

# Highly-selective and high-speed Claisen rearrangement induced with subcritical water microreaction in the absence of catalyst†‡

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Highly-selective, high-speed aromatic and aliphatic Claisen rearrangement was shown to give the corresponding product in an excellent yield induced by subcritical water microreaction in the absence of catalyst.

## Introduction

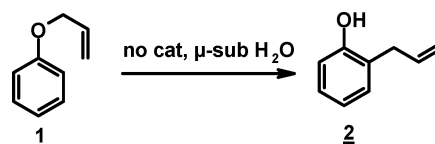
The Claisen rearrangement is a fundamental organic reaction for the production of a large variety of important intermediates and fine chemical products.<sup>1</sup> Continuous efforts have been devoted to the development of a catalytic Claisen rearrangement with Lewis acids, such as  $\text{BCl}_3$ ,<sup>1a,2a</sup>  $\text{R}_2\text{AlCl}$ <sup>2b</sup> and  $\text{PdCl}_2(\text{MeCN})_2$ ,<sup>2c</sup> to replace environmentally damaging processes which consume energy due to long reaction times and generate a large amount of solvent waste.<sup>1b</sup>

The Claisen rearrangement of allyl phenyl ether (**1**) to *o*-allylphenol (**2**) has been tested as a non-catalytic reaction model in a batchwise process to provide essential knowledge of [3,3] sigmatropic reactions (Table 1, entries 1–4).<sup>3</sup> For example, in a solvent-free conventional heating method, **2** was produced with an 85% yield at 220 °C, ambient pressure and in long reaction time of 6 h.<sup>3a</sup> While in a similar batchwise process, but using subcritical water ( $\text{subH}_2\text{O}$ ), the yield of **2** was 84% in a shorter reaction time of 10 min, at 240 °C and 3.4 MPa.<sup>3b</sup> In the same process, as the temperature increases to 245 °C and the reaction time to 60 min, the yield of **2** decreased to 45% due to the formation of by-products like 2-hydroxypropylphenol and 2-methylcoumaran. Furthermore, at 250 °C, 4.0 MPa and 60 min, 2-methylcoumaran was exclusively formed in a 72% yield.<sup>3c</sup>

Considering the solvent-free microwave heating process, **2** was obtained in a poor yield of 21% at 325–361 °C, 0.1 MPa and 10 min. However, the yield of **2** was drastically improved to 92%

using DMF as solvent at 300–315 °C, 0.1 MPa and in a shorter reaction time of 6 min.<sup>1b</sup>

Herein, we report a new highly efficient non-catalytic Claisen rearrangement using a microreaction system in  $\text{subH}_2\text{O}$ , as shown in Scheme 1.



Scheme 1

The prefix “micro”, applied to chemical micro processing, is generally defined as a continuous flow through regular domains with characteristic fluid channels of the “sub-millimetre” range,<sup>4</sup> hence the term “micro” will be used hereafter (see the ESI).<sup>‡</sup>

The concept of this methodology is based on the assumption that  $\text{subH}_2\text{O}$  itself could work as a Lewis acid,<sup>5a</sup> but also that the dielectric constant ( $\epsilon$ ) could be controlled in the  $\text{subH}_2\text{O}$  region<sup>6,5b,c</sup> through the adjustment of the pressure and temperature.<sup>7</sup> The  $\text{subH}_2\text{O}$  microreaction system can provide a continuous operation characterized by an instantaneous heating and a subsequent quenching of the substrates with vigorous mixing, which leads to a high-speed Claisen rearrangement as well as preventing the consecutive hydrolysis and pyrolysis of the substrate and product. The obtained results confirm the feasibility of this approach and provide an insight for the function of water as a Lewis acid in the  $\text{subH}_2\text{O}$  water region. They also demonstrate that the selectivity and separation procedure is effective compared to other methods, such as conventional organic solvents or solvent-free conditions.

## Results and discussion

In an exploratory study, the Claisen rearrangement of **1** ( $0.77 \text{ mol kg}^{-1}$ ) to **2** was carried out in a  $\text{subH}_2\text{O}$  microreaction system (see ESI)<sup>‡</sup> as a test reaction.

At first, to determine the appropriate reaction conditions, the yield of **2** was plotted against the temperature, at a fixed pressure of 5 MPa and residence time of 81 s (see ESI, Fig. S1).<sup>‡</sup> At around 265 °C, **2** was produced in the maximal yield of 73% with a 74% selectivity and without any sequential by-products, such as 2-hydroxypropylphenol and 2-methylcoumaran. When the pressure was changed to 10 MPa, under the same temperature of 265 °C and residence time of 81 s, the change in the product yield was minimal (76%) and within the experimental error limit

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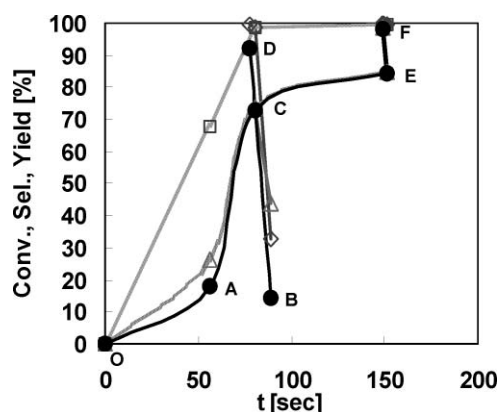
**Table 1** Claisen rearrangement from **1** to **2** by various methods

Entry	Method	Reactor type	Cat.	Solvent	Conc./mol kg <sup>-1</sup>	T/°C	P/MPa	Reaction time	Sel. (%)	<b>2</b> yield (%)	Reference
1	CH <sup>a</sup>	B <sup>c</sup>	—	—	7.5	220	0.1	6 h	—	85	1b and 3a
2	subH <sub>2</sub> O	B	—	H <sub>2</sub> O	0.29	240	3.4	10 min	—	84	3b
3	MW <sup>b</sup>	B	—	—	—	325–361	0.1	10 min	—	21	1b and 3c
4	MW	B	—	DMF	—	300–315	0.1	6 min	—	92	1b and 3c
5	μ-SF <sup>d</sup>	F <sup>f</sup>	—	—	6.9	265	5	360 s	68	37	This work
6	μ-subH <sub>2</sub> O <sup>e</sup>	F	—	H <sub>2</sub> O	0.77	265	5	81 s	74	73	This work
7	μ-subH <sub>2</sub> O	F	—	H <sub>2</sub> O	0.27	265	5	149 s	98	98	This work

<sup>a</sup> Conventional heating. <sup>b</sup> Microwave heating. <sup>c</sup> Batchwise reactor. <sup>d</sup> Microreaction-solvent-free. <sup>e</sup> Microreaction with subH<sub>2</sub>O. <sup>f</sup> Flow reactor.

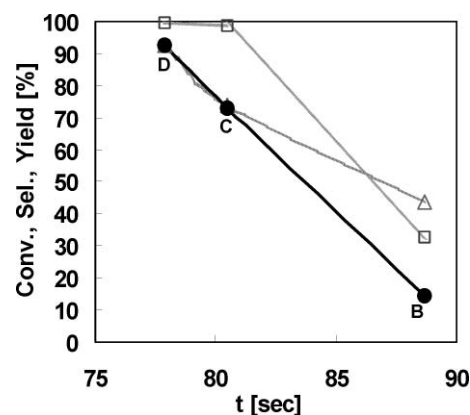
(see ESI, Fig. S2).<sup>‡</sup> Therefore, 5 MPa was adopted as the optimal pressure at 265 °C and residence time of 81 s.

The residence time can be changed by the substrate flow rate and/or the water flow rate in a microreaction system. Fig. 1 exhibits the variation of residence time with conversion, selectivity and yield, at 265 °C and 5 MPa. The variation of the substrate flow rate from 0.25 to 0.75 g min<sup>-1</sup> at a fixed water flow of 4.97 g min<sup>-1</sup> results in an increase in the yield of **2** that follows an S-shaped trend with respect to the residence time (Fig. 1; line O–A–C–E). For example, the yield of **2** was 73% at a residence time of 81 s and a substrate flow rate of 0.49 g min<sup>-1</sup> (Fig. 1; point C). The yield was increased to 88% as the residence time and the substrate flow rate was changed to 152 s and 0.25 g min<sup>-1</sup>, respectively (Fig. 1; point E). Interestingly, increasing the water flow rate from 4.97 to 6.96 g min<sup>-1</sup> at a fixed substrate flow rate of 0.49 g min<sup>-1</sup> increased the yield of **2** to 95% with a 92% selectivity at 78 s (Fig. 1 and Fig. 2; point D); and, amazingly, when the substrate flow rate was changed to 0.25 g min<sup>-1</sup>, **2** was exclusively produced with 98% yield and selectivity at 149 s (Fig. 1; point F). Hence, it is possible to obtain **2** with very high yields without any acid catalyst nor even any organic solvent.



**Fig. 1** Residence time vs. conversion (square), selectivity (triangle) and yield (filled circle) for the Claisen rearrangement of allyl phenyl ether (**1**) with subH<sub>2</sub>O at 265 °C and 5 MPa. Each point corresponds to the following water flow rates (g min<sup>-1</sup>) and substrate flow rates (g min<sup>-1</sup>); O (0.00, 0.00), A (4.9, 0.75), B (2.49, 0.49), C (4.97, 0.49), D (6.96, 0.49), E (4.97, 0.25) and F (6.96, 0.25). See also Fig. 2 for an enlargement of the region near points B, C and D.

In a typical procedure, a stream of **1** is placed across a high-speed flow of subH<sub>2</sub>O and the resulting mixture is introduced into a microreactor, where the Claisen rearrangement proceeds rapidly as a result of the vigorous mixing caused by a turbulent



**Fig. 2** Residence time (78 to 89 s) vs. conversion (square), selectivity (triangle) and yield (filled circle) for the Claisen rearrangement of allyl phenyl ether (**1**) with H<sub>2</sub>O with a substrate flow rate of 0.49 g min<sup>-1</sup>, at 265 °C and 5 MPa. Each point corresponds to the following water flow rates (g min<sup>-1</sup>) and substrate flow rate (g min<sup>-1</sup>); B (2.49, 0.49), C (4.97, 0.49) and D (6.96, 0.49).

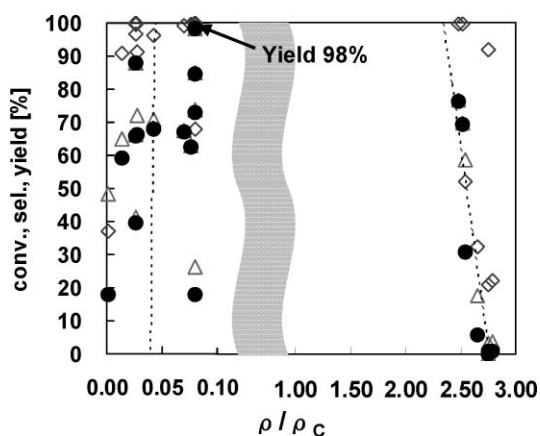
flow with a Reynolds number of around  $1.7 \times 10^4$ . The Claisen rearrangement occurs exclusively by the 'on-water' mechanism.<sup>8</sup> No significant side reactions, such as hydrolysis, hydration, or pyrolysis occurred, which leads to a conversion, selectivity and yield for **2** of above 98%. After the conversion is completed, at around 265 °C and 5 MPa with a reaction time of 149 s (Fig. 1), the product **2** accumulates at the bottom of the aqueous solution and can be obtained in a nearly pure state by being easily, and almost quantitatively, isolated by phase separation.

Table 1 summarizes the results obtained under various reaction conditions. Solvent-free microreaction without H<sub>2</sub>O was also conducted using the same microreaction system to reveal the effect of subH<sub>2</sub>O. **2** was obtained in a poor yield of 37% at 265 °C, 5 MPa and 360 s (Table 1, entry 5); therefore, subH<sub>2</sub>O was proved to be an important factor to accelerate the reaction with an excellent yield of 98% (Table 1, entry 7). Furthermore, these yields could be grouped according to specific densities, which is a ratio of the estimated density against the critical density of water ( $\rho_c = 0.314$  g cm<sup>-3</sup>), into two groups: liquid or gas phase subH<sub>2</sub>O.<sup>7b</sup> The most effective reaction took place in gas phase subH<sub>2</sub>O which gave **2** in an excellent yield (Fig. 3). This finding is related to the change in dielectric constant, as the reaction seems to prefer the region of low dielectric constants (see ESI, Fig. S3).<sup>‡</sup> Obviously, this enhancement in the low polarity region of subH<sub>2</sub>O should be distinguished from the

**Table 2** Johnson–Claisen rearrangement from **3** and **4** to **5** with the subH<sub>2</sub>O system

Entry	Method	Reactor type	Cat. (eq.)	Solvent	Conc./mol kg <sup>-1</sup>	T/°C	P/MPa	Reaction time	Sel. (%)	Yield (%)	Reference
1	CH <sup>a</sup>	B <sup>b</sup>	C <sub>3</sub> H <sub>11</sub> CO <sub>2</sub> H (0.13eq)	—	3.13	100–166	0.1	6 h	—	86–88	3d
2	μ-SF <sup>c</sup>	F <sup>c</sup>	—	—	6.90	265	5	18 min	40	40	This work
3	μ-subH <sub>2</sub> O <sup>d</sup>	F	—	H <sub>2</sub> O	0.10	265	5	284 s	95	95	This work

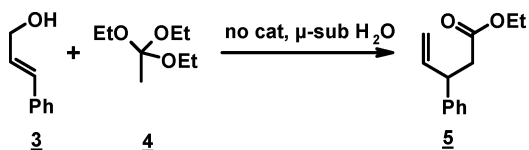
<sup>a</sup> Conventional heating, molar ratio **3** : **4** = 1.0 : 1.13. <sup>b</sup> Batchwise reactor. <sup>c</sup> Microreaction-solvent-free, molar ratio **3** : **4** = 1.0 : 1.0. <sup>d</sup> Microreaction with subH<sub>2</sub>O, molar ratio **3** : **4** = 1.0 : 1.0. <sup>e</sup> Flow reactor.



**Fig. 3** Specific density vs. conversion (square), selectivity (triangle) and yield (filled circle) of the Claisen rearrangement of allyl phenyl ether (**1**) with subH<sub>2</sub>O at various temperatures and pressures.

rate acceleration using high polarity solvents in a conventional heating process.<sup>1d</sup>

In order to extend the application of the present reaction system, the method was also applied to the aliphatic Claisen rearrangement, Johnson–Claisen rearrangement,<sup>1c</sup> for the preparation of ethyl 3-phenyl-4-penten-2-ate (**5**) from cinnamyl alcohol (**3**) and triethyl *ortho*-acetate (**4**)<sup>3d</sup> (Scheme 2), which is a multi-step process including the formation of diethyl ether from **3** and **4** and the elimination of ethanol, followed by a Claisen rearrangement of vinyl allyl ether. An excellent yield of 95% for **5** was obtained using subH<sub>2</sub>O under similar conditions as described before and in the absence of any catalyst, which was superior to the solvent-free microreaction and conventional methods (Table 2).



**Scheme 2**

It has to be mentioned that the water molecules in the subH<sub>2</sub>O would play a catalyst-like role by transferring a proton along locally formed hydrogen bonds with the substrate,<sup>9a</sup> which leads to a lowering of the energy for the bond cleavage and bond formation.<sup>9b</sup> The role of water in the intermolecular hydrogen transfer has also been supported by quantum chemical calculations.<sup>9c</sup>

E-factor<sup>10b</sup> and energy consumption, as well as yield and selectivity, are important parameters in green chemistry<sup>10</sup> and were inspected for this reaction as represented in Scheme 1 (see ESI, Fig. S4–S6).<sup>†</sup> Conventional heating showed a low E-factor, even at longer reaction times, and a large energy consumption, but the product **2** was obtained with a good yield of 85%. While microwave heating in DMF attained a high yield of 92% in a shorter reaction time and with lower energy consumption, it resulted in a high E-factor due to the non-reusable DMF in the reaction mixture. In contrast, the subH<sub>2</sub>O microreaction is superior to the other processes with an excellent yield of 98% at a shorter reaction time (149 s), with a low E-factor of 0.02 due to the reusable water, and a low energy consumption of 414 kJ kg<sup>-1</sup>. Therefore, the Claisen rearrangement with the subH<sub>2</sub>O microreaction was confirmed as a green process. The Claisen rearrangement with the subH<sub>2</sub>O microreaction system can easily be extended to various substrates and work in this direction is underway.

## Conclusion

We have developed a high-speed, highly-selective aromatic and aliphatic Claisen rearrangement in the absence of catalyst with the use of a flow-type subH<sub>2</sub>O microreaction system, with an excellent selectivity, over 90%, at a temperature of 265 °C, pressure of 5 MPa and residence time between 149–284 s. This system nicely demonstrates the potential benefits resulting from the combination of the subH<sub>2</sub>O properties and microprocess for the Claisen rearrangement. Finally, it seems worth noting that this approach induced by a subH<sub>2</sub>O microreaction system is environmentally benign, and therefore, it draws general attention for “green” organic synthesis.

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