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Flow chemistry: Imidazole-based ionic liquid syntheses in micro-scale

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ABSTRACT

The quarternization of an N-atom in the 1-methyl-imidazole with different alkylating agents was investigated to form so-called Ionic Liquids. (3-Chloropropyl)-trimethoxysilane, 1-chlorobutane, diethyl sulfate and methyl trifluoromethanesulfonate were used as alkylating agents. Reaction kinetics range from very slow to instantaneous and the reaction heat from endothermal to extremely exothermal respectively. The reactions were performed under flow conditions using different types of microstructured reactors as well as pre-structurized reactants in the micro-scale. Unusual heat management with integrated heat pipes allow safer performing of highly exothermal reactions with comparably high throughput.

1. Introduction

Microreactors are most commonly understood as flow-through systems containing internally three-dimensional structures ranging from micro- to millimeter size. Compared to conventional technology, significantly larger specific surface-to-volume ratios and, consequently superior heat exchange properties can be achieved [1]. Also, the micro-structurized internals allow pre-shaping the reactant fluid flow to ensure an increased mass transfer, a minimized backmixing and better temperature- and residence time control. But focusing on the microstructured internals of a reactor is only one aspect of chemical micro-processing. Also single droplets provide very small reaction volumes. The definition of 'microreactor' should also be extended to free falling or flowing droplets surrounded by another liquid or even gas.

To perform a chemical reaction close to the kinetic limit is the essential aim of chemical micro-processing. Such kind of free (non-encased) flow is already realized, e.g. as impinging jets [2,3], levitated droplets [4], spinning disk reactors [5,6], or spray. At least, chemical micro-processing is better defined as a part of "chemistry in flow", which allows to apply unusual process regimes, e.g. high temperature or pressure [7,8].

It is well-known, that the conventional syntheses of imidazole-based Ionic Liquids (IL) can cause problems due to the fast kinetics of the alkylation and the released heat within a very short time. The reaction is mostly performed by slowly adding an alkylating agent to the bulky amine (or even vice versa), to avoid hot-spot formation or thermal runaway. One way to control the temperature of highly exothermic reactions is to slow it down. This can be achieved by diluting the reactants with solvents and/or slowly adding of one of the reactants to the other. Long reaction times and the use of large volumes of solvents increase both production risks and also costs.

All microstructured reactor based IL syntheses are performed in a continuous flow. The reactants are pumped, preheated and mixed, and the reaction takes place by a subsequent flow-through a heated or cooled array of microstructured channels. A more simple system uses a single tube or capillary instead of a channel array immersed in a thermostat bath to control reaction temperature. Some alternative processing procedures, either completely solvent free or conducted with a solvent recirculation are exemplarily used for the quarternization of 1-methyl imidazole (**1**).

The reaction rates range from slow to instantaneous and the reaction enthalpy from very low to highly exothermal ((I) to (IV)):

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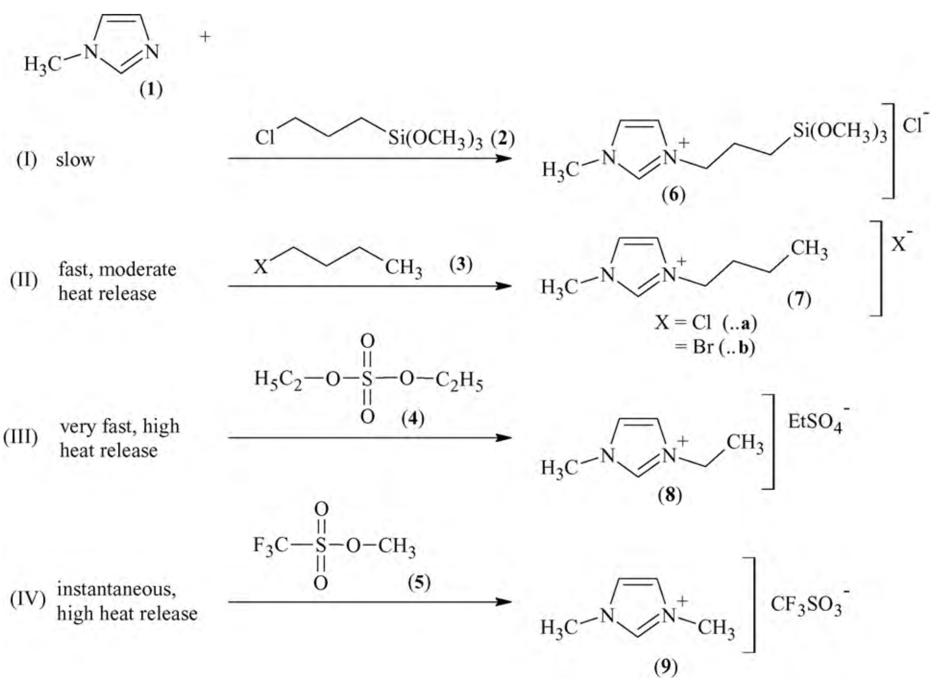

2. Experimental

1-Methylimidazole (**1**) (CAS 616-47-7; 99%), toluene (CAS 108-88-3; p.a.), (3-chloropropyl)trimethoxysilane (**2**) (CAS 2530-87-2; 98+%), 1-bromobutane (**3b**) (CAS 109-65-9; 99%), 1-chlorobutane (**3a**) (CAS 109-69-3; 99+%), and diethyl sulfate (**4**) (CAS 64-67-5; 99%) were purchased from ACROS ORGANICS, Geel, Belgium. Methyl trifluoromethanesulphonate (**5**) (CAS 333-27-7; 98%) was delivered from ABCR GmbH, Karlsruhe, Germany.

Continuous and nearly pulsation-free (volume flow deviation approx. 0.3% [9]) feed of the reactants were realized by using preparative HPLC pumps (Varian PrepStar^{TM}, SD-1, 50 mL-Ti pump heads).

Proton 300 MHz ^{1}H NMR spectra were measured either in deuterated chloroform or dimethyl sulfoxide (DMSO) on a Bruker^{TM} AC 300 spectrometer. IR measurements were made with FT-IR Thermo Nicolet 380 spectrometer equipped with an ATR-probe supplied from Infrared Fiber Sensors Co. Aachen, Germany.

NiCrNi thermocouples were used for temperature measurements combined with a Voltkraft^{TM} K204 (Conrad Electronic, Hirschau, Germany) data logger.

Sovents and excess of reactants were removed by a vacuum short path distillation device (KDL-1, UIC GmbH, Alzenau, Germany).

3. Slow reactions with negligible heat release; reaction (I)

N-3-(3-Trimethoxysilylpropyl)-1-methyl imidazolium chloride (**6**) is synthesized from 1-methyl imidazole (**1**) and (3-chloropropyl)-trimethoxysilane (**2**) in batch for 24 h under reflux of toluene [10–14]. The reaction rate at room temperature is negligible. (3-Chloropropyl)-trimethoxysilane (**2**) tends to decompose at higher temperatures, and to avoid hydrolysis moisture must be excluded.

To check the possibility to perform this reaction in a continuous way, a monolithic microstructured reactor set-up is used (see Fig. 1). Two home-made syringe pumps (IMM Institut fuer Mikrotechnik Mainz GmbH, Germany) feed the reactants (**1**) and (**2**) into an electrically heated stainless steel reactor (dotted lines in Fig. 2). The reactants are separately pre-heated up to reaction temperature in microchannels with a volume of 28 μL each before mixing by passing an integrated caterpillar micromixer. The mix-

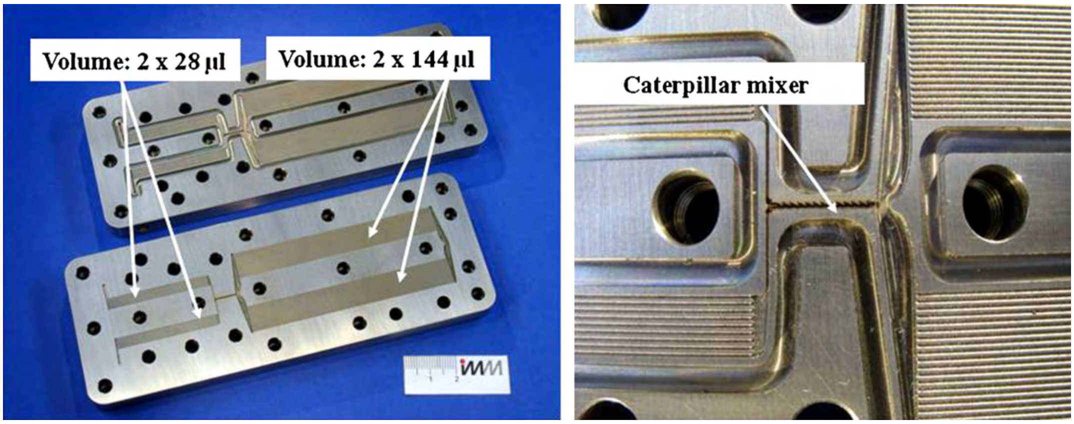

Fig. 1. Stainless steel microstructured reactor. Left: the reactant inlets are located on the left side; the caterpillar mixer (middle) and the channel array providing space for residence time adjustment (right). Right: magnification of the so-called caterpillar mixer made by laser-structurization.

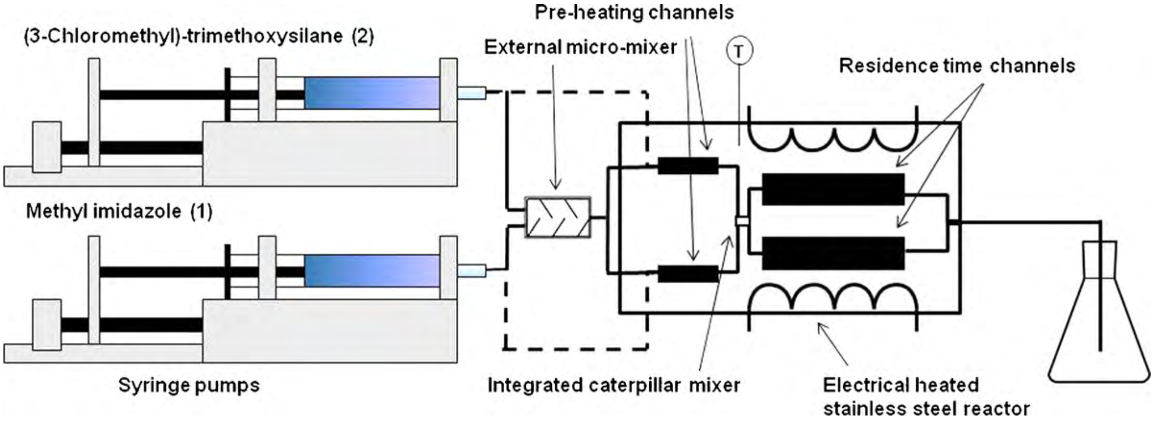

Fig. 2. Schematic reactor set-up for the synthesis of (**7**). Dotted lines indicate flow for pre-heating and internal mixing, and solid lines for external pre-mixing.

ture is subsequently spread into a channel array with an overall volume of 288 μL to provide enough volume for residence time adjustment. Processing in this 'classical' microreactor set-up was not successfully accomplished due to a slow thermal decomposition of (**2**) resulting in a subsequent blockage of the respective pre-heating channels.

The inert behavior of the reaction mixture allows to pre-mix the reactants in an additional static mixer outside of the microstructured reactor (solid lines in Fig. 2). Two different overall flow rates with equimolar ratio of (**1**) and (**2**) and three reaction temperatures were investigated. The remaining concentration of (**1**) was determined by FT-IR ATR as a measure for the conversion. Assuming that the reaction slows down to a negligible rate samples were immediately cooled down to room temperature after leaving the reactor. The highest conversion was achieved for a temperature of 200 °C and a flow rate of 27 $\mu\text{L}\,\text{min}^{-1}$. The product appears as very viscous pale yellow oil.

Assuming only traces of side products, the yield for the crude product corresponds with the conversion of (**1**) depending on the reaction temperature (see Table 1).

4. Fast reactions with moderate heat release; reaction (II)

1-Butyl-3-methylimidazolium chloride (**7a**) and the respective bromide (**7b**) are widely used at present in batch synthesis, i.e. by mixing an equimolar ratio of the reactants at low temperatures, resulting in long reaction times ranging from hours to days [16,17]. Due to the heat release of the reaction and the fast reaction kinetics, often solvents like THF, ethanol or toluene are used. A comprehensive summary is given in [16]. It is remarkable that the reaction mixture becomes bi-phasic: an ionic liquid (**7a/7b**) phase and an alkylhalide phase (**3a/b**). The solubility of (**3a/b**) in (**7a/7b**) is low and the concentration of (**1**) in both phases depends on its partition coefficient. The reaction volume can then be assumed as an inactive ionic liquid phase enriched with (**1**) and an active akylhalide phase where the reaction takes place [16]. However, for a 98% conversion at 66 °C a very long reaction time of about 70 h is required due to this bi-phasic behavior [16,17]. The activation energies for the synthesis of (**7b**) are approx. 82.2 $\text{kJ}\,\text{mol}^{-1}$ [16], and approx. 78.4 $\text{kJ}\,\text{mol}^{-1}$ for (**7a**) [18] respectively.

The moderate heat release allows a safe batch processing in the lab-scale. Taking the fast 2nd order kinetic into account [16], and the limited reaction temperatures caused by the boiling points of the alkylhalides (**7a**/**7b**), these reactions should be predestinated for performing in microstructured reactors under continuous flow conditions. Surprisingly, only a few publications were found for processing in microstructured reactors under continuous flow conditions [18,19].

Fundamental investigations for the reaction (II) using 1-bromobutane (**7b**) were made by Waterkamp et al. [19] in a flow-through microstructured reactor system consisting of a vortex-type micromixer with 450 μm channel width and serial connected tubes with a total volume of 306 mL. Colorless (**7b**) could be achieved by processing in a reactor with two different temperature levels ranging from 65 °C to 85 °C and an 8-fold excess of 1-bromobutane (**3b**). With residence times up to 48 min, 97% conversion (**1**) and a purity of 99% could be achieved [19,20].

Since 1-chlorobutane (**3a**) is less expensive than the respective bromo-compound (**3b**), an experimental procedure for the synthesis of (**7a**) is of common interest. From the mechanistic kinetic model, the kinetic of the reaction (II) should be slower for the reactant (**3a**) compared to (**3b**). To overcome the limitation of mass transfer of in the bi-phasic reaction and to shorten the reaction time from several hours for batch processing down to minutes an adapted microstructured reactor and a suitable protocol are required.

The used experimental set-up is schematically shown in Fig. 3. To ensure a long-time constant flow, the substances (**1**) and (**3a**) were pumped with preparative HPLC pumps into a modified OSBP-system (IMM Institut fuer Mikrotechnik Mainz GmbH). This OSBP-system consists of a thermostated bath where pre-heating tubes, micromixer and residence time tubes are immersed in a heat transfer liquid together. For pre-heating 1/16″ stainless steel tubes were used and connected to a commercial available HPLC mixer (Knauer Smartmix$^{\text{TM}}$). To avoid evaporation of 1-chlorobutane (**3a**) (Bp. 76–77 °C) at temperatures up to 150 °C the reaction must be continuously performed under pressure of about 6–7 bar.

Fast and efficient mixing on the micro-scale is an already solved problem. But the reaction of (**1**) and (**3a**) turns from a well-mixed solution to a bi-phasic system by subsequent coalescence.

Table 1
Conversion of (**1**) depending on flow rates and reactor temperatures in mass%. The concentration of (**1**) is determined by FT-IR.

Flow rate [μL/min]	Residence time [min]	C_{MIM} 170 °C [%]	C_{MIM} 180 °C [%]	C_{MIM} 200 °C [%]
53	6.5	89.7	92.3	97.6 (98.4)[a]
27	13.0	94.2	95.6	>99[b]

[a] The results are in accordance with external validation by HPLC measurement [15].
[b] Remaining (**1**) could not be detected.

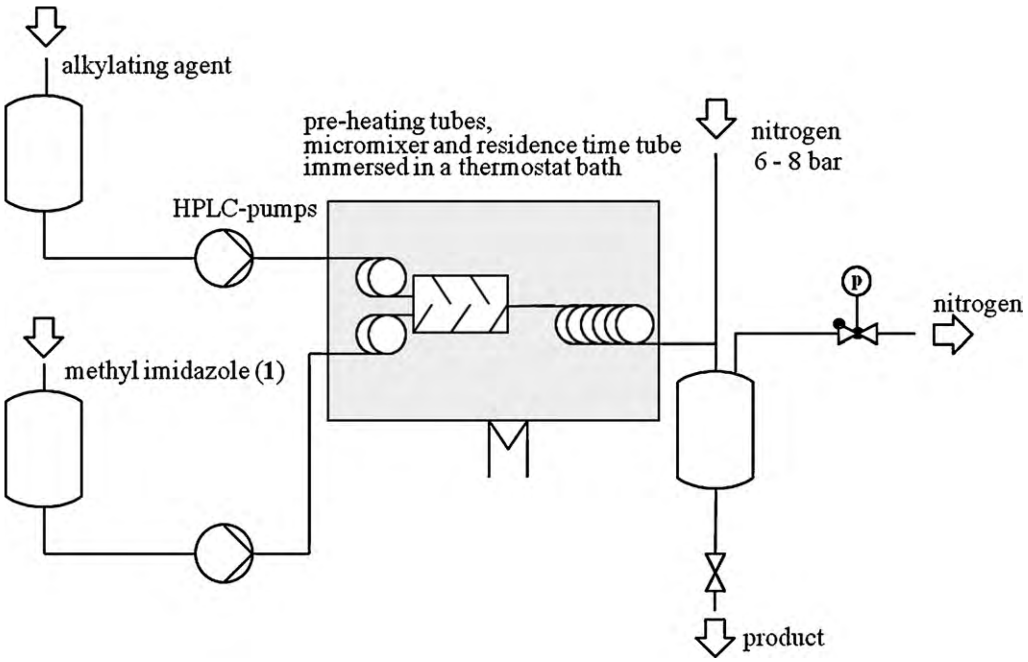

Fig. 3. Reactor flow scheme of a micro-mixer – tube reactor set-up. Mixer and tube are immersed in a thermostat bath. The tubes at the entrance of the micro-mixer are long enough to heat up the reactants prior entering the mixer. A back-pressure valve keeps the higher pressure inside the set-up constant.

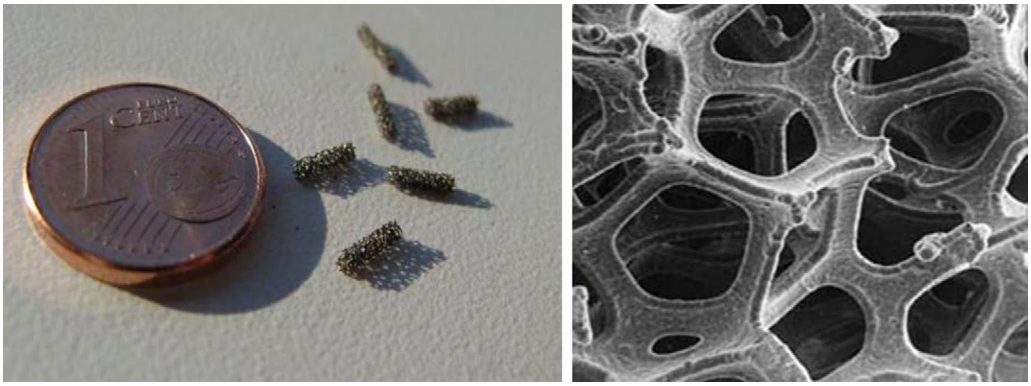

Fig. 4. Nickel foam (Recemat^{TM})packing material with a diameter of about 2.1 mm (left) and SEM image (right).

In microchannels both phases form active an inactive plugs which avoid a completion of the reaction in a short time. To provide residence time, two different 1/8″ stainless steel capillaries, 300 mm long (fittings not included), with an inner diameter of 2.1 mm were used. One is filled with nickel foam (Recemat^{TM}), with approx. 4% filling level, to avoid plug flow, i.e. to sustain the dispersion as long as it flows through the residence time tube (see Fig. 4). For comparison the reaction was performed in a second unfilled capillary.

The formed product was collected in a 50 mL Swagelok^{TM} cylinder equipped with a sample valve. The whole system was connected to a N_2 supply line and a pressure regulation valve kept the pressure between 6 and 7 bar. The reaction conditions and experimental results are given in Table 2.

Samples were taken from the sample valve, immediately cooled and diluted to stop further reaction. To monitor the reaction, the conversion of (**1**) was used and sufficiently determined by the ratio of the integrated ^{1}H NMR signals of (**1**) and (**3**).

As expected, higher reaction temperatures lead to a remarkable decrease of reaction time. Compared to 50 h batch processing at 66 °C [16] similar conversion of about 70–80% could be achieved within less than half an hour.

Table 2
Reaction condition and experimental results for the reaction (II). Highlighted in grey are the values for the unfilled tube.

Experiment	A	B	C	D	E
Temperature [°C]	145	145	150	150	150
Pressure [bar]	6	6	7	7	7
Molar ratio [(**3**):(**1**)]	1.2	1.92	2.0	1.0	0.5
Volume flow [ml min^{-1}]	0.82	1.01	1.38	1.42	1.35
Residence time tube volume [ml]	26	26	15	15	15
Residence time [min]	31.7	25.7	10.9	10.6	10.7
Conversion (**1**) [%]	87	70	77	82	49 (98 based on (**3**))

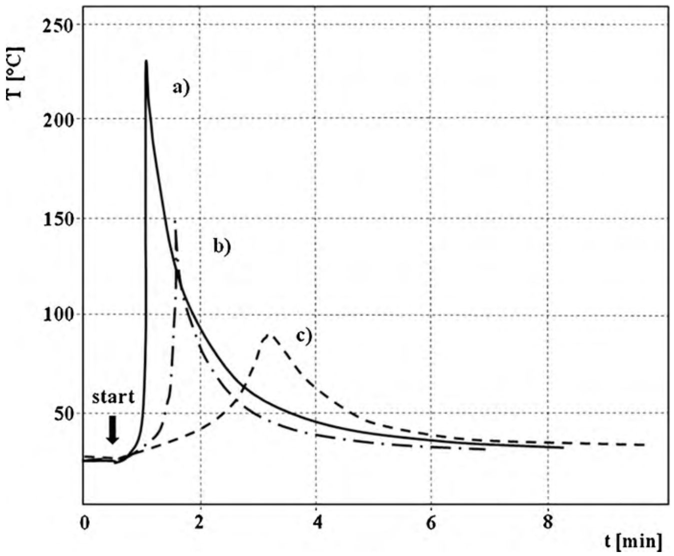

Fig. 5. Recorded time resolved reaction temperature changes for the reaction (III) in batch. (a) Non-diluted reaction mixture, (b) diluted with 5 mL toluene, (c) diluted with 10 mL toluene.

Some different results can be observed between the experiments (A/B – unfilled residence time tubes), and (C/D/E – filled with nickel foam). A comparison of (B) and (C) gives a 7% higher conversion for (C) for 42% of the reaction time. A similar result is found for the comparison of (A) and (D); the conversion for the experiment (D) is only 5% less compared to (A) if the reaction time is 33% decreased. Even taking deviations of temperature, pressure and volume flow into account, the results indicate that the conversion of dispersion for the flow inside the residence time tube influences the reaction by stabilizing the interfacial area between the active part containing ((**3a**) and less (**1**)) and the inactive part containing ((**7a**) and the majority of (**1**)). By flowing through the nickel foam a permanent mixing and therefore an exchange of reactants takes place.

The remaining excess of reactants can be removed by short path vacuum distillation and the remaining crude product (**7a**) crystallizes immediately to a white-brownish solid. The product can be further purified by recrystallization to get a colorless substance with a melting point of 56–58 °C. The melting point is lower than given in literature (~70 °C (http://www.sigmaaldrich.com/catalog)) due to incorporation of moisture from air.

5. Very fast reactions with high heat release; reaction (III)

The reaction of 1-methylimidazole (**1**) with diethyl sulfate (**4**) to 1-ethyl-3-methylimidazolium ethylsulfate (**8**) is very fast and highly exothermal [21] compared to the synthesis of (**7a/b**). The exothermal behavior of this single-phase reaction can be checked by a simple experiment: 4.0 mL (0.5 mol) of (**1**) is mixed as fast as possible with 6.6 mL (0.5 mol) (**4**) at room temperature. The time resolved reaction temperature changes were recorded with a digital thermometer (Voltcraft, K204, Conrad Electronics) with a sampling rate of one per second (Fig. 5).

After an initial period of about 5–10 s the reaction accelerates and a nearly adiabatic temperature rise up to 240 °C within 2–3 s ((solid line a) in Fig. 5) for the solvent-free mixture can be observed. A discolored brown viscous liquid of (**8**) is the result of this thermal runaway (Fig. 5).

Diluting with a solvent is an appropriate method to control the reaction rate [22]. By adding 5 mL toluene to the reaction mixture at ambient temperature also a steep temperature rise was observed. But the solvent could cool the reaction mixture by boiling under reflux and a peak temperature of about 150 °C could be observed. This temperature is higher than the boiling temperature of toluene indicating that the whole solvent is evaporated. Nevertheless a cooling effect of the cooled toluene reflow avoids temperatures above 200 °C. The color of the obtained product is now slightly yellow after removing the toluene by short path vacuum distillation (see Fig. 5).

By a further increase of the toluene partition an intrinsic cooling by evaporation of the solvent takes place and the temperature of the reaction mixture does not exceed the boiling point. With 10 mL toluene the reaction temperature could be kept by far below the boiling point of the solvent. By this procedure a colorless ionic liquid (**8**) could be obtained after removing the toluene.

An overall second order kinetics with an activation energy of 89 kJ mol^{-1} [23] and a reaction enthalpy of 130 kJ mol^{-1} was determined [24]. Modeling this reaction with given parameters [23], a 99.7% conversion of equimolar amount of reactants is achieved in 2.6 min at a temperature of 100 °C. Unfortunately, the reaction slows down dramatically by a decrease of reaction temperature, e.g. the rate constant decreases by a factor of 2.2 if the reaction temperature is decreased from 100 °C down to 90 °C [23].

A continuous flow synthesis in microstructured reactors is advantageous due to the excellent heat transfer properties of such devices [23–26]. The reactants are cooled, mixed and subsequently transferred into efficient micro-heat exchangers of plate architecture or to external thermostated tubes with small inner diameters to ensure efficient cooling or even heating for reaction completion. But even by efficient external cooling a radial temperature rise is predicted for a full developed laminar flow profile [25].

Therefore, a reactor system composed of a microstructured mixer closely connected to an efficient micro-heat exchanger with plate architecture allows intense cooling of the reaction mixture at the beginning of the reaction. This section is followed by a series of tubular reactors with step-wise increased diameters ranging from millimeter to centimeter scale. Both, the heat exchanger and the tubular reactor sections, are separately controlled by individual thermostats. The throughput of this reactor system can be possibly increased by a numbering up of the reactor set-up [27,28].

But some advantageous properties of processing in microstructured reactors are counterbalanced by design and engineering issues, e.g. the inaccuracy of the volume flow, or a cost intensive cooling and heating periphery. Assuming that the used mixer provides a very fast and perfect mixing by lamination of fluid sheets and/or secondary flow behavior, the flow inside a single micro-tube, channel or array of channels is non-turbulent, also indicated by the small Reynolds numbers. The proposed advantage of the laminar flow inside microchannels becomes quite contrary if remarkable volume-flow deviations take place. The absence of forced backmixing leads to undefined molar ratios of reactants, in particular if an equimolar feed is required. In the best case, an incomplete conversion can be determined. But also a safety problem can arise for highly exothermal reactions when reaction takes place partly in the withdrawal vessel.

To reduce risks and drawbacks an alternative set-up is shown in Fig. 6 combining the advantages of processing in batch and microstructured reactors. Well-known from batch processing the evaporation heat of a solvent with a comparable low boiling point (toluene) is used for intrinsic cooling of a reaction mixture. In our case, a structurized reaction mixture, e.g. droplets or spray formed by a nozzle with microstructured internals, acts as a multitude of very small batch systems. The droplets itself are microreactors, where the initial and critical part of the reaction takes place, intrinsically cooled by partial evaporation of the solvent.

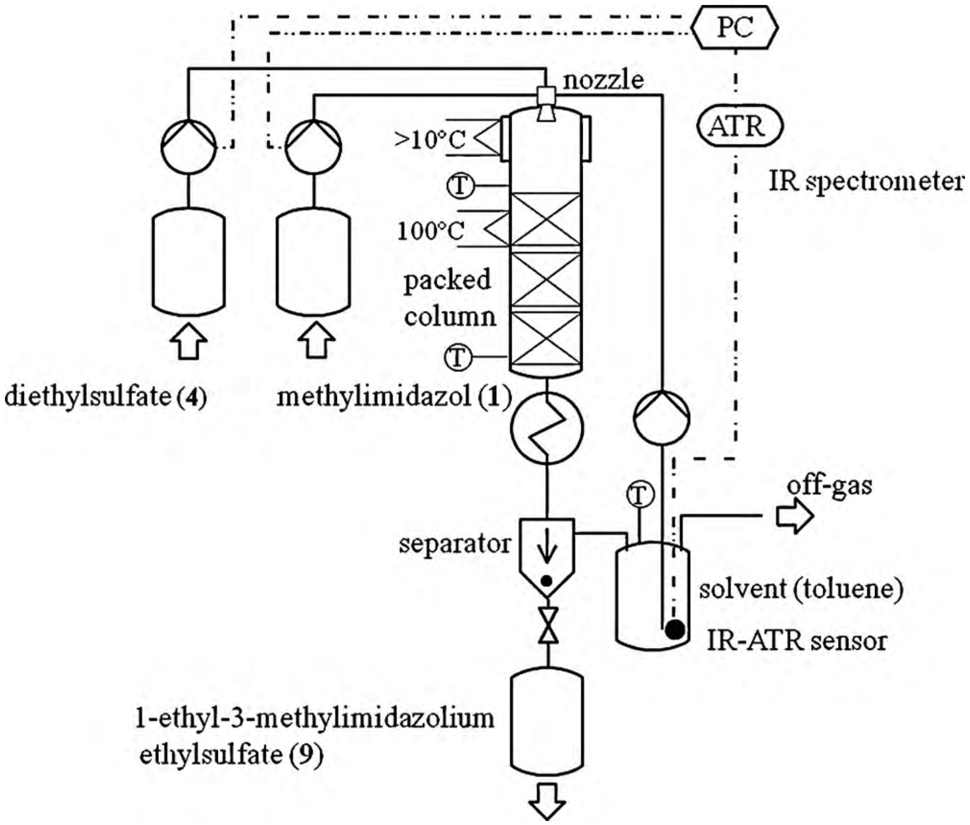

Fig. 6. Schematic of the continuous flow lab-scale plant used for reaction (III) (see also DE 10 2008 032 593.3; 11th August 2008).

The key parts of this system are:

- an external heated column partly filled with glass or ceramic rings as packing material,
- a nozzle for structuring the reaction mixture (Fig. 7),
- IR-ATR spectrometer to monitor the reaction.

Two preparative HPLC pumps feed the reactants (**1**) and (**4**) to the nozzle where they were mixed with toluene, which is pumped from the solvent vessel and subsequently dropped or sprayed in the empty space of the head of a heated column (inner diameter 8 mm; length 400 mm). Due to the fast heat transfer the reaction starts immediately while the droplets are free flying downwards

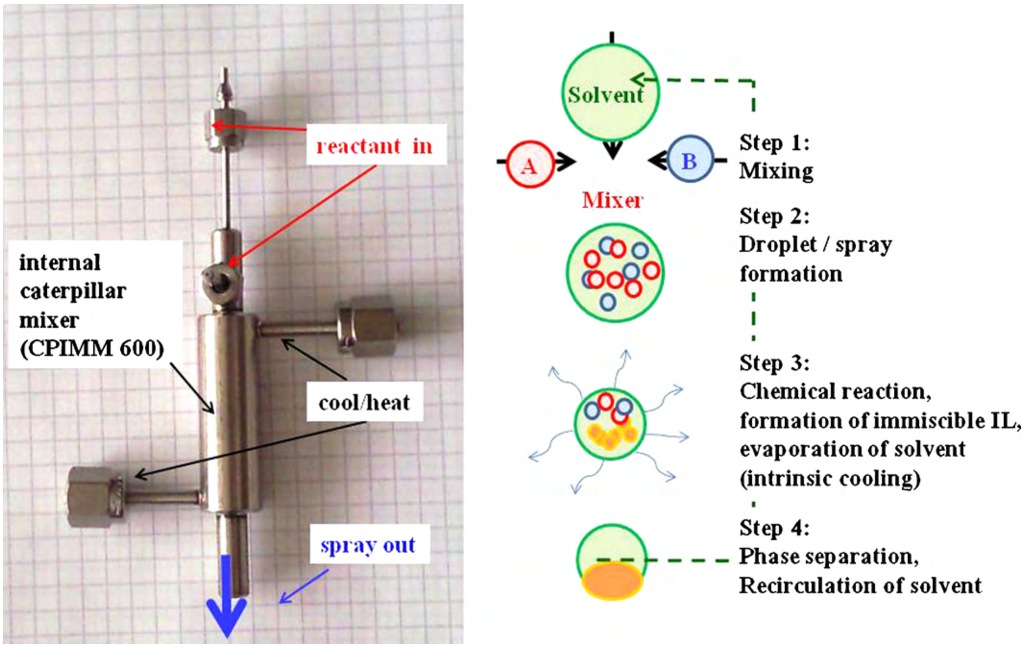

Fig. 7. Spray/droplet nozzle with integrated caterpillar mixer (left). Principle of performing the reaction in droplets by adding an additional solvent (right).

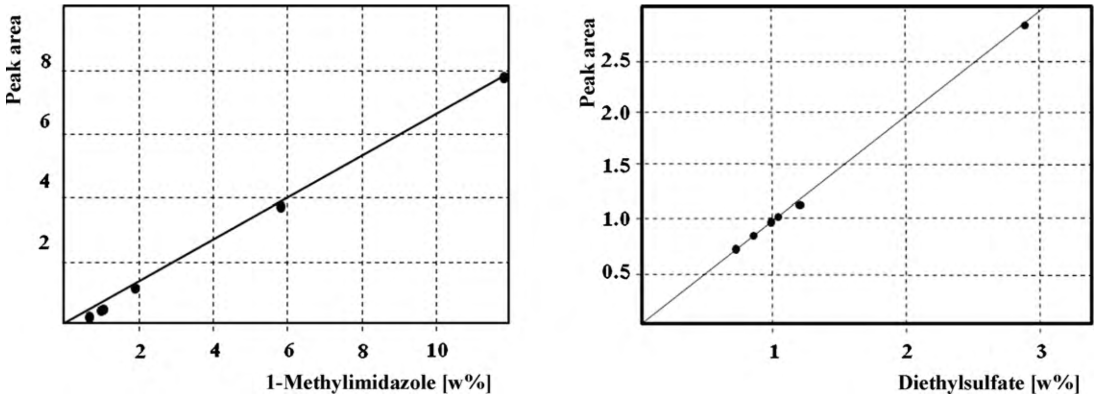

Fig. 8. Right: IR measurement calibration curve for different concentrations of (**6**) in toluene (peak area at 920 cm^{-1}). Left: IR measurement calibration curve for different concentrations of (**1**) in toluene (peak area at 1230 cm^{-1}).

indicated by a partial evaporation of toluene and a visible second phase formation. The evaporated solvent heats up the droplets or spray while it is cooled down below the boiling point. An additional cooling device on top of the column avoids an emission of evaporated solvent. During the passage through the heated packing of the column the temperature of the reaction mixture is kept constant at 100 °C. The residence time in the packed column is not well defined compared to microchannel or tube reactors and also backmixing takes place which does not influence the product (**8**) quality. After leaving the column, the reaction mixture is cooled down to ambient temperature. The formed two phases, the product (**8**) and toluene, are separated by a phase-separator.

The raw product (**8**) is collected and the toluene, which is possibly contaminated with traces of reactants, is transferred to the solvent vessel. Similar to the reaction (II) an excess of (**1**) is dissolved in (**8**), while an excess of (**4**) is transferred to the toluene phase. An unwanted and dangerous shift of the reaction to the separator or the solvent vessel can be monitored by an increase of temperature. Optional, an IR-ATR probe can be used to determine traces of unconverted reactants (compare Fig. 8).

This situation can appear by deviations of the volume flow or malfunction of pumps. The unconverted material is re-delivered to the nozzle and the control system can balance the molar ratios of (**1**) and (**4**) by changing the volume flow of the respective pump (dotted lines in Fig. 6). For the lab-scale investigation the IR-ATR measurement and pump control was manually done.

The overall flow rate was adjusted to ensure an average residence time of about 6.5 min ((**1**): 0.5 mL min^{-1}; (**4**): 0.826 mL min^{-1}; 6.3 mmol each; toluene: 1.0 mL min^{-1}). The yield was determined to 97.9% by HPLC for the raw product [15]. The raw product is a colorless viscous liquid which turns to pale yellow after purification by vacuum thin layer distillation at 110 °C and at 0.2 mbar.

A simple scale-up is possible by increasing the volume flow through the nozzle and an adaption of the column size to provide necessary residence time. By using the above mentioned set-up the volume flow of the reactants was increased by a factor of four ((**1**): 2.0 mL min^{-1}; (**4**): 3.3 mL min^{-1}; 25.2 mmol each) and the toluene volume flow was set to 5.0 mL min^{-1}, resulting in a yield of 93.1% (HPLC). Due to the too short residence time, remarkable amounts of (**4**) could be detected in the toluene phase as well as respective amounts of (**1**) in the product (**8**). It is obvious that also the size of the column must be increased to ensure the necessary residence time for completion of the reaction.

6. Instantaneous reactions with high heat release; reaction (IV)

The reaction (IV) is known as instantaneous even at room temperature, and due to the 2nd order kinetics the majority of the reaction heat is released immediately [23,29]. Discoloration due to overheating the reaction mixture can be observed as side reaction.

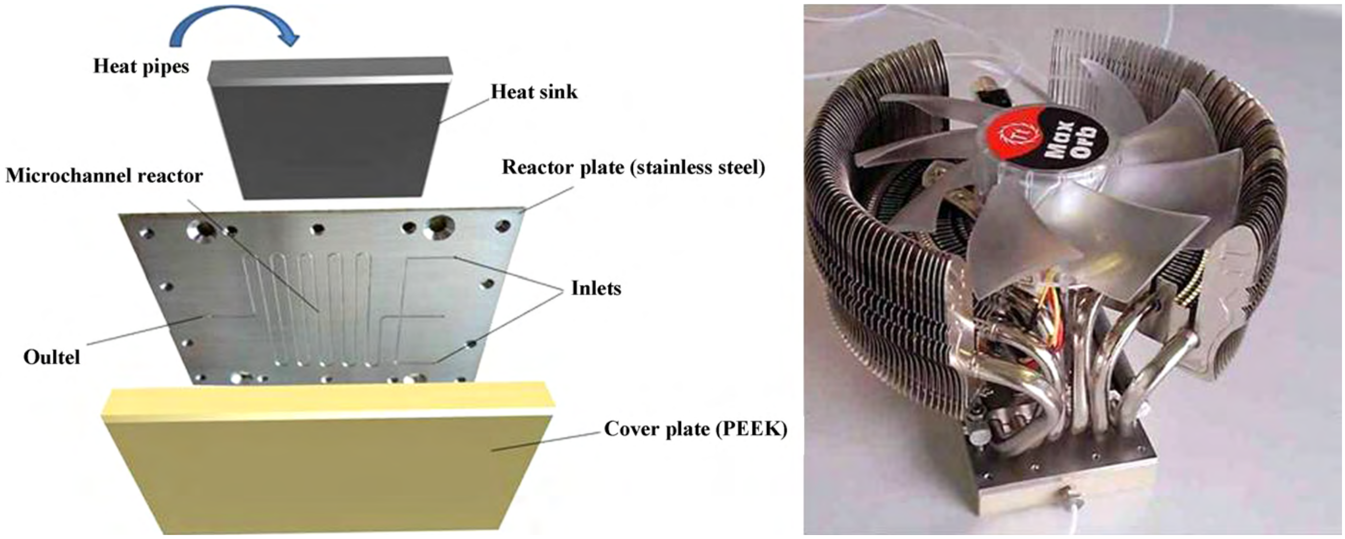

Fig. 9. Schematic of the microstructured reactor (left). Image of the mounted heat pipe on the reactor (right). The fan was not in use during the experiments.

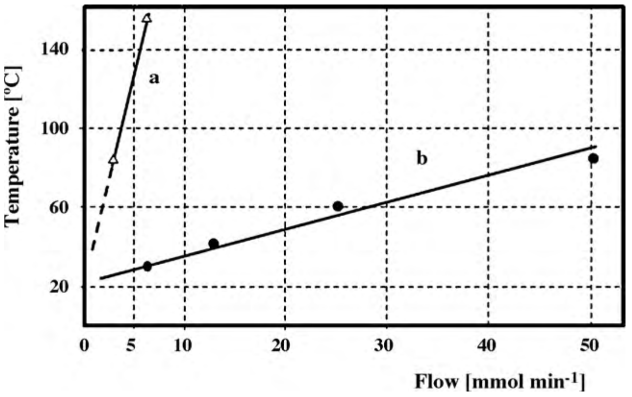

Fig. 10. Temperatures measured directly at the outlet of the microstructured reactor depending on the volume flow rate ((**1**):(**5**) in mL min^{-1}). (a) Without cooling: 0.25:0.356 and 0.5:0.7; (b) with mounted heat pipe: 0.5:0.7; 1.0:1.42; 2.0:2.85; 4.0:5.7.

In general, the reaction (IV) is performed in batch under extensive cooling and by very slowly adding of methyl trifluoromethanesulfonate (methyl triflate) (**5**) to (**1**) to form 1,3-dimethylimidazolium trifluoromethanesulfonate (**9**). Due to the high amount of instantaneously released heat, processing times of hours or even days were reported to keep the reaction under control. For comparison, the synthesis of 1-ethyl-3-methylimidazolium-triflate is prepared in batch [30–33] by use of additional solvent [34], by anion exchange [35], or processing in supercritical CO_2 [36].

The reaction heat removal is crucial for this reaction. It should be fast and directly at the point of release. Therefore, a combination of a heat pipe (Thermaltake^{TM} CL-P0369, Taiwan (http://www.tt-germany.com/)) and a microstructured reactor were used to perform this highly exothermal reaction under safe conditions, as was previously described in detail in this journal [37].

Fig. 9 shows a schematic of the used system. As a microstructured reactor a stainless steel plate (1.4435) equipped with a simple static micromixer, and single 300 × 500 μm^2 wide and 400 mm long channel (0.6 mL volume) is used. The reactor plate is covered by a PEEK plate which provides the connectors for inlets and outlet. The area above the microchannel is covered with the heat sink of the heat pipe.

The reaction (IV) was performed by an equimolar feed ratio of (**1**) and (**5**), i.e. with different volume flow rates (see Fig. 10). It can be derived from this figure, that performing reaction (IV) in a non-externally cooled reactor is impossible even at low flow rates. The temperature exeeds by far the boiling point of (**5**) and stable flow conditions cannot be achieved. Equipping the microstructured reactor with the heat pipe mentioned above, the volume flow rates could be increased up to 4.0:5.7 mL per minute without losing thermal control of the reaction. For further increase of flow rates the heat pipe has to work with an actively cooled heat pipe system using a fan with a controlled speed relying on the actual heat release.

Up to flowrates of 2.85:2.0 mL per minute the ^{1}H NMR spectra of the raw products indicate a complete conversion of (**1**) to (**9**). The product appears as a yellowish viscous liquid which crystallizes at room temperature in colorless needles with a melting point of 30–32 °C (32–34 °C [32]).

7. Conclusions

The investigated reactions follow in principle the same mechanism, a quarternization of an N-atom in the imidazole ring by an alkylating agent. For all reactions protocols for performing in batch are available. But dependent on the alkylating agent, some drawbacks can be detected:

(I): requires long reaction times at higher temperatures. The alkylating reactant is sensitive to moisture and decomposes also at high temperatures. It is important to point out that the residence time seems to be responsible for discoloration and product quality.
(II): is exothermal but with a comparably slow kinetic. Higher temperatures can reduce the processing time dramatically but due to the low boiling point of the alkylating agent pressure must be applied.
(III): is highly exothermic but an extensive cooling slows down the reaction. Dilution of the reaction mixture by a solvent is common, but the reaction becomes bi-phasic. Also an enrichment of non-reacted substances in the product has the potential for unwanted thermal overshooting in the withdrawal vessel und must be avoided for safety reasons under all circumstances.
(IV): is an instantaneous reaction with extremely fast and high reaction heat release. A batch processing seems to be only possible by an extensive dilution. Even this requires a long reaction time and, in addition, the processing takes place in a two-phase system similar to reaction (III).

Flow chemistry cannot provide a solution for all mentioned problems, but it gives possibilities to overcome major drawbacks of batch processing. In detail:

(I) Can be performed at higher temperatures up to 200 °C which reduces necessary residence time. The product quality increases due to less discoloration, the avoidance of decomposition of (**2**) by air and moisture. By processing in flow the thermal load of the formed product can be remarkably decreased, but the main advantages of microstructured reactors, i.e. the superior heat- and mass transfer properties do not have a remarkable impact on this reaction.
(II) Higher reaction temperatures and higher pressure allows to shorten residence time. In the case of a dispersed multi-phase flow coalescence can be avoided by performing the reaction in flow-through suitable packed tubes.
(III) Small droplets and intrinsic cooling by evaporation heat of the solvent reduces risks caused by thermal overshooting. Deviation of volume flows can be leveled by backmixing within the column packing. Also an automated monitoring of the complete system by IR measurement increases the safety aspects of this reaction.
(IV) The extremely fast reaction requires immediate and efficient cooling. Heat pipes provide a dynamic cooling, i.e. the cool rating can be adapted to the instant heat release.

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