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Hydrogen-Bond-Promoted Hetero-Diels−Alder Reactions of Unactivated Ketones

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The [4 + 2] cycloaddition reaction between dienes and carbonyl-group-containing compounds provides one of the most direct methods for the synthesis of six-membered oxygen heterocycles. Although these hetero-Diels−Alder reactions have been studied extensively,[1] due to the prevalence and biological importance of oxygen heterocycles,[2] their scope is limited. Nearly all such cycloadditions have been reported with aldehydes, and, even then, they require special reaction conditions, such as high temperature, high pressure, or Lewis acid catalysis.[1a,3] For steric and electronic reasons, the ketone carbonyl group is a much poorer heterodienophile than the aldehyde carbonyl group, such that there are very few reports of successful hetero-Diels−Alder reactions of simple ketones.[1,4,5a] We report here the first examples of hydrogen-bond-promoted acceleration of hetero-Diels−Alder reactions and the use of such catalysis to carry out the hetero-Diels−Alder reactions of simple, unactivated ketones.

While investigating the solvent effect for the hetero-Diels−Alder reaction between aldehydes and 1-amino-3-siloxybuadiene,[5] we observed a significantly higher reaction rate in chloroform than in other aprotic organic solvents. To more precisely assess the solvent effect, we examined the rate of the hetero-Diels−Alder reaction between diene **1** and *p*-anisaldehyde (**2**) in several different solvents (Table 1). It is clear from the data that the rate differences do not correlate with the solvent's dielectric constant: the reaction in chloroform was 10 times faster than that in the more polar solvent, acetonitrile. The higher rate in chloroform cannot simply be explained by invoking catalysis from trace amounts of acid in chloroform, since the same rate was observed even after rigorous purification of the solvent. Moreover, the addition of triethylamine or a catalytic amount of HCl did not affect the rate one way or another.[6] The increased reaction rate in chloroform, we concluded, could arise from a C−H···O hydrogen bond between chloroform and the carbonyl oxygen,[7,8] which would render the carbonyl group a stronger heterodienophile (Figure 1).

As the data show, the cycloadditions are accelerated to a much greater extent in protic solvents, in which the OH group is expected to form a strong hydrogen bond to the aldehyde oxygen.[9,10] Thus, the hetero-Diels−Alder reaction of **1** and anisaldehyde is 630 times faster in deuterated 2-propanol than in deuterated THF, which corresponds to a $\Delta\Delta G^{\ddagger}$ of −3.77 kcal/mol.

Importantly, the activation provided by hydrogen-bonding solvents is sufficient that even simple ketones, generally considered unreactive,[1] undergo the hetero-Diels−Alder reaction. We initially examined the hetero-Diels−Alder reaction of cyclohexanone (**4a**) and diene **1** in chloroform (Table 2). Remarkably, although slow, the cycloaddition with this unactivated ketone proceeded cleanly and gave, upon acetyl chloride-mediated elimination of the amino group, the desired spiro-fused dihydropyrone in 45% yield, along with *E*-4-(*N*,*N*-dimethylamino)-3-buten-2-one (**5**).[11] As anticipated, the cycloaddition was considerably faster in protic solvents. The reaction went to completion in 1 day in *t*-BuOH and, upon acetyl chloride workup, afforded the expected spiro product in 71% yield. Solvents with less shielded hydroxyl groups were more effective at accelerating the hetero-Diels−Alder reaction.

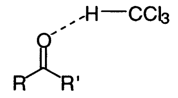
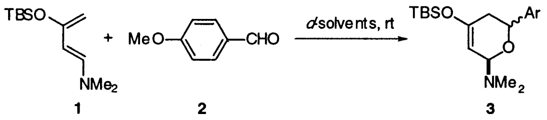


Figure 1.

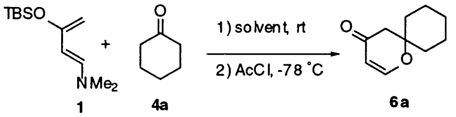
Table 1. Rates of HDA Reactions in Different Solvents



entry	solvent	dielectric constant[a]	rate constant (*k*)[b]	relative rate
1	THF-d_8	7.6	1.0×10^{-5}	1
2	benzene-d_6	2.3	1.3×10^{-5}	1.3
3	acetonitrile-d_3	37.5	3.0×10^{-5}	3.0
4	chloroform-*d*	4.8	3.0×10^{-4}	30
5	*tert*-butyl alcohol-d_{10}	10.9	2.8×10^{-3}	280
6	isopropyl alcohol- d_8	18.3	6.3×10^{-3}	630

[a] For the corresponding undeuterated solvent, at 25 ± 5 °C . [b] Kinetics measured by NMR integration using internal standard.

Table 2. Reactions of Cyclohexanone and **1** in H-Bonding Solvents



entry	solvent	time (h)	solvolysis (%)[a]	yield (%)[c]
1	chloroform	48	20−25	45
2	*tert*-butyl alcohol	24	<5	71
3	isopropyl alcohol	3	10−15	60
4	ethanol	0.5	∼50[b]	30
5	methanol	0.5	∼40[b]	0
6	2-butanol	5	<5	78

[a] Percentage of hydrolysis was calculated by NMR integration. [b] Significant amount of other type of decomposition took place as well as hydrolysis. [c] Yields refer to isolated, chromatographically purified products, except for entries 4 and 5, where the yield was based on NMR integration of cycloadduct.

The reaction went to completion in just 3 h in 2-propanol, but the desired cycloadduct was accompanied by a significant amount (10−15%) of the solvolysis byproduct, **5**. Diene solvolysis predominated in ethanol and methanol. The results show that although better hydrogen-bonding alcohols promote faster reactions, they also

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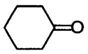
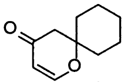
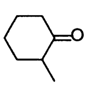
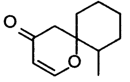
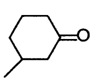
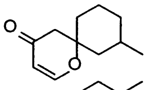
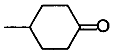
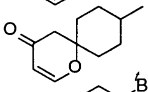
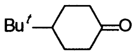
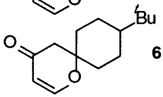
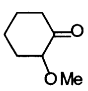
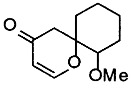
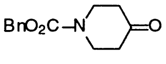
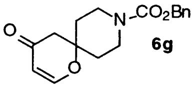
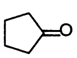
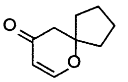
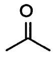
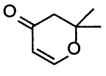
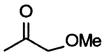
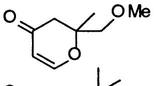
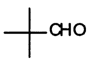
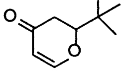
Table 3. Cycloaddition Reactions of Diene **1** and Unactivated Ketones

entry	ketone	time[a]	product	ratio	yield (%)[c]
1		5 h	 **6a**		78
2		4d	 **6b**		35
3		5.5 h	 **6c**	4.2:1	75
4		5.5 h	 **6d**	2.8:1	74
5		5.5 h	 **6e**	3:1	76
6[b]		8 h	 **6f**	1.5:1	81
7		3 h	 **6g**		82
8		19 h	 **6h**		41
9		30 h	 **6i**		40
10		6 h	 **6j**		33[d]
11		1.5 h	 **6k**		77

[a] All reactions were carried out 0.5 mmol scale in 0.5 mL of 2-butanol, using 2 equiv of the ketone. [b] The ketone was dissolved in 0.2 mL of benzene. [c] Yields refer to chromatographically purified products. [d] An equal amount of the Mukaiyama aldol side product was formed. See ref 5a.

solvolyze the diene. The use of 2-butanol (entry 6) provided a good compromise: the reaction was reasonably fast and was accompanied by little of the solvolysis byproduct.

This hydrogen-bond-promoted protocol represents the first general method for achieving the hetero-Diels−Alder reactions of unactivated ketones (Table 3). The reactions were carried out conveniently by mixing the diene and the ketone in 2-butanol and letting the resulting solution stir at room temperature for the indicated time. The alcohol was removed in vacuo and replaced with dichloromethane. After the solution was cooled to −78 °C, acetyl chloride was added, and the resulting solution was subjected to an aqueous workup and chromatographic purification. This simple, one-pot procedure allowed the preparation of a variety of structurally novel spiro-dihydropyrones in good yields.

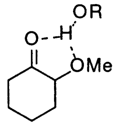


Figure 2.

These hetero-Diels−Alder reactions are sensitive to steric and electronic variations in the ketone. Whereas the reaction of diene **1** and cyclohexanone went to completion in just 5 h, the reaction with 2-methylcyclohexanone was only ca. 50% complete after 4 d (entry 2). By contrast, 2-methoxycyclohexanone was comparable in reactivity to cyclohexanone (entry 6). Evidently, the inductive effect of the methoxy group and its capacity to hydrogen bond override the steric effect (Figure 2). Substituents at the 3 or 4 positions of cyclohexanones do not retard the reaction (entries 3 and 4). In general, six-membered-ring ketones were more effective as heterodienophiles than other ketones (cf. entries 8−10). Finally, the hetero-Diels−Alder reaction of the hindered aldehyde, pivaldehyde, is greatly accelerated in a hydrogen-bonding solvent (entry 11).[12]

The results above demonstrate that the hetero-Diels−Alder reactions are greatly accelerated in hydrogen-bonding solvents. This activation protocol represents an attractive and operationally simple alternative to conventional Lewis acid catalysis. The extension of this hydrogen bond acceleration concept to asymmetric synthesis remains to be explored.

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Supporting Information Available: General experimental procedures for the HDA reactions shown and spectroscopic data for the products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) Even if there were a trace amount of acid in the solvent, it would be neutralized by the basic nitrogen in the cycloadduct.
(7) The rate of the hetero-Diels−Alder reaction in deuteriochloroform was the same (within experimetal error) as that in chloroform.
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(11) Diene **1** is readily hydrolyzed or solvolyzed, affording **5**.
(12) The corresponding reaction in chloroform was considerably slower and afforded the product in 54% product after 2 days (ref 5a).

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