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FEATURE

Synthetic chemistry in microreactors

It has been claimed that microreactors may one day replace the round-bottom flask. Get past the hype and microreactors are starting to get noticed by academia and industry for the synthesis of organic molecules.

What and why of microreactors

Microreactors are microfluidic devices where chemical reactions are performed in very narrow channels (typically 100–500 μm). Microreactors can be constructed from a variety of materials including metals, glass, silicon and organic polymers using microfabrication techniques (wet-, ion- and laser-etching; hot embossing and moulding methods). These devices are continuous flow reactors where reactants are mixed, or treated, in a continuous process.

What are the benefits of performing organic reactions in small and, at times, expensive and complex microfluidic devices? Summarised here are the main advantages of using microreactors often proclaimed in presentations and the literature.

Safety

Safety is probably the most commonly discussed benefit of the use of microreactors and one that covers a variety of different aspects. For instance, on-site and on-demand production of hazardous or unstable chemicals using microreactors can eliminate transport and storage issues. Microreactors have a very high surface area to volume ratio compared to conventional laboratory-scale glassware (10000–50000 m^2/m^3 v. approx. 100 m^2/m^3) and as such have very high rates of heat transfer. Because reaction volumes within individual channels are very small the heat generated can be dissipated quickly. Reactions that are highly exothermic can be performed without the same level of cooling typically used with conventional apparatus, and in the most extreme cases, reactions that cannot be readily performed because they would lead to explosive thermal runaway can be undertaken in a microreactor.

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Controlled conditions

As a direct consequence of the precise rapid mixing and the high level of thermal transfer, reactions in microreactors can be more controlled compared to conventional systems, and as such reaction selectivity and yield can be improved, particularly where by-products form due to reaction hot-spots. Short residence times within microreactors can also limit the opportunity for products to degrade. Microreactors are continuous flow reactors, so if the conditions, such as temperature of the system, do not change, continuous operation of the reactor should not affect the progress of the reaction (e.g. yield or selectivity). Thus the simplest way to produce more product is to run the reactor for a longer period of time. Because microreactors allow for synthesis on a small scale (short run times) high throughput chemical synthesis for the production of compound libraries is possible.

Scale-out not scale-up

Scaling-up the production from the laboratory to a pilot-plant scale requires process development, which may mean a redesign of the synthetic pathway to suit the larger scale. In the case of microreactors, the size of the reactor (channel dimensions) is not increased, the number of microreactors (or microchannels) is increased. This replication process (or 'numbering-up') can involve either replicating the entire microreactor device or, more commonly, increasing the number of reaction channels connected in parallel. For instance, a microreactor system might consist of one channel, *x* parallel channels on a single plate, or a stack of *y* plates each containing *x* channels in parallel. So while individual channels are on the micro-scale involving very small volumes of reagents, an entire microreactor system consisting of a large number of parallel channels can be much larger and capable of handling large volumes of reagents. The advantage of device replication as a route to increased production is that once a synthesis is optimised for a single microreactor (or channel) it is optimised for a 'pilot plant' full of microreactors. No further process development is required for increased production.

Microreactors in action

In recent years, significant advances have occurred in the application of microreactors to synthetic organic chemistry. Of particular note is the diversity of reactions (and associated techniques and conditions) performed in microreactors, some of which are summarised in Table 1. The selected examples in this article

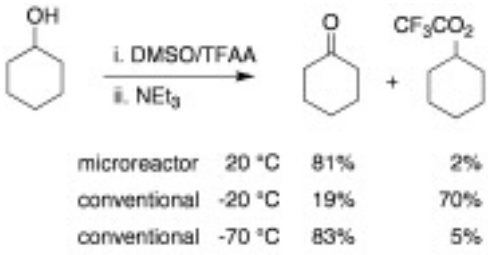
Table 1. Flexibility of microreactors

Reactions	Techniques and variables
Alkylation and acylation	Wide temperature ranges < –100°C to > 300°C
Oxidation	Microwave irradiation
Nitration	Photochemistry
Halogenation with fluorine, chlorine and bromine	Electrochemical synthesis
Lithiation and Grignard reactions	Homogeneous and heterogeneous catalysis
Hydrogenation	Enzymatic transformations
Dehydration	Biphasic systems (liquid–liquid, gas–liquid)
Glycosylations	Supported reagents and catalysts
Diels–Alder	Solventless reactions
Wittig	
Diazotisation and diazo coupling	
Enamine synthesis	
Aldol condensation	
Michael addition	
β-peptide synthesis	
Chiral resolutions of epoxides	
Free-radical, RAFT and ATRP polymerisations	
Heck, Suzuki, Kumada, Sonogashira and Stille reactions	
Nanoparticle and colloid synthesis – Au, CdSe, silica, polymers	

illustrate some of the advantages previously mentioned. A number of recent reviews cover in much more detail the diverse applications of microreactors to synthetic chemistry.[1–5]

Swern oxidation at room temperature

The Swern oxidation to convert an alcohol to a ketone or aldehyde, using dimethyl sulfoxide (DMSO) and trifluoroacetic anhydride (TFAA) is typically performed at low temperatures (< –50°C), which can be a prohibitive condition on larger scales. At higher temperatures by-product formation can be significant due to the instability of the intermediate formed from the reaction of DMSO and TFAA. Using a series of micromixers the oxidation of cyclohexanol has been conducted at room temperature to afford cyclohexanone in high yield (Scheme 1).[6] In comparison, when the reaction was performed in conventional laboratory apparatus comparable yields were obtained only when the reaction was conducted at –70°C. The fast mixing, efficient temperature control and short residence time of the initially formed DMSO–TFAA reaction intermediate were attributed to the effectiveness of the system.



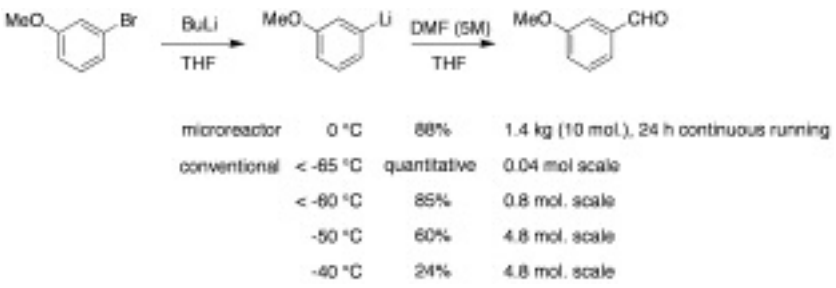
Scheme 1. Swern oxidation in a microreactor versus conventional laboratory apparatus.

Organometallic chemistry

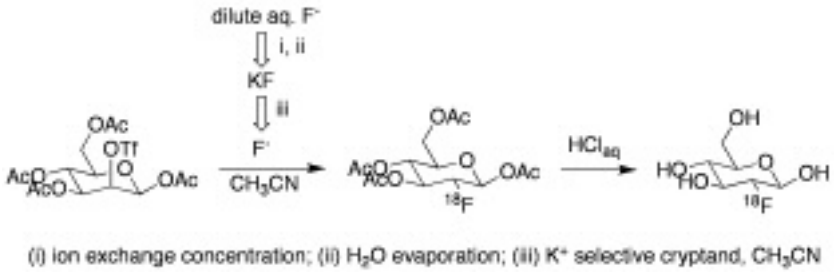
Microreactor systems are also amenable to organometallic chemistry. Using a microreactor system at 0°C with very short residence times 3-methoxybenzaldehyde was prepared in high yield (88%), and with continuous operation of the microreactor over 24 h 1.4 kg of the product was isolated (Scheme 2).[7] The short residence times (11 s for first step; 9 s for second step) minimised decomposition of the unstable aryl lithium intermediate. When the reaction was attempted using batch (conventional) methods, equivalent yields could only be obtained on much smaller scales and at lower temperatures. Scaling up the reaction using conventional methods proved difficult, because prolonged reagent addition times were required to maintain the low reaction temperatures.

Radiolabelled synthesis

As a proof of concept for on-site and on-demand chemical production a single automated microreactor was developed to prepare 2-deoxy-2-[^{18}F]fluoro-D-glucose (Fig. 1, Scheme 3),[8] which is commonly used in positron emission tomography (PET) imaging. A number of consecutive processes occur in the microreactor, including concentration of a dilute [^{18}F]fluoride solution (obtained



Scheme 2. Synthesis of 3-methoxybenzaldehyde using microreactor versus conventional methods.



Scheme 3. Automated microreactor preparation of 2-deoxy-2-[^{18}F]fluoro-D-glucose.

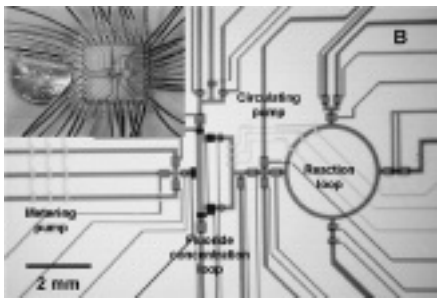


Figure 1. The microreactor used in the preparation of 2-deoxy-2-[^{18}F]fluoro-D-glucose. (From reference 8. Reprinted with permission from the American Association for the Advancement of Science (AAAS).)

from a cyclotron) using an ion-exchange resin; solvent exchange from water to acetonitrile; fluoride substitution of the triflate group on a D-mannose triflate in dry acetonitrile; solvent exchange back to water; and finally deprotection by acid to afford the desired material. The entire process is completed in the microreactor within 14 minutes ([^{18}F]fluoride $t_{1/2}$ = 110 min), producing the radiolabelled material more quickly and in higher yield and purity compared to conventional automated synthesisers.

Increased production

A common perception is that only small quantities of materials can be prepared in microreactor systems, but the scale-out (not scale-up) nature of microreactors has enabled the use of microreactor systems for the production of commercial quantities of chemicals, with both improvements in safety and reaction efficiency. A microreactor pilot plant in China is safely producing nitroglycerin (from glycerin and nitric and sulfuric acids – a highly exothermic reaction that for obvious reasons requires very careful temperature control) continuously at 10–15 kg/h, with reactor flow rates exceeding 100 L/h.[9] Sigma-Aldrich can produce methylenecyclopentane at a rate of 300 g/h with 70% conversion and no by-product formation, whereas conventional techniques afforded material with up to 30% of the more thermodynamically stable 1-methylcyclopentene by-product which proved difficult to separate.[10] A microreactor system (Fig. 2), developed by DSM Fine Chemicals (Austria) and the Institute for Micro Process Engineering (Forschungszentrum Karlsruhe, Germany), operating over a 10-week period produced approximately 300 tonnes of a polymer precursor![11]

Catalysis

Numerous metal-based catalytic reactions have been performed in microreactors including hydrogenation, oxidation, dehydration and coupling reactions.[1,3] For the most part, the metal catalysts have been either homogeneous catalysts or heterogeneous catalysts where metal/metal oxide films or metal species on inert supports (e.g. palladium on silica) have coated or filled the reactor channels.

Because microreactors are continuous flow devices, the use of homogeneous catalysts requires a constant supply of catalyst during the run time of the reactor. The use of supported homogeneous catalysts with microreactors enables access to the benefits of improved homogeneous catalysts, such as high activity and selectivity, combined with the advantage that the catalyst is retained in the reactor, allowing reuse of the catalyst and reduced contamination of the product. Methods of incorporating supported homogeneous catalysts into the channels of microreactors are still very much under investigation. To date, the majority of investigations

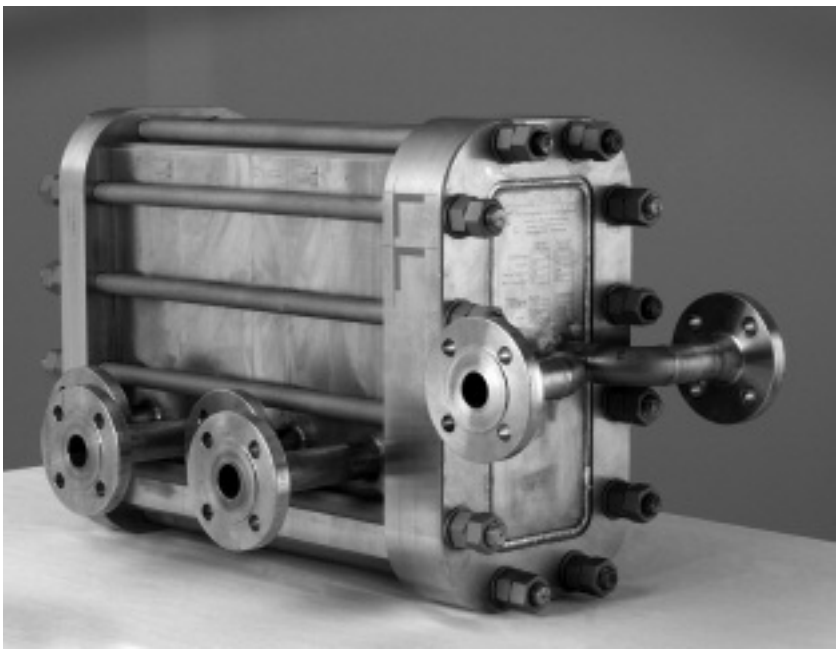


Figure 2. A scaled-out microreactor unit (65 cm long and weighing 290 kg) with thousands of microchannels, capable of liquid flow rates of 1700 kg/h. (Reprinted with permission. Copyright Forschungszentrum Karlsruhe.)[11]

into supported homogeneous catalysts and microreactors have focused on the placement of the catalysts in cartridge or tubular reactors using polymeric beads, silica powders or monolithic support materials.[12–14]

Future of microreactors

Microreactors do not produce only microlitre quantities of products. They can produce larger quantities of materials and in many cases via synthetic routes that have not been scalable using conventional techniques. A number of companies worldwide produce commercial microreactor systems, including Cellular Process Chemistry (Germany), Velocys (USA), Epigem (UK), Ehrfeld Mikroteck (Germany) and MiniFab (Melbourne, Australia). Companies that are exploring microreactor technologies include, but are not limited to, Clariant, Sigma-Aldrich, Bayer, Degussa, Dupont, BASF, Merck, Johnson & Johnson, Dow, GlaxoSmithKline and Pfizer.

Will microreactors replace round-bottom flasks? The field of microreactors for organic synthesis is a little over a decade old and with continued exploration more chemical methodologies will be tested in microreactors. It is clear by the advancements over the past decade that fine-chemical and pharmaceutical companies will increase their use of microreactor technologies as rapid reaction optimisation and rapid reaction scaling is possible. However, the use of microreactors is not without its difficulties and one of the biggest problems in their use is due to channel blockages by solids (although this is an area of continued research and there are examples of particle synthesis in microreactors). As a consequence of such problems careful selection of reaction conditions is needed before microreactors can be used. For synthetic organic chemists microreactors are probably not suited to the exploration of the unknown, but rather for the improvement of syntheses that may have been first performed in a round-bottom flask.

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