Micro reactors: a new tool for the synthetic chemist

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This review focuses on the use of micro reactors as tools in synthetic organic chemistry, aiming to highlight the many advantages associated with their use, in particular their ability to synthesise products in high yield, purity and, where relevant, selectivity.

Introduction

Current production technology is based on the scale-up of successful laboratory-scale processes. This approach is however flawed as at each stage of the scale-up, reactor modifications result in changes to the surface to volume ratio, which often have a profound effect on the thermal and mass transportation properties of the reaction. As a result of these variations, it is often necessary to re-optimise the process at each stage of scale-up, leading to severe delays; consequently the route from laboratory to production is both time-consuming and expensive.

Micro reaction technology has been proposed as a means of addressing this problem as laboratory scale reactions may be performed and optimised using a single reactor and in order to achieve production, multiple reactors may be employed in parallel (Fig. 1).[1] From a production perspective this approach to scale-out, rather than scale-up, is advantageous as it enables changes in production volume to be rapidly implemented, by simply increasing or decreasing the number of devices employed. Furthermore, in comparison to a production plant where reactors are frequently configured for a single function, this system flexibility is both advantageous and cost effective as it enables the demands of the customer to be met with ease.

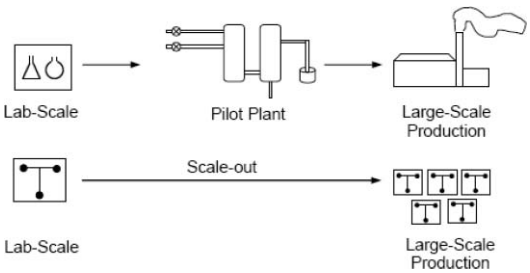

Fig. 1 Schematic comparing the traditional and continuous flow approaches to large-scale production.

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Dr Paul Watts graduated from the University of Bristol in 1995 with a first class BSc in chemistry. He continued his studies at Bristol, obtaining a PhD in bio-organic natural product chemistry under the supervision of Professor Tom Simpson FRS and Professor Chris Willis. His PhD focused on the synthesis of isotopically labelled compounds, for use in determination of biosynthetic pathways to polyketide-derived natural products. Paul subsequently worked as a post-doctoral research associate at The University of Hull, where he investigated organic synthesis in micro reactors. In February 2002, he was appointed as an academic at The University of Hull where he now leads the micro reactor group, which consists of 3 post-doctoral researchers and 7 PhD students. He is interested in organic chemistry, catalysis, biocatalysis and electrosynthesis in micro reactors and has published more than 50 papers in the area.

Paul Watts

Charlotte Wiles

Dr Charlotte Wiles studied at The University of Hull where she obtained her PhD in 2003, entitled 'organic synthesis in micro reactors'. Her post-doctoral research currently focuses on improving reaction efficiency as a function of incorporating solid-supported reagents and catalysts into micro fabricated reactors.

Laboratory scale micro reactors

Micro reactors basically consist of a network of channels formed in a substrate such as silicon, quartz, metal or polymer, which may be fabricated using a wide variety of techniques.[1] With respect to synthetic applications, glass or metal micro reactors are most commonly employed. To perform chemical syntheses within such reactors reagents are brought together in a predetermined sequence, in a designated region of the channel network, where they are mixed and reacted.

For newcomers to the field of micro reaction technology, the easiest way to manipulate fluids through a micro channel network is through the use of pumps, such as syringe pumps. This technique also enables the system to be integrated with on-line analytics, such as HPLC, providing an automated system suitable for reaction optimisation.[2] One disadvantage associated with the use of mechanical pumping techniques is that the large external pumps often dwarf the reaction system itself. This can be addressed by the integration of miniaturised pumps within the reactor, however these microfabricated components increase reactor complexity and can be prone to wear and tear. In contrast, the use of non-mechanical pumping mechanisms, which rely on the direct transfer of energy, are advantageous as they are inherently simple, contain no moving parts, enable pulse-free, low flow rates to be obtained and are readily miniaturised. Of these techniques, the most popular non-mechanical pumping mechanism used for fluidic handling within micro fabricated devices is electroosmotic flow (EOF).[3] In order to manipulate fluids using EOF, electrodes are inserted into the reagent reservoirs, as illustrated in Fig. 2, through which an electric field is applied.

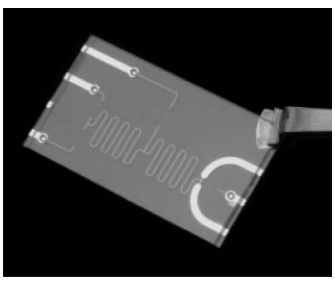


Fig. 2 Glass micro reactor with integrated platinum electrodes, enabling the generation of EOF along with on-line conductivity measurements.

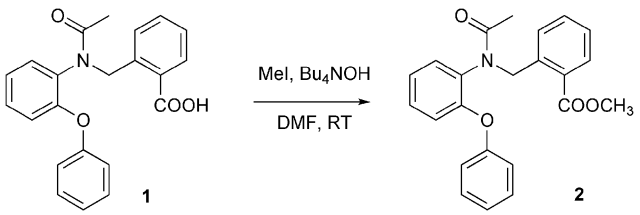
Compared to the use of mechanical micro pumps, field induced flow is advantageous as the electric field acts as both a pump and a valve, providing control over the direction and magnitude of fluid flow. In addition, the technique is readily automated enabling the use of complex flow regimes such as stopped flow. The main disadvantage of this approach however is that the pumps' performance is directly linked to the properties of the fluid contained within the micro channel.

Chemical synthesis within micro reactors

A significant research program is now underway to establish the benefits that micro reactors can bring to the field of synthetic organic chemistry and although many micro reactions have been reported over the past decade,[4–8] for the purpose of this emerging area article, we have focused on those examples that illustrate enhanced reaction efficiency. Further details may be found in the accompanying article by Wirth *et al.*[9]

Rapid reaction optimisation

Micro reaction technology enables the rapid optimisation of reaction conditions, an example of this was recently reported by Lu *et al.*[10] whereby the effect of flow rate on the methylation of a benzodiazepine ligand **1** was investigated (Scheme 1). The authors reported that operating the reaction at a flow rate of 10 μl min^{-1} resulted in a low yield of product (*ca.* 10%), but by decresing the flow rate (hence increasing the residence time of the reactants) to 1 μl min^{-1}, the yield was increased to 53% (Fig. 3).



Scheme 1 Methylation of benzodiazepine ligand **1**.

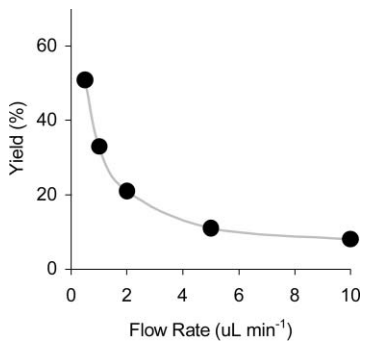
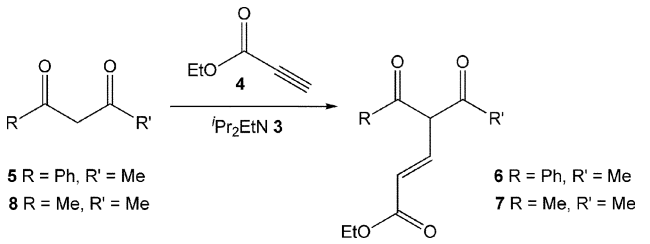


Fig. 3 Effect of flow rate on the methylation of a benzodiazepine ligand **1** in a micro reactor.

Based on these preliminary results, the authors went on to illustrate that they could employ radiolabelled methyl iodide ($^{11}CH_3$) in the reaction to enable the synthesis of a PET radioligand. This example demonstrates that reactions can not only be optimised rapidly, but in this particular example that the reaction may be optimised using non-labelled alkylating agent before it is substituted with a more expensive and radioactively labelled counterpart. The principle was further developed by Gillies and co-workers,[11,12] whereby a glass micro reactor was employed for the incorporation of radiolabels into Annexin-V. Cheng-Lee and co-workers[13] more recently demonstrated the fabrication of an integrated micro fluidic system capable of performing the multi-step synthesis of 2-[^{18}F]FDG.

Whereas Lu and coworkers[10] improved the efficiency of the reaction by reducing the flow rate, an alternative approach is to use the technique of stopped flow. Wiles *et al.*[14] reported the preparation of 1,3-diketone enolates, using an organic base **3**, and their subsequent reaction with a variety of Michael acceptors, such as **4**, to afford 1,4-addition products within a micro reactor (Scheme 2).

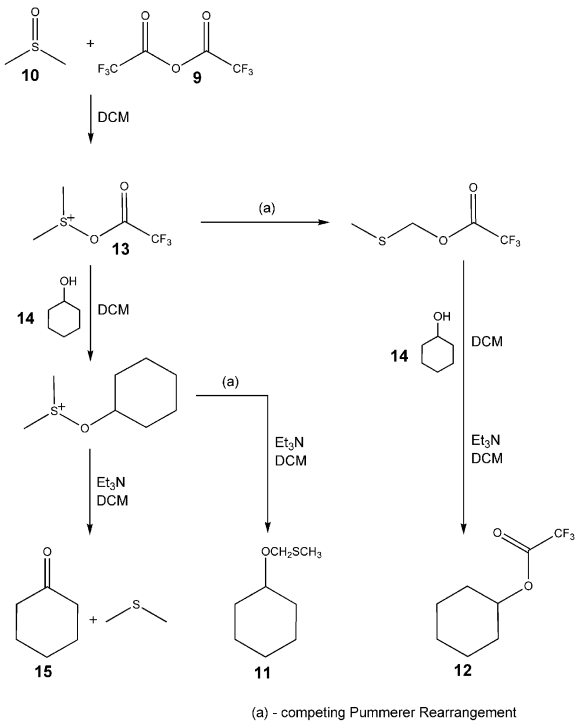


Scheme 2 Michael addition performed under EOF.

When using a continuous flow of reagents **4** and **5**, only 15% conversion to the product **6** was observed, compared with 56% adduct **7** when diketone **8** was employed. The authors however demonstrated enhancements in conversion through the implementation of a stopped flow technique; this procedure involved the mobilisation of reagents through the device whilst employing a periodic stopping of the reagent streams (*via* removal of the applied field), prior to re-mobilisation of the reagents upon application of a voltage. Using a regime of 2.5 s on and 5 s off, the authors report a 19% increase in conversion to adduct **6**; while lengthening the stopped flow period further to 10 s, resulted in quantitative conversion to (*E*)-4-benzoyl-5-oxohex-2-enoic acid ethyl ester **6**. The procedure was subsequently repeated for the synthesis of adduct **7**, in which a regime of 2.5 s on and 5 s off resulted in an increase in conversion to 95% (*E*)-4-acetyl-5-oxohex-2-enoic acid ethyl ester **7**. The authors proposed that the observed increase in conversion, when employing stopped flow, was due to an effective increase in residence time within the device enabling accommodation of the different reaction kinetics; this approach is clearly relevant to those wishing to study reaction kinetics.

Improved selectivity in chemical reactions

Yoshida and co-workers[15] reported a series of Moffat–Swern oxidations within a micro reactor. As Scheme 3 illustrates when employing trifluoroacetic anhydride **9** as the activating agent for DMSO **10**, the Pummerer rearrangement is an inevitable side reaction, which leads to the undesirable formation of by-products **11** and **12**. In order to suppress these side reactions, batch reactions are typically performed at reduced temperatures; for example at −70 °C only 10% **11** and 5% **12** were obtained, compared with 2% **11** and 70% **12** when the reaction was performed at −20 °C. The authors proposed that by conducting the reaction in a micro reactor, where rapid mixing and precise temperature control is attained, increased reaction temperatures could be employed whilst maintaining reaction selectivity. With this in mind, the micro reactor set-up was submerged in a cooling bath and the reagents supplied to the reactor using a series of syringe pumps. To perform a reaction, solutions of DMSO **10** and trifluoroacetic anhydride **9** in DCM were introduced into the micro reactor from two separate inlets, the reagents subsequently reacted to afford the intermediate **13**, prior to the addition of cyclohexanol **14** in DCM. The reagents were again mixed and reacted in a second reactor prior to the addition of Et_3N in DCM before collection of the reaction products at 30 °C. Using this approach, the authors investigated the effect of reaction temperature (−20 to 20 °C) and reagent residence time (0.01 to 2.4 sec) on the synthesis of cyclohexanone **15**, comparing the results obtained to a standard batch reaction (−20 °C).



Scheme 3 Moffat–Swern oxidations within a micro reactor.

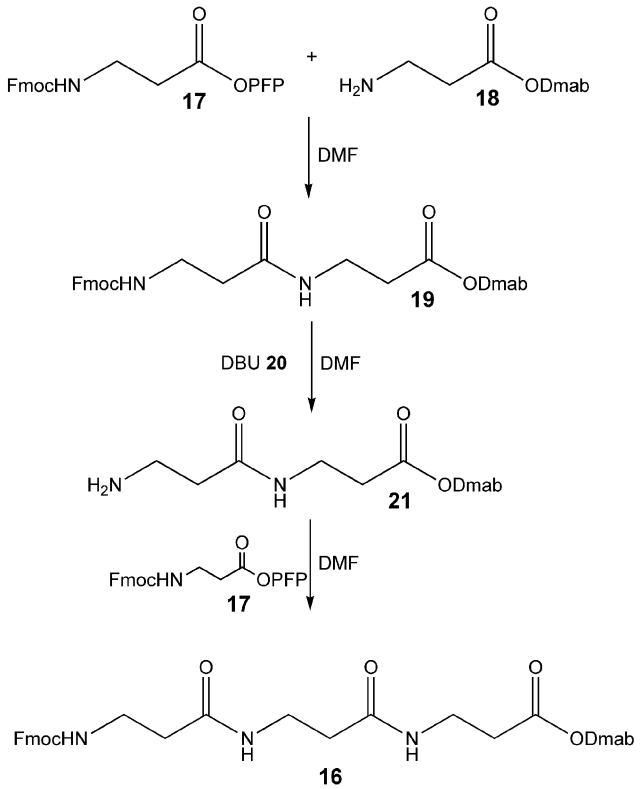
As Table 1 illustrates, the authors obtained comparable conversions and selectivities to batch, even when the micro reactions were performed at room temperature; an observation that is attributed to the short residence time employed for the generation of the reactive intermediate **13**.

Multi-step reactions

In addition to an array of single step reactions, Watts *et al.*[16] reported the synthesis of a tripeptide **16**, demonstrating the first solution phase multi-step synthesis within an EOF-based micro reactor. As Scheme 4 illustrates, the synthesis involved coupling a pentafluorophenyl ester **17** and an amine **18** to prepare a dipeptide **19**, which was further reacted with DBU **20** to effect Fmoc deprotection. The resulting amine **21** was subsequently reacted, *in situ*, with a second equivalent of pentafluorophenyl ester **17** to afford the desired tripeptide **16**, obtaining 30% conversion (over three steps). The approach clearly demonstrates the ability to control both the spatial and temporal evolution of reaction intermediates, enabling efficient, multi-step processes to be performed in continuous flow reactors. Although the example presented demonstrates the generation of relatively non-toxic

Table 1 Effect of reaction temperature on the oxidation of cyclohexanol **14**

	Batch reactor	Micro reactor		
Residence time/sec	*N/A*	2.4	0.01	0.01
Temperature/°C	−20	−20	0	20
Total conversion (%)	86	88	90	81
Cyclohexanone **15** (%)	19	88	89	88
By-product **11** (%)	2	6	7	5
By-product **12** (%)	70	5	1	2



Scheme 4 Multi-step peptide synthesis.

intermediates, the technique could be readily applied to the synthesis of toxic intermediates, providing a safe, scalable route to reactions that cannot currently be performed on a large-scale.

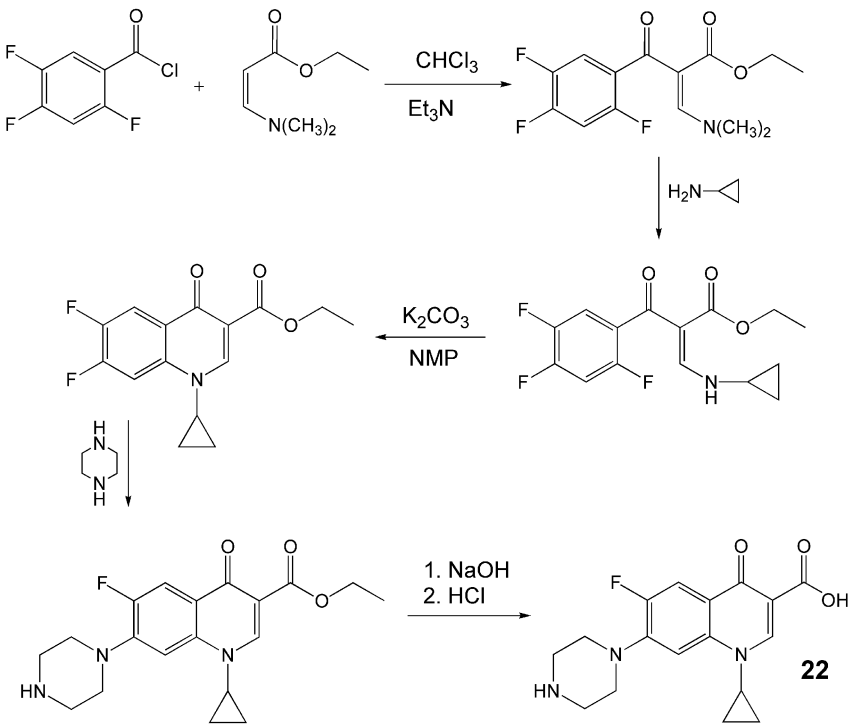
Schwalbe *et al.*[17] subsequently performed the multi-step synthesis of ciprofloxacin **22** within a micro reactor, demonstrating one of the most complex micro fluidic reactions investigated to date (Scheme 5).

Synthesis of analytically pure compounds

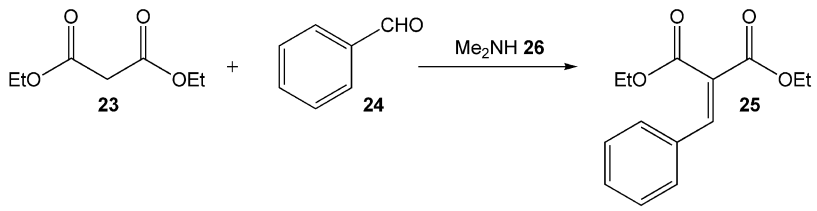
Although different approaches to compound purification have been evaluated within micro reactors, including electrophoretic separation[18] and liquid–liquid extraction,[19] in the vast majority of cases the products tend to be purified, off-line, using traditional techniques such as solvent extraction and chromatography; this clearly detracts from the advantages of conducting the reactions within micro reactors.

Wiles and co-workers[20] recently reported the Knoevenagel condensation within a micro reactor, demonstrating the quantitative conversion of diethyl malonate **23** and benzaldehyde **24** to 2-benzylidenemalonic acid diethyl ester **25** in quantitative conversion (Scheme 6); the product **25** however remained contaminated with dimethylamine **26**.

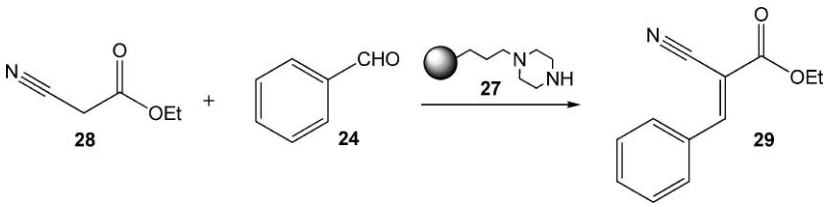
In order to circumvent this problem, the authors investigated the incorporation of a solid-supported base **27** into the micro reactor, enabling the synthesis of analytically pure compounds without the need for additional product purification. Again, EOF was used to mobilise the reagents, ethyl cyanoacetate **28** and benzaldehyde **24** through the packed-bed where they condensed to afford 2-cyano-3-phenyl-acrylic acid ethyl ester **29** in 99% conversion (Scheme 7).[21] Using the optimised reaction conditions, a range of aldehydes and activated methylenes were investigated; in all cases excellent product yields and purities were obtained. The authors concluded that the supported reagents suffered less physical damage when



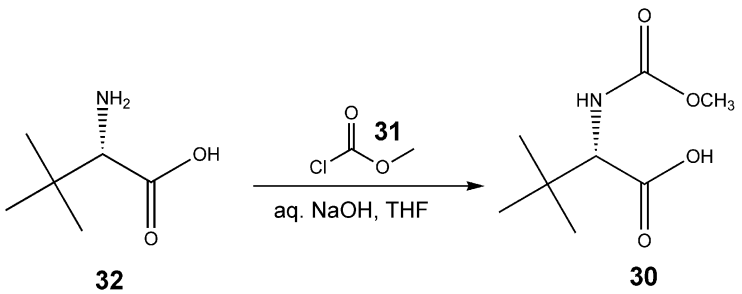
Scheme 5 Synthesis of ciprofloxacin **22** in a micro reactor.



Scheme 6 Solution phase Knoevenagel reaction in a micro reactor.



Scheme 7 The use of immobilised reagents for the synthesis of analytically pure compounds in a micro reactor.



Scheme 8 Continuous flow synthesis of carbamates.

used within the flow reactor, compared to their use in conventional stirred/shaken reactors, resulting in extended reagent lifetimes.

Other reactions conducted in micro reactors incorporating supported reagents include acetalisations,[22] oxidations[23] and the multi-step synthesis of the natural product oxomaritidine.[24]

Large-scale manufacture

Although the use of micro reaction technology is well documented within the academic environment, few papers in the open literature describe their industrial use. A recent paper by Zhang *et al.*,[25] from Johnson and Johnson Pharmaceuticals, reported the use of a stainless steel CYTOS micro reaction system to perform a series of reactions employing unstable intermediates and high reaction temperatures for the synthesis of kilogram quantities of product. One such example was the synthesis of *N*-methoxycarbonyl-L-*tert*-leucine **30** (Scheme 8) *via* the addition of methyl chloroformate **31** to L-*tert*-leucine **32** in the presence of aqueous NaOH. Conducting the reaction in a flow reactor, at −40 °C, resulted in the synthesis of *N*-methoxycarbonyl-L-*tert*-leucine **30** in 91% yield affording a throughput of 83 g hr^{-1}.

Conclusions

In conclusion, we have demonstrated numerous advantages associated with micro reaction technology including: rapid reaction optimisation, reduced reaction times, enhanced conversions, reduced by-product formation, the ability to generate and react reagents formed *in situ*, along with increased reaction selectivity compared to conventional stirred reactor methodology. Consequently, the application of micro reaction technology is of great environmental importance as it has the potential to reduce the quantity of raw materials required, along with efficiently converting them into the desired product with minimal generation of side products and waste. In addition, this approach enables stringent control of reaction conditions, such as temperature, reducing the risk associated with thermal runaway and subsequent explosion.

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