Applications of Flow Synthesis in Medicinal Chemistry

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Flow Synthesis: Vision and Objectives

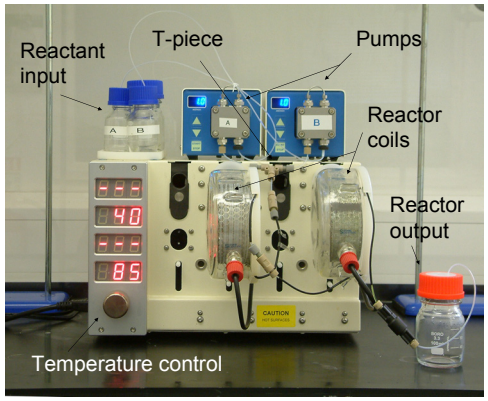
Although chemical synthesis in flowing systems is well established as a technique in manufacturing, particularly in the bulk chemical industry, it has only recently attracted attention in pharmaceutical research as a methodology with potential to expand accessible chemical space and aid scale up of drug like compounds (see box).

Over the last year, an expanding selection of instrumentation for flow synthesis aimed at the medicinal chemist has allowed us to investigate the applications of this methodology.

The R4 bench-top flow synthesis system is designed for both homogenous flow chemistry in tube reactors and heterogeneous flow chemistry using reagents, catalysts or scavengers on immobilised supports within Omnifit column reactors. Up to four reactors can be mounted on the system, using a flexible combination of both tube and column reactors mounted in series or in parallel. Tube reactors are available in various sizes from 0.5ml to 10ml volume and Omnifit column reactors in sizes from 6.6mm ID x 50mm length to 15mm ID x 150mm length can be used .

Each reactor position can be independently heated from ambient to 150ºC using a hot-air system. Forced cooling to ambient is also possible using unheated air, allowing both rapid cooling and some temperature control over exothermic reactions. Two Knauer HPLC type pumps are provided, with flow rates from 0.05ml/min to 10ml/min. The pumps are stable to all commonly used organic solvents but not to strong mineral acids such as HCl. The system pressure is controlled using simple HPLC-type back-pressure regulators – a 100psi and a 40psi version were supplied for this study.

The system has an in-built controller with a large format display panel for temperature setting and display. Remote control is also possible through the RS232 input.



During a 10 week trial, chemistry was conducted on the Vapourtec R4 to assess its usability and utility in a medicinal chemistry environment.

Why Flow Chemistry?

Controllability of reaction variables

- Controlled exposure to reactive environment can minimise product decomposition and by-product formation
- Flow rate is used to control reaction time and stoichiometry
- Multistep reactions are possible – no intermediate isolation

Small reaction volume

- Efficient heat transfer (accurate reaction temperature control)
- Efficient mass transfer (fast, predictable mixing)
- Increased safety when working with high energy intermediates
- Local concentration effects can improve the efficiency of solid supported reagents

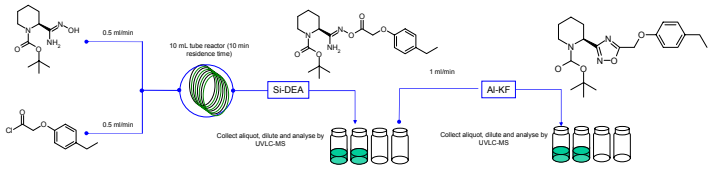
Reproducibility during scale up

- Produce more by flowing for longer
- Whole reaction mixture experiences the set conditions (*cf* batch reactor)

Example 1: Oxadiazole Synthesis

The scheme illustrates chemistry that has been successfully applied in a two step batch process to access oxadiazoles. The first step is an acylation that proceeds at room temperature in near quantitative yield. The second step also proceeds at room temperature with fluoride catalysis, such as TEAF, in acetonitrile. The two processes cannot be done in 'one-pot' since the bases and their hydrochloride salts prevent the fluoride catalysis from working.

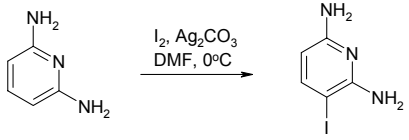
The reaction was adapted for flow using a supported base (DEA on silica) and potassium fluoride on alumina. The conversion for each step was shown to be essentially quantitative by LC/MS.



Example 2: Iodination

The iodination of 1,5-diaminopyridine is used to give a key intermediate in a medicinal chemistry programme.

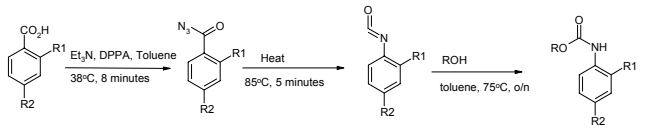
The batch conditions (0.5 eq. I_2 and Ag_2CO_3, DMF, 0°C, 20 hours) gave a mixture of both mono- and di-iodinated products (30% yield of mono) and required two chromatography steps to isolate clean mono-iodinated material.



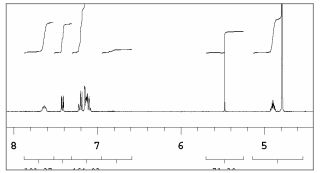
The synthesis under flow conditions was investigated using an Omnifit packed column reactor. The diaminopyridine (0.2M DMF) and iodine (0.2M DMF) were pumped at room temperature through a column reactor filled with solid silver carbonate to give a residence time of 12mins. NMR analysis of the crude material gave a ratio of 7:2:1 mono:di-iodinated:starting material. The crude material was triturated with MeOH to give 98% pure mono-iodinated material with no chromatography.

Example 3: Curtius Rearrangement

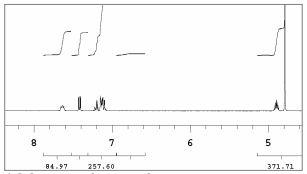
The Curtius can be problematic to scale due to formation of the potentially explosive azidoketone intermediate and the evolution of gas. Performing the reaction in flow allows the formation and rearrangement of small quantities of the azidoketone making the reaction safer to perform on scale. The carboxylic acid and DPPA/Et_3N were mixed using a T piece and flowed at 35°C for 8 minutes to form the azidoketone. This was then flowed into another reactor at 85°C for 5 minutes before quenching with an alcohol at 75°C to form the carboxamide. The maximum quantity of azidoketone in the first reactor at any moment was 7mmoles, the maximum quantity of nitrogen evolved during the second step was 2.5mmoles.



The reaction was performed on 10mmole and 100mmole scales using identical reaction conditions but just leaving the reactions on for longer. The reaction profile of the products was identical and the isocyanate was formed in >80% yield. The reaction could have been scaled further, e.g. 1mole of isocyanate could have been prepared using the same conditions in 33 hours.



10 mmole scale



100 mmole scale

Conclusion

The Vapourtec R4 was found to be simple to use and suitable for preparation of material in the mg to gram scale. The trial reactions indicated that flow chemistry is potentially useful for improving selectivity through ease of control of stoichiometry, mixing and heat transfer. The use of packed columns also allows multi-step reactions where reagents are incompatible. Finally, small reactor volumes allow potentially hazardous reactions to be carried out and scaled up without increasing the amount of reactive intermediate in process at one time. This gives access to reactions at scales that would normally be considered unsafe in a research environment.