Flow Synthesis: Reaction Optimisation and Scale-up in Meso-reactors

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Introduction

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

The current drug discovery paradigm is represented in Figure 1.

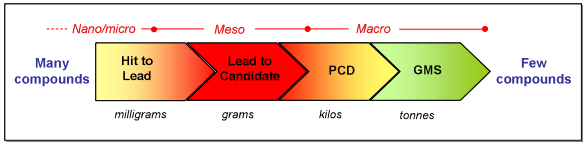


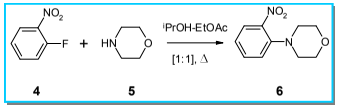
Figure 1. Drug Discovery Paradigm

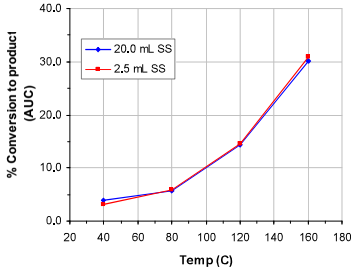
A key decision point is reached when the candidate molecule is first evaluated in man. Therefore, any approach which reduces the cycle time in getting to this point is desirable from the perspective of reducing early stage R&D costs.

The potential to scale-up continuous flow chemistries from mgs to the 100s of grams required to assess safety in man, without the need to modify the synthetic route, has the attractive potential to save both time and money.

However, the lack of simple commercially available instruments to allow medicinal and process chemists to evaluate a wide range of continuous flow chemistries has previously hindered progress in this area. FlowSyn™ was specifically designed to fulfil this need.

Reaction Optimisation and Scale-up



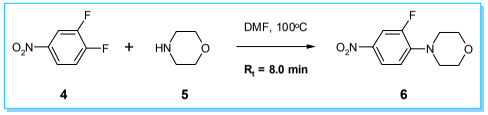


To minimise the consumption of reagents and intermediates it is desirable to perform reaction optimisation in flow on a small scale and to then scale by increasing the size of the flow reactor. A pre-requisite, therefore, is that the results obtained on both scales should be identical.

FlowSyn™ was used to obtain the reaction profiles shown in Figure 2, where it can be seen that the reaction optimisation results, obtained using a 2.5 mL tubing reactor, contrast closely with the experiments performed in a 20 mL reactor.

Example 1: SN_{Ar} Synthesis of a Zyvox® Intermediate

Upjohn's Linezolid (Zyvox®) was the first example of a new class of MRSA active oxazolidinone antibiotics. The first step in a synthesis of this drug is the SN_{Ar} reaction between morpholine and the fluoronitrobenzene **4**.



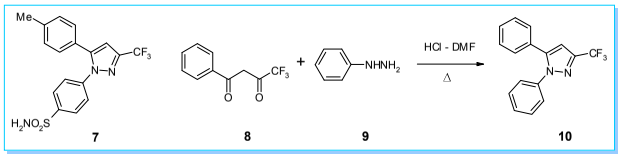
This reaction was optimised in flow on a small scale using FlowSyn™ fitted with a 2.5 mL SS reactor and then the reaction was scaled-up in a 20 mL tubing reactor to afford **6** with a throughput of approx **100 g** every 3 hours.

Figure 3.

The desired product was conveniently isolated by directing the outflow of the flow reactor into a collection vessel containing water to precipitate the product.

Collection and drying of the suspended orange solid afforded the desired nitroaniline **6** in 98% isolated yield and > 99% purity.

Example 2: Knorr Pyrazole Synthesis.



Pyrazoles are a common drug-like structural motif (e.g. Celecoxib® **7**), and condensation reactions are well-suited to implementation in flow chemistry. As shown in Table 1, the reaction of the 1,3-dione **8** with phenyl hydrazine **9** was profiled on a small scale over a range of conditions in the FlowSyn™ using a 2.5 mL PTFE tubing reactor that was resistant to the acidic reaction conditions required.

Table 1.

	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*
Conc^n [A]	0.20	0.20	0.20	0.20	0.20	0.20	**0.40**	0.40
Conc^n [B]	0.22	0.22	0.22	0.22	0.22	0.22	**0.44**	0.44
R_t (min)	10.0	10.0	10.0	10.0	5.0	5.0	**5.0**	5.0
Flow A (mL/min)	0.10	0.10	0.10	0.12	0.24	0.20	**0.20**	0.24
Flow B (mL/min)	0.15	0.15	0.15	0.13	0.26	0.30	**0.30**	0.26
Temp (°C)	40	70	100	100	100	100	**100**	100.0
Pressure (psi)	30	30	30	30	30	30	**30**	30.0
% s/m (1)	79	16	0	3	9	2	**0**	3
% product (3)	21	84	95	93	88	94	**96**	93

Optimal flow conditions were determined to be those in *Exp. 7* under which 96% conversion to the pyrazole **10** was achieved at 100°C with only a 5 min residence time. Minimal (4%) conversion to the alternate regioisomer accounted for the remaining starting material, but this impurity was removed when the desired product was isolated by precipitation from water.

A throughput of **10.5 g/h** was achieved when these conditions were scaled up by simply fitting a 20 mL tubing reactor to the FlowSyn™ and increasing the flow rates to obtain the same residence time.

Summary

FlowSyn™ is an accessible meso-scale continuous flow reactor. It constitutes a useful tool for optimising and scaling-up continuous flow chemistries of drug-like intermediates typically encountered in early stage drug discovery campaigns.

Acknowledgements

Uniqsis gratefully acknowledge the expert support and assistance of Grant Instruments Ltd in designing and developing FlowSyn™.