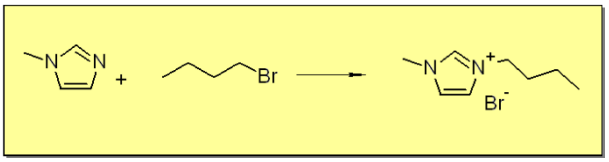
Application Note 24:

Solvent Free Synthesis of an Imidazolium based Ionic Liquid Under Continuous Flow Conditions

Produced by Vapourtec

Abstract

This example illustrates the use of the Vapourtec R-Series to safely control the highly exothermic synthesis of the first generation ionic liquid [bmim]Br as well as handling the highly viscous product.



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Background

In the past decade the use of ionic liquids (IL) as a replacement for conventional molecular solvents has tremendously increased.

Features that make IL's attractive for use in organic synthesis in general and catalytic processes in particular are

- their insignificant vapor pressure (even at high temperatures),
- non-flammability,
- high thermal, chemical and electrochemical stability,
- high solvating properties
- ease of recycling.

Another important feature is the possibility of tuning their physical and chemical properties by varying the nature of the anion and side chain.

The production of ionic liquids in high purity, which is essential for their application, is a challenge as the exothermic nature of the alkylation step can lead to low purities. Insufficient mixing in conventional batch synthesis is also a major problem for large scale synthesis. These hot spots manifest as colorization of the product. In order to maximize yield and minimize by-product formation, therefore, good mixing is required,

along with efficient heat exchange to control the reaction temperature. Here the development of a simple clean, high yielding but versatile approach to the synthesis of an ionic liquid is described.

Reaction Optimization

To minimize the need for purification and work up, the ionic liquid solvent was to be synthesised solvent free. All reagents were therefore used neat as supplied from Aldrich. Both the 1-methyl-1H-imidazole and the n-bromobutane were pumped easily using the Vapourtec R-2 pumps.

Setup (Optimization)

The flow system setup combined the R2 pump module and R4 reactor module with the reactor configured as shown in Fig 1.

A 10 mL stainless steel tubing reactor was installed along with a variable back pressure regulator (BPR) fitted in-line between the reactor outflow and the collection valve.

The system was primed with EtOAc. The system was set in the pump configuration allowing the materials to be introduced directly through the pumps.

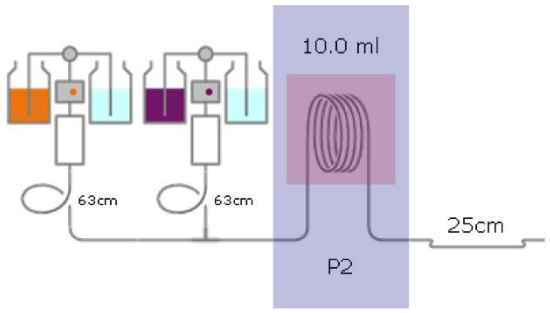

Fig 1 - Pump and reactor setup (illustration exported from flow control software)

The system pumped the reagents neat,

Reagent A: 1-methyl-1H-imidazole (Aldrich 336092, 99%, purified by redistillation, CAS 616-47-7)

Reagent B: n-bromobutane (Aldrich B59497, ReagentPlus®, 99%, CAS 109-65-9.

The collection valve 'Collect' output was directed into 20 mL glass vials.

Summary of conditions

System solvent:	EtOAc
Reagent A:	neat 1-methy-1H-midazole
Reagent B:	neat n-bromobutane
Flow rate A:	variable (238 – 1000 µL/min)
Flow rate B:	variable (262 – 1000 µL/min)
Stiochiometry A:B:	variable 1.0 eq and .1 eq alkylating reagent.
Reactor volume:	10 mL Stainless Steel
Reactor temperature:	80 - 180 °C
Back pressure regulator:	variable

Method (Optimization)

1. The system was flushed with EtOAc at 2.5 mL/min per pump and checked for leaks before pumping any reagents.
2. Priming the pumps with EtOAc: Both selection valves were set to 'Solvent' and the pumps were primed with EtOAc at 1.0 mL/min per pump.
3. 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 connecting the valves to stock bottle 1 was filled with Reagent A. The

selection valve was set back to 'Solvent' and EtOAc pumped through the lines for 2 minutes. The same process was repeated with line 2, Reagent B to fill the second reagent line.

4. Reaction optimization: A selective range of conditions were run manually. Residence times of 5, 10 and 20 minutes were run at two variations of amine stoichiometry (1.0 eq and 1.1 eq) in a 10 ml reactor at a range of temperatures; 80, 100, 110, 140, 150 and 180 °C.
5. Work-Up and Analysis: Any excess of the bromobutane that was present in the collected material was decanted and an aliquot of the crude reaction mixture was taken for NMR analysis. The crude was then dried under high vacuum at 90 °C for 6 hrs. After this time a further sample was taken for analysis.

Running the Reaction (Optimization)

Optimal conversion was observed at 110 °C with a residence time of 10 mins and 1.1 eq of n-bromobutane. A slight excess of the alkylating reagent was required for full conversion to the desired product.

Scale up

After the optimum conditions were determined from the initial reaction optimization experiments, it was decided to process a larger volume of material to establish whether the heat control and clean synthesis could be run continuously.

Method (scaleup)

40 ml of reagent A (502 mmol) was processed and the steady state region collected as described by Flow Commander dispersion profile over ~80 mins.

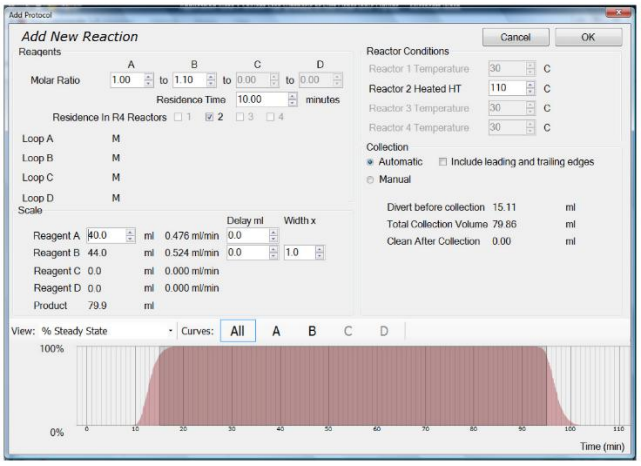

Fig 2 – Flow control software setup for scale up experiment

Results (Scaleup)

After the work up procedure detailed above and drying overnight (101g, 92% yield and 100% purity by NMR) of the desired product was isolated.

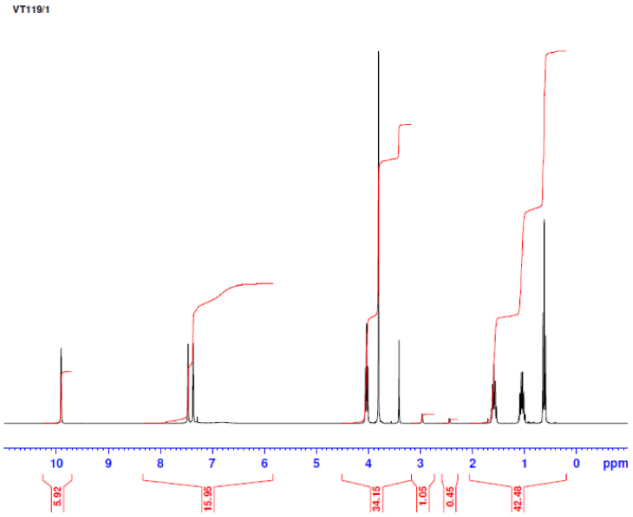

Figure 3; NMR (300 MHz, 1 H, $CDCl_3$); Large scale experiment at 110 °C, 1:1.1, 10 mins residence time.

It is also worth noting the significant increase in viscosity of the IL being synthesized:

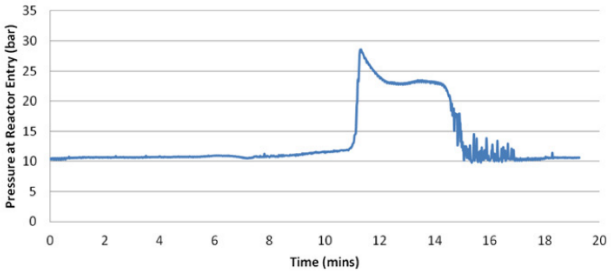

Fig 4. Back pressure measured before reactor showing increase when switching to reagents and creating viscous ionic liquid product

Theoretical larger scale

As demonstrated in Vapourtec application note 4, it is possible to connect the maximum of 4 x 10 ml tube reactors in series and apply the same reaction conditions developed with a single reactor (in this case 10 min residence time, 110 °C and 1.1 eq of amine). This results in a 4x scale up giving a theoretical throughput of 1.61 M/hr potentially achieving a mass transfer of 300 g/hr (7.2 kg/day) at 90% yield.

It should be noted that this experiment has not yet been attempted.

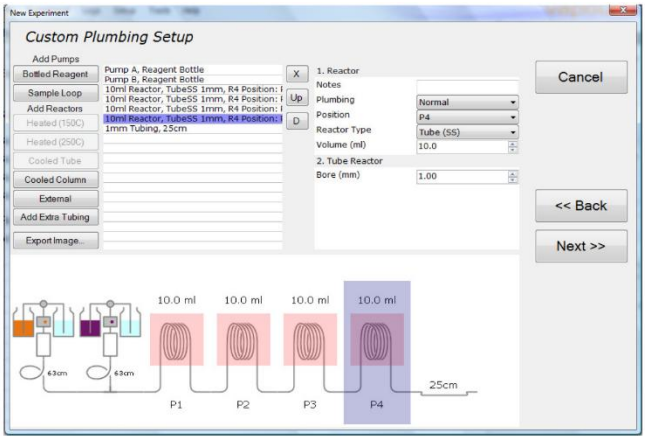

Fig 5. Flow control software experiment setup with 4 reactors in series

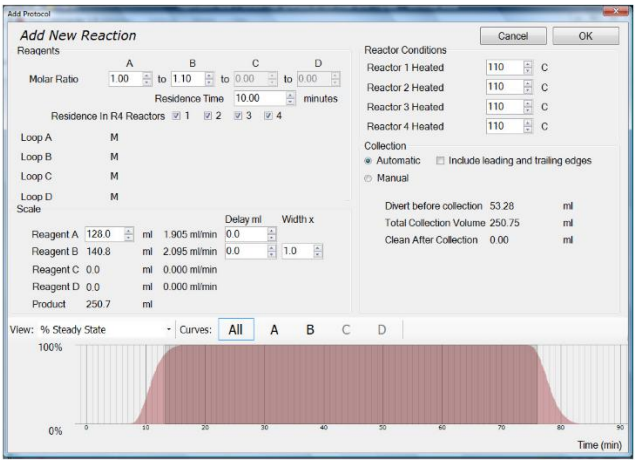

Fig 6. Flow control software reaction setup for larger volume.

Results & Discussion

From the optimization experiments it was clear that there was a set of conditions that gave the cleanest, non-colored material.

Initial experiments looked at temperature and residence time keeping the stoichiometric ratio of reagents at 1:1.

At the lower temperature of 80 °C over the selected residence times of 5, 10 and 20 mins the amount of ionic liquid produced relative to the amount of bromobutane seen was low. The ionic liquid is formed as a viscous oil, if the conversion was low increased amounts of the immiscible alkylating reagent were collected and could be seen sitting on top of the product. At temperatures above 110 °C the ionic liquid formed began to color indicating degradation or by-product formation. As the temperature was increased the color darkened from a pale straw to a deeper orange. Between 100 and 110 °C, a colorless material forming was observed that was relatively high yielding after drying.

NMR (300 MHz, 1 H, $CDCl_3$) analysis of these initial results show that at a 1:1 ratio of the reagents the imidazole is present in all experiments. At 80 °C the relative purity by NMR of product to imidazole is only 62%. Above 100 °C the purity increases and is constant at 75% at temperatures up 180 °C. It should be noted that the product formed was not extracted as described in some processes but dried under vacuum and temperature. This only removed the residue system solvent and alkylating reagent.

To increase the yield of the product and ensure that that the 1-methylimidazole was fully consumed a short series of experiments were run, increasing the stoichiometric ratio of the reagents, 1-methylimidazole against n-bromobutane, to 1:1.1. As previously observed, temperatures of up to 110 °C gave no coloration in the initial experiments and these reactions were run at 110 °C at 5, 10 and 15 mins residence time.

As expected the increased amount of the alkylating reagent gave full conversion of the 1-methylimidazole to the desired ionic liquid by NMR after decanting the excess bromobutane and drying. The dried material crystallized on standing to give a colorless solid. At 5mins residence time the yield was a modest 78%, this increased to a very good yield of 92% at 10 mins and 94% at 15 mins.

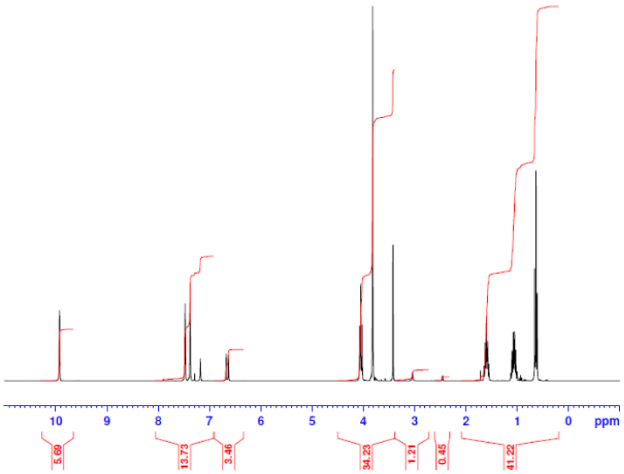

Fig 7 NMR (300 MHz, ^1H, $CDCl_3$); 110 °C, 1:1, 10 mins residence time.

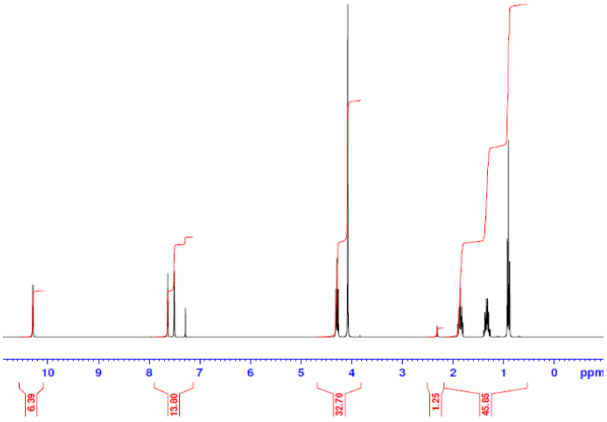

Fig 8 NMR (300 MHz, ^1H, $CDCl_3$); 110 °C, 1:1.1, 10 mins residence time.

The NMR data shows the complete disappearance of the imidazole double doublet at 6.7 ppm by adding an excess of the alkylation reagent.

It should be noted that the exotherm generated on reaction of the two components could be observed (and even quantified) using the flow control software. An exothermic reaction is visible as a decrease in the power supplied to the reactor heating system (displayed and logged digitally) when switching from solvent to reagent.

At the higher flow rates of the short residence time experiment a significant exotherm was clearly observed. An exotherm of this nature may not be controllable by a traditionally stirred batch reactor but was controlled safely and easily by the Vapourtec apparatus.

A thermocouple was placed at the mixing T-piece (which was external to the temperature controlled zone of the reactor manifold) to check the exothermic event at mixing. No temperature increase was seen, so it it seems clear that no temperature control was required at mixing, and the heat was all dissipated downstream when the mixture was raised to target reaction temperature

(Vapourtec do offer the "internal mixer" reactor in which the mixer ***is*** inside the temperature controlled zone, but it was in this case not called for).

Conclusion

This study demonstrates the capability of the Vapourtec R-Series system to allow difficult to scale in batch reactions to be developed and optimized quickly, and then safely scaled up in flow. It should be stressed that due to the exothermic nature of this reaction, it could not be carried out at the temperatures obtained here in traditionally stirred batch reactors.

A simple continuous flow process for the synthesis of ionic liquids has been demonstrated. This versatile approach lends itself to the production of a wide variety of further combinations of side chain and anion. This approach meets the demands for highly pure products and lends itself well to preparing large amounts of material on demand.

Acknowledgements

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www.flowchemistrysolutions.co.uk