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Microwave-mediated Biginelli reactions revisited. On the nature of rate and yield enhancements

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The microwave-mediated Biginelli dihydropyrimidine synthesis was reinvestigated using a purpose-built commercial microwave reactor with on-line temperature, pressure, and microwave power control. Transformations carried out under microwave heating at atmospheric pressure in ethanol solution show no rate or yield increase when the temperature is identical to conventional thermal heating. In the case of superheating by microwave irradiation at atmospheric pressure the observed yield and rate increases are rationalized as a consequence of a thermal (kinetic) effect. Under sealed vessel conditions (20 bar, 180 °C) the yield of products is decreased and formation of various byproducts observed. The only significant rate and yield enhancements are found when the reaction is performed under "open system" conditions where the solvent is allowed to rapidly evaporate during microwave irradiation. However, the observed rate and yield enhancements in these experiments are a consequence of the solvent-free conditions rather than caused specifically by microwave irradiation. This was confirmed by control experiments of the solventless Biginelli reaction under microwave and thermal heating.

Introduction

During the past decade the number of publications and reviews that have advocated the advantages and the use of microwave irradiation to carry out organic synthesis has increased significantly.[1–5] Microwaves generate rapid intense heating of polar substances with consequent significant reductions in reaction times, cleaner reactions that are easier to work up, and in many cases higher yields. In fact, some reactions that do not occur by classical heating or that occur in very low yields can be performed in high yields under microwave irradiation.[1–5] The reasons for the observed rate enhancements in microwave-assisted transformations in comparison to conventional heating are not fully understood and some authors have postulated a specific "non-thermal microwave effect" for those effects which can not be rationalized as a simple consequence of superheating of solvents.[2]

Despite the lack of a detailed theoretical understanding, four different experimental techniques to perform microwave-assisted organic synthesis have emerged: (i) reactions carried out in organic solvents in an open system at atmospheric pressure,[1–3] (ii) reactions in organic solvents using sealed vessels at elevated temperature/pressure,[1–3] (iii) solvent-free ("dry media") protocols that eliminate the use of solvents and/or employ inorganic solid supports as reaction media,[4] and (iv) phase transfer catalysis (PTC) conditions in the absence of organic solvent.[5] For reactions carried out in standard organic solvents at atmospheric pressure it is particularly difficult to explain the significant rate and yield enhancements that have been claimed in several cases, without invoking a "non-thermal microwave effect".[6] The situation is further complicated as most of these studies have been carried out using domestic unmodified microwave ovens, which do not allow the direct measurement of temperature or pressure, and due to the uneven field distribution inside the cavity make any reproduction or comparison with conventional heating experiments difficult.

The controversy[2,6] about the existence of a "non-thermal microwave effect" has prompted us to reinvestigate the microwave-assisted variation of the classical solution-phase Biginelli dihydropyrimidine synthesis. Two independent reports by Gupta *et al.*[7] and Dandia *et al.*[8] have appeared in the literature, that describe considerable enhancements in both yields and reaction rates for this particular multicomponent process, when compared to conventional thermal heating under otherwise identical reaction conditions. Herein we present a detailed study on the microwave-mediated Biginelli reaction under a variety of experimental conditions employing a commercially available, purpose-built microwave reactor.

Results and discussion

The venerable Biginelli dihydropyrimidine synthesis has attracted considerable attention in recent years.[9–15] This multicomponent process involves the one-pot cyclocondensation of a β-ketoester with an aryl aldehyde and urea (or thiourea) component under strongly acidic conditions according to the mechanism outlined in Scheme 1.[11] Unfortunately, the original protocol (ethanol, catalytic HCl, reflux) provides only low to moderate yields of the desired dihydropyrimidine targets (DHPMs) **8**, in particular when substituted aromatic aldehydes or thioureas are employed.[10,12] The publications by Gupta[7] and Dandia[8] describe 26 examples of microwave-enhanced solution-phase Biginelli reactions employing ethyl acetoacetate (**5**), (thio)ureas **2** (X = O, S), and a wide variety of aromatic aldehydes **1** as building blocks. Upon irradiation of the individual reaction mixtures (ethanol, catalytic HCl) in an open glass beaker inside the cavity of a domestic microwave oven the reaction times were reduced from 2–24 hours of conventional heating (80 °C, reflux) to 3–11 minutes under microwave activation (*ca.* 200–300 W).[7,8] At the same time the yields of DHPMs **8** obtained by the authors were markedly improved compared to those reported earlier using conventional conditions (see below).

In order to determine the existence of a nonthermal microwave effect we have repeated the above experiments employing a purpose-built multimode microwave batch reactor from Milestone Inc. (ETHOS 1600 series).[13] This instrument features a built-in magnetic stirrer, direct temperature control of the reaction mixture with the aid of a shielded thermocouple, and

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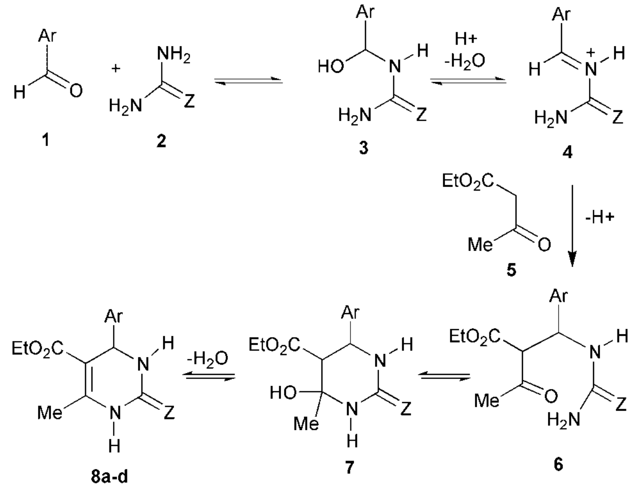
Table 1 Published yield and rate enhancements for the microwave-mediated Biginelli syntheses of DHPMs **8a–d** (according to refs. 7 and 8)

DHPM[a]	Yield (%) MW[b]	Yield (%) CONV[c]	Reaction time/min MW[b]	Reaction time/min CONV[c]	References MW[b]	References CONV[c]
8a	90	78.5	3.5	180	7	14*a*
8b	96	46.9	3	120	7	14*a*
8c	90	42	3	120	7	14*c*
8d	78.4	24	4	—	8	15

[a] For substitution patterns, see Scheme 1. [b] MW = microwave heating (domestic microwave oven, open beaker, *ca.* 200–400 W). [c] CONV = conventional thermal heating (oil bath, reflux).



8a, Z = O, Ar = phenyl
8b, Z = O, Ar = 3,4-dimethoxyphenyl
8c, Z = S, Ar = phenyl
8d, Z = S, Ar = 3-nitrophenyl

Scheme 1

software that enables online temperature/pressure control by regulation of microwave power output. This microwave reactor can either be fitted with standard glassware and a reflux condenser for operation at atmospheric pressure, or equipped with a sealed PFA vessel for carrying out reactions at elevated pressure (see Experimental section).

Out of the microwave-mediated Biginelli condensations presented by Gupta and Dandia[7,8] we have selected four representative examples (**8a–d**, Scheme 1) for our studies. Apart from the original DHPM **8a** reported by Biginelli,[9] these include cases where the reported yield increases upon microwave irradiation were most pronounced (**8b–d**, Table 1). In terms of molar equivalents of reactants and catalyst, both publications essentially followed the optimized conditions for the Biginelli reaction as reported by Folkers *et al.*[14]

As a starting point in our investigation we have tried to mimic the experiments performed by Gupta *et al.*[7] for the synthesis of DHPM **8a** under microwave irradiation. Instead of using a domestic-type microwave oven we have employed the ETHOS 1600 microwave reactor with standard Pyrex glassware and a reflux condenser fitted through the roof of the microwave cavity. The temperature of the stirred reaction mixture was monitored directly by a shielded thermocouple inserted into the solution. The same amounts and proportions of reactants (urea, benzaldehyde, ethyl acetoacetate), solvent (ethanol), and catalyst (concentrated HCl) were used as indicated by Gupta *et al.*[7] To our disappointment, the yield of DHPM **8a** after 10 min of irradiation at 400 W was only 15%, the remainder consisting of unchanged starting materials (see Experimental). The reaction temperature during the 10 min period was *ca.* 98 °C, indicating a strong superheating effect by microwave irradiation.

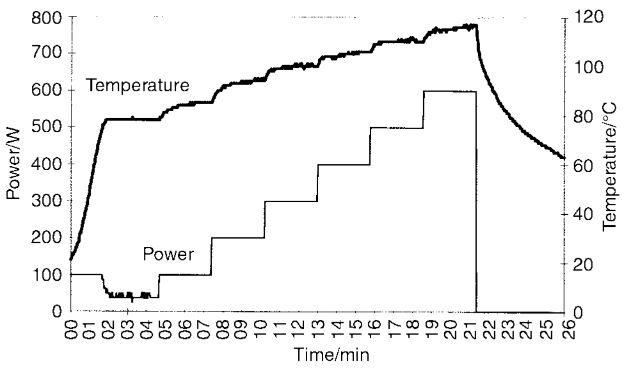


Fig. 1 Dependence of superheating of ethanol on microwave power output (shielded thermocouple, Milestone Ethos 1600 microwave reactor).

Superheating of solvents at atmospheric pressure is a common phenomenon when dealing with microwave heating of polar organic solvents.[16] For ethanol the superheating effect has been reported to be between 5 to 24 °C, depending on reactor type, experimental conditions (glassware, boiling chips, wall surface) and microwave input power.[17] The origin of this superheating effect has been rationalized in terms of an "inverted heat transfer" effect (from the irradiated medium towards the exterior) preventing the onset of nucleate boiling.[16] We have determined the superheating effect for absolute ethanol using the ETHOS 1600 microwave reactor under the same experimental conditions (amount of solvent, glassware, magnetic stirring *etc.*) that were employed in all normal pressure syntheses described in the following sections. Fig. 1 shows the dependence of the changes in solvent temperature (*i.e.* measured in the liquid phase) on the microwave input power. For the initial 5 minutes the temperature was set to 80 °C with a maximum input power of 100 W. As seen in Fig. 1 this temperature is reached in *ca.* 2 min; for the remaining 3 min the power is automatically reduced to *ca.* 40 W to keep the temperature at 80 °C. For the period 5–18 min a nominal temperature of 130 °C was preselected. This ensures that the system will continuously operate at the maximum selected output power. For 100 W the temperature increased to 85 °C, for 200 W to 94 °C *etc.* until at 600 W a temperature of 116 °C was reached. From 200 W onwards an intense reflux of the solvent was observed.

In order to investigate the effect of microwave irradiation on the Biginelli reaction in more detail, the synthesis of DHPMs **8a–d** was carried out under the following set of experimental conditions: (i, CONV) by conventional thermal heating (reflux, 80 °C, 3 h); (ii, MW-A) by microwave heating (80 °C, 3 h); and (iii, MW-B) by microwave superheating (400 W, reflux, 3 h). We anticipated that any significant differences in yields and rates between thermal and microwave heating *using the same temperature of 80 °C* (conditions CONV and MW-A) would provide a strong indication as to the existence of a "non-thermal microwave effect". Since the final reaction products, DHPMs **8a–d**, are virtually insoluble in cold ethanol the amount of

Table 2 Comparison of yields obtained in thermal and microwave-mediated Biginelli reactions (reflux conditions)

	Yield (%)		
DHPM[a]	CONV[b]	MW-A[c]	MW-B[d]
8a	78	80	80
8b	49	54	75
8c	29	33	35
8d	<1	<1	<1

[a] For substitution patterns, see Scheme 1. [b] CONV = conventional thermal heating (oil bath, reflux, 80 °C, 3 h). [c] MW-A = microwave heating (*ca.* 30 W, 80 °C, 3 h). [d] MW-B = microwave superheating (400 W, 3 h).

precipitated pure product provided an easy measure for the reaction yield (see Experimental section).

For the microwave heating experiments at 80 °C (MW-A) a maximum microwave power of 50 W was selected. The effective average power used over the 3 h period was *ca.* 30 W. The results of these comparative studies are summarized in Table 2. As can be seen by inspection of the thermal (CONV) and 80 °C microwave experiments (MW-A), yields are essentially identical. The small increase in yield on going from the thermal to the microwave runs (2–5%) may be rationalized either in terms of an inaccuracy of the temperature measurement, or by the formation of localized, microwave-induced "hot spots" that escape the macroscopic measurement of bulk solution temperature.[2] Whatever the reason for these small deviations an appreciable "non-thermal microwave effect" evidently was not observed.[18]

For the superheating experiments (MW-B) the results are similar, with the exception of DHPM **8b**. Here, a significantly improved yield of 75% was obtained, as compared to 49% in the thermal run. By performing a second thermal experiment (80 °C) in which the reaction time was extended from 3 h to 12 h - also yielding 75% of **8b** - it was demonstrated that the yield increase in the superheating experiment is associated with an increase in the reaction rate going to higher temperatures (*ca.* 90 °C in the superheating experiment). This is supported by the mechanistic assumption that for an electron-rich aldehyde (*i.e.* 3,4-dimethoxybenzaldehyde), one would expect the reaction rate for the rate limiting mechanistic steps (**1**→**3**, **4**→**6**)[11] to be lower as compared to the phenyl case **8a** (Scheme 1). Therefore a longer reaction time in the thermal run has the same effect as a higher temperature in the superheating experiment. In sharp contrast, no significant increase in yield was observed for DHPM **8c** when the reaction time under thermal conditions was extended from 3 h to 12 h. The isolated yield of 36% agrees nicely with the yield obtained for **8c** in the superheating experiment (35%, Table 2). In our hands, for DHPM **8d** only trace amounts of products were produced in all three experimental variations (isolated by flash chromatography). Most of the reaction mixture consists of unreacted starting materials in addition to a number of unidentified byproducts in small amounts.[15] Biginelli reactions involving thioureas and substituted aromatic aldehydes notoriously produce low yields of DHPMs.[10,15]

Since the microwave irradiation experiments performed under atmospheric pressure described above failed to show the postulated[7,8] significant rate and yield enhancements, we have also carried out experiments in sealed vessels. In order to observe possible rate enhancements under pressure we have repeated the synthesis of DHPM **8a** under microwave irradiation using a sealed PFA reactor instead of reflux conditions (MW-C, see Experimental section). Experiments were carried out at 120 °C, 150 °C, and 180 °C for various periods of time. In a typical experiment (Fig. 2), the maximum temperature was set to 180 °C (500 W preselected maximum power) which led to a maximum pressure of 20 bar. In order to allow for adequate mixing of reagents the temperature was first brought to 100 °C within 2 min with intense stirring and then kept in this range for an additional 2 min. After ramping the temperature to 180 °C within 3 min, the temperature was kept at 180 °C for 1 h (average microwave power *ca.* 100 W). During that period the pressure gradually increased to 20 bar. Once the irradiation was stopped temperature and pressure rapidly decreased. After a cooling period of 20 min the system was opened and the reaction stopped by inserting the PFA container into an ice-bath. By analysis of the reaction mixture by TLC and ^{1}H NMR it became evident that various undesired side reactions had occurred under these more drastic conditions, and that the yield of DHPM **8a** had decreased significantly. Work-up of the reaction mixture yielded 37% of DHPM **8a** and 28% of dihydropyridine **9** among other unidentified by-products. The formation of dihydropyridine **9** can be rationalized in terms of an acid-catalyzed hydrolysis of urea to carbon dioxide and ammonia, the latter then reacts with ethyl acetoacetate and benzaldehyde in a classical Hantzsch-type fashion to produce **9** (Scheme 2).[19]

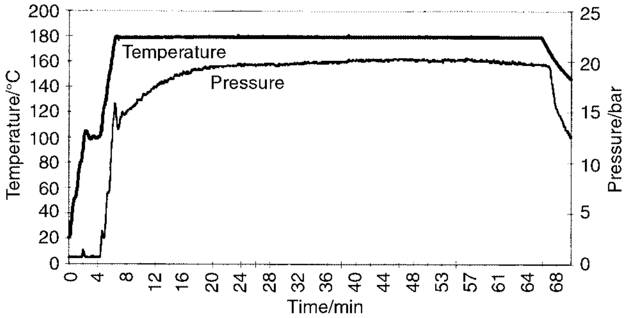
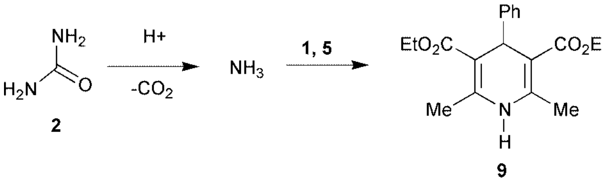


Fig. 2 Temperature *versus* pressure profile for the microwave-mediated Biginelli synthesis of dihydropyrimidine **8a** under sealed vessel conditions. The average microwave power used (not shown) was *ca.* 100 W.



Scheme 2

Since none of the experimental conditions used above did allow us to reproduce the yield or rate enhancements reported by Gupta and Dandia (Table 1),[7,8] we have ultimately chosen to repeat the Biginelli syntheses of **8a**–**d** in a domestic microwave oven in glass beakers following as closely as possible the published protocols by these authors (MW-D). Domestic microwave ovens, however, have several significant drawbacks that make the reproducibility of results troublesome,[4a] in addition to safety concerns as sparks are common in microwave systems.[20]

One of the most striking differences between the superheating experiments described above and microwave irradiation runs using the conditions of Gupta[7] and Dandia[8] (see Experimental section) is the substantial evaporation of volatile solvent (*i.e.* ethanol) that occurred employing the latter protocol. Even using short irradiation cycles (10–20 s) the loss of solvent was substantial. In fact, after several cycles of irradiation and cool-off periods most of the solvent had evaporated (even considering that a 5-fold amount of ethanol was used as compared to the standard thermal[14a] protocol). Although it is difficult to adequately reproduce the experimental conditions reported by Gupta[7] and Dandia[8] (given the differences in domestic microwave magnetron design) it becomes evident that such evaporation effects are unavoidable no matter what type of equipment is used. The yields of DHPMs **8a**–**d** that were obtained using the

Table 3 Comparison of yields obtained in thermal and microwave-mediated Biginelli reactions (open system conditions)

DHPM[a]	Yield (%) MW-D[b]	MW-E[c]	THERM[d]
8a	78	50	62
8b	78	53	50
8c	58	62	67
8d	50	53	50

[a] For substitution patterns, see Scheme 1. [b] MW-D = microwave heating (ethanol), 5 min total reaction time (20 s 800 W/15 s cool-off period cycles). [c] MW-E = microwave heating (no solvent), 5 min total reaction time (20 s 800 W/15 s cool-off period cycles). [d] THERM = conventional thermal heating (no solvent), 30 min, 120 °C bath temperature.

above "open system" conditions are given in Table 3 (MW-D). As can be seen, substantial rate and/or yield increases were observed for all examples, as compared to the microwave experiments carried out under reflux conditions (MW-A, MW-B, Table 2). Although we could not quite reproduce the extremely high yields reported by Gupta[7] and Dandia[8] (Table 1) a substantial increase was nevertheless observed in most cases, in particular for the generally low-yielding examples involving thioureas, *i.e.* DHPMs **8c**,**d**. The above results can be readily rationalized by assuming that in a more concentrated reaction medium the reaction proceeds considerably faster.[6] In addition, in an open reaction system the 2 equivalents of water that are formed during the course of the reaction are removed from the reaction mixture by codistillation with the solvent. Since some of the key reaction steps for the Biginelli dihydropyrimidine synthesis can be formulated as equilibrium processes (Scheme 1) this may drive the reaction in the desired direction. In contrast, using a reflux condensor (MW-A, MW-B), or a sealed vessel system (MW-C), the eliminated water is not removed from the reaction mixture.

Using the MW-B conditions we have noticed that towards the final irradiation cycles (after 3–4 min total reaction time) all the solvent had been evaporated and that microwave irradiation was essentially performed on a neat mixture of reagents. At this point we considered abandoning the use of solvent altogether and running the microwave-mediated Biginelli reaction as a so-called "dry-media" or solvent-less process.[21] In the solvent-free microwave Biginelli reaction (MW-E), the three building blocks were simply mixed in a beaker, and after the addition of catalytic amounts of concentrated HCl the reaction mixture was irradiated in the domestic microwave oven. Again, the use of irradiation cycles, rather than continuous irradiation proved beneficial. Upon continuous irradiation (800 W) for 1–2 min extensive decomposition took place and product yields were decreased significantly. The reaction temperature exceeded 120 °C under these conditions whereas the use of the same irradiation cycles as under MW-D (Table 3) gave rise to a maximum temperature of *ca.* 90 °C (measured immediately after irradiation with a conventional thermometer). The yields of DHPMs **8a**–**d** obtained under conditions MW-E are summarized in Table 3 (not optimized). In general, yields were in the same range as under the solvent conditions MW-D, with somewhat lower yields for the runs involving urea (*i.e.* DHPMs **8a**,**b**). We attribute these slightly lower yields to non-homogeneous reaction conditions in the early stages of the process, *i.e.* the low solubility/miscibility of urea (as compared to thiourea) with the other components. We have recently shown that this problem can be overcome by using polyphosphate ester (PPE) as a non-volatile reaction mediator.[21a] We also note that the use of a solid support (*e.g.* alumina or silica) apparently is not necessary.[21b]

In order to compare the specific influence of microwave heating on the solvent-free process (MW-E) we have carried out the same reaction under thermal conditions by conventional heating of the neat reactants in an oil bath at 120 °C bath temperature (reaction temperature *ca.* 90 °C) (THERM). Apart from the somewhat longer reaction times, DHPMs **8a**–**d** were formed in comparable yields (Table 3). The advantages of the solvent-free variation of the Biginelli reaction are immediately evident if one compares the yields for DHPM **8d** obtained under solvent conditions (Table 2) and under solvent-free conditions (Table 3). Only on using solvent-free processes—independent of the use of microwave or conventional heating—can a meaningful yield of **8d** be obtained.

Conclusions

The experiments described in this article were aimed at confirming the existence of specific "non-thermal microwave effects" that have been the subject of intense discussion for the last couple of years.[2,6] As a model reaction we have chosen the well-known Biginelli dihydropyrimidine synthesis for which several microwave-promoted protocols have been reported recently.[7,8,21] For reactions carried out in solvents in a homogeneous medium at atmospheric pressure (Table 2) the following conclusions emerge. (i) There is no appreciable difference in reaction rates and yields between reactions carried out under microwave irradiation (MW-A) and thermal heating (CONV) *at identical temperatures*. (ii) The difference in reaction rates/yields upon using superheated solvents (MW-B, *i.e.* for DHPM **8b**) is a consequence of the higher reaction temperature of the reaction medium and can be rationalized in terms of a conventional thermal (kinetic) effect (as opposed to a "non-thermal effect"). (iii) For processes carried out in sealed vessels under microwave irradiation (MW-C) a strong superheating effect is observed (*i.e.* 180 °C, 20 bar), however, due to the formation of various by-products this particular method is synthetically impractical. (iv) The only substantial rate and yield enhancements are found for reactions that are carried out either in the absence of solvent (MW-E), or using solvent under "open system" conditions[7,8] where the solvent is rapidly evaporated during irradiation but provides homogeneity in the initial phase of the reaction (MW-D). The observed rate and yield enhancements under these conditions are a consequence of the more concentrated reaction medium, in addition to product water being removed from the equilibrium (Scheme 1). We therefore can not confirm the existence of a "specific" or "non-thermal" microwave effect in these processes. In fact, our thermal comparison studies (THERM, Table 3) show that more or less identical yields are observed when the neat reagents are heated in an oil bath. The only difference is the somewhat longer reaction times that are due to the slower heat transfer involved in conventional heating.

Experimental

General procedures and materials

Melting points were determined on a Gallenkamp melting point apparatus, Mod. MFB-595 and are uncorrected. IR spectra were recorded on a Perkin-Elmer 298 spectrophotometer as KBr pellets. ^{1}H and ^{13}C NMR spectra were obtained on a Varian XL-200 Gemini instrument at 200 MHz and 50 MHz, respectively (*J* values are given in Hz). Micro-analyses were obtained on a Fisons Mod. EA 1108 elemental analyzer. Reactions were monitored by thin layer chromatography (TLC) on 0.2 mm silica gel F-252 (Merck) plates. Flash chromatography was performed with silica gel 60 (40–63 µm, Aldrich) using mixtures of light petroleum (bp 40–60 °C) and ethyl acetate as eluent. For all Biginelli syntheses absolute ethanol (Merck, p.a.) was used as solvent. Benzaldehyde was distilled *in vacuo* before use. All other reagents were purchased from Aldrich Chemical Co. and used without further purification. For solvent-less procedures (MW-E, THERM) solid components were employed as grained powders.

Microwave irradiation experiments

A) Milestone ETHOS 1600 batch reactor.[22] The multimode microwave reactor has a twin magnetron (2 × 800 W, 2455 MHz) with a maximum delivered power of 1000 W in 10 W increments. A rotating microwave diffuser ensures homogeneous microwave distribution throughout the plasma coated PTFE cavity (35 cm × 35 cm × 35 cm). For normal pressure operations (MW-A, MW-B) standard glassware (100 cm^3 three-necked Pyrex round-bottomed flask) with a water-cooled reflux condensor fitted on top of the cavity was used. For experiments carried out in sealed vessels (MW-C) 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 both normal pressure and sealed vessel operation. During experiments, time, temperature, pressure, and power were monitored/controlled with the "easy-WAVE" software package (Vers. 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.

B) Domestic microwave oven. For the microwave irradiation experiments described in MW-D and MW-E (Table 3) a conventional (unmodified) household microwave oven equipped with a turntable was used (Panasonic NN-3356/3306, 2450 MHz, 800 W max power).¶ **CAUTION:** Heating flammable solvents in an open container inside the cavity of a standard microwave oven (MW-D) represents a severe fire hazard due to the occurrence of sparks in such environments.[20] However, we have encountered no incidence of this in the *ca.* 50 runs carried out for this project.

Superheating of ethanol (Fig. 1)

Ethanol (20 cm^3) was placed in a 100 cm^3 three-necked round-bottomed flask and was irradiated with magnetic stirring inside the cavity of the ETHOS 1600 microwave reactor with the microwave power indicated in Fig. 1. A reflux condenser was fitted on top of the microwave cavity. Intense reflux was observed at >200 W. The maximum temperatures, measured in the liquid phases, dependent on the microwave output power were: 100 W, 85 °C; 200 W, 94 °C; 300 W, 101 °C; 400 W, 106 °C; 500 W, 111 °C; 600 W, 116 °C.

Reaction conditions CONV (Table 2)

A mixture of ethyl acetoacetate **5** (75 mmol, 9.75 g), the appropriate aldehyde **1** (50 mmol), (thio)urea **2** (50 mmol), absolute ethanol (20 cm^3), and concentrated HCl (100 μL, *ca.* 4 drops) was placed in a 100 cm^3 three-necked round-bottomed flask and heated at reflux (80 °C measured inner temperature) with magnetic stirring for 3 h. After solid $NaHCO_3$ (100 mg) was added (in order to quench the acid-catalyzed Biginelli reaction) the mixture was allowed to stand at 4 °C for 3 h. During that time the solid DHPMs **8a**–**c** precipitated from the reaction mixture, and were subsequently filtered, washed with ice-cold ethanol, and dried at 50 °C. In the case of DHPM **8d** the solvent was evaporated, and the crude mixture subsequently purified by flash chromatography (silica gel, toluene–ethanol 9:1). ^1H NMR (200 MHz) measurements of **8a**–**d** confirmed their purity to be >95%. For yields, see Table 2.

Reaction conditions MW-A (Table 2)

A mixture of the appropriate reagents, ethanol, and HCl (for amounts, see CONV) was irradiated inside the cavity of the ETHOS 1600 microwave reactor for 3 h at 80 °C at the maximum power level of 50 W using the same glassware as described in conditions CONV above. The average software-controlled microwave power used was *ca.* 30 W in order to keep the reaction temperature at 80 °C. Work-up as described above yielded DHPMs **8a**–**d** (see Table 2).

Reaction conditions MW-B (Table 2)

A mixture of the appropriate reagents, ethanol, and HCl (for amounts, see CONV) was irradiated under intense reflux (superheating) inside the cavity of the ETHOS 1600 microwave reactor for 3 h at 400 W using the same glassware as described in conditions CONV above. Work-up as described above yielded DHPMs **8a**–**d** (see Table 2).

Reaction conditions MW-C (Fig. 2)

A mixture of ethyl acetoacetate **5** (38 mmol, 4.94 g), benzaldehyde **1** (25 mmol, 2.65 g), urea **2** (25 mmol, 1.50 g), absolute ethanol (10 cm^3), and concentrated HCl (50 μL) was taken inside a 100 cm^3 PFA sealed reaction vessel. After ramping the temperature to 180 °C within 7 min (Fig. 2) the temperature was kept at 180 °C (20 bar) for 1 h. After cooling down the reaction container in an ice-bath for 20 min the system was vented and the PFA vessel subsequently kept at 4 °C at atmospheric pressure for 3 h. Filtration of the precipitated solid gave DHPM **8a** in 37% yield (2.40 g) and >95% purity (^1H NMR). Evaporation of the mother liquor followed by flash chromatography (silica gel, hexane–ethyl acetate 1:1) produced DHP **9** (1.75 g, 28% yield) among other unidentified products.

Reaction conditions MW-D (Table 3)

A mixture of ethyl acetoacetate **5** (15 mmol, 1.95 g), the appropriate aldehyde **1** (10 mmol), (thio)urea **2** (10 mmol), absolute ethanol (25 cm^3), and concentrated HCl (30 μL) was taken in a 100 cm^3 Pyrex glass beaker and irradiated inside the cavity of the domestic microwave oven. This setup was irradiated for 20 s at full power (800 W) followed by a 15 s cooling period. This 35 s irradiation/cooling cycle was repeated 9 times (total reaction time 5 min). During that period substantial loss of solvent by evaporation was observed. In the final cycles (after 3–4 min) irradiation was essentially performed on a solvent-less system as judged by the measured weight-loss of the reaction vessel. After standing for 1–2 h at room temperature, the solid reaction mixture was titurated with ice-cold ethanol (5 cm^3). The DHPMs **8a**–**d** were filtered, washed with ice-cold ethanol, and dried. For yields see Table 3. ^1H NMR (200 MHz) measurements of these products confirmed their purity to be >95%.

Reaction conditions MW-E (Table 3)

A mixture of ethyl acetoacetate **5** (15 mmol, 1.95 g), the appropriate aldehyde **1** (10 mmol), (thio)urea **2** (10 mmol), and concentrated HCl (30 μL) was taken in a 50 cm^3 Pyrex glass beaker and irradiated inside the cavity of the domestic microwave oven using the same irradiation cycles as under MW-D. Work-up as described above yielded DHPMs **8a**–**d** (see Table 3).

Reaction conditions THERM (Table 3)

A mixture of ethyl acetoacetate **5** (15 mmol, 1.95 g), the appropriate aldehyde **1** (10 mmol), (thio)urea **2** (10 mmol), and concentrated HCl (30 μL) was taken in a 50 cm^3 round-

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¶ We note that domestic microwave ovens always operate at the maximum power level, even if a lower power level is selected. For the Panasonic instrument, for example, a preselected level of 250 W will result in cycles of 6 s of irradiation at 800 W, followed by an irradiation pause of 16 s. This makes the reproduction of literature experiments performed in domestic ovens at power levels other than the maximum level somewhat troublesome. We therefore recommend use of the maximum available power level (continuous irradiation) with user-selected irradiation pauses, if desired.

bottomed flask and inserted into a preheated oil bath (120 °C bath temperature). After stirring for 30 min (reaction temperature *ca.* 90 °C) the mixture was allowed to cool to room temperature. Work-up as described above yielded DHPMs **8a**–**d** (see Table 3).

Spectroscopic data for products

Ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (8a). Mp 206–207 °C (from ethanol) (lit.,[14a] 202.4 °C); ν_{max}/cm^{-1} 3240, 3110, 1725, 1700, 1645; δ_H (200 MHz, DMSO-d_6) 1.12 (t, J = 7.5 Hz, 3H), 2.28 (s, 3H), 4.03 (q, J = 7.5 Hz, 2H), 5.17 (d, J = 3.0 Hz, 1H), 7.22–7.41 (m, 5H), 7.78 (br s, 1H), 9.22 (br s, 1H).

Ethyl 4-(3,4-dimethoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (8b). Mp 177–179 °C (from ethanol) (lit.,[14a] 178–178.5 °C); ν_{max}/cm^{-1} 3240, 3110, 1725, 1705, 1625 cm^{-1}; δ_H (200 MHz, DMSO-d_6) 1.17 (t, J = 7.5 Hz, 3H), 2.32 (s, 3H), 4.09 (q, J = 7.5 Hz, 2H), 3.85 (s, 6H), 5.38 (d, J = 3.0 Hz, 1H), 6.75–6.90 (m, 3H), 5.90 (br s, 1H), 8.33 (br s, 1H).

Ethyl 6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (8c). Mp 205–207 °C (from ethanol) (lit.,[14c] 207–208 °C); ν_{max}/cm^{-1} 3340, 3180, 3100, 1670, 1580; δ_H (200 MHz, DMSO-d_6) 1.12 (t, J = 7.5 Hz, 3H), 2.31 (s, 3H), 4.02 (q, J = 7.5 Hz, 2H), 5.20 (d, J = 3.0 Hz, 1H), 7.20–7.41 (m, 5H), 9.68 (br s, 1H), 10.31 (br s, 1H).

Ethyl 6-methyl-4-(3-nitrophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (8d). Mp 208–209 °C (from ethanol) (lit.,[15] 206–207 °C); ν_{max}/cm^{-1} 3180, 1715, 1660, 1595, 1530; δ_H (200 MHz, DMSO-d_6) 1.12 (t, J = 7.5 Hz, 3H), 2.33 (s, 3H), 4.05 (q, J = 7.5 Hz, 2H), 5.35 (br s, 1H), 7.65–7.73 (m, 2H), 8.08–8.27 (m, 2H), 9.80 (br s, 1H), 10.55 (br s, 1H).

Diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (9). Mp 154–156 °C (lit.,[23] 158–160 °C); δ_H (200 MHz, DMSO-d_6) 1.12 (t, J = 7.5 Hz, 6H), 2.28 (s, 6H), 3.98 (q, J = 7.5 Hz, 4H), 4.85 (s, 1H), 7.18 (m, 5H), 8.80 (br s, 1H).

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