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Microwave Chemistry

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Microwave Effects in Organic Synthesis: Myth or Reality?**

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temperature monitoring

Since the first published reports in 1986[1] on the use of microwave irradiation to "accelerate" organic chemical transformations, there has been considerable speculation and discussion of this effect. Much of the debate has centered around the question whether the observed effects can in all instances be rationalized by purely thermal/kinetic phenomena (thermal microwave effects) arising from the rapid heating and high bulk reaction temperatures attained with microwave dielectric heating, or whether some effects are connected to so-called specific or nonthermal microwave effects.[2,3] Unfortunately, the definitions of what constitutes a specific or nonthermal microwave effect are somewhat vague and different scientific communities may in fact have different definitions.[3] Most scientists today will agree that the energy of the microwave photon is far too low to directly cleave molecular bonds, and that therefore microwaves cannot "induce" molecules to undergo chemical reactions upon direct absorption of electromagnetic energy, as opposed to ultraviolet and visible radiation (photochemistry).[3] However, in the organic chemistry community claims of the existence of nonthermal microwave effects persist.[2] These effects have been postulated to result from a direct, often stabilizing interaction of the electromagnetic field with specific molecules, intermediates, or even transition states in the reaction medium, which is not connected to a macroscopic change in reaction temperature.[2,3] It has been argued, for example, that the presence of an electric field affects the orientation of dipolar molecules or intermediates and hence changes the pre-exponential factor A or the activation energy (entropy term) in the Arrhenius equation for certain types of reactions.[2,3] Furthermore, a similar effect has been proposed for polar reaction mechanisms, where the polarity increases going from the ground state to the transition state, resulting in an enhancement of reactivity by a decrease of the activation energy.[2,3] Specific microwave effects are caused by the uniqueness of the microwave dielectric heating mechanisms and include, for example,

1) the superheating effect of solvents at atmospheric pressure,
2) the selective heating of, for example, strongly microwave-absorbing heterogeneous catalysts or reagents in a less polar reaction medium (and effects resulting from the differential/selective heating of bi- or multiphasic liquid/liquid systems),
3) the formation of "molecular radiators" by direct coupling of microwave energy to specific reagents in homogeneous solution (microscopic hotspots), and
4) the elimination of wall effects caused by inverted temperature gradients.[3]

It should be emphasized that any rate enhancements of this type are essentially still the result of a thermal phenomenon (that is, a change in temperature compared to heating by standard convection methods), although it may be difficult to determine the exact temperatures experimentally.

Specific as well as nonthermal microwave effects can be influenced by the electromagnetic field strength—the higher the field strength, the more pronounced the effect—and can be, at least in theory, largely independent of the bulk reaction temperature.[2,3] It should be noted that a clear differentiation between specific and nonthermal microwave effects following the definitions stated herein is not always expressed in the literature. Today, it is generally agreed that in most instances the observed effects in microwave-assisted organic reactions are the result of purely (bulk) thermal phenomena.[4,5] Microwave chemistry relies on the ability of the reaction mixture to efficiently absorb microwave energy, taking advantage of microwave dielectric heating phenomena such as dipolar polarization and ionic conduction mechanisms.[6] This results in rapid internal heating (in-core volumetric heating) by the direct interaction of electromagnetic irradiation with the molecules in the reaction mixture.[6] The use of sealed-vessel microwave reactors therefore allows reaction mixtures to be heated very rapidly to temperatures far above the boiling point of the solvent under atmospheric conditions (300 °C/30 bar). Such temperature profiles may in some cases

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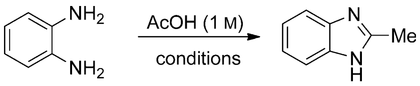
be difficult—if not impossible—to reproduce using standard methods of conductive heating.[4,5] The very rapid heating and sometimes extreme temperatures observed in microwave chemistry make it apparent that based on applying the Arrhenius relationship [$k = A\ \exp(-E_a/RT)$], transformations that require several hours when performed in a solvent at reflux temperature may reach completion in a few minutes, or even seconds, using superheated solvents in a sealed-vessel, autoclave-type, microwave reactor (see Scheme 1).[4,5,7] The higher reaction temperatures and more rapid heating typically experienced in microwave-assisted transformations may in some instances also lead to altered product distributions compared to those obtained with conventional heating at reflux in an oil bath, or even open up entirely new reaction pathways not seen at lower temperatures.[4,5,8] Such purely thermal phenomena can also explain why in many cases microwave-assisted reactions performed at an optimized reaction temperature have been found to be cleaner, leading to less byproducts than the conventionally heated processes carried out at the (often suboptimal) reflux temperature of the solvent.[4,5]



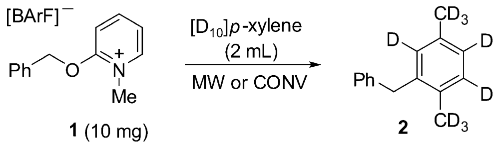
conditions (T/p)		t
CONV	25 °C / -	9 weeks
CONV	60 °C / -	3 d
CONV	100 °C / -	5 h
MW	130 °C / 2 bar	1 h
MW	160 °C / 4 bar	10 min
MW	200 °C / 9 bar	3 min
MW	270 °C / 29 bar	1 s

Scheme 1. Thermal microwave effects in the synthesis of 2-methylbenzimidazole. The condensation reaction can be accelerated, in agreement with the Arrhenius relationship ($A = 3.1 \times 10^8$, $E_a = 73.43\ \mathrm{kJ\,mol^{-1}}$), from a reaction time of 9 weeks at room temperature, to 5 h at reflux conditions (CONV, ca. 100 °C), to 1 s in a sealed-vessel microwave reactor at 270 °C (Ref. [7]).

In contrast to these undisputed thermal microwave effects, specific or nonthermal microwave effects are more difficult to rationalize (see above), and their existence/nonexistence is the subject of constant debate in the scientific community. These effects have sometimes been identified in the context of using rather unusual processing conditions involving, for example, open-vessel microwave chemistry, or a technique referred to as simultaneous cooling, where the reaction vessel is concurrently cooled from the outside while being irradiated with microwaves.[9,10] However, in many cases where specific/nonthermal microwave effects have been claimed, a subsequent careful reinvestigation has revealed that experimental artifacts mainly connected to erroneous temperature measurements and agitation/stirring of the reaction mixture were responsible for the originally observed phenomena.[10–15] Importantly, during the past few years it has been recognized that the general practice of using external IR temperature sensors in microwave reactors that record the outer surface temperature of the reaction vessel—not the internal reaction temperature—is highly problematic when reliable on-line temperature data are required, as in kinetic experiments connected to the investigation of microwave effects.[10–12,14–16] Internal, fast-responding fiber-optic (FO) temperature probes are far better suited to accurately monitor the actual reaction temperature during the microwave irradiation process, in particular for strongly microwave-absorbing and/or viscous reaction mixtures.[16] One of the main problems in investigating microwave effects therefore clearly is connected to the fact that it is rather difficult to perform appropriate control experiments comparing microwave with conventionally heated processes using oil baths or autoclave devices, since in order to be scientifically meaningful, both sets of experiments must be conducted at the exact same temperature, including a careful adjustment of heating and cooling profiles.[10–12] Other parameters such as vessel geometry, stirring speed, and the method of temperature monitoring must also be closely matched in order to ensure scientifically valid results.[10–12] In this context, the use of a reaction vial made out of strongly microwave-absorbing silicon carbide has proven extremely valuable in investigating the existence/nonexistence of specific/nonthermal microwave effects in the past few years. Evaluating a wide variety of chemical transformations,[7,13] not limited to organic synthesis,[17] we have not been able to substantiate the existence of a specific/nonthermal microwave effect for any of the investigated chemical transformations, not even for those cases where such effects have previously been described or would be expected.

Based on our experience in studying microwave effects during the past decade,[10–13,17,18] we were rather confident that nonthermal microwave effects in organic chemistry do not exist. In our hands, when reinvestigated using proper control of the process parameters (in particular temperature and stirring efficiency), all previously reported nonthermal microwave effects turned out to be purely thermal in nature, and ultimately the consequence of erroneous temperature measurement. For specific microwave effects, the situation is not as clear-cut, although also in this case we have been largely unsuccessful in demonstrating any genuine and synthetically relevant effects,[19] for example as a result of selective catalyst heating phenomena,[11c,12] or the elimination of wall effects.[11d,13] Although a number of recent studies have cast significant doubt on the existence of nonthermal and some types of specific microwave effects, surprisingly, such microwave effects are still being reported on a regular basis. Herein, we describe a detailed reinvestigation of two recently published cases of microwave effects that are allegedly not connected to a purely bulk temperature phenomenon (i.e., a thermal microwave effect). In both instances it has been claimed that microwave irradiation leads to significant enhancements in reaction rate or product yields that cannot be duplicated by conventional conductive heating at the same temperature. By presenting the results of our studies in this Essay, we endeavor to highlight frequently made experimental errors and pitfalls when microwave-heated chemical transformations are performed, and identify some of the misconceptions related to this nonclassical heating technology.

In a recent article published in *Chemical Science,* Dudley and co-workers reported the thermal Friedel–Crafts benzylation of [D_{10}]*p*-xylene using the 2-benzyloxy-1-methylpyridinium salt **1** as a precursor (Scheme 2).[20] At elevated temperatures, **1** undergoes rate-determining unimolecular thermolysis to generate a benzyl cation, which subsequently reacts with the arene in an electrophilic aromatic substitution. This completely homogeneous reaction was carried out in an excess of [D_{10}]*p*-xylene, employing either oil-bath or microwave heating under a variety of different conditions.[20] Remarkably, the authors found that when the Friedel–Crafts benzylation shown in Scheme 2 was performed at the same apparent reaction temperatures (in the range of 80–100 °C), conversions under microwave conditions were significantly higher than those in the oil-bath experiments. For example, at 80 °C after a reaction time of 250 min a conversion of roughly 25 % was achieved with conventional heating, whereas the microwave experiment had already progressed to about 90 % completion.[20] Similarly, after 30 min at 100 °C the corresponding conversions were approximately 25 % (oil bath) and 90 % (microwave), respectively.[20] For the "100 °C" experiments the actual reaction temperature recorded for the microwave experiments was not even 100 °C as the microwave power of the reactor (200 or 300 W) was not sufficient to heat the reaction mixture to the desired temperature.



Scheme 2. Friedel–Crafts benzylation of [D_{10}]*p*-xylene using **1** as precursor. $BArF^-$ = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate.

The central hypothesis of the authors in explaining these unusual findings relates to the fact that the ionic substrate in this reaction (i.e., **1**) is highly polar in nature whereas the solvent (the only other component in the reaction mixture) is completely microwave transparent. Employing microwave-transparent quartz reaction vials,[21] the authors suggest that under these conditions the reaction shown in Scheme 2 can be "microwave-actuated", in other words, specifically influenced by microwave irradiation in ways that cannot be duplicated by conventional heating.[20] Although the publication does not provide a definite scientific rationale for the observed phenomenon, it is suggested that the pre-exponential factor A in the Arrhenius equation may be influenced by "incident microwave irradiation", increasing the molecular collisions of the polar substrate **1**, thereby leading to enhanced reactivity.[20] The proposed effect perhaps can best be classified as a specific microwave effect involving selective heating of a strongly microwave-absorbing species in a homogeneous reaction mixture ("molecular radiators").[2,3]

A key argument made by Dudley and co-workers to rationalize the obtained data is that the microwave power itself is of crucial importance for the progress of the reaction. The authors therefore performed an additional series of experiments in which the benzylation reaction was carried out under reflux conditions in a round-bottomed flask employing both types of heating modes (toluene was used instead of [D_{10}]*p*-xylene in this experiment). This procedure, in principle, has two major advantages:

1) The reaction can be performed with a constant level of microwave power instead of in temperature-control mode where the magnetron output power is typically reduced once the desired temperature has been reached. If microwave power (i.e., the electric field strength) is indeed an important factor, this will be noticeable in the progress of the reaction.
2) The reaction temperature will be much easier to control, as the boiling point of the reaction mixture is a physical constant and should be the same regardless of whether microwave or conventional heating is applied. In fact, benzylation in refluxing toluene at 110–111 °C using 300 W constant microwave power led to higher conversion than that achieved in the oil-bath experiment at the same apparent reaction temperature (67 % versus 36 % after 30 min; 86 % versus 68 % after 60 min).[20]

The results described in the Dudley paper are indeed remarkable and at first sight strongly suggest the occurrence of a genuine specific or nonthermal microwave effect (as heralded in a subsequent news feature in *Chemistry World*).[22] We were therefore interested in repeating the experiments reported by Dudley and co-workers to provide an independent verification of these claims. In their work, the authors took great care to ensure similar reaction conditions in the microwave experiments and the oil-bath runs. The exact same reaction volumes and reaction vessels were employed for both sets of experiments and efficient agitation was ensured by magnetic stirring. However, despite the significant body of evidence pointing to the importance of monitoring the internal reaction temperature by using fiber-optic probes (see above), the authors instead relied on external calibrated IR sensor technology to estimate the actual reaction temperatures during their microwave experiments. Although the authors—correctly—point out that in this particular instance with a low-viscosity, fully homogenous reaction mixture, FO technology is not necessary, we note that our experience in studying microwave effects over the past decade strongly indicates that only internal FO temperature-sensing technology can provide accurate information on genuine reaction temperatures during microwave-assisted reactions.

We have repeated the key experiments described by Dudley and co-workers, duplicating the reaction conditions and experimental setups reported in the original reference.[23] The only difference is that in our experiments the reaction temperature in both the microwave and oil-bath runs was carefully monitored by accurate and fast responding internal FO probes. As can be seen from the data shown in Figure 1, we obtained exactly the same conversions for the benzylations using microwave and oil-bath heating at both 80 °C and 100 °C using [D_{10}]*p*-xylene as the solvent.[23] Since our data sets more closely correspond to the conversions reported by Dudley and co-workers for their oil-bath experiments, we

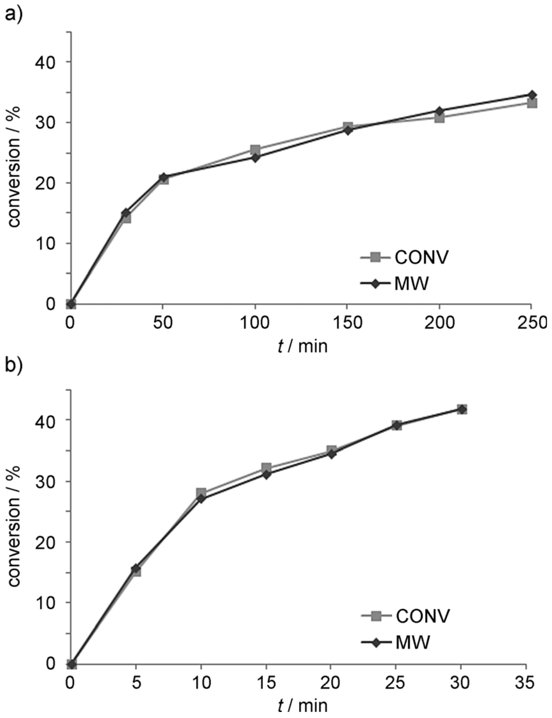
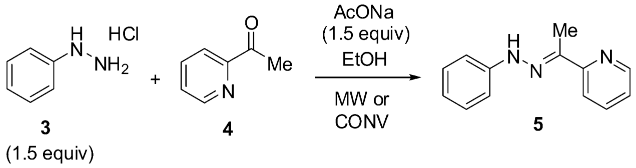


Figure 1. Conversion of **1** to **2** in [D_{10}]*p*-xylene (Scheme 2) at 80 °C (a) and 100 °C (b) using conventional heating in a preheated oil bath (CONV) or microwave heating (MW) in a single-mode reactor (CEM Discover). Conversions were determined by ^{1}H NMR spectroscopy by taking aliquots at specific time intervals as described in Ref. [20]. The reaction temperature for both oil-bath and microwave experiments was adjusted using internal fiber-optic temperature probes. For the 100 °C experiments, the average values from three experiments are given (standard deviations are presented in the Supporting Information).

assume that the actual reaction temperatures in their microwave runs must have been significantly higher than the values recorded using external IR sensor technology.[24] This hypothesis is also supported by the fact that the applied average microwave power in the Dudley experiments is considerably higher than the values in our experiments, even though the same type of microwave reactor was used.[24]

In addition, we have also repeated the originally reported benzylation experiment using reflux conditions with toluene as a solvent and with 300 W of constant magnetron output power (see above).[20] Again, in our hands, the conversions after 15 min (23 %), 30 min (43 %), and 60 min (67 %) were more or less identical to those achieved using conventional heating in a preheated oil bath (21 %, 41 %, and 67 %, respectively).[23] Again, the use of internal FO temperature sensors was critical in order to ensure similar temperature regimes in the oil-bath and microwave reflux experiments.[24] Key to achieving comparable conditions in the two types of experiments was the use of boiling chips that prevent superheating under microwave conditions.[23] Having repeated both the temperature control and constant microwave power experiments we are convinced that the discrepancies in conversions between oil-bath and microwave heating reported by Dudley et al. are associated with erroneous temperature measurements during the microwave-irradiated reactions.[24] Clearly, in our hands no evidence for any type of specific or nonthermal microwave effects could be obtained.

The second example involves a publication by La Regina and co-workers in *ACS Combinatorial Science* in 2011 describing the preparation of a variety of pyridinyl *N*-arylhydrazones by classical hydrazone synthesis using microwave technology.[25] The optimization of reaction conditions and main discussion on the possible role of microwave irradiation were performed employing phenylhydrazine hydrochloride (**3**) and 2-acetylpyridine (**4**) as the model reaction using ethanol as the solvent and and sodium acetate as the base (Scheme 3). Initial trials with sealed vessels employing standard microwave irradiation in a temperature range of 80–130 °C for 3–5 min led to very low product yields (3–15 %). When the exact same reaction was performed under open-vessel reflux conditions (ca. 80 °C) for 5 min a product yield of 50 % was obtained. This yield could be further increased to 98 % by simultaneously cooling the reaction mixture with compressed air under otherwise identical reaction conditions.[25] The authors ascribe this remarkable effect of simultaneous cooling[9] to the prevention of "microwave overheating" by continuous removal of latent heat from the reaction mixture, thereby avoiding the alleged decomposition of starting materials and/or reaction products.[25] If verified, the results presented in this study would clearly indicate some sort of not purely thermal microwave effect, with the bulk reaction temperature (always 80 °C) only playing a minor role. Notably, all microwave experiments were performed using external IR temperature sensors.



Scheme 3. Formation of hydrazone **5** from phenylhydrazine **3** and ketone **4**.

In repeating the transformation shown in Scheme 3 using the exact same reaction stoichiometry and reagent concentrations as given in the original report, we noticed that hydrazine hydrochloride **3** reacts essentially spontaneously with ketone **4** at room temperature.[23] Stirring the reaction mixture for 5 min at room temperature provided hydrazone **5**, which precipitated in analytical purity, in 85 % yield. Apparently, there is no need to heat this reaction. Nonetheless, we additionally performed a variety of different heating experiments (40–130 °C) using either oil-bath or microwave heating in closed or open vessels applying proper internal FO temperature-sensing technology.[23] In essence, the results were always identical: the desired hydrazone **5** was obtained in roughly 85 % yield within 5 min. We were not able to detect any decomposition of the hydrazone product at elevated temperature. It is therefore apparent that there is no special microwave effect of any kind involved in this chemistry, and that the use of open-vessel microwave processing or applying simultaneous cooling does not lead to any apparent advantages.[24]

From these experiments, in particular those reported by Dudley et al., it is quite apparent that the use of internal FO temperature probes in microwave chemistry is absolutely essential when accurate reaction temperatures are required. External IR temperature sensors are simply too unreliable for a variety of reasons.[24] In particular, when the simultaneous cooling technique is applied (as in the La Regina example),[9] external IR sensors should not be used under any circumstances, since the IR sensor may record a significantly lower temperature (reflecting the vessel's surface temperature) than the actual temperature of the reaction mixture inside the reaction vessel.[10–12] Arguably, an optimum representation of the genuine reaction temperature in a microwave-heated reaction can be obtained by a system that *simultaneously* records both external (calibrated) IR and internal FO temperatures.[16] The key advantage of performing a microwave heating experiment with dual IR/FO temperature measurement is that the temperature is recorded concurrently at two different positions of the reaction vessel. Any significant deviation between the two temperature values will point to the occurrence of temperature gradients in the reaction mixture, and therefore to mass- and/or heat-transfer problems.[16]

Another general factor of critical importance in this context is stirring. Microwave dielectric heating in single-mode reactors invariably results in regions of high and low field intensity,[26] which in turn will lead to hot and cold spots in the heated medium.[11] If sufficient mass transfer (e.g. stirring/agitation) cannot be ensured, temperature gradients may result, leading to the observed differences in the recorded FO and IR temperatures. A very valuable tool in this context can be a built-in camera that allows direct observation of stirring efficiency[27] and of other important events occurring in the reaction mixture (i.e., arcing phenomena).[19]

In their publications, the Dudley and La Regina groups describe open-vessel microwave experiments in solvents at reflux.[20,25] One may argue that this in some way defeats the purpose of working under microwave conditions: it is not possible to superheat the solvent above its boiling point (cf. Scheme 1), since the maximum reaction temperature that can be attained under these conditions will be—in principle, not taking superheating at atmospheric conditions into account—limited to the boiling point of the solvent. Clearly, the use of an open-vessel setup would only make sense if one suspects the occurrence of specific or nonthermal microwave effects, where bulk temperature is not critical, but microwave power and thus electromagnetic field strength are. Indeed, the arguments for the use of this setup in both the Dudley and La Regina papers are in both cases mainly connected to the fact that more microwave power can be administered to the reaction mixture. In both cases this hypothesis ultimately proved to be unfounded. If one accepts that nonthermal microwave effects do not exist and specific microwave effects are relatively rare, then to operate a microwave reactor under reflux conditions at the boiling point of the reaction mixture does not appear to be a particularly useful method, since the results obtained under these conditions can typically be duplicated easily by conventional conductive heating using heating mantles or oil baths. The same arguments have to be made about the simultaneous cooling technique, which in principle also allows microwave chemistry experiments to be performed at increased power levels.[9] In the absence of a specific/nonthermal microwave effect the application of this technique will not alter the chemistry in any way.

Our general experience in the field of microwave-assisted organic chemistry is therefore that ultimately, in the overwhelming majority of examples, it is only the bulk reaction temperature that governs the outcome of a chemical transformation under microwave conditions. The applied microwave power and thus the electric field strength have little or no direct influence on chemical reactivity, apart from controlling the heating rate of the process.[10–13,17,18,28] In other words, the effects reported for most microwave-irradiated chemical transformations can be rationalized by purely thermal/kinetic phenomena, and thus ultimately fall into the category of thermal microwave effects.[29] Specific microwave effects related to selective heating phenomena can sometimes be observed for very carefully selected examples, but are a relatively rare occurrence and perhaps of little practical relevance to synthetic organic chemistry.[3,19] Importantly, we firmly believe that the existence of genuine nonthermal microwave effects is a myth, as all our attempts to verify these often claimed "magical" microwave effects during the past decade have failed.[10–13,17,18] Similar to the two case studies presented herein essentially proposing some sort of a specific microwave effect, when carefully conducted control experiments were performed—paying meticulous attention to all relevant process parameters—the proposed effects vanished.

Why are nonthermal and specific microwave effects still being reported in the literature ? In our opinion, most of today's commercially available laboratory microwave reactors are not very well suited to study microwave effects.[30] These instruments were essentially designed to "rapidly generate compounds", not to perform accurate kinetic investigations. Therefore, in most instances, these microwave reactors are not equipped with the temperature-sensing technology and software algorithms that are needed to accurately control and monitor reaction temperature during a microwave chemistry experiment (taking all eventualities such as viscosity increases, exothermic behavior, and changes in the microwave absorptivity of the reaction mixture into account). As highlighted above, the reliable monitoring of reaction temperature is nontrivial but absolutely critical to the investigation of microwave effects. In addition, most chemists have only a limited understanding of the underlying physical principles behind electromagnetic wave–material interactions,[31] and are also not familiar with the way in which scientific microwave reactors operate.[26] In our opinion, it is mainly the combination of these three factors that have led to the confusion and speculation on the existence of microwave effects in the chemical literature, and to a situation where the literature now is full of erroneous reports that cannot be independently verified.

It is perhaps worth mentioning that the debate on microwave effects in organic chemistry is not new, and was already the subject of debate in *Angewandte Chemie* ten years ago.[32] Even at that time, the existence of nonthermal microwave effects was essentially refuted. From our perspective, after more than a decade of intense research in this area, we must now conclude that nonthermal microwave effects simply do not exist. Undoubtedly, there will be many more claims to the existence of these effects in organic chemistry (and in other fields) in the future. Unless those claims are independently verified, we would caution the scientific community against taking the existence of those effects for granted. We sincerely hope that this Essay will help the scientific community to accept the fact that microwave chemistry is not "voodoo science",[33] but in essence an incredibly effective, safe, rapid, and highly reproducible way to perform an autoclave experiment under strictly controlled processing conditions.[34,35]

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[34] In this context, we believe that a general change in terminology would also appear appropriate. The use of expressions like "microwave-accelerated" and "microwave-induced" for chemical transformations performed in a microwave reactor imply that it is the microwaves themselves, i.e., the electromagnetic field, that accelerates or induces the chemical reaction. This is clearly misleading if one assumes that any reaction enhancement is due to a thermal microwave effect. We therefore favor the use of the well-accepted expression "microwave-assisted", although in reality probably "microwave-heated" would be most appropriate. Similarly, statements often found in the literature along the lines of "microwave versus thermal conditions" should be avoided as they will cause confusion.

[35] Another myth that exists in the scientific community is that microwave heating is energy efficient and therefore "green". This is typically not the case, in particular not for small-scale laboratory reactors. For a critical discussion, see: J. D. Moseley, C. O. Kappe, *Green Chem.* **2011**, *13*, 794.