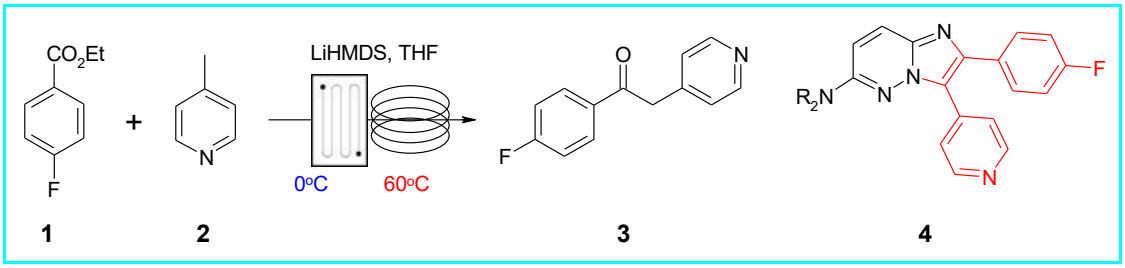
Asynt - Application Note 25:
Standalone Cold Coil: Low Temperature Metalation



Introduction:

Metalations are typically performed at very low temperature (often -78°C) in batch with slow addition of the organometallic base in order to control the exothermic nature of such reactions and to ensure that unstable or reactive metalated intermediates persist. In flow, the improved control of mixing and temperature, will often ensure that similar (or improved) reaction outcomes can be achieved more conveniently at higher temperatures.

This Application Note describes how FlowSyn can be used with the addition of a separate 'Cold Coil' reactor module fitted with a static mixer chip to run a metalation/quench reaction described in the literature[1] for the preparation of intermediates (eg **3**) useful for the synthesis of kinase inhibitor chemotypes (eg **4**).

The literature procedure has been further optimised on the FlowSyn to increase throughput. Further optimisation is also possible.

- The strong organolithium base is pumped directly into the reactors *without* the need to use sample loops to protect the pumps.
- A static mixer chip and small extended residence coil, both cooled to 0°C using the standalone 'Cold Coil' reactor module attached to an external chiller are used to control the initial exothermic metallation reaction with LiHMDS.
- The use of an external mechanical chiller ensures that stable low temperatures can be maintained for many hours without the need to refill baths with cardice.
- The reaction mixture is then incubated in a 2nd coil reactor @ 60°C to (i) reduce residence time R_t, (ii) help to keep the reaction product in solution, and (iii) *increase overall throughput*.

Method:

System solvent: Tetrahydrofuran (freshly distilled anhydr.).

Stock solution A: 1M LiHMDS in THF (19.8 mL; 19.8 mmol).

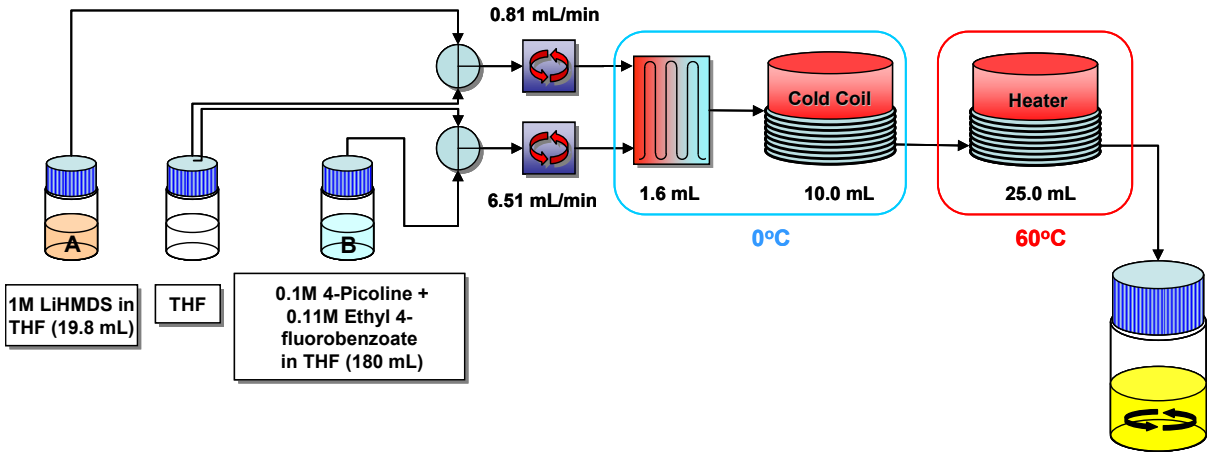
Stock solution B: Ethyl 4-fluorobenzoate (3.02 g, 18.0 mmol) and 4-picoline (1.84 g, 19.8 mmol)) diluted to 180 mL with anhydr. THF (0.10/0.11M).

Notes *(see photograghs):*

- All reagent solutions were inerted under N_2 and stored in oven-dried bottles.
- The system was flushed with anhydrous THF (100 mL) to remove residual moisture before commencing the experiment.
- No BPR was fitted to the outflow.
- The metalated reaction product is quite insoluble, therefore to minimise blockages, the outflow was directed straight into the waste bottle and manually moved over to the collection bottle just as the reaction product could be seen (yellow/orange) to be leaving the 25 mL coil reactor.

- The product was collected in a 1000 mL bottle containing hexanes (400 mL).
- A stainless steel needle was inserted into the stock bottle of 1M LiHMDS .
- Pumpheads were fitted with a Backwash Kit (UQ-7210).

Schematic:



Configuration:

System Configuration			
RH reactor:		**LH reactor:**	
Type:	Coil	Type:	None
Material:	LT PTFE	Material:	N/A
Volume:	36.6 ml	Volume:	0.0 ml
Max Temp:	100°C	Max Temp:	N/A
System Dead Volume:	0.00 ml	Heat Exchanger:	No
Minimum Pressure:	5 psi	Pump Start Delay:	5 s
Maximum Pressure:	200 psi	Pressure Units:	psi
Pressure Threshold:	Off	Equil. Flow Rate:	1.0 ml/min
Wash Flow Rate:	10.0 ml/min		

Auto Set Up			
Inlet A:	Bottle	Coil Residence Time:	00:05:00
Inlet B:	Bottle	Column Residence Time:	00:00:00
Volume A:	20 ml	Total Flow Rate:	7.32 ml/min
Volume B:	180 ml	Pre Collect:	0.00 ml
A:B Ratio:	1:9.0	Post Collect:	10.0 ml
Coil Temp:	60C	Final Wash:	30.0 ml
Column Temp:	18C	Intermediate Wash:	0.00 ml

Throughput = 12.2 g/h (40.0 mmol/h)

When the reaction was complete the product was collected by filtration to afford a yellow solid which was washed with hexanes (3 x 20 mL). The solid was dissolved in water (200 mL) and extracted into EtOAc (3 x 50 mL). The dried organic extracts were evaporated *in vacuo* to afford the product **3** as a yellow powder (5.0 g; 92%).

HPLC: R_t = 1.87min (R_t(s/m) = 2.04min, 0.20min): 100% purity @ 254nm.

^{1}H-NMR ($CDCl_3$; 400Hz): 4.30 (2H, s), 7.1-7.2 (4H, m), 8.0-8.1 (2H, m), 8.58 (2H, dd, J = 4.8).

Figure. Preparation of intermediate **3** using FlowSyn fitted with a 'Cold Coil' and Static Mixer Chip.

References:

1. F. Venturoni, N. Nikbin, S. V. Ley and I. R. Baxendale, *Org. Biomol. Chem.*, **2010** DOI: 10.1039/b925327k