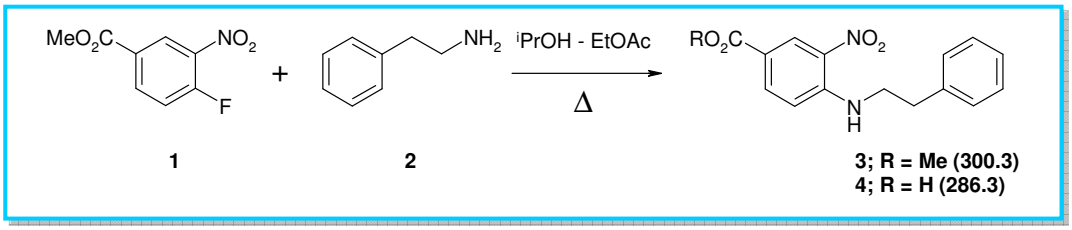
FlowSyn™ Application Note 1:
SN_{Ar} Reaction



Method:

System solvent: [2:1] ^{i}PrOH/EtOAc
Stock solution A: 0.1M Methyl 4-fluoro-3-nitrobenzoate **1** (3.98g, 20 mM) in [2:1] ^{i}PrOH-EtOAc (200 mL).
Stock solution B: 0.11M 2-Phenylethylamine **2** (2.66g, 22 mM) in [2:1] ^{i}PrOH-EtOAc (200 mL).

A variable BPR was fitted and this was adjusted manually to maintain a system pressure of 150 psi at steady state throughout all flow experiments.

a. Flow Optimisation using 'Manual Control' Interface

1. FlowSyn™ was fitted with a 2.5 mL stainless steel (SS) tubing reactor cassette, and the heating unit was tensioned to ensure optimal thermal contact.
2. The inlets were both set to 'Solvent', the outlet was set to 'Waste', and the system was calibrated by running each pump at 1.00 mL/min for 5 min and collecting the outflow in a measuring cyclinder. The measured volumes were entered into the 'Configuration' screen. [In this case, Pump A was found to be running 8% too fast and 5.40 mL was collected. Therefore '1.08 mL' was entered in the 'Configuration' screen for Pump A].
3. A series of flow experiments were performed to profile the SN_{Ar} reaction shown above as follows:

Pump A:	0.12 mL/min
Pump B:	0.12 mL/min
Residence time (R_t):	10 min
Backpressure:	150 psi
Temperature:	40, 80, 120, 160°C

4. In each case, the flow reactor was allowed to equilibrate to the set temperature with the selection valves set to 'Solvent'. The valves were then set to 'Reagent' and the system was allowed to reach steady state for 1.5 reactor volumes (15 min) before a sample (2 drops) was collected in a mass spec. vial containing MeCN (0.7 mL) and 10% HCl (0.1 mL) to stop the reaction.
5. The next temperature was entered and the process was repeated at 80, 120 and 160°C, and the samples were analysed by UVLC-MS (AUC relative **1**).
6. Finally, the selection valves were again set to 'Solvent', the temperature was set to 20°C, and the system was flushed and allowed to cool down to ambient with the cooling gas on for approximately 0.5 h.

Temp (ºC)	% s/m 1	% prod. 3	% acid 4
40	25.9	74.1	0.0
80	6.1	93.9	0.0
100	1.7	97.2	1.1
120	**0.0**	**98.2**	**1.8**
160	0.0	98.0	2.0

Figure 2. Reaction optimisation data.

The optimisation data obtained is shown in Figure 2. As would be expected, conversion to the desired product **3** increases with temperature. However, interestingly, at the higher temperatures ester hydrolysis begins to form the corresponding acid **4** as an undesirable byproduct. The optimal temperature appears to lie between 80 and 120°C and **not** at the highest temperature of 160°C – as might have been supposed for this reaction. Therefore an additional experiment was performed at 100°C. However, at 100°C some unreacted starting material **1** remained and therefore, in this case, 120°C was selected as the optimum temperature for scale-up.

b. Flow Scale-up using 'Manual Control' Interface

1. FlowSyn™ was fitted with a 20 mL SS tubing reactor, and the heating unit was tensioned to ensure optimal thermal contact.
2. The selection valves were set to 'Solvent' and the system was primed to remove all air bubbles - running the pumps at 2.5 mL/min before the pumps were again calibrated at 1.00 mL/min as above [no further adjustments were necessary, in this case].
3. The following flow parameters were entered and the system was allowed to equilibrate for approx. 10 min.

Pump A:	1.00 mL/min
Pump B:	1.00 mL/min
Residence time (R_t):	10 min
Backpressure:	150 psi
Temperature:	120°C

4. The input selection valves were set to 'Reagent' and the system was allowed to run to 'Waste' whilst attaining steady state for 15 min before the collection valve was set to 'Collect'.
5. The outflow was collected for 150 min (equiv. to 15 mmol of **3**).
6. Finally, the collection valve was set to 'Waste', the input selection valves were set to 'Solvent', the temperature was set to 20°C, and the system was allowed to cool to ambient temperature with the cooling gas switched on for approx. 60 min. The pumps were switched off after 20 min flushing through.
7. The collected product solution was evaporated *in vacuo* to leave a yellow solid which was washed on a filter with water (2 x 20 mL), 10% HCl (2 x 10 mL), water (2 x 20 mL), and hexanes (2 x 20 mL) before drying o/n @ 60°C *in vacuo* to leave **3** as a yellow powder (4.25g, 94%): m.p. = 101 - 102°C.
   Throughput = 6.0 mmol/h (1.80g/h).

UVLC-MS (ESI +ve): (*m/z* 301.1 (MH^+)); R_t = 3.56 min, >99%;

IR (ATR): 3359(m), 2949(w), 1708(s), 1622(s), 1566(m), 1519(m), 1435(s), 1280(s), 1230(s), 1145(m), 911(w), 757(m), 697(s) cm^{-1};

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 8.80 (d, J=3, 1H), 8.30 (brs, 1H), 7.95 (dd, J=7, 1H), 7.3-7.1(5) (m, 5H), 6.78 (d, J=7, 1H), 3.80 (s, 3H), 3.55 (m, 2H), 2.95 (t, J=7, 2H).

Supplementary Information:

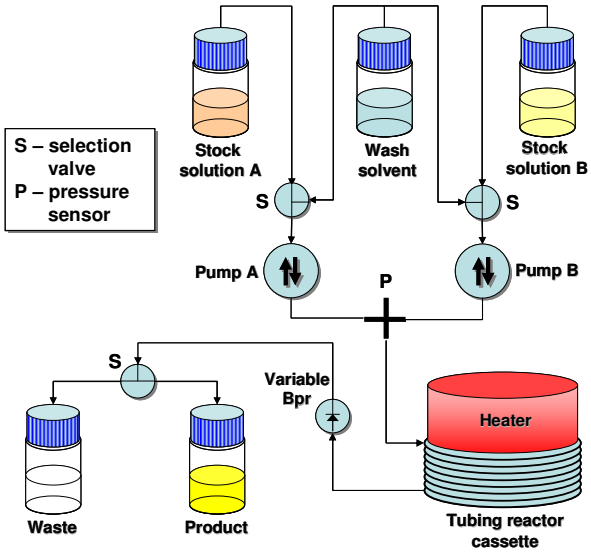


Figure 3. Schematic FlowSyn™ configuration used.

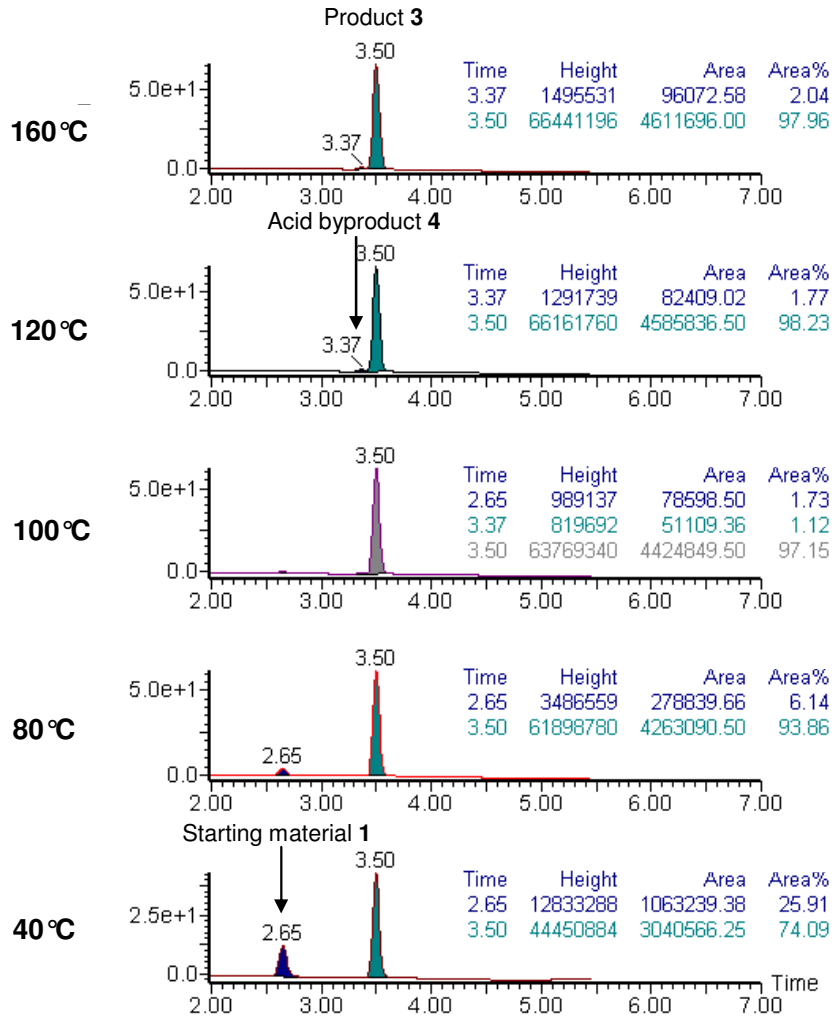


Figure 4. Primary experimental data: UVLC-MS traces (MicroMass v4.0 with peak smoothing).

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