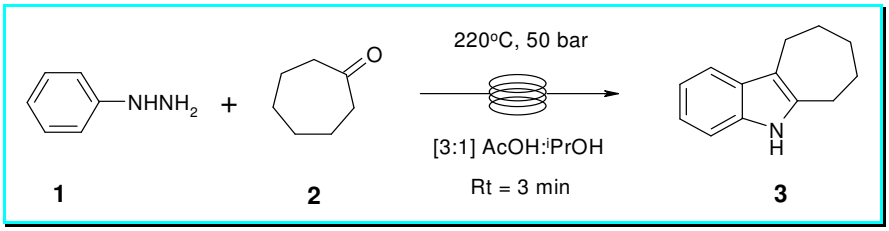
FlowSyn™ Application Note 16:
Fischer Indole Synthesis



Objective:

The rate of the Fischer indole synthesis can be significantly increased by running at high temperature and pressure under conditions similar to those encounter in a batch microwave reactor.
However, in a continuous flow device, the quantity of material produced is limited only by the length of time the instrument is run for.
In addition, product isolation, as in this case, can frequently be facilitated by direct precipitation from water, the product being collected by filtration followed by drying *in vacuo*.

Method:

System solvent: [3:1] AcOH:^{i}PrOH.
Stock solution A: 1.00M phenylhydrazine (5.40g, 50.0mmol diluted to 50ml) in [3:1] AcOH:^{i}PrOH.
Stock solution B: 1.05M cycloheptanone (5.88g, 52.5mmol diluted to 50ml) in [3:1] AcOH:^{i}PrOH.

- ^{i}PrOH was added to the acetic acid as a co-solvent to aid solubility in the flow reactor.
- The 'Collect' outlet tubing was directed into a glass bottle containing ice-water (250ml) positioned on a magnetic stirrer.
- A 500psi BPR (tan/green) was fitted.

Configuration:

System Configuration			
RH reactor:		**LH reactor:**	
Type:	Coil	Type:	None
Material:	Steel	Material:	
Volume:	20.0 ml	Volume:	
Max Temp:	260°C	Max Temp:	
System Dead Volume:	0.60 ml	Heat Exchanger:	Yes
Minimum Pressure:	0 psi	Pump Start Delay:	30 s
Maximum Pressure:	1000 psi	Pressure Units:	psi
Pressure Threshold:	Off		
Wash Flow Rate:	5.0 ml/min	Equil. Flow Rate:	0.5 ml/min

Auto Set Up:

Auto Set Up			
Inlet A:	Bottle	Coil Residence Time:	00:3:20
Inlet B:	Bottle	Column Residence Time:	00:00:00
Volume A:	40 mL	Total Flow Rate:	6.00 mL/min
Volume B:	40 mL	Pre Collect:	0.0 ml
A:B Ratio:	1:1	Post Collect:	0.0 ml
Coil Temp:	220C	Final Wash:	10.0 ml
Column Temp:	80C	Intermediate Wash:	0.0 ml

Results:

The observed sytem pressure during the experiment was 725psi. When the experiment was complete, the collection bottle was chilled (ice/water) and the precipitate collected on a filter. The solid was washed with cold [3:1] ^{i}PrOH-water(2 x 30ml), water (30ml) and hexanes (30ml) and dried *in vacuo* to afford the indole **3** as a beige powder (g, %), which could be sublimed to give colourless platelets: mp 145-146^{o}C.

HPLC: 100% (214-270nm).

NMR (400MHz; CDCl3): 1.6-1.8 (m, 6H), 1.8-2.0 (m, 2H), 2.6-2.9 (m, 4H), 7.05-7.15 (m, 2H), 7.2.25-7.35 (m, J=4, 4Hz, 1H), 7.45-7.55 (m, 1H), 7.5-7.8 (brs, 1H).

^{13}CMR (100Hz; CDCl3): 24.5, 27.5, 28.8, 29.5, 31.8, 110.0, 113.6, 117.4, 119.2, 120.5, 129.5, 134.2, 136.9.

LCMS ($M+H^{+}$): 186.3

211 bis Avenue Kennedy - BP 1140 - 03103 Montluçon - France
Tél : 33 (0) 4 70 03 88 55 - Fax : 33 (0) 4 70 03 82 60
e-mail : interfine@mail.interchim.fr
www.interchim.com