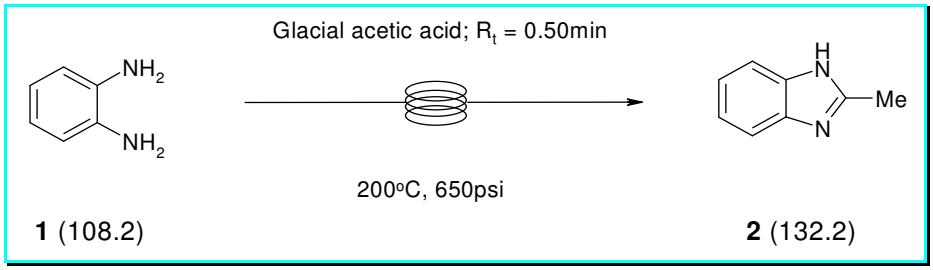
FlowSyn™ Application Note 23:
Heterocyclic Synthesis: 2-Methylbenzimidazole



Introduction:

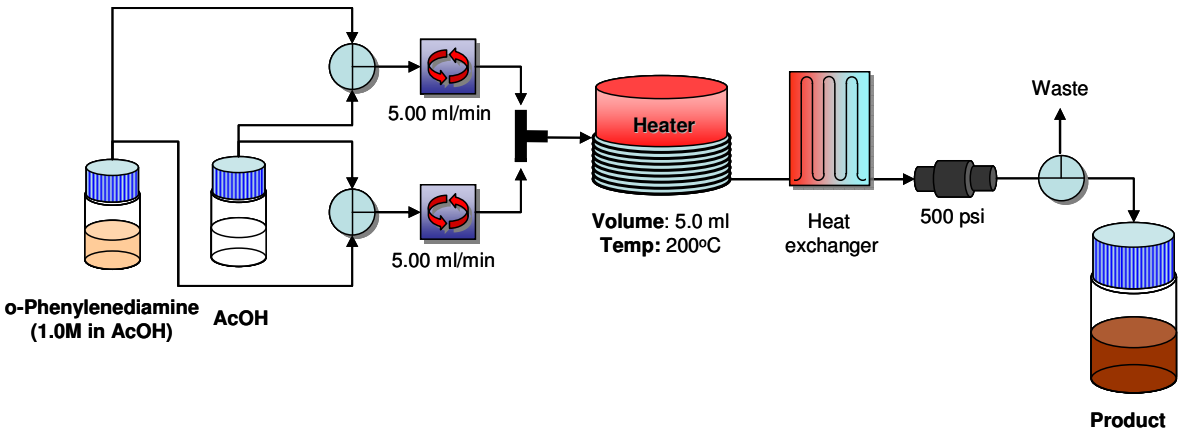
Many useful reactions in chemical synthesis can be considerably accelerated when run at high temperature under microwave-assisted conditions. However, for scale-up the need to empty and refill conventional batch microwave vessels coupled with repetitive heating up and cooling down cycles is both inconvenient and decreases throughput. Under these circumstances, the translation of high temperature microwave protocols to continuous flow processes offers tangible advantages both in terms of reduced operational complexity and increased throughput.
Heterocyclic synthesis is a case in point, and in this Application Note we describe the continuous flow synthesis of 2-methylbenzimidazole which can be achieved in 30 seconds at 200°C under continuous flow-through conditions in the FlowSyn.

Method:

System solvent: Acetic acid.
Stock solution A/B: o-Phenylenediamine (43.2g, 0.40 moles) diluted to 400mL in acetic acid to produce a 1M solution.

- o-Phenylenediamine was dissolved by briefly warming to approx 50°C in acetic acid with stirring and then cooling to room temperature in a sonicator.
- The FlowSyn was fitted with a 5ml stainless steel coil reactor and the system pressure was controlled using a 500psi fixed back pressure regulator.

Schematic:



FlowSyn Set Up:

System Configuration			
RH reactor:		**LH reactor:**	
Type:	Coil	Type:	None
Material:	Steel	Material:	
Volume:	5.0 ml	Volume:	
Max Temp:	150°C	Max Temp:	
System Dead Volume:	0.60 ml	Heat Exchanger:	Yes
Minimum Pressure:	0 psi	Pump Start Delay:	5 s
Maximum Pressure:	1000 psi	Pressure Units:	psi
Pressure Threshold:	Off		
Wash Flow Rate:	10.0 ml/min	Equil. Flow Rate:	1.0 ml/min

Auto Set Up			
Inlet A:	Bottle	Coil Residence Time:	00:00:30
Inlet B:	Bottle	Column Residence Time:	00:00:00
Volume A:	200 ml	Total Flow Rate:	10.0 ml/min
Volume B:	200 ml	Pre Collect:	0.00 ml
A:B Ratio:	1:1	Post Collect:	10.0 ml
Coil Temp:	200C	Final Wash:	10.0 ml
Column Temp:	50C	Intermediate Wash:	0.00 ml

Throughput = 79.2g/h

When the reaction was complete the product was isolated by evaporating the excess acetic acid *in vacuo* to leave a dark viscous oil. The oil was neutralised with half-saturated potassium carbonate solution with stirring (gas evolution!) to precipitate a beige solid. The solid was collected by filtration, washed on the filter with water (3 x 80ml) and dried at 60°C *in vacuo* to afford 2-methylimidazole as a beige solid (49.0g; 93%).

HPLC: R_t = 0.18min (R_t(s/m) = 0.17min): 100% purity @ 254nm.

^{1}H-NMR ($CDCl_3$; 400Hz): 7.45 (m, 2H), 7.15 (m, 2H), 2.55 (s, 3H): 98% purity.