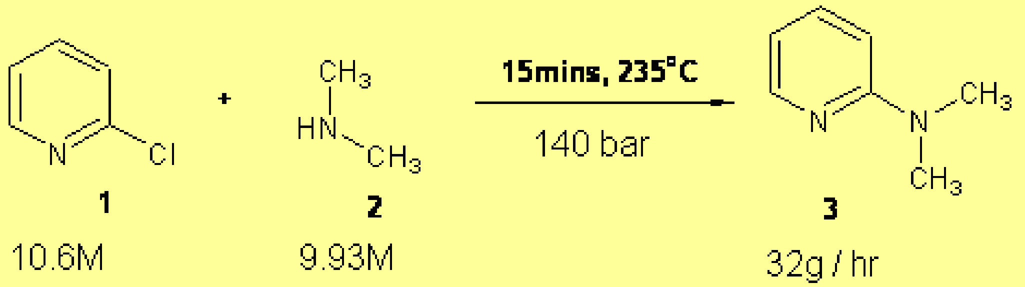
Application Note 32: High Pressure and Temperature Process Scale S_NAr Reaction under Solvent Free Conditions using Liquefied Dimethylamine.

This application note illustrates the use of the Vapourtec R-Series system to run reactions under solvent free (neat) conditions and it's ability to pump liquefied gases at high temperatures and pressures. This expands on work carried out in Application note 29 (where a game changing throughput of material from a bench top system was demonstrated).

By harnessing the higher temperatures and pressures available and again running the reaction solvent free it is possible to carry out uncatalysed amination of 2-chloropyridine in throughput previously unavailable.

Using the Vapourtec High Pressure Pump Module when carrying out reactions of this nature removes limitations associated with batch pressure reactors (e.g. Parr 'bombs').



Scheme 1

Background

The ability of continuous flow chemistry to offer scalable reactions is well documented. The Vapourtec R-Series system is proven to be able to scale optimized reactions from one reactor to multiple reactors in series allowing chemists to increase the throughput on the system and generate larger volumes of material. This increased mass transfer can also be achieved by increasing the concentration of the reactant/reagent solutions. However there is often a critical concentration where the reagent or product becomes insoluble. This is a major limitation in being able to carry out reactions in a continuous flow manner. If reactants could be pumped neat and products kept flowing throughout the system , amount of material that could be generated would massively increase.

Application note 23 showed the advantage of being able to process dissolved dimethylamine (2.0M in MeOH) at higher temperatures and pressure removing the chemist from the limitations of the fixed volume pressure vessel. If gases of this type could be pumped in their liquid form, the concentration of the reactions could again be increased and therefore throughput could be increased while maintaining precise control of reaction stochiometry.

Dimethylamine is a highly flammable liquefied gas with a low boiling point of 7°C and is generally encountered as a solution in water or an organic solvent at concentrations up to around 40%. Dimethylamine is used in the production of several industrially significant compounds and the synthesis of many agrichemical and pharmaceutical products. Aminopyridines are also found in a number of chemical applications ranging from pharmaceuticals and agricultural products to florescent dyes and as transition metal complex ligands.

The amination of electron deficient 2-halopyridines under nucleophillic aromatic substitution (S_NAr) conditions is well precedented. Buchwald-Hartwig couplings and nickel catalyzed reactions are very efficient but generate undesirable waste from a green perspective. Uncatalysed reactions of this type generally require harsh conditions and are carried out in pressurized vessels or under microwave conditions over periods of days. We demonstrate in this application the ability to perform this chemistry solvent free, uncatalysed over a short residence (reaction) time, pumping neat dimethylamine and controlling the salt formation with no detrimental effect.

2-Chloropyridine (density 1.205 g/cm^3) is liquid at room temperature and is easily pumped with the Vapourtec R2 system. The desired product from the S_NAr reaction, *N*,*N*-dimethylpyridin-2-amine has a boiling point of 191°C and is also a liquid at room temperature.

Dimethylamine is supplied in its neat gaseous form in canister's at low pressures, ~3bar. By inverting the canister and maintaining the temperature of the gas canister 10°C above the pump head enables us to easily introduce dimethylamine in its liquid state into the Vapourtec R2 pump system.

The obvious problem here is the salt formation as it will quickly form a solid in our system. This was overcome by the addition water to the reaction mixture via a third pump directly after the mixing of the reagents. Dimethylamine hydrochloride is highly miscible with water. In this example the calculated minimum amount of water needed from application note 31.was used.

By calculating the minimum amount of water needed to dissolve 1mol of dimethylamine hydrochloride relative to the starting material 2-chloropyridine we limit the amount required and limit any possible hydrolysis side reactions. It should be noted none of the pyridin-2-ol was observed as a result of hydrolysis.

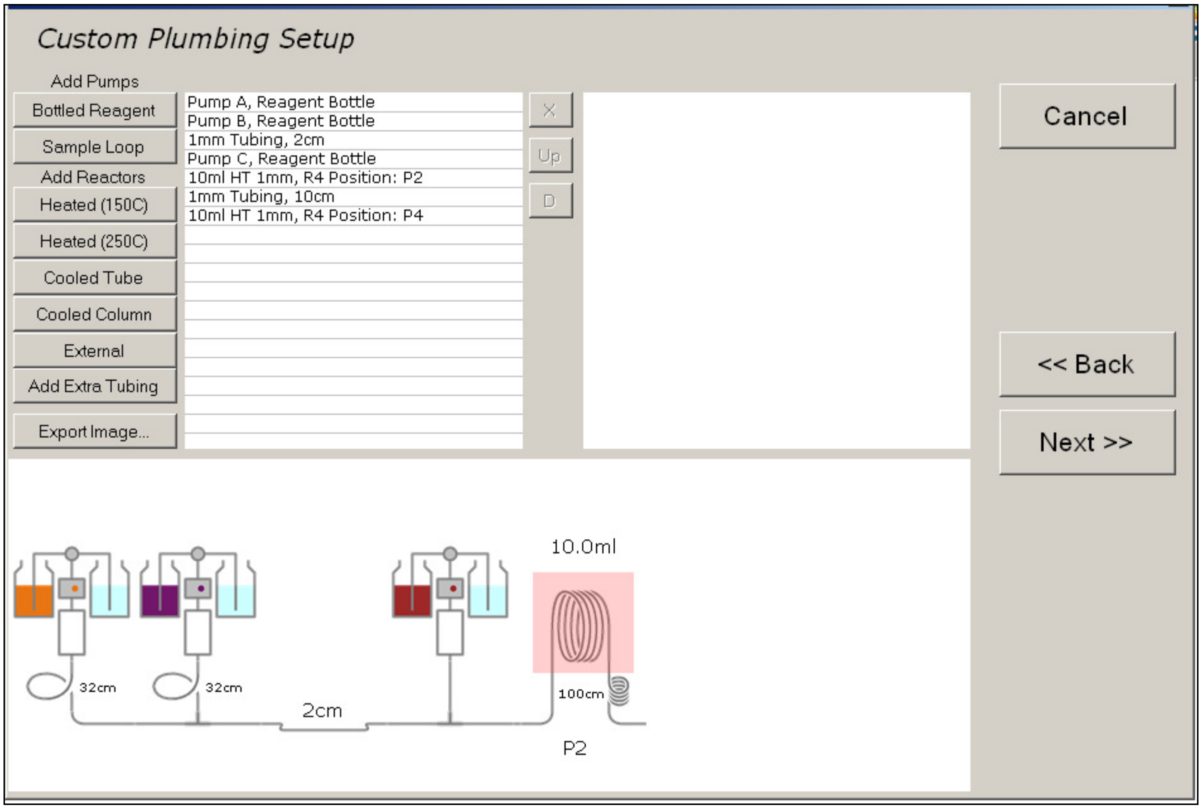
Method (Optimisation).

As stated above, the aim was to demonstrate the continuous pumping with no detrimental solid formation of a neat, solvent free reaction and to demonstrate the safe pumping of dimethylamine in its liquid state.

Setup

The flow reactor was configured using a combination of the **R2 High Pressure** pump module and **R4** reactor module as shown in Figs 1. It should be noted the third pump is connected in-line with the reactants almost directly after mixing.

A 10 mL SS reactor was installed with a connecting tube in series with 2 x 1000 psi BPR. The elution outflow was collected directly from the last BPR via a short length of tubing.



Custom Plumbing Setup

Pump A, Reagent Bottle
Pump B, Reagent Bottle
1mm Tubing, 2cm
Pump C, Reagent Bottle
10ml HT 1mm, R4 Position: P2
1mm Tubing, 10cm
10ml HT 1mm, R4 Position: P4

Fig 1 - FlowCommander™ setup of reactors

NB. The temperature of the dimethylamine canister was maintained ~10°C above the pump head by means of a tape heater. The canister was inverted and clamped securely and connected directly to the inlet tubing of pump B bypassing the solvent/reagent valve.

See schematic overleaf.

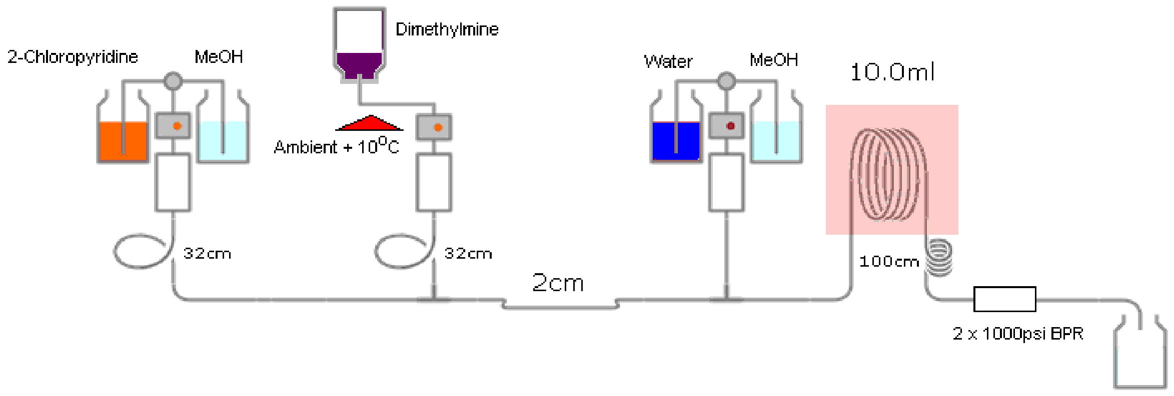


Fig 2. Schematic showing complete equipment layout

All reagents were used neat as supplied from Aldrich;

Reagent A
2-Chloropyridine (Aldrich C69802, CAS 109-09-1)

Reagent B
Dimethylamine (Aldrich 295280, CAS 124-40-3)

Reagent C
Water (Aldrich 34877, CAS7732-18-5)

System Parameters

System solvent:	Methanol
Reagent A:	neat 2-Chloropyridine (10.6M)
Reagent B:	neat Dimethylamine (14.9M) NB. After mixing with water (reagent C) the effective concentration is 9.93M
Reagent C:	Water
Flow rate A:	variable (199 – 298 µL/min)
Flow rate B:	variable (312 – 468 µL/min
Flow rate C:	variable (156 – 234 µL/min
Stiochiometry A:B	1:2.2
Reactor volume:	10 mL SS reactor.
Reactor temperature:	*variable* 200 - 250 ℃
Back pressure regulator:	2 x 1000 psi (total 140 bar) Upchurch bpr

Then the optimization reactions followed the sequence of event listed below;

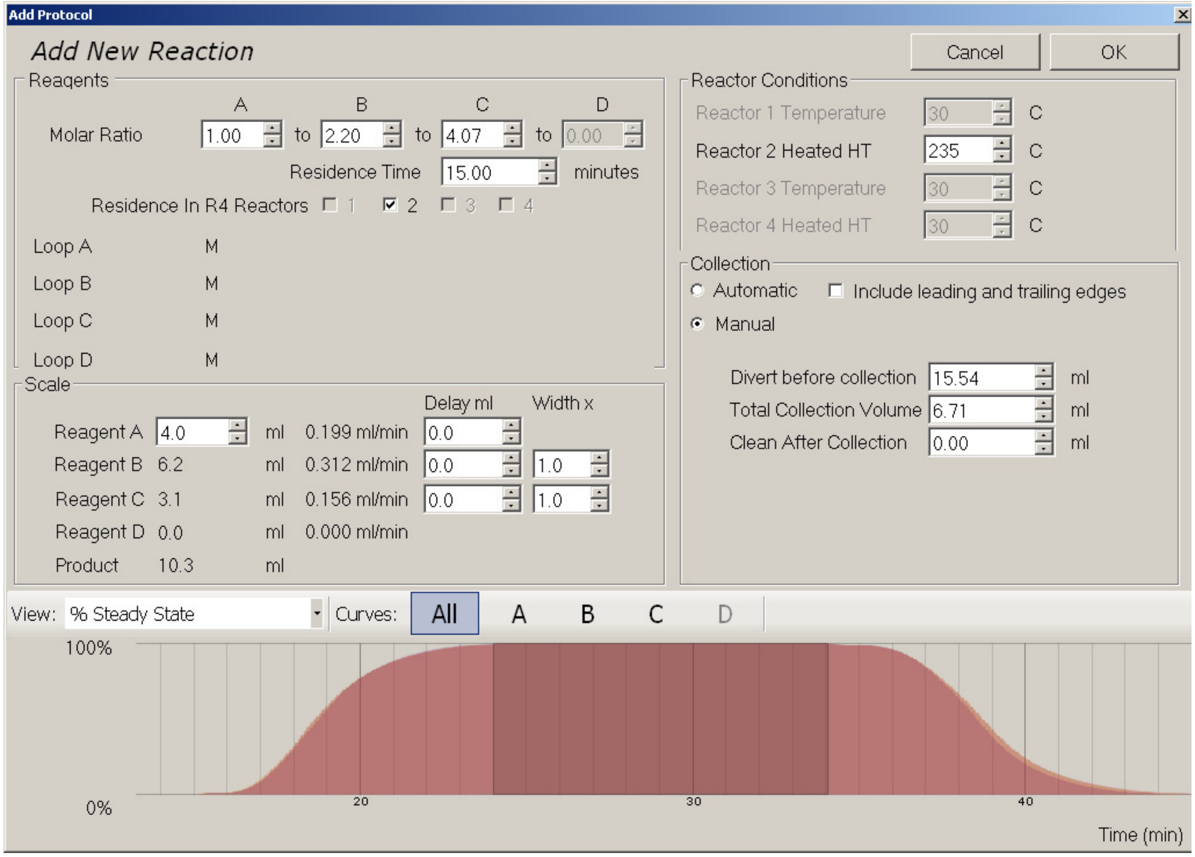
1) *Priming the pumps with Methanol (MeOH):* Selection valves 1,3 were set to 'Solvent' and the pumps were primed with MeOH at 1.0 mL/min per pump.
2) *Priming the pumps with reagents:* The selection valve for line 1 was set to 'Reagent', the pumps set to 1 mL/min and the line from stock bottle 1 to the selection valve was filled with **Reagent A.** The selection valve was set back to 'Solvent' and MeOH pumped through the lines for 2 minutes.
3) **Reagent B was primed with care.** The canister was fitted with a needle valve and connected directly to the inlet tubing of pump B. The prime valve was fitted a PFA tube fed directly into a flask containing methanol. The needle valve was opened to show liquid dimethylamine in the tubing. Opening the prime valve and pumping at a low flow rate (100ul/min) allows the pump to be primed and excess dimethylamine to be captured in the methanol solution safely. After priming was complete the prime valve was tightly closed.
4) Pump 3 was primed via the prime valve and allowed to pump at 1.0ml/min for 5mins.
5) *Reaction optimisation:* A selective range of conditions were run using FlowCommander™. Residence times of 10 and 15 minutes were run at with a fixed stoichiometry (2.2eq Dimethylamine) in a 10ml reactor at 200, 235 and 250°C. A 4ml aliquot of reagent A (42.45mM substrate 1) was reacted in each experiment.
6) *Work-Up and Analysis:* The collection stream was directed into a flask containing water. The resulting partition was extracted with diethyl ether x 3, the combined organic extracts washed with brine, dried (Magnesium sulfate) and the filtrate concentrated in-vacuo.

The water content was assumed to be similar to that calculated in previous application note 31. This was measured by dissolving 1g amine hydrochloride in the minimum amount of water. For every 1mol of 2-chloropyridine reacted 1mol amine hydrochloride is produced. Assuming 100% completion of our reaction we calculate the amount of water required to dissolve the salt. In this example this gave rise to a 2:1 ratio of amine to water (9.93M).

Initial reaction conditions of 200°C, 10minute residence time and 2.2eq of dimethylamine showed (after extraction of the eluent with diethyl ether) an incomplete reaction with substrate 1 still present. Increasing the system temperature to 250°C under the same conditions showed all of substrate 1 consumed but the formation of a number less polar by-products (unclassified).

At 10mins ~5% of the starting material 1 was observed at 235°C, increasing the residence time to 15mins show a near quantitative conversion. It should be noted that no significant exotherm was observed through FlowCommander™ running these reactions solvent free.

Fig 3 shows the FlowCommander™ reaction setup for this reaction.



Add Protocol

Add New Reaction

Reagents

	A		B		C		D
Molar Ratio	1.00	to	2.20	to	4.07	to	0.00

Residence Time 15.00 minutes

Residence In R4 Reactors ☐ 1 ☑ 2 ☐ 3 ☐ 4

Loop A M

Loop B M

Loop C M

Loop D M

Scale

				Delay ml	Width x
Reagent A	4.0	ml	0.199 ml/min	0.0	
Reagent B	6.2	ml	0.312 ml/min	0.0	1.0
Reagent C	3.1	ml	0.156 ml/min	0.0	1.0
Reagent D	0.0	ml	0.000 ml/min		
Product	10.3	ml			

Reactor Conditions

Reactor 1 Temperature	30	C
Reactor 2 Heated HT	235	C
Reactor 3 Temperature	30	C
Reactor 4 Heated HT	30	C

Collection

○ Automatic ☐ Include leading and trailing edges

● Manual

Divert before collection	15.54	ml
Total Collection Volume	6.71	ml
Clean After Collection	0.00	ml

View: % Steady State

Fig 3 . Reaction setup showing

- **reaction conditions**
- **predicted dispersion profile at the collection point**

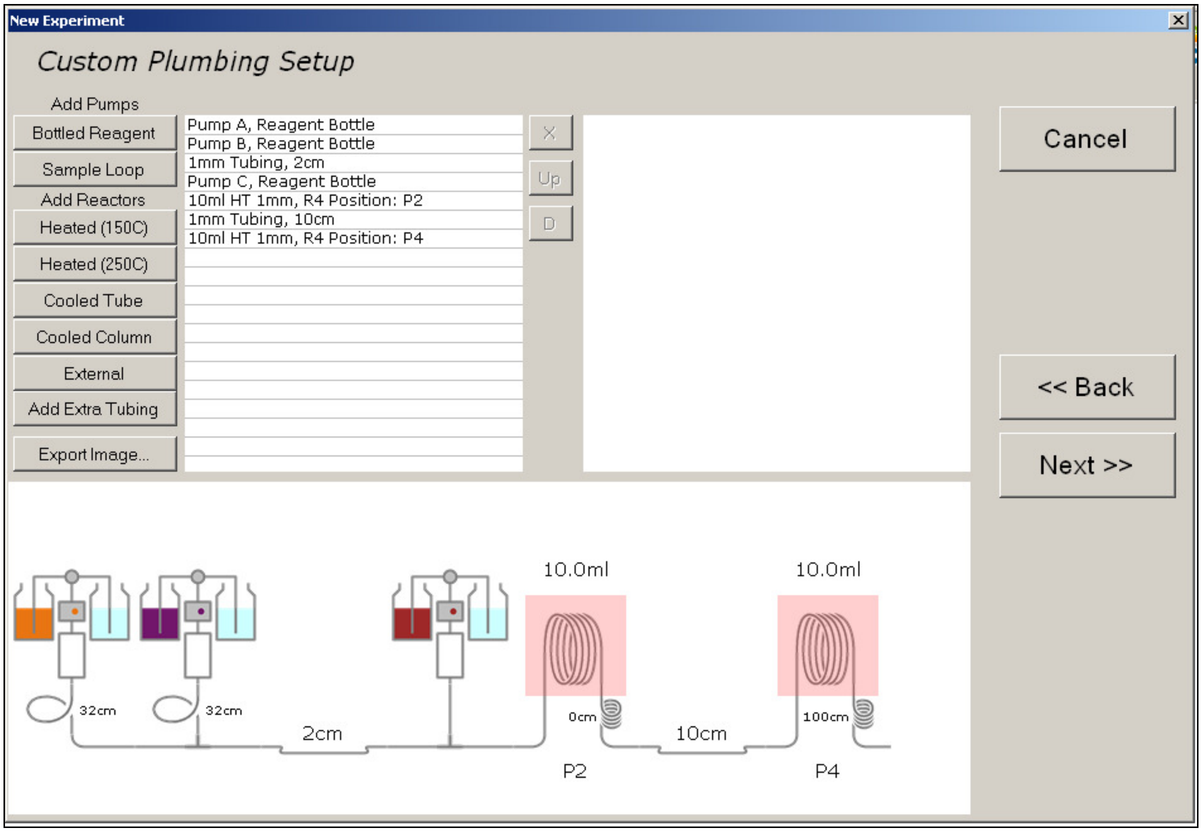
Method (Scale Up Conditions)

As described the optimum reaction conditions for reacting a small 4ml aliquot were 235°C, 15mins residence time with 2.2eq dimethylamine.

With the success of running the reaction neat through the system and observing quantitative conversion at steady state conditions it was decided to scale the conditions to further increase the mass transfer of the reaction. As described previously the Vapourtec R-Series has the capability to run multiple reactors in series. By placing a second high temperature SS reactor in series it was that a two fold increase in the flow rate could be achieved under the same conditions. Experimenting with this proved the same quantitative conversion could be achieved with a combined residence time of 15minutes. The first HT reactor was used without its usual post cooling coil and the two reactors were linked with an insulated stainless steel tube.

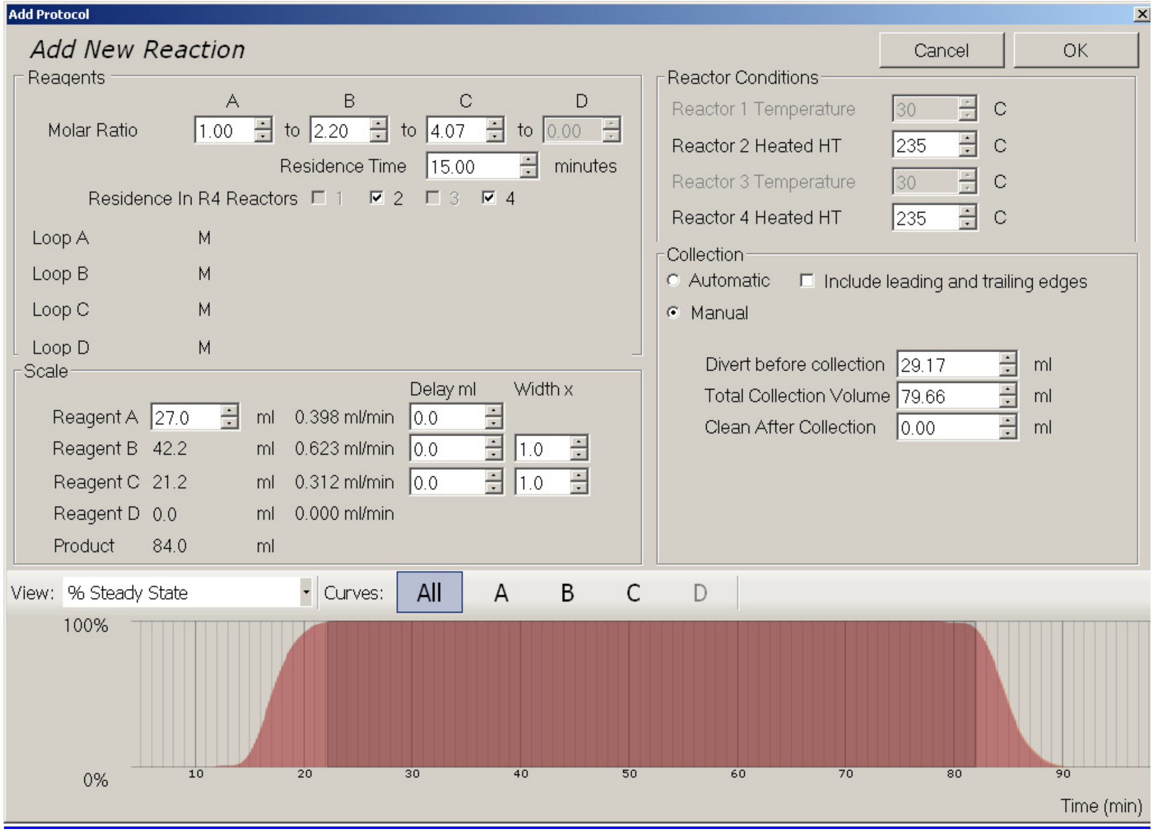
Applying the optimum reaction conditions (235°C, 15mins residence time with 2.2eq piperidine) a 21ml aliquot was reacted over 60minutes.

Setup



Pump A, Reagent Bottle
Pump B, Reagent Bottle
1mm Tubing, 2cm
Pump C, Reagent Bottle
10ml HT 1mm, R4 Position: P2
1mm Tubing, 10cm
10ml HT 1mm, R4 Position: P4

Fig 4 – Flow Commander Setup for scale-up experiment



Add New Reaction

Reagents

	A		B		C		D
Molar Ratio	1.00	to	2.20	to	4.07	to	0.00

Residence Time 15.00 minutes

Residence In R4 Reactors ☐ 1 ☑ 2 ☐ 3 ☑ 4

Loop A M

Loop B M

Loop C M

Loop D M

Scale

				Delay ml	Width x
Reagent A	27.0	ml	0.398 ml/min	0.0	
Reagent B	42.2	ml	0.623 ml/min	0.0	1.0
Reagent C	21.2	ml	0.312 ml/min	0.0	1.0
Reagent D	0.0	ml	0.000 ml/min		
Product	84.0	ml			

Reactor Conditions

Reactor 1 Temperature	30	C
Reactor 2 Heated HT	235	C
Reactor 3 Temperature	30	C
Reactor 4 Heated HT	235	C

Collection

○ Automatic ☐ Include leading and trailing edges

● Manual

Divert before collection	29.17	ml
Total Collection Volume	79.66	ml
Clean After Collection	0.00	ml

View: % Steady State

Fig 5 – FlowCommander reaction set-up for scale up experiment

All reagents were used neat as supplied from Aldrich;

Solution A
2-Chloropyridine (Aldrich C69802, CAS 109-09-1)

Solution B
Dimethylamine (Aldrich 295280, CAS 124-40-3)

Solution
Water (Aldrich 34877, CAS7732-18-5)

System Parameters

System solvent:	Methanol
Reagent A:	neat 2-Chloropyridine (10.6M)
Reagent B:	neat Dimethylamine (14.9M) NB. After mixing with water the effective concentration is 9.93M
Reagent C:	Water
Flow rate A:	398 µL/min
Flow rate B:	623 µL/min
Flow rate C:	312 µL/min
Stiochiometry A:B	1:2.2
Reactor volume:	2 x 10 mL SS reactor.

Reactor temperature: 235 ℃

Back pressure regulator: 2 x 1000 psi (total 140 bar) Upchurch BPR

Then the optimization reactions followed the sequence of event listed below;

1) *Priming the pumps with Methanol (MeOH):* Selection valves 1,3 were set to 'Solvent' and the pumps were primed with MeOH at 1.0 mL/min per pump.
2) *Priming the pumps with reagents:* The selection valve for line 1 was set to 'Reagent', the pumps set to 1 mL/min and the line from stock bottle 1 to the selection valve was filled with **Reagent A.** The selection valve was set back to 'Solvent' and MeOH pumped through the lines for 2 minutes.
3) **Reagent B was primed with care.** The canister was fitted with a needle valve and connected directly to the inlet tubing of pump B. The prime valve was fitted a PFA tube fed directly into a flask containing methanol. The needle valve was opened to show liquid dimethylamine in the tubing. Opening the prime valve and pumping at a low flow rate (100ul/min) allows the pump to be primed and excess dimethylamine to be captured in the methanol solution safely. After priming was complete the prime valve was tightly closed.
4) Pump 3 was primed via the prime valve and allowed to pump at 1.0ml/min for 5mins.
5) *Work-Up and Analysis:* The collection stream was directed into a flask containing water. The resulting partition was extracted with diethyl ether x 3, the combined organic extracts washed with brine, dried (Magnesium sulfate) and the filtrate concentrated in-vacuo.

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Results - Scale Up Experiment.

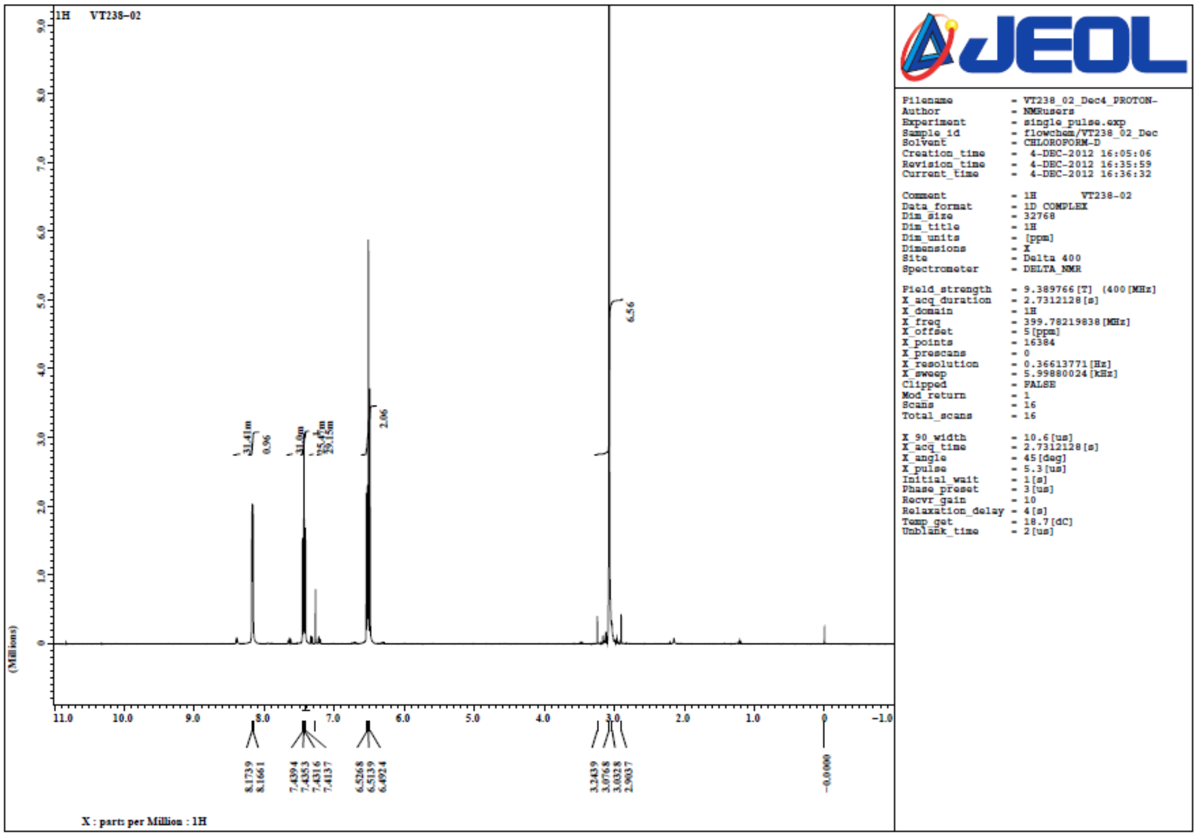
27 ml (32.54g) of **Reagent A** (2-Chloropyridine; 0.287mol) was processed and collected over ~60 mins as shown above. After work-up of the concentrated crude material, a pale yellow oil was isolated which corresponded to the desired product. Yield = 32.04g, 91% (isolated yield)

Extrapolating this experiment we can predict a yield of 770g/ 24hrs under continuous reaction conditions.

See overleaf for NMR analysis.

NMR Analysis

VT238-02 Scale-Up Experiment
^{1}H NMR



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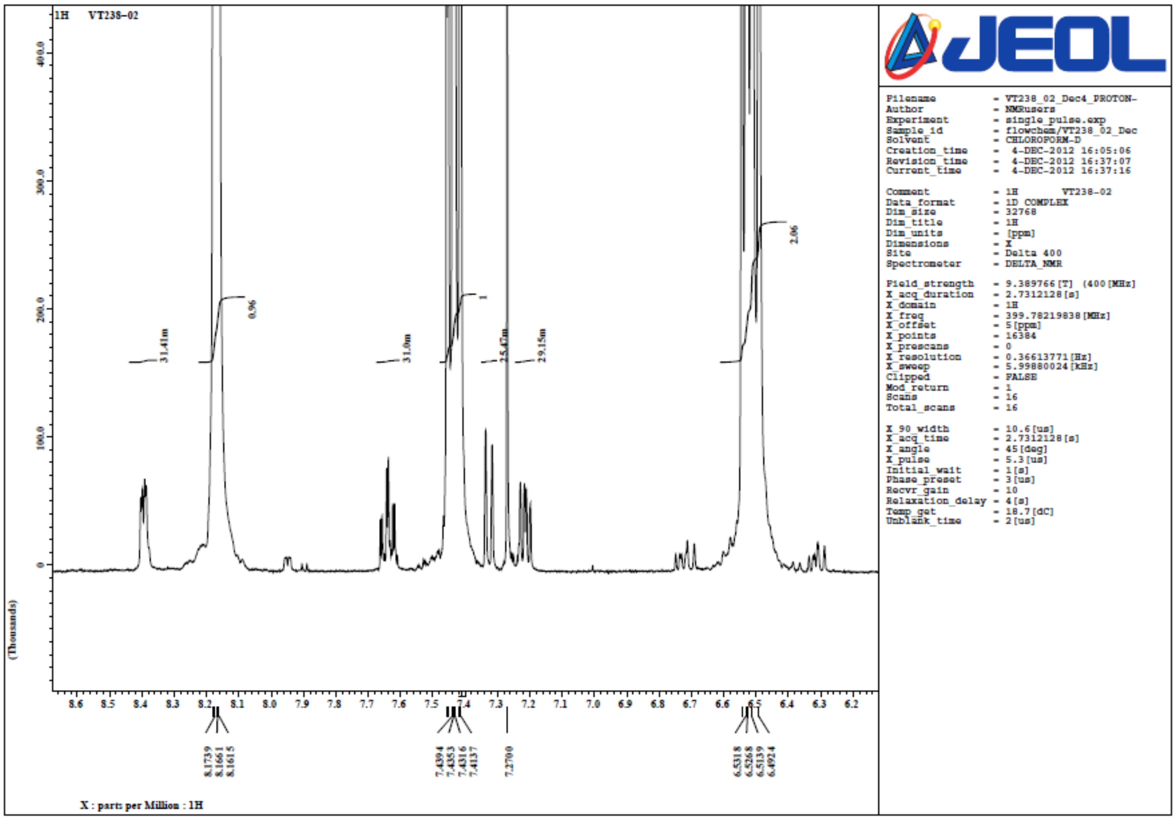

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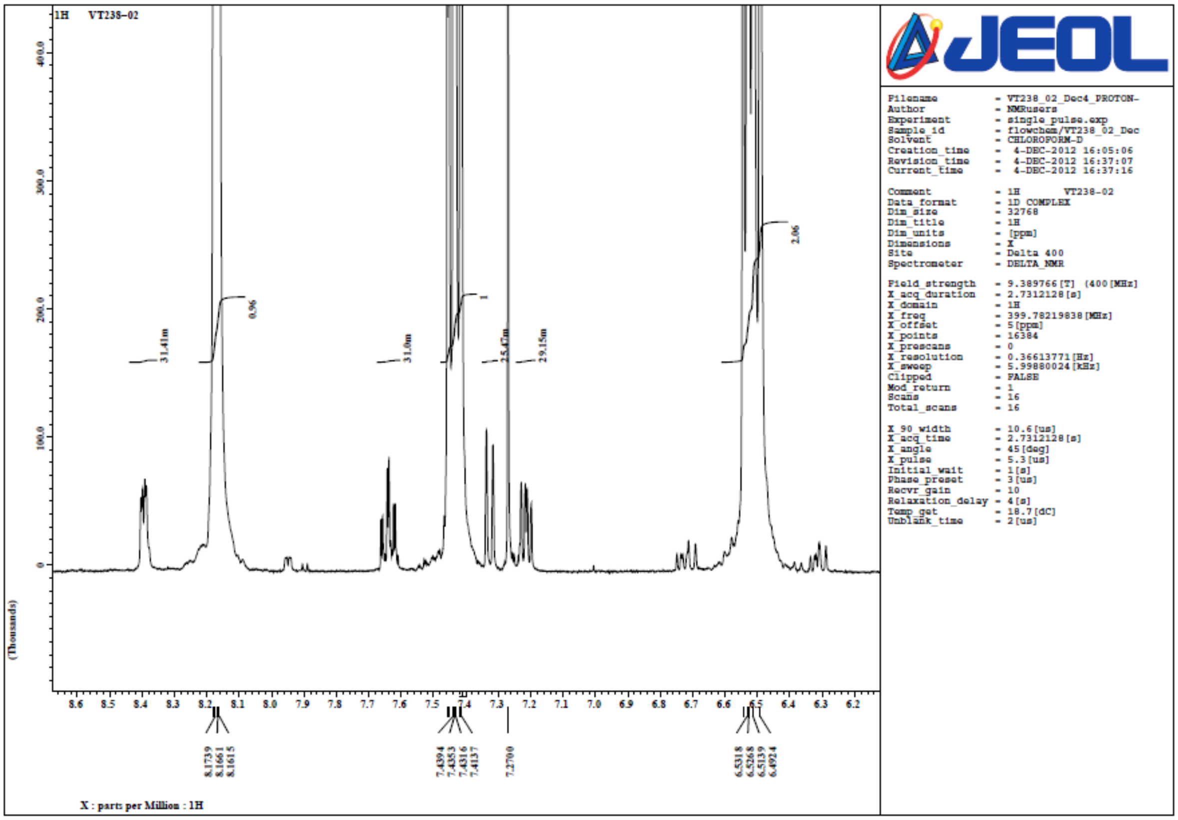

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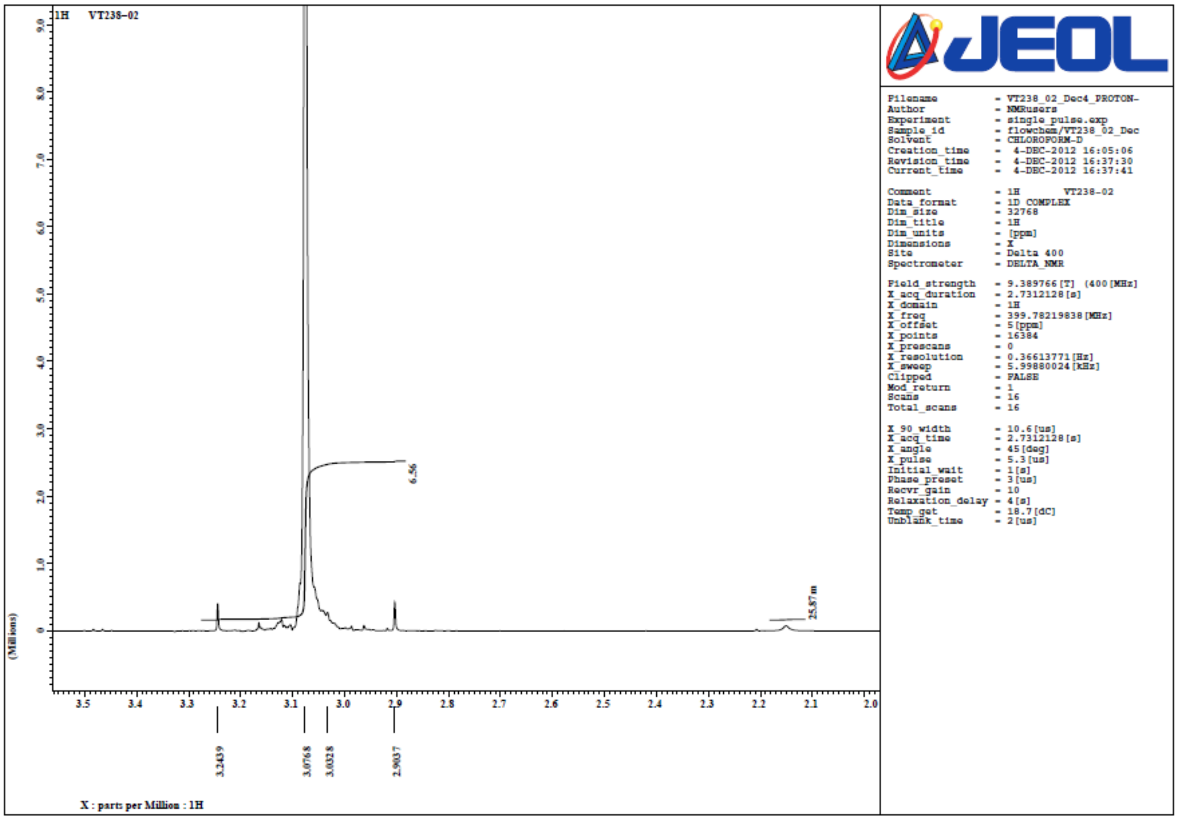

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Conclusion

The work detailed in this report demonstrates the ability of the Vapourtec R-Series to carry out solvent free reactions in a safe and stable manner. The control of the salt formation throughout the system was controlled by addition of the minimum amount of water. This removes the main issue previously found with solid matter blocking the reactor and lends itself to a wider range of applications.

By minimizing the amount of solvent used to the small amount of system solvent needed to prime the reactor loop, this method has been demonstrated to be greener than alternative approaches. In addition, carrying out these reactions without catalyst removes metal residue and ligand waste from the process and reduces cost. The most significant aspect of this application is the proven ability to pump liquefied gases safely and efficiently through the Vapourtec R2 High Pressure system. Being able to handle gases in their liquid state under pressure expands the scope of chemistry available to chemists. At the high pressures used it was possible to switch system solvents from the NMP previously used to MeOH, which adds to green credentials of the reaction.

With yields and scalability potentially greater than conventional methods this moves the Vapourtec R-Series out of the laboratory and into the hands of process chemists.

Acknowledgements

Vapourtec would like to thank Andrew Mansfield of Flow Chemistry Solutions Ltd
for his assistance with this application note

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www.flowchemistrysolutions.co.uk