vapourtec
precision flow chemistry

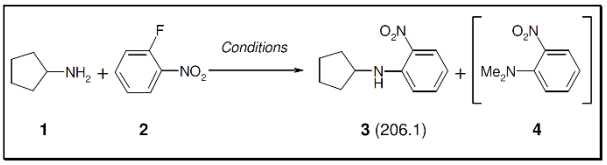
Application Note 1:

Reaction Profiling using a 'Dual-Core™' Tubing Reactor

Produced by Vapourtec

Abstract

This Application Note illustrates, using an SNAr reaction as a simple example, how a continuous flow tubing reactor containing a dual core can be used for reaction profiling, using the smaller capacity reactor to minimize sample wastage, to obtain optimal reaction conditions that may be directly scaled-up in the larger reactor.



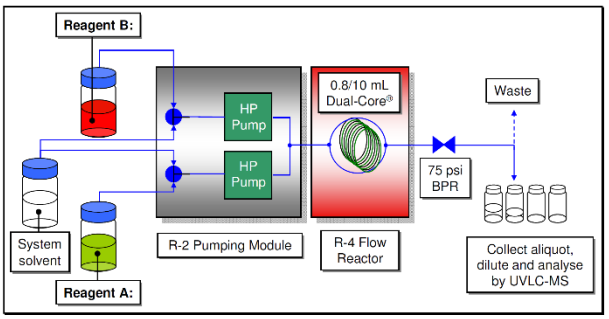


Figure 1. Actual and schematic Dual-Core™ flow reactor configurations.

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Method

The flow reactor was assembled using a combination of the R-2 Pump Module and R-4 Reactor Module as shown in Figure 1. A Dual-Core™ Tubing Reactor (810 µL/10.2 mL) was installed and a 75 psi BPR fitted to the reactor outflow. A short length of 0.5 mm id tubing connected this to a waste collection bottle. The System Solvent Bottle was filled with either DMF or [1:1] EtOAC-EtOH, and the Reagent Stock Bottles A and B were filled with solutions of 2-fluoronitrobenzene and cyclopentylamine in the same solvent respectively.

Setup

System solvent:	DMF or [1:1] EtOH-EtOAc
Reagent A:	0.2M 2-fluoronitrobenzene 2 (2.1 mL in 37.9 mL solvent)
Reagent B:	0.2M/0.4M cyclopentylamine 1 (1.95/3.9 mL in 48.1/36.1 mL solvent)
Flow rate A:	variable
Flow rate B:	variable
Reactor volume:	810 µL/10.2 mL (1.0 mm id)
Reactor temperature:	40-120 °C
Back pressure regulator:	75 psi

Optimisation of Flow Conditions ('Dual-Core™' Reactor)

Using the Dual-Core™ Tubing Reactor, exploratory experiments may be conveniently performed on smaller amounts of material prior to committing to a preparative run, without the need to change the experimental setup. In this case the reactor used had a scale-up factor of 12.6 fold.

Typically, a range of values are selected to investigate different experimental parameters. This may be guided by design of experiment principles (e.g. using software such as Design-Expert®). The objective is to profile the reaction and gain an indication of those parameters that lead to an optimal outcome. Depending on the situation, this may, for example, be to limit the stoichiometric excess of an expensive reagent, to deliver a high purity product, or to maximize yield. In this illustrative example the effects of temperature, flow rate (reactor residence time), stoichiometry and solvent were studied.

Approximately 40 µL aliquots were collected and immediately diluted in mass spec vials filled with MeCN (600 mL) containing 10% HCl (50 mL) to stop the reaction prior to UVLC-MS analysis. The primary analytical data obtained is tabulated in the Appendix, along with a typical set of UVLC-MS traces. The data is summarised here graphically in Figure 2.

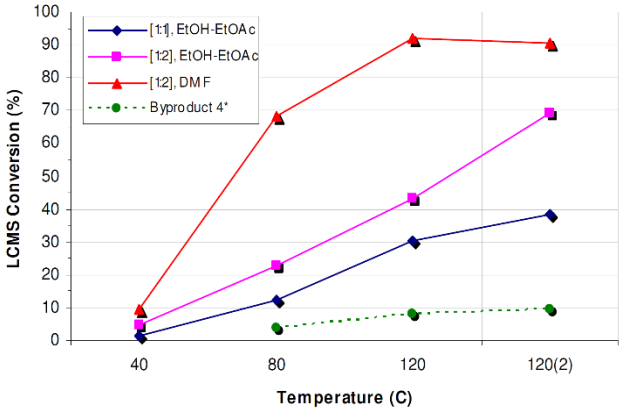


Figure 2. SNAr reaction profile determined using a Dual-Core™ reactor. N.b. * The impurity 4 is only formed when using DMF as the reaction solvent; (2) Refers to data with an extended retention time of 25 min.

Discussion

From the graph (Figure 2), it is apparent that some of the factors studied had a significant effect on the outcome of the SNAr reaction. In fact, a wide range of conversions distributed between 1% and 92% were observed.

Concentration: In this example, a single concentration (0.1M in [2]), equivalent to a throughput of 1.0 g per hour in the larger 10.2 mL co-wound reactor, was chosen. In general, it is beneficial to perform flow chemistry at a higher concentration than the corresponding batch reaction in order to increase throughput. However, care should be taken to ensure that this does not result in precipitation of the reaction product and subsequent blockage of the flow reactor.

Temperature: At close to room temperature the reaction is very slow. As expected, increasing the temperature results in a corresponding increase in conversion to the desired product 3. In particular, it is beneficial to perform this reaction above 80 °C, i.e in excess of the boiling point of the EtOAc-EtOH

solvent mixture. Such superheated conditions can be readily and safely attained in the continuous flow reactor.

Time: At the highest temperature studied (120 °C), extending the residence time in the flow reactor from 12.5 min to 25 min (values 120(2)) increases conversion in the EtOAc-EtOH solvent system. However, when using DMF at elevated temperature, decomposition of the solvent liberates dimethylamine and leads to an increase in the amount of the corresponding SNAr byproduct 4, and a decrease in conversion to the desired product 3.

Stoichiometry: Increasing the amount of cyclopentylamine present from [1:1] to [1:2] (cyan line vs blue line) was found to enhance conversion to product 3.

Solvent: The reaction was performed in both DMF and a [1:1] mixture of EtOH and EtOAc. A key requirement is to ensure that all materials remain solvated whilst passing through the flow reactor. Although alcoholic solvents are popular media for SNAr reactions, at the concentrations employed here, the addition of EtOAc as cosolvent is necessary to ensure that homogeneity of the reaction mixture is maintained throughout. In an attempt to minimize the formation of the byproduct 4 (which is apparently dependent upon both residence time and temperature), some additional experiments were conducted (Figure 3). In the event, at both 120 °C with a decreased residence time of 8.25 min, and at 80 °C with an extended residence time of 25 min, a less desirable reaction profile with a significant quantity of starting material remaining unconverted to product was observed.

In reality, DMF might well be substituted by NMP at this point. This would eliminate the formation of the byproduct 4 completely. Nevertheless, this particular example illustrates well how a reaction profile can be straightforwardly altered under continuous flow conditions by manipulation of various experimental parameters. Even a relatively small number of experiments can quickly yield important information that leads to an improved overall reaction profile.

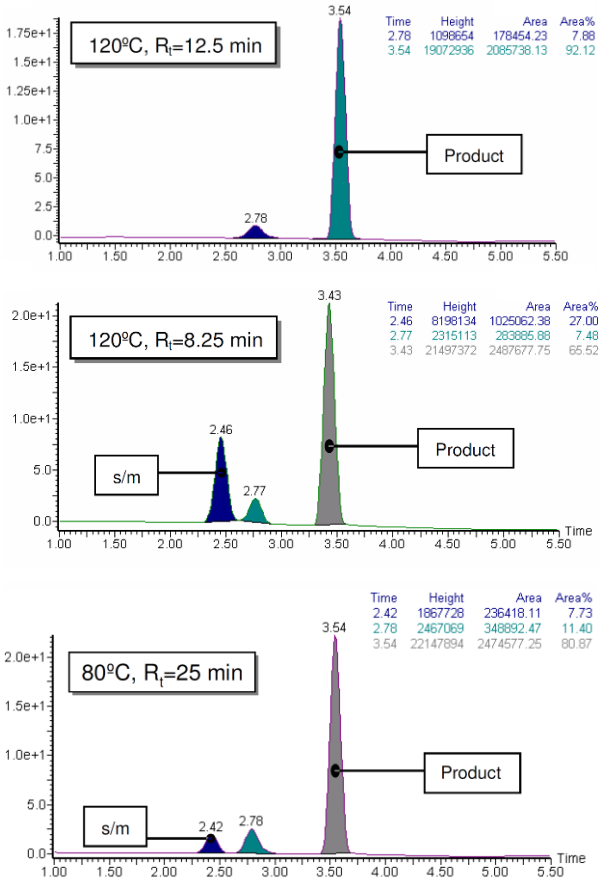


Figure 3.

Comparison with scale-up (810 µL→10.2 mL).

To demonstrate that, when using the Dual-Core™ tubing reactor, the reaction profile obtained on a small scale is representative of that observed on scale-up, the previous SNAr experiment performed in DMF at 80 °C (Rt = 12.5 min) was scaled up 12.6 fold and repeated in the larger co-wound 10.2 mL tubing reactor.

The UVLC-MS results are shown in Figure 4. At steady state, allowing for experimental error, a good correlation (± 3% with respect to the formation of product) between the data obtained in the two tubing reactors was obtained.

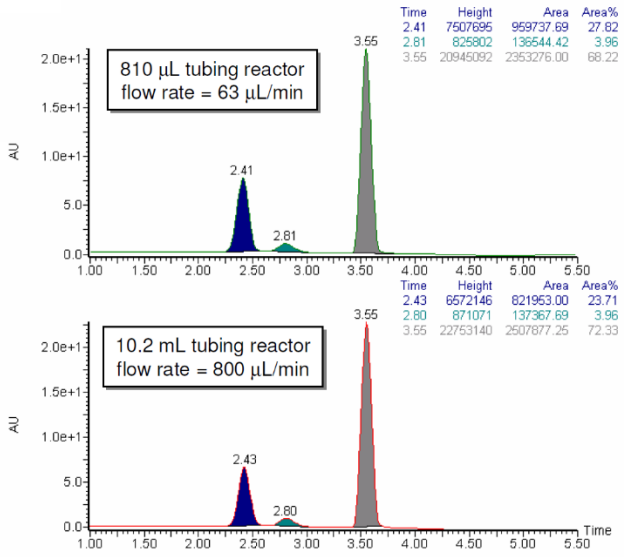


Figure 4.

Contrasting tubing reactors of different sizes.

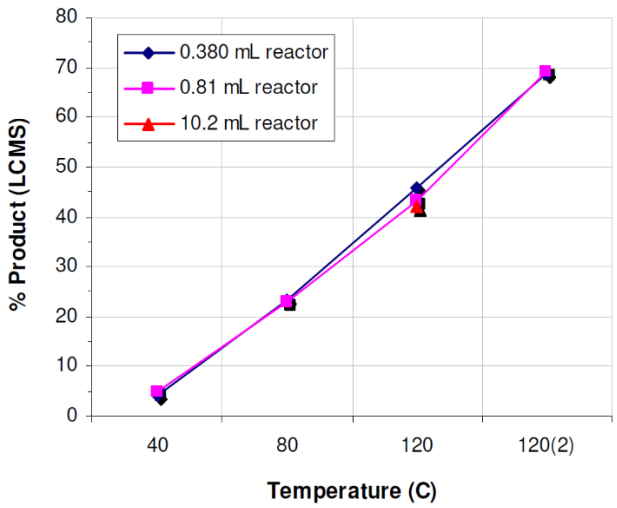
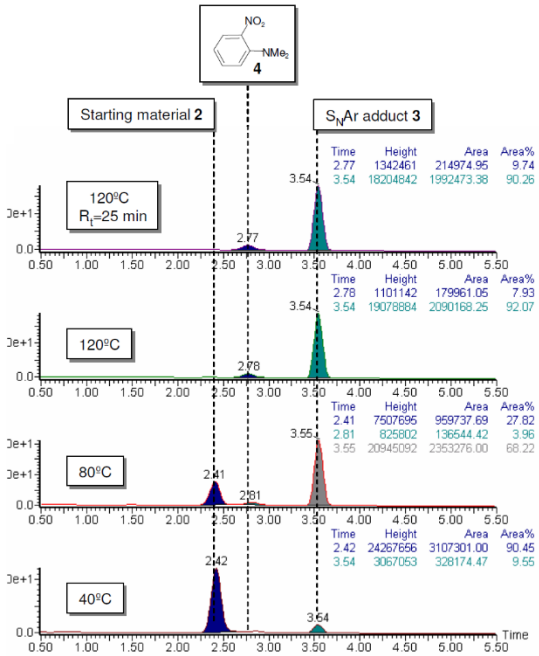


Figure 5.

By using tubing reactors of different internal volumes, a single R-4 has the capability to perform direct scale-up over 2 orders of magnitude. For instance, a 400 µL reactor can be replaced by four 10 mL reactors (total volume = 40 mL) on the same R-4. To demonstrate viability, the above SNAr reaction was conducted in a 370 µL (id = 0.5 mm), 0.81 mL (id = 1.0 mm) and a 10.2 mL (id = 1.0 mm) reactor. To economize on material, only a single data point was collected at the largest scale (120 °C) (Figure 5). The data points obtained are in close agreement.

Appendices



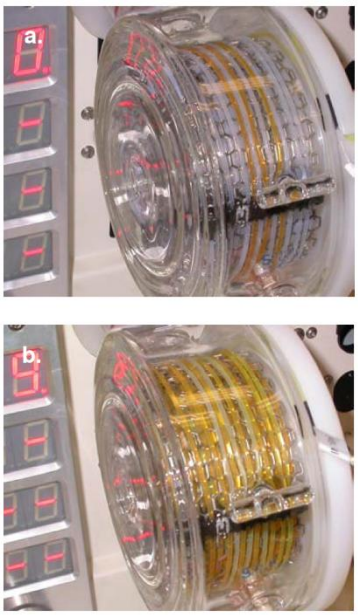


Figure 6. Using the 'Dual-Core™' tubing reactor for reaction optimization. (a) 810 µL reactor. (b) 10.2 mL reactor.

Table 1. Reaction optimization data obtained using the Dual-Core™ tubing reactor.

Entry	Temp (C)	(uL/min)		(M)				(% LCMS)	
		Flow A	Flow B	[A]	[B]	Solvent	s/m	Byproduct	Product
1	40	32	32	0.2	0.2	EtOH-EtOAc	98.7	–	1.3
2	80	32	32	0.2	0.2	EtOH-EtOAc	87.7	–	12.3
3	120	32	32	0.2	0.2	EtOH-EtOAc	69.7	–	30.3
4	120*	16	16	0.2	0.2	EtOH-EtOAc	61.5	–	38.5
5	40	32	32	0.2	0.4	EtOH-EtOAc	95.3	–	4.7
6	80	32	32	0.2	0.4	EtOH-EtOAc	77.2	–	22.8
7	120	32	32	0.2	0.4	EtOH-EtOAc	56.9	–	43.1
8	120*	16	16	0.2	0.4	EtOH-EtOAc	38.3	–	69.1
9	40	32	32	0.2	0.4	DMF	90.5	0	9.5
10	80	32	32	0.2	0.4	DMF	27.8	4	68.2
11	120	32	32	0.2	0.4	DMF	0	7.9	92.1
12	120*	16	16	0.2	0.4	DMF	0	9.7	90.3

Table 2. Reaction conversion data obtained comparing tubing reactors of different internal dimensions (0.380 µL, 0.5mm id; 0.810 µL, 1.0mm id; 10.2 mL, 1.0mm id).

Entry	Temp (C)	Rt (min)	(M)			Product 3 (% LCMS)		
		Residence time	[A]	[B]	Solvent	0.38 mL	0.81 mL	10.2 mL
1	40	12.5	0.2	0.4	EtOH-EtOAc	4.3	4.7	
2	80	12.5	0.2	0.4	EtOH-EtOAc	23.2	22.8	
3	120	12.5	0.2	0.4	EtOH-EtOAc	45.8	43.1	42.1
4	120(2)	25	0.2	0.4	EtOH-EtOAc	68.9	69.1	