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Vortex fluidic promoted Diels-Alder reactions in an aqueous medium

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ABSTRACT

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Vortex fluidics

The loss of aromatic stabilization energy is the main cause for the much slower Diels–Alder cycloaddition reactions involving aromatic molecules relative to reactions involving aliphatic compounds.¹ Anthracene is a versatile unit in building structural diversity and a plethora of reactions exist for modifying and functionalizing its ring systems.² An example of this diversity is the ability for anthracene to act as a highly conjugated diene in the Diels–Alder reaction for a diverse range of dienophiles, adding across the 9 and 10 positions.³

Several strategies have been developed to promote Diels–Alder reactions of inert aromatic compounds. In general, approaches used to overcome the resonance energy of the starting material in Diels–Alder reactions can be divided into two categories: (i) where there is relief of strain in distorted aromatic cores which compensates for the loss in aromaticity,^{4,5} and (ii) the use of harsh conditions such as high temperatures and pressures, or the use of strong Lewis acids that can enhance orbital interactions.^{6–9} Catalysis of Diels–Alder reactions through formation of supramolecular assemblies is becoming increasingly popular. Large molecules containing a cavity (e.g., cyclodextrins¹⁰ or related basket¹¹ or capsule-like¹² structures) can bind both Diels–Alder reagents simultaneously and promote their reaction. The same principle accounts for catalysis by antibodies¹³ and enzymes.¹⁴

Fujita et al. reported that using an aqueous organopalladium cage, unusual regioselectivity was observed in the Diels–Alder coupling of anthracene and maleimide guests. Intriguingly, this cage

promoted the reaction at the terminal 1,4-position rather than the central 9,10-position of the anthracene ring.¹⁵ Moreover, they found another similar bowl-shaped host attaining efficient catalytic turnover in coupling the same substrates with the conventional regiochemistry. In the present contribution we have developed the use of a thin film microfluidic platform, namely a vortex fluidic device (VFD) in providing constant 'soft energy' for promoting Diels–Alder reactions of anthracenes substituted at the 9,10-positions in high molar ratio aqueous media.

'Soft energy' provided within a thin film microfluidic platform, namely a vortex fluidic device (VFD), is

effective in accelerating and promoting Diels-Alder reactions in the absence of any catalyst. Diels-Alder

cycloadducts generated from different 9-substituted anthracenes and N-maleimides are formed in high

yield in an aqueous medium using the confined mode of operation of the VFD.

We recently developed the VFD as a thin film microfluidic device with high Reynolds numbers. This contrasts with conventional microfluidic devices involving moving of liquids through channels, which have low Reynolds numbers.¹⁶ The VFD is an attractive alternative because it has dynamic thin films where there is intense shear, with high mass and heat transfer,¹⁷ in contrast to traditional batch processing. VFD processing has proven capability in exfoliating graphene from graphite,¹⁸ disassembling molecular capsules of *p*-phosphonic acid calix[5]arene,¹⁹ controlling the growth of palladium nano-particles on carbon-nano-onions²⁰ forming graphene-algae hybrid materials,^{21,22} controlling the pore size and wall thickness of mesoporous silica at ambient temperature,²³ and controlling the polymorphs of calcium carbonate.²⁴ We have also reported the use of the VFD in controlling reactivity and selectivity in organic synthesis for a series of triarylpyridines²⁵ and calix[4]arenes.²

The VFD can operate under a confined mode or a continuous flow mode, depending on the nature and reactivity of the starting materials. The continuous flow mode has relatively short residence times which can be an issue for some organic reactions, and





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contrast with the confined mode which is not residence time dependent. In the confined mode of VFD processing, as the 10 mm diameter tube containing a finite volume of liquid rotates, a dynamic thin fluid film forms on the wall of the tube where there is intense shear, at least for tilt angles $\theta > 0^\circ$. The average thickness of the fluid film depends on the processing parameters, including rotational speed, θ and the volume of the liquid.²⁵ The present work focuses on using the confined mode of operation of the VFD to promote Diels–Alder reactions involving anthracenes and maleimides, establishing the ability to effect the reactions in media with a high mole fraction of water, without the need for catalysts, and with relatively short reaction times.

Initially, our efforts were directed at the typical cycloaddition reaction between 9-hydroxymethylanthracene (1a) and N-phenylmaleimide (2a) in water. For reasons of cost, safety, and environmental concerns, water is a desirable solvent for chemical reactions, and the study of organic reactions in aqueous solvent has an intriguing history.²⁷ The pioneering work of Breslow et al. established that Diels-Alder reactions proceed faster (as high as 700-fold) and have a higher endo/exo selectivity in water than in organic solvents.¹⁰ The small size and high polarity of water molecules, as well as the three-dimensional hydrogen bonded network system of bulk water, provide some unique properties which include a large cohesive energy density, high surface tension, and a hydrophobic effect.²⁸ These unique properties are believed to be responsible for the rate and selectivity enhancements of Diels-Alder reactions. The main difficulty of the above reaction was the low solubility of the anthracene in water, which was addressed by the addition of a suitable alcohol as a co-solvent, ca. 10%. The effect of addition of different alcohols has been studied extensively by Blokzijl et al.^{29,30} They reported that a number of Diels–Alder reactions show an increase in rate upon addition of small amounts (a few mol%) of suitable alcohols. This trend has been explained by assuming an enhancement of hydrophobic interactions in such media. The alcohol molecules are expected to promote the water structure, which in turn favors the entropic contribution of hydrophobic interactions.³¹ Breslow et al. also studied the reaction between substituted 9-hydroxymethyl-anthracene and maleimides in alcohol-water mixtures, establishing that a small amount of an alcohol co-solvent does not interfere with the ability of water to solvate ionic transition states (activated complexes), but that the co-solvent is recruited to help solvate the hydrophobic portions. The induced solubility perturbations reflect the solvation of the reactants by the co-solvent. Overall, they successfully correlated the rate constant with the solubility of the starting materials for each Diels-Alder reaction. From these relations the change in solvent accessible surfaces between initial state and activated complex was estimated.³¹ Fujita et al.¹⁵ described the same reaction of 1a and 2a using a self-assembled coordination cage which decreased the entropic cost of the reaction. Unfortunately, using either a batch or control experiment at 90 °C for 5 h in water, resulted in incomplete reaction with only trace amounts of product formed.¹

Use of the VFD to prepare **3a** from the starting materials **1a** and **2a** was investigated (Scheme 1). A 10 mm diameter glass tube with a cap was used to carry out the reaction in the confined mode. The reaction parameters of speed and tilt angle for VFD were fixed at 7000 rpm and 45° , respectively, which were optimized processing parameters for previous studies on the use of the VFD in organic reactions.²⁵ Experimentally, the substrates **1a** and **2a** were mixed together in water or water with a small mole fraction of ethanol, and the temperature and reaction time were varied to optimize the conversion. We first took both reactants **1a** and **2a** in water in the VFD at 50 °C for 1 h. However, this resulted in incomplete formation of **3a** (Table 1, entry 1). On the other hand, a 9:1 water/ethanol solvent system at 50 °C for 10 min (entry 2),



Scheme 1. Diels-Alder reaction for optimizing the VFD operating parameters.

 Table 1

 Reaction conditions for preparing cycloadduct 3a

Entry	Temp (°C)	Time (min)	Solvent	Reaction mode ^a	Conversion (%)
1	90	60	H ₂ O	VFD	0
2	50	10	H ₂ O/EtOH ^b	VFD	67
3	50	20	H ₂ O/EtOH ^b	VFD	78
4	50	30	H ₂ O/EtOH ^b	VFD	91
5	60	10	H ₂ O/EtOH ^b	VFD	70
6	50	30	H ₂ O/EtOH ^b	Batch	15

 $^a\,$ VFD is in the confined mode, at 45° tilt angle, and 7000 rpm. $^b\,$ 10% ethanol in water.

resulted in almost 67% conversion into the cycloadduct **3a** (determined by ¹H NMR spectroscopy). The reaction time was then increased from 10 min to 30 min (entries 3 and 4) and the percent conversion into product gradually increased up to 91%. When the reaction temperature was increased from 50 °C to 60 °C for 10 min, we observed only a slight increase in conversion 70% to **3a** (entry 5). As a control, we conducted the best replicated reaction conditions (entry 4) in a batch mode process and interestingly, only a very low conversion was observed (entry 6). It is noteworthy that in every case we produced only the central 9,10-cycloadduct, with no evidence for any terminal 1,4-cycloadduct.

Inside the reaction tube of the VFD both centrifugal and gravitational forces are active at the 45° tilt angle. According to fluid dynamics, Stewartson/Ekman layers are formed in the thin films created at this angle.¹⁸ The intense shear layers in dynamic thin film accelerate the Diels-Alder reaction which results in higher yields of 3a. The choice of rotating speed of the VFD is also important for promoting this reaction. In previous studies,²⁵ we reported that a higher speed favors the progress of organic reactions, but interestingly, here we found changing the speed had little effect on the reaction outcome (Fig. 1). Indeed for a tilt angle of 45° the yield increases as speed increases, to almost quantitative conversion at 5000 rpm, with then a slight reduction for even higher speeds. This discontinuity is becoming evident for a number of applications of the VFD, including a discontinuity for the simple dimerization of cyclopentadiene, although this is in the absence of any solvent.²⁵ Clearly this is a special phenomenon which warrants a detailed understanding of the fluid dynamics and will feature in a separate study.

After establishing the optimized results for 9-hydroxymethylanthracene and *N*-phenylmaleimide, the scope of the Diels–Alder reactions for different 9-substituted anthracenes and different *N*substituted maleimides was investigated (Scheme 2 and Table 2). Overall the results showed that there was high conversion into the expected 9,10-cycloadducts **3b-i**, except for 9-carboxylic acid anthracene **3j**. It may be the presence of the electron-withdrawing carboxylic acid moiety on the anthracene ring that inhibits this reaction.

In summary, we have developed a highly efficient and more benign methodology using a high mole fraction aqueous medium with ethanol in a microfluidic platform for Diels–Alder reactions,



Figure 1. Percent conversion for the reaction in Fig. 1, using the VFD at 45° tilt angle, θ , as the speed is varied.



Scheme 2. General scheme for the reactions in Table 2.

Table 2 Synthesis of compounds 3 under VFD at 50 °C, 5000 rpm, and 45° tilt angle for 30 min

Entry	R ¹	R ²	Product	Conversion (%)
1	-CH ₂ OH	Ph	3a	99
2	-CH ₃	Ph	3b	99
3	-CH ₂ OH	Cyclohexyl	3c	91
4	-CH ₃	Cyclohexyl	3d	93
5	-CH ₂ OH	Bn	3e	95
6	-CH ₃	Bn	3f	98
7	-CH ₂ OH	n-Pr	3g	97
8	-CH ₃	n-Pr	3h	99
9	-CHO	Ph	3i	53
10	-CO ₂ H	Ph	3j	0

with significantly reduced processing times. We believe this method has the ability to play an integral role in the chemical synthesis sector from an environmental, quality, safety, and economical perspective.

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Supplementary data

Supplementary data (General experimental, data and copies of ¹H NMR and ¹³C NMR spectra of new compounds) associated with this article can be found, in the online version, at http://dx.doi.org/ 10.1016/j.tetlet.2014.02.077.

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