Microwaves lend a hand

Researchers offer examples of microwave-assisted synthesis taking hold in everyday lab practices.

BY MICHAEL J. COLLINS

The use of microwave chemistry has grown rapidly, as evidenced by the 450 articles published on the subject in 2003 alone. Several compounds produced via microwave synthesis are now entering late-stage development, and new applications in peptide synthesis, low-temperature (–100 to 35 °C) reactions, and enzymatic digestions are being explored.

Using a microwave system rather than conventional heating methods allows chemists to perform reactions in minutes, instead of hours, and offers higher yields and cleaner chemistries. In addition, chemists are discovering reactions that they can only achieve in a microwave synthesis system.

It became readily apparent at the 2nd International Microwaves in Chemistry Conference—held recently in Orlando, FL, and sponsored by CEM Corp. (*www.cem.com*)—that medicinal chemists are approaching the point where instrumentation for microwave-assisted organic synthesis is becoming as commonplace as oil baths.

"Microwaves are becoming a standard instrument in research laboratories in academia and industry," said Peter Seeberger, professor of organic chemistry at the Swiss Federal Institute of Technology (*www.ethz.ch*) and a speaker at the conference. The meeting included 17 others speaking on topics ranging from applications in carbohydrate chemistry to catalyst-free reactions, as well as new developments in microwave technology.

Seeberger, well known for his work in carbohydrate chemistry, spoke on the use of microwave synthesis for oligosaccharide reactions. He has successfully integrated microwave synthesis instrumentation into his laboratory and now uses the technology in the preparation of building blocks for oligosaccharide assembly, in the introduction and removal of protecting groups, and in the preparation of linkers to make carbohydrate chips and carbohydrate arrays.

He has also synthesized molecules that cannot be accessed under conventional heating methods, such as a central tetrasaccharide module he included in his conference presentation. Seeberger's current research includes work on a malaria vaccine candidate.

Nicholas Leadbeater, assistant professor of chemistry at the University of Connecticut, discussed transition-metal-free approaches to organometallic reactions. These included successful palladium-free Suzuki and Sonogashira cross-coupling reactions in water using a phase-transfer catalyst. Such reactions are widely used in the pharmaceutical industry, and Leadbeater's work presented a new and possibly cost-saving approach to traditional organometallic reactions.

Keynote speaker Brian Warrington, vice president of technology development chemistry at GlaxoSmithKline (*www.gsk.com*), gave a thought-provoking presentation on the future of high-throughput drug discovery. Known in the pharmaceutical industry for his visionary views, Warrington has identified key technologies and measured their impact in creating new drugs.

Microwave synthesis has become an accepted method and is playing an increasingly larger role in medicinal chemistry. The last hurdle to overcome—namely a lack of systems—is leading many pharmaceutical companies to build the cost of the instrumentation into their budgets for both new and existing laboratory facilities.

For example, one major pharmaceutical company has decided to integrate microwave synthesis into its drug discovery program and has determined it will need to provide one manual microwave-synthesis system for every four chemists and one automated microwave-synthesis system for every eight.

Companies are finding that the rapid-optimization capabilities of microwave synthesis are giving them the means to better utilize their research personnel resources, enabling 1 chemist to do the work of 15 in a quarter of the time. This frees the other chemists to pursue alternate drug targets and allows promising compounds to move faster to the next development stage.

New technology developments are also leading to new discoveries. The research that pharmaceutical companies and universities are conducting on the simultaneous cooling technology developed by CEM led to several published works last year.

At the meeting, Jian (Jack) Chen, senior scientist at Procter & Gamble Pharmaceu-

Microwave-assisted chemistry can increase yields and cut time

	Conventional method		Microwave-assisted	
Reaction	Time, h	Yield, %	Time, min	Yield, %
Biginelli condensation	12–14	15–60	5	60–90
Heck coupling	20	68	3	68
Mitsunobu reaction	18	65	5	78
Sonogashira coupling	12	80	25	97

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ticals (*www.pg.com*), discussed the results of his work with simultaneous cooling. By externally cooling a reaction vessel with compressed air while simultaneously administering microwave irradiation, more energy can be applied directly to the chemical reaction. The occurrence of side products and thermal degradation of heat-sensitive reaction components and intermediates can also be avoided by removing excess thermal energy with this technology.

Chen had tried various microwave methods for α-ketoamide synthesis, achieving at best only a 45% yield. When he performed this same reaction at 100 W with simultaneous cooling for both steps, the reaction yield was 74% in 2 min. In addition to publishing data on α-ketoamide synthesis (*Tetrahedron Lett.* **2003,** *44,* 8873), Chen has used simultaneous cooling in the synthesis of acyltetrazoles.

CEM reported on advances in microwave technology, including a stop-flow, scale-up system that can synthesize milligram to 500-g quantities without adjusting the original 10-mL chemistry. The system can handle solid-supported reagents and catalysts, slurries, and highly viscous fluids. The company presented several reactions supporting the system's capabilities, including a stop-flow Suzuki reaction with a 5-min residence time at 120 °C that produced 50 g of product with an 85% yield in 3.3 h.

In addition, the company presented a new subambient microwave-synthesis system and a microwave peptide synthesizer. With the subambient system, chemists can perform microwave reactions in low-temperature (–100 to 35 °C) conditions. This technique may prove to be very important to researchers performing carbohydrate chemistry or using highly reactive species. CEM's microwave peptide synthesizer also offers the ability to produce higher-purity peptides in as little as 2.5 h, much less than conventional systems taking hours or days.

Although peptide synthesis is all automated now and can be done using solid-phase techniques, the reaction times still are lengthy, explained Stephen Caddick, professor of organic chemistry and chemical biology at University College in London. "And, because of the difficulties of purification of peptides and characterization of peptides, there's quite a lot of trial and error involved," he added. "So the use of the microwave-accelerated approach is going to be important."

In addition to gains in speed and yield, advances in microwave chemistry have begun to address scalability, solid-phase synthesis, and continuous flow. The degree to which chemists accept microwave-assisted synthetic methods will depend on several factors, including cost and accessibility to new instrumentation, the breadth of reactions and applications addressed, and, as researchers make the transition, a growing familiarity with the technology.

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