cl_2CO^{-1}$ 3540 m, 3390 w sh.

   Spectral data of 10 ^1H NMR (δ, D_6 benzene, 250 MHz) 6.76 J = 5.9 Hz, 1H), 5.97 (dd J = 5.9, 1.8 Hz, 1H), 4.76 (m, 1H), 4.76 (d J = 6.3 Hz, 1H), 3.13 (d, J = 6.3, 1H), 2.80 (m, 2H), 2.45 (dd J = 13.6, 7.3, 1H), 2.32 - 2.15 (m, 2H), 2.12 (dt J = 2.93, 7.8, 1H), 1.92 (dd J = 13.6, 5.0 Hz, 1H), 1.60 - 1.49 (m, 2H), 1.42 ddd, J = 11.3, 4.5, 2.5, 1H), 1.11 (dd J = 11.4, 7.3, 1H); IR(CH_2Cl_2) 3560 W, 3380 m.
6. T. Okamoto and Y. Kawazoe Chem. Pharm. Bull. 11 643 (1963).
7. R. A. Firestone and M. A. Vitale, J. Org. Chem. 46 2160 (1981), Firestone has noticed that increasing solvent viscosity increased the rates of some intramolecular reactions. He reasoned that acceleration of reactions that are independent of intermolecular collisions would occur to a greater extent in solvents that minimize translational motion of molecules thereby localizing the internal energy in the vibrational modes. While we realize that many other variables are changed when a different solvent is used one might speculate that more highly ordered solvents will favor an intramolecular reaction that has a high negative entropy of activation.

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