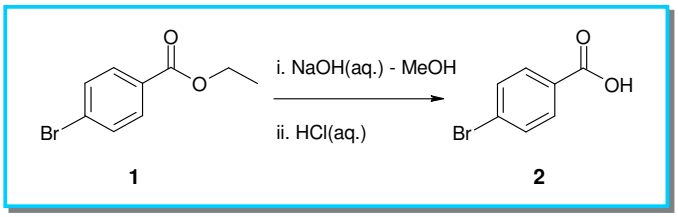
FlowSyn™ Application Note 2: Ester Hydrolysis



Method:

System solvent: 10% aqueous MeOH.
Stock solution A: 0.20M Ethyl 4-bromobenzoate **1** (4.58g, 20.0 mM) in 10% aqueous MeOH (100 mL).
Stock solution B: 0.50M Sodium hydroxide (2.00g, 50.0 mM) in water (100 mL).

A fixed back-pressure regulator was fitted (5 bar) and this was used in all experiments.

a. Flow Optimisation using 'Manual Control' Interface

1. FlowSyn™ was fitted with a 2.5 mL Teflon (PTFE) 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, both pumps were found to be running too fast (5.20 mL was collected in each case). Therefore '1.04 mL' was entered in the 'Configuration' screen for both pumps].
3. A series of flow experiments were performed under 'Manual Control' to profile the hydrolysis (Figure 1). The first four experiments examined the effect of varying the reaction temperature. In the final two experiemnts, the effect of decreasing the residence time and altering the reaction stoichiometry was briefly evaluated in an attempt to increase throughput.
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 before a sample (2 drops) was collected and quenched with MeCN (0.7 mL) and 10% HCl (0.1 mL) to stop the reaction in a ms vial.
5. 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 temperature with the cooling gas on for approximately 0.5 h.
6. The samples were analysed by UVLC-MS (AUC relative **1**).

Rt (min)	10.0	10.0	10.0	10.0	**5.0**	5.0
Flow A (mL/min)	0.15	0.15	0.15	0.15	**0.25**	0.20
Flow B (mL/min)	0.10	0.10	0.10	0.10	**0.25**	0.30
Stoichiometry [A:B]	1.67:1.0	1.67:1.0	1.67:1.0	1.67:1.0	**2.5:1.0**	3.75:1.0
Temp (°C)	20	40	60	80	**80**	80
Pressure (psi)	50	50	50	50	**50**	50
% s/m	44[a]	40[a]	2	0	**0**	0
% prod.	56	60	98	100	**100**	100

Figure 1. Reaction optimisation data. [a]Transesterification leads to a mixture of methyl and ethyl esters.

The optimisation data obtained is shown in Figure 1 and illustrates that whilst transesterification is a competing process at lower temperatures, above approximately 60°C complete hydrolysis to the desired product **2** occurs. At 80°C, it is possible to increase the throughput by halving the reactor residence time and adjusting the stoichiometry to compensate. The conditions shown in red (column 5) were selected for scale-up and corresponds to a throughput of 24 mmol/h.

b. Flow Scale-up using 'Start Experiment' Interface

FlowSyn™ is equipped with a program that allows unattended operation and is able to run a flow experiment automatically, stopping the instrument when the reaction is complete. This was used to perform an 8 fold scale-up flow hydrolysis of **1** under the conditions optimised above.

1. FlowSyn™ was fitted with a 20 mL PTFE tubing reactor cassette, and the heating unit was tensioned to ensure optimal thermal contact.
2. The 'Collect' outflow from the collection valve was directed into a bottle containing stirring 1M hydrochloric acid (250 mL) to precipitate the reaction product **2** and thereby facilitate product isolation.
3. The selection valves were set to 'Reagent' and the reagent lines were primed.
4. The selection valves were set to 'Solvent' and the system was primed to remove all air bubbles. The pumps were calibrated at 1.00 mL/min as previously [no further adjustments were necessary, in this case].
5. The following flow parameters were entered into the 'Setup Experiment' screen.

Reactors:	Coil	**Reaction Time:**	5.00 min (00:05:00)
Coil Type:	Teflon	**Total Flow Rate:**	4.00 mL/min
Coil Temp:	80°C	**Volume A:**	60 mL
Col. Temp.	0°C	**Volume B:**	60 mL
Pressure:	70 psi	**A:B Ratio:**	1.0:1
Inlet A:	R	**Post Collect:**	20.0 mL
Inlet B:	R	**Post Wash:**	30.0 mL

6. Press 'Run Experiment'. FlowSyn™ equilibrates to the set temperature and then runs the flow experiment andfinally cleans the system by flushing with system solvent.
7. The precipitated product was collected by filtration and washed with water (3 x 30 mL) before drying o/n @ 70°C *in vacuo* to leave **2** as a white powder (2.19g, 92%): m.p. = 250 - 252°C. **Throughput = 24.0 mmol/h.**

UVLC-MS (ESI -ve): (*m/z* 199.0, 201.0 ($M-H^-$)); R_t = 2.96 min, >99%;

IR (ATR): 2848(m), 2674(w), 2564(w), 1680(s), 1587(m), 1425(m), 1319(m), 1396(m), 1012(w), 757(w) cm^{-1};

^{1}H NMR (d^6-DMSO, 400 MHz): δ_H 13.20 (brs, 1H), 7.82 (d, J=7, 2H), 7.67 (d, J=7, 2H).

Supplementary Information:

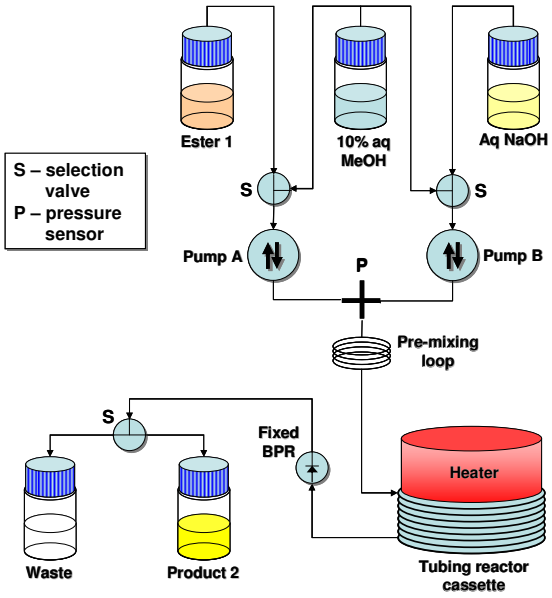


Figure 2. Schematic FlowSyn™ configuration used.

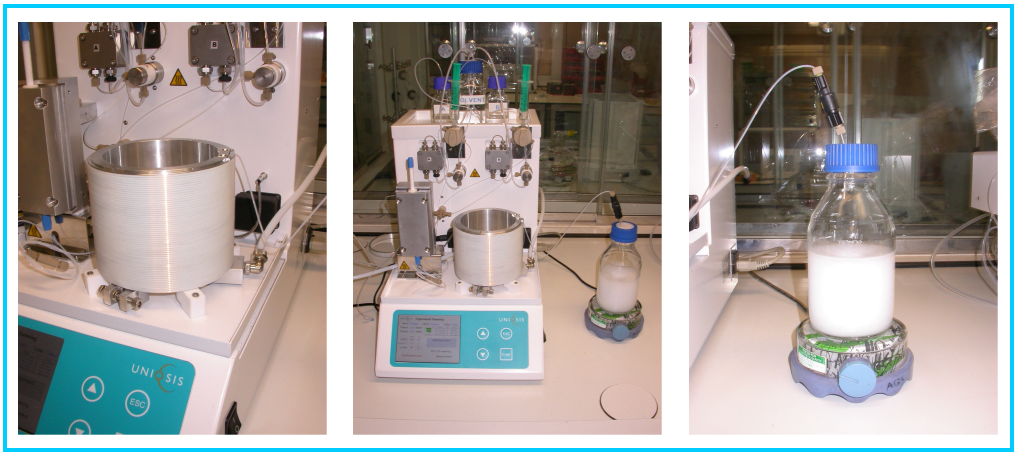


Figure 3. Images of scale-up experiment (Nb. Covers removed from the heater for clarity).

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