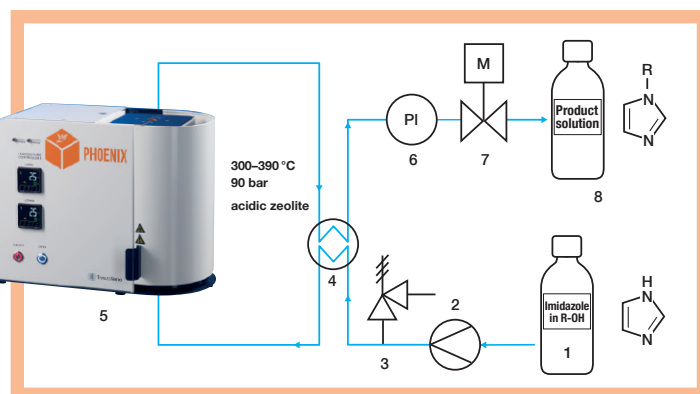




A continuous flow process for the green and sustainable production of N-alkyl imidazoles



Introduction

Ionic liquids have gained great interest during the last three decades due to their green and sustainable behavior along with their added versatility as solvents in inorganic and organic reactions as well.¹ *N*-Alkylimidazole derivatives are key intermediates for the synthesis of quaternary ionic liquid salts. However, many of the *N*-alkylated imidazole compounds are commercially available but their price is often prohibitively high. The nature of the alkyl side-chain on the imidazole ring affects the solubility of materials in the ionic liquid and might even alter reactivity. Nevertheless, due to their low prices the most frequently used ionic liquids are 1-ethyl-3-methylimidazolium (EMIM) and 1-butyl-3-methylimidazolium (BMIM) salts.

The present application note discusses the results of Fekete *et al.* on the synthesis of *N*-alkylimidazoles in the Phoenix Flow Reactor™ using acidic zeolite catalyst mixtures in flow (Scheme 1).²

Instrumentation

The reactions were carried out in ThalesNano's Phoenix Flow Reactor™ which is a versatile instrument for high temperature reactions in continuous flow.³ The reactor can operate in either heterogeneous or homogeneous mode giving chemists a modular tool to perform reactions from ambient temperature up to 450 °C. Applying elevated pressure up to 200 bar ensures that the organic solvents are kept in the liquid phase well above their boiling point.

Figure 1. Schematic representation of the process

1 – Adding vial with starting solution, 2 – HPLC pump, 3 – Overpressure safety valve, 4 – Counter-flow heat exchanger, 5 – Phoenix Flow Reactor™, 6 – Pressure sensor, 7 – Pressure regulator, 8 – Product collection vial.

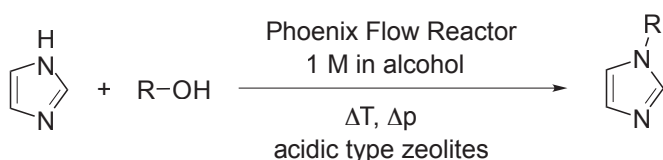
The reactions detailed in this application note were carried out using stainless steel cartridges filled with a mixture of zeolites and silica. An HPLC pump provided the liquid flow through the sealed catalyst bed and through the opposite flow heat exchanger before the solution left the instrument through an automatic back pressure regulator.

Experimental

RISK ASSESSMENT AND HAZARDS

Avoid contact with hot parts of the system. Above 250 °C it is mandatory to connect the heat exchanger and a safety valve to the system to prevent overpressure and possibility of injury. Liquids over 90 °C may cause damage to the back pressure sensor. Connect a tube to the outlet of the relief valve and place it in a flask to collect the released liquid/gas in case of over pressurization. Never open the system at high temperature/high pressure, the uncontrolled release of high pressure liquid can potentially come into contact with the operator. Always work in a ventilated fume hood to prevent inhalation of organic solvent vapors. Zeolites might generate a significant pressure drop when used with primary alcohols. It is recommended to wash the cartridge with a low flow rate before changing to working parameters. Heating the cartridge with constant flow should lower the experienced pressure drop on the column.

Scheme 1. General scheme of the *N*-alkylation reaction.



GENEAL PROCEDURE FOR THE SYNTHESIS OF N-ALKYL IMIDAZOLES

A 1 M solution of imidazole (6.8 g in 100 mL solution) was prepared in the corresponding alcohol (reagent grade, Molar Chemicals), which fulfilled the role of the solvent and reactant at the same time. BASF-F160 Zeolite (8 g, pH=3.0, 98% acid-leached bentonite) and silica (3.4 g, 60 Å, Molar Chemicals) were cautiously mixed together. A ½" × 250 mm (outer diameter × length) cartridge was charged with the catalyst mixture. The cartridge was placed in the Phoenix Flow Reactor and was pretreated with the corresponding alcohol at 0.5 mL/min flow rate. The reaction temperature (300–390 °C), the pressure (90 bar), and flow rate (1.00–1.25 mL/min) were then set. The solution of the starting material was passed through the reactor. A simple work up by evaporation of the solvent gave the N-alkylated imidazole in >90% yield. Analysis of the product was carried out by GC-MS (Agilent 6530 series II) and ¹H-NMR (Bruker, 300 MHz) spectroscopic analysis.

Results and discussion

The work by Fekete *et al.* focused on the production of different N-alkylated imidazoles and reaction optimization in flow.² Following the work of Ono and Gitis,⁴ the catalyst screening focused on acidic type of minerals. The BASF-F160 acidic zeolite proved to be the most effective (Scheme 1, Table 1), however other acidic materials, such as Montmorillonite K10 (Sigma, pH= 2.5–3.5) provided good results too (not shown on Scheme). Zeolite BASF-F160 provided excellent yields with longer primary alcohols (Table 2), despite that these alcohols have higher pK_a values and therefore exhibited lower reactivity. The scope of the reaction was extended to other amines, e.g. piperidine and pyrrolidine, using *n*-butanol as solvent and alkylating agent (Scheme 2).

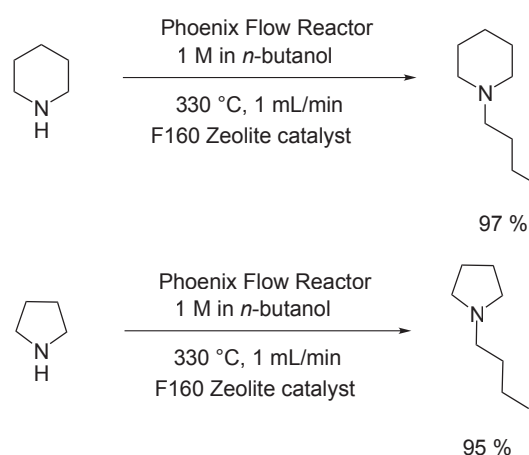
Alcohol	Catalyst		c (M)	T (°C)	V _{flow} (mL/min)	¹ H-NMR yield (%)
	Zeolite F160 (g)	Silica (g)				
Ethanol	8.00	3.4	1	350	1	>99
			2	350	1	92
			2	360	1	>99
			2	380	1.25	>99

Table 1. Reaction conditions optimization with ethanol.

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Alcohol	Catalyst		c (M)	T (°C)	V _{flow} (mL/min)	¹ H-NMR yield (%)
	Zeolite F160 (g)	Silica (g)				
<i>n</i> -butanol	8.0	3.4	1	390	1	98
<i>n</i> -pentanol	8.0	3.4	1	390	1	98
<i>n</i> -octanol	8.0	3.4	1	390	1	93

Table 2. Alkylation of imidazole with different primary alcohols.



Scheme 2. *n*-Butylation of piperidine and pyrrolidine (isolated yields are given).

Conclusion

The alkylation of imidazole on fixed bed acidic zeolite catalysts proved to be very efficient in flow. A range of N-alkyl imidazole derivatives were prepared with an 8–14 g/hour productivity in good-to-excellent yields. The key advantages of the process are

- the simple work-up (evaporation or vacuum distillation);
- the possibility of reusing the solvent;
- clean procedure by water is being the only side-product.

Overall, this method gives easy excess to ionic liquid precursors.

Acknowledgement

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