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A TWO STEP, NON-STEREOSPECIFIC CATION RADICAL DIELS-ALDER REACTION

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Abstract:
The cation radical Diels-Alder cycloadditions of *cis*- and *trans*-1-propenyl aryl ethers to 1,3-cyclopentadiene, catalyzed by tris(4-bromophenyl)aminium hexachloroantimonate in dichloromethane solution, are found to be non-stereospecific, in contrast to the stereospecificity observed in other cation radical Diels-Alder reactions previously studied. These and supporting experiments indicate that, in this particular system, the reaction occurs by a two step mechanism.

Keywords: aryl propenyl ethers; cation radicals; Diels-Alder cycloadditions

The 1,3-cyclohexadiene (diene)/2,4-hexadiene (dienophile) system was the first reaction system for which the stereochemistry of a cation radical Diels-Alder reaction was determined.[1] In the case of all three geometric isomers of 2,4-hexadiene the reactions were observed to be >98% stereospecific. More recent studies of the stereochemistry of the cation radical Diels-Alder addition of *cis*- and *trans*-1,2-diaryloxyethenes to 1,3-cyclopentadiene and also to 1,3-butadiene have provided analogous results.[2] While these results are consistent with a concerted (albeit highly non-synchronous) cycloaddition mechanism, they do not rigorously exclude the possibility of a two step mechanism in which the second (cyclization) step is faster than stereorandomizing bond rotations. Very recent theoretical studies suggest that, at least in the prototype cation radical Diels-Alder system (s-*cis*-1,3-butadiene cation radical/ethene), this is in fact the case.[3] Experimental studies involving CIDNP have also generated evidence for distonic cation radical intermediates in cation radical Diels-Alder reactions.[4] For this reason we became interested in investigating the stereochemistry of a cation radical Diels-Alder reaction in a system in which the carbocation moiety of the distonic cation radical intermediate is highly stabilized and therefore more likely to have a lifetime sufficient to permit stereorandomizing bond rotations.

The *cis* and *trans* isomers of both 4-methyl- and 4-methoxyphenyl 1-propenyl ether were prepared by treating the corresponding allyl ethers with palladium chloride in dichloromethane at room temperature for several days until the isomerization to the propenyl ethers was complete (GC). In the case of the 4-methyl compound, the isomerization required *ca.* 2 days, whereas with the 4-methoxy compound it required 10 days. The mixture of *cis*- and *trans* -1-propenyl aryl ethers (*ca.* 60% *cis*:40% *trans*) was then subjected to silica gel chromatography using

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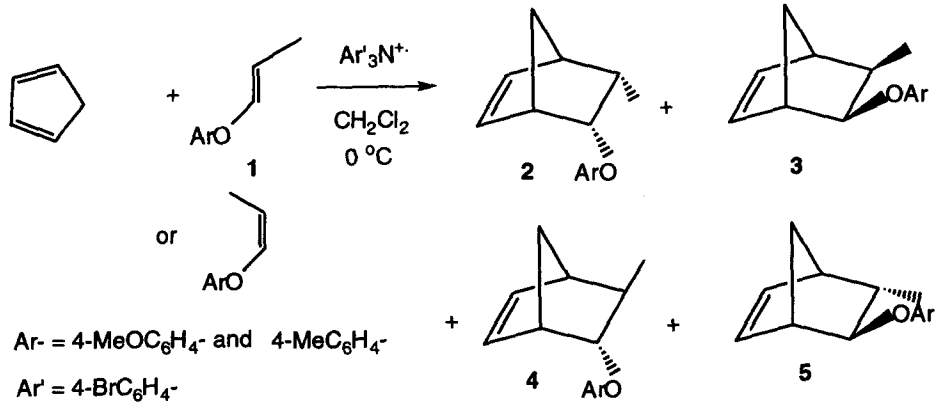
petroleum ether: dichloromethane (15:1) as the eluent. These compounds were found to be >98% pure and were fully characterized by proton and carbon NMR and by HRMS.[5] The corresponding unsubstituted phenyl 1-propenyl ethers were not purified, since their reactions with 1,3-cyclopentadiene appeared to be much less efficient than those of the derivatives having electron donating substituents.

The reactions of the 4-methoxyphenyl 1-propenyl ethers (**1**) were studied most extensively. The reaction of either *cis*-**1** or *trans*-**1** with 1,3-cyclopentadiene under the usual aminium salt conditions proved to be extemely inefficient because of competition with facile acid catalyzed reactions. However, when a two phase dichloromethane:water (20:1) solvent system was employed in order to extract strong acids which may be present in the aminium salt and/or which are generated during the reaction, from the dichloromethane solution, the reaction cleanly produced the Diels-Alder adducts **2-5** in 59% yield from *trans*-**1** (total yield of separated

SCHEME 1

Non-Stereospecific Addition of Aryloxy Cis- and Trans-1-Propenyl Ether

Cation Radicals To 1,3-Cyclopentadiene



purified adducts). GC measurements showed that the yields in the case of *cis*-**1** are comparable to those from *trans*-**1**. To our knowledge, this is the first time in which such a two phase system has been employed in conjunction with the aminium salt method, but this modification appears to have considerable promise in other synthetic applications of this chemistry. It is, however, necessary to employ a larger amount of the aminium salt than conventionally (*ca*. 60-100 mol %). The structures of the four Diels-Alder adducts were determined by proton NMR, COSY, and NOESY spectra, as well as HRMS (Scheme 1).[6] The composition of the adducts obtained from *cis*-1 was found to be 89% *cis* [44% *cis,endo*(**2**)and 45% *cis,exo*(**3**)] and 11%*trans*[5% *trans,endo* (**4**) and 6% *trans,exo*(**5**)]. The Diels-Alder adducts obtained from *trans*-**1** were found to be 71% *trans* (43% **4** and 28% **5**) and 29% cis (9% **2** and 20% **3**). Analogous results were found for the 4-methyl compound using GC. However, the individual adducts were much more difficult to purify in this latter instance.

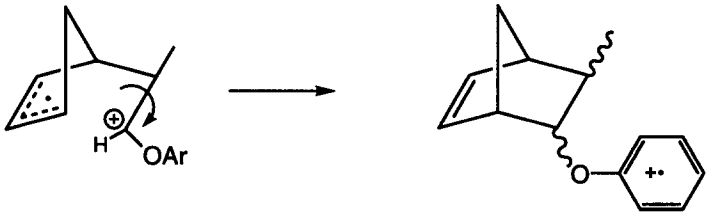
To verify that the product mixture was not generated by subsequent rearrangement or decomposition of primary products, either Diels-Alder or cyclobutane products, the corresponding reactions were also carried out both for short reaction times (5 s) in the absence of the aqueous phase (after which time only a 5-10% conversion of reactants to adducts was achieved) and, independently, in the presence of an excess of a hindered base, 2,6-di-*tert*-butylpyridine. In both cases product mixtures were obtained which were quite similar to those reported above. In each case it was verified by GC that geometric isomerization of the recovered starting material was insignificant.

Although it appears highly unlikely that unimolecular isomerization of the intermediate *cis* or *trans* cation radical could compete with the extremely rapid cycloaddition, this possibility was investigated by carrying out the reaction in the presence of very large excesses (20 fold) of cyclopentadiene.. Under these reaction conditions, the same product mixtures were obtained as had been previously observed. Finally, the observation that very similar product distributions were observed when the reaction was carried out with initiation by photosensitized electron transfer (dicyanobenzene, acetonitrile) or anodic oxidation (reticulated vitreous carbon,acetonitrile:dichloro-methane) remove the possibility that the aminium salt might ionize the substrates by a unique mechanism involving electrophilic attack followed by bond rotation and then homolysis.

The results of this stereochemical study therefore clearly indicate that the additions of the cation radicals of *cis*- and *trans*-1-propenyl aryl ethers to 1,3-cyclopentadiene are stepwise processes involving an intermediate distonic cation radical in which the carbocationic site is very appreciably stabilized by the electron donating aryloxy function (Scheme 2). Given the apparent involvement of this kind of intermediate it is of

SCHEME 2

The Stepwise Mechanism Involving A Distonic Cation Radical Intermediate



special interest that Diels-Alder adducts strongly predominate in this reaction , as opposed to cyclobutane adducts. It does appear that a small amount of at least one other adduct, which could not be fully purified, is formed in this reaction, and it appears likely that this is indeed a cyclobutane adduct. Nevertheless, it is clear that these latter adducts are minor products of the reaction, even at very short reaction times. This suggests that the distonic cation radical is preferentially formed in a conformation which favors cyclization at the diene terminus.

The question of whether some cation radical Diels-Alder reactions occur in a fully concerted manner, without the intervention of distonic cation radical intermediates remains an interesting one. Reactions which are highly stereospecific are clearly the best candidates for a concerted mechanism. However, as has been noted, stereospecificity in itself is not a rigorous proof of concert. It will also be of interest,if such mechanisms are operative, to determine what is their range of operation, and what are the factors which favor concerted as opposed to two step cycloaddition. Research into these questions is continuing in this laboratory.

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References and Notes.

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[5] *Synthesis of Cis- and Trans-***1**. 4-Methoxyphenyl allyl ether (27.4 g,0.167 mol) was dissolved in 50 mL of dichloromethane, followed by the addition of palladium(II) chloride (0.27 g). The solution was stirred at room temperature and checked periodically by GC to determine the progress of the reaction. After 10 days the conversion was essentially quantitative. A portion (6.9 g) of this 60:40 *cis:trans* mixture was then subjected to silica gel chromatography using petroleum ether:dichloromethane (15:1) as the eluent. The pure *cis* isomer was obtained iin 22% yield (1.53 g), the pure *trans*-isomer in 13% yield (0.87 g), along with 3.5 g of a mixture of the two isomers: ^{1}H NMR (CDCl3), *cis*: δ 1.69 (dd,3H,J=6.84,1.69 Hz),3.76(s,3H),4.78(m,1H,J=6.81), 6.28(dd,1H,J=5.98,1.7),6.87(m,4H); *trans*: δ 1.63 (dd,3H,J=6.86,1.62), 3.76(s,3H),5.27 (m,1H, J=6.89), 6.35 (dd,1H,J=12.16,1.63),6.86(m,4H).

[6] *Diels-Alder Reaction of trans-1 with 1,3-Cyclopentadiene.* To 80 mL of dichloromethane and 4 mL of water was added 0.31 g (1.89 mmol) of *trans*-1 and 1.25 g (18.9 mmol) of 1,3-cyclopentadiene. After cooling to 0 °C, 1.54 g (1.89 mmol) of tris(4-bromophenyl)aminium hexachloroantimonate was added, with stirring . The reaction mixture was quenched after 2 minutes with saturated potassium carbonate in methanol , washed three times with water, and extracted with dichloromethane . The isomer mixture was analyzed by GC and the individual diastereoisomers separated by silica gel chromatography. Characterization of the four isomers is provided as supplementary material.