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Microwave-Assisted Reactions in Organic Synthesis—Are There Any Nonthermal Microwave Effects?

Nikolai Kuhnert*

Introduction

The development of resource- and environmentally friendly processes in terms of sustainable chemistry has become a focal point in chemical research in recent years. Of particular importance is a reduction in the amounts of solvents and hazardous substances required, and the more efficient use of energy.[1, 2] Synthetic chemists have neglected alternative sources of heat for chemical reactions, and still rely on isomantles, oil, sand and water baths, or heatguns as heating devices.

The use of microwave (MW) irradiation as a source of heat in synthetic chemistry offers a promising alternative. Microwaves differ from conventional heat sources, in that the solvents or reactants are directly heated without heating the reaction vessel. By conventional methods, the vessel is heated and this then transfers the heat by convection. Microwave heating is more efficient in terms of the energy used, produces a higher temperature homogeneity, and is considerably more rapid than conventional heat sources. The first application of microwave irradiation in chemical synthesis was published in 1986.[3] It is worth noting that the first commercial household microwave oven was introduced to the market in 1954, and that the transfer of microwave technology into the chemistry laboratory has taken the unusually long time of over three decades. In typical microwave ovens, the magnetrons (microwave generators) produce a microwave wavelength of 12.25 cm, which corresponds to a frequency of 2.45 GHz. The basic theory underlying the interaction of microwaves with macroscopic matter was formulated by von Hippel[4] and, for the basic equations, the reader is referred to this work and to an excellent overview by Mingos.[5]

Over the last decade, microwave-assisted chemistry has matured into a highly useful technique and provides an interesting alternative for heating chemical reactions. The large number of publications clearly indicates the development of this area of chemistry.[6–11]

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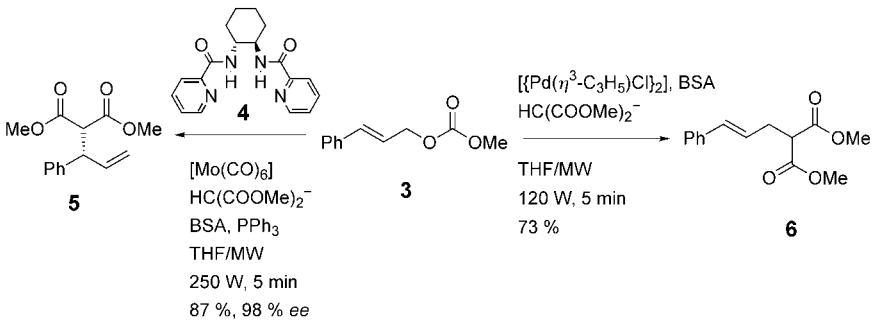
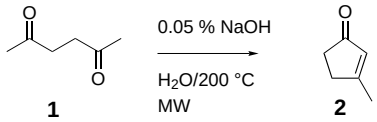
Microwave techniques in synthetic chemistry often elicit a dramatic increase of the reaction rate and yields. An impressive example was reported by Loupy et al., who observed an increase in yield from 2% to 95% under microwave conditions, in the Leuckart reductive amination.[12] These rate and yield enhancements have been suggested by some to be caused by specific, nonthermal microwave effects.[13–15] This article will report the current state of microwave chemistry and highlights the latest experiments, which for the first time allow a direct comparison between the microwave and thermal procedures. This comparison allows the first clear conclusions to be drawn in the discussion about nonthermal microwave effects.



Scheme 2. Transition-metal-catalyzed reactions under microwave conditions. [17] BSA = *N*,*O*-Bis-(trimethylsilyl)acetamide.

Prior to the discussion of special microwave effects, I would like to introduce two representative examples of microwave chemistry that illustrate the confusion caused by an uncritical consideration of published results and lead to an overestimate of the capabilities of the method. Work by the Strauss group has focused on the use of water under microwave conditions.[16] In a high-pressure reactor, water temperatures of 200–300 °C can be reached by rapid microwave heating. Under these high temperatures, the dielectric constant of water changes considerably and water behaves as a "pseudo-organic solvent". The cyclization of the 1,4-diketone **1** in 0.05% NaOH solution at 200 °C yields the 2-cyclopentenone **2** (Scheme 1) within 15 minutes.[16]



Scheme 1. Cyclizations in water under aqueous conditions.[16]

Hallberg and co-workers have shown that a molybdenum-catalyzed allylic substitution of the carbonate **3** and dimethylmalonate can be performed under microwave heating with a shortened reaction time, excellent stereoselectivity, and excellent yield to give the regioisomeric products **5** and **6.** By use of the enantiomerically pure ligand **4**, mostly **5** is formed, but in the presence of palladium catalysts, **6** is the main product (Scheme 2).[17] Careful monitoring of the reaction temperature revealed that the reaction proceeded at 220 °C in THF, far above the boiling point of this solvent under normal pressure. This temperature was achieved by an effect termed "microwave flash heating" by the authors.

Both examples illustrate the differences between the reaction conditions of thermal and microwave conditions, and underline the difficulties in such a comparison. Under microwave conditions, the reactions proceed in closed vessels at considerable pressure, far above the boiling points of the solvents. Any rate acceleration in these cases might be caused by the high reaction temperature and the changes of the physical properties of the solvent. However, as no direct comparison with a thermal procedure under comparable conditions was undertaken, some room remains for speculation about nonthermal microwave effects.

Instrument Design and History

Most microwave chemistry is still performed in multimodal household ovens. For a long time, these instruments have been treated with scepticism and are of limited use. Synthetic chemistry in such commercial household ovens is heavily criticized as it suffers from a low reproducibility.[11] Furthermore, microwave work using household ovens centers around the use of polar solvents such as alcohols, water, DMF, and DMSO, or mixtures of these. As a result, uncontrolled heating of the reaction mixtures occurs, usually accompanied by a considerable build-up of pressure in closed reaction vessels, or rapid evaporation of the solvent in open vessels; these effects often turn microwave synthetic chemistry in these ovens into a hazardous adventure. Recent advances in instrumentation design, in particular the design of dedicated microwave ovens for organic synthesis, have improved the situation enormously. The ovens for organic synthesis use a monomodal cavity and the microwave beam is focused onto the sample using a waveguide. In this way, the interaction between the microwave field and the reaction mixture is well controlled and can easily be optimized. An elegant demonstration of the optimization of reaction conditions with respect to temperature, pressure, reaction time, and solvent in the microwave-assisted Hantzsch dihydropyridine synthesis was recently reported by Öhberg and Westman.[18] Figure 1 illustrates the basic set up of the two alternative microwave ovens.

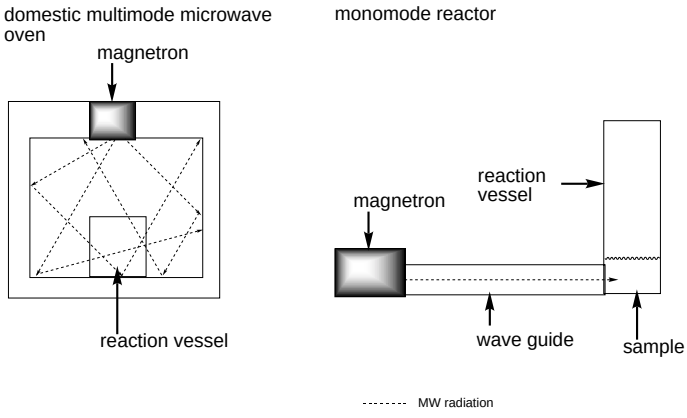


Figure 1. Schematic representation of a household microwave oven and an oven designed for synthesis.

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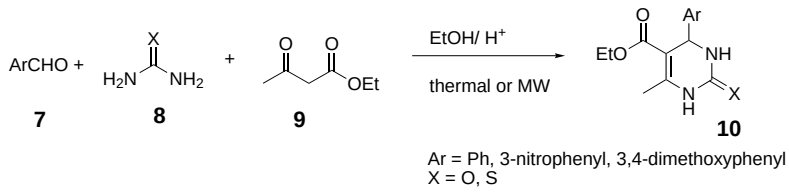
In the microwave oven for synthesis, the reaction temperature can be monitored and controlled using a fiber-optic temperature probe or, alternatively, the surface temperature can be monitored using an IR thermometer, which allows the maintenance of a constant reaction temperature. Pressure can be monitored in sealed systems, and the ovens can be fitted with reflux condensers to realize conventional reflux processes in open vessels. Additionally, mechanical stirring can effectively suppress localized superheating and bumping (delayed boiling). These additional features mean that individual reactions can be easily optimized, are reproducible, have a low energy useage, and result in better chemical yields and faster reactions. Most importantly, the reaction conditions are well defined and allow a direct comparison of microwave heating with conventional thermal heating. This instrumentation is now readily available at affordable prices for routine laboratory use.

Rate Enhancements and Nonthermal Effects

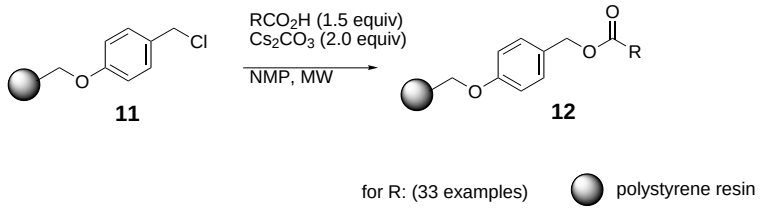
Kappe and Stadler have now for the first time made a direct comparison between microwave heating and thermal heating under almost identical conditions. In their first contribution,[19] they revisited the Bignelli reaction, for which two microwave protocols have been published; these both report increased yields and shorter reaction times.[20, 21] In this three-component coupling reaction, an aromatic aldehyde **7**, a urea or thiourea derivative **8**, and ethylacetoacetate (**9**) condense to form a dihydropyrimidine **10** (Scheme 3).

Careful comparisons of the conventional thermal with the microwave-assisted reaction revealed the following finding: there was no appreciable difference in the reaction rates between reactions carried out under thermal heating or microwave heating at identical temperatures. The differences in rates and yields observed between thermal and microwave heating can be fully attributed to higher reaction temperatures in the microwave methods. The advantages of the microwave method are thus based only on a conventional thermal effect. In sealed vessels, appreciable superheating is observed (e.g. ethanol 180 °C at 20 bar), which leads to the formation of undesired side-products, rather than to an improvement of the reaction in terms of yield and rate. Increased yields are obtained by using a conventional household microwave oven and can be rationalized in terms of increased concentration of the reactants caused by rapid evaporation of the solvent and water, which acts as a driving force in the condensation.



Scheme 3. Bignelli reaction under microwave conditions.[19]

In a second publication, Kappe and Stadler turned their attention to microwave-assisted, solid-supported chemistry.[22] As a model reaction, they investigated the Cs_2CO_3-mediated ester formation with Wang resin-bound benzoyl chloride (**11**; Scheme 4). Again, no appreciable nonthermal effects could be observed by comparing the microwave-heating and thermal-heating reactions at the same temperature. The increased efficiency observed for the microwave method in comparison to procedures published earlier can be attributed to a direct rapid heating and the use of NMP as a high boiling polar solvent, ideally suited to the microwave conditions. However, the authors have discovered one of the most promising niches for microwave chemistry. In the synthesis of combinatorial libraries on solid supports, an increase in reaction rates and efficiency would improve the otherwise rather sluggish and slow reactions. Other drawbacks of thermal solid-supported chemistry, such as degradation of the polymer support caused by long reaction times, are avoided.



Scheme 4. Solid-phase reaction under microwave conditions. [22] NMP = *N*-Methylpyrrolidinone.

Summary and Outlook

Because of the thorough work of Kappe's group, the comparison of thermal- and microwave-heating methods is possible for the first time. It can be cautiously concluded (see below) that all speculation of special and nonthermal effects in microwave heating has no basis. The reported increased reaction rates and yields have lost their magic; they can be rationalized by taking into account increased temperatures caused by superheating or concentration effects. I strongly hope that all future publications in microwave chemistry will follow Kappe's example and thoroughly account for the observed improvements in reaction rates and yields.

Recent work by Jones and co-workers, however, [23] might open up a completely different question in microwave chemistry. Although not explicitly stated, their work on the heterogeneous deuteration of indole derivatives shows that there is a difference in the selectivity for deuterium incorporation between thermal-[24] and microwave-heating methods. Whereas in homogenous reactions under microwave conditions, the selectivity essentially follows the thermal pattern,[25] it seems to be possible to alter the selectivity in heterogeneous reactions. It is left open to interpretation, whether a special microwave effect has to be taken into account in these heterogeneous reactions.

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Biosynthesis of Polyunsaturated Fatty Acids by Polyketide Synthases

Ursula Kaulmann and Christian Hertweck*

Nature's virtuosity of linking and tailoring simple carboxylic acid monomers to give a huge structural diversity of polyketide and fatty acid metabolites has been a fascinating subject for interdisciplinary research since the early works of Collie at the start of the 20th century.[1] During the past few decades a large body of knowledge has been established by using modern molecular biology methods, from which a deeper insight into the processes employed in fatty acid and polyketide biosynthesis has been gained.[2–4] Both biosynthetic pathways have strong homologies in the chemical mechanisms involved in chain extension and in the common pool of simple precursors (acetyl-CoA, malonyl-CoA),[5, 6] as well as in the character of the enzymes used for chain propagation and processing.[2, 7] In general, polyketides and fatty acids are constructed by repetitive decarboxylative Claisen ester condensations of an acyl-CoA starter unit with (methyl)malonyl-CoA units catalyzed by a β-ketoacyl synthase (KS). This process usually involves a (malonyl)acyl transferase (MAT/AT) and an acyl carrier protein (ACP). In fatty acid biosynthesis, subsequent β-oxo processing by a keto reductase (KR), dehydratase (DH), and an enoyl reductase (ER) generally yields a fully saturated acyl backbone. In contrast to this, the reductive steps in polyketide biosynthesis are partly or fully omitted, thus giving rise to a more complex pattern of functionalization. The elongation/reduction cycles are repeated until a defined chain length is obtained. The thioester-bound substrate is then released from the enzyme complex and may be subjected to further tailoring, such as desaturation (especially fatty acids), oxidation, glycosylation, or methylation (especially polyketides).[8] On the basis of genetic analyses and the architecture of the proteins employed, fatty acid synthases (FASs) and polyketide synthases (PKSs) are both generally classified into two types: type I, in which the active sites are linearly arranged on a large module, and type II, which consists of a dissociable complex of small, discrete monofunctional proteins.[9, 10] Despite remarkable similarities in their setup and functions, PKSs and FASs are clearly distinct in their detailed programming at the amino acid level, and—more importantly—they constitute a branch point between primary and secondary metabolism. It is thus a matter of speculation that both pathways diverged at an early stage during evolution.

In view of this knowledge, a recent discovery that long-chain polyunsaturated fatty acids (PUFAs) can be biosynthesized by bacterial polyketide synthases is ground-breaking news.[11] PUFAs have long been known as essential membrane components in the brain and retina[12, 13] as well as precursors of signaling molecules, such as the prostaglandins, thromboxanes, and leukotrienes,[14, 15] but—until recently—they were believed to be produced exclusively by eukaryotic organisms, not by bacteria. Recently, several research groups have independently identified PUFAs, such as eicosapentaenoic acid (EPA, 20:5n3), docosahexaenoic acid (DHA, 22:6n3), and arachidonic acid (AA, 20:4n6), from various psychro-

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