Control of Mixing and Temperature using a Mesoscale Flow Reactor

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Introduction

Continuous flow chemistry continues to gain in popularity as an alternative to more traditional batch synthesis techniques.

This is largely attributable to the fact that the use of long tubular reactors having small cross-sectional dimensions leads to much improved control of both temperature and mixing. This in turn leads to high reproducibility and more straightforward scale-up to produce large quantities of material 'on demand'.

On a small scale, good control of mixing can typically be achieved by relying upon diffusion in narrow channels. In these cases, a simple 'T'-mixer is adequate.

However, for higher throughput applications, or where diffusion is slow, the use of a static mixer to promote efficient turbulent mixing is necessary.

Uniqsis have designed a range of glass static mixer blocks with narrow channels incorporating active mixing geometries that benefit from both diffusional and turbulent mixing, are chemically inert and function as very efficient heat exchangers.

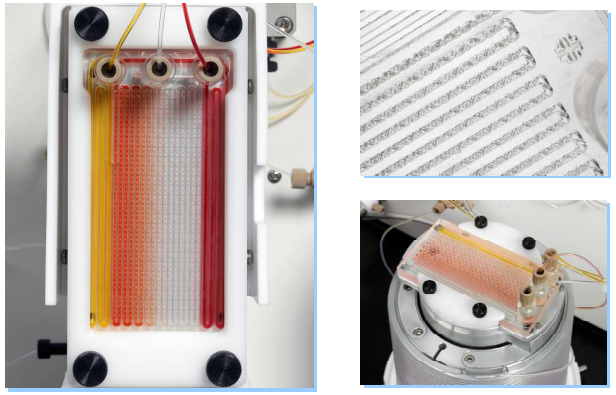
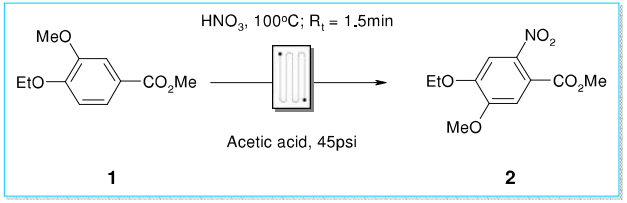


Figure 1. Glass Static Mixer Block (2.0 ml).

- The Uniqsis 2.0 ml *glass static mixer block* can be used as small mixer/reactor for ***reaction optimisation*** on a small scale.
- Attach to a larger volume coil reactor (residence time unit) to permit ***direct scale-up*** simply by a proportional increase in flow rate so as to maintain the same reactor residence time.

Example 1: Nitration

The combination of acetic and nitric acids is a relatively mild method for nitration, but is well suited to continuous flow implementation in that by operating at elevated temperature, short reaction times and high selectivity can be achieved whilst minimising the amount of corrosive (and potentially explosive) hot nitrating mixture present in the reactor at any one time.



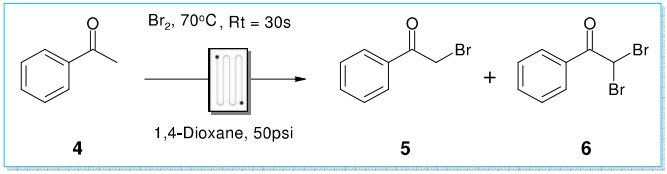
The nitrated product **2** was isolated directly in 85% yield by precipitation from water as shown in Figure 2.

Figure 2. Nitration underway in a mixer chip, collecting the reaction product by direct precipitation from water.

In this example, the 2.0 ml mixer block used as the flow reactor was able to deliver a throughput of **6.0 g/h**.
However, this could be increased to **60 g/h** by extending the mixer block with a 14 ml PTFE coil reactor and increasing the total flow rate to 10.3 ml/min (R_t = 1.5 min).

Example 2: Bromination

Electrophilic bromination is a useful reaction in synthesis. However, when molecular bromine is used as the electrophile (under adventitious acidic conditions) it can be difficult to control both the exothermic addition and to prevent subsequent *bis*-bromination of the desired *mono*-brominated product.



A series of flow-through conditions were investigated using the automated *FlowSyn Multi-Experiment Package* to quickly profile the bromination reaction.

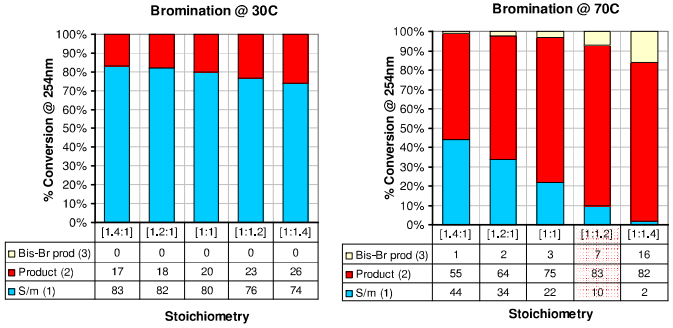
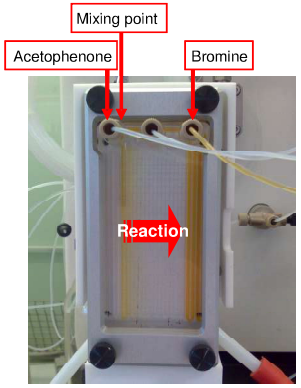


Figure 3. Profiling electrophilic bromination under flow-through conditions.

The results are represented in Figure 3 and show how the reaction can be performed very rapidly as a titration at 70°C whilst still affording a good product ratio.

A throughput of **6.9 g/h** was achieved using the static mixer block alone. This could be increased to **28 g/h** by attaching a 5.0 ml PTFE coil reactor as an extended residence time unit (total flow rate = 13.2 ml/min; R_t = 30 s).



Summary

A glass static mixer block has been found to be a versatile addition to FlowSyn that affords excellent mixing and temperature control. The mixer can be used alone as a small volume reactor for reaction optimisation, and subsequently for direct scale-up by attachment to a coil reactor residence time unit.