Microwave-Assisted Organic Synthesis in Near-Critical Water at 300 °C – A Proof-of-Concept Study

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Microwave-assisted organic synthesis in near-critical water (NCW) in the 270–300 °C temperature range has been investigated in a dedicated multimode microwave reactor utilizing heavy-walled quartz reaction vessels. Several different known transformations such as the hydrolysis of esters or amides, the hydration of alkynes, Diels–Alder cycloadditions, pinacol rearrangements, and the Fischer indole synthesis were successfully performed in microwave-generated NCW without the addition of an acid or base catalyst.

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Introduction

Chemical processes often employ large amounts of hazardous and toxic solvents. The choice of pursuing a low-waste route and reusable reaction media to minimize the economic cost and environmental impact of a chemical process is becoming ever more urgent for the future, so there is pressure on organic chemists to investigate clean, economical, and environmentally safer methodologies. One of the most promising approaches uses water as an alternative reaction medium.[1]

Synthetic organic reactions in aqueous media at ambient or slightly elevated temperatures (<100 °C) have become of great interest, since water often displays unique reactivity and selectivity as a solvent for organic reactions,[1–3] exploiting, for example, so-called hydrophobic effects.[4–5] Chemical processing in water is also possible under "superheated conditions" (>100 °C) in sealed vessels because of the favorable changes that occur in the chemical and physical properties of water at high temperatures and pressures.[6] Water around its critical point (374 °C, 221 bar) possesses properties very different from those of ambient liquid water and is attracting increased attention as a medium for organic chemistry.[7] Supercritical water (SCW, >374 °C) has been studied extensively for materials synthesis, waste destruction, plastics recycling, coal liquefaction, and biomass processing,[7,8] though its application for preparative organic synthesis is somewhat limited due to its degenerative properties.

In contrast, the so-called near-critical (also termed subcritical) region of water, at temperatures between 200–300 °C (NCW), is of greater importance to organic synthesis.[7] High-temperature near-critical water (NCW) under autogenic pressure provides a more favorable reaction medium for organic synthesis than does water under supercritical conditions (>374 °C). At 250 °C, water has a density and a polarity similar to those of acetonitrile at room temperature. The dielectric constant of water (ε') drops rapidly with temperature, and at 250 °C has fallen from 78.5 (at 25 °C) to 27.5.[6]

Most importantly, the ionic product (dissociation constant) of water is increased by three orders of magnitude on going from room temperature to 250 °C.[6] NCW can therefore act as an acid, base, or acid-base bicatalyst without the need for costly and cumbersome neutralization and catalyst regeneration. These different aspects of high-temperature water chemistry have recently drawn increased attention from the synthetic community and have been extensively reviewed.[7]

Another area in organic synthesis that is receiving increasing attention in recent years is the use of microwave energy to heat reaction mixtures. Since the first reports on the use of microwave heating to accelerate organic chemical transformations by the groups of Gedye[9] and Giguere/Majetich[10] in 1986, more than 2500 articles in the area of microwave-assisted organic synthesis (MAOS) have been published.[11] Not only is direct "in-core" microwave heating able to reduce chemical reaction times from hours to minutes, but it is also known to reduce side reactions, increase yields, and improve reproducibility. The exact nature or even existence of a "special microwave effect" is still a matter of debate.[12]

Notably, there is a growing number of publications advocating the use of microwave energy to heat reaction mixtures utilizing water as solvent,[13] a field originally pioneered by C. R. Strauss in the mid 1990s.[14] In principle, thanks to its properties, water is an excellent solvent for

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microwave-assisted organic synthesis. Although it has a dielectric loss factor that puts it into the category of a medium microwave absorber, it heats up sufficiently upon microwave irradiation (2.45 GHz) in the 20–150 °C region (see below). Because of the technical limitations of many of today's commercially available sealed vessel microwave reactors[15] most of the previously published studies on microwave-assisted water chemistry were restricted to reaction temperatures below 200 °C and circa 20 bars pressure.[13,14] In fact we are not aware of any publications on MAOS in water above 260 °C. The potential of any synergistic effects between microwave irradiation and near-critical water chemistry (MW-NCW chemistry) has therefore not been explored.

Here we demonstrate the feasibility of performing microwave-assisted organic synthesis in near-critical water in the 270–300 °C temperature range for the first time. A dedicated multimode microwave reactor (2.45 GHz, 1400 W) was utilized for this purpose, allowing reactions to be performed in water as solvent in heavy-walled quartz reaction vessels on 15–400 mL scales with operation limits of 80 bars of pressure and temperatures close to 300 °C. A variety of different types of chemical transformations were investigated as model reactions in order to study the general feasibility of MW-NCW chemistry in this temperature range.

Results and Discussion

Generation of Microwave-Heated Near-Critical Water

The heating characteristics of a particular material (e.g., a solvent) under microwave irradiation conditions are dependent on the dielectric properties of the material. The ability of a specific substance to convert electromagnetic energy into heat at a given frequency and temperature is determined by the so-called loss tangent tan δ.[11] A reaction medium with a high tan δ value is required for efficient absorption and, consequently, for rapid heating. In comparison with other solvents, water can be regarded only as a medium microwave-absorbing solvent at 20 °C.[11]

Because of the dramatic changes in its dielectric properties at higher temperatures, it becomes very difficult to heat water by microwave energy at higher temperatures. In fact, SCW is transparent to microwave radiation, and it therefore initially proved difficult to reach the desired target temperature of 300 °C in preliminary investigations involving the microwave irradiation of pure water.

It is well known that the dielectric loss of a solvent such as water can be significantly increased by the addition of small amounts of, for example, inorganic salts.[17,18] We therefore conducted microwave heating experiments to compare pure water and dilute aqueous solutions (0.01–0.05 M) of sodium chloride.[17] These experiments were carried out in a single-mode cavity microwave reactor (20 bar pressure limit), with use of an accurate fiber-optic temperature measurement device[19] and a microwave-transparent quartz reaction vessel. As shown in Figure 1, constant irradiation with 150 W power produced a marked difference in heating profiles between pure water and a 0.03 M sodium chloride solution. While the water sample reached only circa 130 °C after 90 s of irradiation, the dilute salt solution was easily heated to 190 °C, at which point irradiation was aborted by the system due to the pressure limit of the instrument (20 bar) being exceeded. A sodium chloride concentration of 0.03 M proved to be optimal: while at lower salt concentrations the heating was less efficient, there was little change in the heating profile on going from 0.03 M to, for example, a 0.04 or 0.05 M concentration.

For the chemistry applications described below it can be assumed that the comparatively low salt concentrations

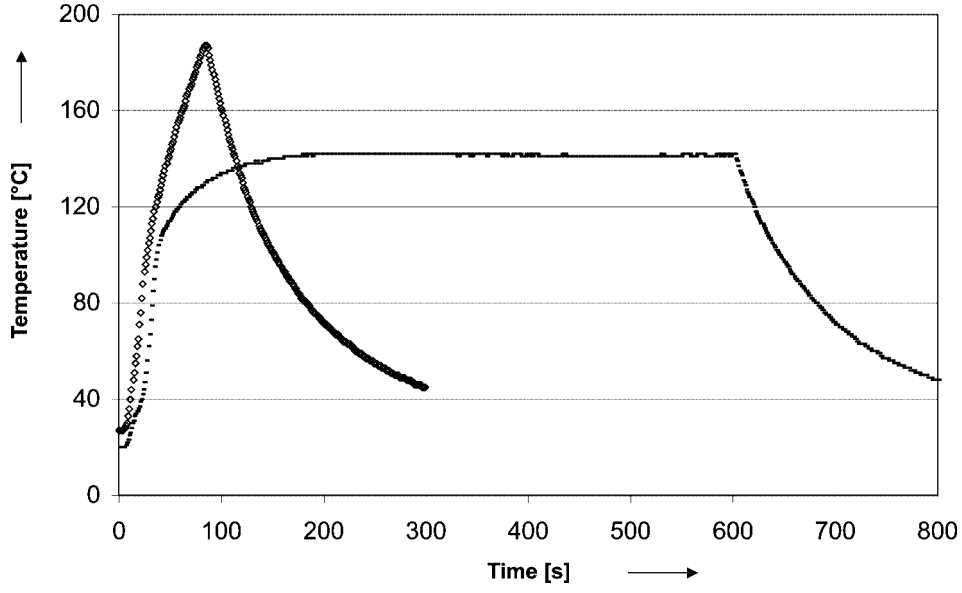

Figure 1. Microwave heating profiles for pure water (–) and 0.03 M sodium chloride solution (◊) at constant 150 W power. Single-mode irradiation, 5 mL sample volume, fiber-optic temperature measurement, sealed 10 mL quartz reaction vessel, magnetic stirring (see Exp. Sect.).

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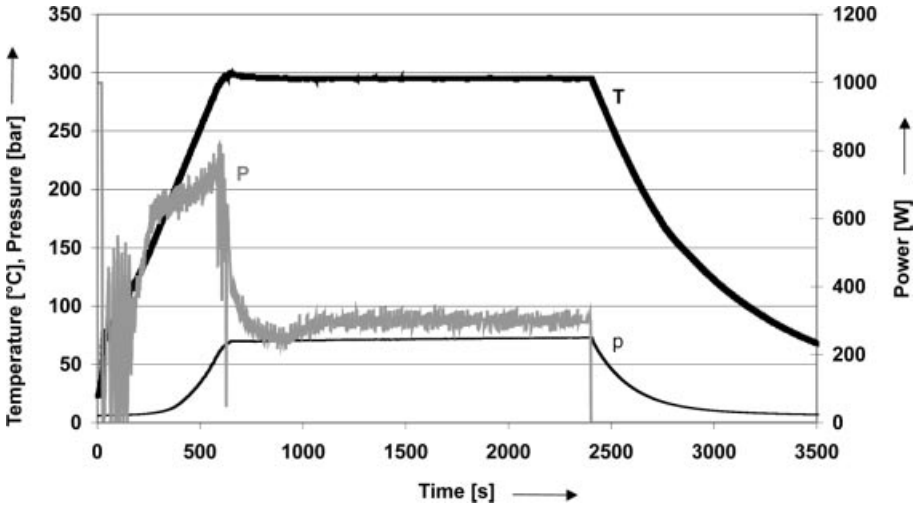


Figure 2. Heating curve for the generation of near-critical water (NCW) under microwave conditions in a multimode microwave reactor: 15 mL water (0.03 M NaCl), set temperature 296 °C, max. power 1000 W, ramp time 10 min. T = temperature, P = Power, p = pressure. The maximum pressure was 80 bar. The temperature was measured with a gas balloon thermometer.

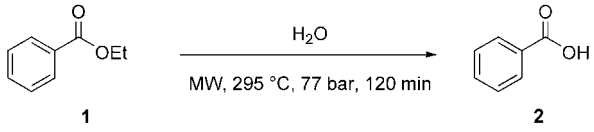
(0.03 M, 0.18 w/w%) would not significantly influence the reactivity of the near-critical water medium[20] but would mainly improve microwave absorbance by ionic conduction.[18]

Employing a 0.03 M sodium chloride solution, we next proceeded to generate NCW in a multimode microwave system (see Exp. Sect. for details on instrumentation). As can be seen in Figure 2, a reaction temperature of 296 °C (corresponding to the maximum allowed pressure of 80 bars) could be reached after a 10 min programmed ramp time. A maximum peak power of 800 W was used during the heating period. After the set temperature had been reached, the magnetron power regulated itself down to circa 300 W to maintain the 296 °C temperature for 30 min. With the same instrumentation the 296 °C temperature could be maintained for several hours at a 15–400 mL scale. All experiments in the following sections were therefore performed in HPLC grade water doped with small amounts of sodium chloride (0.03 M).

Having established the feasibility of generating microwave-heated near-critical water at circa 300 °C for prolonged periods of time, we next investigated specific chemical transformations under these unique conditions.

Hydrolysis of Ethyl Benzoate and Benzamide

In general, the hydrolysis of esters and amides is only possible in the presence of strong mineral acids or bases, producing considerable amounts of waste acid and salt. With employment of NCW or SCW, ester hydrolyses are possible without the addition of acid or base, as demonstrated previously by, for example, the groups of Vogel[6] and Eckert.[21] It is assumed that the dominant reaction mechanism for the hydrolysis of esters above the critical temperature of water (SCW) is the direct nucleophilic attack of water at the carbonyl carbon atom of the ester, whereas in the near-critical region (NCW) an autocatalytic $A_{ac}2$ mechanism is operative.[6] For the hydrolysis of benzoic esters in NCW (250–300 °C) Eckert and co-workers suggest an autocatalytic mechanism, since benzoic acid is one of the products (Scheme 1).[21] The acidity of NCW seems sufficient to initiate hydrolysis of the benzoate and formation of the benzoic acid autocatalytic species.[6,21] Under conventional thermal conditions, 80% conversion to benzoic acid was achieved at 250 °C after 4 h.[21]



Scheme 1. Hydrolysis of ethyl benzoate in NCW.

Our optimization studies involving microwave-generated near-critical water (MW–NCW) produced comparable results. While no reaction was observed at temperatures below 200 °C, complete hydrolysis (>99% HPLC conversion) of ethyl benzoate to benzoic acid was experienced after 2 h at 295 °C, resulting in an isolated product yield of 95%. Upon cooling, most of the benzoic acid precipitated from the aqueous reaction medium and could be simply collected by filtration.

The hydrolysis of benzamide (Scheme 2) under NCW conditions has been investigated on several occasions, most notably by the groups of Katritzky[22] and Vogel.[23] Katritzky and co-workers[22] studied this hydrolysis with conventional thermal heating, both in superheated cyclohexane and in NCW. In cyclohexane at 250 °C after 5 d, 74% of the starting benzamide, 22% of benzonitrile by-product, and only 4% of the desired benzoic acid were isolated. In NCW under the same conditions (250 °C, 5 d) an 83% yield of benzoic acid was obtained, along with small amounts of decarboxylated product (benzene) and 17% of reisolated starting material.[23]

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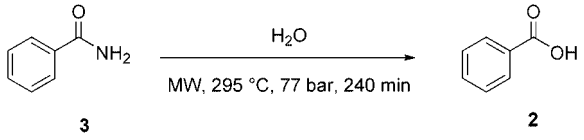
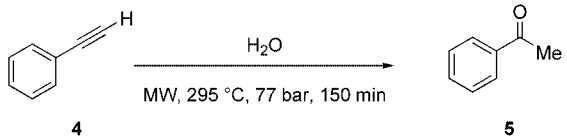


Scheme 2. Hydrolysis of benzamide in NCW.



Scheme 3. Hydration of phenylacetylene to acetophenone with NCW.

In previous work we have demonstrated that benzamide can be hydrolyzed cleanly to benzoic acid in 20% or 5% (v/v) sulfuric acid under sealed vessel microwave irradiation conditions.[24] At a reaction temperature of 180 °C, for example, 7 min of microwave heating in 5% sulfuric acid were required to achieve complete hydrolysis, comparing favorably with a 12 h reaction time at 100 °C (reflux conditions in an oil bath).[24] Increasing the concentration of sulfuric acid to 20% resulted in shorter reaction times (2 min at 180 °C), whereas again no reaction was observed in the absence of an acid catalyst, even at temperatures as high as 220 °C.[24]

With our MW-NCW technology it now proved possible to hydrolyze benzamide completely to benzoic acid at 295 °C within 4 h (>99% HPLC conversion), resulting in a 92% isolated product yield. Use of reaction times of less than 4 h gave incomplete transformations. No by-products such as benzonitrile or benzene could be detected. It can be assumed that the ammonium hydroxide formed during the hydrolysis autocatalyzes this reaction.[23]

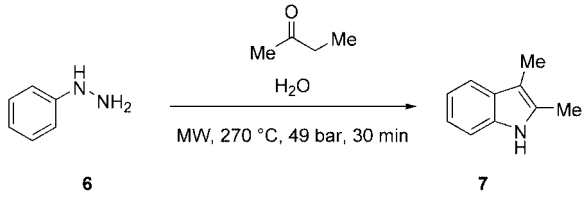
Hydration of Phenylacetylene

According to Katritzky, treatment of phenylacetylene with pure, thermal NCW (250 °C) produces a complex reaction mixture:[25] after 5 d, the desired hydrolysis product acetophenone (Scheme 3) had been formed in 51% yield, along with dimeric and trimeric self-condensation products such as phenylnaphthalenes and triphenylbenzenes.[25] Alternatively, Strauss and co-workers employed dilute aqueous acid (0.5 M sulfuric acid) in an autoclave to facilitate the addition of NCW to phenylacetylene at 280 °C, affording the corresponding acetophenone in 90% yield within 1 h.[26] Clean, acid-catalyzed hydrolysis of alkynes to ketones also occurs in the presence of acidic metal salts such as $CuCl_2$, $SnCl_2$, or $AuBr_3$.[27] In 2004, Vasudevan and Verzal reported on the hydration of a variety of alkynes (including phenylacetylene) in pure water under microwave conditions at 200 °C.[28] Within 20 min, most of the studied terminal arylalkynes had been completely transformed into the desired acetophenones. In our hands these results could not be reproduced, mainly because it proved impossible to heat water to 200 °C under the single-mode microwave conditions specified by the authors (cf. Figure 1). At the maximum obtainable temperature of 175 °C no conversion to acetophenone was observed.

In our hands the complete conversion (HPLC, 215 nm) of phenylacetylene to acetophenone in MW-NCW required at least 150 min at 295 °C (Scheme 3), with small amounts of dimeric and trimeric self-condensation products[25] being detectable by GC-MS analysis. The exact isolated product yield of the hydration reaction was determined by precipitation of the ketone with 2-(2,4-dinitrophenyl)hydrazine, providing a 78% yield of the corresponding hydrazone.

Fischer Indole Synthesis

The preparation of indoles is of significant interest owing to the broad applications of this heterocyclic core.[29–32] Strauss and co-workers[33,34] investigated the microwave-assisted preparation of indoles in NCW below 260 °C. In a prototype multimode microwave reactor,[14] 2,3-dimethylindole was obtained from phenylhydrazine and butanone by the Fischer indole synthesis in pure water as solvent (Scheme 4). Optimal conditions involved heating at 222 °C for 30 min, providing a 67% yield after workup.[33] When 1 M sulfuric acid was used instead of water, the yield was comparable but the reaction could be completed in 1 min.



Scheme 4. Fischer indole synthesis from phenylhydrazine and butanone in NCW.

In an attempt to reproduce Strauss's conditions, we indeed obtained full conversion of the phenylhydrazine at 222 °C after 30 min in MW-NCW, but a 28% yield (HPLC) of an unknown by-product or intermediate was observed in addition to the desired indole. The optimized conditions with our experimental setup involved microwave heating of a mixture of phenylhydrazine and 2-butanone (2.0 equiv.) in water to 270 °C for 30 min, providing a comparatively clean and quantitative HPLC conversion to the desired product. Purification by silica gel chromatography allowed the isolation of pure 2,3-dimethylindole in 64% yield.

Pinacol Rearrangement

The pinacol rearrangement is known to be catalyzed by strong acids in conventional methods and has attracted attention as a basic way of producing aldehydes and ketones.

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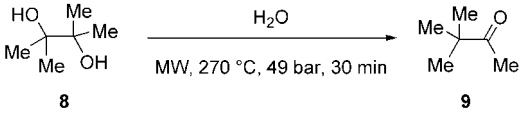
The classical method for the production of pinacolone from pinacol (Scheme 5) requires boiling of the alcohol in 25% sulfuric acid for 3 h.[35] The reaction is significantly accelerated by raising the temperature to the near-critical and supercritical water region and can be performed without addition of an acid catalyst in these media.[36] As described by Ikushima and co-workers,[36] pinacolone is the sole product of the rearrangement of pinacol in NCW and SCW (300–450 °C), but in the very limited temperature region around the critical point (374 °C) at 375–380 °C dehydration of pinacol (**8**) to 2,3-dimethyl-1,3-butadiene also occurs. Other authors have observed the quantitative rearrangement of pinacol to pinacolone at 275 °C in near-critical deuterium oxide within 1 h.[37] With our MW–NCW method, full and clean conversion (GC-MS) was achieved within 30 min at 270 °C. The product was isolated (76%) by transformation of the ketone into the corresponding hydrazone by treatment with 2-(2,4-dinitrophenyl)hydrazine. At a temperature of 200 °C the rearrangement in water under microwave conditions was extremely sluggish, producing only a 14% yield of pinacolone after 20 min. Since neither the starting material nor the product is acidic, it is safe to assume that here NCW itself is acting as the "acid" catalyst for this rearrangement.[6,7]



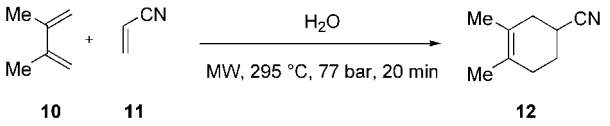
8 **9**

Scheme 5. Rearrangement of pinacol to pinacolone in NCW.

Diels–Alder Reaction

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 both reaction rates and selectivity of these [4π+2π] cycloadditions.[38] In the early 1980s, Breslow and Grieco independently reported that the use of water as a solvent medium for Diels–Alder reactions significantly influenced the reaction rate.[2] In 1997, Korzenski and Kolis first performed Diels–Alder cycloaddition reactions in NCW. While reactions below 280 °C were unsuccessful, several Diels–Alder products were obtained in the 290–340 °C temperature region.[39] Hirata and co-workers[40] subsequently demonstrated that for Diels–Alder cycloadditions in SCW the reactions are accelerated because of increased thermal activation and the reaction yield is increased dramatically due to the enhanced solubilities of the starting materials in relation to those in ambient water. Hydrophobic effects[4,5] apparently play no role at these high temperatures, where water is acting as a pseudo-organic solvent.

As part of our investigations we reproduced the addition between 2,3-dimethylbutadiene (**10**) and acrylonitrile (**11**) (Scheme 6), previously reported under NCW conditions by Korzenski and Kolis.[39] While only trace amounts of products were formed in water at 200 °C with use of sealed vessel microwave heating, full conversion was achieved at 295 °C within 20 min with employment of 2 equiv. of the diene.



10 **11** **12**

Scheme 6. Diels–Alder cycloaddition between diene **10** and dienophile **11** in NCW to give the cycloadduct **12**.

Conclusion and Outlook

We have successfully demonstrated that it is technically feasible to perform microwave synthesis in water on scales from 15–400 mL at temperatures of up to 300 °C and 80 bars of pressure in a dedicated multimode microwave reactor. This significantly extends the accessible temperature/pressure range for microwave-assisted organic synthesis in relation to the currently used single-mode microwave instrumentation (250 °C, 20 bar). For all the investigated model reactions in this proof-of-concept study it was possible to reproduce or improve previous results, as shown by comparison of previously published data obtained from thermal near-critical water (NCW) experiments with the results obtained in microwave-generated near-critical water (MW–NCW) under autogenic pressure conditions. In most cases the unique strongly acidic properties of NCW were exploited to perform transformations that would normally require the presence of a strong acid. It therefore appears that MW–NCW technology is ideally suited to perform organic synthesis in this high-temperature region, combining the advantages of microwave chemistry (rapid, direct in-core heating) with the benefits of using water as solvent under near-critical conditions. At this point it is not clear how the irradiation with microwave frequencies (dipolar polarization and ionic conduction heating mechanism) may be affecting the unique properties of water near its critical point (reduced strength of hydrogen bonding, increased local proton concentration).[36] Future work will be directed towards study of a variety of different chemical processes under MW-NCW conditions and to investigation of the physicochemical peculiarities of water under these conditions.

Experimental Section

General: Melting points were obtained with a Gallenkamp melting point apparatus (Model MFB-595) in open capillary tubes. ^{1}H NMR spectra were recorded with a Bruker AMX 360 instrument at 360 MHz in the solvents indicated. Chemical shifts (δ) are expressed in ppm downfield from TMS as internal standard. The letters s, d, dd, t, q, and m are used to indicate singlet, doublet, double doublet, triplet, quadruplet, and multiplet. Analytical HPLC analysis was performed with a Shimadzu LC-10 system, fit-

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ted with LC10-V T(AP) pumps, an autosampler (Sil-10AXL), and a dual wavelength UV detector set at 215 and 254 nm. Analytical liquid chromatographic separations were carried out on a C18 reversed-phase analytical column, LiChrospher 100 RP-18 (E. Merck, 119 × 3 mm, particle size 5 μm) at 25 °C with a mobile phase A: water/acetonitrile, 90:10 (v/v) + 0.1% TFA and B: acetonitrile + 0.1% TFA (gradient grade quality HPLC solvents were purchased from Acros; TFA was of analytical reagent grade, Aldrich) at a flow rate of 0.5 mL·min^{-1}. The following gradient was applied: linear increase from solution 30% B to 100% B in 7 min, hold at 100% solution B for 2 min. GC-MS measurements were performed with a Hewlett–Packard model 6890 instrument fitted with an HP 5973 mass-selective detector.

Materials: All chemicals were purchased from Sigma–Aldrich or Acros and were used without further purification. A 0.03 M NaCl solution in HPLC gradient grade water (Acros, code: A/0627/17, batch: 0436331) was used as a solvent for all MW-NCW reactions.

Microwave Chemistry. Single-Mode Reactor:[19] The heating curve displayed in Figure 1 was recorded with a CEM Discover System from CEM Corporation. Reactions were performed in custom-made quartz vessels (capacity 10 mL) sealed with septa. The pressure was controlled through a noninvasive "intellivent™" pressure probe on the surface of the septum. The temperature of the contents of the vessel was monitored through a fiber-optic probe inserted into the reaction vessel within a sapphire immersion well. The experiments were performed with use of a stirring option through which the contents of the vessel (5 mL sample volume) were stirred by means of a rotating magnetic plate located below the floor of the microwave cavity and a Teflon-coated magnetic stir bar in the vessel. **Multimode Reactor:**[41] The NCW experiments were carried out in a SYNTHOS 3000 multimode microwave reactor from Anton Paar GmbH. The instrument was fitted with two magnetrons, operating at a frequency of 2.45 GHz with continuous microwave output power from 0 to 1400 W. The cavity (dimensions: w × d × h, 45 × 42 × 35 cm) was fitted with an eight-vessel rotor, with 80 mL quartz glass vessels (max. filling volume ca. 60 mL) dedicated for reactions at high pressure (80 bar controlled pressure) and temperatures (300 °C). The quartz vessels rested inside protecting air cooling jackets made of PEEK. They were capped with special seals and a protective PEEK cap. The seals comprised a release valve that could be manually operated and allowed the pre-pressurization of the vessel through a connection port with a syringe adapter. The individual vessels were placed in the corresponding rotor, fixed by screwing down the upper rotor plate, and the rotor was finally closed with a protection hood. Accurate temperature measurement was achieved by inserting a gas balloon thermometer into one reference vessel. Additionally, the surface temperatures of all vessels could be monitored by IR thermography. Pressure was monitored by a load-cell-type simultaneous hydraulic pressure-sensing system for all vessels, with monitoring of the highest pressure level and pressure increase. Both pressure and temperature data were transferred to the microwave control unit in wireless fashion by an infrared LED on the rotor. The reactor's built-in electronics allowed reaction control in a temperature vs. time mode. After irradiation, the rotor was cooled to approximately 40 °C within 20 min by venting of air through cooling gaps surrounding the reaction vessels. The system was equipped with various safety features/devices, including a solvent detection system, and shutdown mechanisms in case of a too rapid temperature or pressure increase in one of the reaction vessels. Each vessel was fitted with a pressure release seal designed to vent at 120 bar of pressure, avoiding rupture of the vessel.

General Procedure for all MW-NCW Experiments: A quartz vessel (80 mL) fitted with a Teflon-coated stirring bar (2.0 cm) was charged with NaCl solution (0.03 M, 15 mL) and the appropriate reactants (see below for details). The vessel was sealed and inserted into the 8-position rotor at position 1. Another 80 mL quartz vessel was fitted with an identical stirring bar and filled with NaCl solution (0.03 M, 15 mL). After sealing, this vessel was placed at position 5. Additionally, two empty sealed vessels were placed at positions 3 and 7 (as the rotor top plate contains the hydraulic system for simultaneous pressure sensing it is important to charge the rotor symmetrically; four fitted positions are necessary to achieve a flat position of the plate to guarantee accurate pressure measurement). After the vessels had been fixed by tightening the screws of the rotor top plate, the temperature probe was inserted into vessel 1. Finally, the rotor was closed with the protection hood and placed inside the cavity of the microwave reactor.

Hydrolysis of Ethyl Benzoate (1) and Benzamide (2): Ethyl benzoate (**1**; 1.05 g, 1.00 mL, 6.97 mmol) or benzamide (**2**; 605.0 mg, 5.00 mmol) were added to the NaCl solution (0.03 M) in vessel 1. The reaction mixture was heated at 295 °C for 120 min (240 min in the case of **2**) by use of an 8 min linear heating ramp. After having been cooled to 40 °C by an air-flow (20 min), the vessel at position 1 was removed from the rotor. The reaction mixture (containing precipitated benzoic acid) was basified with Na_2CO_3 (20%), whereupon the precipitate dissolved. The basic solution was then extracted with $CHCl_3$ (4 × 20 mL) to remove traces of any unreacted starting material. After acidification of the aqueous phase, benzoic acid (**3**) precipitated and the acidic aqueous phase was subsequently extracted with diethyl ether (4 × 20 mL). The ether fractions were combined, dried with $MgSO_4$, and concentrated, providing 803.8 mg (95%) of pure (>99% HPLC at 215 nm) benzoic acid as colorless crystals. In the case of benzamide, benzoic acid was obtained in 92% yield (563.6 mg) and >99% HPLC purity. m.p. 120–122 °C (ref.[42] m.p. 121–122 °C). ^{1}H NMR (360 MHz, $CDCl_3$): δ = 7.50 (t, J = 7.6 Hz, 2 H), 7.64 (t, J = 7.3 Hz, 1 H), 8.14 (d, J = 7.8 Hz, 2 H) ppm. MS (neg. APCI): m/z = 121.0 [M – 1]$^-$ (M = 122.12).

Hydration of Phenylacetylene (4): Freshly distilled phenylacetylene (**4**; 0.46 g, 0.50 mL, 4.55 mmol) was added to the NaCl solution (0.03 M) in vessel 1. The reaction mixture was heated at 295 °C for 150 min with employment of an 8 min linear heating ramp. After having been cooled to 40 °C by an air-flow (20 min), the vessel at position 1 was removed from the rotor. A solution of 2-(2,4-dinitrophenyl)hydrazine (1.0 g, 5.05 mmol), H_2SO_4 (concd., 7.0 mL), and methanol (25 mL; ***CAUTION:*** exothermic reaction of H_2SO_4 with methanol!) was added to the aqueous reaction mixture. The precipitate was filtered off, washed with aqueous $NaHCO_3$ (5%) and distilled water, and placed in a drying oven (50 °C) overnight to provide 1.07 g (78%) of the corresponding hydrazone as an orange solid (HPLC purity: >99%). m.p. 240–241 °C (ref.[43] m.p. 240 °C). ^{1}H NMR (360 MHz, $CDCl_3$): δ = 2.49 (s, 3 H), 7.48 (t, J = 3.8 Hz, 3 H), 7.87–7.90 (m, 2 H), 8.16 (d, J = 9.6 Hz, 1 H), 8.38 (dd, J = 10.8 Hz, 1 H), 9.19 (d, J = 2.5 Hz, 1 H), 11.37 (s, 1 H) ppm. MS (pos. APCI): m/z = 301.1 [M + 1]$^+$; (neg. APCI): m/z = 299.2 [M – 1]$^-$ (M = 300.28).

Fischer Indole Synthesis of 2,3-Dimethyl-3*H*-indole (7): Phenylhydrazine (**6**; 1.09 g, 0.99 mL, 10.06 mmol) and butan-2-one (1.45 g, 1.80 mL, 20.15 mmol) were added to the NaCl solution (0.03 M) in vessel 1. The reaction mixture was heated to 270 °C by employment of an 8 min linear heating ramp and was then irradiated at 270 °C for an additional 30 min. After having been cooled to 40 °C by an air-flow (20 min), the vessel at position 1 was removed from the

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rotor. The aqueous reaction mixture was extracted with diethyl ether (4 × 20 mL). The combined ether fractions were then dried with $MgSO_4$ and after removal of the solvent the product was purified by dry column flash chromatography with dichloromethane as an eluent to furnish 0.93 g (64%) of indole **7** as a colorless solid (HPLC purity: >99%). m.p. 101–102 °C (ref.[44] m.p. 105.5–106.5 °C). ^{1}H NMR (360 MHz, DMSO): δ = 2.13 (s, 3 H), 2.29 (s, 3 H), 6.97–6.88 (m, 2 H), 7.19 (d, J = 7.9 Hz, 1 H), 7.33 (d, J = 7.6 Hz, 1 H), 10.6 (s, 1 H) ppm. MS (pos. APCI): m/z = 146.2 [M + 1]$^+$ (M = 145.21).

Rearrangement of Pinacol (8): Pinacol (**8**; 360 mg, 3.05 mmol) was added to the NaCl solution (0.03 M) in vessel 1. The reaction mixture was heated to 270 °C by employment of a 7 min linear heating ramp and was then irradiated for an additional 30 min at 270 °C. After having been cooled to 40 °C by an air-flow (20 min), the vessel at position 1 was removed from the rotor. A solution of 2-(2,4-dinitrophenyl)hydrazine (700 mg, 3.53 mmol), H_2SO_4 (concd., 4 mL), and methanol (20 mL; ***CAUTION:*** exothermic reaction of H_2SO_4 with methanol!) was added to the aqueous reaction mixture. The precipitate was filtered off, washed with aqueous $NaHCO_3$ (5%) and distilled water, and placed in a drying oven (50 °C) overnight to provide 647.6 mg (76%) (HPLC purity: >99%) of the corresponding hydrazone as an orange solid. m.p. 119–120 °C. ^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.25 (s, 9 H), 2.05 (s, 3 H), 7.98 (d, J = 9.7 Hz, 1 H), 8.33 (d, J = 9.7 Hz, 1 H), 9.16 (d, J = 2.4 Hz, 1 H), 11.03 (s, 1 H) ppm. MS (pos. APCI): m/z = 281.1 [M + 1]$^+$ (M = 280.29).

Diels-Alder Reaction of 2,3-Dimethylbutadiene (10) and Acrylonitrile (11): 2,3-Dimethylbutadiene (**10**, 1.31 g, 1.80 mL, 15.9 mmol) and acrylonitrile (**11**, 0.40 g, 0.50 mL, 7.60 mmol) were added to the NaCl solution (0.03 M) in vessel 1. The reaction mixture was heated to 295 °C by employment of an 8 min linear heating ramp and was then irradiated at 295 °C for an additional 20 min. After having been cooled to 40 °C by an air-flow (20 min), the vessel at position 1 was removed from the rotor. The aqueous reaction mixture was extracted with diethyl ether (5 × 20 mL). The combined ether fractions were then re-extracted with cold water and dried with $MgSO_4$. After removal of the solvent, the product was purified by dry column flash chromatography with dichloromethane as an eluent and iodine on silica gel for detection, which produced 664 mg (65%) of cycloadduct **12** as a yellowish oil (HPLC purity: >99%). ^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.63 (s, 6 H), 1.81–2.26 (m, 6 H) 2.78–2.80 (m, 1 H).[45] MS (pos. APCI): m/z = 136.1 [M + 1]$^+$ (M = 135.21).

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[1] C.-J. Li, T.-H. Chan, *Organic Reactions in Aqueous Media*, Wiley, New York, NY, **1997**.
[2] a) R. Breslow, *Acc. Chem. Res.* **1991**, *24*, 159–164; b) P. A. Grieco, *Aldrichim. Acta* **1991**, *24*, 59–66; c) C.-J. Li, *Chem. Rev.* **1993**, *93*, 2023–2035.
[3] U. M. Lindström, *Chem. Rev.* **2002**, *102*, 2751–2772.
[4] W. Blokzijl, J. B. F. N. Engberts, *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1545–1579.
[5] B. Widom, P. Bhimalapuram, K. Koga, *Phys. Chem. Chem. Phys.* **2003**, *5*, 3085–3093.
[6] a) P. Krammer, H. Vogel, *J. Supercrit. Fluids* **2000**, *16*, 189–206; b) P. Krammer, S. Mittelstädt, H. Vogel, *Chem. Eng. Technol.* **1999**, *22*, 126–130.
[7] a) D. Bröll, C. Kaul, A. Krämer, P. Krammer, T. Richter, M. Jung, H. Vogel, P. Zehner, *Angew. Chem.* **1999**, *111*, 3180–3196; b) P. E. Savage, *Chem. Rev.* **1999**, *99*, 603–621; c) M. Siskin, A. R. Katritzky, *Chem. Rev.* **2001**, *101*, 825–836; d) A. R. Katritzky, D. A. Nichols, M. Siskin, R. Murugan, M. Balasubramanian, *Chem. Rev.* **2001**, *101*, 837–892; e) N. Akiya, P. E. Savage, *Chem. Rev.* **2002**, *102*, 2725–2750; f) H. Weingärtner, E. U. Franck, *Angew. Chem. Int. Ed.* **2005**, *44*, 2672–2692.
[8] a) S. Minett, K. Fenwick, L. Stenmark, *Spec. Chem. Mag.* **2001**, *21*, 30–32; b) X.-H. Qi, Y.-Y. Zhuang, Y.-C. Yuan, W.-X. Gu, *J. Hazard. Mater.* **2002**, *90*, 51–62; c) G. Del Re, G. Di Giacomo, *Desalination* **2001**, *138*, 61–64; d) S. Baur, H. Schmidt, A. Kraemer, J. Gerber, *J. Supercrit. Fluids* **2005**, *33*, 149–157.
[9] R. Gedye, F. Smith, K. Westaway, H. Ali, L. Baldisera, L. Laberge, J. Rousell, *Tetrahedron Lett.* **1986**, *27*, 279–282.
[10] R. J. Giguere, T. L. Bray, S. M. Duncan, G. Majetich, *Tetrahedron Lett.* **1986**, *27*, 4945–4948.
[11] Review: C. O. Kappe, *Angew. Chem. Int. Ed.* **2004**, *43*, 6250–6284; Books: a) A. Loupy, *Microwaves in Organic Synthesis*, Wiley-VCH, Weinheim, **2002**; b) P. Lidström, J. P. Tierney, *Microwave-Assisted Organic Synthesis*, Blackwell Scientific, **2005**; c) C. O. Kappe, A. Stadler, *Microwaves in Organic and Medicinal Chemistry*, Wiley-VCH, Weinheim, **2005**.
[12] a) A. de la Hoz, A. Diaz-Ortiz, A. Moreno, *Chem. Soc. Rev.* **2005**, *34*, 164–178; b) L. Perreux, A. Loupy, *Tetrahedron* **2001**, *57*, 9199–9223; c) N. Kuhnert, *Angew. Chem. Int. Ed.* **2002**, *41*, 1863–1866; d) C. Strauss, *Angew. Chem. Int. Ed.* **2002**, *41*, 3589–3590.
[13] a) V. Molteni, M. M. Hamilton, L. Mao, C. M. Crane, A. P. Termin, D. M. Wilson, *Synthesis* **2002**, 1669–1674; b) P. S. Baran, D. P. O'Malley, A. L. Zografos, *Angew. Chem. Int. Ed.* **2004**, *43*, 2674–2677; c) N. E. Leadbeater, M. Marco, *J. Org. Chem.* **2003**, *68*, 888–892; d) L. Bai, J.-X. Wang, Y. Zhang, *Green Chem.* **2003**, *5*, 615–617; e) J.-X. Wang, Z. Liu, Y. Hu, B. Wei, L. Bin, *Synth. Commun.* **2002**, *32*, 1607–1614; f) N. E. Leadbeater, M. Marco, B. J. Tominack, *Org. Lett.* **2003**, *5*, 3919–3922; g) . P. Appukkuttan, W. Dehaen, E. Van der Eycken, *Eur. J. Org. Chem.* **2003**, 4713–4716; h) N. Kaval, K. Bisztray, W. Dehaen, C. O. Kappe, E. Van der Eycken, *Mol. Diversity* **2003**, *7*, 125–133; i) R. K. Arvela, N. E. Leadbeater, H. M. Torenius, H. Tye, *Org. Biomol. Chem.* **2003**, *1*, 1119–1121; j) D. Villemin, M. J. Gomez-Escalonilla, J.-F. Saint-Clair, *Tetrahedron Lett.* **2001**, *42*, 635–637; k) T. A. Bryson, J. J. Stewart, J. M. Gibson, P. S. Thomas, J. K. Berch, *Green Chem.* **2003**, *5*, 174–176; l) T. A. Bryson, J. M. Gibson, J. J. Stewart, H. Voegtle, A. Tiwari, J. H. Dawson, W. Marley, B. Harmon, *Green Chem.* **2003**, *5*, 177–180; m) R. K. Arvela, N. E. Leadbeater, M. S. Sangi, V. A. Williams, P. Granados, R. D. Singer, *J. Org. Chem.* **2005**, *70*, 161–168.
[14] The group of C. R. Strauss developed a prototype multimode microwave batch reactor (MBR) for performing organic synthesis and in the 1990s studied a variety of organic chemical transformations in microwave-heated water as solvent in the 200–260 °C temperature range. This reactor is currently not a commercial product for these high temperature/pressure specifications. See ref.[33,34] for details.
[15] The majority of microwave-assisted organic reactions today are performed in so-called single-mode reactors, which have a pressure limit of 20 bars, thereby limiting the reaction temperature for water as solvent to 200 °C. See refs.[11,16] for more details.
[16] B. Hayes, *Microwave Synthesis*, CEM Publishing, Matthews, NW, **2002**.
[17] E. Neas, M. Collins, *Introduction to Microwave Sample Preparation: Theory and Practice* (Eds.: H. M. Kingston, L. B. Jassie), American Chemical Society, Washington, DC, **1988**.

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[18] a) C. Gabriel, S. Gabriel, E. H. Grant, B. S. Halstead, D. M. P. Mingos, *Chem. Soc. Rev.* **1998**, *27*, 213–224; b) D. M. P. Mingos, D. R. Baghurst, *Chem. Soc. Rev.* **1991**, *20*, 1–47.
[19] N. E. Leadbeater, S. J. Pillsbury, E. Shanahan, V. A. Williams, *Tetrahedron* **2005**, *61*, 3565–3585.
[20] L. A. Torry, R. Kaminsky, M. T. Klein, M. R. Klotz, *J. Supercrit. Fluids* **1992**, *5*, 163–168.
[21] H. P. Lesutis, R. Gläser, C. L. Liotta, C. A. Eckert, *Chem. Commun.* **1999**, *20*, 2063–2064.
[22] A. R. Katritzky, A. R. Lapucha, *Energy Fuels* **1990**, *4*, 555–561.
[23] A. Krämer, S. Mittelstädt, H. Vogel, *Chem. Eng. Technol.* **1998**, *21*, 494–500.
[24] a) A. Stadler, S. Pichler, G. Horeis, C. O. Kappe, *Tetrahedron* **2002**, *58*, 3177–3183; b) G. Horeis, S. Pichler, A. Stadler, W. Gössler, C. O. Kappe, *Fifth International Electronic Conference on Synthetic Organic Chemistry (ECSOC-5)*, September 1–30, **2001**, http://www.mdpi.net/ecsoc-5/e0000/e0000.htm.
[25] A. R. Katritzky, F. J. Luxem, M. Siskin, *Energy Fuels* **1990**, *4*, 518–524.
[26] J. An, L. Bagnell, T. Cablewski, C. R. Strauss, R. W. Trainor, *J. Org. Chem.* **1997**, *62*, 2505–2511.
[27] a) K. S. Jerome, E. J. Parsons, *Organometallics* **1993**, *12*, 2991–2993; b) E. Mizushima, K. Sato, T. Hayashi, M. Tanaka, *Angew. Chem. Int. Ed.* **2002**, *41*, 4563–4565.
[28] A. Vasudevan, M. K. Verzal, *Synlett* **2004**, 631–634.
[29] D. L. Hughes, *Org. Prep. Proced. Int.* **1993**, *25*, 609–632.
[30] H. M. Hugel, D. J. Kennaway, *Org. Prep. Proced. Int.* **1995**, *27*, 1–31.
[31] J. T. Fitzpatrick, R. D. Hiser, *J. Org. Chem.* **1957**, *22*, 1703–1704.
[32] B. Robinson, *The Fischer Indole Synthesis*, Wiley, Chichester, **1982**, pp. 642–653.
[33] a) C. R. Strauss, R. W. Trainor, *Aust. J. Chem.* **1995**, *48*, 1665–1692; b) C. R. Strauss, *Aust. J. Chem.* **1999**, *52*, 83–96.
[34] K. D. Raner, C. R. Strauss, R. W. Trainor, J. S. Thorn, *J. Org. Chem.* **1995**, *60*, 2456–2460.
[35] J. Boeseken, W. R. Van Tonningen, *Recl. Trav. Chim. Pays-Bas* **1920**, *39*, 187–190.
[36] a) Y. Ikushima, K. Hatakeda, O. Sato, T. Yokoyama, M. Arai, *Angew. Chem. Int. Ed.* **1999**, *38*, 2910–2914; b) Y. Ikushima, K. Hatakeda, O. Sato, T. Yokoyama, M. Arai, *J. Am. Chem. Soc.* **2000**, *122*, 1908–1918.
[37] B. Kuhlmann, E. M. Arnett, M. Siskin, *J. Org. Chem.* **1994**, *59*, 3098–3101.
[38] U. Pindur, G. Lutz, G. Otto, *Chem. Rev.* **1993**, *93*, 741–761.
[39] M. B. Korzenski, J. W. Kolis, *Tetrahedron Lett.* **1997**, *38*, 5611–5614.
[40] Y. Harano, H. Sato, F. Hirata, *J. Am. Chem. Soc.* **2000**, *122*, 2289–2293.
[41] A. Stadler, B. H. Yousefi, D. Dallinger, P. Walla, E. van der Eycken, N. Kaval, C. O. Kappe, *Org. Process Res. Dev.* **2003**, *7*, 707–716.
[42] C. J. Salomon, E. G. Mata, O. A. Mascaretti, *J. Org. Chem.* **1994**, *59*, 7259–7266.
[43] M. Behforouz, J. L. Bolan, M. S. Flynt, *J. Org. Chem.* **1985**, *50*, 1186–1189.
[44] M. Akazome, T. Kondo, Y. Watanabe, *J. Org. Chem.* **1994**, *59*, 3375–3380.
[45] J. B. Lambert, D. E. Marko, *J. Am. Chem. Soc.* **1985**, *107*, 7978–7982.

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