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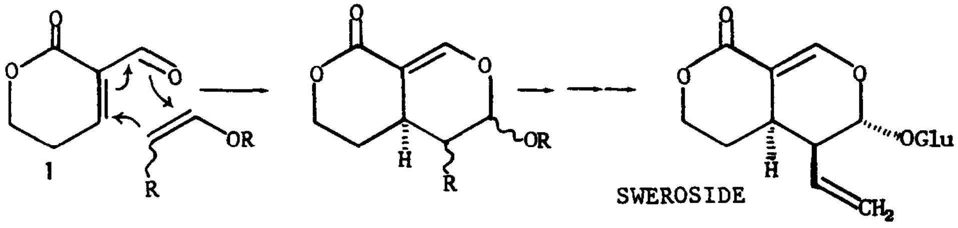
DIELS-ALDER REACTIONS OF 2-ACETYL-2-CYCLOHEXENONE WITH ENOL ETHERS AND EMAMINES

Barry B. Snider[1]

Department of Chemistry, Princeton University
Princeton, New Jersey 08544

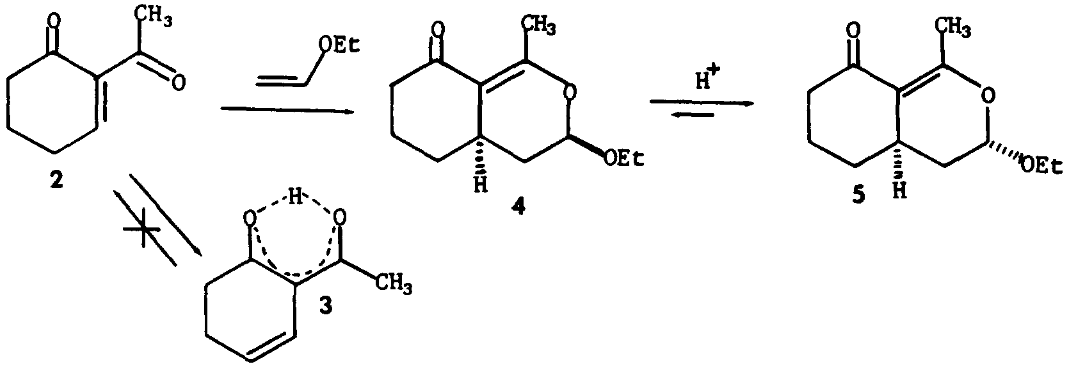
Summary: 2-Acetyl-2-cyclohexenone (2) undergoes inverse electron demand Diels-Alder reactions with enol ethers at 25°C. The adduct in which the oxygen adds endo is favored. Trans substituted enol ethers are ≈35 times as reactive as the cis isomer. Enamines react immediately with 2 at 25°C.

Inverse electron demand Diels-Alder reactions of carbonyl compounds provide an attractive route to 3,4-dihydro-2H-pyrans.[2] We were interested in exploring the reactions of 1 with enol ethers as a route to sweroside.[3] We have recently shown that α,β-unsaturated carbonyl compounds activated by electron withdrawing groups in the α position are reactive dienes in inverse electron demand Diels-Alder reactions.[4] However, compounds such as 1 are unstable toward tautomerization.[5] It was therefore of interest to determine whether α,β-unsaturated carbonyl compounds of this type can be used as dienes in the Diels-Alder reaction.



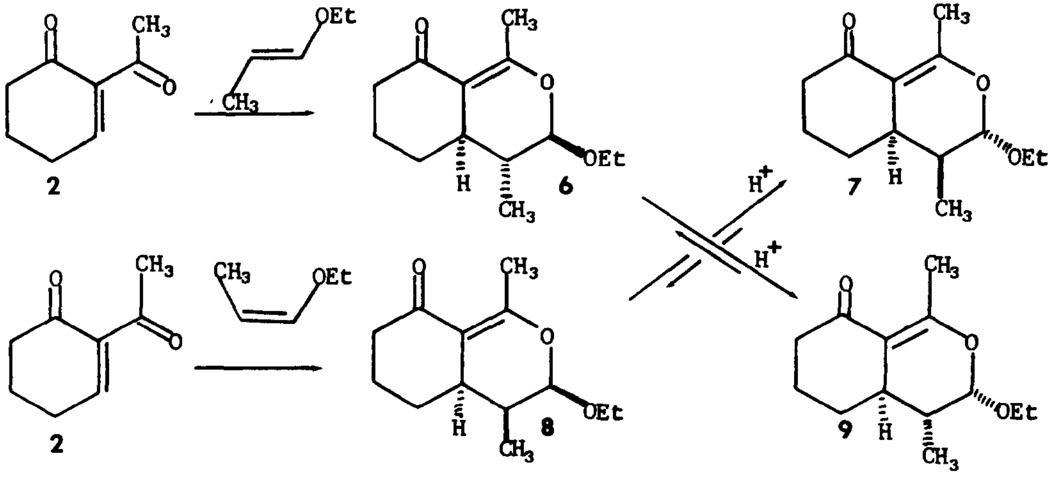
The Diels-Alder reactions of readily available 2-acetyl-2-cyclohexenone (2)[5] with enol ethers and enamines were investigated. Treatment of 2 (≈ 75% pure, contaminated with 10% of 3) with excess ethyl vinyl ether, either neat or in $CDCl_3$, for 24 hr at 25°C gives a 75% yield of the endo Diels-Alder adduct 4, mp 53-57°C, containing less than 5% of the exo isomer 5.[6] Acid catalyzed isomerization by traces of HCl in $CDCl_3$ leads to a 70:30 equilibrium mixture of 5 and 4.

Reaction of 2 with 5 eq of a 70:30 mixture of *Z*- and *E*-1-propenyl ethyl ether for 48 hr at 25°C gives a 70% yield of an 83:13:6 mixture of 6, 7 and 8.[6] Isomerization of 6 by traces of HCl gives a 2:1 equilibrium mixture of 9[6] and 6.

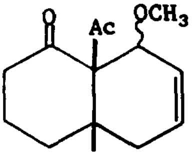


Isomerization of 7 gives a 3:1 equilibrium mixture of 7 and 8. The isomers with an axial ethoxy group, 7 and 9, are more stable because of the anomeric effect. The reaction of 2 with *E*-1-propenyl ethyl ether for 48 hr results in a 70% yield of an 86:14 mixture of 6 and 7. The reaction of 2 with *Z*-1-propenyl ethyl ether is very slow, giving a 30% yield of a 3:1 mixture of 8 and 9 in 30% yield along with 50% of 3 after 28 days at 25°C. In both cases the major isomer results from endo addition of the ethoxy group.

Since the stereochemistry of the dienophile is preserved in the Diels-Alder reaction, the ratio of isomers formed from the mixture of ethyl propenyl ether isomers indicates that the trans isomer is 35 times as reactive as the cis isomer. The much greater reactivity of trans substituted dienophiles has been noted in Diels-Alder reactions and [3+2] cycloadditions.[7] This phenomena does not appear to have been observed in inverse electron demand Diels-Alder reactions.[2,8] In this case, steric inhibition of resonance in the cis isomer does not occur. Shrinkage of the bond angles of the dienophile from 120° to 109° during the reaction, resulting in compression of the van der Waals radii of the eclipsed cis substituents is probably responsible for the unreactivity of the cis isomer.



Enone 2 reacts as a dienophile with 1-methoxy-*trans*-1,3-butadiene to give a 78% yield of a 55:45 mixture of octalones 10. Treatment of 2 with 1-methoxy-*cis*-1,3-butadiene[9] results in the formation of a complex mixture of unidentified products. Treatment of 2 with 1-methoxy-*cis*-1-buten-3-yne results in the formation of conjugate addition of product 11 in 70% yield.



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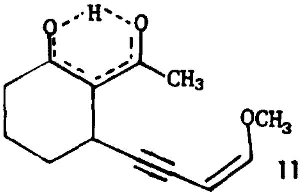

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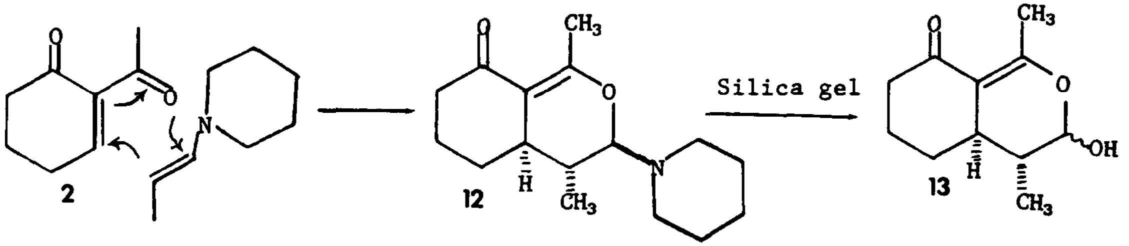
No reaction occurs between 2 and styrene, 2,3-dimethyl-2-butene, *cis*-β-methoxystyrene, 3-ethoxy-2-cyclohexenone, *E*-or *Z*-1-propenyloxytrimethylsilane,[10] or dihydropyran. After long reaction times, at high temperatures, or in the presence of base, 2 isomerizes to 3. Isomerization of 2 to 3 appears to be irreversible, since treatment of 3 in ethyl vinyl ether for 24 hr at 80°C gives no 4 or 5.

Enamines were investigated in an attempt to find other dienophiles that would react with 2 faster than 2 isomerizes with 3. Enone 2 reacts exothermically with 1-(*E*-1-propenyl)piperidine[11] at 25°C giving a ≈ 90% yield of Diels-Alder adduct 12[6] in which the nitrogen added endo. Unlike the reaction of 2 with *E*-1-propenyl ethyl ether, only a single adduct is formed. Attempted purification of 12 by chromatography on silica gel gives an 81% yield of 13[6], mp 86-89°C, as a 1:1 mixture of isomers. Thus the adducts from enamines which are obtained in high yield can be converted easily to 2-hydroxy-3,4-dihydropyrans.



α,β-Unsaturated carbonyl compounds activated by electron withdrawing groups in the α-position undergo facile inverse electron demand Diels-Alder reactions with enol ethers and enamines at 25°C. The products formed should be useful for the synthesis of secoiridoids and their analogs.

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6. The characteristic NMR spectral data ($CDCl_3$) for the Diels-Alder adducts are given below: 4, δ 4.97 (dd, 1, J = 3, 9 Hz), 2.20 (d, 3, J = 2 Hz); 5, δ 5.13 (dd, 1, J = 2.5, 2.5 Hz), 2.25 (d, 3, J = 2 Hz); 6, δ 4.58 (d, 1, J = 8.5 Hz), 2.20 (d, 3, J = 2 Hz), 1.06 (d, 3, J = 7 Hz); 7, δ 4.80 (d, 1, J = 1.7 Hz), 2.25 (d, 3, J = 2 Hz), 0.83 (d, 3, J = 7 Hz); 8, δ 4.96 (d, 1, J = 2 Hz), 2.20 (d, 3, J = 2 Hz), 0.86 (d, 3, J = 7 Hz); 9, δ 4.88 (d, 1, J = 2.5 Hz), 2.20 (d, 3, J = 2 Hz), 1.03 (d, 3, J = 7 Hz); 12, δ 4.22 (d, 1, J = 10 Hz), 2.15 (s, 3), 1.01 (d, 3, J = 7 Hz); 13, δ 5.26 (d, 0.5, J = 2.4 Hz), 4.87 (d, 0.5, J = 8.4 Hz), 2.17 (s, 3), 1.11 (d, 1.5, J = 7 Hz), 1.07 (d, 1.5, J = 7 Hz).
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