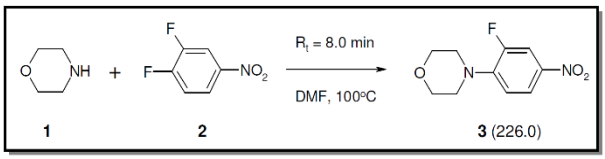
Application Note 3:

Scale-up SNAr using Single 12 mL Tubing Reactor

Produced by Vapourtec

Abstract



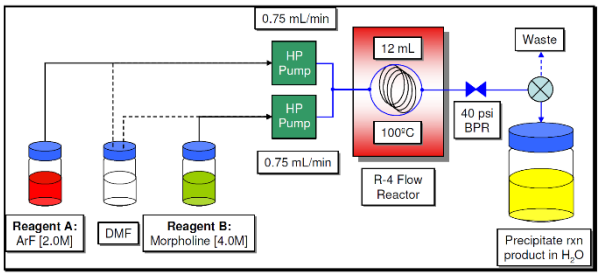


Figure 1. Schematic Flow Reactor configurations.

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Method

The flow reactor was configured using a R-4 Flow Reactor Module and 2 Knauer A120 high pressure pumps as shown in Figure 1. The pumps were connected to a 12 mL tubing reactor via a T-piece. Each pump was connected to the T-piece through a 100psi BPR. A 'T' pressure release safety valve fitted with a 250 psi BPR was fitted between the T-piece and the tubing reactor. The outflow from the tubing reactor was directed into either a 100 mL Duran waste collection bottle or into a 5 L Duran product collection bottle filled with 4 L of water, which was placed on a magnetic stirrer and stirred at approximately 600 rpm. A manual 2-position 3 way valve from used to direct the outflow to either 'waste' or collect. A 40 psi BPR was connected inline between the tubing reactor outflow and the selection valve.

Setup

Scale:	450 mmol
System solvent:	DMF
Reagent A:	2.0 M 3,4-Difluoronitrobenzene 2 (55.0 mL) in DMF (195 mL)
Reagent B:	4.0M Morpholine 1 (87.0 mL) in DMF (163 mL)
Flow rate A:	0.75 mL/min
Flow rate B:	0.75 mL/min
Reactor volume:	12 mL
Reactor temperature:	100 °C
Back pressure regulator:	40 psi
Residence time:	**8 mins**
Throughput:	**20 g/h**

A flow reactor was configured using a combination of the R-2 Pump Module and R-4 Reactor Module as shown in Scheme 1. A Dual-Core™ tubing reactor with calibrated reactor volumes of 810 µL and 10.2 mL was installed. In this optimization study, in order to minimize the consumption or reagents, only the smaller volume tubing reactor was used. A 75 psi BPR was fitted to the reactor outflow and this was connected to a waste collection bottle with a short length of 0.5 mm id tubing.

Flow Reaction:

1. Priming the pumps: The pump inlet tubes were placed in the DMF system solvent reservoir, and the pumps were primed using a syringe connected to the pump outlets.

2. The tubing reactor outflow was directed to 'waste' and both pumps were switched 'on' at 2.00 mL/min until fill the flow reactor was filled with solvent and no bubbles appeared in the outflow.

3. Priming the reactors: The pumps were switched 'off' and the inlet tubes were inserted into the bottles containing Reagents A and B respectively. The tubing reactor was set to 100 °C, and the pumps were each set to 0.75 mL/min and switched 'on'.

4. Attaining steady state: When the reactor temperature had stabilized at 100 °C, the flow was directed to 'waste' for a further 12 mins (1.5x tubing reactor internal volume; this collected material could be recycled if desired) to ensure that steady state had been reached before the collection valve was switched to the 5 L Duran bottle and product collection commenced.

5. Running the reaction: The SNAr product 3 was collected continuously for 5 h.

6. Flushing the system: After 5 h, the collection valve was set to 'waste' and the R-4 temperature was set to 30 °C. The pumps were temporarily stopped, the inlet tubes were inserted into the solvent reservoir, and the pumps were restarted. The system was flushed with DMF for 12 mins (2x system volume), by which time it had cooled to 30 °C.

Work up:

The precipitate was isolated by filtration, washed with water on the filter (3 x 500 mL), air dried, washed with hexanes (3 x 200 mL) and then dried under high vacuum at 40 °C for 18 h to afford the SNAr adduct 3 as a yellow powder (101 g; 99%, [>99% purity]).

LC-MS (ESI +ve): (m/z 227.0 (MH+)); Rt = 2.75 min, >99%;1H NMR (400MHz, CDCL3): dH 7.98 (ddd, J, 1H), 7.92 (dd, J, 1H), 6.91 (t, J, 1H), 3.86(t, J, 2H), 3.27(t, J, 2H).

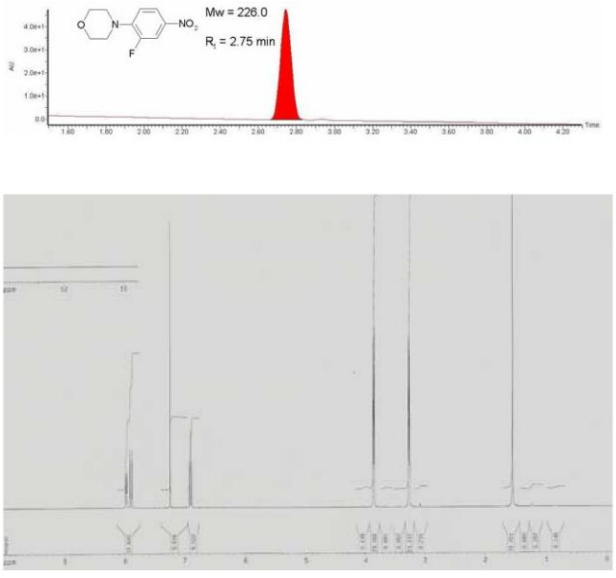

Figure 2. LC-MS data and 1H NMR spectrum for 3.