Silicon Carbide Passive Heating Elements in Microwave-Assisted Organic Synthesis

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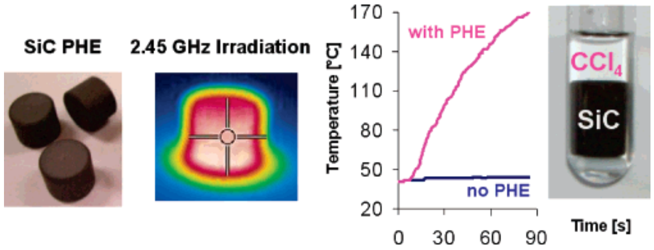

Microwave-assisted organic synthesis in nonpolar solvents is investigated utilizing cylinders of sintered silicon carbide (SiC)—a chemically inert and strongly microwave absorbing material—as passive heating elements (PHEs). These heating inserts absorb microwave energy and subsequently transfer the generated thermal energy via conduction phenomena to the reaction mixture. The use of passive heating elements allows otherwise microwave transparent or poorly absorbing solvents such as hexane, carbon tetrachloride, tetrahydrofuran, dioxane, or toluene to be effectively heated to temperatures far above their boiling points (200−250 °C) under sealed vessel microwave conditions. This opens up the possibility to perform microwave synthesis in unpolar solvent environments as demonstrated successfully for several organic transformations, such as Claisen rearrangements, Diels−Alder reactions, Michael additions, *N*-alkylations, and Dimroth rearrangements. This noninvasive technique is a particularly valuable tool in cases where other options to increase the microwave absorbance of the reaction medium, such as the addition of ionic liquids as heating aids, are not feasible due to an incompatibility of the ionic liquid with a particular substrate. The SiC heating elements are thermally and chemically resistant to 1500 °C and compatible with any solvent or reagent.

Introduction

The use of microwave energy to heat chemical reactions has become an increasingly popular technique in the scientific community, as evidenced by the large number of review articles and books published on this subject.[1−3] In many instances, controlled microwave heating under sealed vessel conditions has been shown to dramatically reduce reaction times, increase product yields, and enhance product purities by reducing unwanted side reactions compared to conventional synthetic methods.[1−3] Although there is still considerable debate and speculation on the nature and/or the existence of so-called “nonthermal” microwave effects that could provide a rationalization for some of the observed phenomena,[3] there is little doubt that microwave heating will become a standard technique in most laboratories within a few years. The many advantages of this enabling technology have not only been exploited for organic synthesis (MAOS)[1−3] and in the context of medicinal chemistry/drug discovery,[4] but have also penetrated fields such

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[1] Books: (a) *Microwave-Enhanced Chemistry. Fundamentals, Sample Preparation and Applications*; Kingston, H. M., Haswell,S. J., Eds.; American Chemical Society: Washington, DC, 1997. (b) *Microwaves in Organic Synthesis*; Loupy, A., Ed.; Wiley-VCH: Weinheim, Germany, 2002. (c) Hayes, B. L. *Microwave Synthesis*: *Chemistry at the Speed of Light*; CEM Publishing: Matthews, NC, 2002**.** (d) *Microwave-Assisted Organic Synthesis*; Lidström, P., Tierney, J. P., Eds.; Blackwell Publishing: Oxford, UK, 2005**.** (e) Kappe, C. O.; Stadler, A. *Microwaves in Organic and Medicinal Chemistry*; Wiley-VCH: Weinheim, Germany, 2005.

[2] Recent reviews: (a) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250 and references therein. (b) Hayes, B. L. *Aldrichim. Acta* **2004**, *37*, 66. (c) Roberts B. A.; Strauss C. R. *Acc. Chem. Res.* **2005**, *38*, 653.

[3] (a) De La Hoz, A.; Diaz-Ortiz, A.; Moreno, A. *Chem. Soc. Rev.* **2005**, *34*, 164. (b) Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199. (c) Kuhnert, N. *Angew. Chem., Int. Ed.* **2002**, *41*, 1863. (d) Strauss, C. R. *Angew. Chem., Int. Ed.* **2002**, *41*, 3589.

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as polymer synthesis,[5] material sciences,[6] nanotechnology,[7] and biochemical processes.[8]

Microwave chemistry generally relies on the ability of the reaction mixture to efficiently absorb microwave energy, taking advantage of "microwave dielectric heating" phenomena such as dipolar polarization or ionic conduction mechanisms.[9] In most cases this means that the solvent used for a particular transformation must be microwave absorbing. The ability of a specific 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.[9] 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.

In general, solvents used for microwave synthesis can be classified as high ($\tan \delta > 0.5$, 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 ($\tan \delta < 0.1$, for example: chloroform, ethyl acetate, THF, dichloromethane, toluene, hexane).[2,9] Other common solvents without a permanent dipole moment such as carbon tetrachloride, benzene, and dioxane are more or less microwave transparent. Therefore, microwave synthesis in low-absorbing or microwave-transparent solvents is often not feasible, unless either the substrates or some of the reagents/catalysts are strongly polar and therefore microwave absorbing, raising the overall dielectric properties of the reaction medium to a level that allows sufficient heating by microwaves. Since this is not always the case, many nonpolar solvents, that have proven to be very useful and are popular in conventional chemistry, are potentially precluded from use as solvents in microwave synthesis.

To overcome the problem of low microwave absorption, the original solvent choice for a particular reaction sometimes has to be compromised, requiring a change to a more polar, better microwave absorbing solvent instead. A recent example was reported by Maes and co-workers in the context of a scale-up study involving a microwave-assisted Buchwald−Hartwig amination.[10] While the amination was successfully optimized and run on a small scale (1 mmol) in toluene at 150 °C, a solvent change to the significantly more polar trifluoromethylbenzene was required for carrying out the same reaction on a larger scale in the same microwave instrument (max power 300 W) due to the poor microwave coupling characteristics of toluene ($\tan \delta = 0.040$).[10]

Alternatively, instead of switching entirely to a polar solvent it sometimes suffices to add small quantities of a strongly microwave absorbing (polar) solvent to an otherwise low absorbing solvent or reaction mixture to achieve similar effects. As has been demonstrated by Ondruschka and co-workers,[11] a 20% solution of 2-propanol in hexane absorbs microwave irradiation with an efficiency that is comparable to that of pure 2-propanol ($\tan \delta = 0.799$), with hexane being nearly microwave transparent ($\tan \delta = 0.020$). Similarly, dilute solutions of standard inorganic salts can be used to dramatically improve the comparatively moderate microwave absorbance of water ($\tan \delta = 0.123$).[9,12,13]

One of the most elegant techniques in this context is the use of room temperature ionic liquids, which are very strongly microwave absorbing, as heating aids. As has been demonstrated by Ley and co-workers in 2001, the addition of only small amounts of an ionic liquid (ca. 5%) sufficed to modify the dielectric properties of toluene to an extent that superheating to high temperatures (200−220 °C) by microwaves in a sealed vessel reactor became possible.[14] Subsequent detailed studies by Leadbeater,[15] Ondruschka,[16] and others[17] established the general usefulness of this methodology for microwave-assisted organic synthesis employing nonpolar solvents.[18]

It is obvious, however, that all of the above-mentioned "invasive" methods have a severe disadvantage in that the polarity of the original solvent system is inadvertently being modified. Clearly, there are situations where it is desirable or even a necessity to perform a particular reaction in a genuinely nonpolar solvent in the absence of any polar additives. In particular, the use of ionic liquids is sometimes incompatible with certain reaction types and even small amounts of an ionic liquid may prevent specific reaction pathways (see below).[15,19] Furthermore, recent evidence suggests that under high-temperature microwave irradiation conditions some ionic liquids will decompose in the presence of nucleophiles.[20]

Looking for noninvasive alternatives, we have explored the use of passive heating elements (PHEs) as additives to poorly

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(19) Silva, A. M. G.; Tomé, A. C.; Neves, M. G. P. M. S.; Cavaleiro, J. A. S.; Kappe, C. O. *Tetrahedron Lett.* **2005**, *46*, 4723. In the particular cycloaddition studied in this paper it was found that small amounts of an ionic liquid (bmimPF$_6$) used as doping reagent led to complete decomposition of the starting material and therefore inhibited the desired reaction pathway.

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microwave absorbing reaction mixtures. PHEs are chemically inert and strongly microwave absorbing materials (“microwave susceptors”) that transfer the generated thermal energy to the nonpolar solvent through conduction and convection to allow efficient heating. The use of such devices, available in a variety of different sizes and geometric forms, is not uncommon in the field of analytical chemistry and in microwave-assisted solvent extractions where the use of nonpolar solvents is often required to extract specific target analytes.[21] In microwave-assisted organic synthesis (MAOS) their use so far has been extremely rare and is not well documented.[22]

Here we describe the use of a novel and superior type of passive heating element for microwave chemistry, made from sintered silicon carbide that is chemically completely inert, strongly microwave absorbing, and due to its high melting point (ca. 2700 °C) and very low thermal expansion coefficient can be employed at extremely high temperatures. In this article we demonstrate the practical use of this virtually indestructible and fully recyclable material in microwave-assisted organic synthesis and highlight its application for a variety of different transformations employing both single-mode and multimode microwave reactors.

Results and Discussion

Temperature Measurements. To carefully explore the heating characteristics of nonpolar solvents in the presence and absence of PHEs or other doping agents, we first investigated the use of a suitable reaction vessel and temperature measurement device for our studies. On the basis of our previous experience with low-absorbing solvents under microwave conditions,[24] it became rather obvious that the standard Pyrex reaction vessels used in the currently available single-mode microwave instruments are not microwave transparent and will absorb a significant amount of microwave energy, thereby acting as “passive heating elements” in their own right.[24−26] This was easily demonstrated by comparing the heating profiles of microwave transparent carbon tetrachloride in a standard microwave Pyrex vessel and in a custom-made quartz vessel of exactly the same geometry. Irradiating a 4 mL sample of solvent in a single-mode instrument at 150 W constant magnetron output power for 5 min led to no measurable increase in the solvent temperature with use of the quartz vessel, whereas the temperature of the carbon tetrachloride was raised to 109 °C in the Pyrex vessel by conductive heating via the hot glass surface (Figure S1 in the Supporting Information). To be sure to monitor the correct temperature of the solvent (and not of the vessel) we have employed a fiber-optic probe directly immersed into the solvent contained in the reaction vessel,[13,26] and not the standard method of monitoring the outside surface temperature of the microwave vessel by a calibrated remote IR sensor. In case of a microwave transparent medium contained in the self-absorbing Pyrex vessel, the indirect IR method typically records a higher (erroneous) temperature value as compared to the direct temperature measurement in the reaction vessel by a fiber-optic probe (Figure S2 in the Supporting Information). For most of our subsequent experiments this combination of microwave transparent quartz reaction vessels and direct fiber-optic temperature measurements was utilized.[13] For high microwave absorbing reaction media (polar solvents or mixtures containing passive heating elements), however, the use of quartz vessels and fiber-optic probes is not required (Figure S3 in the Supporting Information).

To compare the efficiency of passive heating elements with the invasive techniques described above and to provide a consistent data set for the different methods, we first set out to reevaluate several of the known heating aids used in microwave synthesis using the validated experimental setup described above. The results of those studies investigating the heating characteristics of carbon tetrachloride doped with various amounts of ethanol, water doped with NaCl or tetrabutylammonium bromide (TBAB), and mixtures of the ionic liquid *N*-butyl-*N*′-methylimidazolium hexafluorophosphate (bmimPF$_6$) with hexane are discussed in detail in the Supporting Information (Figures S4−S8). Indeed, all those methods allow the rapid heating of otherwise low-absorbing solvents to practically useful temperatures by microwave irradiation. In particular ionic liquids are very powerful heating aids for microwave synthesis as already reported by several research groups,[14−18] but we find their use in conjunction with nonpolar solvents sometimes to be problematic.[27]

Passive Heating Elements. Because of the inherent disadvantages of employing invasive heating aids that change the polarity of the solvent system, and additionally may contaminate the reaction mixture in an undesired way, we have subsequently looked at the performance of passive heating elements (PHEs) in raising the temperature of nonpolar solvents under microwave irradiation conditions. A careful evaluation of the currently

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[22] To the best of our knowledge, the utilization of such heating inserts (generally made out of fluoropolymers doped with graphite or carbon black, ref 29) in the context of microwave synthesis has to date only been mentioned in footnotes in three recent publications dealing with microwave-assisted pericyclic rearrangements in nonpolar solvents by the groups of Davies and Barriault, respectively (ref 23).

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[24] Garbacia, S.; Desai, B.; Lavastre, O.; Kappe, C. O. *J. Org. Chem.* **2003**, *68*, 9136.

[25] A similar observation was made by Maes and co-workers with reaction vessels used in a multimode microwave instrument. See ref 10 for details.

[26] Leadbeater, N. E.; Pillsbury, S. J.; Shanahan, E.; Williams, V. A. *Tetrahedron* **2005**, *61*, 3565.

[27] While investigating the behavior of ionic liquids under microwave irradiation conditions we discovered one additional problem of using these materials in conjunction with nonpolar solvents. In many instances the ionic liquid will not be soluble in the nonpolar solvent, even at higher temperatures. While this may be of advantage for subsequent product isolation (the product being extracted to the nonpolar solvent), this creates a significant problem in terms of temperature measurement and reproducibility under microwave conditions. By heating a biphasic system consisting of immiscible solvents with vastly different loss tangents, differential heating will occur (ref 28). Depending on where and how the “reaction temperature” is measured, different values will be obtained (Figure S8 in the Supporting Information). The problem is aggravated by the fact that (single-mode) microwave reactors from different vendors either measure the temperature by IR sensor from the bottom or from the side, therefore in one case measuring the temperature of the (very hot) ionic liquid phase, in the other case monitoring the temperature of the (cooler) organic layer for the same process. We therefore recommend to use ionic liquids that are soluble in the solvent system of choice in order to avoid these problems (see refs 17 and 24).

available materials Weflon and Carboflon,[29] both originally developed for microwave-assisted solvent extraction and applications in multimode microwave reactors, proved that these passive heating elements were able to sufficiently raise the temperatures of toluene, carbon tetrachloride, and a variety of other nonpolar solvents under the carefully controlled single-mode microwave conditions described above (Figure S9 in the Supporting Information). Both materials consist of a fluoropolymer (for example Teflon) doped with varying amounts of strongly microwave absorbing graphite or carbon black. Since both types of PHEs are based on an organic polymer, however, they do not withstand temperatures of more than 240 °C. In fact, we find that the prolonged and repeated use of this material in high power density[30] single-mode cavities is limited to about 200 °C bulk temperature of the solvent. Due to the comparatively slow transfer of heat by conduction to the surrounding solvent, superheating the strongly microwave absorbing material to temperatures far above the measured bulk temperature is possible,[31] leading to deformation and degradation of the polymer.

In view of our interest in microwave chemistry at temperatures as high as 300 °C[13] we required access to a more resistant material. Silicon carbide (SiC) has long been known to be thermally and chemically resistant, and a strong microwave absorber (also termed "microwave susceptor").[32] Several articles describe the use of SiC as a microwave susceptor in material sciences, aiding, for example, in the rapid microwave-assisted synthesis of superconducting MgB_2 at temperatures close to 800 °C,[33] or in the microwave sintering of ZrO_2 ceramics.[34] In fact, because of its high melting point (ca. 2700 °C) and resistance, SiC crucibles have been used for the microwave melting of aluminum, copper, and nuclear waste glass.[35] Sintered silicon carbide has a very low thermal expansion coefficient and no phase transitions that would cause discontinuities in thermal expansion. All these properties make SiC an ideal candidate for the development of PHEs for microwave-assisted organic synthesis. The material for the current application consists of cylinders of 2000 °C sintered silicon carbide that are stable to corrosion and temperatures up to 1500 °C. For maximum flexibility, the overall shape of the cylinders (10×18 mm^2) was designed in such a way to allow their application in both single-mode and multimode microwave instruments (see Figure S10 in the Supporting Information for further details).[36]

TABLE 1. Temperatures of Nonpolar Solvents Attained by Microwave Irradiation in the Presence and Absence of SiC Passive Heating Elements[a]

solvent	tan δ[b]	*T* without SiC (°C)[c]	*T* with SiC (°C)	time (s)[d]	bp (°C)
CCl_4	n.d.	40	172	81	76
dioxane	n.d.	41	206	114	101
hexane	0.020	42	158	77	69
toluene	0.040	54	231	145	111
THF	0.047	93	151	77	66

[a] Single-mode sealed vessel microwave irradiation, 150 W constant magnetron output power, 2 mL solvent, sealed 10 mL quartz (pure solvent) or Pyrex (solvent with PHE) reaction vessel, magnetic stirring. Starting temperature 40 °C. The individual heating profiles are reproduced in the Supporting Information (Figure S11). [b] Data from ref 2a. [c] After 77−145 s of microwave irradiation (see footnote d). [d] Time until the maximum pressure limit of the instrument (20 bar) was reached and the experiment had to be aborted (with SiC).

The performance of the SiC PHEs was investigated with the experimental setup described above. The data presented in Table 1 clearly show that solvents with a very small tan δ value (tan δ < 0.04: CCl_4, dioxane, hexane) are not heated under microwave conditions at all if microwave transparent reaction vessels are used, even in small volumes in a single-mode microwave reactor that provides a considerable power density.[30] Solvents with a low tan δ value (tan δ 0.04−0.10: toluene, THF) are heated to some extent. In contrast, all solvents—even a microwave transparent solvent such as CCl_4—can be rapidly heated to high temperatures in the presence of the SiC heating element. It has to be noted that the temperatures given in Table 1 for microwave heating in the presence of SiC do not represent the highest possible temperature attainable, but merely the temperature at which the experiments had to be aborted since the pressure limit of the microwave reactor (ca. 20 bar) was reached (the temperatures therefore reflect the boiling point of the particular solvent, see also Figure S11 in the Supporting Information). By using different instrumentation with higher pressure limits, significantly higher solvent temperatures can be obtained (see Figure S12 in the Supporting Information).

Microwave Synthesis with Passive Heating Elements. Having shown the general feasibility of SiC heating elements as highly resistant and practical heating aids for nonpolar solvents under microwave conditions, their application in a variety of different chemical transformations was subsequently investigated.

a. Claisen Rearrangement. The Claisen rearrangement, the [3,3] sigmatropic rearrangement of allyl vinyl ethers that allows the preparation of γ,δ-unsaturated carbonyl compounds,[37] is a synthetically very valuable transformation. Numerous useful applications of the Claisen and related reactions in organic synthesis have been reported in the past.[37] In general, thermal Claisen rearrangements require high temperatures and proceed quite slowly. Therefore, not surprisingly, numerous reports on microwave-assisted Claisen and related rearrangements have appeared in the literature.[1,2,23,37,38] We were particularly attracted by a recent study by Ley and co-workers, who reported the microwave-assisted Claisen rearrangement of a simple allyl aryl

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(28) For a case of differential microwave heating involving a chloroform/water biphasic system, see: Raner, K. D.; Strauss, C. R.; Trainor, R. W.; Thorn, J. S. *J. Org. Chem.* **1995**, *60*, 2456.

(29) Weflon and Carboflon are commercially available heating inserts from Milestone s.r.l. (www.milestonesci.com) and CEM Corp. (www.cem.com).

(30) (a) Nüchter, M.; Ondruschka, B.; Weiss, D.; Beckert, R.; Bonrath, W.; Gum, A. *Chem. Eng. Technol.* **2005**, *28*, 871. (b) For a detailed discussion of commercially available microwave reactors and the difference between single-mode and multimode cavities, see ref 1e, Chapter 3, pp 29−55.

(31) (a) Bogdal, D.; Lukasiewicz, M.; Pielichowski, J.; Miciak, A.; Bednarz, Sz. *Tetrahedron* **2003**, *59*, 649. (b) Lukasiewicz, M.; Bogdal, D.; Pielichowski, J. *Adv. Synth. Catal.* **2003**, *345*, 1269.

(32) (a) *Properties of Silicon Carbide*; Harris, G. L., Ed.; Institute of Electrical Engineers: London, UK, 1995. (b) *Silicon Carbide*: *Recent Major Advances*; Choyke, W. J., Matsunami, H., Pensl, G., Eds.; Springer: Berlin, Germany, 2004. (c) *Advances in Silicon Carbide Processing and Applications*; Saddow, S. E., Agarwal, A., Eds.; Artech House Inc.: Norwood, MA, 2004.

(33) Dong, C.; Guo, J.; Fu, G. C.; Yang, L. H.; Chen, H. *Supercond. Sci. Technol.* **2004**, *17*, L55.

(34) Lasri, J.; Ramesh, P. D.; Schachter, L. *J. Am. Ceram. Soc.* **2000**, *83*, 1465.

(35) Sturcken, E. F. *Ceram. Trans.* **1991**, *21*, 433.

(36) SiC passive heating elements are available from Anton Paar GmbH (www.anton-paar.com).

(37) Martín Castro, A. M. *Chem. Rev.* **2004**, *104*, 2939.

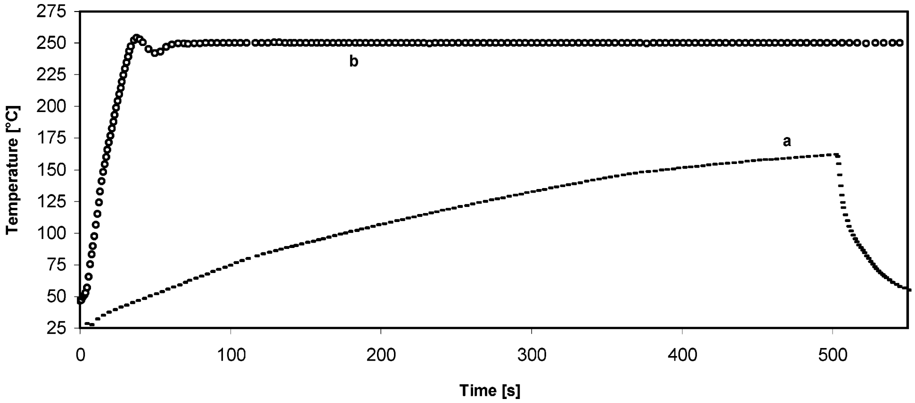
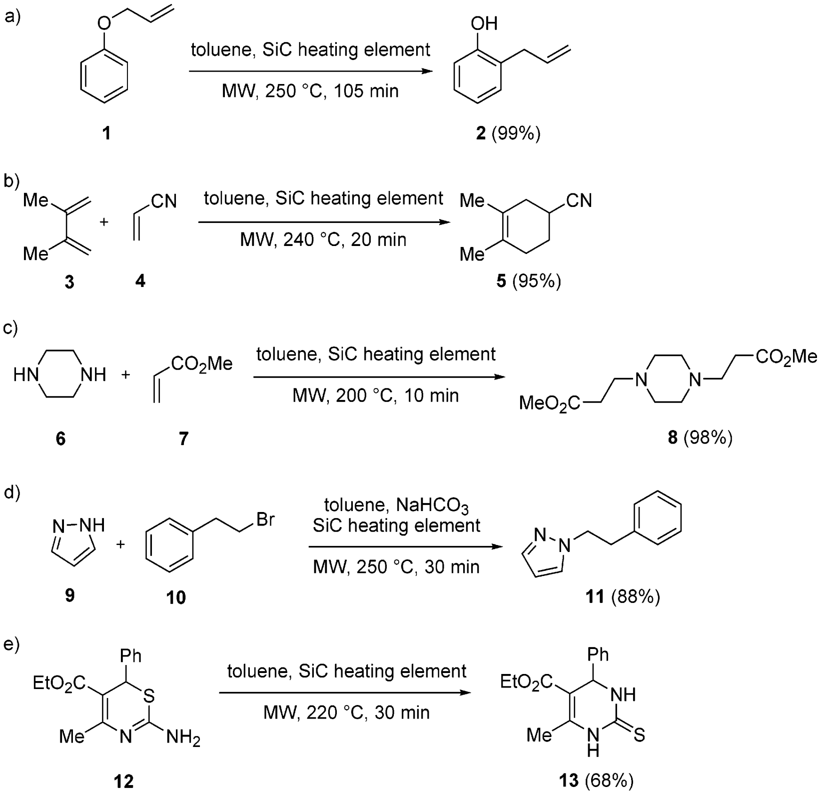


FIGURE 1. Heating profiles for a microwave-heated 0.2 M solution of allyl phenyl ether in toluene (2.0 mL). Experiments were carried out with a single-mode microwave instrument in a 10 mL sealed Pyrex vessel with magnetic stirring (IR temperature measurement). Profile a: Reaction mixture without heating element (300 W constant power, 250 °C preselected maximum temperature, see ref 40). Profile b: Reaction mixture with an SiC heating element (300 W maximum power, 250 °C preselected maximum temperature).

SCHEME 1. Microwave-Assisted Organic Synthesis in Nonpolar Solvents with Passive Heating Elements



ether using an ionic liquid−toluene solvent system.[38] A 97% yield of the rearranged product could be obtained by three successive 15 min irradiations at 220 °C, employing toluene doped with the ionic liquid 1-butyl-3-methylimidazolium hexafluorophosphate (bmimPF$_6$) as solvent. To test the usefulness of the passive heating element concept in this process, we investigated the closely related rearrangement of allyl phenyl ether (**1**) using microwave irradiation (Scheme 1a). Under conventional thermal conditions this rearrangement requires reaction times of many hours at high temperatures.[37,39] In the event, an attempt of heating a solution of the allyl ether in toluene under single-mode microwave conditions failed. Due to poor absorption properties of toluene (Table 1) and the unpolar character of substrate **1**, the overall loss tangent of the reaction mixture was not high enough to permit significant dielectric heating by microwave irradiation at 2.45 GHz. Even by taking advantage of a self-absorbing Pyrex reaction vessel, the highest observed temperature of the reaction mixture of 160 °C was not high enough to induce the thermal Claisen rearrangement **1** → **2** (conversion <1%) (Figure 1, profile a).[40] In contrast, by adding a SiC passive heating element the desired reaction temperature of 250 °C was easily reached within 30 s

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(38) Baxendale, I. R.; Lee, A.-I.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **2002**, *16*, 1850.

(39) (a) Tsai, T.-W.; Wang, E.-C.; Li, S.-R.; Chen, Y.-H.; Lin, Y.-L.; Wang, Y.-F.; Huang, K.-S. *J. Chin. Chem. Soc.* **2004**, *51*, 1307. (b) Van, T. N.; Debenedetti, S.; Kimpe, N. D. *Tetrahedron Lett.* **2003**, *44*, 4199.

(40) A safety feature of the single-mode reactor aborts the experiment if the preset temperature cannot be reached after a few minutes with full power. This also prevents overheating and damage of the magnetron.

(13 bar pressure) and full conversion to the allyl phenol **2** was obtained within 105 min (Figure 1, profile b).[41]

This method, allowing the reaction to proceed in a completely unpolar environment, provided the rearranged product in high yield and purity, with almost no side reactions detectable by HPLC and ^{1}H NMR analysis. It should be noted that the use of fluoropolymer-based heating inserts[22,23,29] is not possible here, due to the high temperatures and extended reaction times (see above). For comparison purposes we also studied the same reaction using the bmimPF$_6$–toluene solvent system similar to the conditions reported by Ley.[38] By using the "invasive" ionic liquid as heating aid, the rearrangement **1** → **2** also proceeded smoothly under comparable time/temperature conditions. With the passive heating element protocol, workup simply involved removal of the SiC cylinder by filtration or with the aid of tweezers and subsequent evaporation of solvent. In the case of ionic liquids, purification typically involves solid-phase extraction or chromatography.[14–18]

b. Diels–Alder Reactions. Diels–Alder $4\pi + 2\pi$ cycloaddition reactions arguably belong to the most useful synthetic transformations known. These pericyclic processes are employed extensively for the production of polycyclic ring systems, and are also used widely in the field of natural product synthesis.[42] Not unlike the Claisen rearrangement, pericyclic Diels–Alder cycloadditions are often carried out in an unpolar solvent, unless the possibility for reaction enhancement by solvent effects or catalysis exists.[43] Numerous Diels–Alder processes have been studied under microwave conditions due to the long reaction times and elevated temperatures often required.[1,2] For assessing the performance of the SiC heating element, we have chosen the cycloaddition between 2,3-dimethylbutadiene (**3**) and acrylonitrile (**4**) to provide the cyclohexene adduct **5** (Scheme 1b). Again, these particular[13] (and closely related) cycloaddition reactions have been previously studied under microwave conditions, including protocols involving ionic liquid-doped solvents.[15] Similar to the situation in the case of the Claisen rearrangement described above, we were able to carry out the cycloaddition in toluene as solvent at 240 °C using the SiC heating element. After 20 min of total irradiation time, a near-quantitative yield (95%) of pure product was obtained by simply removing the heating element and evaporating the volatiles under reduced pressure. Similar yields were obtained by running the reaction at 250 °C for 10 min. Again, virtually no product (<2% conversion) was obtained without the heating element (maximum reached temperature 170 °C after 7 min).[40] These data compare very favorable with the conventional process that requires several hours of heating in solvents such as 1,2-dichloroethane at 100 °C.[44]

The cycloaddition reaction described in Scheme 1b was carried out on a 2 mmol scale with a high power density single-mode microwave reactor[30] providing a 300 W maximum magnetron output power. A critical factor for the success of microwave heating technology is the ability to scale-up reactions to larger volumes.[1,2] This is often done in multimode reactors which feature significantly larger microwave cavities.[10,45] Although the magnetrons used in such instruments nominally have a larger power output (1000–1400 W), these reactors provide a significantly lower power density (power per volume).[30] As recently reported by Maes and co-workers (see above), a nonpolar solvent system that may be appropriate for a particular transformation on a small scale may not prove suitable for a larger scale experiment—either in the same or a different instrument—due to insufficient absorption and magnetron power.[10] We were therefore particularly interested to investigate the performance of the SiC heating elements in a scale-up experiment involving a multimode microwave reactor. Thus, the cycloaddition described in Scheme 1b was run on a 100 mmol scale in a multivessel rotor reactor[13,45] in four 100 mL sealed Teflon vessels each containing 25 mL of toluene, one 10 × 18 mm^2 SiC cylinder, and the two substrates. Gratifyingly, despite the more than 10-fold difference of the solvent/heating element ratio and the decreased microwave power density, the four passive heating elements were able to heat the ca. 100 mL reaction mixture to the optimized reaction temperature of 240 °C without any problem within ca. 7 min (Figure S13).[46] Product yields and purities in this 50-fold scale-up run after 20 min at 240 °C were the same as those in the small scale experiment.

c. Michael Additions. As an additional example to test the concept of passive heating elements in microwave synthesis we looked at a bimolecular addition reaction involving somewhat more polar substrates as in the two previous transformations. We have chosen the Michael addition of methyl acrylate (**7**) and piperazine as nucleophile (**6**) (Scheme 1c).[47] By using once again nonpolar toluene as the solvent, the bis-Michael adduct **8** was obtained within 10 min at 200 °C in 98% isolated yield from piperazine and 4 equiv of methyl acrylate. The reaction could also be performed with 2 equiv of the Michael acceptor, albeit providing a somewhat lower isolated product yield. Despite the presence of the protic piperazine base, microwave absorbance of the reaction mixture was not sufficient to allow efficient heating by microwave irradiation in the absence of the SiC heating element. After 7 min of irradiation with 300 W constant power the maximum temperature was 170 °C and only very low conversion to the final product was observed.[40] Full conversion to **8** at room temperature in toluene requires 2 days.

d. *N*-Alkylation Reactions. The three transformations discussed so far (Scheme 1a–c) demonstrate the usefulness of the passive heating element concept. Reactions that are preferably run in a nonpolar, low microwave-absorbing solvent system (here toluene) can be conducted efficiently in this solvent by adding a strongly microwave absorbing inert heating element. Without adding the heating element, there is practically no conversion to product since the required onset temperatures

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[41] Similar to the results by Ley (ref 38) we find that pulsed microwave heating (6 cycles of 15 min irradiation at 250 °C) gave better results (>99% conversion) than one continuous irradiation cycle for 90 min (92% conversion). This microwave pulsing effect was not investigated further, however.

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[46] The efficiency of the SiC passive heating elements in heating larger amounts (100 mL) of a variety of nonpolar solvents in multimode environments was studied in detail. These data are reproduced in the Supporting Information (Figure S12). There is also an important safety aspect that needs to be considered. It is not advised to heat non- or low-absorbing reaction mixtures for prolonged periods of time in microwave reactors. This leads to the magnetron continuously operating at the maximum power level trying to reach the selected set temperature (cf. Figure S14), and ultimately can result in overheating and damage of the magnetron (see ref 40) or destructive coupling of microwave irradiation with sensitive instrument and/or vessel parts.

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cannot be reached. Using this technique, there is no need to change the solvent or to add a polar additive such as an ionic liquid. It should be noted, however, that in principle (despite technical difficulties)[27] in all the cases described so far, these processes can also be performed by using invasive ionic liquids as microwave heating aids at similar temperatures, as previously reported in the literature.[15,38]

We therefore wanted to test the heating element concept in a more challenging case where it has been explicitly stated that the use of ionic liquids as additives is not possible. A case in point are *N*-alkylations with alkyl halides as reagents. According to Leadbeater, the alkylation of pyrazole with alkyl halides in toluene in the presence of a standard dialkyl imidazolium hexafluorophosphate ionic liquid is not possible.[15] At the elevated temperatures used in the alkylation protocol, the ionic liquid was completely destroyed within a few seconds by reaction with the alkyl halide reagent.[15] In our hands, the same reaction (Scheme 1d), when carried out with the SiC passive heating element instead of an ionic liquid, readily provided the desired alkylated pyrazole **11** in high yield. By using $NaHCO_3$ as a mild base to neutralize the formed HBr,[48] full conversion was achieved within 30 min at 250 °C resulting in an 88% isolated product yield after purification by chromatography. Note that the optimized cylindrical geometry of the SiC heating element allows for stirring of the heterogeneous reaction mixture with a magnetic stir bar (see Figure S10 for details).

e. Dimroth Rearrangement. A final example involves the high-temperature rearrangement of a heterocycle bearing a nucleophilic free amino group. This again is a case where the use of high-temperature microwave heating is expected to be beneficial, but an ionic liquid cannot be used as a heating aid due to the presence of a nucleophilic group.[15,20] We have recently reported the generation of functionalized 2-amino-1,3-thiazine libraries via combinatorial protocols.[49] These types of 1,3-thiazine heterocycles generally undergo thermal, uncatalyzed rearrangement to the thermodynamically more stable pyrimidine-2-thions.[50,51] In the case of thiazine **12**, differential scanning calorimetry measurements indicated that in the solid state the onset temperature for rearrangement to pyrimidine **13** (Scheme 1e) lies above 180 °C. Since this strictly thermal Dimroth rearrangement[51] does not require any protic or other catalysts we wanted to perform the rearrangement in a nonpolar environment using toluene as solvent. The optimized conditions involved heating a solution of thiazine **12** in toluene together with a SiC heating element at 220 °C for 30 min, providing a 68% product yield after recrystallization of the crude material. There was no reaction without added heating element (max temperature after 4 min: 140 °C)[40] and, importantly, in the presence of an ionic liquid the solution turned completely black after a few minutes of microwave heating and led to a complex product mixture.

Conclusion and Outlook

In summary, we have shown that nonpolar organic solvents which are low microwave absorbers can be heated to very high temperatures in the presence of so-called passive heating elements (PHEs) made out of strongly microwave absorbing and chemically inert sintered silicon carbide (SiC). This technique now allows the use of nonpolar solvents in microwave-assisted synthesis. In contrast to the well-known use of ionic liquids as heating aids in microwave synthesis, this technique is truly chemically noninvasive and does not change the polarity or other properties of the solvent system. We have successfully demonstrated that passive heating elements can be used in cases where ionic liquids are incompatible with one of the substrates and for a variety of other synthetic transformations. Furthermore, the use of SiC cylinders is also more practical since the noninvasive heating elements can be mechanically removed very easily and no purification from any ionic liquid is required. The particular SiC material utilized herein is mechanically, thermally, and chemically resistant up to 1500 °C. The heating elements are therefore compatible with any solvent or reagent, virtually indestructible, and can be reused unlimited without loss of efficiency. The SiC cylinders can be employed in both single-mode and multimode microwave reactors and provide the additional benefit that instruments can be operated at lower power levels—and thus inherently safer—due to the higher overall absorption of microwave energy by the contents of the reaction vessel.

There is one interesting aspect associated with the use of passive heating elements that needs to be discussed, however. The SiC insert very strongly absorbs microwave energy and subsequently transfers the generated heat via conduction phenomena to the reaction mixture. This means that most of the "microwave heating" using this technology essentially occurs by conventional conduction and convection principles, similar to an oil-bath experiment generating a hot surface and temperature gradients. In addition, it has to be assumed that there is only a very little possibility for any direct interaction of the microwave field with specific molecules in the reaction medium—virtually excluding the possibility of any nonthermal microwave effects[3]—since most of the energy will be absorbed by the heating element and not by the surrounding solution. Therefore, it appears that many of the presumed benefits of microwave synthesis may be lost by using this technique.[52] In our hands, however, this method has worked very well and we have not seen any obvious disadvantages in using the heating elements for the chemical transformations we have studied and presented herein. The aim of the present work was to investigate silicon carbide material as novel and useful passive heating elements for microwave-assisted organic synthesis. We plan to scrutinize

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(52) It has to be considered, however, that in many cases of microwave-assisted synthesis with nonpolar media the reaction vessel also functions as a "passive heating element" (self-heating of the glass vessels, see Figures S1 and S14) and that there are several recent examples where the indirect heating of reaction containers by microwaves was achieved by coating the vessel with a thin metal film that proved critical for the success of the investigated transformations. For example, see: (a) He, P.; Haswell, S. J.; Fletcher, P. D. I. *Lab Chip* **2004**, *4*, 38. (b) He, P.; Haswell, S. J.; Fletcher, P. D. I. *Appl. Catal., A* **2004**, *274*, 111. (c) Comer, E.; Organ, M. G. *J. Am. Chem. Soc.* **2005**, *127*, 8160. (d) Stadler, A.; Kappe, C. O. *Org. Lett.* **2002**, *4*, 3541. There are also cases where reaction containers, i.e., deep well plates made out of Weflon material, have been used successfully in microwave synthesis: (e) Macleod, C.; Martinez-Teipel, B. I.; Barker, W. M.; Dolle, R. E. *J. Comb. Chem.* **2006**, *8*, 132. (f) Nüchter, M.; Ondruschka, B. *Mol. Diversity* **2003**, *7*, 253. (g) See also: Lin, Q.; O'Neill, J. C.; Blackwell, H. E. *Org. Lett.* **2005**, *7*, 4455.

the more subtle consequences of using these materials relating to microwave effects in detail in the future.

Experimental Section

2-Allylphenol (2, Scheme 1a). A 10 mL microwave vessel equipped with a Teflon-coated stir bar and a SiC heating element cylinder was filled with 2 mL of toluene and 49 mg (0.36 mmol, 0.05 mL) of allyl phenyl ether (**1**). After the vessel was sealed, the sample was irradiated for 105 min at 250 °C. The reaction mixture was subsequently cooled to 50 °C by compressed air, the vessel was opened, and the SiC cylinder was removed. Evaporation of the solvent under reduced pressure resulted in 49 mg (quantitative, HPLC homogeneity at 215 nm: >95%) of rearranged product **2** as a yellowish oil. ^{1}H NMR (360 MHz, $CDCl_3$) δ 3.45 (d, $J = 1.30$, 2 H), 5.00 (s, 1H), 5.16−5.20 (m, 2 H), 5.99−6.08 (m, 1H), 6.82−7.17 (m, 4H).[53]

3,4-Dimethylcyclohex-3-enecarbonitrile (5, Scheme 1b). Small scale: A 10 mL microwave vessel equipped with a Teflon-coated stir bar and a SiC heating element cylinder was filled with 2 mL of toluene, 334 mg (4.0 mmol, 0.46 mL) of 2,3-dimethylbutadiene (**3**), and 105 mg (2.00 mmol, 0.13 mL) of acrylonitrile (**4**). After the vessel was sealed, the sample was irradiated for 20 min at 240 °C. The reaction mixture was subsequently cooled to 50 °C by compressed air, the vessel was opened, and the SiC cylinder was removed. Evaporation of the solvent and excess butadiene provided 256 mg (95%) of cycloadduct **5** as a pale yellow oil (HPLC homogeneity at 215 nm: 99%). **Large scale:** Four 100 mL Teflon reaction vessels each equipped with a 2 cm stir bar and a SiC heating element cylinder were individually filled with 25 mL of toluene, 4.1 g (50 mmol, 5.65 mL) of 1,3-dimethylbutadiene (**3**), and 1.32 g (25 mmol, 1.64 mL) of acrylonitrile (**4**). The vessels were sealed and placed in a 16 vessel rotor system and subsequently irradiated for 20 min at 240 °C in a multimode reactor (Figure S13). After the vessels were cooled to 50 °C and the contents of the four reaction were combined, solvent and excess butadiene were evaporated to provide 13.1 g (97%) of cycloadduct **5** as a pale yellow oil (HPLC homogeneity at 215 nm: 99%). ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.63 (s, 6 H), 1.83−2.26 (m, 6 H), 2.77−2.79 (m, 1 H).[13]

3-[4-(2-Methoxycarbonylethyl)piperazin-1-yl]propionic Acid Methyl Ester (8, Scheme 1c). A 10 mL microwave vessel equipped with a Teflon-coated stir bar and a SiC heating element cylinder was filled with 2 mL of toluene, 172 mg (2.0 mmol) of piperazine (**6**), and 688 mg (8.0 mmol, 0.72 mL) of methyl acrylate (**7**). After the vessel was sealed, the sample was irradiated for 10 min at 200 °C. The reaction mixture was subsequently cooled to 50 °C by compressed air, the vessel was opened, and the SiC cylinder was removed. Evaporation of the solvent and excess methyl acrylate provided crude bis-adduct **8**, which was subsequently purified by dry column flash silica gel chromatography with methanol as an eluant to yield 503 mg (98%) of pure adduct **8** as colorless solid. Mp 53 °C (lit.[54] mp 55 °C). ^{1}H NMR (360 MHz, $CDCl_3$) δ 2.51 (t, $J = 7.6$ Hz, 12 H), 2.70 (t, $J = 7.3$, 4 H), 3.69 (s, 6 H);[55] MS (positive APCI) m/z 259 [M + 1].

1-Phenethyl-1*H*-pyrazole (11, Scheme 1d). A 10 mL microwave vessel equipped with a Teflon-coated stir bar and a SiC heating element cylinder was filled with 2 mL of toluene, 136 mg (2.0 mmol) of pyrazole (**9**), 0.84 mg (1.0 mmol) of $NaHCO_3$, and 185 mg (1.0 mmol, 0.14 mL) of (2-bromoethyl)benzene (**10**). After the vessel was sealed, the sample was irradiated for 30 min at 250 °C. The reaction mixture was subsequently cooled to 50 °C by compressed air, the vessel was opened, and the SiC cylinder was removed. Evaporation of the solvent and purification of the crude product by dry column silica gel flash chromatography with a 1:1 mixture of petroleum ether and ethyl acetate as an eluant provided 152 mg (88%) of product **11** as a pale yellow oil (HPLC homogeneity at 215 nm: 97%). ^{1}H NMR (360 MHz, DMSO-d_6) δ 3.08 (t, $J = 7.4$ Hz, 2 H), 4.33 (t, $J = 7.4$ Hz, 2 H), 6.16 (t, $J = 1.7$ Hz, 1 H), 7.13−7.27 (m, 5 H), 7.43 (s, 1 H), 7.57 (d, $J = 1.7$ Hz, 1 H);[48] MS (positive APCI) m/z 173.0 [M + 1] ($M = 172.23$).

Ethyl 1,2,3,4-Tetrahydro-6-methyl-4-phenyl-2-thioxopyrimidine-5-carboxylate (13, Scheme 1e). A 10 mL microwave vessel equipped with a Teflon-coated stir bar and a SiC heating element cylinder was filled with 2 mL of toluene and 69 mg (0.25 mmol) of ethyl-2-amino-4-methyl-6-phenyl-6*H*-1,3-thiazine-5-carboxylate (**12**).[49] After the vessel was sealed, the sample was irradiated for 30 min at 220 °C. The reaction mixture was subsequently cooled to 50 °C by compressed air, the vessel was opened, and the SiC cylinder was removed. Evaporation of the solvent and recrystallization of the crude product from acetonitrile provided 47 mg (68%) of pyrimidine **13** as a colorless solid. Mp 201 °C (lit.[56] mp 206 °C). ^{1}H NMR (360 MHz, DMSO-d_6) δ 1.10 (t, $J = 7.1$ Hz, 3 H), 2.29 (s, 3 H), 4.00 (q, $J = 7.1$ Hz, 2 H), 5.17 (d, $J = 3.3$ Hz, 1 H), 7.20−7.37 (m, 5 H), 9.66 (s, 1 H), 10.34 (s, 1 H).[56]

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Supporting Information Available: Description of general experimental and microwave procedures, heating profiles for solvents and reaction mixtures under single-mode and multimode microwave irradiation conditions, and images of passive heating elements. This material is available free of charge via the Internet at http://pubs.acs.org.

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