FlowSyn™: An Integrated Bench-top Continuous Flow Reactor

Mark Ladlow, Otman Benali, Samantha Dunnage, Martyn Fordham and Paul Pergande

Uniqsis Ltd., 29, Station Rd, Shepreth, Cambs., SG8 6GB, UK.

www.asynt.com

Introduction

Continuous flow-through chemistry is an emerging technology for early stage drug discovery that has broad applicability in reaction optimisation and scale-up.

In comparison to conventional batch processes key advantages include:

- Enhanced thermal and mass transfer leading to improved controllability of reaction temperatures and mixing.
- Increased reaction rates and yields running under superheated conditions analogous to those achieved in microwave reactors.
- High reproducibility resulting in facilitated scale-up.
- Improved safety attributable to reduced instantaneous reaction volumes.

FlowSyn™

FlowSyn™ is an integrated bench-top continuous flow reactor specifically designed to make flow chemistry accessible to all (Figure. 2).

The unit is able to deliver two independent reagent solutions at a pre-determined pressure to either a heated (ambient - 250ºC) tubing reactor and/or a column reactor under full control using a simple graphical user interface (Figure. 1).

Reagents are introduced either from reagent stock bottles or by loop injection using the integrated injection valves.

A range of interchangeable tubing and column reactor modules of various sizes are available to provide maximum flexibility.

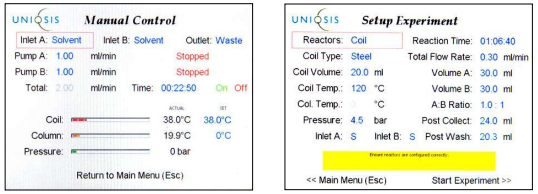


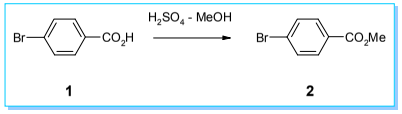
Figure 3.

Electrically operated valves control the input and output flow streams and simple unattended experiments can be programmed to run automatically, collecting the reaction product under steady-state conditions and then stopping the instrument when the experiment is complete.

Figure 2. FlowSyn™

Example 1: Accelerated Esterification under Superheated Conditions.

In this simple example, the esterification of 4-bromobenzoic acid **1** in MeOH containing 1.5% sulfuric acid was studied.



Initially, a series of small scale experiments were performed under steady state conditions to profile the effect of temperature and reaction time (residence time R_t).
As shown in Figure. 3, by running the reaction at 120°C and 75 psi complete conversion to methyl 4-bromobenzoate **2** ('aniseed') could be achieved in only 10 min. in the flow reactor.

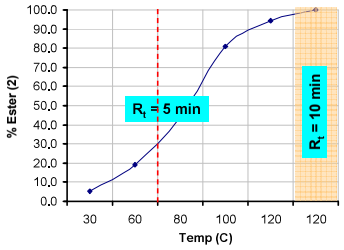
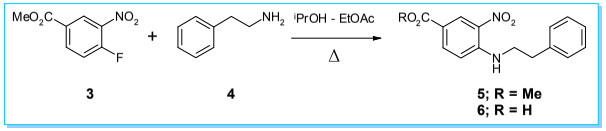


Figure 3.

In contrast, the corresponding batch process, which is limited to 65°C at reflux, is much less efficient. Only a 25% conversion to **2** was obtained in a similar 10 min.

Example 2: Aromatic Nucleophilic Substitution

Nucleophilic aromatic substitution is a useful reaction in synthesis, particularly in the preparation of kinase inhibitors. The aniline **5** was needed on a gram scale as an intermediate in a combinatorial library synthesis.



The reaction was optimised on a small scale in flow using a 2.5 mL tubing reactor (Figure 4).

In the presence of a 10% excess of amine **4**, all the fluoronitrobenzene **3** was consumed within 10 min above 120°C. However, at higher temperatures (> 90°C) a competing hydrolysis of the desired product **5** to the corresponding acid **6** was apparent.

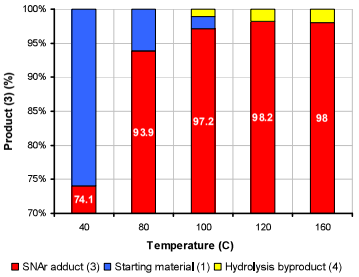


Figure 4.

Suitable optimised conditions were determined to be: R_t = 10 min, T = 120ºC, and under these conditions the reaction was straightforwardly scaled using a 20 mL tubing reactor to afford 10g of **5** in approx 5.5h.

Summary

FlowSyn™ has been shown to be a useful integrated tool for performing meso-scale flow chemistries. Reactions may be optimised on a small scale and then reproducibly scaled up to produce larger quantities of material within a short period of time.

Acknowledgements

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