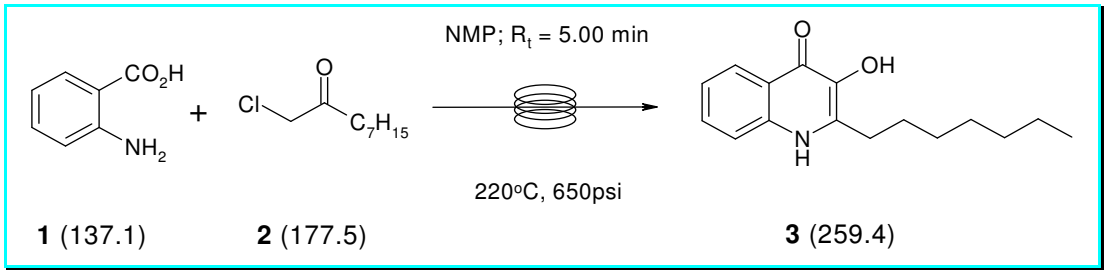
FlowSyn™ Application Note 24:
Heterocyclic Synthesis: 3-Hydroxy-4-quinolones



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.

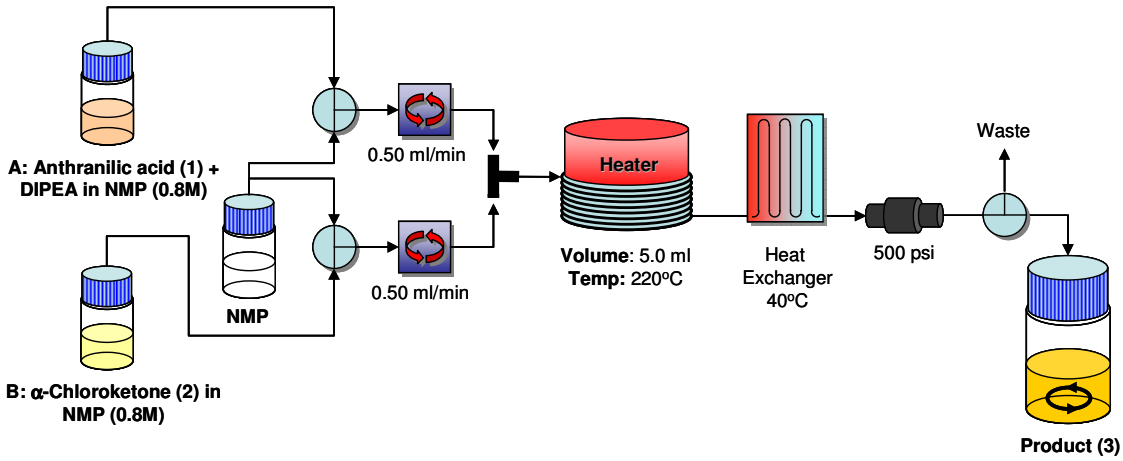
Heterocyclic synthesis is a case in point, and in this Application Note we describe the continuous flow synthesis of the 3-hydroxy-4-quinolone PQS (*Pseudomonas* quinolone signal). This molecule is used by *Pseudomonas* in quorum sensing and is a useful 'tool' compound in this area of research. The synthesis of PQS can be readily achieved in multi-gram quantities at 220 °C under continuous flow-through conditions in the FlowSyn.

Method:

System solvent: *N*-Methyl-2-pyrolidone (NMP).
Stock solution A: Anthranilic acid **1** (4.10 g, 30.0 mmol) and *N*,*N*-diisopropylethylamine (6.00 mL, 36.0 mmol) made up to 37.5 mL in NMP (0.80M).
Stock solution B: 1-Chloro-2-nonanone **2** (80 %, 4.45 g, 20.0 mmol) made up to 25 mL in NMP (0.80M)

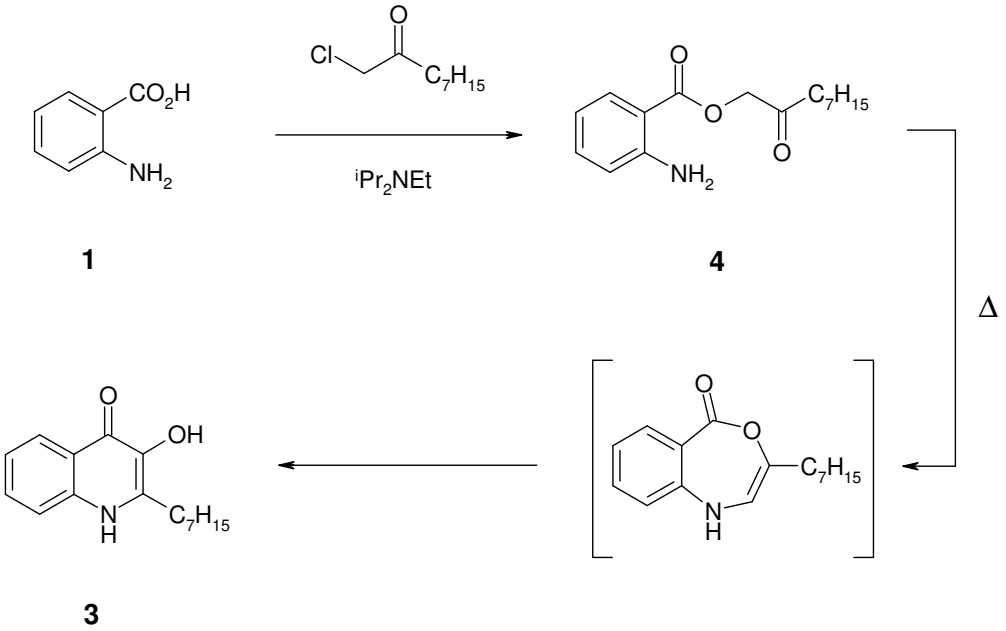
- The 1-chloro-2-nonanone was prepared by a Grignard reaction on the corresponding Weinreb amide and used without further purification (> 80 % purity).
- The FlowSyn was fitted with a 5ml stainless steel coil reactor and the system pressure was controlled using a 500 psi fixed back pressure regulator.
- The heat exchanger was cooled by connection to a low pressure laboratry nitrogen line (< 1 bar).
- The product was collected by directing the flow reactor outflow into a bottled containing stirring ice-water (300 mL).

Schematic:



Reaction Optimisation:

This synthesis was originally performed in a mono-modal microwave batch reactor and an initial reaction profiling study was therefore performed in the microwave prior to transferring this protocol to the FlowSyn continuous flow reactor for scale-up.
Homogeneous batch microwave chemistry typically translates directly into flow and therefore this use of both batch microwave and conventionally heated flow-through equipment presents a good paradigm for reaction optimisation and scale-up.

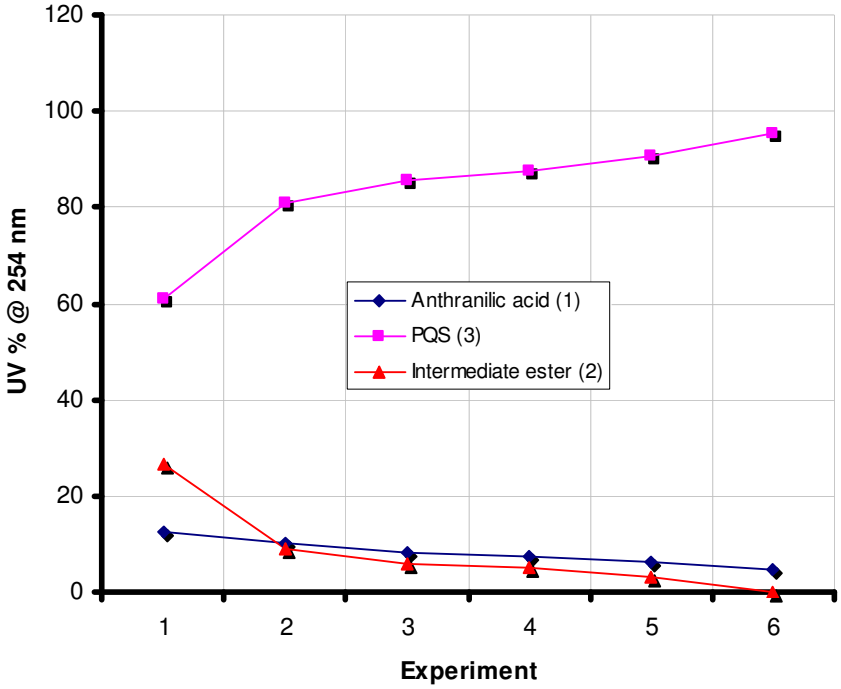


The reaction occurs through the formation of an intermediate ester **4** which rearranges at higher temperatures into the desired hydroxyquinolone **3**. The intermediate can be isolated and processed separately if desired.

Reaction profiling in the MW suggested optimal conditions to be 5 min @ 220 °C in the presence of a 10% excess of the chloroketone. Under these conditions only a small amount of residual anthranilic acid was evident in the UV-HPLC analysis and all the intermediate ester **4** was converted to product **3**.

	Ratio A:B	Temperature	R_t (min)	% S/m 1	% Product 2	% Intermediate 3
1	[1:1]	140 °C	5 min	12.5	60.8	26.7
2	[1:1]	160 °C	5 min	10.2	80.8	9.0
3	[1:1]	180 °C	5 min	8.3	85.7	6.0
4	[1:1]	200 °C	5 min	7.4	87.6	4.9
5	[1:1.1]	220 °C	5 min	6.3	90.7	3.0
6	[1:1.1]	220 °C	5 min	4.7	95.3	0.0

Table 1: Batch microwave reaction profiling data.



Graph 1: Batch microwave reaction profiling data.

FlowSyn Set Up:

System Configuration			
RH reactor:		**LH reactor:**	
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:	15 psi	Pump Start Delay:	5 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			
Inlet A:	Bottle	Coil Residence Time:	00:05:00
Inlet B:	Bottle	Column Residence Time:	00:00:00
Volume A:	19 ml	Total Flow Rate:	1.00 ml/min
Volume B:	21 ml	Pre Collect:	0.00 ml
A:B Ratio:	1:1.1	Post Collect:	2.00 ml
Coil Temp:	220C	Final Wash:	5.00 ml
Column Temp:	40C	Intermediate Wash:	0.00 ml

Throughput = 5.8 g/h (25 mmol/h)

The product was collected by filtration of the aqueous suspension that formed in the Collection bottle and washed on the filter with water (3 x 30 mL) and hexanes (1 x 30 mL). The filter cake was air-dried to afford the hydroxyquinolone **3** as a brown free-flowing powder (3.48 g, 82 %).

HPLC: R_t = 3.23 min (R_t(s/m) = 1.89 min): 96% purity @ 254 nm.

IR (ATR; υ_{max}): 3249, 2949, 2924, 2849, 1639 cm^{-1}.

^{1}H-NMR (d^6-DMSO; 400Hz): 11.42 (br s, 1H), 8.10 (d, J = 8 Hz, 1H), 8.00 (br s, 1H), 7.55 – 7.52 (m, 2H), 7.24 – 7.19 (m, 1H), 2.74 (t, J = 7.5 Hz, 2H), 1.68 (q, J = 7.5 Hz, 2H), 1.40 – 1.20 (m, 8H), 0.86 (t, J = 7.0 Hz, 3H).

The product could be recrystallised from ethyl acetate to give PQS **3** as white crystals.