Diels-Alder Reactions Using
Supercritical Water As An Aqueous Solvent Medium

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Abstract: A variety of Diels-Alder reactions have been performed in supercritical water as a reaction medium. The rapid reaction of Diels-Alder reactions of cyclopentadiene and various electron poor dienophiles such as diethyl fumarate and acrylonitrile is observed in supercritical water, and leads to high yields of clean products without added catalysts. © 1997 Elsevier Science Ltd.

The Diels-Alder reaction is the most widely employed synthetic method for the production of polycyclic ring systems. In view of the importance of the method for the preparation of natural and synthetic products, there is increasing interest in the development of special methods and catalysts to enhance reaction rates as well as selectivity of the $[4\pi + 2\pi]$-cycloadditions.[1] In the early 1980's, Breslow and Grieco separately reported that using water as a solvent media for Diels-Alder reactions significantly influenced the rate of reaction.[2] However the aqueous phase naturally limits the reagents to polar ionic compounds, or requires special additives. The unique properties of supercritical water (SCW),[3] and our current research program involving organic reactions in SCW,[4] led us to explore the possibility of performing Diels Alder reaction in supercritical water for the first time.

The properties of supercritical water are much different than those of water at ambient conditions and correlate strongly with density. Water reaches supercritical conditions at 374°C and 221 atm (3200 psi). Under these conditions, its dielectric constant decreases dramatically to a value similar to that of toluene, and renders a great majority of organic molecules completely soluble in supercritical water. It is not actually necessary for water to reach its actual critical point for it to become a suitable solvent for organic reactions. For example, at 300°C the critical point of the benzene/water mixture is surpassed and the two compounds are completely miscible.[5] Other hydrocarbons exhibit similar behavior in this subcritical region. For example, we found that cyclopentadiene and ethylacrylate become sufficiently soluble in H_2O to react completely at approximately 280°C, almost 100°C below the critical point. In fact, all of the reactions we have studied thus far can take place in this subcritical region of water.

Water is also a non toxic, inexpensive, readily available solvent and easily separated from most organic products. However, the use of SCW as a *solvent* in organic synthesis remains largely unexplored and deserves proper investigation.[4,6] SCW is particularly attractive because of the observation of unusual effects of water on the rates of cycloaddition reactions.[2,3] In this paper we report that SCW is an attractive

medium for Diels Alder synthesis, and that the reaction times of a variety of cycloaddition reactions are enhanced significantly in SCW relative to reactions run under more conventional conditions.

Exploratory reactions were run in 316 stainless steel reaction vessels with cone and thread fittings and an internal volume of 10.1mL, designed to withstand temperatures and pressures up to 400°C and 20,000 psi respectively. All reactions described here were run using supercritical or near critical water as the solvent. In a typical reaction, 4 mL of water and a total of 0.5 mL of starting materials were added to the vessel. The vessel was assembled and placed in a tube furnace preheated to 375°C. Depending on the solubility properties of the starting materials, the reactions were heated from 0.5 to 2.0 hours. The organic products were extracted into ether and analyzed by GC-MS or HPLC. All successful reactions were further scaled-up to 3mL of reactants in a larger volume stainless steel reaction vessel. All results were similar to those of the smaller volume reactions.

A number of reactions were studied using 1,3-butadienes, but in order to examine the scope and limitations of this chemistry, the size and position of the substituent on the conjugated diene were varied as well as the nature of the dienophiles. Most of the reagents used in these experiments are, of course, completely immiscible in water under ambient conditions. The results are listed in Table 1.
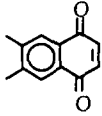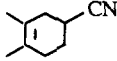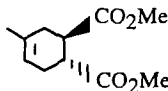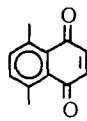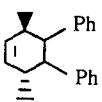
Steric hindrance plays a role in the final outcome of these reactions. For instance, when 1,4-diphenyl-butadiene is reacted with sterically hindered dienophiles such as trans-stilbene, no reaction takes place. Similarly, when cis-trans-hexadiene is used with almost any dienophile the result is a relatively low product yield. However, as the steric hindrance of the system decreases from tetraphenylethylene to styrene, the product yield increases from 5% to 49%.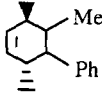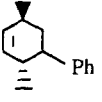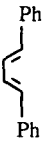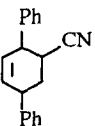 When substituents are on the 2 or 3 position of the butadiene the reaction gives modest to excellent yields of product as seen from Table 1. In the case where a cyclohexene derivative is the expected product, reaction conditions sometimes favors the loss of 2 equivalents of H_2 to yield the aromatic species, especially in the case where an oxidant such as benzoquinone is the dienophile.

It was previously reported that the cycloaddition of cyclopentadiene (1) with the unsaturated carboxylic acid derivatives diethyl-fumarate (2) and diethyl-maleate (5) using an ethanol-water co-solvent mixture along with bakers' yeast as the catalyst led to appreciable stereoselectivity.[7] After 48 hours at 37°C the reaction gave (3) and (6) in 74% and 78% yields respectively.
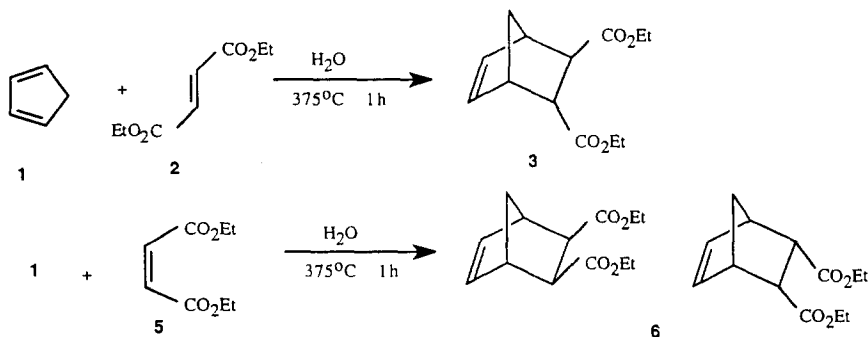
However, using SCW as a solvent in the absence of any catalyst, we obtained yields of 10% and 86% of (3) and (6) respectively after one hour. Although the yield for the endo/exo-2,3-diethylester-5-norbornene,(3), mixture is low, the cis diene (diethyl-maleate) formed an equal mixture of both isomers of 6 in excellent yield. Using the same reaction conditions the norbornene derivative (9) was synthesized from cyclopentadiene and ethyl acrylate in approximately 80% yield after two hours.

Table 1. Diels-Alder reactions using water as the reaction media.

	Diene	Dienophile	Rxn Conditions	Major Product	% Yield
(a)		acrylonitrile	30 min; 303°C		88%
(b)		quinone	30 min; 310°C		86%
(c)		acrylonitrile	25 min; 293°C		100%
(d)		diethylfumarate	60 min; 337°C		84%
(e)		quinone	60 min; 334°C		17%
(f)	II II	tetraphenylethylene	60 min; 334°C	N.R.	--
(g)	II II	trans-stilbene	60 min; 334°C		5%
(h)	II II	methylstyrene	60 min; 334°C		26%
(i)	II II	styrene	60 min; 334°C		49%
(j)		trans-stilbene	120 min; 373°C	N.R.	--
(k)	II II	styrene	120 min; 371°C	N.R.	--
(l)	II II	acrylonitrile	35 min; 307°C		95%

This compared to a 93% yield after 5 hours at room temperature in a 5M $LiClO_4$ and diethyl ether solution.[8] In contrast to the usual isomeric ratios of endo and exo adducts, our experiment showed an almost 1:1 endo-exo ratio, compared to the results from the lithium solution above, which contained an 8:1 endo-exo ratio.
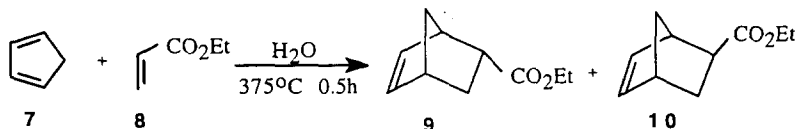
A time and temperature study using methyl acrylate, **8**, and cyclopentadiene, **7**, indicates that as the reaction initially reaches supercritical conditions, the endo/exo ratio is almost equal. However, the reaction undergoes reversion upon heating, reestablishing an equilibrium with a higher endo/exo ratio.

Table 2. Time and temperature study of **7 + 8** revealing increased stereoselectivity of endo configuration

Reaction Time(min.)	Final Temperature(°C)	Endo/Exo Ratio **9/10**
15	195	1.7
30	281	1.3
60	330	1.8
90	343	2.1
120	356	2.4
240	375	3.0

To confirm the importance of SCW as a reaction solvent, all reactions were run under the same conditions without solvent. Reactions were never as clean and never gave as high yields as in SCW. In most cases the reagents tend to polymerize upon heating, and solidified inside the reaction vessel. In addition, reactions run in water at temperatures below 280°C led to no reaction. Thus we have demonstrated that Diels-Alder reactions can be performed cleanly in high yield, using supercritical water as an aqueous reaction medium, eliminating the need for organic solvents while increasing reaction rate.

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