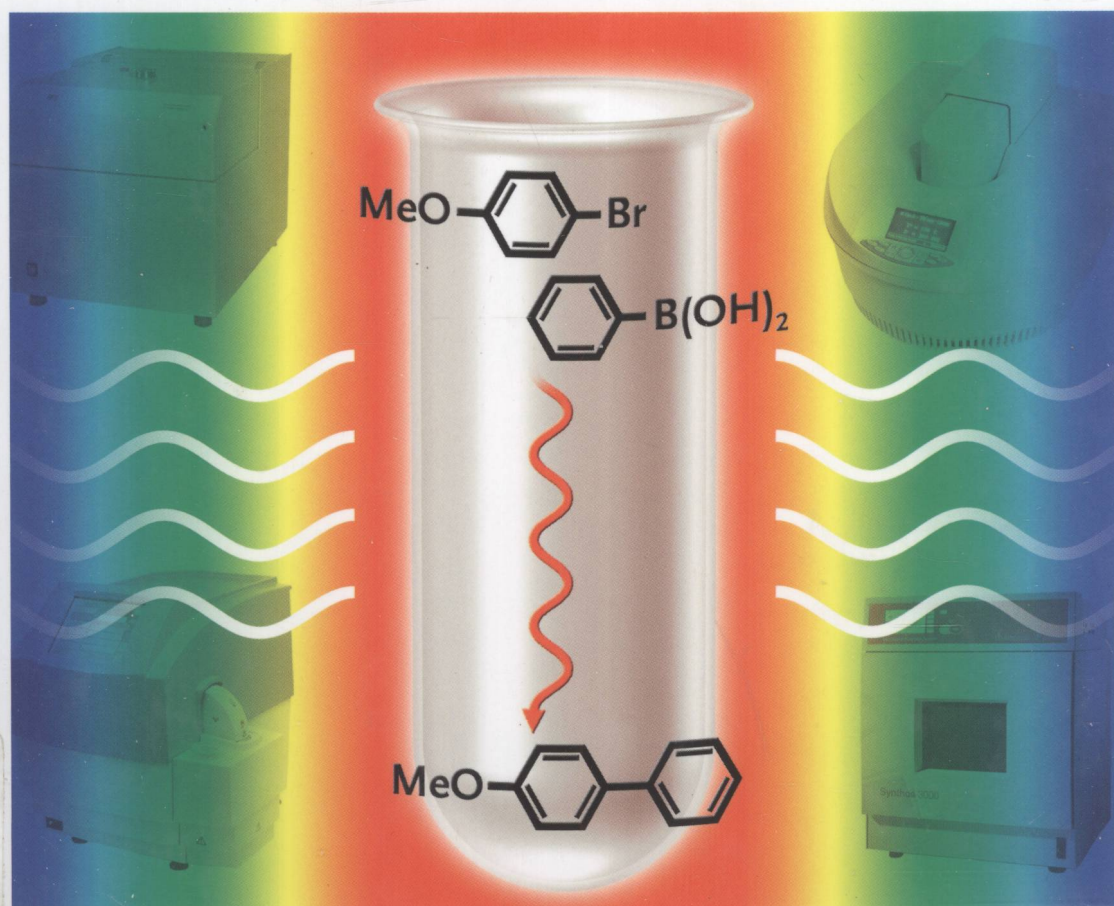


C. Oliver Kappe, Doris Dallinger,
and S. Shaun Murphree

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Practical Microwave Synthesis for Organic Chemists

Strategies, Instruments, and Protocols



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and S. Shaun Murphree*

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Preface

Today, a large body of work on microwave-assisted organic synthesis is available in the published and patent literature. Close to one hundred review articles, several books, and online databases already provide extensive coverage of the subject for the specialist reader. The goal of the present book is to provide an introductory treatise for beginners, a sort of “How To Get Started” guide. Apart from a few articles in the *Journal of Chemical Education*, very little introductory and practical hands-on information on controlled microwave chemistry has been presented in a textbook style format.

This fact has prompted the publication of the present work “*Practical Microwave Synthesis for Organic Chemists – Strategies, Instruments, and Protocols*” which serves both the beginner and the more experienced microwave user. A major motivation for writing this treatise has been the continuous and enthusiastic feedback obtained from scientists during conferences and short courses on microwave synthesis organized by the authors. In particular, the very popular MAOS conference series organized since 2003, in combination with practical hands-on or classroom-style training courses, has led to a collection of questions and comments from the attendees and has stimulated the design and concept for this book. It has been written mainly with the microwave novice in mind. Several chapters are specifically designed for beginners, such as undergraduate or graduate students in academia, or industrial scientists getting started in microwave-assisted organic synthesis.

Following a brief introduction (Chapter 1), Chapter 2 details the basic concepts of microwave dielectric heating theory and provides insight into the current understanding of microwave effects. In Chapter 3 a comprehensive review of most of the commercially available single-mode and multimode microwave reactors for organic synthesis is presented. Chapter 4 provides an extensive overview of the different microwave processing techniques that are available today, while Chapter 5 contains many useful tips for the microwave novice, including a “Frequently Asked Questions” Section. The last chapter of the book (Chapter 6) contains a collection of carefully selected and documented microwave experiments that may also be used by scientists in academia to design a course on microwave-assisted organic synthesis. All examples have been tested by advanced undergraduate students in the course of a

special “Microwave Chemistry Lab Course” during the spring of 2007 at the University of Graz.

Writing this book would have been impossible without considerable assistance from all the members of the Christian Doppler Laboratory for Microwave Chemistry (CDLMC) in Graz. All past and present members are acknowledged for their invaluable contributions over the years. Special thanks go to Jennifer M. Kremsner, Toma N. Glasnov, Hana Prokopcová, Bernadett Bacsa, Jamshed Hashim, Tahseen Razzaq and Florian Reder for their help in assembling the practical examples presented in Chapter 6. The students taking part in the “Microwave Chemistry Lab Course” are particularly acknowledged for their engagement and valuable input. In this context the authors wish to thank the Fulbright Commission and the Austrian–American Educational Commission for supporting the international collaboration leading to the development of this practical course. Thanks are also due to the microwave equipment vendors for providing detailed information and high resolution graphics of their instruments. In this context, the support of Alexander Stadler (Anton Paar GmbH), Martin Keil (Biotage AB), Axel Schöner (CEM Corp.) and Mauro Ianelli (Milestone s.r.l.) is acknowledged.

Graz
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May 2008

*C. Oliver Kappe and Doris Dallinger,
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1

Microwave Synthesis – An Introduction

While fire is now rarely used in synthetic chemistry, it was not until Robert Bunsen invented the burner in 1855 that the energy from this heat source could be applied to a reaction vessel in a focused manner. The Bunsen burner was later superseded by the isomantle, oil bath or hot plate as a source of applying heat to a chemical reaction. In the past few years, heating chemical reactions by microwave energy has been an increasingly popular theme in the scientific community. Since the first published reports on the use of microwave irradiation to carry out 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 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 related 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. The statement that, in principle, any chemical reaction that requires heat can be performed under microwave conditions has today been generally accepted as a fact by the scientific community.

The short reaction times provided by microwave synthesis make it ideal for rapid reaction scouting and optimization of reaction conditions, allowing very rapid progress through the “hypotheses–experiment–results” iterations, resulting in more decision points per unit time. In order to fully benefit from microwave synthesis one has to be prepared to fail in order to succeed. While failure could cost a few minutes, success would gain many hours or even days. The speed at which multiple variations of reaction conditions can be performed allows a morning discussion of “What should we try?” to become an after lunch discussion of “What were the results?” Not

surprisingly, therefore, many scientists, both in academia and in industry, have turned to microwave synthesis as a frontline methodology for their projects.

Arguably, the breakthrough in the field of MAOS on its way from laboratory curiosity to standard practice started in the pharmaceutical industry around the year 2000. Medicinal chemists were among the first to fully realize the true power of this enabling technology. Microwave synthesis has since been shown to be an invaluable tool for medicinal chemistry and drug discovery applications since it often dramatically reduces reaction times, typically from days or hours to minutes or even seconds [5]. Many reaction parameters can therefore be evaluated in a few hours to optimize the desired chemistry. Compound libraries can then be rapidly synthesized in either a parallel or (automated) sequential format using microwave technology [5]. In addition, microwave synthesis often allows the discovery of novel reaction pathways, which serve to expand “chemical space” in general, and “biologically-relevant, medicinal chemistry space”, in particular.

In the early days of microwave synthesis, experiments were typically carried out in sealed Teflon or glass vessels in a domestic household microwave oven without any temperature or pressure measurements [1]. Kitchen microwave ovens are not designed for the rigors of laboratory usage: acids and solvents corrode the interiors quickly and there are no safety controls. The results were often violent explosions due to the rapid uncontrolled heating of organic solvents under closed vessel conditions. In the 1990s several groups started to experiment with solvent-free microwave chemistry (so-called dry-media reactions), which eliminated the danger of explosions [10]. Here, the reagents were pre-adsorbed onto either a more or less microwave transparent inorganic support (i.e., silica, alumina or clay) or a strongly absorbing one (i.e., graphite), that additionally may have been doped with a catalyst or reagent. Particularly in the beginning of MAOS, the solvent-free approach was very popular since it allowed the safe use of domestic microwave ovens and standard open vessel technology. While a large number of interesting transformations using dry-media reactions have been published in the literature [10], technical difficulties relating to non-uniform heating, mixing, and the precise determination of the reaction temperature remained unsolved, in particular when scale-up issues needed to be addressed.

Alternatively, microwave-assisted synthesis was, in the past, often carried out using standard organic solvents under open vessel conditions. If solvents are heated by microwave irradiation at atmospheric pressure in an open vessel, the boiling point of the solvent typically limits the reaction temperature that can be achieved. In order to nonetheless achieve high reaction rates, high-boiling microwave absorbing solvents were frequently used in open-vessel microwave synthesis [11]. However, the use of these solvents presented serious challenges during product isolation and recycling of solvent. In addition, the risks associated with the flammability of organic solvents in a microwave field and the lack of available dedicated microwave reactors allowing adequate temperature and pressure control were major concerns. The initial slow uptake of microwave technology in the late 1980s and 1990s has often been attributed to its lack of controllability and reproducibility, coupled with a general lack of understanding of the basics of microwave dielectric heating.

In particular, the use of kitchen microwave ovens in combination with non-reliable temperature monitoring devices led to considerable confusion in the microwave chemistry community in the late 1990s and has given MAOS a bad reputation and the stigma of a “black box” science. The majority of organic chemists at that time were not taking microwave chemistry seriously and the discussion and irritation around the topic of “microwave effects” has probably contributed to this situation [12]. Historically, since the early days of microwave synthesis, the observed rate-accelerations and sometimes altered product distributions compared to oil-bath experiments led to speculation on the existence of so-called “specific” or “non-thermal” microwave effects [13]. Such effects were claimed when the outcome of a synthesis performed under microwave conditions was different from the conventionally heated counterpart at the same apparent temperature. Reviewing the present literature it appears that today most scientists agree that, in the majority of cases, the reason for the observed rate enhancements is a purely thermal/kinetic effect, that is, a consequence of the high reaction temperatures that can rapidly be attained when irradiating polar materials in a microwave field, although clearly effects that are caused by the uniqueness of the microwave dielectric heating mechanism (“specific microwave effects”) must also be considered. While for the chemist in industry this discussion may seem futile, the debate on “microwave effects” is undoubtedly going to continue for many years in the academic world. Because of the recent availability of modern dedicated microwave reactors with on-line accurate monitoring of both temperature and pressure, some of the initial confusion on microwave effects has subsided. This can also be attributed, to some extent, to the fact that microwave synthesis today is mostly carried out in solution phase using organic solvents, where the temperature of the reaction mixture can generally be adequately monitored.

Controlled MAOS in sealed vessels using standard solvents – a technique pioneered by Strauss in the mid 1990s [14] – has thus celebrated a steady comeback since the year 2000 and today clearly is the method of choice for performing microwave-assisted reactions. This is evident from surveying the recently published literature in the area of microwave-assisted organic synthesis (Figure 1.1). In addition to the primary and patent literature, many review articles [3–19], several books [2], special issues of journals [20], feature articles [21], online databases [22], information on the world-wide-web [23], and educational publications [24, 25] provide extensive coverage of the subject. Among the about 850 original publications that appeared in 2007 describing microwave-assisted reactions under controlled conditions, a careful analysis demonstrates that in about 90% of all cases sealed vessel processing (autoclave technology) in dedicated single-mode microwave instruments has been employed. A recent survey has, however, found that as many as 30% of all published MAOS papers still employ kitchen microwave ovens [26], a practice banned by most of the respected scientific journals today. For example, the American Chemical Society (ACS) organic chemistry journals will typically not consider manuscripts describing the use of kitchen microwave ovens or the absence of a reaction temperature, as specified in the relevant publication guidelines [27].

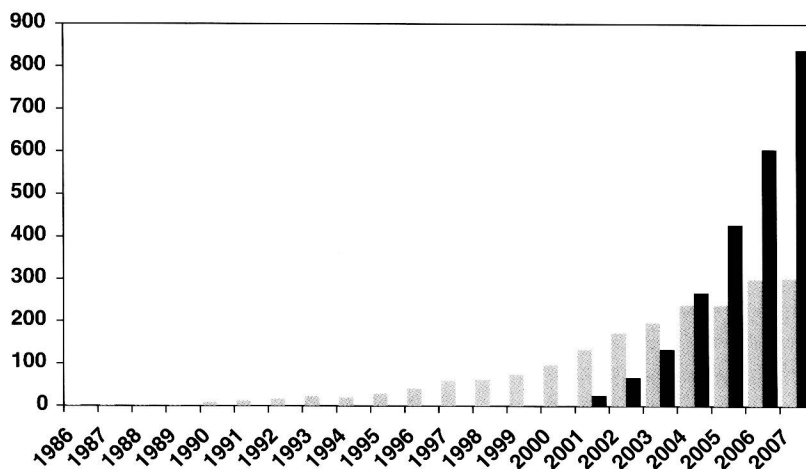


Figure 1.1 Publications on microwave-assisted organic synthesis (1986–2007). Gray bars: Number of articles involving MAOS for seven selected synthetic organic chemistry journals (*J. Org. Chem.*, *Org. Lett.*, *Tetrahedron*, *Tetrahedron Lett.*, *Synth. Commun.*, *Synthesis*, *Synlett*. SciFinder Scholar keyword search on

“microwave”). The black bars represent the number of publications (2001–2007) reporting MAOS experiments in dedicated reactors with adequate process control (about 50 journals, full text search: microwave). Only those articles dealing with synthetic organic chemistry were selected.

Recent innovations in microwave reactor technology now allow controlled parallel and automated sequential processing under sealed vessel conditions, and the use of continuous or stop-flow reactors for scale-up purposes. In addition, dedicated vessels for solid-phase synthesis, for performing transformations using pre-pressurized conditions and for a variety of other special applications, have been developed. Today there are four major instrument vendors that produce microwave instrumentation dedicated to organic synthesis. All these instruments offer temperature and pressure sensors, built-in magnetic stirring, power control, software operation and sophisticated safety controls. The number of users of dedicated microwave reactors is therefore growing at a rapid rate and it appears only to be a question of time until most laboratories will be equipped with suitable microwave instrumentation.

In the past, microwave chemistry was often used only when all other options to perform a particular reaction had failed, or when exceedingly long reaction times or high temperatures were required to complete a reaction. This practice is now slowly changing and, due to the growing availability of microwave reactors in many laboratories, routine synthetic transformations are now also being carried out by microwave heating. One of the major drawbacks of this relatively new technology remains the equipment cost. While prices for dedicated microwave reactors for organic synthesis have come down considerably since their first introduction in the late 1990s, the current price range for microwave reactors is still many times higher

than that of conventional heating equipment. As with any new technology, the current situation is bound to change over the next several years and less expensive equipment should become available. By then, microwave reactors will have truly become the “Bunsen burners of the twenty first century” and will be standard equipment in every chemical laboratory.

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