ORGANIC LETTERS

2006
Vol. 8, No. 24
5545−5547

Rate Enhancement of Diels–Alder Reactions in Aqueous Perfluorinated Emulsions

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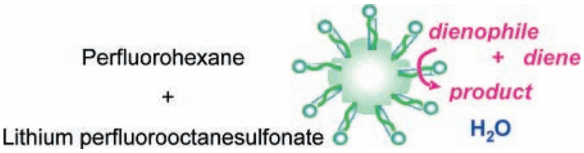
Received September 20, 2006

ABSTRACT



A marked acceleration property for the Diels–Alder reaction was observed in an aqueous micellar system composed of perfluorohexane and lithium perfluorooctanesulfonate. The reaction rate increased with the concentration of the equimolar mixture of PFH and LiFOS, and the rate in 500 mM PFH and 500 mM LiFOS was about 100-fold greater than that in water without the fluorous field. After completion of the reaction, the products were simply extracted from the aqueous reaction mixture using *n*-hexane.

Recently, the use of water as a reaction solvent has received considerable attention in synthetic organic chemistry due to its unique physical and chemical properties.[1] By utilizing these properties, it is possible to realize reactivity or selectivity that cannot be attained in organic solvents. It is well-established that the rates of certain Diels−Alder reactions in aqueous media show dramatic acceleration relative to those in organic solvents.[2] Over the years, this has been ascribed to various factors such as hydrophobic association of the reacting partners,[3] micellar catalysis,[4] solvophobicity,[5] high internal solvent pressure,[6] cohesive energy density,[7] solvent polarity,[8] and hydrogen bonding.[9] In addition, similar rate acceleration of Diels−Alder reactions has been observed in fluorous solvents.[10] It has been shown that fluorocarbon solvents have poor miscibility and lower solvation power than ordinary nonpolar organic liquids ("fluorophobic effect") and that these highly fluorinated solvents have solvophobic properties that are similar to those observed in water. The unique properties of fluorous compounds have also been applied in the synthesis of fluorous-tagged organic compounds, allowing rapid reactions and separations.[11]

The property of exclusivity shown by fluorous solvents and water toward numerous organic substrates, however, may

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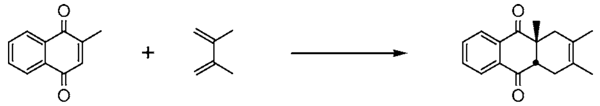
10.1021/ol0623116 CCC: $33.50

limit the reaction efficiency and productivity because the solubility of substrates in these solvents is generally very low, causing precipitation or aggregation in solution. It was expected that the creation of a wide interfacial area between a fluorous phase and aqueous media might cause the substrates to remain in the interface, accelerating their intermolecular reactions, due to repulsion from both sides (fluorous and aqueous phase). On the basis of these assumptions, we identified significant acceleration of Diels−Alder reactions in fluorous micelles and microdroplets formed by perfluorohexane (PFH) and lithium perfluorooctanesulfonate (LiFOS)[12] in water, as an example of the hypothesized substrate-exclusive biphasic reaction fields.

Initially, the media effect on the rate of the Diels−Alder reaction between 2-methylnaphthoquinone **1** and 2,3-dimethyl-1,3-butadiene **2** was examined (Table 1).

Table 1. Media Effect for the Initial Rates of Diels−Alder Reaction between **1** and **2**



1 **2** **3**

condition	reaction rate^a (μM/h)	condition	reaction rate^a (μM/h)
PFH	0.25	water	1.40
n-hexane	0.38	aq SDS (100 mM)	3.87
diethyl ether	1.00	aq TFE (100 mM)	3.80
methanol	1.27	aq LiOTf (100 mM)	1.15
acetonitrile	1.60	aq LiOS (100 mM)	2.35
dichloromethane	3.16	aq LiFOS (100 mM)	11.6
toluene	0.73	neat^b	<0.2

^{a} The initial reaction rate was estimated from the generation of the product **3** in the reaction mixture of **1** (0.1 mmol) and **2** (0.4 mmol) in 10 mL of each reaction medium over 24 h at 25 °C. ^{b} A mixture of **1** (0.1 mmol) and **2** (0.4 mmol) in the absence of solvent.

The reaction rate was very low in ordinary organic solvents, PFH, and water. Even in the presence of aliphatic-chain surfactants such as sodium dodecyl sulfate (SDS) and lithium octanesulfonate (LiOS), no remarkable acceleration was observed. In aqueous 2,2,2-trifluoroethanol (TFE), substrates showed low solubility in the aqueous dispersion. However, in the presence of LiFOS, the aqueous Diels−Alder reaction was moderately accelerated. As no accelerating effect was observed for lithium trifluoromethanesulfonate (LiOTf), it was suggested that the formation of perfluorinated micelles in aqueous media should be effective for the acceleration of the Diels−Alder reaction.

On the basis of the expectation of rate enhancement properties in perfluorinated moieties, we then attempted to construct perfluorinated microdroplets using PFH as a core fluorous liquid and LiFOS as an emulsifier. Sonication of the equimolar mixture of PFH and LiFOS resulted in the formation of a small-sized, stable fluorinated dispersion. To the particle dispersion were then added **1** and **2** with stirring at 25 °C.

Surprisingly, the Diels−Alder reaction of **1** and **2** was dramatically accelerated in the aqueous equimolar dispersion of PFH and LiFOS (Table 2). The reaction rate increased with the concentration of the equimolar mixture of PFH and LiFOS, and the rate in 500 mM PFH and 500 mM LiFOS was about 100-fold greater than that in water without the fluorous field.

Table 2. Initial Rates of Diels−Alder Reaction between **1** and **2** in Aqueous Fluorous Emulsions

LiFOS (mM)	PFH (mM)	*n*-hexane (mM)	reaction rate^a (μM/h)
–	–	–	1.40
100	–	100	2.10
100	–	–	11.6
100	100	–	42.4
200	200	–	84.8
500	500	–	142.5

^{a} The initial reaction rate was estimated from the generation of the product **3** in the reaction mixture of **1** (0.1 mmol) and **2** (0.4 mmol) in 10 mL of each reaction medium over 24 h at 25 °C.

For a mixture of 500 mM PFH and 500 mM LiFOS, the Diels−Alder reaction was almost complete after standing for 72 h at 25 °C (yield of 98%, with 2% recovered starting material **1**; Figure 1 shows the initial rates and yields). It was revealed that the sonicated mixture of PFH and LiFOS in water formed a stable, fine emulsion of 0.37 μm mean diameter (measured by a laser-scattering droplet analyzer). Both **1** and **2** showed low miscibility with PFH and water; the exclusive property of the aqueous/fluorous interface effectively accelerates the desired cycloadditions.

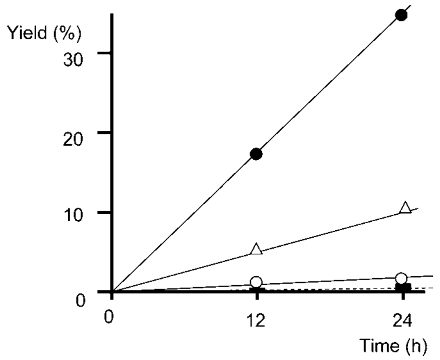


Figure 1. Initial rates of Diels−Alder reaction. Conditions: compounds **1** (0.1 mmol) and **2** (0.4 mmol) in 10 mL of water. ●, 500 mM LiFOS/PFH aqueous. △, 100 mM LiFOS/PFH aqueous. ○, 100 mM LiFOS aqueous. ■, water.

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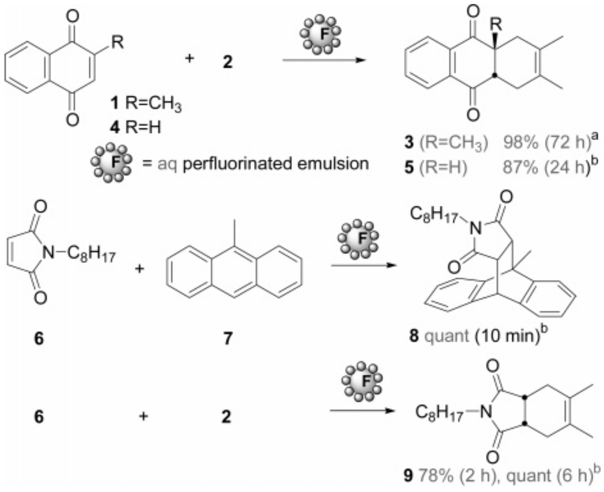
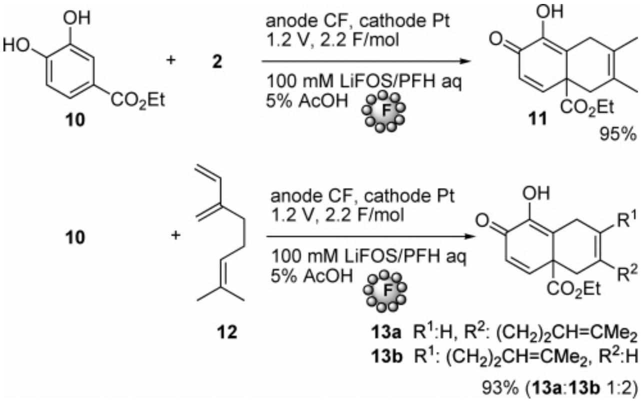
Scheme 1. Diels−Alder Reactions in the Perfluorinated Emulsion



[a] 500 mM LiFOS/PFH. [b]100 mM LiFOS/PFH.

Scheme 2. Anodic Diels−Alder Reactions in the Perfluorinated Emulsion



Using the fluorinated micellar system, it was shown that some typical Diels−Alder reactions could proceed even under very mild aqueous conditions (Scheme 1). In the absence of the perfluorinated droplets, those products were obtained in 15−60% yield. In addition, as several kinds of micellar systems effectively work as electrolytic reaction fields in which surfactants play a role as supporting electrolytes,[13] we undertook the further challenge of applying the system to the anodic Diels−Alder reaction of in situ generated unstable quinone intermediates. Scheme 2 shows the electrochemical oxidation of ethyl 3,4-dihydroxybenzoate **10** (0.06 mmol) in the presence of dienes (0.24 mmol) in 100 mM LiFOS/PFH in 0.5% aqueous acetic acid, using carbon felt (CF) as the anode and Pt as the cathode in an undivided cell (2.2 F/mol). After completion of electrolysis, the desired cycloadducts were obtained in excellent yield. On the other hand, in the absence of the fluorous micelle dispersion, in which just LiOTf (100 mM) was added as a supporting electrolyte, the desired cycloadducts were obtained only in 20% yield, along with decomposed byproducts and recovered starting material **10**. The results indicate that this fluorous micellar reaction system enables direct electron transfer and acceleration of cycloaddition of anodically generated dienophiles and dienes, avoiding decomposition or reduction of the unreacted unstable quinone intermediates.

After completion of the reaction, the products were simply extracted from the aqueous reaction mixture using *n*-hexane. As the fluorinated surfactant shows low emulsifying properties with aliphatic alkanes in water, phase separation was easily accomplished, enabling reuse of the aqueous perfluorinated surfactants.

In conclusion, an equimolar mixture of LiFOS and PFH, which formed fine droplets in water, was shown to lead to marked acceleration of Diels−Alder reactions, including those using an in situ electrogenerated unstable dienophile. In this way, it is possible to carry out these reactions without heating or the use of Lewis acids. This reaction system not only will be beneficial in terms of environmental and green chemistry but also constitutes a new aspect of synthetic chemistry in water.

Acknowledgment. This work was financially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology (MEXT).

Supporting Information Available: Experimental procedures and characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0623116

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