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Microwave Synthesis: a new wave of synthetic organic chemistry

by Robert England

Microwave-assisted synthesis is set to change organic chemistry for good. The technology is generally applicable to syntheses in medicinal and combinatorial chemistry, and compared to conventional methods offers enhanced speed, reproducibilty and scalability. This technique solves many of the challenges currently facing pharmaceutical chemists and todays easy-to-use instrumentation, integrated robotics and verified synthesis methods are designed to provide a complete lab solution.

Only 3 years ago, microwave synthesis was not a meaningful technology for most organic chemists. Spurred by early reports of ultra-fast synthesis using microwave irradiation (reactions are completed in minutes compared to hours and days), some adventurous chemists had attempted to apply domestic microwave ovens to organic synthesis, only to find, at best, unpredictable synthesis results, and at worst, themselves cleaning up the lab after an unexpected explosion.

Domestic and many industrial microwave ovens were not designed to run chemical reactions, in much the same way as a mobile telephone, albeit a microwave transmitter, was not designed to warm up food. A multi-mode oven provides an uneven microwave field density (Figure 1), which is inadequate for the task of chemical synthesis.

The first purpose-built microwave synthesiser was launched in 2000. This device was designed to produce a uniform microwave field, regardless of the content of the vessel, with typical lab-scale samples: between 0.5 ml and 5 ml. Equipped to monitor and control the temperature of the reaction, and to safeguard against explosions by substantial safety mechanisms, this microwave synthesiser could produce ultra-fast (reactions taking typically 5 minutes), highly reproducible and safe synthesis results.

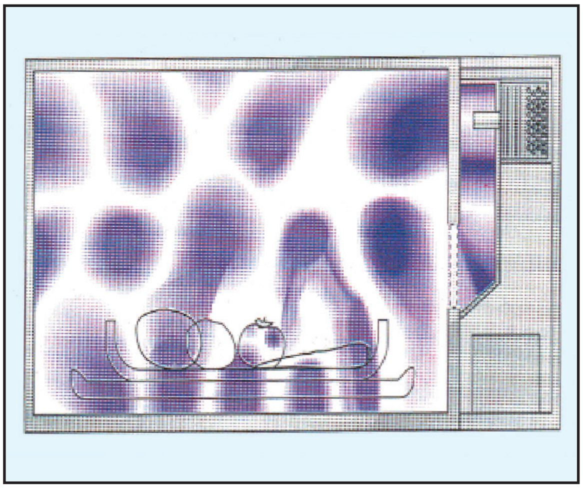

Figure 1. Microwave field in a domestic microwave oven, showing the typical uneven pattern of hot spots (shown here in purple) and cold spots.

Reactions are more reproducible when heated by microwaves largely because the heating process is uniform and highly controlled (Figure 3). In addition, the reaction temperature is accurately monitored and controlled.

In contrast to heating by conventional means, microwave irradiation raises the temperature in the reaction volume simultaneously, without intervention through the vessel wall (Figure 4). This means that synthesis proceeds uniformly throughout the reaction vessel, reaching completion simultaneously. This effect also influences the general scalability of reactions as an identical temperature profile can be achieved regardless of the volume of the vessel.

Productive, reproducible chemistry

3 years on from the introduction of the first commercial microwave synthesiser, regular users of the technique are reporting that up to 40% of all explorative chemistry is now being performed in this way, and estimates suggest that more than 10,000 microwave reactions are run per week. Many of these users are in the pharmaceutical and biotech industries. Figure 5 shows a typical modern microwave synthesiser, with sample transfer facilities to eliminate the tedium of manually changing vials every 5 minutes. Microwave-assisted synthesis is well on its way to becoming a cornerstone of modern chemistry development.

Microwave-assisted synthesis is, in many ways, superior to traditional heating. The ability to elevate the temperature of a reaction well above the boiling point of the solvent increases the speed of reactions by a factor of 10-1,000. Reactions are thus completed in minutes or even seconds. Yields are generally higher and the technique may provide a means of synthesising compounds that is not available conventionally.

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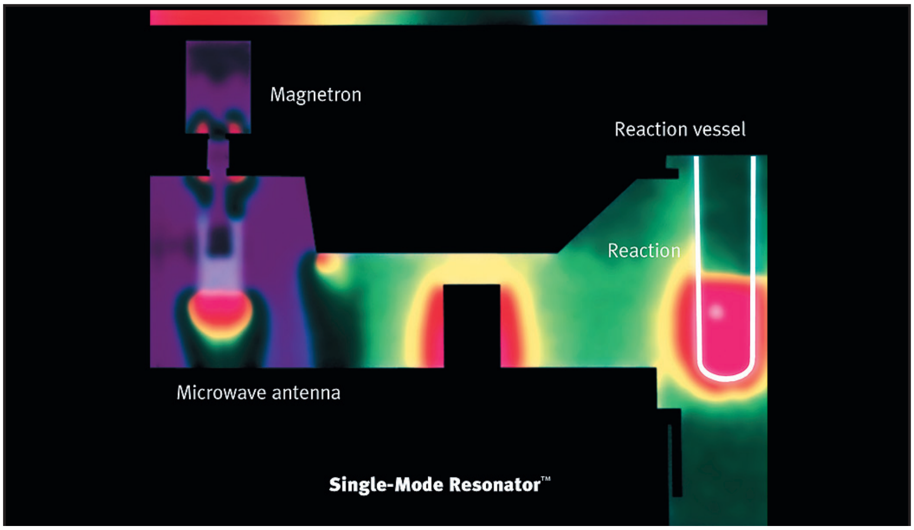

Figure 2. The Single-Mode Resonator design generates an even heating pattern in a lab-scale sized reaction vessel, leading to a high degree of synthesis reproducibility.

Pharmacuetical lead optimisation

The speed of microwave synthesis is ideal for developing compounds in the lead optimisation phase of pharmaceutical development. Here, synthetic chemists apply diverse synthesis methods iteratively to develop candidate drugs from lead compounds. The fast reaction times that microwave synthesis provides give an ideal response time for chemists to work out new chemistries and develop proprietary compounds.

Reaction times are incredibly short, thus a reaction procedure can be fully optimised in an hour, and the scope of the reaction can then be tested with a diverse set of substrates in the following hour. A fully optimised procedure and a range of products is produced in the time it takes to run a single conventional reaction.

Knowledge bases for microwave synthesis

From the outset, it was clear that the reproducibility and speed of microwave-assisted synthesis would be an ideal foundation on which to build a knowledge base for organic synthesis. Speed would contribute to the rapid development of methods, and reproducibility is essential to make the data worthwhile in somebody else's hands. A database of reproducible and, as mentioned earlier, scalable synthesis methods was previously unimaginable in organic chemistry.

There is also a general need for a knowledge base of microwave synthesis methods because chemists need a reference source to get them started with this technology. Microwave synthesis imposes a sufficiently different set of requirements compared to traditional synthesis methods (e.g. considerations of the microwave-absorbing characteristics of solvents; optimisation of reagents to work at elevated temperatures; or even the ability to run chemistry in water), that to really take advantage of the technique, new synthetic methods are warranted.

To address this, the Personal Chemistry company has developed Emrys PathFinder, a database of verified synthesis methods directed at addressing the needs of medicinal chemistry. The company has also developed a knowledge management system for pharma and biotech companies, Coherent Synthesis, which allows researchers to develop and share their own methods. This management system allows pharmaceutical R&D departments to immediately reap the productivity benefits of microwave synthesis, and to efficiently apply the knowledge to shortcut future development projects by re-application of the rapidly accumulated chemistry knowledge.

Furthermore, Personal Chemistry has developed 11 reaction kits for common transformations, containing pre-dispensed chemicals and optimised methods to further improve the quality and productivity of chemistry development.

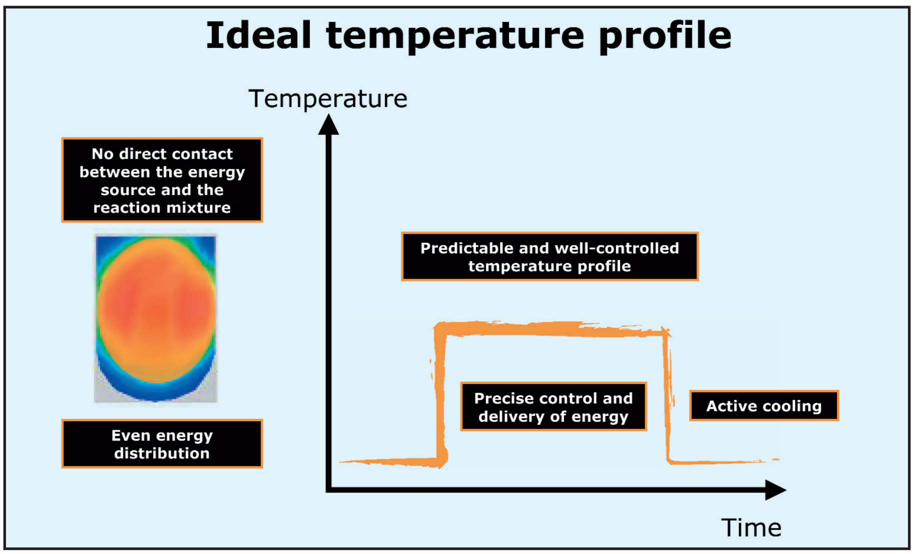

Figure 3. Microwave irradiation can generate an "ideal" temperature profile, allowing reactions to be initiated and quenched efficiently and reproducibly.

Coherent synthesis

The short definition of Coherent Synthesis is knowledge-based microwave synthesis for lead compound development. This system captures the synergy from ultra-fast and highly reproducible organic synthesis, verified methods, automated knowledge accumulation, and the efficiency gained from a software-based chemistry workflow platform. The result is a major boost in both quality and productivity at every stage of chemistry development projects. In May 2002, more than 3,000 fully optimised, verified and robust methods based on microwave synthesis were released. These can be searched from every chemist's desktop computer to support lead compound development.

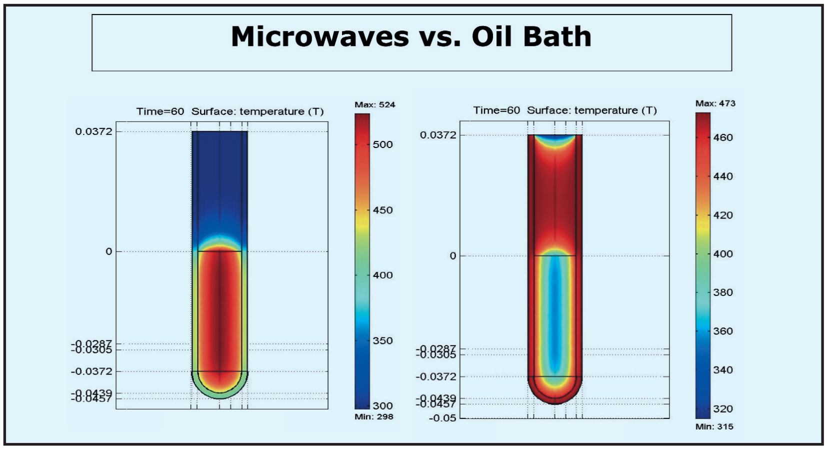

Figure 4. The temperature profile after 60 seconds as affected by microwave irradiation (left) compared to treatment in an oil-bath (right). Microwave irradiation raises the temperature of the whole reaction volume simultaneously, whereas in the oil heated tube, the reaction mixture in contact with the vessel wall is heated first. Temperature scale in Kelvin. "0" on the vertical scale indicates the position of the meniscus.

Most of the methods in the database were developed by the company directly, but they have also received significant contributions from a scientific partnership program, which includes Steven Ley (Cambridge University, UK), Mark Bradley (Southampton University, UK) and Barry Sharpless (Scripps Institute, La Jolla, USA). The methods include everything from "textbook" chemistry to innovative means of synthesising heterocyclic libraries. The short turnaround time that the verified methods provide, in combination with the microwave technology and levels of automation available, means that compounds and libraries can be synthesised on demand.

All of the top 20 pharma and biotech companies have been quick to invest in microwave technology and most of them have several knowledge-sharing systems at sites all over the globe. Many of these companies are now using Coherent Synthesis on a regular basis, and would like it to become a global chemistry knowledge sharing system. As the systems were originally based on industry standards like Oracle and Accelrys' Accord Chemistry Cartridge, this future development is possible.

Summary

Only a year back, one of the major objections to microwave synthesis was that there weren't any solutions to scale-up the chemistry - it was a dead end. Further investigations into this issue have shown that the opposite is true - that scalability is actually one of the technology's major strengths. The systems described above give similar conditions over orders of magnitude of volume. Thus if it is possible to synthesise 10 mg of a compound in Personal Chemistry's instrument, it is almost trivial to synthesise 100 g. Therefore the difficulties that were previously experienced when trying to convert a benchtop method into a large scale operation are avoided. This spring, the Personal Chemistry company is launching 2 new scale-up products and microwave chemistry synthesis services to serve customer's scale-up needs.

Figure 5. Chemist working with Emrys Optimizer

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