Melinda Fekete, László Kocsis*, György Dormán, Richard V. Jones and Ferenc Darvas

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

DOI 10.1515/gps-2015-0146
Received December 18, 2015; accepted April 14, 2016; previously published online May 14, 2016

Abstract: *N*-alkyl imidazoles are the basic components of the widely used and studied imidazolium ionic liquids. The need for these materials multiplied since the field of ionic liquids has been gaining more and more importance. Our aim was to develop a continuous flow method for the *N*-alkylation of imidazole that provides the alkylated derivatives with high productivity and selectivity, using only cheap, preferably green starting materials. Herein, we report a novel method for the preparation of *N*-alkyl imidazoles over a zeolite catalyst using high temperature and pressure in a heterogeneous catalytic flow reactor. The yield and selectivity exceeded 95% for *n*-chain alcohols while the residence time was kept at 13 min, thus, the productivities were between 9 g/h and 14 g/h. The only side product in the reaction is water, thus, the process expresses high atom economy.

Keywords: continuous flow; high pressure flow reactor zeolite; high temperature; ionic liquid; *N*-alkyl imidazoles.

1 Introduction

N-alkyl imidazoles gained interest in the last two decades when their salts, the 1,3-dialkylimidazolium ionic liquids, became widely investigated. Although *N*-alkyl imidazoles are commercially available, their high price is a limiting factor of their further application. The only exception to this is 1-methylimidazole, which is widely available for a low price. The price of these compounds dramatically increases with the chain length: while 100 ml of *N*-methylimidazole costs only 28 € (Sigma-Aldrich), the price of 5 ml of *N*-octylimidazole is above 300 € (Sigma-Aldrich).

Based on these cost differences, *N*-methylimidazole is the most widely used starting material in the 1,3-dialkylimidazolium ionic liquid syntheses based on its quaternization reaction with alkyl halides [1]. Imidazolium ionic liquids are attractive solvent candidates in many chemical processes, including catalysis [2, 3], organic reactions [4, 5] and nanoparticle synthesis [6, 7]. One of the advantages of ionic liquids is their tunable properties: changing the cation, the alkyl substituent or the anion can lead to ionic liquids with completely different physicochemical properties [8, 9]. Despite this often-mentioned fact, tailoring the ionic liquids for a given chemical problem is not common in research. The most studied ionic liquids are 1-alkyl-3-methylimidazolium – especially the 1-ethyl-3-methylimidazolium and 1-butyl-3-methylimidazolium (BMIM) – salts, due to their relatively low price and wide availability.

In a chemical reaction, the side chain length and polarity of the imidazolium ionic liquid can significantly influence the solubility of reactants. In the biphasic Difasol process, octenes are selectively produced [10] from butenes using [BMIM $AlCl_4$] ionic liquid with selectivities over 90%. The length of the alkyl chain is crucial to obtain good selectivity: while butenes are soluble, octenes are not miscible with the applied ionic liquid; thus, higher oligomers are not produced in the biphasic system.

Imidazolium-based ionic liquids display a pronounced self-organization in the solid, liquid and even in the gas phase [9, 11]. Double-tailed ionic liquids form interlocking chains [12] in their crystal structure that might affect the selectivity of a catalytic reaction. Wang et al. [13] attempted to use symmetrically substituted, long-chain imidazolium ($C_{12}C_{12}IM$) ionic liquid that previously showed a liquid crystalline structure [14]. A structurally similar, *N*-heterocyclic carbene catalyst, ($NiCl_2[C_{12}C_{12}IM]_2$) was added to the ionic liquid in order to achieve higher selectivity towards linear olefin oligomers in the ordered liquid crystalline structure.

In another approach, epoxidation of cyclooctene was achieved with high yield and selectivity (>99%) using a supported ionic liquid catalyst [15]. Here, the imidazolium cation bearing an octyl group was grafted (chemically bound) onto the silica surface, while peroxotungstate anions served the catalytic activity.

As the above-mentioned examples show, the alkyl chain substituent of the imidazolium ionic liquid has

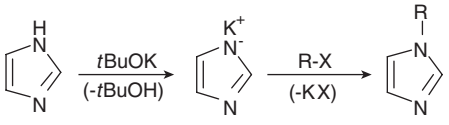
***Corresponding author: Lászlo Kocsis,** ThalesNano Inc. Záhony u. 7., Budapest 1031, Hungary, e-mail: laszlo.kocsis@thalesnano.com
Melinda Fekete, György Dormán, Richard V. Jones and Ferenc Darvas: ThalesNano Inc. Záhony u. 7., Budapest 1031, Hungary

a significant effect on the chemical reaction. Having a cheap source of the different *N*-alkylated imidazoles is highly desired in the ionic liquid synthesis and for their further application.

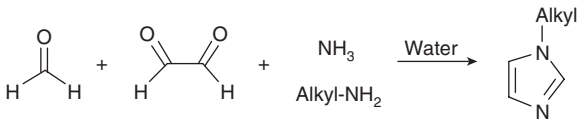
In a conventional, typical laboratory scale process, the imidazole is reacted with an alkyl halide in the presence of a strong base (Scheme 1). This is a well-established method, but the usage of alkyl halide and base (for example tBuOK, NaOMe or NaH) makes the process expensive on the industrial scale. The atom efficiency of this process is low, as one mole side product (depending on the base) and one mole salt is produced. In addition, the reaction becomes slow with long alkyl chain chlorides. However, the more reactive alkyl bromide or iodide derivatives are even less economical.

Industrial methods describe [16, 17] the synthesis of *N*-alkyl imidazoles *via* ring closure with ammonia, formaldehyde, glyoxal and the corresponding alkyl amine (Scheme 2). This reaction would provide good atom efficiency; however, it might be difficult to lead the reaction selectively toward the *N*-alkylated product. Also, the process requires the storage and usage of poisonous materials such as formaldehyde, amines and ammonia.

There are a few descriptions in the literature for the alkylation – particularly methylation and ethylation – of imidazole using minerals [18–20] as catalyst in gas phase reactions. Ono et al. [19] reported about the vapor phase alkylation of 4(5)-methylimidazole over Y-zeolites. Similarly, Gitis et al. found [20] HNaY zeolites to be suitable catalysts for the vapor phase methylation of imidazole and 2-methylimidazole. However, such vapor phase reactions cannot provide high enough productivity for a fine chemical scale production, while they are not feasible in a laboratory environment. In addition, it has never been attempted to extend the protocol for other – long chain or branched – alcohols.



Scheme 1: Typical laboratory synthesis of *N*-alkyl imidazoles.



Scheme 2: Synthesis of alkyl imidazoles with ring closure.

2 Materials and methods

In our work, a high temperature-high pressure continuous flow reactor (Phoenix Flow Reactor, ThalesNano Inc., Budapest, Hungary) was used that can be easily be implemented in a fume hood. The alkylation process over the zeolite was generalized for n_C>2 alcohols (Scheme 3).

The Phoenix Flow Reactor is a bench-top module that can house a loop or a fixed-bed unit and allows reactions up to 450°C and 200 bar. The high pressure is kept constant with the help of a pressure valve, thus allowing the chemicals to stay in the liquid phase at temperatures above the boiling point. The liquid-phase reaction allows chemists to have higher through-put of reactants as well as easy reaction handling.

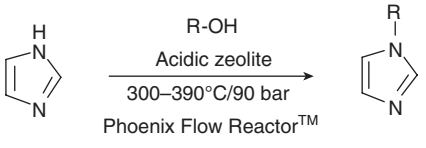
A stainless steel cartridge (9 mm×250 mm) was filled with catalyst material and placed into the Phoenix reactor (Figure 1). Both ends of the cartridge were sealed with titanium frits (2 µm pore size). An HPLC pump was connected to the inlet of the cartridge *via* a 2 ml heat exchanger loop. The outlet of the catalyst cartridge was connected to a pressure controller valve *via* the heat exchanger. Collection of the samples was carried out manually, or by the help of a fraction collector. Connector tubing was made of stainless steel, with an inner diameter of 1 mm.

3 Results and discussion

First, we focused our attention on the reaction between ethanol and imidazole in order to explore the potential of our system. Thus, a 1 M solution of imidazole was prepared in ethanol; ethanol having the role of solvent and reactant at the same time.

Based on the former work of Ono et al. [19] and Gitis et al. [20], only acidic type minerals were tested. We focused our work on the BASF F160 Zeolite (pH=3.0, 98% acid-leached bentonite) catalyst, however, preliminary tests with Montmorillonite K10 (Sigma, pH=2.5–3.5) showed that other, acidic type minerals could be similarly efficient.

Conversion values were determined by nucleic magnetic resonance (NMR) (picoSpin 45 MHz or Brucker 300 MHz). Samples were also double-checked by gas chromatography-mass spectrometry (GC-MS) (Agilent 5975C, HP5/MSUI column) in order to identify any side products.



Scheme 3: One-step continuous flow synthesis of *N*-alkyl imidazoles.

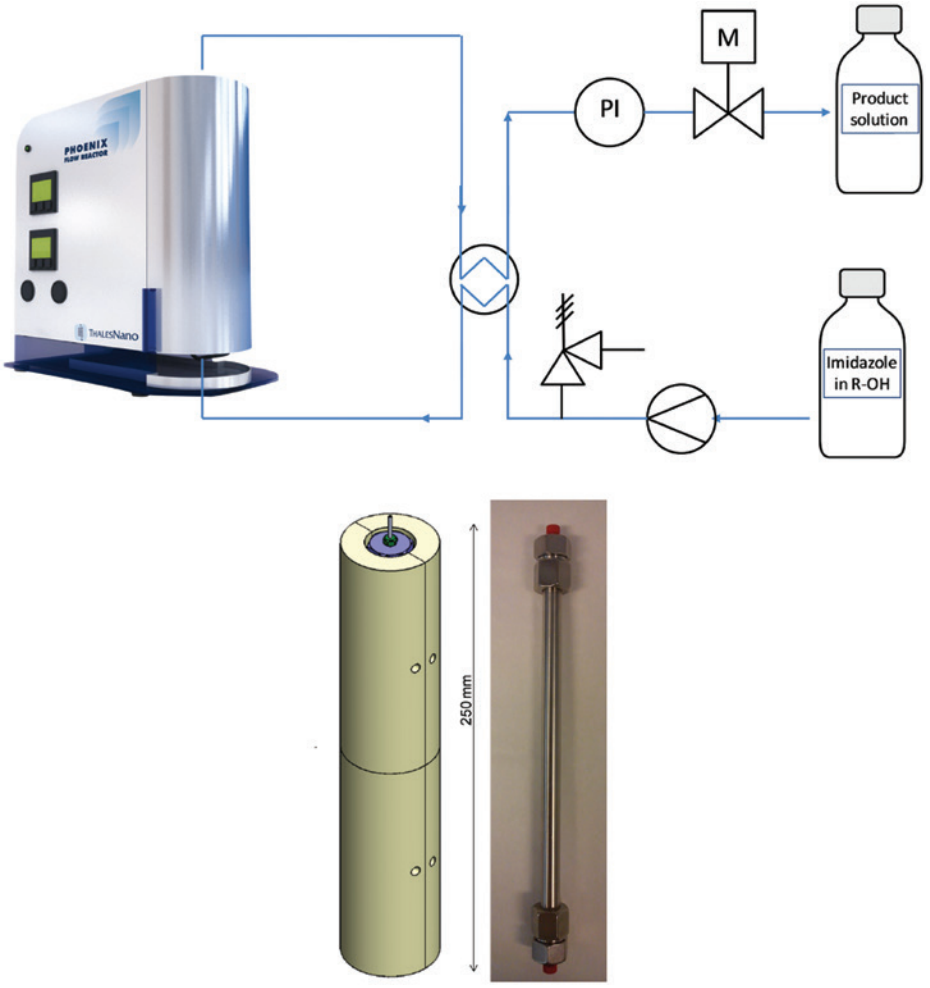


Figure 1: Experimental set-up for the continuous flow *N*-alkylation of imidazole. Below: reactor tube (right) and reactor tube within the heating element of the reactor (left).

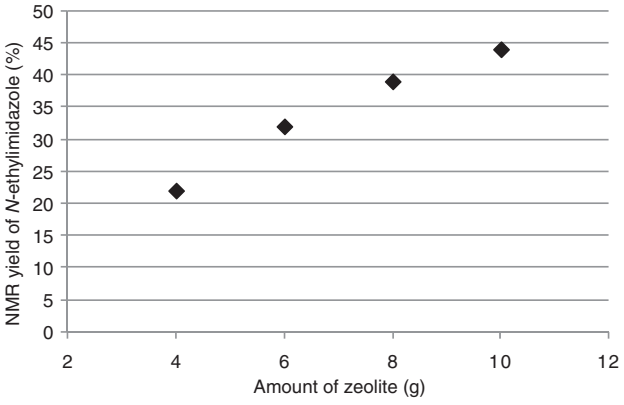
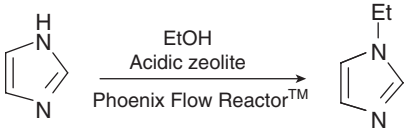


Figure 2: Effect of catalyst amount on the reaction of imidazole and ethanol. Reaction conditions: 1 M solution, 300°C, 90 bar, 1 ml/min flow rate. Residence time was kept at 13 min in each case.

First, different zeolite amounts were compared. To be able to always fill the same reactor, the applied acidic catalyst was mixed with an inert material, silica gel (Silica gel 60, 63–200 um, Merck). Thus, we kept the void volume of the reactor constantly at 13 ml. Silica alone was tested and found to give conversions under 1%.



Scheme 4: Alkylation of imidazole with ethanol.

The amount of catalyst has an almost linear effect on the reaction rate (Figure 2). Importantly, selectivity of the reaction was >99% and in each case, no side products were observed.

As we aimed to optimize the reaction (Scheme 4), different temperatures (Figure 3), flow rates and concentrations were also investigated. In the examined temperature range, the conversion showed a linear increase with the temperature. For the given 1 M imidazole solution the optimal temperature is above 340°C.

The reaction was not influenced by the applied pressure; the same results were obtained at 50 bar and 90 bar. After this observation 90 bar pressure was used in all experiments.

In order to increase the productivity of the system, the concentration of the solution was also varied (Table 1). Although more concentrated solutions showed a lower conversion rate, complete conversion of the 2 M reaction mixture was reached at 360°C or above. Thus, without any further optimization, a productivity of 14.4 g/h was achieved. To our satisfaction, the reaction was selective for *N*-ethylimidazole and side products were not observed even at the applied high temperatures.

3.1 Long-chain alcohols

As was proven by the above experiments, the Zeolite F160 is a suitable catalyst for the alkylation of imidazole. The catalyst is stable at the applied conditions and provides excellent conversion and selectivity. Based on these results, we decided to extend the reaction to longer chain alcohols. These, due to their higher pK_a values, exhibited somewhat lower reactivity. Nevertheless, at 390°C even the reaction with *n*-octanol was close to completion (Table 2).

These results suggested that the found conditions could be applied to other linear alcohols as well, as long as the alcohol was a liquid. The high concentration of solute and the relatively short residence time allowed us to reach good productivity values for these imidazoles. Without any further scale-up of the system, the following productivities were obtained:

The space time yield (Table 3) obtained here agrees well with those of the typical fine chemical manufacture [21]. In addition, the productivity of our bench-top system can be easily increased with scale-up, since scaling up a fixed bed reactor is a relatively easy task [22].

The reaction requires a simple vacuum distillation as work-up, and the distilled alcohol can be recycled and reused. In addition to the product, only one equivalent of

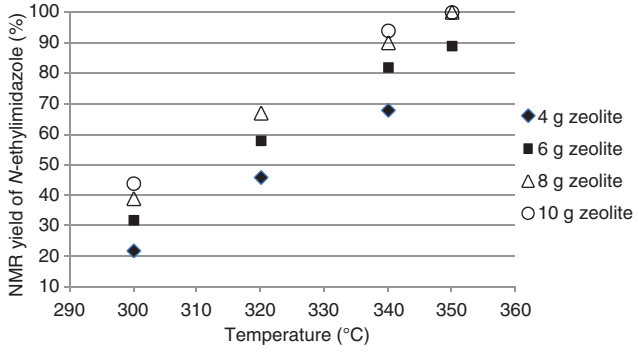


Figure 3: Reaction conditions: 1 M solution, 1 ml/min flow rate, 90 bar pressure. Residence time was kept at 13 min.

Table 1: Process intensification of the reaction.[a]

Alcohol	Catalyst		c (M)	T (°C)	V_{flow} (ml/min)	NMR yield[b] (%)
	Zeolite F160 (g)	Silica (g)				
Ethanol	8.0	3.4	1	350	1	>99
			2	350	1	92
			2	360	1	>99
			2	380	1.25	>99

[a]Reaction conditions: 13 ml void volume, 90 bar pressure. Yields and selectivities were >99%, based on 45 MHz picoSpin nuclear magnetic resonance (NMR) and gas chromatography-mass spectrometry (GC-MS).
[b]Based on 45 MHz picoSpin NMR data.

Table 2: Reaction parameters and results with *n*-alcohols.[a]

Alcohol	Catalyst		c (M)	T (°C)	V_{flow} (ml/min)	NMR[b] yield (%)
	Zeolite F160 (g)	Silica (g)				
n-Butanol	8.0	3.4	1	350	1	77
			1	370	1	93
			1	390	1	98
			1	**390**	**1.25**	**97**
			1	350	1	62
n-Pentanol	8.0	3.4	1	370	1	85
			1	**390**	**1**	**98**
			1	390	1.25	96
			1	370	1	84
n-Octanol	8.0	3.4	1	370	1.25	77
			1	390	1.25	91
			1	**390**	**1**	**93**

[a]Reaction conditions: 13 ml void volume, 90 bar pressure. Selectivities were found >97%, based on gas chromatography-mass spectrometry (GC-MS) data.
[b]Based on 300 MHz nuclear magnetic resonance (NMR).

Table 3: Theoretical productivity and space time yield values based on the best reaction parameters (See Table 2, bold).

N-alkyl imidazole	c (M)	V_{flow} (ml/min)	Productivity[a] (g/h)	Space time yield (kg/h*l)
Ethyl	2	1.25	14.4	1.1
Butyl	1	1.25	9.1	0.7
Pentyl	1	1	8.1	0.62
Octyl	1	1	10.0	0.77

[a]Conversion values (<100%) were considered in the calculation.

water was produced in the reaction, thus the atom efficiency of this process is very good.

In the reaction mixture, only small amounts of dialkyl ethers and alkenes were identified originating from the alcohol. Importantly, no alkyl-chain isomerization occurred in the reactions.

3.2 Scope and limitations

Based on their lower acidity, secondary alcohols showed decreased reactivity than primary alcohols. In addition, at the applied temperature, secondary alcohols lose water in an elimination reaction. As a consequence, we observed notable gas production during the reactions and water as a separate phase in the reaction of 2-butanol (gas formation was noticed with primary alcohols as well, but to a much lower extent).

Interestingly, the reaction was found to be less selective; in the reaction of 2-propanol and 2-butanol, several side products were observed. The GC-MS analysis showed that *C*-alkylation as well as double-alkylation occurred. Due to the small relative amount of these side products, they were not isolated and analyzed. Presumably, the forming alkene (1-propene and 2-butene) alkylates the imidazole ring but with a different reaction mechanism. However, the method is still feasible and the product can be purified by a simple distillation.

Furthermore, *N*-alkyl imidazoles were prepared in 100–150 ml reaction scale under the optimized conditions (Tables 4 and 5, bold lines) and isolated *via* vacuum distillation. The products were obtained as colorless or slightly yellowish liquids with the following isolated yields and purity as shown in Table 6.

Table 4: Reaction conditions and results with branched alcohols.[a]

Alcohol	c (M)	T (°C)	V_{flow} (ml/min)	Conversion[b] (NMR, %)	Selectivity[b] (NMR, %)
2-Butanol	1	350	1	63	68
	1	350	1.25	51	82
	1	370	1	60	67
	1	**370**	**0.75**	**73**	**76**
2-Propanol	2	350	1	51	86
	2	350	0.75	59	83
	2	370	0.75	78	88
	1	350	1	77	91
	1	350	0.75	81	90
	1	**360**	**0.75**	**85**	**88**

[a]Reaction conditions: 13 ml void volume, 90 bar pressure. Catalyst loading: 8.0 g zeolite with 3.4 g silica.
[b]Based on 300 MHz nucleic magnetic resonance (NMR) spectra. Side products bearing NH are not well detectable in our gas chromatography-mass spectrometry (GC-MS) method thus selectivity was determined by NMR in these cases.

Table 5: Isolated yield and purity of *N*-alkyl imidazoles.

N-alkyl imidazole	Isolated yield (%)	Purity % (GC-MS)
Ethyl	**90**	>99
Butyl	**92**	99
Isopropyl	**80**	94
But-2-yl	**68**[a]	99
Pentyl	**92**	>99
Octyl	**76**	98

[a]Higher conversion and selectivity was reached here than during the optimization, possibly due to the long (~125 min) reaction time. Boiling points and nucleic magnetic resonance (NMR) chemical shift of the products were in agreement with those of the literature.
GC-MS, Gas chromatography-mass spectrometry.

3.3 Reaction with other amines

In order to evaluate the synthetic utility of the procedure, next to imidazole, piperidine and pyrrolidine were tested in the zeolite-catalyzed reaction. Typical lab-scale synthesis of these compounds is similar to the alkylation of imidazole (Scheme 1), although milder conditions are sufficient. A catalytic synthesis route with ethanol is also described over $RuCl_3$ and Rh complexes [23, 24]. However, the Ru and Rh catalysts are more costly compared to zeolite, which can limit the utility of these synthesis routes.

Using our method, both piperidine and pyrrolidine reacted with *n*-butanol with good conversion and high selectivity, giving the desired *N*-alkylated products (Table 5).

N-butylpiperidine and *N*-butylpyrrolidine were isolated as their HCl salts (Table 7), after adding a calculated amount of HCl solution, and consequent evaporation.

3.4 Longevity

From the previous experiments we suspected that the Zeolite F160 catalyst has a stable behavior over a long period of time. In order to prove this observation, a longevity test was performed. The reaction of imidazole with *n*-butanol (Scheme 5) was carried out for an overall period of 24 h (1500 ml solution). The Phoenix Flow Reactor was connected to a Gilson FC 204 fraction collector and 30 ml samples were taken during the 24 h.

Table 6: Reaction conditions and results with other amines.[a]

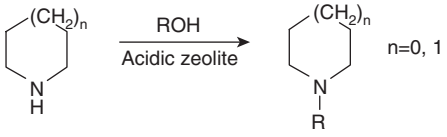
Amine	Alcohol	c (M)	T (°C)	V_{flow} (ml/min)	Conversion (GC, %)	Selectivity (GC, %)
Piperidine	2-Butanol	1	280	1	8	79
		1	320	1	72	91
		1	330	1	94	97
		1	**340**	**1**	**>99**	**97**
Pyrrolidine		1	280	1	75	89
		1	**330**	**1**	**>99**	**95**

[a]Reaction conditions: 13 ml void volume, 90 bar pressure. Catalyst loading: 8.0 g zeolite with 3.4 g silica.
The bold values refer to the optimized conditions (highest conversion and selectivity).

Table 7: Isolated yield of *N*-butylpiperidine and *N*-butylpyrrolidine.

Product	Isolated yield (%)
N-butylpiperidine	**97**
N-butylpyrrolidine	**89**[a]

[a]Short-path distillation.



Scheme 5: Alkylation of piperidine and pyrrolidine.

Figure 4 shows the conversion and selectivity of the reaction over the 24 h period. It is clearly visible that conversion as well as selectivity shows a rather constant value. The stable performance of the catalyst makes this alkylation process a considerable alternative for *N*-alkyl imidazole manufacturing.

3.5 Mechanism of the reaction

The reaction of imidazole and alcohol might be very similar to the industrially important methylamine formation. The amination of methanol with ammonia over zeolites has been extensively researched and several reaction mechanisms have been suggested [25–27].

Chen et al. [26] proposed that weakly adsorbed methanol reacts with an ammonium ion through protonation of methanol by an ammonium ion and subsequent interaction of the ammonia nitrogen with the carbon atom of the protonated methanol. Corbin et al. [27] suggested that the mechanism of methylamine formation is an S_N2 attack of the weakly adsorbed ammonia on the protonated

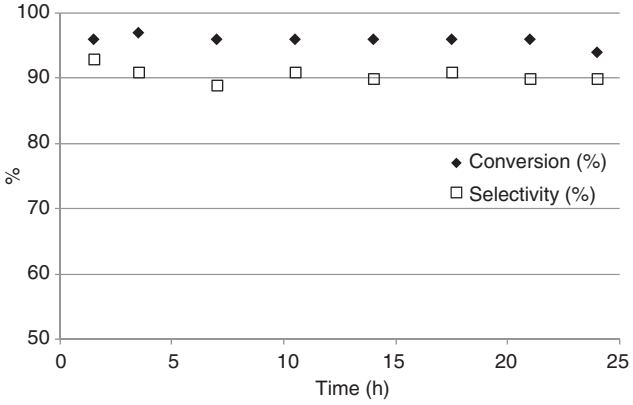


Figure 4: Longevity experiment of imidazole and butanol. Reaction conditions: 13 ml void volume, 90 bar pressure, 1 ml/min flow rate, 390°C. Catalyst loading: 8.0 g zeolite with 3.4 g silica. Conversion and selectivity were determined based on 300 MHz nuclear magnetic resonance (NMR).

methanol. The proton source can be the zeolite hydrogen or the ammonium ion.

We assume that a similar mechanism is valid for the alkylation of imidazole, piperidine and pyrrolidine with alcohols. The nucleophilic substitution-like mechanism ensures the selectivity on the nitrogen atom. The idea is supported by the fact that in this particular mechanism, isomerization of the alkyl group is not likely and such a phenomenon was indeed not observed by us.

The side products we experienced in the reaction of secondary alcohols were identified as *C*-alkylated imidazoles. We presume that such a product is formed in the reaction of imidazole with alkene rather than with alcohol. This can be better understood based on the mechanism of alkylation of benzene by alkene over zeolite [28]. In both cases, chemisorption of the alkene on the zeolitic Bronsted acidic site occurs and a geometry very close to a carbenium ion is formed. The reaction is in essence an alkylation of protonated alkene by the aromatic ring (benzene or imidazole).

4 Conclusion

In this paper, we demonstrate a continuous flow process for the production of *N*-alkyl imidazoles. The reaction takes place in a fixed-bed reactor between imidazole and an alcohol over the acidic zeolite catalyst at a temperature >300°C. The only chemical the process requires is the solvent-and-reagent alcohol. The elaborated method provides conversion and selectivity >95% for *n*-chain alcohols. With the applied bench-top size flow reactor,

productivities between 9 g/h and 14 g/h were reached. The only side product in the reaction is water, thus, it is a high atom economy synthesis route. The catalyst shows excellent longevities over 20 h that makes the synthesis even more efficient. Reaction of secondary alcohols results in somewhat lower, but reasonable conversion and selectivity values.

Furthermore, the method was extended for non-aromatic cyclic amines as well: pyrrolidine and piperidine were converted selectively into the *N*-alkylated derivatives with high yields.

References

[1] Gordon CM, Muldoon MJ. In *Ionic Liquids in Synthesis*, 2nd ed., Wasserscheid P, Welton T, Eds., Wiley-VCH Verlag: Weinheim, 2008, Vol. 1, p 7–32.
[2] Parvulescu VI, Hardacre C. *Chem. Rev.* 2007, 107, 2615–2665.
[3] Sheldon R. *Chem. Commun.* 2001, 37, 2399–2407.
[4] Yanai H, Ogura H, Taguchi T. *Org. Biomol. Chem.* 2009, 7, 3657–3659.
[5] Morrison DW, Forbes DC, Davis JH. *Tetrahedron Lett.* 2001, 42, 6053–6055.
[6] Cimpeanu V, Kočevar M, Parvulescu VI, Leitner W. *Angew. Chem*. 2009, 121, 1105–1108.
[7] Redel E, Krämer J, Thomann R, Janiak C. *J. Organomet. Chem.* 2009, 694, 1069–1075.
[8] Holbrey JD, and Rogers RD. In *Ionic Liquids in Synthesis*, 2nd ed., Wasserscheid P, Welton T, Eds., Wiley-VCH Verlag: Weinheim, 2008, Vol. 1, p 57–72.
[9] Dupont J, Suarez PAZ. *Phys. Chem. Chem. Phys.* 2006, 8, 2441–2452.
[10] Bourbigou HO, Favre F. In *Ionic Liquids in Synthesis*, 2nd ed., Wasserscheid P, Welton T, Eds., Wiley-VCH Verlag: Weinheim, 2008, Vol. 2, p 464–488.
[11] Gozzo FC, Santos LS, Augusti R, Consorti CS, Dupont J, Eberlin MN. *Chem.-Eur. J*. 2004, 10, 6187–6193.
[12] Wang X, Heinemann FW, Yang M, Melcher BU, Fekete M, Mudring AV, Wasserscheid P, Meyer K. *Chem. Commun.* 2009, 45, 7405–7407.
[13] Wang X, Sobota M, Kohler FTU, Morain B, Melcher BU, Laurin M, Wasserscheid P, Libuda J, Meyer K. *J. Mater. Chem.* 2012, 22, 1893–1898.
[14] Sobota M, Wang X, Fekete M, Happel M, Meyer K, Wasserscheid P, Laurin M, Libuda J. *ChemPhysChem.* 2010, 11, 1632–1636.
[15] Yamaguchi K, Yoshida C, Uchida S, Mizuno N. *J. Am. Chem. Soc.* 2005, 127, 530–531.
[16] *US pat.* Process for manufacture of imidazoles. 6177575, 2001.
[17] *US pat.* Preparation of 1-substituted imidazoles. 4450277, 1984.
[18] *US pat.* Production of substituted imidazoles. 3652581, 1972.
[19] Ono Y, Izawa Y, Fu ZH. *Chem. Commun.* 1995, 31, 9.
[20] Gitis KM, Neumoeva GE, Isagulyants GV. *Chem. Heterocyc. Compd.* 1994, 30, 547–550.
[21] Klemm E. Heterogeneous Catalytic Engineering, *Topical Workshop, Catalysis*, Stuttgart, April 12, 2011.
[22] Donati G, Paludetto R. *Catal. Today* 1997, 34, 535–547.
[23] Bitsi G, Schleiffer E, Antoni F, Jenner G. *J. Organomet. Chem.* 1989, 373, 343–352.
[24] Grigg R, Mitchell TRB, Sutthivaiyakit S, Tongpenyai N. *Chem. Commun.* 1981, 611–612.
[25] Veefkind VA, Lercher JA. *Appl. Catal. A-Gen.* 1999, 181, 245–255.
[26] Chen DT, Zhang L, Kobe JM, Yi C, Dumesic JA. *J. Mol. Cat.* 1994, 93, 337–355.
[27] Corbin DR, Schwarz S, Sonnichsen GC. *Catal. Today* 1997, 37, 71–102.
[28] Rozanska X, van Santen RA. In *Handbook of Zeolite Science and Technology*, Auerbach SM, Carrado KA, Dutta PK, Eds., CRC Press: Boca Raton 2003, p 1000–1058.

Bionotes

Melinda Fekete

Melinda Fekete received her PhD in 2004 from Budapest University of Technology and Economics where she also spent 3 postdoctoral years. Between 2012 and 2014 she worked at ThalesNano Inc., Budapest, as a senior research scientist. Presently, she is a Research Fellow at the University of Greifswald, Germany. She gained experience in the synthesis of biologically active nitrogen-heterocycles *via* Pd-catalyzed cross-coupling reactions and heterogeneous catalytic flow reactions. She published 11 scientific papers in international journals.

László Kocsis

László Kocsis holds a PhD in Organic Chemistry from the Eötvös Lóránd University, Budapest, Hungary (2008). In 2004, he began working as a research chemist at the Reanal Finechemical Company in Budapest, Hungary. In 2011 he joined ThalesNano Inc., Budapest as Head of Chemistry. He has experience in the synthesis of amino acid derivatives and peptides, heterogeneous catalysis and reactions under continuous flow conditions. He is the co-author of 10 publications.

György Dormán

György Dormán obtained his PhD from the Technical University of Budapest in 1986. After graduation, he worked at Sanofi-Chinoin in Budapest. In 1988–1989 he spent a postdoctoral year in the UK and between 1992 and 1996, he was a Visiting Scientist at SUNY, Stony Brook, NY, USA. Between 1999 and 2008, he served ComGenex/AMRI as a Chief Scientific Officer. Since 2008, he has been responsible for the scientific innovation of ThalesNano. In 2011, he became honorary Professor at University of Szeged. He is an author of 85 scientific papers.

Richard V. Jones

Richard V. Jones was appointed as the CEO of ThalesNano Inc., Budapest in April 2012. He joined ThalesNano in 2004 where he started as Chief Research Chemist, helping to develop the chemistry on the R&D 100 Award winning H-Cube and other flow reactors. Prior to ThalesNano, Richard was at Biofocus Discovery, UK and worked on the synthesis of several kinase and G-protein-coupled-receptor (GPCR) inhibitor based compound libraries. Richard studied chemistry at the University of Bristol, UK where he graduated with honors in 1999.

Ferenc Darvas

Ferenc Darvas is one of the pioneers in combinatorial chemistry and founded the first European corporation, ComGenex, in 1992. In mid-2000, he turned to flow reaction technologies and as an inventor, initiated and co-developed H-Cube, the first bench top hydrogenator at ThalesNano, Inc. He holds PhD degrees in organic chemistry and computer science. He is a co-author of the first graduate text book on Flow Chemistry (De Gruyter). He is currently teaching as a guest professor at Florida International University, Miami, FL, USA.