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Microwave-enhanced reactions under open and closed vessel conditions. A case study

Alexander Stadler, Sonja Pichler, Gabriela Horeis and C. Oliver Kappe*

Institute of Organic Chemistry, Karl-Franzens-University Graz, Heinrichstrasse 28, A-8010 Graz, Austria

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Abstract—Important differences have been observed when performing microwave-enhanced organic transformations, using open and closed vessel conditions. For the hydrolysis of benzamide with sulfuric acid in sealed vessels, where no volatile products are formed, no appreciable difference in reaction performance as a function of the filling volume of the vials or the reaction scale were detected. However, in the cyclocondensation of tetrahydroquinoline with substituted malonic esters, where 2 equiv. of ethanol are formed, the outcome of the reaction under sealed vessel conditions is critically dependent on the scale of the reaction.

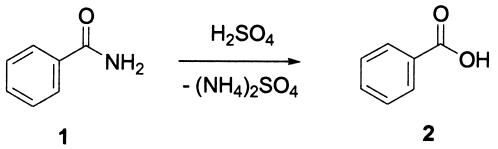
1. Introduction

High-speed microwave-enhanced chemistry has attracted a considerable amount of attention in recent years. Since the first report on the use of microwave heating to accelerate organic chemical transformations by Gedye and co-workers in 1986,[1,2] more than 1000 articles have been published in the area of microwave-enhanced organic synthesis.[3] In fact, it is becoming evident that rapid microwave protocols can be developed for a large number of chemical transformations requiring heat. The main benefits of performing reactions under microwave irradiation conditions are the significant rate enhancements and the higher product yields that can frequently be observed. While different hypotheses have been proposed to account for the observed rate enhancements under microwave irradiation, a generally accepted rationalization remains elusive.[4] Regardless of the origin/existence of a special microwave effect, microwave-enhanced chemistry can be extremely efficient and is applicable to a broad range of practical synthesis.[3–8] Although many of the early pioneering experiments in microwave-enhanced organic synthesis have been carried out in domestic unmodified microwave ovens, the current trend clearly is to use dedicated instruments for chemical synthesis, in particular for processes involving organic solvents.[3] Most of today's commercially available microwave reactors feature built-in magnetic stirrers, direct temperature control of the reaction mixture with the aid of fiber-optic probes, shielded thermocouples or IR sensors, and software that enables on-line temperature/pressure control by regulation of microwave power output.[3] In general, regardless of the specific microwave reactor employed, microwave-enhanced processes can be carried out either under sealed vessel or under open vessel (atmospheric pressure) conditions. In this article, we deal with the specific advantages and disadvantages resulting from the use of either of the two methods. We also report on scale-up characteristics and on the use of so-called multimode versus monomode microwave instruments.

2. Results and discussion

2.1. Hydrolysis of benzamide

As a suitable model reaction for studying some of the effects outlined above we have chosen the acid hydrolysis of benzamide (**1**) to benzoic acid (**2**) (Scheme 1). In fact, this transformation was the first microwave-enhanced organic reaction published in the literature.[1,2] In 1986, Gedye and co-workers reported on this hydrolysis under microwave conditions, employing sealed Teflon vessels in an unmodified domestic microwave oven.[1] A six-fold rate enhancement, i.e. a reduction of the hydrolysis time from 1 h to 10 min, was observed for this particular process as compared to classical reflux conditions. Due to the nature of microwave dielectric heating,[9] accurate temperature measurements using conventional means of temperature determination during the irradiation process were not



Scheme 1.

Keywords: microwave-enhanced chemistry; hydrolysis; cyclocondensations; 4-hydroxy-2(1*H*)-quinolones; non-thermal microwave effects.

* Corresponding author. Tel.: +43-316-3805352; fax: +43-316-3809840; e-mail: oliver.kappe@uni-graz.at

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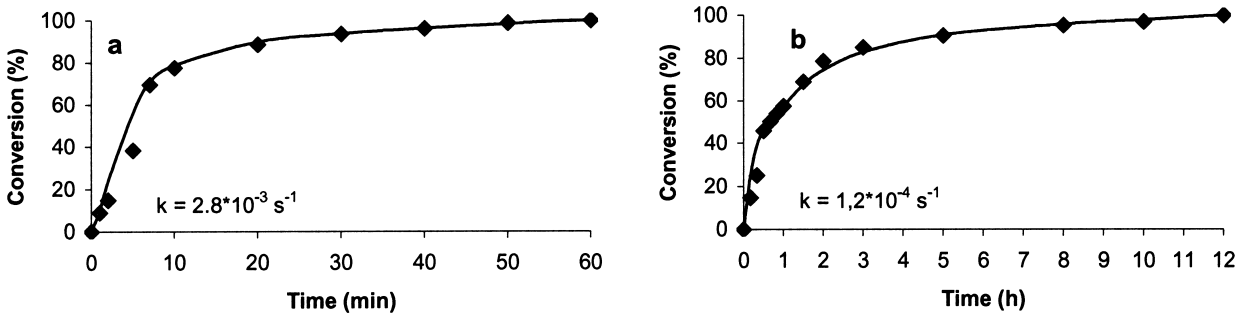


Figure 1. Kinetics of the hydrolysis of benzamide (**1**) at ca. 100°C in 20% (v/v) (a, left) and 5% (v/v) sulfuric acid (b, right). Hydrolysis rates were determined by HPLC analysis (see Section 4).

possible at that time. Therefore, the reason for the observed rate enhancement was not fully understood and these results (as many others that followed later) contributed to speculation on the existence of so-called non-thermal or specific microwave effects.[4] In order to have accurate data for comparisons at hand, we first investigated the hydrolysis of benzamide under classical thermal reflux conditions (~100°C). Experiments were run both with the originally specified[1,2] 20% (v/v) sulfuric acid, in addition to 5% (v/v) sulfuric acid. The data so obtained are presented in Fig. 1. Thus, complete hydrolysis of benzamide at 100°C under atmospheric pressure conditions requires ca. 1 h in 20% and 12 h in 5% sulfuric acid.

We next turned our attention to hydrolysis reactions under sealed vessel conditions using heating by microwave irradiation. For these small-scale experiments a monomode instrument with integrated robotics interface for automated use (see Section 4) was employed.[10] In contrast to the original work by Gedye et al.,[1,2] here both direct temperature and pressure measurements were possible. After a few optimization runs using the same reaction mixture composition as described by Gedye et al.[1,2] we discovered that employing 140°C as reaction temperature complete conversion to benzoic acid could be achieved within 7 min (Table 1), corresponding nicely to the rate-enhancement data given in the original publication.[1,2] Making use of the automated sequential processing capabilities of the microwave reactor,[10] this hydrolysis reaction could rapidly be further optimized to arrive at conditions where complete hydrolysis is possible within only 1–2 min (e.g. by increasing the reaction temperature to 180°C) (Table 1). The reaction time here is specified as the total irradiation time, thus including the rapid microwave flash heating period until the 180°C preselected reaction temperature was reached. The actual reaction time at 180°C is therefore considerable shorter (Fig. 2). Active gas jet cooling allows the mixture to be cooled very efficiently. In addition we also carried out microwave-enhanced hydrolysis reactions involving 5% sulfuric acid. Here, 140°C reaction temperature proved to be insufficient to hydrolyze benzamide within a reasonable time (Table 1). However, increasing the temperature to 180°C allowed complete hydrolysis of benzamide within 7 min. Comparing the results of thermal and microwave-enhanced hydrolysis rates, significant rate enhancements (10–100-fold) could indeed be achieved for both the 20 and 5% sulfuric acid runs. Impressive as these numbers may seem, they are not surprising at all if one considers the significantly higher confirmed reaction temperatures under which these processes took place, and the fact that these temperatures are rapidly obtainable in sealed vessels utilizing microwave technology.[3] Performing this reaction under open vessel microwave irradiation conditions would not be expected to lead to any significant rate enhancement (due to the aqueous medium), apart from what can be attributed to the well-known, but comparatively small microwave superheating effect at atmospheric pressure.[11]

Table 1. Conversion rates (%) for the microwave-enhanced hydrolysis of benzamide under different reaction conditions (sealed vessels)

Time (min)	20% H_2SO_4			5% H_2SO_4		
	140°C	160°C	180°C	140°C	160°C	180°C
1	25	72	95	9	37	73
2	71	95	>99	31	62	79
5	95	>99	–	51	90	96
7	>99	–	–	64	91	>99
10	–	–	–	83	>99	–

Hydrolysis rates were determined by HPLC analysis (see Section 4).

The above experiments involving microwave-enhanced hydrolysis in monomode instruments involved 2.0 mL of solvent in glass process vials designed for a filling volume of 2.0–5.0 mL. In order to cover a variable range of different reaction volumes we have also carried out experiments in the smaller of the two types of available process vials, designed for reaction volumes of 0.5–2.0 mL (see

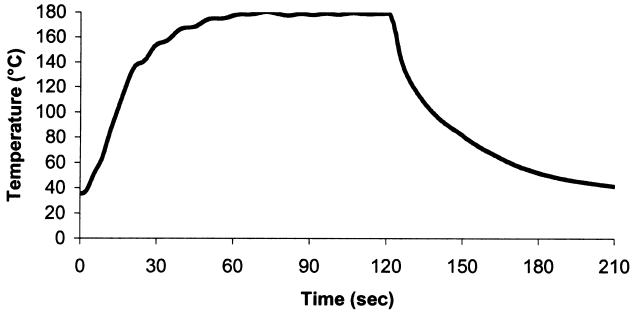


Figure 2. Heating profile for the benzamide hydrolysis at 180°C in 20% sulfuric acid under sealed vessel/microwave irradiation conditions. Microwave flash heating (300 W, 0–50 s), temperature control using the feedback from IR thermography (constant 180°C, 50–120 s), and active cooling (120–210 s).

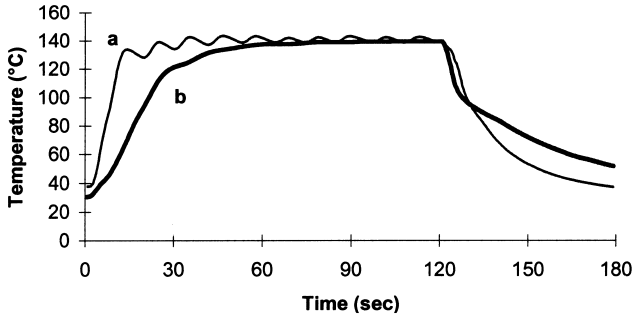


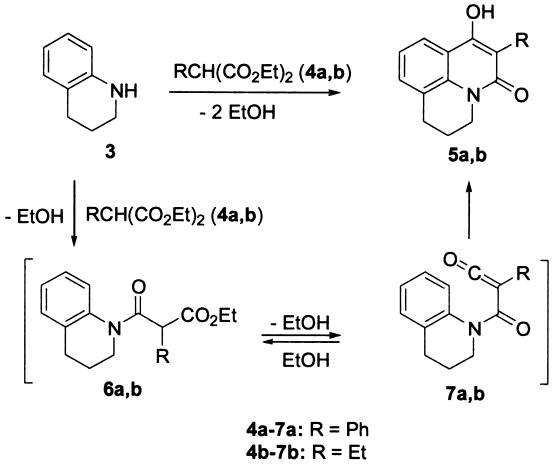
Figure 3. Heating profiles for the benzamide hydrolysis at 140°C in 20% sulfuric acid under sealed vessel/microwave irradiation conditions; (a) for 0.5 mL reaction volume (small process vial); (b) for 5.0 mL reaction volume (large process vial). For very small volumes (curve a) the temperature equilibration is not as smooth as for larger solvent volumes (curve b).

Section 4). Therefore a series of experiments involving hydrolysis of 100 mg/mL of benzamide in 20% sulfuric acid was carried out using 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, and 5.0 mL volume of sulfuric acid in the appropriate vials. Irradiation of all these reaction mixtures using the optimized conditions (140°C, 7 min) led to quantitative hydrolysis of benzamide. The maximum pressure, depending on the type of vial and the volume, was 5–8 bar. To get more accurate information on the reproducibility and scale-up characteristics of this process we have also run a set of experiments involving only 2 min of irradiation time (140°C), i.e. for an incomplete hydrolysis (see Table 1), in the solvent range indicated above (0.5–5.0 mL). The hydrolysis data were spread out ±10% around the 71% value found for the 2.0 mL run (cf. Table 1), the higher rates (70–80%) generally being obtained for the lower solvent volumes, and vice versa. This is not surprising if one considers the difference in the heating profiles between, e.g. a 0.5 and 5.0 mL run (Fig. 3), where a distinctly faster heating to the desired final temperature is observed for smaller volumes. Apart from these comparatively small deviations no appreciable difference in reaction performance depending on the filling volume of the vials was detected. It should be pointed out that the filling volume may be a major concern when performing microwave chemistry with systems lacking temperature or pressure control, or when working outside the specified volume ranges.

Another issue in microwave-enhanced synthesis is the use of dedicated multimode versus monomode cavities.[3] In the so-called multimode instruments (conceptually similar to a domestic oven), the microwaves that enter the cavity are being reflected by the walls and the load over the typically large cavity. A mode stirrer ensures that the field distribution is as homogeneous as possible. In the much smaller mono- or single-mode cavities, only one mode is present and the electromagnetic irradiation is focused directly through an accurately designed wave-guide onto the reaction vessel mounted in a fixed distance from the radiation source. We were therefore interested to investigate if the relatively small-scale reaction conditions that were optimized in the monomode instrument (see above) could be successfully transformed to a multimode reactor, capable of processing much larger volumes. In this context we have carried out the hydrolysis of benzamide in an ETHOS Synth Labstation (see Section 4),[12] employing a 100 mL sealed perfluoroalkoxy Teflon (PFA) reaction vessel. Again, the use of this set-up allowed direct temperature and pressure monitoring, as well as stirring of the reaction mixture. Using the same concentrations (100 mg benzamide/mL sulfuric acid) and reaction conditions successful hydrolysis runs were carried out with 10, 25, and 50 mL volume, i.e. hydrolyzing up to 5 g of benzamide. Runs were carried out at 140°C (20% sulfuric acid) and 180°C (5% sulfuric acid), leading to complete hydrolysis within 10 min. Although the heating and cooling profiles for the two reactors were different, these experiments demonstrate that conditions can be successfully taken from one microwave platform to another, going from 0.5 to 50 mL in scale, and from a monomode to a multimode system. In particular, the fact that there was no active cooling incorporated with the multimode reactor (heating profiles not shown) made a more quantitative comparison impossible.

2.2. 4-Hydroxy-2-quinolinones by cyclocondensation

In order to investigate in detail the effect of open- versus closed vessel conditions in microwave-heated chemical transformations we next turned our attention to a second model reaction, namely the formation of 4-hydroxyquinolin-2-(1*H*)-ones **5a,b** from anilines (i.e. **3**) and malonic esters (Scheme 2).[13] Note that here, in contrast to the first model reaction, 2 equiv. of a volatile byproduct (ethanol) are formed, that under normal (atmospheric pressure) conditions are simply distilled off.[13,14] At least one of the ethanol molecules may be involved in an equilibrium type process (**6**→**7**, Scheme 2), and preventing removal of ethanol from the reaction mixture, i.e. by using a closed vessel, may drive the reaction along undesired pathways.[13] The desired synthesis is conventionally difficult to achieve, mainly because of the high temperatures required (250–350°C). Such high temperature conditions are crucial here in order to generate the key α-oxoketene intermediates **7** which subsequently cyclize to the desired quinolinones **5**.[15,16] Therefore the rapid heating and high-temperature processing capabilities offered by microwave technology seemed to be ideally suited for this type of chemistry. Furthermore, carrying out the reaction sequence in a closed vessel would assure that the desired high-temperatures



Scheme 2.

could be reached, regardless of the boiling points of solvents or reagents employed.

With these issues in mind we have carried out the following sets of microwave experiments involving the reaction of diethyl phenylmalonate (**4a**) with tetrahydroquinoline (**3**) using 1,2-dichlorobenzene (DCB) as solvent. DCB is a solvent ideally suited for this process as it is microwave absorbing due to its dielectric properties[9] and also dissolves both starting materials, whereas the quinolinone products **5** are virtually insoluble at room temperature. This facilitates product isolation and, e.g. provided 4-hydroxy-2-quinolinone **5a** in analytical purity directly upon cooling of the reaction mixture. All initial experiments were carried out in the monomode reactor using sealed vessel conditions at the maximum operable temperature of 250°C (Table 2). A number of optimization runs were carried out involving equimolar amounts of starting materials in varying concentrations at 250°C. In one series of experiments, the effect of irradiation time on the yield was studied for runs involving 2.0 mmol of reagents and 2.0 mL of DCB. Not surprisingly, the yield increased from 54 to 78% on going from 5 to 30 min of irradiation time (entries 1–4). In another set of experiments (entries 5–7) the effect of starting material concentration on the observed yields was investigated keeping the irradiation time (10 min) and amount of solvent (2.0 mL) constant. We were surprised to find that there is a significant dependence of the yield on the amount of reagents used in this process. Apparently, the lower is the amount of starting materials, the higher the yield. At first glance these results may indicate a relationship between dilution and yield. However, we attribute this unexpected effect to the pressure built-up in the reaction vessel. Monitoring the pressure in the vial, it became evident that the larger the amount of material in the vial the higher the pressure that was formed in the sealed vessel, going from 3.6 bar (1.0 mmol) to 7.4 bar (4.0 mmol). Clearly, the pressure build-up in the vial is a result of the ethanol eliminated during the reaction.[13] In an effort to increase the available head-space in the sealed reaction vessels and to check for possible dilution effects we have performed another set of experiments, varying the amount of solvent for a 1.0 mmol reagents run (entries 8–12). The results obtained clearly indicate that there is no dilution effect at play here. The optimum yield (91% isolated yield in 10 min) was achieved for a 1.0 mmol composition of reagents in 0.5 mL of DCB (entry 12). Similar high yields were also obtained without solvent, but here the isolated product was not in an analytical state of purity (entry 13). It should be pointed out that for the corresponding conventional, thermal protocol, reaction conditions involving several hours of heating in an oil bath at 220–300°C (without solvent) were reported providing similar high yields (94%).[14] We also note that while this work was in progress, a microwave-enhanced synthesis of 4-hydroxy-2-quinolinones appeared in the literature, involving the solvent-less fusion of anilines and malonic esters in open vessels employing a dedicated multimode reactor.[17] Interestingly, the authors specifically point out that it was 'essential to work in open vessels', and that 'in a closed vessel the reaction does not proceed at all'.[17] For comparison purposes we have therefore carried out the synthesis of **5a** under open vessel, solvent-free, microwave conditions using the monomode reactor (entry 14, see Section 4). In agreement with the published work[17] we find that this method provides a high yield of product, albeit not in analytical purity since DCB cannot be used as solvent (see above). It is important to note, however, that here—in contrast to sealed vessel conditions—one is not limited by the amount of material in the vial, since there is no pressure build-up (entries 14 and 15). Therefore, for larger scale synthesis the atmospheric pressure conditions are evidently preferred. On the other hand, one has to keep in mind that large-scale experiments in open vessels will release significant amounts of flammable ethanol into the microwave cavity which presents a severe safety hazard.

To further address the issue of open- versus closed reaction vessels we have studied another example of the above cyclocondensation process, involving diethyl ethylmalonate (**4b**) as building block.[13] In contrast to the corresponding phenylmalonate, the ethylmalonate has a significantly lower boiling point (208°C for **4b**[18] versus 285°C for **4a**;[19] 245°C for **3**[20]) which makes the preparation of quinolinone **5b** under conventional conditions troublesome.[13] Indeed, in a control experiment using oil-bath heating (250°C bath temperature) (Table 3, entry 1), only traces of the desired

Table 2. Optimization runs for the microwave-promoted synthesis of 4-hydroxyquinolin-2-(1*H*)-one **5a** under sealed and open vessel conditions (250°C, monomode reactor)

Entry	(**3**)/(**4a**) (mmol)	DCB[a] (mL)	Time (min)	Yield (%)
1	2.0	2.0	5	54
2	2.0	2.0	10	67
3	2.0	2.0	20	72
4	2.0	2.0	30	78
5	1.0	2.0	10	76
6	2.0	2.0	10	67
7	4.0	2.0	10	60
8	1.0	4.0	10	54
9	1.0	3.0	10	65
10	1.0	2.0	10	76
11	1.0	1.0	10	84
12	1.0	0.5	10	91
13	1.0	–	10	90
14[b]	2.0	–	10	92
15[b]	4.0	–	10	90

[a] Solvent: 1,2-dichlorobenzene (DCB).
[b] Open vessel in the monomode reactor (see Section 4).

Table 3. Comparison of thermal- versus microwave-heated synthesis of quinolinone **5b** under sealed and open vessel conditions (20 min reaction time)

Entry	Method	(**3**)/(**4b**) (mmol)	DCB (mL)	Yield (%)
1	CONV[a]	2.0	1.0	<5%
2	CONV[a]	2.0	–	40
3	MW[b]	2.0	1.0	37
4	MW[b]	2.0	0.5	49
5	MW[b]	2.0	–	75
6	MW[b]	4.0	–	34
7	MW[c]	2.0	–	75
8	MW[c]	4.0	–	75
9	CONV[d]	2.0	–	71

[a] Open vessel, pre-heated oil-bath (250°C).
[b] Sealed vessel microwave irradiation (250°C).
[c] Open vessel microwave irradiation (250°C).
[d] Open vessel, pre-heated oil bath (290°C).

product were obtained when the reaction was carried out in 1,2-dichlorobenzene (DCB) as solvent. This is not surprising, since here the boiling point of DCB (180°C) will prevent the reaction mixture from reaching the required high temperatures. When the same experiment was carried out in a solvent-free manner, a moderate yield of 40% of **5b** was obtained (entry 2). It should be noted that the temperature of the reaction mixture reached only ca. 225°C at the end of the 20 min period with concomitant removal of volatile ethanol from the reaction vessel. In a further set of experiments the cyclocondensation reaction was carried out under sealed vessel conditions using the monomode microwave reactor (entries 3–6). Similar to the results described with the phenyl analog (Table 2), there was a distinct correlation between the amount of solvent (entries 3–5) and starting materials (compare entries 5 and 6) used, and the yield of product. Again, the lower is the total amount of material in the vial (i.e. the larger the head-space and the lower the pressure build-up) the higher the yield. For quinolinone **5b** the best result (75% isolated yield) was obtained using solvent-free conditions at 2.0 mmol concentration of starting materials (entry 5). Using microwave dielectric heating in sealed vessels the desired reaction temperature of 250°C was rapidly reached within 3 min, in contrast to thermal heating utilizing an oil bath, preheated to 250°C, where the maximum reachable temperature was 225°C. Directly comparing the conventional and the microwave solvent-free runs (entries 2 and 5, respectively), it seems that the significantly higher yield in the latter experiment may be rationalized by the rapid heating possible under microwave conditions (microwave-flash heating), and the significantly higher final temperature that is obtained by direct 'in core' microwave heating. In order to address this issue further, we have carried out additional experiments in open vessels. Similar to the phenyl analog **5a** (Table 2) open vessel microwave runs at 250°C produced exactly the same yield as closed vessel experiments at lower concentrations (entries 7 and 8). Apparently, the lower boiling point of malonate **4b** does not play a major role here. In a final experiment we have tried to mimic the rapid heating and high temperatures obtainable by microwave irradiation by performing the cyclocondensation in a preheated oil bath at 290°C. Under these conditions the heating profile of the reaction was virtually identical to the microwave runs (open or closed vessel conditions) leading to a temperature of ca. 245°C in the process vial within 3 min. Not surprisingly, a yield of 71% of isolated pure product was obtained (entry 9). Therefore, by simulating the rapid heating possible utilizing microwave heating by conventional methods, it is indeed possible to obtain a similar high yield as in the microwave-heated experiments! One has to be aware, however, that the current transformations were carried out on a relatively small scale (2.0–4.0 mmol). It may in fact not be possible to reproduce the crucial rapid heating profiles experienced herein on a significantly larger scale, in particular not with conventional heating methods.

3. Conclusion

In the present article, we have described the differences observed in carrying out microwave-enhanced organic transformations under sealed vessel and open vessel conditions. In the first example, the hydrolysis of benzamide (**1**) to benzoic acid (**2**) in sulfuric acid (Scheme 1), no volatile reaction products are formed and this transformation can be performed successfully under a variety of sealed vessel conditions. The outcome of the reaction is *not* dependent on the filling volume in the vial as long as similar heating profiles can be achieved. Therefore this process can be scaled-up from 0.5 to 50 mL volume without a significant change in process time, even switching microwave platforms (monomode to multimode). In the second example, the condensation of tetrahydroquinoline (**3**) with malonates **4**, 2 equiv. of ethanol are formed during the cyclocondensation process (Scheme 2). This leads to a significant pressure build-up in the sealed reaction vessel, which has a marked effect on the progression of the reaction (Tables 2 and 3), and makes the scale-up of these processes under sealed vessel conditions troublesome. However, these condensation reactions can also be carried out successfully under open vessel conditions in a microwave heated, solvent-free experiment. That way, the volatile reaction product is removed rapidly from the reaction mixture and therefore from the equilibrium (Scheme 2).

In summary, we have demonstrated that care must be taken in deciding on the appropriate reaction conditions in microwave-heated organic transformations. While sealed vessel reactors provide the important convenience and advantage that the reaction temperature is not limited by the boiling point of the solvent or reagent, in some cases the closed vessel conditions can also present a severe problem as demonstrated herein.[21] We believe that this is particularly relevant for those processes where equilibria are involved, and where volatile molecules can otherwise be removed from the reaction vessel.

We would also like to point out that in the studies reported herein we have not observed any non-thermal or specific microwave effects.[4] All rate enhancements described in this work can be rationalized on the basis of the increased reaction temperatures.

4. Experimental

^{1}H NMR spectra were obtained on a Bruker AMX 360 instrument at 360 MHz. FTIR spectra were recorded on a Mattson Instruments Unicam FTIR 7000 spectrophotometer using the KBr pellet method. Micro-analyses were obtained on a Fisons Mod. EA 1108 elemental analyzer. Benzamide (**1**), tetrahydroquinoline (**3**), malonates **4**, 1,2-dichlorobenzene (DCB) and sulfuric acid were obtained from Aldrich Chem. Co. and used without further purification.

4.1. Microwave instrumentation

Monomode reactor: Smith Synthesizer™ (Personal Chemistry AB).[10] The system operates at a frequency of 2.45 GHz with continuous microwave irradiation power from 0–300 W. The reaction vials (Smith Process Vials™) are glass-based ca. 10 mL tubes, sealed with Teflon septa and an aluminum crimp top. Vials for 0.5–2.0 and 2.0–5.0 mL filling volume (total volume 8.3 and 11.0 mL, respectively) are available, both equipped with appropriate

stirring bars. The process vials are moved in an automated fashion by a gripper incorporated to the platform. Inside the cavity, applying the pressure sensor as additional seal, the vials can be exposed to 20 bars of pressure and 250°C. Temperature is measured by infrared thermometry on the outer surface of the process vial. The microwave output power is regulated by the software algorithm, so that the preselected maximum temperature is maintained for the desired reaction time. After the irradiation period the reaction vessel is cooled down rapidly (approx. 60 s) to ambient temperature by compressed air (gas jet cooling). For experiments in open vessels, the Teflon septa were omitted during capping of the vials. **Caution**: note that this is not an approved method of operation for the microwave instrument. Care must be taken since volatile and/or flammable organic material may enter the microwave cavity.

Multimode reactor: ETHOS Synth Labstation (Milestone Inc.).[11] The multimode microwave reactor has a twin magnetron (2×800 W, 2.45 GHz) with a maximum delivered power of 1000 W in 10 W increments (pulsed irradiation). A rotating microwave diffuser ensures homogeneous microwave distribution throughout the plasma coated PTFE cavity (35 cm×35 cm×35 cm). For the experiments carried out in sealed vessels a 100 mL PFA reaction vessel contained in a single high-pressure HPR1000 rotor block segment was employed. Built-in magnetic stirring (Teflon-coated stirring bar) was used in all operations. During experiments, time, temperature, pressure, and power was monitored/controlled with the 'easyWAVE' software package (Version 3.2). Temperature was monitored with the aid of a shielded thermocouple (ATC-300) inserted directly into the corresponding reaction container. For experiments in sealed vessels a pressure sensor (APC-55) was additionally employed.

4.2. Monitoring benzamide hydrolysis

As benzamide (**1**) and benzoic acid (**2**) are virtually insoluble in 4°C water and sulfuric acid, the reaction products could be simply isolated by suction after standing for several hours in a refrigerator and washed with cold water. For all kinetic investigations described herein a HPLC method was developed based on the analysis of reprecipitated material after cooling (>95% recovery). After drying, equivalent amounts of material were dissolved in a minimum amount of acetonitrile and filled up to 10 mL with water. That solution was injected into the HPLC (HP Series 1050), Column LiChrospher 100 RP-18 (5 μm) 119 mm×3 mm, E. Merck, Darmstadt, Germany), using a gradient of (acetonitrile/water 5:95)/(acetonitrile) 7:3 (0–2 min) and acetonitrile (2–10 min) as the mobile solvent. The elution resulted in a retention time of 2.5 min for benzamide and 3.7 min for benzoic acid. For reference purposes some samples were also worked-up according to the method described by Gedye et al.[2] involving extraction methods. In our hands both methods gave virtually identical results.

4.3. Thermal hydrolysis of benzamide (Fig. 1)

Mixtures of 3.0 g (24.8 mmol) of benzamide (**1**) in 30 mL of 20% (v/v) sulfuric acid were heated under reflux (100°C) with stirring for 90 min. After 1, 2, 5, 7, 10, 20, 30, 40, 50, 60 and 90 min, aliquots were taken from the reaction mixture and the exact conversion rates were determined by HPLC measurements as described in Section 4.2. Complete conversion (>99%) at reflux temperature (100°C) required 60 min. An identical experiment was carried out with 5% (v/v) sulfuric acid involving heating for 24 h. Conversion rates were determined for 10, 20, 30, 40, 50, 60, 90 min and 2, 3, 5, 8, 10, 12, 14, 16 and 24 h. Complete conversion (>99%) required 12 h.

4.4. Microwave-enhanced hydrolysis of benzamide (Table 1)

A. Monomode reactor. Mixtures of 200 mg (1.65 mmol) of benzamide (**1**) and 2.0 mL 20% (v/v) sulfuric acid were filled in large Smith Process Vials™. After the vials were sealed and placed in the Smith Synthesizer microwave cavity they were irradiated sequentially using the conditions given in Table 1. Conversion rates were determined by HPLC measurements as described in Section 4.2. Identical experiments were carried out, employing 2.0 mL of 5% (v/v) sulfuric acid and for volumes from 0.5–2.0 mL (small vial), and 2.0–5.0 mL (large vial) using the same concentration of benzamide (100 mg/mL).

B. Multimode reactor. Mixtures of 100 mg benzamide/mL of sulfuric acid (20 and 5% (v/v), respectively) were placed in the 100 mL sealed PFA Teflon vessel and successful hydrolysis runs were carried out with 10, 25, and 50 mL volume. The 20% mixtures were irradiated at 140°C (700 W maximum power), the 5% mixtures at 180°C (800 W maximum power) for 10 min. Cooling after the irradiation was performed by placing the vessel in an ice bath. At ca. 80°C the vessel was opened and the mixture was allowed to stand in a refrigerator (4°C) for several hours to enable complete crystallization of product. Conversion rates were determined by HPLC measurements as described in Section 4.2.

4.5. Cyclocondensation of tetrahydroquinoline (3) and malonic esters (4a,b) (Tables 2 and 3)

A. Monomode reactor. Equimolar amounts of tetrahydroquinoline (**3**) and the corresponding malonic esters **4a** or **4b** (1.0–4.0 mmol) were placed in the appropriate reaction vial. 1,2-Dichlorobenzene as a solvent was added in 0–4.0 mL range. Individual vessels were sealed, placed in the microwave cavity and irradiated at 250°C for 5–30 min. After rapid gas jet cooling the crude precipitated products were diluted with ca. 1.0 mL of hexanes and allowed to stand in the refrigerator for approximately 1 h. The precipitate was filtered by suction and dried in vacuo. In case of the open vessel experiments, the reaction vials were placed in the microwave cavity without sealing (alumina crimp top without Teflon septum).

B. Thermal heating (Table 3, entry 2). A mixture of 266 mg (2.0 mmol) of tetrahydroquinoline (**3**) and 376 mg (2.0 mmol) of ethyl diethylmalonate was placed in a small Smith Process Vial™. The fiber optic probe was inserted and the vessel was placed in a pre-heated oil bath (250°C bath temperature). The temperature inside the vessel reached

225°C within 90 s and the mixture was further heated at this temperature for 20 min and subsequently cooled using a water bath. The reaction mixture was diluted with 1.0 mL of hexanes and allowed to stand in the refrigerator for approximately 1 h. The precipitate was filtered by suction and dried in vacuo. This procedure yielded pure **5b** in 40% yield.

4.5.1. 1-Hydroxy-2-phenyl-6,7-dihydro-5*H*-benzo[*ij*]-quinolizin-3-one (5a). Mp 221–222°C (lit.[14] 220°C). ^{1}H NMR (DMSO-d_6) δ 2.00 (t, J=7.0 Hz, 2H), 2.95 (t, J=7.0 Hz, 2H), 4.02 (t, J=7.0 Hz, 2H), 7.13–7.87 (m, 8H), 9.96 (s, OH). IR (KBr): ν 3200, 1625, 1605, 1565 cm^{-1}. Anal. calcd: C, 77.96%; H, 5.45%; N, 5.05%. Found: C, 78.21%; H, 5.55%; N, 4.98%.

4.5.2. 1-Hydroxy-2-ethyl-6,7-dihydro-5*H*-benzo[*ij*]quinolizin-3-one (5b). Mp 192–193°C (lit.[22] 294–295°C). ^{1}H NMR (DMSO-d_6) δ 1.01 (t, J=7.5 Hz, 3H), 1.97 (t, J=6 Hz, 2H), 2.60 (q, J=7.5 Hz, 2H), 2.91 (t, J=6 Hz, 2H), 4.01 (t, J=6 Hz, 2H), 7.10 (t, J=8.0 Hz, 1H), 7.29 (d, J=8.0 Hz, 1H), 7.78 (d, J=8.0 Hz, 1H), 9.94 (br s, OH). IR (KBr): ν 3200, 1630, 1605, 1570 cm^{-1}. Anal. calcd: C, 73.34%; H, 6.59%; N, 6.11%. Found: C, 73.55%; H, 6.43%; N, 6.01%.

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