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The Diels-Alder Reaction of 1-Azadienes. The Effect of an α-Cyano Substituent

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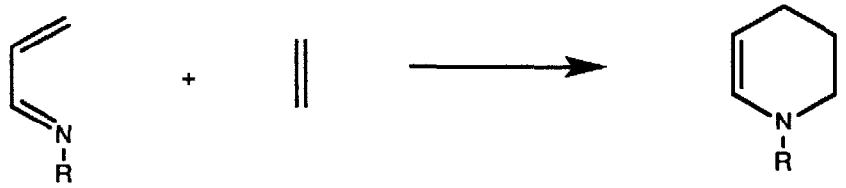
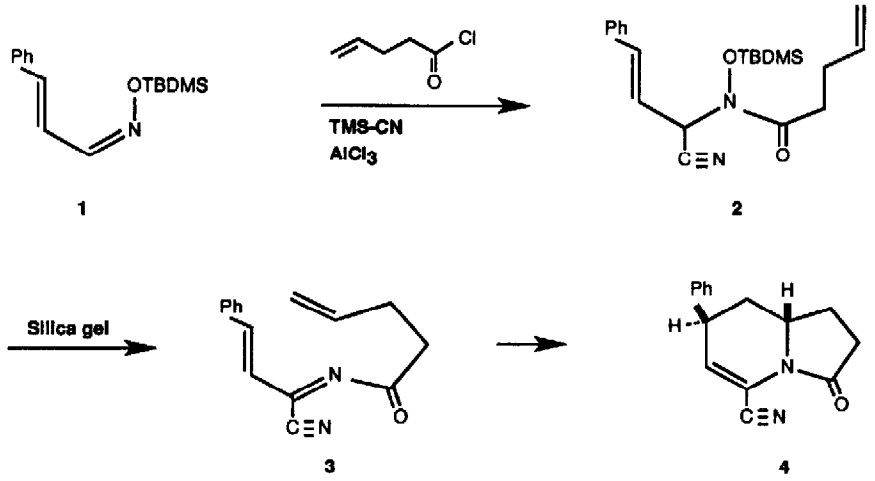
Abstract: N-Acyl-α-cyano-1-azadienes have been observed to be reactive and *anti* selective dienes in the intramolecular hetero Diels-Alder reaction.

The Diels-Alder reaction of 1-azadienes is potentially a powerful method for the preparation of six membered nitrogen heterocycles. It has the known advantages of Diels-Alder reactions of producing, in one step, two new σ-bonds, a six membered ring and three stereogenic centers whose relative configurations are readily controlled. In addition, the Diels-Alder reaction of 1-azadienes creates an endocyclic enamine, a desirable functional group for further structural elaboration.[1] Until recently, however, the Diels-Alder reaction of 1-azadienes was an unknown transformation of general utility in synthetic chemistry.[2] Among the reasons for the lack of useful Diels-Alder reactions of 1-azadienes, the less favorable thermodynamics of this reaction compared to the all carbon system[3] and the instability of the endocyclic enamine derivative in the product with respect to polymerization are undoubtedly important. Studies concerned with the development of 1-azadienes as reactants in the Diels-Alder reaction must contend with these problems.



A few years ago we reported[4] that N-acyl-1-azadienes participated in the Diels-Alder reaction. We illustrated the utility of this process by successfully applying it to the total synthesis of (–)-deoxynupharidine.[5] Presumably, the N-acyl function on the 1-azadiene serves to both lower the activation energy[6] for the process and to stabilize the enamine derivative[7] in the product. Because of the reactivity of the N-acyl-1-azadienes with respect to polymerization, these studies owed their success to the use of flash vacuum thermolysis[8] for both the generation of the N-acyl-1-azadienes and their Diels-Alder reactions.

The introduction of an α-cyano substituent on the 1-azadiene offers the possibility of considerably expanding the synthetic utility of the Diels-Alder reaction of 1-azadienes. The ability of a cyano group to behave both as a π-electron withdrawing substituent and a leaving group is not shared by many functionalities. These properties can be extensively exploited in the Diels-Alder reaction of 1-azadienes. (1) The cyano group should lower the activation energy of the elimination reaction for the formation of the 1-azadiene. (2) The cyano group should accelerate the Diels-Alder reaction by further lower the LUMO of the 1-azadiene enhancing the interaction with the HOMO of the dienophile. (3) The cyano group should stabilize the N-acyl imine with respect to processes involving nucleophilic addition to the imine such as polymerization and possibly allow for condensed phase intermolecular Diels-Alder reactions. (4) Because α-cyanoamines possess an acidic hydrogen and behave as iminium ion equivalents this functional group is useful for further structural elaboration. The utility of these reactions have been beautifully demonstrated by Husson and co-workers in the development of the CN,(RS) method for alkaloid total synthesis.[9]



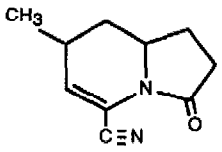
We envisioned that an efficient and reasonable strategy to the desired N-acyl-α-cyano-1-azadiene could involve addition of cyanide ion to an oxime followed by acylation of the intermediate α-cyano hydroxyl amine. This process was accomplished by treating the silyl protected *anti* oxime derivative **1**[10] of cinnamaldehyde with trimethylsilylcyanide and pent-4-enoyl chloride in methylene chloride using aluminum chloride as a catalyst at room temperature for 12 hrs. Concentration of the reaction mixture *in vacuo* followed by flash chromatography resulted in the development of a yellow band that proved to be the N-acyl-α-cyano-1-azadiene **3**[11] contaminated by a small amount of the Diels-Alder adduct. The Diels-Alder reaction was driven to completion by refluxing the azadiene **3** in dry benzene for two hrs. This three step process, (a) formation of the α-cyanohydroxyl amine, (b) elimination to give the N-acylimine and (c) the Diels-Alder reaction proceeded in 54% overall yield from the protected oxime derivative of cinnamaldehyde.

Also of interest is the observation that the presumably less stable stereoisomer (4) with the phenyl substituent *cis* (pseudo axial) to the hydrogen atom at C-5 is the major product (>25:1).[12] This is a significant and useful preference for the Diels-Alder proceeding through the *anti* or *exo* transition state.

The intramolecular Diels-Alder reaction of the analogous azadiene[4] without the α-cyano substitution under flash vacuum thermolysis conditions gave a 3:1 mixture of stereoisomers. It has been suggested that substituents at C-3 of the all carbon dienes raise the activation energy of the *endo* pathway, which is consistent with these results. However, in the absence of kinetic data it is difficult to determine whether the large proportion of the reaction proceeding through *exo* transition state is due to the temperature[13] or a greater *exo* selectivity of the α-cyano-1-azadiene.[14]

The preference for the *exo* transition state appears to be much greater for the N-acyl-1-azadienes than analogous all carbon systems.[15] We believe this is due to the stereoelectronic requirements of the developing amide bond. Molecular modeling[16] suggests that orbital overlap of the nitrogen lone pair and the carbonyl group is more favorable in the *exo* transition state.

We have also applied the above scheme to prepare the Diels-Alder adducts **5**, **6** and **7**. The diminished *exo* selectivity of **6** is also consistent with the developing interaction between the nitrogen lone pair and the carbonyl group being important in the transition state. Because the oxygen lone pairs of **6** can interact with the carbonyl group the interaction of the nitrogen lone pair becomes energetically less important.[17]



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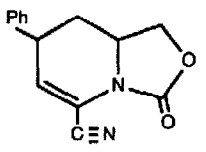

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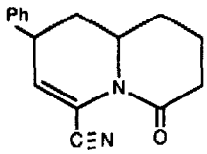

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CIS/TRANS RATIO	19:1	8:1	15:1

In summary, a method has been developed for the preparation of N-acyl-α-cyano-1-azadienes and it has been demonstrated that these compounds readily participate in the Diels-Alder reaction.

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References and Footnotes

(1) (a)*Enamines: Synthesis, Structure and Reactions,* Cook, A. G., Ed., Marcel Dekker: New York, 1988 (b) Stevens, R. V. *Acc. Chem. Res.* **1977**, *10*, 193. (c) Wenkert, E. *ibid.* **1968**, *1*, 78.

(2) For two recent reviews on the Diels-Alder reaction of 1-azadienes see: (a) Boger, D. L.; Weinreb S. M. *Hetero Diels-Alder Methodology in Organic Synthesis,* Academic Press: Orlando, FL. 1987. (b) Kametani, T.; Hibino, S. *Adv. Heterocyclic Chem.,* **1987**, *42*, 246.

(3) Ciganek, E. *Org. React.*, **1984**, *32*, 1.

(4) Cheng, Y-S; Lupo, A. T., Jr.; Fowler, F. W. *J. Am. Chem. Soc.* **1983**, *105*, 7696.

(5) Hwang, Y.; Fowler, F. W. *J. Org. Chem.* **1985**, *50*, 2719.

(6) There are at least two possible roles the N-acyl function can play to lower the activation energy. There is a gain of 15-20 kcal/mole of stabilization energy due to formation of the amide functionality in the product, part of which is available to the transition state. The N-acyl function also lowers the LUMO of the azadiene increasing a stabilizing interaction with the HOMO of the dienophile.

(7) Endo cyclic enamines without substituents on the double bond are extremely reactive. For example, see: Fowler, F. W. *Reactivity of Reduced Pyridines*, in *Comprehensive Heterocyclic Chemistry*, McKillop, A., Boulton, A. J., Eds., Pergamon Press: Oxford, Vol. 2, 1984, pp 365-394.

(8) Magrath, J.; Fowler, F. W. *Tetrahedron Lett.* **1988**, *29*, 2171.

(9)(a) Jimonet, P.; Grierson, D. S.; Husson, H.-P. *Tetrahedron Lett.* **1987**, *28*, 6179. (b) Grierson, D. S.; Royer, J.; Guerrier, L. Husson, H.-P. *J. Org. Chem.* **1986**, *51*, 4475. (c) Arseniyadis S.; Huang, P. Q.; Husson, H.-P. *Tetrahedron Lett.* **1988**, *29*, 1391.

(10) Although both the *syn* and *anti* oxime derivatives react in this process, the much greater reactivity of the *anti* oximes make them the preferred reactants.

(11) Experimental data on the azadiene **3** and the Diels-Alder adduct **4**: IR (film) 2930, 2210, 1715, 1620, 1405, 1260, 970, 835 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.44-2.52(q, J=7.2, 2H), 2.65-2.69(t, J=7.2, 2H), 5.05-5.17(m, 2H), 5.81-5.94(m, 1H), 6.81-6.86(d, J=16.1, 1H), 7.26-7.59(m, 5H), 7.65-7.70(d, J=16.1, 1H); MS m/s (relative intensity) 239 (0.5), 238 (1.6, M^+), 183 (1.7), 129 (100), 102 (44.3), 55(8.4).

Diels-Alder adduct **4**: Mp 133-134 °C; IR (KBr) 3070, 2220, 1705, 1615, 1400 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.65-1.73(m, 1H), 1.83-1.94(m, 1H), 2.13-2.19(m, 2H), 2.46-2.51(m, 2H), 3.58-3.68(m, 1H), 3.77-3.80(t, J=5.4, 1H), 6.08-6.09(d, J=5.0, 1H), 7.13-7.39(m, 5H); ^{13}C-NMR ($CDCl_3$) δ 25.0, 30.4, 36.1, 38.9, 51.0, 111.1, 113.6, 126.9, 126.9, 127.7, 128.5, 142.3, 171.0; MS m/s (relative intensity) 239 (18.3), 238 (100, M^+), 183 (87.7), 155 (32.2), 140 (23.7), 128 (19.9), 115 (30.9), 105 (25.6), 103 (13.5), 91(45.4), 77(20.6), 55 (17.4); Anal. Calcd. for $C_{16}H_{14}N_2O$: C, 75.60; H, 5.92; N, 11.76. Found: C, 75.51; H, 5.95; N, 11.67.

(12) The coupling constant for the vinyl hydrogen is 5.0 Hz. Molecular mechanics calculations (reference 16) predict a coupling constant of 4.8 Hz for **4** and 2.7 Hz for its diastereoisomer. The coupling constants for the products of analogous *exo* and *endo* transition states were 6 and 1 Hz respectively (see reference 4).

(13) The Diels-Alder reactions of azadienes generated under flash vacuum thermolysis conditions occur at approximately 550 °C.

(14) It is known that substitutents at the 3-position of the diene produce a greater degree of exo selectivity (see reference 3, p. 25).

(15) Craig, D. *Chem. Soc. Rev.*, **1987**, *16*, 187.

(16) The molecular modeling was performed using the macromodel program developed by W. C. Still at Columbia University. The Diels-Alder transition states used were previously suggested by K. N. Houk and co-workers: (a) Brown, F. K.; Houk, K. N. *Tetrahedron Lett.* **1985**, *26*, 2297-2300. (b) Brown, F. K.; Houk, K. N. *Tetrahedron Lett.* **1984**, *25*, 4609-4612. The molecular modeling studies suggest the *exo* transition state to be 5.2 kcal/mole more stable than the *endo*.

(17) A diminished interaction of a nitrogen lone pair of a carbamate compared to an amide is reflected in the rotational barriers which are generally higher for the amides compared to carbamates (*Dynamic Nuclear Magnetic Resonance Spectroscopy*, Jackman, L. M.; Cotton, F. A., Eds., Academic Press: New York, 1975, p. 209 ff)

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