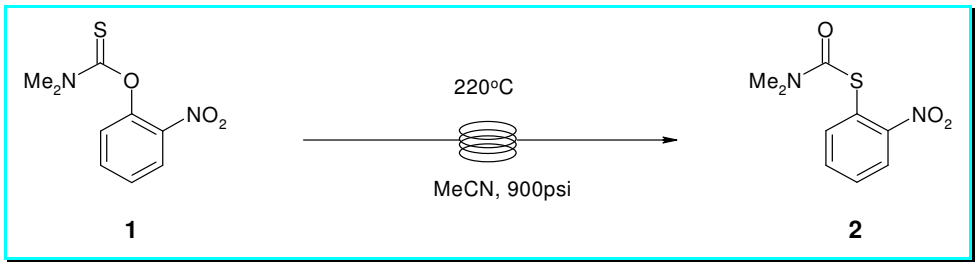
FlowSyn™ Application Note 17: Newman Kwart Rearrangement



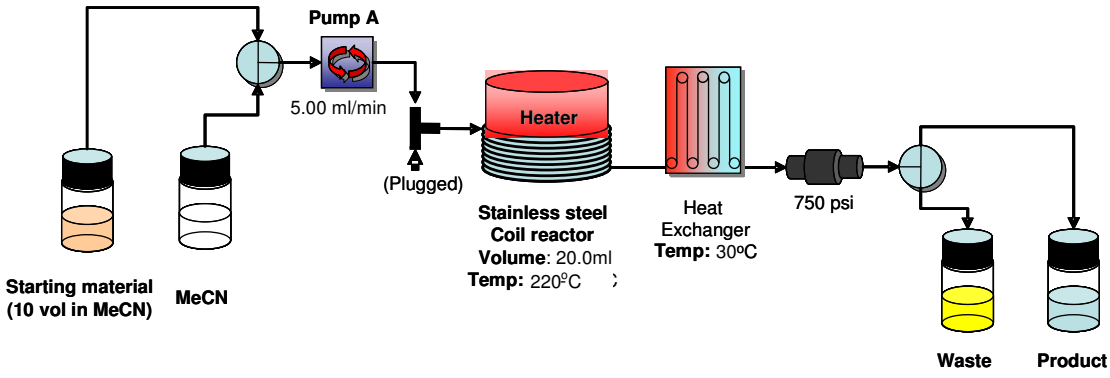
Introduction:

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**.

Method:

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

- A 750psi fixed back-pressure regulator was fitted (tan/blue).
- FlowSyn was fitted with a 20ml Stainless Steel coil reactor.
- The output from the coil reactor was passed through the heat exchanger (set to 30°C) on the back of the column module before connecting to the BPR. A N_2 gas feed was connected.
- 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.



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			
LH Reactor		**RH 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

The **Experiment Set Up Page** was programmed as follows:

Auto Set Up			
Inlet A:	Bottle	Coil Residence Time:	00:04:00
Inlet B:	Bottle	Column Residence Time:	00:00:00
Volume A:	100 mL	Total Flow Rate:	5.00 mL/min
Volume B:	0.00 ml	Pre Collect:	2.5 ml
A:B Ratio:	N/A	Post Collect:	15.0 ml
Coil Temp:	220C	Final Wash:	10.0 ml
Column Temp:	30C	Intermediate Wash:	0.0 ml

Total Reaction Time: 00:28:12

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

LC-MS: R_t = 2.62min (R_t(s/m) = 2.83min); 100% purity (220-300nm).

NMR ($CDCl_3$): δ 7.85 (1H, dd, J = 7.5, 1.2 Hz), 7.65 (1H, d, J = 7.5 Hz), 7.40-7.55 (2H, m), 3.05 (3H, brs), 2.95 (3H, brs)ppm.

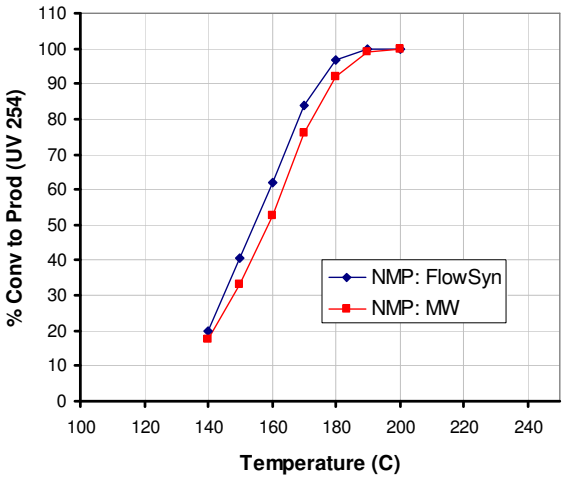
Throughput = 30g/h

Appendix:

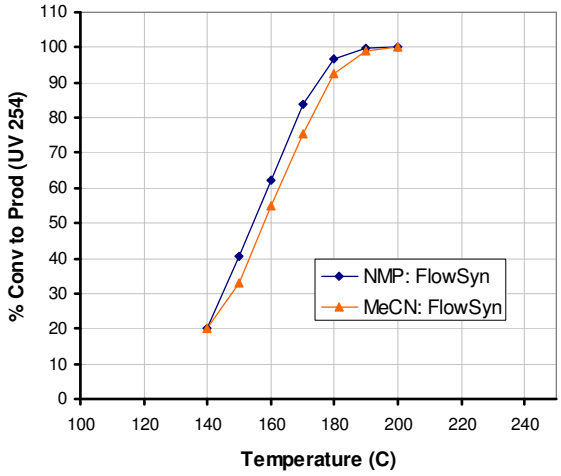
The reaction rate of the NKR is determined by the electronic demand on the aromatic ring such that even for optimally electron deficient examples (eg. the 2-nitro analogue used herein), reaction temperatures in excess of 150°C are required to observe any conversion to rearranged product **2**. This high temperture rearrangement is therefore often performed in the microwave. As such, the reaction can be inconvenient to scale up.

However, as shown above, the reaction works equally well in the FlowSyn continuous flow reactor (Graph 1). Now, the reaction can be readily scaled simply by running 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
- under these conditions, 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

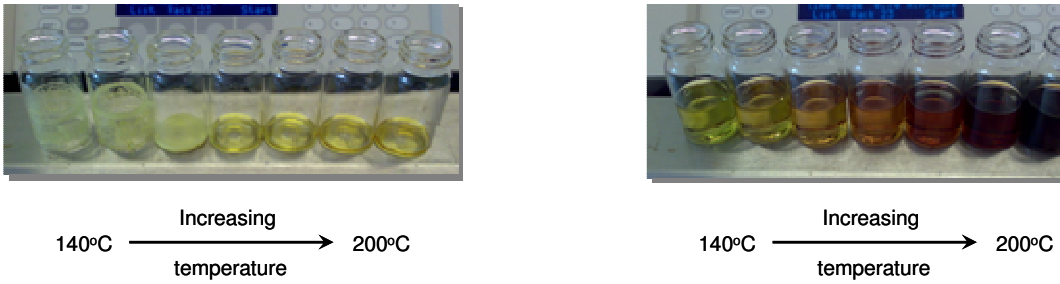


Figure 1: Contrasting NKR performed in MeCN (left) versus NMP (right).

The photographs (Figure 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).

Reaction Optimisation Study:

The temperature dependence study and comparison of the use of MeCN and NMP as solvent were performed using the FlowSyn configured with a Multiple Experiment Package as follows:

- 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 steel coil reactor.

The optimisation/profiling experiments were performed by programming the FlowSyn as follows. The samples obtained were analysed by HPLC and AUCs adjusted using the RRF (relative response factor) for the *S*- vs *O*-analogues to give quantitative integrals @ 254nm.[1]

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:	2.0 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:	2.50 ml
Column Temp:	30C	Intermediate Wash:	0.0 ml

Fraction Collector Set Up			
Fraction Rack:	Optimise	Wait Time:	4.0 ml
		Aliquot Size:	0.03 ml

Temperature Dependence of Conversion for 10min Residence Time:

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	5.0	0.0	Inf:1	140	30	00:10:00	0.50
2	5.0	0.0	Inf:1	150	30	00:10:00	0.50
3	5.0	0.0	Inf:1	160	30	00:10:00	0.50
4	5.0	0.0	Inf:1	170	30	00:10:00	0.50
5	5.0	0.0	Inf:1	180	30	00:10:00	0.50
6	5.0	0.0	Inf:1	190	30	00:10:00	0.50
7	5.0	0.0	Inf:1	200	30	00:10:00	0.50

The above experiments were performed in both MeCN and NMP and the results are shown in Graphs 1-2. The microwave data was obtained using 1ml aliquots of the stock solution in 10ml tubes containing stirbars in a CEM Discover, and the residence times quoted do not take into account ramping and cooling times. *Note:* it was not possible to heat MeCN solutions above 150°C in the MW, even after an extended 10min ramping period. Clearly, this was not a limitation in the FlowSyn.

Additionally, in order to improve throughput on scale-up, we elected to determine optimal conditions that gave complete conversion to the desired product **2** in a residence time of 4min.

Determination of Temperature affording Rt=4min in MeCN

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	5.0	0.0	Inf:1	200	30	00:04:00	1.25
2	5.0	0.0	Inf:1	220	30	00:04:00	1.25
5	5.0	0.0	Inf:1	240	30	00:04:00	1.25

Suitable conditions for scale up were thus determined to be 220°C and Rt=4min.

At higher temperatures, although more rapid reaction rates were obtained, a darker product resulted.

Refences:

1. J. D. Moseley, R. F. Sankey, O. N. Tang, J. P. Gilday; *Tetrahedron*, **2006**, 62, 4685–4689.
2. Drs Jonathon Moseley and Matt Welham (AstraZeneca, Avalon, UK) are gratefully acknowledged for their assistance with this study.