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LEWIS ACID CATALYZED INTRAMOLECULAR DIELS-ALDER CYCLOADDITIONS. A MILD METHOD FOR THE SYNTHESIS OF BICYCLO [n.3.1] BRIDGEHEAD ALKENES

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Summary: Diethyl aluminum chloride is an effective catalyst for the type II intramolecular Diels-Alder cycloaddition.

Lewis acids are commonly employed as catalysts for a variety of pericyclic reactions.[1] The synthetic importance of these reactions is particularly evident in Diels-Alder chemistry where milder reaction conditions and the opportunity to modify both regio- and stereochemistry is well documented.[2]

The influence of Lewis acids on the intramolecular Diels-Alder cycloaddition has also received attention. Although the dramatic and predictable changes in reaction stereochemistry are not in evidence, catalysis in many cases is found to provide substantial rate accelerations.[3] Type II intramolecular Diels-Alder cycloadditions involving dienes joined to the dienophile at the 2-position result in formation of bridgehead alkenes.[4] These cycloadditions frequently require high reaction temperatures and could, therefore, profit measurably from catalysis. Uncertainty regarding the compatability of bridgehead alkenes with Lewis acids was a deterrent to persuing this line of research.

We report here that Lewis acids are effective catalysts for a wide variety of type II intramolecular Diels-Alder cycloadditions and, as a result, make available bridgehead alkenes under very mild reaction conditions. The results are summarized in the table.

A variety of Lewis acids and reaction conditions were surveyed using 4-methylene-hex-5-enyl acrylate (1)[5] as a model substrate. This triene ester undergoes thermal cycloaddition at 139°C ($t_{1/2}$ = 1.8 hr).[6] Although a number of catalysts produced detectable quantities of cycloadduct 2 at or below room temperature ($MgBr_2$,$TiCl_4$,$AlCl_3$), the most effective catalyst was found to be diethyl aluminum chloride.[7] When equimolar amounts of triene ester 1 and Et_2AlCl were stirred at 21°C in CH_2Cl_2 for 4 hr, VPC analysis revealed the bridgehead alkene cycloadduct was formed in 85% yield. An equimolar ratio of catalyst to substrate was found to be optimum, additional catalyst did not accelerate the reaction further and the reaction rate dropped off when a deficiency of catalyst was used. The reaction rate was found to be very sensitive to temperature, after 4 hr at 0^{o}C, only 10% reaction had occurred. A pseudo first order rate constant for the Lewis acid catalyzed cycloaddition was obtained at 21^{o}C, $k = 5.2 \times 10^{-4}$ sec^{-1}.[8] Extrapolation of rate data from the thermal cycloaddition permits a measure of the catalytic rate enhancement, the Lewis acid complexed triene ester is 10^{4} times more reactive than the uncomplexed ester. This rate enhancement is comparable to that found in the bimolecular Lewis acid catalyzed Diels-Alder reaction, estimated in one quantitative study to be 10^{5} (21^{o}C).[10]

Mechanistically, the convention has been to regard Lewis acid catalyzed Diels-Alder cycloadditions as non-synchronous pericyclic reactions.[11,12] Indeed, the rate of catalyzed cycloaddition of triene ester 1 is only slightly influenced by solvent polarity; a change in solvent from pentane to methylene chloride produces less than a threefold change in rate $(k_{CH_2Cl_2}/k_{pentane}) = 2.8$ (19^{o}C).

Interestingly, we have found methylated trienone 7 (entry 4) is considerably more reactive than the non-methylated homolog 3 under Lewis acid catalyzed conditions. This pattern of reactivity is in contrast to their thermal behavior where triene 3 is significantly more reactive than 7.[13] The crossover in diene reactivity may reflect a greater responsiveness of the alkalated diene to an electron deficient dienophile in the catalyzed reaction.[14] The results could also signal the onset of a two step carbonium ion mechanism. Additional evidence, however, will be necessary to permit a distinction between these two alternatives.

As has been found previously, Lewis acids exert only a minor influence on the regioselectivity of intramolecular Diels-Alder reactions.[3] Thermal cycloaddition of triene ester 11 (180^{o}C, 12 hr) yields a mixture of meta and para adducts in a 10:1 ratio. In the presence of Et_2AlCl (1 eq), the cycloaddition is complete after 1 hr at 21^{o}C. The cycloadducts are present in a ratio of 81:19. A slight shift in the direction of the para regioisomer is consistent with that predicted by FMO theory.[16] The magnitude of this shift, however, is not large and may also be accounted for by other factors such as a slight temperature dependence of regioselectivity.[17]

Both mechanistic and synthetic studies of these Lewis acid catalyzed reactions are continuing.

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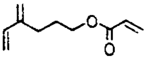
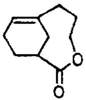
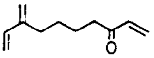
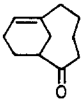
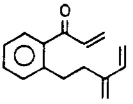
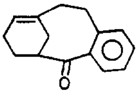
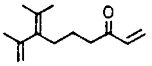
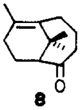
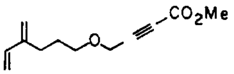
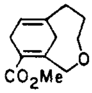
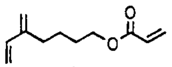
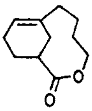
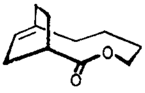
	Triene[a]	Product[a]	Condition[b]	Yield
(1)	 1	 2	CH_2Cl_2, Et_2AlCl, 4 hr 21°C	85(50)
(2)	 3	 4	CH_2Cl_2, Et_2AlCl, 2 hr, 21°C	75
(3)	 5	 6	CH_2Cl_2, Et_2AlCl, 1 hr 21°C	71
(4)	 7	 8	CH_2Cl_2, Et_2AlCl, <5 min 21°C	70
(5)	 9	 10	CH_2Cl_2, Et_2AlCl, 21°C, 12 hr	85
(6)	 11	 12 +  13	CH_2Cl_2, Et_2AlCl 1 hr 21°C	(90)[d]

a. All new compounds give satisfactory spectral data (^1H, ^{13}C, IR, MS).

b. The cycloaddition of trienone 3 serves as a typical experimental procedure. To a stirred solution of 3 (0.35m mol) at 21°C in CH_2Cl_2 (10mL) containing undecane (20μl) as internal standard was added Et_2AlCl (210μl, 0.35m mol, 25% hexane solution) via syringe. After 2 hr the reaction solution was transferred to a cold, saturated $NaHCO_3$ solution (25mL). Product was extracted with pentane (3x20mL), and the organic layer washed with $NaHCO_3$, H_2O then dried ($MgSO_4$). Analysis by GC (2.5m 3% SP2100, T-170°C) indicates cycloadduct 4 present in 75% yield. Cycloadducts were isolated by either preparative GC or by column chromatography.

d. 81:19 mixture of 12:13

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6. The intramolecular Diels-Alder cycloaddition reaction exhibits first order behavior over more than three half-lives. Rate data was obtained in toluene solution (0.06M) by monitoring the disappearance of starting material versus an internal standard.

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8. The rate constant was obtained in CH_2Cl_2 using equimolar amounts of triene ester 1 and diethyl aluminum chloride. The reactive species is assumed to be the 1:1 complex of Lewis acid and triene ester.[9] Thermal cycloaddition of uncomplexed ester is kinetically unimportant under the reaction conditions.

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11. (a) K.N. Houk and R.W. Strozier, J. Am. Chem. Soc., 1973, 95, 4094; (b) N.T. Anh and J. Seyden-Penne, Tetrahedron, 1973, 29, 3259.

12. Under certain conditions, Lewis acid catalyzed Diels-Alder reactions have been suggested to proceed by a two step, ionic mechanism, (a) H. Hirai, J. Polymer Sci., Macromolecular Rev., 1976, 11, 47; (b) H.W. Thompson and D.G. Melillo, J. Am. Chem. Soc., 1970, 92, 3218; (c) T. Inukai and T. Kojima, J. Org. Chem., 1966, 31, 1121.

13. The half-life of trienone 3 is 13 hr at 155°C. Compound 7, on the other hand, underwent only 10% cycloaddition after 72 hr at 185°C.

14. A similar reversal in reactivity has been noted by Sustman[15]. 4-Methyl-1,3-pentadiene (MP) is very similar in reactivity to butadiene in competition experiments with TCNE ($k_{rel} = 1.08$). In competition experiments with the less electron poor dienophile maleic anhydride, MP is inreactive. These results are complicated, however, by the fact that reaction of MP with TCNE yields mixtures of 4+2 and 2+2 cycloadducts indicating an ionic component to this reaction.

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