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Nonthermal Microwave Effects Revisited: On the Importance of Internal Temperature Monitoring and Agitation in Microwave Chemistry

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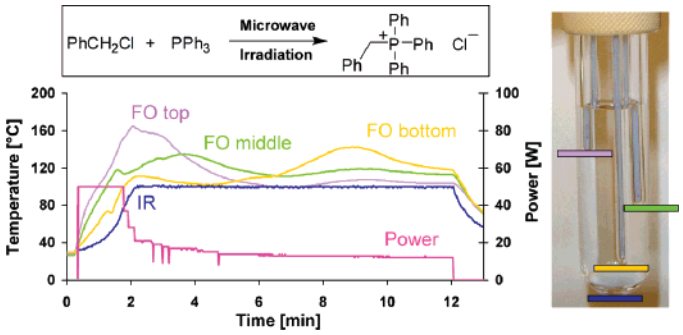

The concept of nonthermal microwave effects has received considerable attention in recent years and is the subject of intense debate in the scientific community. Nonthermal microwave effects have been postulated to result from a direct stabilizing interaction of the electric field with specific (polar) molecules in the reaction medium that is not related to a macroscopic temperature effect. In order to probe the existence of nonthermal microwave effects, four synthetic transformations (Diels−Alder cycloaddition, alkylation of triphenylphosphine and 1,2,4-triazole, direct amide bond formation) were reevaluated under both microwave dielectric heating and conventional thermal heating. In all four cases, previous studies have claimed the existence of nonthermal microwave effects in these reactions. Experimentally, significant differences in conversion and/or product distribution comparing the conventionally and microwave-heated experiments performed at the same measured reaction temperature were found. The current reevaluation of these reactions was performed in a dedicated reactor setup that allowed accurate internal reaction temperature measurements using a multiple fiber-optic probe system. Using this technology, the importance of efficient stirring and internal temperature measurement in microwave-heated reactions was made evident. Inefficient agitation leads to temperature gradients within the reaction mixture due to field inhomogeneities in the microwave cavity. Using external infrared temperature sensors in some cases results in significant inaccuracies in the temperature measurement. Applying the fiber-optic probe temperature monitoring device, a critical reevaluation of all four reactions has provided no evidence for the existence of nonthermal microwave effects. Ensuring efficient agitation of the reaction mixture via magnetic stirring, no significant differences in terms of conversion and selectivity between experiments performed under microwave or oil bath conditions at the same internally measured reaction temperatures were experienced. The observed effects were purely thermal and not related to the microwave field.

Introduction

Since the first published reports on the use of microwave irradiation to accelerate organic chemical transformations by the groups of Gedye and Giguere/Majetich in 1986,[1] more than 3500 articles have been published in this fast-moving and

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(1) (a) Gedye, R.; Smith, F.; Westaway, K.; Ali, H.; Baldisera, L.; Laberge, L.; Rousell, R. *Tetrahedron Lett*. **1986**, *27*, 279. (b) Giguere, R. J.; Bray, T. L.; Duncan, S. M.; Majetich, G. *Tetrahedron Lett*. **1986**, *27*, 4945.

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exciting field, today generally referred to as microwave-assisted organic synthesis (MAOS).[2,3] In many of the published examples, microwave heating has been shown to dramatically reduce reaction times, increase product yields, and enhance product purities by reducing unwanted side reactions compared to conventional heating methods. The advantages of this enabling technology have more recently also been exploited in the context of multistep total synthesis[4] and medicinal chemistry/drug discovery[5] and have additionally penetrated fields such as polymer synthesis,[6] material sciences,[7] nanotechnology,[8] and biochemical processes.[9] The use of microwave irradiation in chemistry has thus become such a popular technique in the scientific community that it might be assumed that, in a few years, most chemists will probably use microwave energy to heat chemical reactions on a laboratory scale.[10]

Regardless of the relatively large body of published work in this area,[1−10] the exact reasons why microwave irradiation is able to enhance chemical processes are still unknown. Since the early days of microwave synthesis, the observed rate-accelerations and sometimes altered product distributions compared to conventionally heated experiments have led to speculation on the existence of so-called "specific-" or "nonthermal" microwave effects.[11,12] Such effects have been claimed when the outcome of a synthesis performed under microwave conditions was different from the conventionally heated counterpart at the same measured reaction temperature.[12] Today, it is generally agreed upon that in many cases the observed enhancements in microwave-heated reactions are in fact the result of purely thermal/kinetic effects, in other words, are a consequence of the high reaction temperatures that can rapidly be attained when irradiating polar materials/reaction mixtures under closed vessel conditions in a microwave field.[11,12] Similarly, the existence of so-called "specific microwave effects" which cannot be duplicated by conventional heating and result from the uniqueness of the microwave dielectric heating phenomenon is largely undisputed.[11−13] In this category fall, for example, (i) the superheating effect of solvents at atmospheric pressure, (ii) the selective heating of, e.g., strongly microwave absorbing heterogeneous catalysts or reagents in a less polar reaction medium, and (iii) the elimination of wall effects caused by inverted temperature gradients.[13]

In contrast, the subject of "nonthermal microwave effects" (also referred to as athermal effects)[11] is highly controversial and has led to heated debates in the scientific community.[12,14] Essentially, nonthermal effects have been postulated to result from a proposed direct interaction of the electric field with specific molecules in the reaction medium that is not related to a macroscopic temperature effect. It has been argued, for example, that the presence of an electric field leads to orientation effects 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.[12] Furthermore, a similar effect has been proposed for polar reaction mechanisms, where the polarity is increased going from the ground state to the transition state, resulting in an enhancement of reactivity by lowering of the activation energy.[12] Significant nonthermal microwave effects have been suggested for a wide variety of synthetic transformations.[12]

It should be obvious from a scientific standpoint that the question of nonthermal microwave effects needs to be addressed in a serious manner, given the rapid increase in the use of microwave technology in chemical sciences, in particular organic synthesis. There is an urgent need to provide a scientific rationalization for the observed effects and to investigate the general influence of the electric field (and therefore of the microwave power) on chemical transformations. This is even more important if one considers engineering and safety aspects once this technology moves from the small-scale laboratory work to pilot or production scale instrumentation.[10]

(2) (a) *Microwaves in Organic Synthesis*; Loupy, A., Ed.; Wiley-VCH: Weinheim, Germany, 2002. (b) Hayes, B. L. *Microwave Synthesis: Chemistry at the Speed of Light*; CEM Publishing: Matthews, NC, 2002. (c) *Microwave-Assisted Organic Synthesis*; Lidström, P., Tierney, J. P., Eds.; Blackwell Publishing: Oxford, U.K., 2005. (d) Kappe, C. O.; Stadler, A. *Microwaves in Organic and Medicinal Chemistry*; Wiley-VCH: Weinheim, Germany, 2005. (e) *Microwaves in Organic Synthesis*, 2nd ed.; Loupy, A., Ed.; Wiley-VCH: Weinheim, Germany, 2006. (f) *Microwave Methods in Organic Synthesis*; Larhed, M., Olofsson, K., Eds.; Springer: Berlin, Germany, 2006. (g) *Microwave-Assisted Synthesis of Heterocycles*; Van der Eycken, E., Kappe, C. O., Eds.; Springer, Berlin, Germany, 2006.

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(10) For reviews on large scale microwave synthesis, see: (a) Kremsner, J. M.; Stadler, A.; Kappe, C. O. *Top. Curr. Chem.* **2006**, *266*, 233. (b) Glasnov, T. N.; Kappe, C. O. *Macromol. Rapid Commun.* **2007**, *28*, 395. (c) Ondruschka, B.; Bonrath, W.; Stuerga, D. In *Microwaves in Organic Synthesis*, 2nd ed.; Loupy, A., Ed.; Wiley-VCH: Weinheim, Germany, 2006; Chapter 2, p 62.

(11) For a more detailed definition and examples for thermal, specific, and nonthermal microwave effects, see: Kappe, C. O.; Stadler, A. *Microwaves in Organic and Medicinal Chemistry*; Wiley-VCH, Weinheim, 2005; Chapter 2, pp 9−28. See also refs 3a and 12.

(12) For leading reviews in the field, see: (a) Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199. (b) Perreux, L.; Loupy, A. In *Microwaves in Organic Synthesis*; Loupy, A., Ed.; Wiley-VCH: Weinheim, Germany, 2002; Chapter 3, pp 61−114. (c) Perreux, L.; Loupy, A. In *Microwaves in Organic Synthesis*, 2nd ed.; Loupy, A., Ed.; Wiley-VCH: Weinheim, Germany, 2006; Chapter 4, pp 134−218. (d) De La Hoz, A.; Diaz-Ortiz, A.; Moreno, A. *Chem. Soc. Rev.* **2005**, *34*, 164. (e) De La Hoz, A.; Diaz-Ortiz, A.; Moreno, A. In *Microwaves in Organic Synthesis*, 2nd ed.; Loupy, A., Ed.; Wiley-VCH: Weinheim, Germany, 2006; Chapter 5, pp 219−277.

(13) It should be emphasized that specific microwave effects 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 experimentally determine the exact reaction temperature in these cases, for example, on the surface of a strongly microwave-absorbing catalyst that is selectively superheated by microwave irradiation. For examples, see refs 11 and 12.

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In continuation of our general interest in microwave effects,[15−17] we herein describe a detailed reevaluation of nonthermal microwave effects and the influence of the microwave field on chemical reactions. For this purpose, we have selected four representative chemical transformations that were previously reported to exhibit significant nonthermal microwave effects (see below). In all four cases, carefully conducted control experiments using conventional heating at the same reaction temperature as monitored during the microwave experiments had previously shown large differences not only in yield/conversion but also in product selectivity. For all examples, the differing results between conventional and microwave heating were rationalized by nonthermal microwave effects and in each case a direct intervention of the electric field in the reaction pathway was suggested. In order to reach a general conclusion on the existence of nonthermal microwave effects, we have reinvestigated these high-profile cases using a specialized fiber-optic temperature probe that allows simultaneous temperature detection at different positions of the reaction mixture.

Results and Discussion

Microwave versus Conventional Heating and Temperature Measurement. In order to accurately compare the results obtained by direct microwave heating with the outcome of a conventionally heated reaction, we have recently described a reactor system that allows us to perform both types of transformations *in the same reaction vessel* and to monitor the internal reaction temperature in both experiments directly with a fiber-optic probe device.[17] Monitoring reaction temperatures in microwave-assisted reactions by conventional infrared sensors on the outside vessel wall is not an acceptable technique if an accurate temperature profile for comparison studies needs to be obtained.[16−18] Our original system utilized a CEM Discover single-mode microwave reactor equipped with a fiber-optic probe provided by the instrument manufacturer for directly monitoring the internal reaction temperature in a 10 mL sealed reaction vessel.[17] This setup can be either immersed into the cavity of the microwave reactor or into a preheated and temperature-equilibrated oil or metal bath placed on a magnetic stirrer/hotplate. In both cases, the software of the microwave instrument is recording the internal temperature. This system has the advantage that the same reaction vessel and the same method of temperature measurement is used. In this way, all parameters apart from the mode of heating are identical, and therefore, a fair comparison between microwave heating and thermal heating can generally be made.[19]

For the high accuracy required for the current study, we have made two significant changes to the measurement system described above. During our recent work employing fiber-optic temperature probes,[16,17] we noticed that the response time of the fiber-optic sensor can be quite long depending both on the type of fiber-optic device used and on the protective shielding employed with the probe. For the standard probe/shielding used in conjunction with the CEM Discover, we have experienced response times up to 13 s before the correct temperature was displayed by the sensor (Figure S1 in the Supporting Information). In some instances, for example, for very fast reactions[20] or for polar reaction media that are very rapidly heated by microwave irradiation (see below), this delay time may lead to an incorrect determination of the actual reaction temperature in the initial phase of the experiment. For the current studies, we have therefore employed an independent fiber-optic probe that minimizes the response time to less than 7 s when using an appropriate shielding device. In exceptional cases, this sensor can also be used without protective shielding providing a correct temperature measurement within less than 1 second (see Figure S1 in the Supporting Information).

Even more important, our previous experience in this field has revealed that the location of the fiber-optic sensor in the microwave-heated reaction vessel is of great importance. For example, we have found that differences of 15−40 °C in the measured temperature can be experienced heating microwave absorbing solvents in standard microwave process vials utilizing a single-mode microwave reactor, depending if the temperature probe is placed close to the bottom or in the middle of the vial.[21] In order to monitor these effects more accurately we have now devised a multiple fiber-optic probe measurement device that can be attached to a standard 10 mL microwave vial allowing simultaneous temperature measurement at up to three different positions inside the reaction vial (Figure 1b).

Using this system, surprisingly large temperature gradients on heating pure organic solvents inside a common single-mode microwave reactor with constant microwave power were revealed. For example, using a sample of 5 mL of NMP as solvent, the temperature difference between the bottom and the middle of the vessel was 30 °C (Figure 1a). These internal temperature gradients could also be detected on the outside surface of the vessel by an IR camera after removing the vessel from the microwave cavity (Figure S2, Supporting Information). Gratifyingly, in the case of NMP these gradients could be minimized (deviation <6 °C) by efficient magnetic stirring of the reaction mixture (Figure S4, Supporting Information). While stirring using the built-in magnetic stirring system is easily possible for a pure solvent, this may not be the case for a heterogeneous or viscous reaction mixture or in case where the reaction is performed under solvent-free or dry-media conditions. In order to verify this point, a similar experiment was performed by heating a sample of Montmorillonite K10 Clay (a commonly used inorganic solid support material for dry-media microwave chemistry)[22] using the same experimental setup. In this case, the temperature gradients could not be eliminated by magnetic

(15) (a) Stadler, A.; Kappe, C. O. *J. Chem. Soc., Perkin Trans. 2* **2000**, 1363. (b) Stadler, A.; Kappe, C. O. *Eur. J. Org. Chem.* **2001**, 919. (c) Strohmeier, G. A.; Kappe, C. O. *J. Comb. Chem.* **2002**, *4*, 154. (d) Garbacia, S.; Desai, B.; Lavastre, O.; Kappe, C. O. *J. Org. Chem.* **2003**, *68*, 9136.

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(19) For related publications using this technique, see: (a) Hostyn, S.; Maes, B. U. W.; Van Baelen, G.; Gulevskaya, A.; Meyers, C.; Smits, K. *Tetrahedron* **2006**, *62*, 4676. (b) Vanier, G. S. *Synlett* **2007**, 131.

(20) For very rapid microwave-assisted reactions in the order of seconds, see: (a) Enquist, P.-A.; Nilsson, P.; Larhed, M. *Org. Lett.* **2003**, *5*, 4875. (b) Leadbeater, N. E.; Smith, R. J. *Org. Lett.* **2006**, *8*, 4589. (c) Leadbeater, N. E.; Smith, R. J.; Barnard, T. M. *Org. Biomol. Chem.* **2007**, *5*, 822. (d) Leadbeater, N. E.; Smith, R. J. *Org. Biomol. Chem.* **2007**, *5*, 2770.

(21) For a theoretical prediction of this effect and modeling of the field distribution in a single-mode cavity, see: (a) Berlan, J. *Rad. Phys. Chem.* **1995**, *45*, 581. (b) Saillard, R.; Poux, M.; Berlan, J.; Audhuy-Peaudecerf, M. *Tetrahedron* **1995**, *51*, 4033. For a previous observation of this phenomenon using a prototype single-mode cavity, see: (c) Kaiser, N.-F. K. Ph.D. thesis, Uppsala University, 2001, p 37.

(22) (a) Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P.; Mathé, D. *Synthesis* **1998**, 1213. (b) Varma, R. S. *Green Chem.* **1999**, 43. (c) Kidawi, M. *Pure Appl. Chem.* **2001**, *73*, 147. (d) Varma, R. S. *Pure Appl. Chem.* **2001**, *73*, 193. (e) Varma, R. S. *Tetrahedron* **2002**, *58*, 1235.

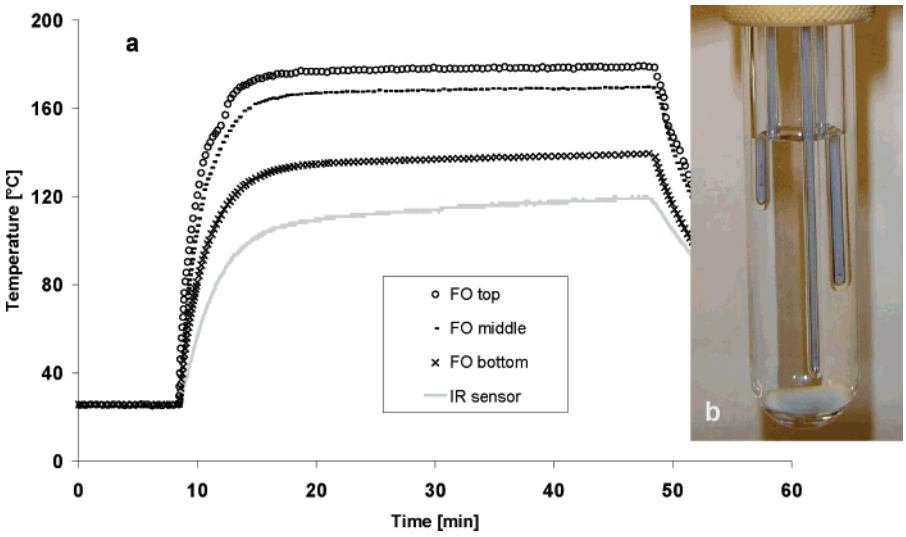


FIGURE 1. (a) Temperature profiles for a sample of 5 mL of NMP contained in a 10 mL quartz vessel equipped with three internal fiber-optic sensors. The sample was irradiated with constant 50 W magnetron output power without stirring for 40 min (CEM Discover). Shown are the profiles for the three internal fiber-optic probes and for the external IR sensor located at the bottom of the instrument (see also Figure S3, Supporting Information). (b) Multiple fiber-optic temperature probe assembly (see the Experimental Section for more details).

stirring since the stirring proved to be inefficient (Figure S5, Supporting Information).[23] It should also be noted that in all cases the calibrated IR sensor shows a significant deviation even from the fiber-optic probe located in close proximity near the bottom of the vessel (see Figure 1b). This once again highlights the problem of using external IR sensors for temperature measurements in microwave-heated vessels.[16−18] The fast responding multiple fiber-optic probe system was also utilized to investigate the effect of simultaneous external cooling by compressed air on the internal temperatures.[24] Also in this case, the significant temperature gradients between the different positions in the vial persisted (Figure S6, Supporting Information). In contrast, a control experiment immersing the fiber-optic probe device shown in Figure 1b (5 mL of NMP) into a preheated oil bath confirmed that no gradients are observed on such as small scale using conventional heating by conduction/convection phenomena, regardless if the mixture was stirred or not (Figure S7, Supporting Information). These temperature monitoring studies demonstrate that microwave heating in high field density single-mode cavities is in fact not as homogeneous as often portrayed[3] and that extreme care must be taken in determining the proper reaction temperature in these experiments, especially in those cases where adequate mixing cannot be assured.[25]

Selection of Chemistry Examples. Having a reliable temperature monitoring system for microwave-assisted reactions in place, we next set out to carefully define a set of appropriate model reactions in order to reevaluate the existence of nonthermal microwave effects in organic synthesis. According to Perreux and Loupy,[12] nonthermal microwave effects are most likely to be observed for reactions that follow polar reaction pathways via polar transition states. It has been suggested that if the polarity of a system is increased from the ground state to the transition state, acceleration can be observed by an increase in the material-wave interactions during the course of the reaction (leading to a stabilization of the polar transition state by the electric field). The most frequently encountered examples involve reactions between neutral molecules where dipoles are developed in the transition state and/or in the product.[12] Second, to observe nonthermal microwave effects transformations should possess high energies of activation with late product-like transition states along the reaction coordinate in agreement with the Hammond postulate.[12]

Another important factor in connection with nonthermal microwave effects is the proper choice of the solvent. Microwave heating generally relies on the ability of the reaction mixture/solvent to efficiently absorb microwave energy, taking advantage of "microwave dielectric heating" phenomena such as dipolar polarization or ionic conduction mechanisms.[26] The ability of a specific material or solvent to convert microwave energy into heat at a given frequency and temperature is determined by the so-called loss tangent (tan δ), expressed as the quotient, tan $\delta = \epsilon''/\epsilon'$, where ϵ'' is the dielectric loss, indicative of the efficiency with which electromagnetic radiation is converted into heat, and ϵ' is the dielectric constant, describing the ability of molecules to be polarized by the electric field.[26] A reaction medium with a high tan δ at the standard operating frequency of a microwave synthesis reactor (2.45 GHz) is required for good absorption and, consequently, for efficient heating.[27] In the case of a high absorbing solvent, most of the

(23) For temperature gradients in the heating of solids under microwave conditions in multimode cavities, see: (a) Stuerga, D.; Gaillard, P. *Tetrahedron* **1996**, *52*, 5505. (b) Bogdal, D.; Bednarz, S.; Lukasiewicz, M. *Tetrahedron* **2006**, *62*, 9440.

(24) Related to the issue of nonthermal microwave effects is the concept that simultaneous external cooling of the reaction mixture (or maintaining subambient reaction temperatures) while heating by microwaves can in some cases lead to an enhancement of the overall process. Here, the reaction vessel is cooled from the outside by compressed air or with the aid of a cooling fluid while being irradiated by microwaves. This allows a higher level of microwave power to be directly administered to the reaction mixture thereby potentially enhancing nonthermal microwave effects that rely on the electric field strength. At the same time, overheating will be prevented by continuously removing heat. For recent examples using this technique, see ref 17 and references cited therein.

(25) For a recent qualitative description of problems resulting from agitation issues in microwave chemistry involving single-mode cavities, see: Moseley, J. D.; Lenden, P.; Thomson, A. D.; Gilday, J. P. *Tetrahedron Lett*. **2007**, *48*, 6084.

(26) (a) Gabriel, C.; Gabriel, S.; Grant, E. H.; Halstead, B. S.; Mingos, D. M. P. *Chem. Soc. Rev*. **1998**, *27*, 213. (b) Mingos, D. M. P.; Baghurst, D. R. *Chem. Soc. Rev*. **1991**, *20*, 1. See also refs 2 and 3.

microwave energy will in fact be absorbed by the solvent and converted into heat, thereby masking any potential nonthermal microwave effects as a result of material-wave interactions. Therefore, the use of nonpolar, low microwave-absorbing solvents or the use of solvent-free conditions has been suggested.[12]

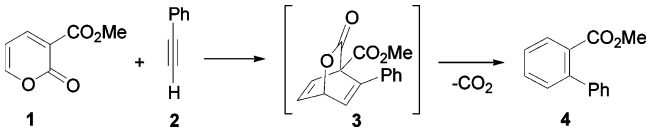
In order to select the most suitable and meaningful examples for our study, we have introduced a number of additional criteria. All chosen published chemistry examples have been conducted in dedicated single-mode microwave reactors utilizing open vessel procedures using temperature control by either built-in IR sensors or fiber-optic probes. The performed control experiments using conventional heating at the same temperature range led to a large difference between the microwave and the conventionally heated run. We have deliberately chosen examples where the reported differences were large in order to minimize the chance of experimental error. In addition, we have selected examples where not only the conversion was different in the microwave run, but in some cases also the product distribution. Because of the inherent difficulties experienced in the temperature measurement using solids under microwave irradiation conditions (see above), dry-media reactions were excluded from our studies. In contrast, we have—where appropriate—selected cases where the reaction mixtures were as homogeneous as possible, using either low-absorbing solvents or solvent-free conditions. This would ensure that the mixtures could be stirred, therefore avoiding potential problems with temperature gradients as described above. Based on all of these criteria, four representative examples for investigating nonthermal microwave effects were chosen. These are discussed in detail in the following sections.

Diels–Alder Cycloaddition of 5-Methoxycarbonyl-2-pyrone and Phenylacetylene. In a 2004 publication, the microwave-assisted cycloaddition of pyrone **1** with phenylacetylene (**2**) was reported.[28] The resulting aromatized product **4** was obtained as a single regioisomer by release of carbon dioxide from the primary cycloadduct **3** (Table 1). The experiment was conducted in an open vessel using the acetylene dienophile in slight excess (1.4 equiv) without added solvent using a dedicated single-mode microwave reactor at 150 °C (calibrated external IR sensor, mechanical stirring). After 3 h of microwave irradiation at 150 °C (temperature control mode), a 64% conversion to product **4** was obtained. Importantly, the exact same experiment when carried out in a preheated oil bath at the same temperature only showed 19% conversion.[28] This significant apparent "microwave effect" was rationalized by the authors taking into account theoretical calculations predicting a strong asynchronicity in the reaction mechanism with a large enhancement in the dipole moments from the ground states to the transition state.[28] Stabilization of polar transition states by the microwave field has been argued to reduce the required energy of activation and therefore to accelerate these transformations.[12]

We have repeated the cycloaddition described in Table 1 using the fiber-optic probe setup shown in Figure 1b to accurately monitor internal reaction temperatures. The same reaction conditions as reported previously were chosen with the exception that the reaction temperature was adjusted to ca. 140 °C instead of 150 °C, since the boiling point of phenylacetylene is 142–144 °C and in our hands experiments at 150 °C internal temperature were difficult to execute. The cycloadditions were performed on a 6.5 mmol scale in a 10 mL Pyrex microwave vial. Since the reaction mixture (ca 2.0 mL) in this particular case is a low viscosity liquid, magnetic stirring was very efficient and therefore only one fiber-optic probe needed to be employed. This allowed us to run the device under open vessel conditions since the formed carbon dioxide vented through the two unused fiber-optic probe inlet ports. For performing the microwave-irradiated experiment the device was introduced into the cavity of the Discover microwave reactor and irradiated at 140 °C for 4 h using the calibrated built-in IR temperature sensor as the lead sensor (temperature control, 80 W maximum magnetron output power). Simultaneously, the true internal reaction temperature was monitored using the fiber-optic probe. In this case, a very good agreement between the external IR and internal fiber-optic temperature sensor was obtained (139.5 vs 141.8 °C average temperature, see Figure S8, Supporting Information). In order to obtain a kinetic profile of the reaction, samples for ^{1}H NMR and HPLC analysis were withdrawn after 30, 60, 90, 150, and 240 min through the unused inlet ports.

For performing the conventionally heated control experiment, the reaction and sample withdrawal regime was repeated, but this time the assembly (Figure 1b) was immersed into a preheated oil bath (140 °C). All other parameters such as reaction scale, stirring speed, and the reaction vessel were kept the same. As shown in Figure S9 (Supporting Information), the internally measured reaction temperatures in the oil-bath and the microwave experiment were nearly identical (141.0 vs 141.8 °C). Based on the previously published data for this reaction (see above), we were surprised to see that in our hands the results in terms of conversion were—within experimental error—nearly identical (Table 1, entries 1–5). No evidence for

TABLE 1. Comparison of Microwave Heating and Conventional Heating for the Diels–Alder Reaction of Pyrone 1 and Phenylacetylene (2)[a]



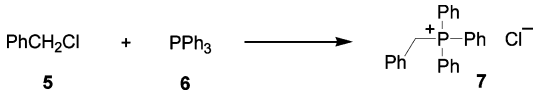
entry	T^b (°C)	time (min)	heating method[c]	conv[d] (%)
1	140	30	oil bath	10
			MW	14
2	140	60	oil bath	20
			MW	23
3	140	90	oil bath	28
			MW	31
4	140	150	oil bath	41
			MW	43
5	140	240	oil bath	54
			MW	57

[a] Pyrone **1** (6.5 mmol) and phenylacetylene (**2**, 9.1 mmol, 1.4 equiv) were reacted neat in a 10 mL microwave process vial (Figure 1b). For further details, see the Experimental Section. [b] Internal reaction temperature measured by fiber-optic sensor. The heating profiles are reproduced in the Supporting Information (Figures S8 and S9). [c] For details of the experimental setup for microwave and oil bath heating, refer to the Experimental Section. [d] Conversion based on ^{1}H NMR analysis of the crude reaction mixture.

(27) Solvents used for microwave synthesis can be classified as high (tan δ > 0.5; for example, ethanol, DMSO, methanol, formic acid), medium (tan δ 0.1–0.5; for example, acetic acid, 1,2-dichlorobenzene, NMP, DMF, water), and low microwave absorbing (tan δ < 0.1; for example, chloroform, ethyl acetate, THF, dichloromethane, toluene, *o*-xylene, hexane). Other common solvents without a permanent dipole moment such as carbon tetrachloride, benzene, *p*-xylene and dioxane can be considered as microwave transparent.

(28) Loupy, A.; Maurel, F.; Sabatié-Gogová, A. *Tetrahedron* **2004**, *60*, 1683.

TABLE 2. Kinetic Analysis of the Alkylation of Triphenylphosphine with Benzyl Chloride under Solvent-Free Conditions Using Conventional Heating[a]



entry	T^b (°C)	time (min)	yield[c] (%)
1	105	10	25
2	105	20	59
3	105	45	78
4	105	90	98
5	120 (156 °C)[d]	10	87
6	150 (210 °C)[d]	10	91
7	170 (253 °C)[d]	10	97

[a] Reactions were performed on a 10 mmol scale in the reaction vessel shown in Figure 1b immersed into a preheated oil bath. [b] Temperature of the preheated oil bath. [c] Isolated yields of pure product (see the Experimental Section for details). [d] Maximum internal temperatures monitored by fiber-optic sensors (see the main text and the Supporting Information for a detailed discussion).

any nonthermal microwave effects could therefore be found in this reaction. The slightly higher conversions seen in the microwave runs (2−4%) may be attributed to the different heating profiles experienced in the very early phase of the microwave heated experiment (Figure S9, Supporting Information).

Additional experiments were aimed at achieving full conversion in this cycloaddition process. For this purpose, the reaction was performed under sealed vessel microwave conditions at higher temperatures using a Discover Labmate microwave reactor including both standard IR temperature and online pressure monitoring. Gratifyingly, a 96% conversion based on ^{1}H NMR measurements was obtained after 3 h at 200 °C, resulting in a 71% isolated product yield of **4** after flash chromatography. It is interesting to note that the pressure build-up in the reaction vessel (ca 7.5 bar) is not preventing the cycloaddition.[29] Again, an identical experiment using oil bath heating provided a more or less identical result (98% conversion, 75% isolated product yield).

Nucleophilic Substitution of Benzyl Chloride with Triphenylphosphine. As a second example, we have chosen the nucleophilic substitution of benzyl chloride (**5**) with triphenylphosphine (**6**) leading to phosphonium salt **7** (Table 2). In contrast to the first example described above, this transformation involves not only a polar transition state but also leads to a polar ionic product.[30] Moreover, the product-like transition state is positioned late along the reaction coordinate.[30] Therefore, according to the current theory on microwave effects outlined above, this transformation involving the reaction of two neutral reagents to give a polar product would be ideally suited for observing a nonthermal microwave effect by dipole−dipole electrostatic interaction/stabilization of the transition state.[12]

Indeed, in a 2004 publication, significant differences between performing the reaction shown in Table 2 in an oil-bath and under microwave conditions were observed.[30] Alkylations have been conducted either solvent-free or using xylene as a microwave-transparent solvent employing dedicated single-mode reactors under open vessel conditions (precalibrated IR and fiber-optic temperature measurement). For example, performing the solvent-free reaction of benzyl chloride (**5**) and triphenylphosphine (**6**) in a preheated oil bath at 100 °C for 10 min, the reaction outcome was very different to the microwave irradiation experiment using the same temperature/time conditions (24 versus 78%, respectively).[30] This experimental difference in favor of the microwave run was rationalized by the occurrence of a nonthermal microwave effect involving the stabilization of the polar transition state by the electric field.[30,31]

During our reevaluation of this transformation, we first concentrated on the solvent-free reaction conditions. A kinetic analysis at 105 °C internal reaction temperature using a preheated oil bath (105 °C) and the experimental setup displayed in Figure 1b is shown in Table 2 (entries 1−4). In our hands, the isolated 25% yield of phosphonium salt **7** after 10 min nicely agrees with the result previously reported (24%).[30] Full conversion at 105 °C providing a nearly quantitative isolated product yield under thermal conditions required 90 min (Table 2, entry 4).

It has to be noted that when immersing the vessel containing the neat mixture of the two starting materials (Figure 1b, ca. 5 mL volume) into the preheated oil bath the reaction mixture becomes completely homogeneous after a few seconds using magnetic stirring. After approximately 1 min, the insoluble phosphonium salt product starts to precipitate from the reaction mixture which ultimately leads to complete solidification of the reaction mixture inside the vessel and failure of the magnetic stirring system (Figure S10, Supporting Information). While at ca. 105 °C bath temperature this does not create a problem, we have observed that at higher bath temperatures (>120 °C) thermal runaways will occur leading to significantly higher internal reaction temperatures than those of the bath fluid (Table 2 and Figure S11, Supporting Information). This is most likely a result of the strongly exothermic character of this alkylation reaction and/or of the heat of crystallization resulting from product precipitation as demonstrated by Differential Scanning Calorimetry (DSC) measurements (Figure S12, Supporting Information). For example, using a 150 °C external oil bath temperature produces an internal peak temperature of 210 °C. Under those conditions high isolated product yields can be obtained within a 10 min reaction time frame (Table 2).

When performing the same solvent-free reaction under microwave irradiation conditions the thermal runaway became a serious issue. Since during the course of the alkylation process, the reaction medium becomes strongly microwave absorbing due to the polar character[26] of the initially still dissolved phosphonium salt **7**, rapid temperature increases are experienced in the first few minutes of the experiment. This is particularly true when comparatively high initial microwave power levels are used. However, even at very low magnetron output power (for example 10 W) thermal runaways were experienced (Figure S13, Supporting Information). As shown in Figure 2, the use of 50 W maximum microwave power leads to significant thermal runaways. Using a maximum set temperature of 100 °C on the CEM Discover instrument (mimicking the previously published conditions),[30] the fiber-optic sensors revealed that the actual internal reaction temperature was significantly higher than the presumed reaction temperature recorded by the IR sensor on the surface of the reaction vessel. In addition, the three

(29) For examples of microwave-assisted transformations that require open vessel processing, see: Razzaq, T.; Kappe, C. O. *Tetrahedron Lett.* **2007**, *48*, 2513 and references cited therein.

(30) Cvengros, J.; Toma, S.; Marque, S.; Loupy, A. *Can. J. Chem.* **2004**, *82*, 1365.

(31) For related examples, see: (a) Kiddle, J. J. *Synth. Commun.* **2001**, *31*, 3377. (b) Kiddle, J. J. *Tetrahedron Lett.* **2000**, *41*, 1339.

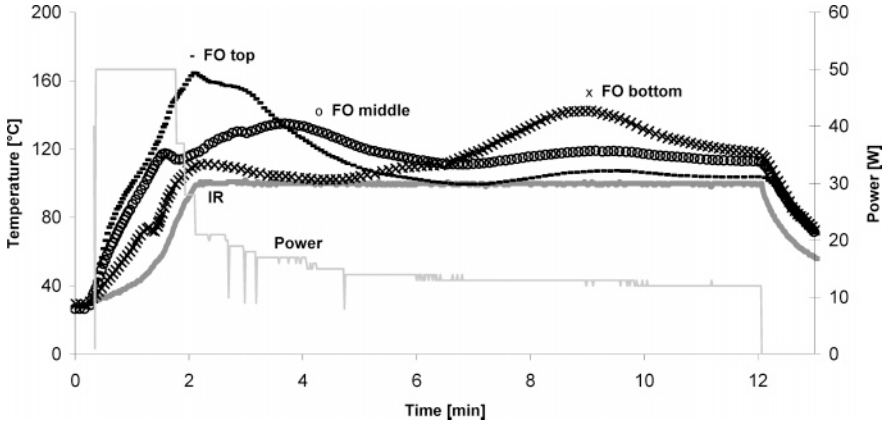


FIGURE 2. Temperature and microwave power profiles for the microwave-assisted solvent-free alkylation of triphenylphosphine with benzyl chloride (Table 2) (CEM Discover single-mode reactor, reaction vessel; see Figure 1b, 50 W maximum magnetron output power, temperature control using the built-in IR sensor). Shown are the profiles for the three internal fiber-optic temperature probes (FO), for the external IR sensor located at the bottom of the instrument (IR), and for the magnetron output power (Power). While the IR sensor controlling the magnetron power continuously measures 100 °C corresponding to the correct set temperature, the internal fiber-optic probes reveal the inhomogeneous temperature distribution within the reaction vessel with a maximum recorded temperature of 165 °C.

internal probes (Figure 1b) displayed considerable differences in the recorded temperature profiles and those experiments furthermore proved difficult to reproduce. This is mainly a result of the inherent temperature gradients experienced in the microwave vessel/cavity (see above) and a consequence of the inability to efficiently stir the reaction mixture once product precipitation takes place (Figure S10, Supporting Information). It is important to point out that without multiple internal temperature monitoring, these severe problems connected to temperature measurement in this particular reaction would not be evident. As can be seen in Figure 2, the standard external IR sensor displays the proper "reaction temperature" of 100 °C which clearly does not represent the true reaction temperature inside the microwave vessel. Not surprisingly, isolated product yields from these microwave experiments were far higher than one would expect from the nominal reaction temperature of 100 °C recorded by the IR sensor. For the experiment shown in Figure 2 (maximum internal temperature 165 °C, ca. 12 min reaction time) a 85% isolated yield of phosphonium salt **7** was obtained, matching the 78% yield previously obtained.[30]

The results described above already indicate that also in this case little evidence for the existence of a nonthermal microwave effect could be found. Since, however, the solvent-free experiments proved difficult to reproduce, we decided to additionally re-evaluate the data previously obtained using *p*-xylene as solvent.[30] As both starting materials are completely soluble in the microwave transparent solvent *p*-xylene, the reaction mixture can be stirred efficiently, even after the insoluble phosphonium salt **7** has precipitated. Using *p*-xylene as solvent for the alkylation described in Table 2, the previous study has found that while the reaction at 140 °C for 30 min in an oil bath resulted in only 11% isolated yield of the phosphonium salt, the microwave experiment using the same conditions led to a 33% product yield.[30] The results of our control experiments between microwave and oil bath heating employing again the multiple fiber-optic probe device are shown in Table 3.

In contrast to the previously published data,[30] we find that for experiments carried out at 140 °C isolated product yields are rather similar between microwave and conventionally heated experiments (1−6% difference in yield). Since here efficient stirring was possible, the IR and fiber-optic probe measurements nicely matched and no temperature gradients developed in the

TABLE 3. Comparison of Microwave Heating and Conventional Heating for the Reaction of Triphenylphosphine with Benzyl Chloride (Table 2) in *p*-Xylene[a]

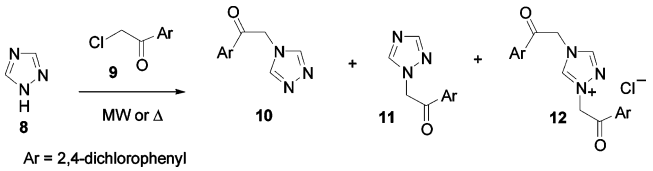
entry	T^b (°C)	time (min)	heating method	yield[c] (%)
1	140	5	oil bath	5
			MW	4
2	140	15	oil bath	11
			MW	8
3	140	30	oil bath	17
			MW	14
			MW (sim cooling)[d]	14
			MW (SiC)[e]	18
4	140	90	oil bath	43
			MW	37
5	200	10	oil bath	53
			MW	56
6	200	30	oil bath	73
			MW	77

[a] Triphenylphosphine (2.0 mmol) and benzyl chloride (2.0 mmol) in 2 mL of *p*-xylene were reacted in a 10 mL microwave process vial (Figure 1b). For further details, see the Experimental Section. [b] Internal reaction temperature measured by two fiber-optic sensors. Some representative heating profiles are reproduced in the Supporting Information (Figure S14). [c] Isolated yields of pure product (see the Experimental Section for details). [d] Applying simultaneous cooling using compressed air (ref 24). [e] In the presence of a SiC passive heating element (ref 16).

reaction vessel (Figure S14, Supporting Information). In addition to the standard temperature controlled microwave runs two additional experiments were performed exposing the reaction mixture to microwave heating at 140 °C for 30 min: (i) By applying the concept of simultaneous cooling of the reaction mixture by compressed air,[24] significantly more microwave power was delivered to the reaction mixture as opposed to the non-cooled experiment (292 versus 105 W) (Table 3, entry 3, see also Figure S14b and S14a, Supporting Information). (ii) Alternatively, the alkylation was also performed in the presence of a strongly microwave absorbing silicon carbide (SiC) material.[16] Since the SiC "passive heating element" is rapidly heated by microwaves, less overall microwave power is used to heat the reaction mixture (51 versus 105 W) (Table 3, entry 3, see also Figure S14c and S14a, Supporting Information).[32]

(32) Kremsner, J. M.; Stadler, A.; Kappe, C. O. *J. Comb. Chem.* **2007**, *9*, 285.

SCHEME 1. Alkylation of 1,2,4-Triazole with 2,2′,4′-Trichloroacetophenone



If the electric field would have any influence on the reaction pathway for this transformation (nonthermal microwave effect), such dramatic differences in the used microwave power would undoubtedly result in a noticeable change in reaction yields. Since this is apparently not the case (Table 3, entry 3) we conclude that no nonthermal microwave effects are present in these reactions. As expected, higher reaction temperatures and prolonged reaction times led to increased product yields, with again no major differences between oil bath and microwave heating being seen (Table 3, entries 5 and 6).

Alkylation of Triazole with 2,2′,4′-Trichloroacetophenone. The phenacylation of 1,2,4-triazole (**8**) with 2,2′,4′-trichloroacetophenone (**9**) was selected as an example for our studies since in this case not only different conversions between oil bath and microwave heating have been experienced, but also the regioselectivity in the alkylation process was found to be strikingly influenced by the mode of heating and the solvent employed (Scheme 1).[33,34] Using polar solvents like pentanol or DMF, no differences in the regioselectivity between conventional and microwave heating at 140 °C were experienced.[33] Employing solvent-free conditions or nonpolar xylene as solvent, however, dramatic differences between the oil bath and the microwave heated alkylations were noted. For example, the alkylation at 140 °C for 20 min in xylene as solvent produced a mixture of the N1- (32%) (**11**), N4- (28%) (**10**), and N1,4-bisalkylated triazoles (40%) (**12**) applying conventional heating (Scheme 1).[33] In contrast, employing single-mode microwave irradiation at the same measured temperature of 140 °C yielded exclusively the N1 isomer.[33] Nearly the same situation was found using solvent-free conditions.[33]

Using our internal fiber-optic temperature monitoring technology, we initially set-out to reproduce the triazole alkylation involving microwave transparent *p*-xylene as solvent. Performing oil bath experiments that allowed us to visually follow the progress of the transformation in the reaction vessel shown in Figure 1b immediately made the inability to efficiently agitate the reaction mixture evident. While 2,2′,4′-trichloroacetophenone (mp 52−55 °C) is soluble in *p*-xylene at room temperature, 1,2,4-triazole (mp 120−121 °C) remains insoluble in the solvent system even in the molten state. This leads to a biphasic mixture that cannot be efficiently stirred using magnetic stirring in combination with the standard 10 mL reaction vessel/stir bar and filling volumes of >1 mL (Figure S15, Supporting Information). Inefficient stirring under microwave conditions may result in temperature gradients inside the reaction vessel (see above) and therefore to inaccurate reaction temperature measurements. In the present case, the situation is further aggravated since the biphasic 1,2,4-triazole/*p*-xylene mixture will be susceptible to differential heating by microwave irradiation.[35]

TABLE 4. Comparison of Microwave Heating and Conventional Heating for the Reaction of 1,2,4-Triazole with 2,2′,4′-Trichloroacetophenone (Scheme 1) in *p*-Xylene[a]

entry	T^b (°C)	time (min)	heating method	N1/N4/N1,4[c] (%)
1	140	20	oil bath	42/33/25
			MW	43/31/26
2	140	60	oil bath	38/32/30
			MW	41/32/28
3	170	20	oil bath	56/20/24
			MW	57/20/23
4	200	20	oil bath	97/1/2
			MW	98/1/1
5	200	40	oil bath	99/0/1
			MW	99/0/1
6	200	60	oil bath	>99/0/0
			MW	>99/0/0

[a] 1,2,4-Triazole (0.9 mmol) and 2,2′,4′-trichloroacetophenone (1.0 mmol) in 0.5 mL of *p*-xylene were reacted in a 10 mL microwave process vial (Figure 1b). For further details, see the Experimental Section. [b] Reaction temperature measured by IR sensor (microwave) and digital thermometer (oil bath fluid). [c] Product distributions based on ^{1}H NMR analysis (Figure S17, Supporting Information).

In order to ensure efficient agitation and reproducibility, we therefore ultimately used a total reaction volume of less than 1 mL inside the reaction vessel (0.5 mL of solvent). Preliminary experiments using 1 mL of solvent demonstrated that here adequate stirring inside the reaction mixture was possible in most cases as indicated by the comparatively good agreement between the measured external IR and internal fiber-optic temperature probes (Figure S16a, Supporting Information). To be confident about efficient agitation inside the closed microwave reactor, the total reaction volume was reduced to 0.5 mL for all subsequent experiments. Because of the low filling volume no internal fiber-optic probe temperature measurement in combination with magnetic stirring was possible, and the determination of reaction temperature here relied exclusively on IR sensor measurements. Using these experimental conditions we could not detect any significant differences between microwave and conventionally heated experiments when running the alkylation reaction at 140 °C for 20 min. In contrast to the previously published results (see above)[33] in both cases nearly identical mixtures of N1-, N4-, and N1,4-bisalkylated 1,2,4-triazole products **10**−**12** (see Scheme 1) were obtained for both heating modes (Table 4, entry 1). The composition of the crude reaction mixture was readily determined by ^{1}H NMR analysis (Figure S17, Supporting Information). Column chromatography using $CHCl_3$/MeOH as eluent in combination with extraction techniques allowed the isolation and full characterization of the pure reaction products.

It has to be noted that the product distribution from our experiments performed at 140 °C (20 min) is in comparatively good agreement with the previously published oil bath data at the same temperature (see above).[33] In order to rationalize the dramatic differences between the published and our microwave runs several additional experiments were performed. As it is evident from the data presented in Table 4, extending the

(33) Loupy, A.; Perreux, L.; Liagre, M.; Burle, K.; Moneuse, M. *Pure Appl. Chem.* **2001**, *73*, 161.

(34) For related examples, see: (a) Pérez, E. R.; Loupy, A.; Liagre, M.; de Guzzi Plepis, A. M.; Cordeiro, P. J. *Tetrahedron* **2003**, *59*, 865. (b) Abenhaim, D.; Diez-Barra, E.; de la Hoz, A.; Loupy, A.; Sánchez-Migallón, A. *Heterocycles* **1994**, *38*, 793.

(35) By microwave irradiating a biphasic system consisting of immiscible solvents/reagents with vastly different loss tangents, differential heating of the two phases will occur. Depending on where and how the "reaction temperature" is measured, different values will be obtained. A case in point are biphasic mixtures of strongly microwave abosorbing ionic liquids and nearly microwave transparent organic solvents. See ref 16 for more details.

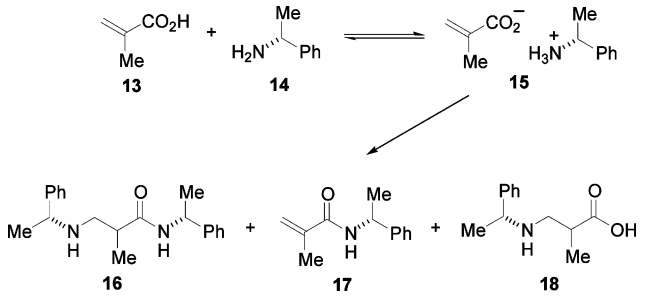
reaction time for the 140 °C run to 60 min led to no significant changes in the product composition (Table 4, entry 2). In contrast, performing the alkylation process at higher reaction temperatures clearly favored the formation of the N1-alkylated triazole **11**, both in microwave and conventionally heated experiments (compare entries 1, 3, and 4). Choosing a reaction temperature of 200 °C (entries 4−6), very high selectivities for the N1-alkylated triazole **11** were obtained. After 60 min at 200 °C only the N1-alkylated triazole **11** was observed in the crude reaction mixture (entry 6) with an overall conversion of ca. 90%.

In this context, it is important to note that the crude mixture of triazoles **10**−**12** isolated from an experiment performed at 140 °C (Table 4, entries 1 and 2) can be cleanly converted into the N1 isomer **11** by heating to 200 °C for 20 min (*p*-xylene, microwaves or oil bath). These results are in good agreement with previously published work on the temperature dependency of 1,2,4-triazole alkylations.[36,37] It has been shown earlier for a closely related system (Scheme 1, Ar = 4-chlorophenyl), that while at lower temperatures a mixture of all three triazole alkylation products is obtained, a higher reaction temperature leads to the almost exclusive formation of N1-alkylated triazole **11**.[36] The thermodynamically more stable N1 isomer is probably formed by bimolecular rearrangement from the *N*4 isomer **10** involving the quaternary triazolium salt **12** as intermediate.[36−38]

Based on the outcome of our experiments, we therefore have no evidence that the alkylation of 1,2,4-triazole shown in Scheme 1 involves a nonthermal microwave effect as previously stated.[33] In our hands, control experiments between microwave and oil bath heating at the same reaction temperature led to comparable results. We believe that the dramatic changes in regioselectivity previously observed in this reaction[33] were the result of inaccurate temperature measurements in the microwave heated experiments, mainly as a consequence of inadequate agitation/differential heating of the biphasic 1,2,4-triazole/xylene reaction mixture.

In addition to the results using *p*-xylene as solvent, we have also re-evaluated the solvent-free alkylation of 1,2,4-triazole (**8**) with 2,2′,4′-trichloroacetophenone (**9**). Heating a mixture of the two components without solvent in an oil bath at 140 °C bath temperature for 20 min (Figure S18, Supporting Information) led to a product composition N1/N4/N1,4 = 30:23:47, in the same range as the previously published values (N1/N4/N1,4 = 36:27:27).[33] As in the alkylation of triphenylphosphine described above, the triazole alkylation shown in Scheme 1 also proved to be exothermic and internal temperature monitoring revealed reaction temperatures as high as 200 °C (Figure S19, Supporting Information) during the initial phases of the 140 °C oil bath experiment. Attempts to reproduce the solvent free triazole alkylation under controlled microwave irradiation conditions proved to be difficult.[39] In all cases, significant thermal runaways were experienced after only a few seconds of microwave irradiation (Figure S20, Supporting Information). We believe that those are related to the formation of strongly microwave absorbing N1,4-bisalkylated triazolium chloride intermediates of type **12**. These salts may behave similar to imidazolium-type ionic liquids and will very rapidly be heated when exposed to microwave irradiation in the liquid or dissolved state.[40] Applying microwave irradiation during the alkylation of 1,2,4-triazole raised the internal reaction temperature to 250 °C within a few seconds (Figure S20, Supporting Information). Under these conditions, mostly the N1-alkylated triazole **11** was formed, but reactions were difficult to control and to reproduce. Heating a mixture of 1,2,4-triazole and 2,2′,4′-trichloroacetophenone in an oil bath to a similar temperature range (for example, 220 °C for 25 min) also provided product mixtures that mainly consisted of the N1-alkylated triazole **11** (>85%).

SCHEME 2. Amidation of Methacrylic Acid with (*R*)-1-Phenylethylamine



Direct Amidation of Methacrylic Acid with (*R*)-1-Phenylethylamine. As a final example for our investigations on nonthermal microwave effects, we have chosen the direct amidation of a carboxylic acid with an amine. Transformations of this type involve two neutral reagents and a neutral product but proceed via highly polar intermediates (ammonium carboxylate salts) and product-like transition states. According to the theory of nonthermal microwave effects outlined above, these amidation processes would be very well suited to exhibit nonthermal microwave effects as a result of a direct stabilizing interaction of the electromagnetic field with the polar transition states.[12] Indeed, there have been several reports in the literature which demonstrated that by using microwave irradiation under solvent-free conditions, direct amide bond formation between a carboxylic acid and an amine can be achieved very efficiently without the use of coupling reagents or other chemical activation methods.[41−43]

The particular example selected for this work involves the amidation of methacrylic acid (**13**) with (*R*)-1-phenylethylamine (**14**) (Scheme 2). This example was chosen since a recent study has shown that different product compositions are obtained when comparing microwave heating and conventional heating in a similar temperature region.[42] Thus, microwave heating of an equimolar mixture of the two starting materials in a dedicated single mode microwave reactor at a monitored temperature of 180 °C (calibrated IR sensor) produced a 90% isolated yield of

(36) Smith, K.; Small, A.; Hutchings, M. G. *Chem. Lett.* **1990**, 347.

(37) For a mechanistic discussion, see: Gautum, O. R.; Carlsen, P. H. J. *Eur. J. Org. Chem.* **2000**, 3745−3748.

(38) Ab initio calculations at the B3LYP/6-31G* level confirmed that the N1 isomer (**11**, Ar = phenyl) is more stable than the N4 isomer (**10**, Ar = phenyl) by ca. 8 kcal/mol.

(39) Difficulties reproducing this reaction in a solvent-free regime under microwave conditions have been recently reported. For more information, see: Lebouvier, N.; Giraud, F.; Corbin, T.; Na, Y.-M.; Le Baut, G.; Marchand, P.; Le Borgne, M. *Tetrahedron Lett.* **2006**, *47*, 6479.

(40) For recent reviews, see: (a) Leadbeater, N. E.; Torenius, H. M.; Tye, H. *Comb. Chem. High Throughput Screen.* **2004**, *7*, 511. (b) Habermann, J.; Ponzi, S.; Ley, S. V. *Mini-Rev. Org. Chem.* **2005**, *2*, 125.

(41) (a) Gelens, E.; Smeets, L.; Sliedregt, L. A. J. M.; Van Steen, B. J.; Kruse, C. G.; Leurs, R.; Orru, R. V. A. *Tetrahedron Lett.* **2005**, *46*, 3751. (b) Perreux, L.; Loupy, A.; Volatron, F. *Tetrahedron* **2002**, *58*, 2155. (c) Massicot, F.; Plantier-Royon, R.; Portella, C.; Saleur, D.; Sudha, A. V. *Synthesis* **2001**, 2441. (d) Vasquez-Tato, M. P. *Synlett* **1993**, 506.

(42) Ianelli, M.; Alupei, V.; Ritter, H. *Tetrahedron* **2005**, *61*, 1509.

(43) (a) Goretzki, C.; Krlej, A.; Steffens, C.; Ritter, H. *Macromol. Rapid Commun.* **2004**, *25*, 513. (b) Ianelli, M.; Ritter, H. *Macromol. Chem. Phys.* **2005**, *206*, 349.

the anticipated methacrylamide **17** after 15 min.[42] This experiment was conducted using the concept of simultaneous cooling.[24] The actual internal reaction temperature was suggested to be ca. 200 °C using a calibration method. In contrast, the conversion to amide **17** in the experiment applying conventional heating at 200 °C was only 12% after the same period of time (15 min) and would not significantly increase by extending the reaction time to 30 min.[42]

A detailed kinetic analysis conducted by the authors has demonstrated that the first (kinetic) reaction product which is produced from the initially formed salt **15** in this transformation is propionic acid **18** which is the result of a (reversible) Michael addition of the amine to methacrylic acid. After ca. 4 min using microwave heating (ca 200 °C) the concentration of the Michael adduct peaked at 50% and subsequently decreased dramatically at the expense of the thermodynamically more stable methacrylamide **17** which was formed in 93% (GC−MS conversion) after 15 min.[42] Interestingly, when the same analysis was performed for the conventionally heated experiment applying a similar temperature profile[44] the concentration of the initially formed kinetic product (Michael adduct **18**) would again decrease after 4 min, but now the major product of the reaction (>80% after 30 min) was amide **16** which is either formed by Michael addition of amine **14** to methacrylamide **17** or by amidation of propionic acid **18** with the amine (Scheme 2). The desired methacrylamide **17** was formed in <20% yield using conventional heating conditions, while amide byproduct **16** was detected in only very small amounts (3.4%) in the microwave experiment.[42]

The authors have suggested that these results cannot be attributed exclusively to the very efficient heating experienced using microwave irradiation, and have rationalized the high selectivity for the formation of methacrylamide **17** from the acid and amine components by arguments relating to the relative hardness of the transition states involved.[42,45] It was proposed that, when competitive reactions are involved, the mechanism occurring via the hardest, most polar transition state (here **13** + **14** → **17**) should be the favored one under microwave irradiation conditions.[12]

A reinvestigation of this solvent-free process using internal fiber-optic temperature monitoring technology again demonstrated the importance of an accurate reaction temperature determination in microwave heated reactions. In order to ensure appropriate agitation, reactions were typically run on a 7.0 mmol scale under sealed vessel conditions using one single fiber-optic temperature sensor. Under these conditions, the homogeneous reaction mixture (ca. 1.5 mL) could be efficiently stirred after the initially formed salt **15** had melted around 130 °C. In our experiments we have tried to as close as possible mimic the conditions previously reported in the literature.[42] After extensive optimization, we were able to achieve a 71% isolated yield of the desired methacrylamide **17** after 15 min of microwave irradiation at a ca. 200 °C IR temperature using simultaneous cooling via a compressed nitrogen flow (Table 5, entry 1).

It became immediately apparent that by using such an experimental protocol the internal temperature was considerably higher than the ca. 200 °C shown by the standard IR sensor. In fact, the fiber-optic probe revealed reaction temperatures that were as much as 60 °C above the recorded external IR temperatures (average temperature 257 °C, see Figure S21, Supporting Information). Additional experimentation has demonstrated that the optimum temperature for the direct amidation process **13** + **14** → **17** appears to be around 260 °C. Higher temperatures (>270 °C) or longer reaction times led to significant product decomposition and byproduct formation, whereas lower temperatures favored the formation of amide **16** (see below). In addition to the "cooled" microwave experiment described above (Table 5, entry 1) we have therefore carried out experiments at the "correct" optimum reaction temperature of ca. 260 °C using (i) microwave heating without simultaneous cooling and (ii) applying conventional heating in a metal bath. As seen from the data presented in Table 5 (entries 1−3), in all three cases the isolated product yields for methacrylamide **17** were rather similar. Moreover, the GC traces for the crude reaction mixtures were more or less identical showing the same impurity profiles (Figure S22, Supporting Information). The main impurity in all cases was amide **16** (Scheme 2). Based on these results, we therefore have no evidence that this direct amidation reaction involves a nonthermal microwave effect as previously assumed.[42] The amount of microwave power used in the experiment - modulated by simultaneous cooling - proved to be irrelevant (94 W versus 173 W with simultaneous cooling). Again, inadequate temperature measurements in the microwave heated experiment, mainly as a consequence of using the simultaneous cooling method in conjunction with IR temperature monitoring,[18] probably led to a misinterpretation of results in the past.[42]

In addition, we have also studied this reaction at a temperature of 200 °C (15 min) in order to compare our results to the previously published data.[42] Indeed, at this substantially lower reaction temperature the main reaction product is amide **16**, with only small amounts of the desired methacrylamide **17** being formed (Table 5). Not surprisingly, there is no substantial difference in yield regardless if the reaction has been processed by microwave heating or conventional heating (Figure S25, Supporting Information). Apparently, the amidation of methacrylic acid (**13**) with (*R*)-1-phenyl-ethylamine (**14**) (Scheme 2) is rather sensitive to the reaction temperature. Here, small changes in the reaction temperature (200 °C versus 250 °C) will lead to a substantially different product distribution.

TABLE 5. Comparison of Microwave Heating and Conventional Heating for the Reaction of Methacrylic Acid (13) with (*R*)-1-Phenylethylamine (14) (Scheme 2)[a]

entry	T^b (°C)	heating method	time[c] (min)	yield[d] (%)
1	257	MW (sim cooling, power control)[e,f]	15	71
2	262	MW (temp control)[f]	15	78
3	263	metal bath (258−268 °C bath temp)[f]	15	75
4	205	MW (temp control)[f]	15	25[g]
5	198	oil bath (200 °C bath temp)[f]	15	19[g]

[a] Methacrylic acid (7.0 mmol) and (*R*)-1-phenylethylamine (7.0 mmol) were reacted without solvent in a 10 mL microwave process vial (Figure 1b). For further details, see the Experimental Section. [b] Average reaction temperature measured by one internal fiber-optic probe. [c] Total reaction/irradiation time. [d] Isolated product yield of methacrylamide **17** after column chromatography. [e] Applying 6 bar of compressed nitrogen (25 °C). [f] Heating profiles and GC−MS chromatograms are reproduced in the Supporting Information (Figures S21−S25). [g] The major product at ca. 200 °C based on GC−MS analysis is amide **16** (see Figure S25, Supporting Information).

(44) In order to mimic the rapid heating profiles observed under microwave conditions, the conventionally heated experiments were conducted using a differential calorimetric scanning (DSC) apparatus.

(45) For further discussion on this reaction, see also the follwowing references: (a) Koopmans, C.; Ianelli, M.; Kerep, P.; Klink, M.; Schmitz, S.; Sinwell, S.; Ritter, H. *Tetrahedron* **2006**, *62*, 4709. (b) Reference 12c, pp 162−164. (c) Reference 12d, pp 254−256.

Accurate online temperature monitoring during microwave experiments is therefore essential.

Concluding Remarks

In summary, we have performed a critical reinvestigation on the existence of nonthermal microwave effects for four carefully selected organic reactions. In all four cases, previous studies have found significant differences in conversion and/or product distribution comparing conventionally heated and microwave-heated experiments performed at the same measured reaction temperature.

Of critical importance for our reevaluation was the introduction of a multiple fiber-optic probe system as accurate temperature measurement device in *both* the microwave and the conventionally heated reactors. Using this technology, we have demonstrated that efficient stirring/agitation of microwave-heated reactions is essential. In contrast to an oil bath experiment, even completely homogeneous solutions need to be stirred when using single-mode microwave reactors. If efficient stirring/agitation cannot be ensured, temperature gradients may develop as a consequence of inherent field inhomogeneities inside a single-mode microwave cavity. The formation of temperature gradients is therefore a particular problem in case of, for example, solvent-free or dry media reactions and for very viscous or biphasic reaction systems where standard magnetic stirring is not effective.

Applying the fiber-optic temperature monitoring device, a critical reevaluation of the four model reactions discussed herein has provided no evidence for the existence of non-thermal microwave effects (see the Results and Discussion). Working at a reaction scale that allowed for an efficient agitation of the reaction mixture via magnetic stirring, no significant differences in terms of conversion and selectivity between experiments performed under microwave conditions and runs conducted in an oil or metal bath at the same internally measured reaction temperature were experienced. The observed effects were purely thermal and not related to the microwave field. Modulating the amount of microwave power delivered to the reaction mixture (for example by applying simultaneous cooling) proved to be ineffective. We believe that the previously observed differences between experiments performed under conventional and microwave heating conditions for these four transformations are in fact the result of inaccurate temperature measurements using external IR sensors. As we have demonstrated, the use of IR sensors is in many cases not appropriate for microwave heated reactions and can easily lead to a misinterpretation of results since the true reaction temperatures during microwave irradiation are not known, in particular for those cases where stirring is problematic and/or where strongly microwave-absorbing polar intermediates or products are formed.

In this context, it has to be noted that it is probably no coincidence that nonthermal microwave effects have in many cases been claimed for processes involving solvent-free/dry media reactions and/or for transformations involving polar reaction intermediates or products (which will strongly absorb microwave energy).[12] Based on the results presented herein, we suspect that in most of the published cases, the observed differences between microwave and conventional heating can in fact be rationalized by inaccurate temperature measurements often using external IR temperature probes, rather than being the consequence of a genuine nonthermal effect. We therefore believe that the concept of nonthermal microwave effects has to be critically reexamined and that a considerable amount of research work will be required before a definitive answer about the existence or nonexistence of these effects can be given.[46]

Experimental Section

Microwave Irradiation Experiments. All microwave irradiation experiments described herein were performed using a single-mode Discover Labmate System from CEM Corp. using standard Pyrex or quartz vessels (capacity 10 mL). Experiments were performed in temperature-control mode where the temperature was controlled using the built-in calibrated IR sensor. In most experiments, the internal reaction temperature was additionally monitored by a multiple fiber-optic probe sensor. The assembly shown in Figure 1b consists of a standard 10 mL CEM process vial (quartz or Pyrex) which is sealed with a special PTFE cap fitted with three quartz tubes (inner diameter = 1 mm, outside diameter = 2 mm) for inserting three individual fiber-optic probes (GaAs principle, Opsens, accuracy ±1.5 °C). The quartz tubes are flexible in height and can be fixed by tightening the three screws on top of the cap. When the main screw (made of PEEK) is tightened, the assembly is sealed and can be operated at temperatures up to 250 °C and a pressure of 20 bar (pressure is not monitored). The whole setup can be introduced in the open-vessel applicator of the CEM Discover using a specially designed PEEK support or immersed into a preheated oil/metal bath.

Diels−Alder Cycloaddition of 5-Methoxycarbonyl-2-pyrone and Phenylacetylene (Table 1). For the kinetic studies, a 10 mL Pyrex reaction vessel equipped with a magnetic stir bar (Figure 1b) was filled with 1.0 g (6.5 mmol) of 5-methoxycarbonyl-2-pyrone (**1**) and 1.0 mL (464 mg, 9.1 mmol, 1.4 equiv) of freshly distilled phenylacetylene (**2**). The vessel was sealed (the PTFE cap was equipped with only one quartz immersion tube allowing sample withdrawal with a syringe through the two open fiber optic inlets) and either immersed in a preheated oil bath or irradiated in a microwave reactor for 240 min (Table 1; Figures S8, S9, Supporting Information). For preparative experiments, a sealed 10 mL Pyrex reaction vessel was filled with 499 mg (3.24 mmol) of 5-methoxycarbonyl-2-pyrone (**1**) and 0.500 mL (464 mg, 4.54 mmol, 1.4 equiv) of freshly distilled phenylacetylene (**2**) and heated for 3 h at 200 °C either with microwave irradiation (IR temperature measurement) or in a preaheated oil bath to reach >96% conversion (^{1}H NMR). The cycloadduct (**4**) could be isolated as a light brown oil (71 and 75% yield, respectively) after column chromatography using CH_2Cl_2 as an eluent: ^{1}H NMR ($CDCl_3$) δ 3.65 (s, 3H), 7.33−7.45 (m, 7H), 7.55 (dt, J = 7.5 Hz, J = 1.4 Hz, 1H), 7.85 (dd, J = 7.7 Hz, J = 1.0 Hz, 1H).[47]

Nucleophilic Substitution of Benzyl Chloride with Triphenylphosphine in *p*-Xylene (Tables 2 and 3). A 10 mL Pyrex reaction vessel equipped with a stir bar (Figure 1b) was filled with a solution of 524 mg (2.0 mmol) of triphenylphosphine (**6**) and 278 μL (253 mg, 2.0 mmol) of benzyl chloride (**5**) in 2 mL of *p*-xylene. For solvent-free experiments, 2.62 g (10 mmol) of triphenylphosphine (**6**) and 1.39 mL (1.27 g, 10 mmol) of benzyl chloride (**5**) were mixed. The reaction mixture was either exposed to microwave irradiation or immersed into a preheated oil bath at different temperatures and times as shown in Tables 2 and 3 (for representative heating profiles, see Figures S11, S13, S14, Supporting Information). After the mixture was cooled to room temperature, the precipitated salt was filtered, washed with cold toluene, and kept in the drying oven at 50 °C overnight to produce pure phosphonium salt **7** (for yields, refer to Tables 2 and 3): mp 332−334 °C (lit.[30] mp 333−337 °C); ^{1}H NMR ($CDCl_3$) δ 5.43 (d,

(46) For a recent study on microwave effects, see: Dressen, M. H. C. L.; van de Kruijs, B. H. P.; Meuldijk, J.; Vekemans, J. A. J. M.; Hulshof, L. A. *Org. Process Res. Dev.* **2007**, *11*, 865.

(47) Kondolff, I.; Doucet, H.; Santelli, M. *Organometallics* **2006**, *25*, 5219.

J = 14.5 Hz, 2H), 7.07−7.08 (m, 4H), 7.57−7.62 (m, 6H), 7.68−7.75 (m, 10H).[30]

General Procedure for the Alkylation of Triazole with Trichloroacetophenone (Table 4). A 10 mL Pyrex vessel equipped with a stir bar (Figure 1b) was charged with a solution of 223 mg (1.0 mmol) of 2,2′,4′-trichloroacetophenone (**9**) in 0.5 mL of *p*-xylene and 62 mg (0.9 mmol) of 1,2,4-triazole (**8**). The reaction mixture was either exposed to microwave irradiation or immersed into a preheated oil bath at different temperatures and times shown in Table 4 (for representative heating profiles, see Figures S16, S19, and S20, Supporting Information). After being cooled to room temperature, the mixture was homogenized with methanol. Subsequently, the organic solvents were removed under vacuum and the conversions determined using ^{1}H NMR spectroscopy (Figure S17, Supporting Information). Isolation via tituration with dioxane and subsequent silica gel flash chromatography using $CHCl_3$/MeOH as eluent provided the pure alkylation products as colorless solids. **10**: mp 175−177 °C; ^{1}H NMR (DMSO-d_6) δ 6.03 (s, 2H), 7.71 (dd, J = 8.4 Hz, J = 1.9 Hz, 1H), 7.86 (d, J = 1.9 Hz, 1H), 8.09 (d, J = 8.4 Hz, 1H), 9.41 (s, 2H); MS (positive APCI) m/z 256 (M + 1, 100). **11**: mp 116−118 °C; ^{1}H NMR (DMSO-d_6) δ 5.84 (s, 2H), 7.64 (dd, J = 8.4 Hz, J = 2.0 Hz, 1H), 7.81 (d, J = 1.9 Hz, 1H), 7.95 (d, J = 8.4 Hz, 1H), 8.02 (s, 1H), 8.53 (s, 1H);[39] MS (positive APCI) m/z 256 (M + 1, 100). **12**: mp 226−228 °C; ^{1}H NMR (DMSO-d_6) δ 6.23 (s, 2H), 6.40 (s, 2H), 7.71−7.76 (dt, J = 8.1 and 1.9 Hz, 2H), 7.89 (dd, J = 5.0 and 1.9 Hz, 2H), 8.13 (dd, J = 8.4 and 1.5 Hz, 2H), 9.35 (s, 1H), 10.28 (s, 1H); MS (positive APCI) m/z 443 (M + 1, 100).

General Procedure for the Amidation of Methacrylic Acid with (*R*)-1-Phenylethylamine (Scheme 2). To a 10 mL Pyrex reaction vessel equipped with a stir bar and charged with 900 μL (846 mg, 7.0 mmol) of (*R*)-1-phenylethylamine (**14**) was added dropwise 595 μL (604 mg, 7.0 mmol) of freshly distilled methacrylic acid (**13**) under ice cooling. In an exothermic reaction, the solid ammonium salt **15** (mp 130−134 °C; ^{1}H NMR ($CDCl_3$) δ 1.51 (d, J = 6.8 Hz, 3H), 1.79 (s, 1H), 4.21 (q, J = 6.8 Hz, 1H), 5.29 (s, 1H), 5.49 (br s, 3H), 5.77 (s, 1H), 7.25−7.38 (m, 5H)) is formed spontaneously, which makes further mixing with the stir bar impossible. Therefore, the starting materials were additionally mixed with a spatula before sealing the reaction vessel as shown in Figure 1b. The salt was subjected to microwave irradiation (140−300 W maximum magentron ouput power, 200 °C set IR temperature), and simultaneous cooling (6 bar of nitrogen) was started immediately after the target IR temperature (200 °C) was reached (Table 5, entry 1, Figure S21, Supporting Information). After 15 min of total irradiation time, the reaction mixture was allowed to cool to room temperature. Subsequent silica gel column chromatography using dichloromethane/methanol (20:1) as eluent resulted in 932 mg (71%) of the final methacrylamide product **17**: mp 88−90 °C (lit.[42] mp 91−92 °C); ^{1}H NMR ($CDCl_3$) δ 1.54 (d, J = 6.9 Hz, 3H), 1.98 (s, 3H), 5.19 (quint, J = 7.2 Hz, 1H), 5.34 (s, 1H), 5.69 (s, 1H), 6.01 (br s, 1H), 7.26−7.39 (m, 5H);[42] MS (positive APCI) m/z 190 (M + 1, 100). Experiments at different temperatures and using conventional heating (Table 5, entries 2−5) were performed in a similar way. The salt **15** was either subjected to microwave irradiation without simultaneous cooling or heated in a preheated bath for 15 min. Data for amide **16**: mp 137−142 °C; ^{1}H NMR ($CDCl_3$) δ 1.19 (d, J = 7.1 Hz, 3H), 1.50 (d, J = 6.9 Hz, 3H), 1.79 (d, J = 6.8 Hz, 3H), 1.91 (br s, 2H), 2.82−2.87 (m, 2H), 3.40−3.49 (m, 1H), 4.21−4.25 (m, 1H), 5.01 (quint, J = 7.3, 1H), 7.22−7.58 (m, 10H); MS (positive APCI) m/z 311 (M + 1, 100).

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Supporting Information Available: Description of general experimental procedures, images, and heating profiles for reactions. This material is available free of charge via the Internet at http://pubs.acs.org.

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