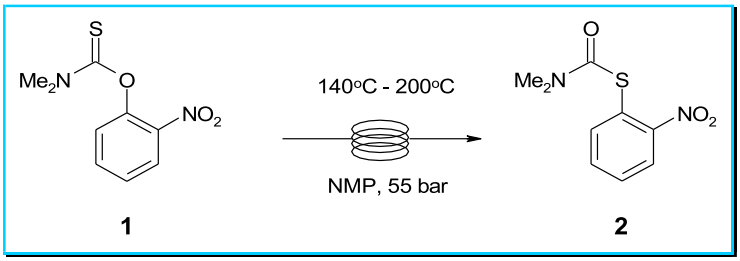
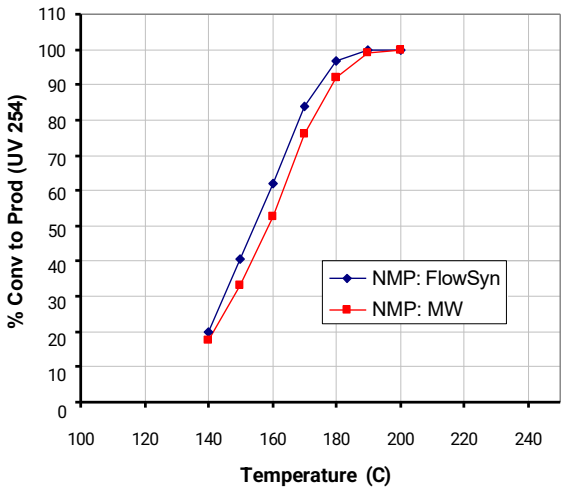
FlowSyn™ Application Note 17: Newman Kwart Rearrangement



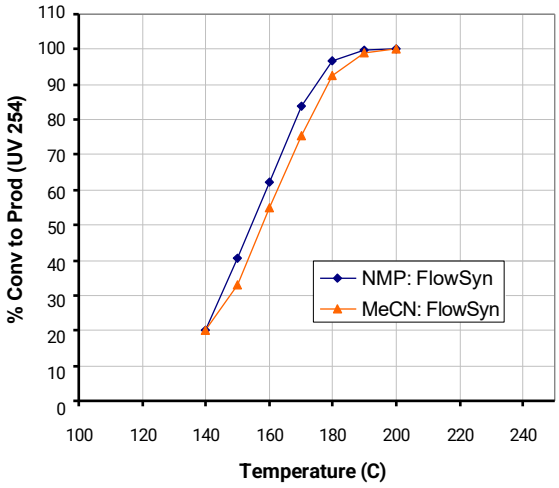
Introduction:

The Newman-Kwart rearrangement is a useful method for converting Ar-O to Ar-S bonds that can be further derivatised following basic hydrolysis of the S-thiocarbamate 2. The reaction rate, and therefore necessary reaction temperature is determined by the electronic demand on the aromatic ring, but is typically in the range requiring the use of microwave heating. As such, the reaction can be inconvenient to scale up.
However, the reaction works equally well in a conventionally heated continuous flow reactor (Graph1). Now, the reaction can be readily scaled simply by running the reactor for longer. Moreover, the higher pressure capability of the FlowSyn permits:

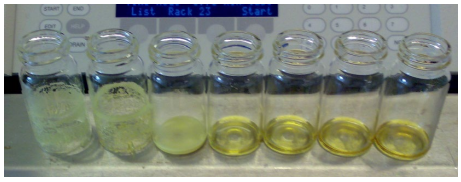
- the use of solvents such as MeCN rather than NMP that can subsequently be easily evaporated to isolate the product (Graph 2) and
- gives a pale yellow oil as opposed to the black product obtained using NMP under identical conditions.



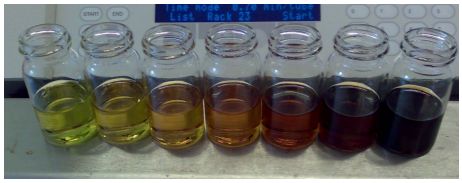
Graph 1: Contrasting a batch microwave with FlowSyn



Graph 2: Contrasting the use of NMP and MeCN as solvent



Increasing
140°C → 200°C
temperature



Increasing
140°C → 200°C
temperature

Figure 1: Contrasting NKR performed in MeCN (left) versus NMP (right).

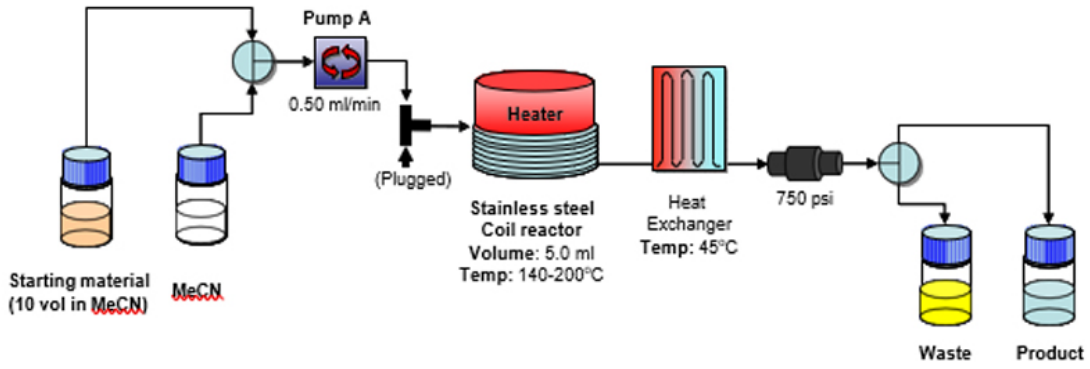
The photographs (Fig. 1) show the collected product samples obtained using FlowSyn fitted with the 'optimise' automation option to produce the temperature dependence studies shown in Graph 2. The samples obtained using acetonitrile are shown on the left, and NMP on the right. The solvent has been removed from the acetonitrile samples and clearly shows how the crystalline starting material is progressively converted to the product – a yellow oil - with increasing temperature (left to right).

Method:

System solvent: Acetonitrile.
Stock solution A: 10 wt% 1 in acetonitrile (10.0g in 100 ml; 0.44M).

- A fixed back-pressure regulator was fitted (750 psi).
- FlowSyn was fitted with a 20ml Stainless Steel coil reactor.
- The output from the coil reactor was passed through the heat exchanger (set to 45°C) on the back of the column module before connecting to the BPR.
- Flow channel B was not used (set Vol B to 0.00ml in Auto Set Up), and was disconnected at the 'T'-mixer and plugged.

1. Scale-up Experiment:



The reagent inlet line 'A' was manually primed up to Selection Valve 'A' with Stock Solution A, and then solvent inlet line 'A' and the flow system was primed with acetonitrile.

The System Configuration Page was programmed as follows:

System Configuration			
Reactor 1		**Reactor 2**	
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:	10 s
Maximum Pressure:	1000 psi	Pressure Units:	psi
Pressure Threshold:	Off		
Wash Flow Rate:	2.0 ml/min	Equil. Flow Rate:	2.0 ml/min

The Experiment Set Up Page was programmed as follows:

Auto Set Up			
Inlet A:	Bottle	Coil Residence Time:	00:10:00
Inlet B:	Bottle	Column Residence Time:	00:00:00
Volume A:	100 mL	Total Flow Rate:	2.00 mL/min
Volume B:	0.00 ml	Pre Collect:	4.0 ml
A:B Ratio:	N/A	Post Collect:	8.0 ml
Coil Temp:	200C	Final Wash:	10.0 ml
Column Temp:	45C	Intermediate Wash:	0.0 ml

Total Reaction Time: 01:09:31

After running the experiment the collected product solution was evaporated *in vacuo* to afford the *S*-thiocarbamate 2 as a pale yellow oil (9.70g; 97%).

LC-MS: Rt = xxmin (Rt(s/m) = yyy);
100% purity (220-300nm(

NMR (CDCl3):

IR (

2. Optimisation Experiment:

- FlowSyn was fitted with a Gilson 203B fraction collector (Automation upgrade required) fitted with an 'Optimisation' sample rack.
- Stock reagent solutions and System Solvent were either NMP or acetonitrile.
- FlowSyn was fitted with a 5.0ml stainless stell coil reactor.

The optimisation/profiling experiments were performed by programming the FlowSyn as follows:

System Configuration			
Reactor 1		**Reactor 2**	
Type:	Coil	Type:	None
Material:	Steel	Material:	
Volume:	5.0 ml	Volume:	
Max Temp:	260°C	Max Temp:	
System Dead Volume:	0.60 ml	Heat Exchanger:	Yes
Minimum Pressure:	0 psi	Pump Start Delay:	10 s
Maximum Pressure:	1000 psi	Pressure Units:	psi
Pressure Threshold:	Off		
Wash Flow Rate:	1.0 ml/min	Equil. Flow Rate:	0.5 ml/min

Auto Set Up			
Inlet A:	Bottle	Coil Residence Time:	00:10:00
Inlet B:	Bottle	Column Residence Time:	00:00:00
Volume A:	5.00 ml	Total Flow Rate:	0.50 ml/min
Volume B:	0.00 ml	Pre Collect:	1.00 ml
A:B Ratio:	N/A	Post Collect:	2.50 ml
Coil Temp:	200C	Final Wash:	2.00 ml
Column Temp:	45C	Intermediate Wash:	0.0 ml
Fraction Rack:	Optimise	Wait Time:	4.0 ml
		Aliquot Size:	0.03 ml

Multiple Experiment Table							
Expt	**Vol A (ml)**	**Vol B (ml)**	**Ratio**	**Coil Temp (°C)**	**Col. Temp (°C)**	**Coil Res Time**	**Flow Rate (ml/min)**
1	2.5	2.5	1:1	140	45	00:10:00	0.50
2	2.5	2.5	1:1	150	45	00:10:00	0.50
3	2.5	2.5	1:1	160	45	00:10:00	0.50
4	2.5	2.5	1:1	170	45	00:10:00	0.50
5	2.5	2.5	1:1	180	45	00:10:00	0.50
6	2.5	2.5	1:1	190	45	00:10:00	0.50
7	2.5	2.5	1:1	200	45	00:10:00	0.50

Further information:

Please visit https://www.asynt.com/product/flowsyn-continuous-flow-reactor/ for further information on the FlowSyn continuous flow reactor used for this paper.

To find out more about our complete range of flow chemistry solutions, please visit: https://www.asynt.com/products/flow-chemistry/