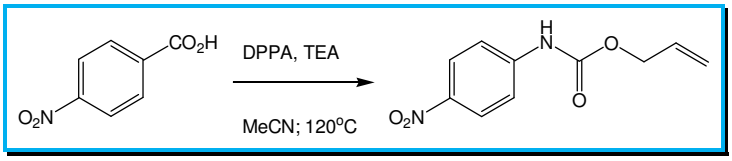
FlowSyn™ Application Note 9: Curtius Rearrangement



Objective:

The Curtius rearrangement is a useful reaction in synthesis that converts carboxylic acids into their corresponding reversed amino derivatives. However, the reaction requires the formation of potentially explosive acyl azides as the precursor to isocyanates that undergo nucleophilic attack to afford the reaction products. Under conventional 'batch' conditions, the scale of the reaction is therefore often limited for safety reasons. This can present a bottleneck in terms of scale-up. Flow chemistry offers an attractive alternative whereby the acyl azide intermediate is continuously processed through to product, preventing its accumulation.

Method:

System solvent: Acetonitrile.
Stock solution A: 4-Nitrobenzoic acid (925 mg; 5.05 mmol), triethylamine (1.40 mL; 10.0 mmol) and allyl alcohol (1.02 µL; 15.0 mmol) in MeCN (50 mL).
Stock solution B: Diphenylphosphorylazide (DPPA: 1.10 mL; 5.1 mmol) in MeCN (50 mL).

A 100 psi fixed back-pressure regulator was fitted and used in all experiments.

Using Automated Experiment Setup

FlowSyn™ is equipped with a program that allows unattended operation and is able to run a flow experiment automatically, stopping and cleaning the instrument when the reaction is complete.

1. FlowSyn™ was fitted with a 14 mL HT PTFE tubing reactor cassette, and the heating unit was tensioned to ensure optimal thermal contact.
2. A 10 cm x 15 mm Column reactor was filled with a [1:1] mixture of Amberlyst A-21 and Amberlyst H-15 resins, and the 'Col Vol' was set to 3.0 mL in the **Configuration Screen**.
3. A 100 psi fixed BPR was connected in-line to the outflow from the tubing reactor before the collection valve.
4. The pumps and inlet lines were primed.
5. The following flow parameters were entered into the 'Auto Set Up' screen.

Inlet A:	Bottle	**Coil Res Time:**	00:20:00
Inlet B:	Bottle	**Col. Res Time:**	00:04:17
Volume A:	10.0 ml	**Tot. Flow Rate:**	0.70 ml
Volume B:	10.0 ml	**Pre Collect:**	3.5 mL
A:B Ratio:	1.0:1.0	**Post Collect:**	14.0 ml
Coil Temp:	120°C	**Final Wash:**	0.0 ml
Col. Temp:	35°C	**Intermed. Wash:**	0.0 mL

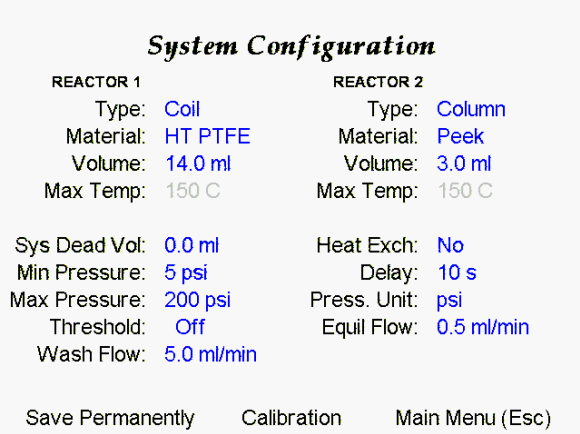
6. Upon pressing 'Run Experiment', FlowSyn™ equilibrates to the set temperature and then runs the flow experiment, before finally cleaning the system by flushing with system solvent ('Wash').
7. The collected product solution was concentrated in vacuo to leave allyl-4-nitrophenyl carbamate as a white solid (198 mg; 88%).

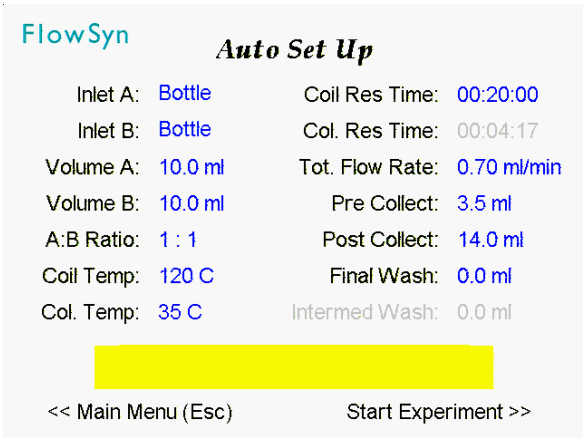
UVLC-MS (ESI +ve): (*m/z* 223.1 (MH^+)); R_t = 3.60 min, >99%;

IR (ATR): 3380 (s), 1730 (s),1685 (m), 1610 (m), 1600 (m), 1545 (s), 1508 (s), 1495 (s), 1320 (s), 1305 (s), 1205 (s), 1110 (s), 1050 (s), 945 (s), 850 (s), 765 (s), 750 (s), cm^{-1}.

^{1}H NMR (d^3-MeCN, 400 MHz): δ_H 8.28 (1H, s), 8.15 (2H, d, *J* = 9.2 Hz), 7.65 (2H, d, *J* = 9.2 Hz), 5.98 (1H, dt, *J* = 17.3, 10.2, 5.8 Hz), 5.40 (1H, ddt, *J* = 17.2, 1.6, 1.6 Hz), 5.30 (1H, ddt, *J* = 10.8, 1.6, 1.6 Hz), 4.65 (2H, d, *J* = 5.6 Hz).

FlowSyn Screenshots:





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