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Subsupercritical Water Generated by Inductive Heating Inside Flow Reactors Facilitates the Claisen Rearrangement

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Abstract Claisen rearrangement of electron-deficient O-allylated phenols, including fluorine-modified phenols, is facilitated in aqueous media at high temperatures and pressures under flow conditions, as opposed to organic solvents. The O-allylation of phenols can be coupled with the Claisen rearrangement in an integrated flow system.

Key words Claisen rearrangement, flow chemistry, fluorobenzenes, inductive heating, supercritical water

The aliphatic version of the Claisen [3,3]-sigmatropic rearrangement¹ has aroused greater interest among synthetic chemists than its aromatic counterpart,² although the latter version still poses considerable challenges. The first rearrangement step of an allyl aryl ether yields an *ortho*-substituted dienone, which then enolizes to an *ortho*-allyl phenol (Scheme 1). The rearrangement can also take place at an *ortho* position, which carries a substituent, followed by a second [3,3]-sigmatropic rearrangement. This Cope rearrangement is sometimes called *para*-Claisen rearrangement and yields the corresponding *p*-allyl phenol.^{2b}



It is postulated that the reaction is of polar nature and therefore can be influenced in polar millieus.³ This is supported by the fact that the speed of allyl *p*-tolylether rearrangement increases when the polarity of the solvent is increased.^{4,5} In recent years water has emerged as a nonclassical solvent for organic reactions and has been studied in detail. It is inexpensive and environmentally friendly and shows unusual properties for influencing reactivities.⁶ This



is particularly evident under supercritical or near supercritical conditions. When the temperature is increased, the relative static permittivity (polarity) decreases from about 80.1 at 20 °C to a value of 27.5 at 250 °C. This dielectric constant is similar to the dielectric constant of acetonitrile or methanol. Another property to be mentioned is the dissociation constant, which drops to a minimum of 11.2 at 250 °C, while the ion product increases with temperature. The maximum value of the ion product is reached under almost critical conditions. Consequently, protons and hydroxide ions are present in higher concentrations, so that this aspect paves the way for the use of water as an in situ produced catalyst for acid- or base-driven reactions. In the near critical range, there is a decrease of hydrogen bonds in water, so that this leads to a decrease of the dielectric constant to a better solubility or at the critical point even to a complete miscibility of organic compounds with water. And thus reactions can be accelerated.^{7,8}

In recent years, we have added inductive heating⁹ to the existing portfolio of enabling technologies in organic chemistry¹⁰ and have shown that it can be ideally combined with fluid dynamics to create high-temperature and high-pressure conditions.¹¹ First studies on sigmatropic rearrangements under flow conditions in organic solvents at 240 °C were described by us.¹² We also demonstrated that water can be heated to near supercritical conditions under fluid dynamics conditions, for example, as a solvent in the continuous synthesis of the atypical antipsychotic drug iloperidone.¹³ Here we report on Claisen rearrangements with fluorinated allyl phenyl ethers that are not known to succeed under classical conditions. An earlier publication by Noel and Hessel already reported on a two-step process for the preparation of 2-allylphenol using bases such as DBU/Amberlyst A21, K₂CO₃, and Amberlyst A26 and this was telescoped with a Claisen rearrangement carried out at 300 °C. However, these studies were based on the use of solvents such as butanol and toluene or were conducted under solvent-free conditions.14,15

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First, a series of allyl phenyl ethers **9–16** was prepared from the corresponding phenols **1–8** under standard conditions (Scheme 2). The substituents R¹ and R² were selected to cover the spectrum from electron withdrawing (**2–7**) to neutral (**1**) to electron releasing (**8**).



The resulting allyl phenyl ethers were next subjected to high-temperature and high-pressure conditions in a flowthrough system, and the results were compared with the corresponding Claisen rearrangements under batch conditions. Microwave irradiation was used to achieve high temperatures and high pressures in batch operations, and the reactions were carried out in a mixture of water/toluene (2:1) in a sealed vial at up to 200 °C for a period of four hours (Scheme 3).



atives **9–16** under batch conditions using microwave radiation as heating concept; isolated yields are given. ^a Determined by NMR spectroscopy, because **18** could not be separated from **10**.

After one, two and four hours, samples were collected and analyzed by GC–MS. It is remarkable that two hours of reaction time were not sufficient to achieve a significant turnover. Thus, allyl phenyl ether **9–16** provided the *ortho*-Claisen products **17–24** in only modest yields. Surprisingly, the conversion with the simplest representative (allyloxy)benzene⁷ resulted in only 10% of the converted product **17**. The next step was to adapt our findings to a tailormade flow system, that is shown in Figure 1 and in Table 1. Here the question of solubility is relevant when organic reactions are carried out in an aqueous medium since flow channels tend to clog. Although the phase boundary in microfluidic devices is already increased, the reaction rates in water are still not sufficient under conventional conditions. Under high-temperature/high-pressure conditions, however, the solvent system can be brought to a point close to critical conditions. As a result, the phase boundary almost completely disappears. In addition, the solubility of organic compounds in the aqueous phase expands, which leads to a dramatic increase in the reaction rate.¹⁴



Figure 1 Laboratory setup of the flow system

The 1/8" steel reactors (coiled, V = 2.4 or 3.2 mL) were heated by embedding it in the homogeneous electromagnetic field induced by a coil-shaped electromagnetic inductor. This was operated under high-frequency conditions (IH-HF 290–320 kHz). The external reactor temperature was determined with an IR pyrometer. In order to ensure high pressures inside the flow system, back-pressure regulators are arranged at the outlet of the flow reactor. The allyl phenyl ethers were fed into the flow system via a sample loop, and the entire system was operated with a piston pump. After a short warm-up phase, the temperature inside the flow system was only affected by the temperature of the solvent entering the reactor, resulting in a small temperature drop of only 5–10°C at the reactor inlet.¹³

It was necessary to optimize the flow conditions for all examples listed in Table 1 and especially for the execution of Claisen rearrangements in water. For example, for allylated phenol 9 we found a reactor temperature of 280 °C and a residence time of 8 min to be ideal, for the chlorine derivative **10** this was 315 °C and a residence time of 3 min. In both cases the isolated yields of products 17 and 18 were 90% in water. We found that in two cases (for 12 and 16) the optimization had to include the avoidance of byproduct formation, especially with respect to para-Claisen products, but also in the case of allyl phenyl ethers 11 ester hydrolysis followed by decarboxylation. Under the optimized conditions, the formation of these byproducts was almost completely suppressed. Fluorinated allyl phenyl ethers 13-15 could also be converted quickly and easily into the Claisen products in water as solvent.

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 Table 1
 Claisen Rearrangement under Flow Conditions in Water and

	Derivative		In water (1 st case)		In dry toluene (2 nd case)	
Entry ^b	R ¹	R ²	Yield ether (%)	Yield Claisen (%)	Yield ether (%)	Yield Claisen (%) ^c
9 → 17	Н	Н	-	90	8	83
10 → 18	Cl	Н	-	90	-	73
11 → 19	COCH ₃	Н	-	92	-	70
12 → 20	$COOCH_3$	Н	-	92	27	62
13 → 21	F	Н	-	78	19	68
14 → 22	Н	F	-	89	26	67
15 → 23	F	F	-	89	55	24
16 → 24	OCH_3	Н	-	71	-	85

^a IH-HF = inductive-heating/high-frequency inductor (300–315 kHz); bpr = back-pressure regulator.

^b Details on conditions (temperature and flow rate): $9 \rightarrow 17$: 280 °C, 0.4 mL/min; $10 \rightarrow 18$: 315 °C, 0.8 mL/min; $11 \rightarrow 19$: 305 °C, 0.9 mL/min; $12 \rightarrow 20$: 265 °C, 0.3 mL/min; $13 \rightarrow 21$: 270 °C, 0.5 mL/min; $14 \rightarrow 22$: 273 °C, 0.5 mL/min; $15 \rightarrow 23$: 245 °C, 1.3 mL/min; $16 \rightarrow 24$: 265 °C, 0.3 mL/min. ^c Isolated yields are reported (for further details and workup, see the Supporting Information).

In Table 1, Claisen rearrangements in water are directly compared with the corresponding transformations performed in dry toluene. In most cases the reactions in toluene were not complete, and the isolated yields of the rearrangement products **17–23** were lower than those obtained in water as a solvent. Only the electron-rich allyl phenyl ether **16** gave better yields of the rearrangement product **24** in toluene compared to water as solvent. These results reveal a promoting effect of water for Claisen rearrangements of allyl phenyl ethers particularly those with electron deficiency.

Next, we investigated the realization of the first step, the O-allylation. Due to the very good mass transfer of flow systems, these are suitable for phase-transfer reactions such as the allylation of sodium phenolates with allyl bromide without the addition of a phase-transfer catalyst. For the O-allylation we designed a flow system consisting of two HPLC pumps. One pump transports allyl bromide in benzene, while the second pump is responsible for the aqueous solution containing the sodium phenolate (their preparation is described in the Supporting Information). Both streams are combined in a T-piece immediately before the inductively heated steel reactor. Due to the low boiling point of allyl bromide, the reaction was carried out under pressure (110–160 bar). The addition of a base to the sodium phenolates resulted in improved yields for the O-allylated phenols, whereby we chose sodium carbonate and sodium hydroxide, respectively. The latter usually showed better results. The optimal conditions for the five examples regarding base, flow rates, temperature, and pressure are shown in Scheme 4.



Scheme 4 O-Allylation of phenols under flow conditions. Method A: phenolates are supplemented with 0.1 M sodium carbonate; method B: phenolates supplemented with 0.1 M sodium hydroxide were pumped at a flow rate of 0.3 mL/min while the allyl bromide was pumped at a flow rate of 0.3 mL/min).

Finally, we turned our focus on the development of a flow system that combines the O-allylation step with the Claisen rearrangement. The correct choice of base was crucial, and it should be noted that an excess of allyl bromide (it decomposes to hydrogen bromide under pyrolytic conditions) proved to be problematic.¹⁵ To achieve the best results, the addition of a hydrochloric acid solution was essential, followed by continuous liquid–liquid extraction to remove the base DBU, and several fixed bed reactors filled with Amberlyst 21 to bind the excess hydrochloric acid were other processes to be included. A two-stage process in water as developed here would avoid these obstacles.

As both individual steps are optimized as continuous processes, these could be telescoped as exemplified for the difluorophenol 7. The first stage was performed in a coil reactor (V = 3.4 mL) at 110 °C. Sodium phenolate 7 and a 1 M allyl bromide solution were combined via a static mixer and then inductively heated in the first steel reactor. The Claisen rearrangement was then carried out in a second reactor (V = 3.2 mL), which was inductively heated to 265 °C, and 2-

allyl-4,6-difluorophenol (**23**) was obtained in 64% isolated yield (Scheme 5).Our studies demonstrate the positive effect of water under almost supercritical conditions on the aromatic Claisen rearrangement. Theoretical calculations have already been made on this topic.¹⁶ These showed that the hydrogen bond between the oxygen atom of the dissolved starting compound and two water molecules is more pronounced in the transition state. Consequently, the presence of water leads to looser, more dissociative, and more polarized transition states. The prerequisite for this would be the formation of a zwitterionic transition state.





It also becomes clear that the rate constant depends on the nature of the substituent. White et al. reported that when the *para* position bears an electron-donating methoxy group and not an electron-withdrawing nitro group, the rate constant (for EtOH/H₂O) increases by a factor of 6.8. Thus, not only the use of a polar solvent but also electrondonating groups lead to an increase in the reaction rate.¹⁷

In conclusion, the Claisen rearrangement is another example of how water can be used advantageously as a solvent in organic reactions under near supercritical conditions.¹⁸ Flow arrangements with high-speed heating technology based on electromagnetic induction provide the ideal environment for achieving rapid Claisen rearrangements of allyl phenyl ethers, including previously unknown examples. Since fluid mechanics is a fundamental technology for modern organic synthesis, this work should open new avenues for applications in the pharmaceutical and perfume industries.

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Supporting Information

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Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1705945. Included are experimental procedures, spectral data and copies of ¹H and ¹³C NMR spectra of all new compounds and intermediates.

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- (18) Two-Step Flow Synthesis of 2-Allyl-4,6-difluorophenol (23) An allyl bromide solution in benzene (1 M) was combined with a 0.1 M aqueous sodium phenolate solution (7, sodium salt) via a static mixer. An additional 0.5 mol/L of sodium hydroxide was added to the aqueous sodium phenolate solution. Both reagents were pumped at a flow rate of 0.3 mL/min through a 1/8" steel reactor (coiled, V = 3.4 mL). The reactor was heated to 110 °C in an oscillating electromagnetic high-frequency field. The reaction mixture was then passed through a second reactor (3.2 mL), which was heated to a temperature of 265 °C at a pressure of 183–184 bar. The reaction mixture was collected over a period of 25 min and extracted with diethyl ether (3 × 10 mL). The combined organic phases were dried over magnesium sul-

fate, filtered, and concentrated under reduced pressure and coevaporated with methanol. The residue obtained was purified by flash chromatography (pentane to pentane/diethyl ether 10%).

2-Allyl-4,6-difluorophenol (24)

Yellow oil (80.2 mg, 0.47 mmol; 64%). ¹H NMR (600 MHz, CDCl₃, CHCl₃ = 7.26 ppm): δ = 6.75–6.71 (1 H, m, H-7), 6.68–6.66 (1 H, m, H-5), 5.98–5.92 (1 H, m, H-2), 5.14–5.10 (2 H, m, H-1), 4.99 (1 H, br s, OH), 3.41–3.40 (2H, m, H-3). ¹³C NMR (150 MHz,

CDCl₃, CDCl₃ = 77.16 ppm): δ = 156.5–154.8 (q, dd, *J* = 240.6 Hz, 11.5 Hz, C-6), 151.4–149.7 (q, dd, *J* = 238.7 Hz, 12.7 Hz, C-8), 138.0–137.9 (q, dd, *J* = 14.0 Hz, 3.5 Hz, C-9), 135.3 (t, C-2), 129.6–129.5 (q, dd, *J* = 8.3 Hz, 2.6 Hz, C-4), 116.9 (s, C-1), 112.0–111.8 (t, dd, *J* = 22.6 Hz, 3.4 Hz, C-5), 102.0–101.7 (t, dd, *J* = 27.2 Hz, 23.0 Hz, C-7), 34.0–33.9 (s, dd, *J* = 3.1 Hz, 1.4 Hz C-3). HRMS (EI): *m/z* calcd for C₉H₈OF₂: 170.0543; found: 170.0543; *R*_f = 0.24 (pentane/Et₂O = 9:1).