Application Note 4:

Scale-up SNAr using 4 Reactor Channels in Series

Produced by Vapourtec

Abstract

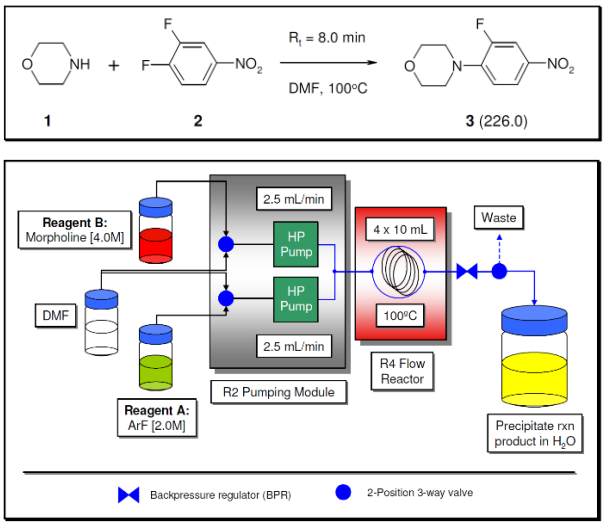

Figure 1. Schematic Flow Reactor Configuration

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Method

The flow reactor was configured using a combination of the R-2 Pump Module and R-4 Reactor Module as shown in Scheme 1. Four Tubing Reactors (10 mL each) were installed and connected together in series. A 40 psi BPR was fitted in-line between the reactor outflow and the collection Valve.

The System Solvent Bottle was filled with DMF, and the Reagent Stock Bottles A and B were filled with solutions of 3,4-difluoronitrobenzene and morpholine in DMF respectively. The Collection Valve 'Collect' output was directed into a 5000 mL glass bottle containing water (4000 L, stirring) to precipitate the reaction product.

Setup

Scale:	450 mmol
System solvent:	DMF
Reagent A:	2.0M 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:	2.5 mL/min
Flow rate B:	2.5 mL/min
Reactor volume:	40 mL (4 x 10 mL coil reactors connected in series)
Reactor temperature:	100 °C

Back pressure regulator:	40 psi
Residence time:	**8 mins**
Throughput:	**68 g/h**

Flow Reaction:

1. Initially, the Collection Valve was set to 'Waste'.

2. Priming the pumps: Both Selection Valves were set to 'Solvent' and the pumps were primed manually using syringes attached to the Selection Valves (set to 'Solvent') with the pumps switched 'on' to fill the pump heads with DMF. Then the Selection Valves were set to 'Reagent' and the lines connecting the valves to the Reagent Stock Bottles were primed using the syringes but, in this case, with the pumps switched 'off'.

3. Priming the Reactors: The Selection Valves were set to 'Solvent', and the reaction parameters were set on the R-2 and R-4. The system was switched 'on' to simultaneously prime and equilibrate the Flow Reactors at 100 °C. After 10 mins, the reactor temperatures remained stable, no air bubbles were observed in the outflow to 'Waste', and the system pressure was observed to be stable at 3.6 bar (combined flow rate = 5.0 mL/min).

4. Attaining steady state: The Selection Valves A and B were simultaneously set to 'Reagent' and the outflow was directed to 'Waste' at the Collection Valve to allow the flow reactor to reach steady state (this material can be recycled).

5. Running the reaction: After 12 mins equilibration (1.5x total internal reactor volume) the Collection Valve was set to 'Collect' (system pressure = 5.8 psi).

6. Flushing the system: After a further 90 mins, the Selection Valves were set to 'Solvent' and the Collection Valve was set to 'Waste'. The reactor temperatures were adjusted to 30 °C 'on the fly', and the system was flushed with DMF as the reactors cooled down for 12 mins.

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 50 °C for 24 h to afford the SNAr adduct 3 as a yellow powder (100.5 g; 99%, [>99% purity]).

LC-MS (ESI +ve): (*m/z* 227.0 (MH^+)); R_t = 2.88 min, > 99%);

^{1}H NMR (400MHz, $CDCL_3$): δH 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).

^{13}C NMR (125MHz, $CDCl_3$): δC 153.2, 150.7, 119.8, 15.7, 111.5, 111.3, 65.4, 48.7.

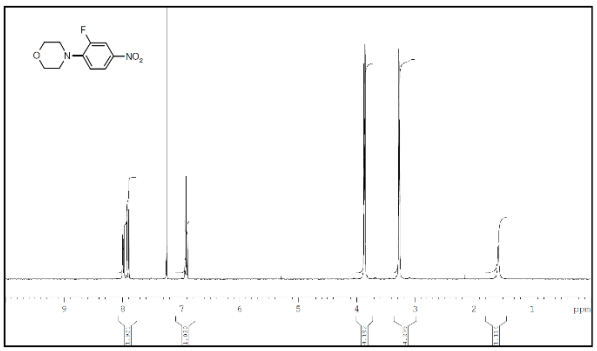

Figure 1. 400MHz ^{1}H NMR Spectrum for 3.

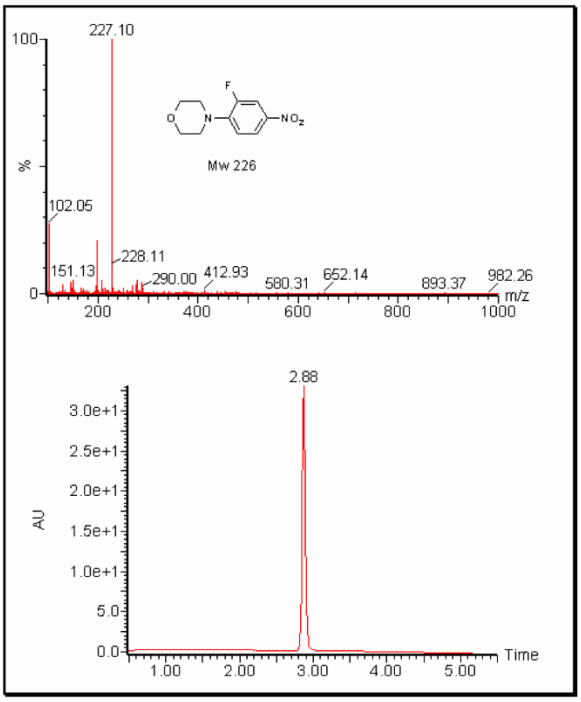

Figure 2. LC-MS Data of S_NAr Adduct 3.

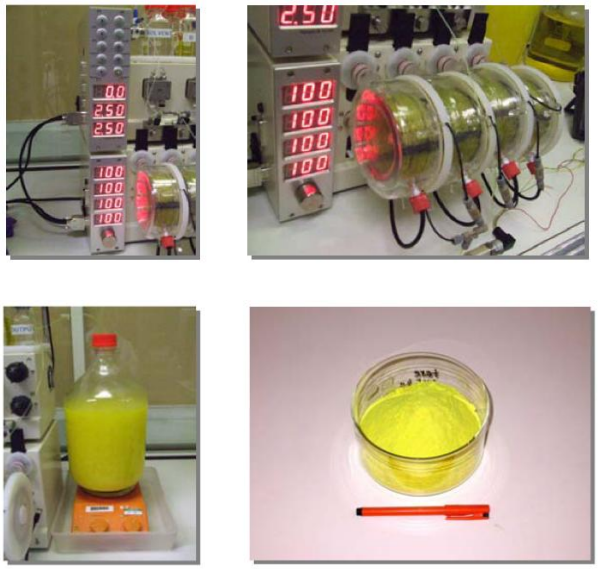

Figure 3. Images of Scale-up Flow Synthesis using the R-2 Pumping Module in Combination with the R-4 Flow Reactor Module (100g/1.5 h).