Organic Process Research & Development **2009,** *13,* 915–923

Reviews

On Scale Up of Organic Reactions in Closed Vessel Microwave Systems

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Abstract:

Scale up of reactions with existing laboratory-scale microwave technologies and factors affecting extension of the scope, including the influences of putative nonthermal microwave "effects," mechanisms of energy transfer, interactions of microwaves with materials, temperature measurement, and reproducibility between systems, are discussed.

Introduction

In 1988, two years after the first publications on microwave-assisted organic synthesis had appeared,[1,2] we constructed the first dedicated continuous microwave reactor.[3] So began two decades of investigations into applications of microwave chemistry at elevated temperature and pressure, primarily with organic solvents. By 1995 a complementary batch reactor had been built,[4,5] and by the turn of the century commercial microwave systems based upon the concepts, patents, and operating principles of our prototypes had become available.[6] Sales for 2003, independently estimated at 89 million U.S. dollars,[7] indicate that such units are widely employed. Moseley et al. recently estimated that about two-thirds of microwave reactions are performed with commercial systems and one-third with domestic ovens.[8] This suggests that, notwithstanding buoyant sales, the market for microwave reactors has not yet fully matured. Popular current applications of the technologies include drug discovery,[9,10] polymer chemistry,[11,12] total synthesis,[13,14] green chemistry,[15,16] materials science,[17,18] nanotechnology,[19] and biochemical processes.[20,21]

Recent work has been directed towards broadening the technical developments,[22] including by scaling down with flow systems[23−28] as presaged in 1994.[29] A key determinant of the scope of microwave chemistry, though, will be the highest scales that can be accommodated. Scale up with existing microwave technologies is discussed herein, and uncertainties regarding extension of microwave capabilities beyond the laboratory scale[21,30−32] are addressed.

Discussion

Organic processes have been scaled up for manufacturing since Perkin began producing Tyrian purple (mauve) more than 150 years ago.[33] Now chemical manufacturing involves an

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(1) Gedye, R.; Smith, F.; Westaway, K.; Ali, H.; Baldisera, L.; Laberge, L.; Rousell, J. *Tetrahedron Lett.* **1986**, *27*, 279.
(2) Giguere, R. J.; Bray, T. L.; Duncan, S. M.; Majetich, G. *Tetrahedron Lett.* **1986**, *27*, 4945.
(3) Strauss, C. R.; Faux, A. F. Method and apparatus for continuous chemical reactions. Australian Provisional Patent No. PJ 0872/88, 1988; U.S. Patent 5,387,397, 1995.
(4) Constable, D.; Raner, K.; Somlo, P.; Strauss, C. *J. Microwave Power Electromagn. Energy* **1992**, *26*, 195.
(5) Raner, K. D.; Strauss, C. R.; Trainor, R. W.; Thorn, J. S. *J. Org. Chem.* **1995**, *60*, 2456.
(6) Roberts, B. A.; Strauss, C. R. *Acc. Chem. Res.* **2005**, *38*, 653.
(7) Ondruschka, B.; Bonrath, W.; Stuerga, D. In *Microwaves in Organic Synthesis*, 2nd ed.; Loupy, A., Ed.; Wiley-VCH: Weinheim, Germany, 2006; Vol. 1, Chapter 2, pp 62−107.
(8) Moseley, J. D.; Lenden, P.; Thomson, A. D.; Gilday, J. P. *Tetrahedron Lett.* **2007**, *48*, 6084.
(9) Larhed, M.; Hallberg, A. *Drug Discovery Today* **2001**, *6*, 406.
(10) Kappe, C. O.; Dallinger, D. *Nat. Rev. Drug Discovery* **2006**, *5*, 51.
(11) Bogdal, D.; Penczek, P.; Pielichowski, J.; Prociak, A. *Adv. Polym. Sci.* **2003**, *163*, 193.
(12) Bogdal, D.; Prociak, A. *Microwave-Enhanced Polymer Chemistry and Technology*; Blackwell Publishing: Oxford, UK, 2007.
(13) Baxendale, I. R.; Ley, S. V.; Nessi, M.; Piutti, C. *Tetrahedron* **2002**, *58*, 6285.
(14) Appukkuttan, P.; Van der Eycken, E. In *Microwave Methods in Organic Synthesis*; Larhed, M., Olofson, K., Eds.; Springer: Berlin, Germany, 2006; Chapter 1, pp 1−47.
(15) Strauss, C. R.; Varma, R. S. In *Microwave Methods in Organic Synthesis*; Larhed, M., Olofson, K., Eds.; Springer: Berlin, Germany, 2006; Chapter 6, pp 199−231.
(16) Varma, R. S. *Green Chem.* **1999**, *1*, 43.
(17) Jhung, S. H.; Jin, T.; Hwang, Y. K.; Chang, J.-S. *Chem.—Eur. J.* **2007**, *13*, 4410.
(18) Barlow, S.; Marder, S. R. *Adv. Funct. Mater.* **2003**, *13*, 517.
(19) Tsuji, M.; Hashimoto, M.; Nishizawa, Y.; Kubokawa, M.; Tsuji, T. *Chem.—Eur. J.* **2005**, *11*, 440.
(20) Collins, J. M.; Leadbeater, N. E. *Org. Biomol. Chem.* **2007**, *5*, 1141.
(21) Van Noorden, R. *Chem. World* **2008**, *5* (10), 40.
(22) Iannelli, M.; Bergamelli, F.; Kormos, C. M.; Paravisi, S.; Leadbeater, N. E. *Org. Process Res. Dev.* **2009**, *13*, 634.
(23) Bagley, M. C.; Jenkins, R. L.; Lubinu, M. C.; Mason, C.; Wood, R. *J. Org. Chem.* **2005**, *70*, 7003.
(24) Comer, E.; Organ, M. G. *J. Am. Chem. Soc.* **2005**, *127*, 8160.
(25) Wilson, N. S.; Sarko, C. R.; Roth, G. P. *Org. Process Res. Dev.* **2004**, *8*, 535–538.
(26) Baxendale, I. R.; Griffiths-Jones, C. M.; Ley, S. V.; Tranmer, G. K. *Chem.—Eur. J.* **2006**, *12*, 4407.
(27) Saaby, S.; Baxendale, I. R.; Ley, S. V. *Org. Biomol. Chem.* **2005**, *3*, 3365.
(28) Smith, C. J.; Iglesias-Siguenza, F. J.; Baxendale, I. R.; Ley, S. V. *Org. Biomol. Chem.* **2007**, *5*, 2758.
(29) Cablewski, T.; Faux, A. F.; Strauss, C. R. *J. Org. Chem.* **1994**, *59*, 3408.
(30) Roberts, B. A.; Strauss, C. R. In *Microwave Assisted Organic Synthesis*; Tierney, J. P., Lidstrom, P., Eds.; Blackwell Publishing: Oxford, UK, 2005; Chapter 9, pp 237−271.
(31) Moseley, J. D.; Woodman, E. K. *Org. Process Res. Dev.* **2008**, *12*, 967.
(32) Kremsner, J. M.; Stadler, A.; Kappe, C. O. In *Microwave Methods in Organic Synthesis*; Larhed, M., Olofson, K., Eds.; Springer: Berlin, Germany, 2006; Chapter 7, pp 233−278.
(33) Garfield, S. *Mauve*; Faber and Faber: London, 2000.

10.1021/op900194z CCC: $40.75

estimated 75,000 to 100,000 products[34] and employs about 12 million people.[35] Industrial chemicals can be grouped according to production volume. Although bulk items predominate in that regard (10^4-10^6 tonne per annum),[36] numerous chemicals are manufactured routinely in lower tonnages. After a century and a half, scale up of conventional laboratory preparations to tonne or multitonne has been well practised.

In contrast, apart from the activities of a limited number of early workers, microwave chemistry in the presence of organic solvents has been conducted with dedicated reactors for less than ten years. Almost always, scales have been less than one kilogram. In the decade from 1986 to 1995, only about 220 microwave chemistry papers were published, and the majority of those dealt with reactions in the absence of solvent.[37] Notwithstanding a wealth of recent literature currently extending to more than 3500 papers and several recent reviews,[38−42] the field remains in its developmental stages.

The rapid growth in interest and activity emanates from advantages offered by microwave over conventional heating, the most significant of which are safety, speed, and convenience. Microwave energy can be introduced remotely, without contact between the source and the chemicals. Energy input to the sample starts or stops immediately that the power is applied or withdrawn. Also, heating rates can be higher than those achieved conventionally if at least one of the components can couple strongly with microwaves,[15,43,44] a feature that can facilitate differential heating in multiphase systems.[37]

As inferred above, the manufactured quantities of individual fine chemicals and pharmaceuticals pale in comparison with those of bulk chemicals.[36] However, fine chemicals and pharmaceuticals can have considerably higher value per unit mass. The number of potential candidates also is orders of magnitude greater. Substances in this category offer *niche* manufacturing opportunities for microwave technologies. Examples from our laboratories include microwave flow processes for manufacture of the iron chelator L1 from maltol, carvacrol from carvone, monomeric alkyl 2-hydroxymethylacrylates from formaldehyde and acrylate esters,[29] and a batch process for the hydrolysis of cellulose to glucose.[37] More recently, the French microwave equipment manufacturer Sairem has developed a prototype flow reactor for the preparation of the cosmetic Laurydone, but apparently, large-scale preparation by that method has not yet occurred.[21] Various companies, though, confidentially produce perfumeries, flavorants, specialty monomers and polymers in commercially available microwave continuous flow and batch systems.

Microwave reactions can be performed batchwise in a single vessel, on volumes ranging from <1 mL up to 3 L or so. In approaches to scaling out instead of up, individual vessels usually numbering between 4 and 20 may be employed for parallel processing in a carousel. Some equipment manufacturers supply systems that enable reaction mixtures in several vessels to be heated in parallel. Stopped or continuous flow systems also may be used.[7,32,45]

That few microwave-assisted reactions have been performed beyond the kilogram scale indicates a plateau in technical development. This may have occurred in part through perceived limitations of the technique as discussed below, but not entirely. Different perspectives of chemists and chemical engineers in chemical discovery and manufacturing respectively, also may have had an influence.[30] A limited knowledge of the reaction conditions may be sufficient to enable synthetic chemists to obtain a desired product in the laboratory. Requirements for scale up, however, differ significantly from those for laboratory chemistry. Precise, optimized data for the conditions are prerequisites. Poorly defined reaction parameters and uncertainty can be potent disincentives. Irreproducibility in some cases and claims of nonthermal microwave "effects"[46−48] appear to have played contributory roles in that regard.

Influence of Reports of Nonthermal Microwave "Effects". Reported microwave "effects" have included higher yields within a given time at the same temperature compared with conventional heating[46] and selectivities dependent upon the method of heating.[49]

In the first comparative kinetics studies involving microwave and conventionally heated reactions, Raner et al. demonstrated that nonthermal "effects" reported by others were erroneous.[50,51] Proponents of nonthermal microwave "effects" subsequently altered their hypotheses to account for those results, but maintained the overriding contention that such effects existed.[46] Recently, Razzaq et al. reinvestigated another series of reactions where nonthermal microwave "effects" had been reported.[52] Although their investigations did not include kinetics studies, they did involve careful replication of the conditions under microwave and conventional heating, as well as comparisons of outcomes. The results supported the conclusions of Raner et al.[50,51] for all cases investigated.

With microwave-assisted synthesis in solvents, heating rates for laboratory-scale reactions typically are in the order of 1−2 °C s^{-1}. Conditions often need to be tightly controlled when heating is rapid. Temperature readings should be accurate, timely, and taken frequently. A feedback mechanism reliant upon temperature readings is commonly employed to regulate the microwave power input and avoid thermal overshoot.

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(34) Purchase, I. F. H. *Pure Appl. Chem.* **2000**, *72*, 1051.
(35) Hildebrandt, B.-U.; Schlottmann, U. *Angew. Chem., Int. Ed.* **1998**, *37*, 1316.
(36) Sheldon, R. *CHEMTECH* **1994**, *24* (3), 38.
(37) Strauss, C. R.; Trainor, R. W. *Aust. J. Chem.* **1995**, *48*, 1665.
(38) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250.
(39) Caddick, S.; Fitzmaurice, R. *Tetrahedron* **2009**, *65*, 3325.
(40) Polshettiwar, V.; Nadagouda, M. N.; Varma, R. S. *Aust. J. Chem.* **2009**, *62*, 16.
(41) Polshettiwar, V.; Varma, R. S. *Chem. Soc. Rev.* **2008**, *37*, 1546.
(42) Larhed, M.; Moberg, C.; Hallberg, A. *Acc. Chem. Res.* **2002**, *35*, 717.
(43) Strauss, C. R. *Aust. J. Chem.* **1999**, *52*, 83.
(44) Strauss, C. R. *Aust. J. Chem.* **2009**, *62*, 3.
(45) Kappe, C. O.; Stadler, A. *Microwaves in Organic and Medicinal Chemistry*; Wiley-VCH: Weinheim, Germany, 2005; Chapter 3, pp 29−55.
(46) Perreux, L.; Loupy, A. In *Microwaves in Organic Synthesis*, 2nd ed.; Loupy, A. Ed.; Wiley-VCH: Weinheim, Germany, 2006; Vol. 1, Chapter 4, pp 134−218.
(47) Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199.
(48) De la Hoz, A.; Diaz-Ortiz, A.; Moreno, A. *Chem. Soc. Rev.* **2005**, *34*, 164.
(49) De la Hoz, A.; Prieto, M. P.; Rajzmann, M.; De Cosar, A.; Diaz-Ortiz, A.; Moreno, A.; Cossio, F. P. *Tetrahedron* **2008**, *64*, 8169.
(50) Raner, K. D.; Strauss, C. R. *J. Org. Chem.* **1992**, *57*, 6231.
(51) Raner, K. D.; Strauss, C. R.; Vyskoc, F.; Mokbel, L. *J. Org. Chem.* **1993**, *58*, 950.
(52) Razzaq, T.; Kremsner, J. M.; Kappe, C. O. *J. Org. Chem.* **2008**, *73*, 6321.

Mixing of the reaction mixture is essential for obtaining accurate temperature readings for the bulk sample.[4,5,37]

The objective of microwave-heated reactions often is to obtain a thermal profile that shows a rapid rise until the required temperature is attained, to maintain that temperature without overshoot for as long as required, and to rapidly cool afterwards (for an early example, see Figure 3 in ref 37). With batch reactors, the features essential for such performance are temperature and pressure measurement, stirring, infinitely variable control of microwave power input, facilities for cooling reaction mixtures, as well as a pressure relief valve.[5,37]

Although most commercial microwave batch reactors now possess these capabilities, the methodologies and efficacies differ, sometimes substantially between systems from various manufacturers.[6,32,45] Reaction conditions obtained from one reactor have not always afforded reproducibility in another, indicating that not all units perform comparably. For factors as fundamental as temperature measurement and sample mixing, Herrero et al. recently reported large variations in temperature (15−40 °C with a fiber-optic thermometer) within samples and lengthy lags in response time (up to 13 s) for readings for reactions performed in a CEM Discover monomodal reactor.[53] Without adequate stirring, temperature gradients in the order of 30 °C between the top and the bottom of the sample were observed, a finding that was consistent with early work.[4] Recent investigators have found that the use of infrared sensors trained on the outer wall of the reaction vessel can afford inaccurate temperature readings for the contents.[54−57] In combination, these findings strongly suggest that with small-scale monomodal units in particular, output data can be subject to significant experimental errors resulting from inadequate temperature measurement and sample mixing, as well as high internal temperature gradients.

Significantly, Perreux and Loupy advocated such reactors for investigation of nonthermal microwave "effects." While noting that accurate control of the temperature (using fiber-optic or infrared detection) was essential, they made no mention of a need for sample mixing.[46] Now, in view of the recently reported technical difficulties associated with controlling reactions in monomodal systems[53−57] and from the discussion above, it could be argued that enhanced rates of reaction brought about by nonthermal microwave "effects" are more open to question than to debate.

Failures and "False" Successes. For preparations where stable products are formed essentially noncompetitively, the risk of thermal decomposition is low. Consequently, sizable systematic errors in measurement of temperature would not adversely affect the outcomes or prevent excellent results from being obtained and reported. For labile products prone to further reaction or decomposition though, high accuracy and control of temperature are essential.[37,43,44] A high failure rate for such processes might be expected in systems possessing inadequate facilities for stirring and/or sensing. A prerequisite for reporting of research results in chemical journals however is that outcomes be no worse than satisfactory. Failed microwave reactions would rarely be published. When "false" successes may be disclosed but real failures cannot, technical deficiencies with specific microwave systems can be masked. This situation appears to hold for some commercial microwave reactors. Apparently, it has not only led workers to report putative nonthermal microwave "effects", but it also may have inhibited scale up.

Comparisons of Reactor Performance. Perhaps as a consequence, several groups have found a need to evaluate individual systems or to compare the performance of microwave reactors from different suppliers.[58−62] Some have investigated a single reaction with various units.[58,59] Others have examined processes involving materials with a range of physical properties including solids (metals, inorganic salts, crystalline organics), liquids (water, organic solvents, ionic liquids), gases (inert or reactants), or combinations thereof.[60−64]

In some cases, reactions performed batchwise in one system were not entirely reproducible in another. Difficulties also were experienced in translating batch conditions to continuous flow processes. Some adverse findings may have been partially attributable to inexperience with the technique. Consideration and discussion of key technical factors affecting microwave reactions appear warranted in that regard.

Mechanisms of Energy Transfer. Sturdy glass or metallic vessels are normally used for conventionally heated reactions. Energy is applied to the outer walls of the vessel and transferred to and through the sample by conduction. Thermal inertia typically is high, so heating and subsequent cooling tend to be slow. Depending upon the nature and size of the vessel, the extent of mixing, conduction, and convection within it, and the temperature of the inner walls, substantial thermal gradients can exist at various locations throughout the sample.[37]

The microwave region of the electromagnetic spectrum lies between infrared and radio frequencies. Some sections within the microwave band are dedicated to essential uses including radar and telecommunications. Disruption of these uses is prohibited by an international convention that has allocated 915 ± 25 MHz, 2450 ± 13 MHz, 5800 ± 75 MHz, and 22125 ± 125 MHz for industrial and scientific microwave heating and drying. Equipment operating at 2450 MHz with a corresponding wavelength of 12.2 cm is most commonly employed in chemistry.[37] Reports on the use of 5800 MHz have recently appeared.[65,66]

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(53) Herrero, M. A.; Kremsner, J. M.; Kappe, C. O. *J. Org. Chem.* **2008**, *73*, 36.
(54) Kremsner, J. M.; Kappe, C. O. *J. Org. Chem.* **2006**, *71*, 4651.
(55) Hosseini, M.; Stiasni, N.; Barbieri, V.; Kappe, C. O. *J. Org. Chem.* **2007**, *72*, 1417.
(56) Nuchter, M.; Ondruschka, B.; Bonrath, W.; Gum, A. *Green Chem.* **2004**, *6*, 128.
(57) Leadbeater, N. E.; Pillsbury, S. J.; Shanahan, E.; Williams, V. A. *Tetrahedron* **2005**, *61*, 3565.
(58) Moseley, J. D.; Lenden, P.; Lockwood, M.; Ruda, K.; Sherlock, J.-P.; Thomson, A. D.; Gilday, J. P. *Org. Process Res. Dev.* **2008**, *12*, 30.
(59) Erdmenger, T.; Paulus, R. M.; Hoogenboom, R.; Schubert, U. S. *Aust. J. Chem.* **2008**, *61*, 197.
(60) Moseley, J. D.; Lenden, P.; Thomson, A. D.; Gilday, J. P. *Tetrahedron Lett.* **2007**, *48*, 6084.
(61) Bowman, M. D.; Schmink, J. R.; McGowan, C. M.; Kormos, C. M.; Leadbeater, N. E. *Org. Process Res. Dev.* **2008**, *12*, 1078.
(62) Bowman, M. D.; Holcomb, J. L.; Kormos, C. M.; Leadbeater, N. E.; Williams, V. A. *Org. Process Res. Dev.* **2008**, *12*, 41.
(63) Pawluczyk, J. M.; McClain, R. T.; Denicola, C.; Mulhearn, J. J., Jr.; Rudd, D. J.; Lindsley, C. W. *Tetrahedron Lett.* **2007**, *48*, 1497.
(64) Glasnov, T. N.; Kappe, C. O. *Macromol. Rapid Commun.* **2007**, *28*, 395.
(65) Horikoshi, S.; Iida, S.; Kajitani, M.; Sato, S.; Serpone, N. *Org. Process. Res. Dev.* **2008**, *12*, 257.

In contrast with conductive or convective heating, microwave energy is transferred primarily by dielectric loss, mainly through dipole rotation and ionic conduction. With dipole rotation, molecules that have permanent or induced dipoles become aligned with the electric field component of the radiation. At 2450 MHz, the field oscillates 4.9×10^9 times per second. Sympathetic agitation generates heat, the intensity of which depends upon the characteristic dielectric relaxation time of the sample. With ionic conduction, dissolved ions migrate with the oscillating electric field. Heat is generated through frictional losses that depend on the size, charge, and conductivity of the ions and on their interactions with the solvent. Compounds with high dielectric constants (e.g., water, ethanol, and ionic liquids) normally absorb readily, while those less polar usually have lower susceptibility. Highly ordered materials tend to be microwave transparent as well as good insulators. Consequently, materials with appropriate physical properties (e.g., polytetrafluoroethylene and quartz) are commonly used in vessels for microwave chemistry.[37]

Effects of Microwaves on Materials. A fundamental aspect of microwave heating, apparently not widely appreciated by chemists, is that the nature and strength of interaction between microwaves and materials can vary at different stages of a process. The susceptibility of reaction mixtures can change with temperature as well as with composition as starting materials are consumed and products formed.[37]

In a monomodal reactor, the sample (usually of mass below 10 g) can be located within the cavity where the electric field strength will be maximal. This allows tuning of the power input and high flux density within the sample. Although so-called "focused microwaves" have been advocated as beneficial through "in core heating", Bogdal elegantly used a thermovision camera to demonstrate the presence of sizable thermal gradients in a sample in a monomodal reactor.[67] When temperature measurements have been less representative, significant variations in readings for the bulk have been found.[53]

Most multimodal reactors have mode stirrers associated with their waveguides so that the direction of delivery of microwaves into the cavity can be varied. The objective is to homogenize the electromagnetic field to eliminate so-called "hot" and "cold" spots where flux densities would be high and low, respectively. This assists in the establishment of a uniform bulk temperature.

Tuning of multimodal cavities can be relatively simple and should be performed frequently in combination with infinitely variable power control, to provide a good match between load and source, with minimal reflected power.[6,37] This can be accomplished under computer control and becomes especially important when the dielectric properties of the sample change during the course of the reaction. Monomodal cavities require frequent tuning, to maintain "focus", and infinitely variable control of microwave power for the same reasons.

Particular care must be exercised when working with materials that become increasingly effective at absorbing microwave energy (i.e. for which the dielectric loss tangent increases) with temperature increase and with reactions that are exothermic.[37,61] Unless the temperature and microwave power are closely controlled, a microwave-driven thermal runaway could result.

Most solvents show a decrease in microwave susceptibility with temperature rise.[37] At high temperatures this could lead to poor matching of the input power with the load, particularly as the supercritical state is approached. In selecting solvents and reaction temperatures this aspect should be carefully considered, as excess input microwave energy can lead to arcing, as discussed below.[37]

Differences in sample size and composition can also affect heating rates. In the latter case, this particularly applies when ionic conduction becomes possible through the addition or formation of salts. For reaction mixtures that are poorly microwave absorbing, susceptors can be added. Such materials include salts,[37] graphite-impregnated Teflon,[68,69] ionic liquids,[70,71] SiC elements,[52,72,73] and graphite alone.[74] These materials absorb the input energy more effectively than the bulk and transfer heat to it mainly by conduction.

Temperature Measurement. Instantaneous temperature measurement of reactions within a microwave field at an affordable price continues to present technical challenges just as it did when Gedye and Giguere began.[1,2] Thermocouples can act as antennae unless they are shielded and/or grounded. Induced currents can lead to heating that would result in false readings, or they could give rise to electrical discharge, referred to as arcing. For microwave chemistry, shielded thermocouples, gas pressure sensors, fiber-optic thermometers, or infrared pyrometry are typically used for temperature measurement.[37] Accuracy depends upon the response time, sensitivity, precision, and location of sensors. Ideally, more than one sensor should be employed, and the response time should be short (preferably less than one second for most applications) with short intervals (again, preferably less than one second) between temperature samplings, particularly when labile materials are involved. Temperature increases in the order of 50 °C or more per second are typical when thermal runaway occurs and sampling of the temperature at multisecond intervals is potentially hazardous in such circumstances.

Fiber-optic thermometers and shielded thermouples are usually held in chemically inert sleeves that are positioned within the reaction vessel. With infrared pyrometry, sensors are located remotely from the sample. Determinations are made typically on the outer wall of reaction vessels and at only one point. A major disadvantage for temperature measurement is that vessels are usually fabricated from materials that are excellent thermal insulators. For safety, the walls are thick, to

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(66) Horikoshi, S.; Hamamura, T.; Kajitani, M.; Yoshizawa-Fujita, M.; Serpone, N. *Org. Process Res. Dev.* **2008**, *12*, 1089.

(67) Bogdal, D.; Bednarz, S.; Lukasiewicz, M. *Tetrahedron* **2006**, *62*, 9440.

(68) Diaz-Ortiz, A.; De la Hoz, A.; Alcazar, J.; Carrillo, J. R.; Herrero, M. A.; Fontana, A.; Munoz, J. D. *Comb. Chem. High Throughput Screening* **2007**, *10*, 163.

(69) Veillet, S.; Tomao, V.; Visinoni, F.; Chemat, F. *Anal. Chim. Acta* **2009**, *632*, 203.

(70) Ley, S. V.; Leach, A. G.; Storer, R. I. *J. Chem. Soc., Perkin Trans 1* **2001**, 358.

(71) Leadbeater, N. E.; Torenius, H. M. *J. Org. Chem.* **2002**, *67*, 3145.

(72) Kremsner, J. M.; Kappe, C. O. *J. Org. Chem.* **2006**, *71*, 4651.

(73) Geuens, J.; Kremsner, J. M.; Nebel, B. A.; Schober, S.; Dommisse, R. A.; Mittelbach, M.; Tavernier, S.; Kappe, C. O.; Maes, B. U. W. *Energy Fuels* **2008**, *22*, 643.

(74) Besson, T.; Thiery, V.; Dubac, J. In *Microwaves in Organic Synthesis*, 2nd ed.; Loupy, A., Ed.; Wiley-VCH: Weinheim, 2006; Vol. 1, Chapter 9, pp 416−455.

enable them to withstand internal reaction pressures in the region of 2−10 MPa at temperatures up to 300 °C. Lag phases may be lengthy when temperature is measured that way. As mentioned above, Herrero et al. found that, in monomodal systems, recorded temperatures were highly dependent upon the positioning of the sensor.[53] Substantial differences in temperature readings were noted when more than one sensor was used. Regardless of their location, temperature sensors should be calibrated regularly. Temperature readings can be validated through the use of a pure liquid such as water and by cross-checking against an independent parameter such as vapor pressure.

Arcing. As mentioned above, excess input microwave energy can result in the buildup of an intense electrical field that can be discharged through an arc. In microwave chemistry, arcing can occur when low-loss samples are being heated, when salt solutions suffer dielectric breakdown, or when suspended metallic materials or sharp edges are present.[37,75,76] Arcing can degrade the inner walls of polymeric reaction vessels, and for processes where scale up is contemplated, conditions that facilitate it should be avoided. Hence, it is desirable to measure forward and reflected power, to have infinitely variable microwave energy input and to employ a load-matching device. The use of a ‘dummy load,’ i.e. a material which can absorb the excess energy but which is held in the microwave zone independently of the reaction mixture can also reduce the risk of arcing. Such techniques are routinely used in large industrial microwave systems typically employed for food processing, mainly to minimize the chances for destruction of the magnetron (microwave generator).

Closed-Vessel Microwave Reactors. Contemporary microwave batch and continuous reactors have been described, discussed, and illustrated extensively elsewhere.[45,58−61] They are used for rapid reactions at significantly higher temperatures than 110 °C, which is 0.6 °C below the bp of PhMe and the upper limit for more than 80% of the processes carried out between 1850 and 2000.[6,44] More reactions may be completed per unit time in fewer vessels than with traditional equipment. Yields may be improved and product mixtures made less complex than with slower processes. Closed-vessel microwave reactors primarily operate by safely raising the temperature up to about 100 °C above the bp of volatile organic solvents, followed ideally by rapid cooling afterwards. At pressures of 2−3 MPa, temperatures in the order of 200 °C are attainable with many solvents that boil below 85 °C at atmospheric pressure. Subsequent removal and recycling of volatile solvents can be relatively straightforward.[5,29,37]

A typical approach to scaling up organic processes involves optimization in the laboratory, advancement of the batch size by about an order of magnitude, reoptimization at that scale, and so on, until the desired scale is attained. In microwave chemistry, with the range of equipment presently available, this may involve batch reactions on scales of 10 mL, 100 mL, and 1 L before transferal of the process to a continuous flow reactor for ultimate production provided that the materials and conditions are suitable.

Obviously other variables besides the method of heating must be considered when optimizing a process. These may include the use of a catalyst (specific type, concentration, phase), selection of reactants and reagents (nature and concentration) and solvents (nature and extent of dilution) to mention just three. With the present report primarily focused upon heating, such aspects are acknowledged but not addressed herein.

Owing to the pressurized operation of most microwave reactors, the breadth of reaction temperatures possible with the usual solvents is significantly extended beyond those available with conventionally heated laboratory glass vessels operating at reflux. As the useable temperature range extends, so do the options for obtaining optimal conditions. Indeed, it is often possible to derive several sets of optima for a given reaction. Longer times may be accepted in return for a lower operating temperature or the use of less catalyst.[37,44] Also, predictive software has been developed to facilitate translation and optimization of conditions, typically within three experiments.[6,44]

Microwave Batch Reactions. In batch reactions, usually the temperature can be increased rapidly to the requisite level and maintained there for as long as necessary. If the mixture is composed exclusively of poorly absorbing components, the temperature will increase more gradually. A useful approximation is that each 10 °C rise in temperature can halve the reaction time. Calculations have indicated that the progress of reaction during the temperature ramp-up stage will be negligible in most cases.[50] In the present context, the upper temperature and the time spent there are the two most influential parameters. For purposes of optimization (rather than for reporting conditions), the reaction time usually should be regarded as that at the upper temperature, not the interval between turning the microwave power on and off. A short reaction time at a higher temperature presents more processing options to the chemist than does a long reaction time at a lower temperature, particularly if the ultimate objective is the development of a flow process.

For introductory information regarding the translation of conditions from conventionally heated reactions to microwave, the reader is referred to the monograph of Kappe and Stadler.[77] A report on scale up of microwave batch reactions to 3 L under pressurized conditions has recently appeared.[22]

A useful starting point for many organic reactions is to heat at 130−150 °C for 5−10 min in a batch reactor. If the reaction goes to completion without decomposition, the remaining task is to establish the minimum time required. This can be done conveniently by halving the time and repeating the reaction at the same temperature. This process should be repeated until some starting material remains in the product mixture. The reaction time can then be extended to midway between the time taken for incomplete reaction and the shortest time determined for complete reaction and so on, until the optimal time is obtained.

On the other hand, if heating at 130−150 °C for 5−10 min affords an incomplete reaction, the temperature can be increased by ~50 °C and the reaction rerun. If complete reaction is obtained, the optimal time can be obtained by following the process outlined in the preceding paragraph. If the process still

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(75) Whittaker, A.; Mingos, D. *J. Chem. Soc., Dalton Trans.* **2000**, 1521.

(76) 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.

(77) For an introduction on this aspect, see: Kappe, C. O.; Stadler, A. *Microwaves in Organic and Medicinal Chemistry*; Wiley-VCH: Weinheim, Germany, 2005; Chapter 5, pp 91−106.

has not gone to completion, the temperature could be increased by a further 50 °C if it falls within the operating scope of the reactor, or near the upper operating temperature of the unit if not. If the reaction still is not complete, it becomes necessary to increase the reaction time at the highest possible operating temperature. Reaction times can be extended by a factor of 2−3 until a desirable outcome has been obtained. The optimal time can be derived by using the process for refinement outlined above.

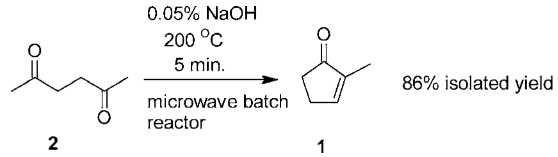
For most reactors, limits for upper operating temperature start at about 230 °C and can be as high as 300 °C, depending on the make of instrument and the manufacturer's specifications. Ability to obtain these temperatures in organic reactions, however, strongly depends upon the corresponding vapor pressure of the solvent. The highest safe operating pressures commonly used are 20 kPa in monomodal and 40−200 kPa in multimodal reactors, depending upon the model employed. In monomodal systems, MeOH and EtOH, for example, could not be used above 160 and 180 °C, respectively, owing to pressure constraints. The respective critical temperatures for those two solvents, 239 and 241 °C, lie near the specified upper temperature limits for most microwave reactors.[78] The critical pressures of MeOH and EtOH, 8 MPa and 6 MPa, respectively,[78] lie within the operating range of some commercial multimodal systems. Under critical or near critical conditions such solvents would be essentially microwave-transparent, however, and care should be exercised in attempting to use them under such conditions, without a dummy load at least.[37]

Scale Up of Batch Reactions. Once optimal conditions have been determined in a microwave batch reactor, reactions usually can be scaled up by at least an order of magnitude each time without difficulty. Several successful examples were recently reported by Bowman et al.[61] An exception involved a Heck reaction, for which the yield decreased upon scale up. The authors attributed this to absorption of the Pd catalyst by the inner wall of the reaction vessel.

In earlier work, we required 3-methyl-2-cyclopentenone (**1**) in high purity (≥99.5%) and on a scale of several hundred grams. It could be made by intramolecular Claisen−Schmidt condensation of 2,5-hexanedione (**2**), residues of which were not easily separable from the product.[79] Under conventional reflux conditions, with NaOH or KOH (1−5% w/v) and reaction times between 15 and 60 min, multigram quantities of **1** could be obtained in 46−53% yield and in high purity (≥99.5%) routinely. Higher yields were not achieved, owing to competing reactions.

With the microwave batch reactor (MBR), the concentration of base required was only 0.05% w/v, and the reaction was carried out at 200 °C for 5 min on a scale of 15.7 g to afford comparably pure product **1** in 86% isolated yield (Scheme 1). Under reflux conditions with the dilute base, a conversion of only 57% was obtained after 18 h, and some polymeric material was formed. At the time, closed, vessel microwave equipment was not commercially available, and others would not have been able to utilize the new method unless it was adapted for use in conventionally heated autoclave reactors.

Scheme 1



To avoid lengthy heating-up periods in the presence of the starting material, the aqueous base (NaOH; 0.05% w/v) was preheated to the required temperature in a 500 mL autoclave, and **2** was injected under pressure into the vessel. At 200 °C, conversions to **1** were 93% after 11 min, a comparable result to that obtained with the MBR, albeit in a longer time. Next, the process was scaled up 10-fold in a 3 L heat-jacketed autoclave reactor. The isolated yield was similar to the returns obtained with both the MBR and the 500 mL autoclave. This and other work[80,81] showed that conditions obtained from microwave processes can be adapted for conventionally heated systems if necessary.

Continuous Flow Microwave Reactor. The continuous microwave reactor was designed to heat reaction mixtures safely, rapidly, and controllably to a designated temperature and then to cool them comparably rapidly afterwards. Operating principles and technical and safety features have been presented.[29] Batch reactors are normally used for one-off synthesis nowadays, so discussion on flow reactors is directed toward scale up to enable the routine preparation of significant amounts of material. Microwave-assisted synthesis under continuous flow conditions was recently reviewed.[64] The two main commercial systems available are the Milestone FlowSYNTH and CEM Voyager, which are depicted schematically in Figures 1 and 2, respectively. The FlowSYNTH was recently described extensively, and its performance appraised.[82] Possessing a 200 mL reaction chamber, it allows reaction mixtures to be stirred while heating and then to be cooled immediately upon exit from the microwave zone. The latter system has a reaction chamber that is an order of magnitude smaller (10 mL) than that of the former, and it does not have capabilities for sample mixing while heating or for rapid postreaction cooling.[64] A continuous flow system recently constructed by Bagley et al. employed CEM hardware.[23] Unfortunately, temperature was measured only at the inlet rather than the outlet of the reaction chamber, suggesting that the thermal data obtained may not have been truly representative of the reaction conditions.

With continuous flow microwave reactors, the time taken to perform a reaction will depend upon the volume of material to be processed and the throughput. Influences include the flow rate, the volume of the vessel in the microwave zone, and the number of passes required. For convenience, we defined the residence time of the reaction mixture in the microwave irradiation zone as the reaction time. The temperature of the reaction mixture immediately upon exit from the microwave

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(78) Lide, D. R. *Handbook of Organic Solvents*; CRC Press: Boca Raton, 1995; pp 205 and 303.

(79) Bagnell, L.; Bliese, M.; Cablewski, T.; Strauss, C. R.; Tsanaktsidis, J. *Aust. J. Chem.* **1997**, *50*, 921.

(80) Bagnell, L.; Cablewski, T.; Strauss, C. R.; Trainor, R. W. *J. Org. Chem.* **1996**, *61*, 7355.

(81) An, J.; Bagnell, L.; Cablewski, T.; Strauss, C. R.; Trainor, R. W. *J. Org. Chem.* **1997**, *62*, 2505.

(82) Moseley, J. D.; Lawton, S. J. *Chim. Oggi.* **2007**, *25* (2), 16.

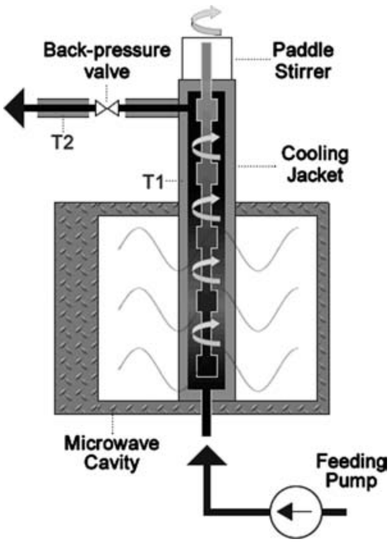


Figure 1

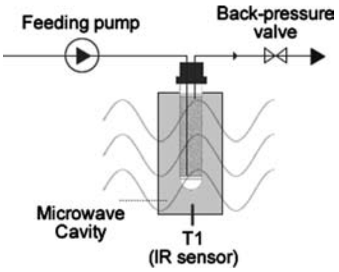
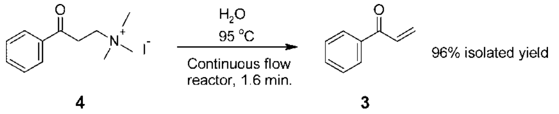


Figure 2

Scheme 2



zone was defined as the reaction temperature, even though thermal gradients would have existed as the material passed through that zone.[29]

Continuous flow microwave reactors share many of the advantages offered by microwave batch systems. An important safety consideration is that heating is direct, and when the power is turned off, thermal input ceases immediately. Another advantage is that only relatively small volumes of material are subjected to processing at any time. This lowers the risk of serious mishap, but should an accident occur, the potential loss of material would be limited to that in the body of the system. Reactions can be sampled and analyzed while a run is in progress and the conditions altered without shutting down. If processes are incomplete after one pass, reaction mixtures may be subjected to multiple passes.

Ready removal of a reaction mixture from a heating zone followed by rapid cooling is highly advantageous for reactions that require heat but produce thermally labile products. This is usually more readily achievable in a flow system than batchwise. In the Hofmann elimination, phenylvinyl ketone (**3**) was produced by passage of a 5% aqueous slurry of *N*-(2-benzoylethyl)-*N*,*N*,*N*-trimethylammonium iodide (**4**) through the microwave zone (Scheme 2).

The cooled aqueous effluent was immediately diluted into chilled Et_2O, precluding polymerization of the monomer and affording nearly quantitative yields. Conventionally performed Hofmann eliminations employed distillation to remove the ketone from the product mixture. Lower yields were obtained than with the microwave method, presumably owing to polymerization of the product.[29]

With the continuous flow technique, the utilization of less aggressive reagents or the same reagent applied in lesser amounts but at high temperatures often proved to be worthy substitutes for the use of aggressive reagents at low temperatures. The esterification of mesitylenecarboxylic acid, for example, employed catalytic amounts of sulfuric acid rather than the 100% required in the traditional Newman method.[83]

The technique is limited mainly by the technical specifications associated with its key elements: pump, valves, tubing, vessel, cooler, sensors, and controllers. It would not be expected to work with highly viscous materials that could not be pumped. Most problems have been concerned with blockages brought about by the presence of insoluble solids, rather than with thermal decomposition. Slurried material in the feed can be processed successfully, however, provided that the solid component is finely powdered and the heterogeneous feed stirred vigorously to prevent settling. Opportunities for success can be enhanced if the solid is consumed during the reaction. Depolymerization of paraformaldehyde to formalin represents a good example.[29]

In some processes solids can be formed. The Finkelstein reaction for example, utilizes the acetone-soluble salt NaI as a starting material and exploits the formation of an acetone-insoluble salt, NaCl, to force a shift in the equilibrium position. The product from an alkyl chloride starting material is the corresponding alkyl iodide. Although possible to perform under flow conditions, the reaction created difficulties brought about by variations in particle size of the salt formed.[29]

A more common problem involves crystallization of the product in the cooler. It may be avoided by cooling the effluent stream in a chilled collection vessel beyond the reactor, by increasing the temperature of the cooler and/or by processing at a faster rate to shorten the cooling time.

Translation of a Microwave Batch Process to a Continuous Flow Process. Several microwave batch reactions have been translated to continuous flow microwave processes and *vice versa*.[5,29,43] Ease of translation depends upon management of logistics mainly involved with continuous processing. The reaction time should be short enough to enable an acceptable rate of output, but not so short that it places undue stress upon the preparation of feedstocks, sampling and analysis, collection of product and workup.

Before proceeding to continuous flow, ideally the reaction should be optimized in a microwave batch reactor. Temperatures and pressures that fall within the safe operating specifications of the flow reactor should be employed. It is preferable for the reaction time to be short, preferably below 10 min and appreciably shorter than that desired for the continuous process. Under flow conditions, the reaction may be slower than its batch counterpart. The temperature of the material at the inlet of the

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(83) Newman, M. S. *J. Am. Chem. Soc.* **1941**, *63*, 2431.

reaction vessel will be lower than that at the exit end. This creates an unavoidable linear thermal gradient in the mixture as it proceeds along the vessel in the microwave zone. Allowance for that can be made when deriving the conditions batchwise. It is also important to ensure that all components of the reaction are compatible with the wettable structural elements of the flow reactor: e.g. HCl and $FeCl_3$ are corrosive, particularly at high temperature and ideally should not contact wettable stainless steel fittings.

For translation of the optimized batch process to continuous operation, a flow rate should be employed that would give the same residence/reaction time as that already determined batchwise. The flow should be established with the reaction feedstock but without applying microwave power. Next, the desired temperature should be set and microwave power applied. With the system filled with the starting solution from the outset, product would not appear in the effluent stream immediately.

In cases where the starting mixture cannot be used to fill the entire system at the outset, it may be possible to employ a solvent initially and switch to the feedstock later. Although this approach may save on valuable starting materials, difficulties can arise if the microwave susceptibilities of the reaction mixture and the solvent differ significantly.

Progress of the reaction can be followed by regular sampling and analysis of the effluent. After a steady state has been attained (this may be expected after about 5 volumes of material have passed through the system), the extent of reaction should be determined. One volume comprises the sum of the internal volumes of the tubing employed, the reaction vessel, and the cooler. If complete, the process would be fully operational.

If the reaction is incomplete, a second pass could be made, followed by additional passes if necessary. During such operations, it is advisible to employ separate vessels for holding the starting material and the product, rather than drawing from and returning to a single vessel. This facilitates sampling, analysis, and assessment of the progress of reaction on a pass-by-pass basis. A multipass process might satisfy the requirements for production in its own right.

If not, it may be necessary to increase the temperature and/or to decrease the flow rate until satisfactory single-pass conditions are obtained. Unlike optimization of batch reactions, iterative changes should involve relatively small changes at a time, preferably no more than 15 °C to the temperature or 5 min to the reaction time. Results from multiple pass runs and from batch wise optimization studies should provide useful guidance as well.

Microwave Processing of Chemicals at Scales above Kilogram. A key role of science and of scientists is to question and accordingly, our microwave reactors met with considerable skepticism at first. Concerns were raised over the potential for microwave leakage, perceived incompatibility between microwaves and solvents, risks of working at pressures above ambient, energy inefficiency, and probable rejection of the technique by the industry. They were widely held, and consequently, the domain remained ours exclusively for a decade.[6,44]

Now, demand for the technology is high, mysterious nonthermal microwave "effects" appear to have been dismissed, and many of the major technical problems have been addressed. The time might seem ideal for scaling up capacity for microwave reactions by at least an order of magnitude above the kilogram level. Doubts have been expressed, however, that scale up may not be feasible owing to insufficient depth of penetration of microwaves,[21,31,62,64] heating rates being too slow to offer advantages,[64] the cost of generating microwave energy being too high,[30,64] and the significant engineering challenges associated with safely heating reactions under pressure in large, microwave-transparent vessels.[64]

With a frequency of 2450 MHz, the depth of penetration of microwaves is in the order of centimeters for many solvents. A crucial advantage however, is that microwaves pass through the walls of the vessel and into the mixture directly, thereby minimizing thermal inertia and degradation on the inner surface. With conventionally heated systems, energy is applied to the outer surface and is transferred to the sample by conduction through the wall. This is the case regardless of scale. Doubts have not been expressed about conventional conductive heating being capable of driving large scale reactions when applied to the outer surface of the containing vessel. If so, they would be summarily dismissed as reactions have been performed that way on the multitonne scale routinely for more than a century. Stirring is employed to distribute the heat through the reaction mixture.

The same could also apply to microwave reactions regardless of the scale on which they were performed. Hence, if sufficient microwave power were introduced to a reaction, one might expect it to heat. Relatively straightforward calculations could establish the microwave power required to give the desired temperature and heating rate. Virtually regardless of the magnitude of the microwave power calculated, existing microwave generators could deliver it. Microwaves are used routinely in food processing for example, on the tens of kilowatt (kW) scale and microwave systems capable of delivering 100 kW and more power are commercially available.[30]

Avoiding Moderate Pressure. If pressures above atmosphere were to present unacceptable risks for reactions on the tonne or multitonne scale, consideration could be given to replacement of volatile organic solvents with ionic liquids. By definition, ionic liquids are comprised totally of ions and have melting points below 100 °C.[84,85] They have no detectable vapor pressure and can dissolve a wide range of inorganic and organic materials. They also can enable new chemistries that are not readily accessible with common low-boiling organic solvents. Most ionic liquids are effective microwave absorbers and their use as solvents imposes no pressure constraints regardless of the temperature employed. In microwave systems, high temperatures may be readily achieved through ionic conduction. Such synergies between microwave technologies and ionic liquids already have been exploited.[86,87] Ionic liquids have also been used as susceptors by addition to nonpolar organic solvents.[70,71]

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(84) Seddon, K. R. *J. Chem. Technol. Biotechnol.* **1997**, *68*, 351.

(85) Earle, M. J.; Seddon, K. R. *Pure Appl. Chem.* **2000**, *72*, 2275.

(86) Leadbeater, N. E.; Torenius, H. M. In *Microwaves in Organic Synthesis*, 2nd ed.; Loupy, A., Ed.; Wiley-VCH: Weinheim, 2006; Vol. 1, Chapter 7, pp 327−361.

(87) Boros, E.; Seddon, K. R.; Strauss, C. R. *Chim. Oggi.* **2008**, *26* (6), 28.

Cost of Microwave Energy. Apart from the perceived difficulties discounted above, there are two main hurdles confronting scale up of microwave reactions beyond the kilogram level. The engineering cost of microwave capacity is based on the installed kilowattage. For domestic and laboratory-scale microwave systems operating at 1 kW or so, the magnetron is air-cooled. Magnetrons of that capacity are bulk produced for applications in domestic ovens and so are relatively inexpensive. Those generating 5 kW and more of microwave power, employ oil-based or water-based cooling. Such systems introduce size, complexity, and substantial cost increases as considerations. In some cases, this problem could be avoided through the use of multiple air-cooled magnetrons, strategically positioned.

As major benefits of microwave processing include high throughputs, automation, clean reactions, and low waste production, the cost of energy is only a relatively minor concern on the laboratory scale. It assumes critical importance though, as production volumes increase. Although reports about the efficiency of microwave reactors on the laboratory scale have been contradictory,[88,89] undoubtedly the efficiency of conversion of electrical energy into microwave power is relatively low (in the order of 50−70% at best) on a higher scale. Thus, for microwave to be preferred over conventionally heated processes (where the energy efficiency typically would be expected to exceed 90%) on a large scale, unique advantages would need to apply. In contrast with their laboratory-scale counterparts, however, larger-scale microwave reactors would be employed for a limited number of specific reactions. Advantages of laboratory-scale microwave heating, such as high-throughput, flexible operation, and automation become less relevant with increasing scale. Consequently, when tonnes of material are required, microwave heating may not be as attractive economically as traditional methods, even if reactors were available.

Conclusion

Strategies have been outlined to facilitate translation of conditions from small to larger batches and from batchwise processes to those employing continuous flow. Provided that the physical properties of the components of reaction are compatible with the specifications of reactors, such progressions should be readily achievable, particularly when data for reaction parameters on a small scale are accurate.

Major constraints to scaling up to the multitonne level do not appear to include claimed nonthermal microwave “effects”, penetration depth of microwaves, or declining heating rates with increasing scale. Technical capabilities exist to introduce tens of kilowatts of microwave power into a sample and to distribute the energy uniformly. The two most significant obstacles involve a high cost of microwave energy per installed kilowatt and relative inefficiency in converting electricity to microwave energy. Breakthroughs in the disciplines of microwave and chemical engineering are eagerly awaited in those areas.

Acknowledgment

With best wishes to Peter Stanetty on the occasion of his 65th birthday.

Received for review July 27, 2009.

OP900194Z

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(88) Gronnow, M. J.; White, R. J.; Clark, J. H.; Macquarrie, D. J. *Org. Process Res. Dev.* **2005**, *9*, 516. Corrigendum: Gronnow, M. J.; White, R. J.; Clark, J. H.; Macquarrie, D. J. *Org. Process Res. Dev.* **2007**, *11*, 293.

(89) Razzaq, T.; Kappe, C. O. *ChemSusChem.* **2008**, *1*, 123.