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Ionic Liquids on Demand in Continuous Flow

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Abstract:

We report on the development of an alternative protocol for the facile, solvent-free synthesis of various novel imidazolium-based ionic liquids (ILs) that affords highly pure products without the necessity of subsequent purification steps. The continuous approach is based on the combination of HPLC pumps with a micromixer and a capillary residence tube. Our system provides a high degree of control over the alkylation reactions due to a high surface-to-volume ratio and superior heat and mass transport. Within the scope of our studies, we focused on ionic liquids containing differently substituted phenyl rings and characterized these compounds with respect to further use for direct application or subsequent reaction sequences. Scale-up can conveniently be achieved by operating several reactors with high continuous throughput in parallel.

Introduction

Ionic liquids are generally understood as fluids that solely consist of ions yet differ from conventional molten salts in a variety of properties.[1] While the latter mostly exhibit high melting points, viscosity, and corrosiveness, the former species are usually liquid below 100 °C and nonvolatile and exhibit an almost negligible vapor pressure. Numerous ionic liquids have been synthesized in the past;[2−5] however this class of compounds only attracted broad attention when hydrolysis-stable compounds with strongly expanded potential for practical applications were introduced in the early 1990s.[6] Within the past 15 years, a wide variety of ionic liquids has been prepared, characterized with respect to both physical and chemical properties, and increasingly used as an alternative to classic organic solvents, as they often show high dissolving power for otherwise sparingly soluble compounds.[1,7,8] The first step in the synthesis of ionic liquids usually involves formation of the cation by quarternization of an amine or phosphane. Variation of the alkylating agent leads to salts with different anions, typically halide ions. The demand for ionic liquids for a variety of synthetic and analytical purposes has been steadily growing in recent years. Due to their inherent nonvolatility, ionic liquids cannot be conveniently distilled prior to use as solvents or reactants. However, very high purity of these compounds is essential for their practical use, which often requires tedious subsequent purification steps, leading to high cost and limited potential for industrial application.

Microstructured reactors have recently attracted increasing interest due to significant benefits originating in very short diffusion pathways and large interfacial contact areas per unit volume (10 000−50 000 m^2/m^3)[9] that result in superior heat and mass transfer compared to conventional lab reactors. Consequently, higher yields and selectivities as well as improved product qualities have been achieved by transferring chemical reactions (especially those that are highly exothermic or endothermic) from classical batch reactors to microstructured devices.[9−14] Higher throughput of products is often conveniently accessible by running several microreactors in a parallel setup. Thus continuous reaction platforms based on micromixing of reactants offer intriguing potential for the preparation of ionic liquids. Waterkamp et al. described the preparation of 1-butyl-3-methylimidazolium bromide in a microstructured reactor and carried out an elegant process intensification study.[15] In another interesting study, Renken et al. reported on the high reactor performance of a microstructured device in the case of a continuously synthesized imidazolium ethylsulfate.[16] Here we present the development of a simple but highly versatile approach for the synthesis of a variety of high purity ionic liquids in a continuous flow reactor equipped with a micromixer, circumventing any additional purification steps.

Experimental Section

Materials. All chemicals were purchased from Acros Organics and used as received. Deuterated DMSO-d_6 was purchased from Deutero GmbH and used as received.

Instrumentation. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, on a Bruker AC and are referenced internally to residual proton signals of the deuterated solvent.

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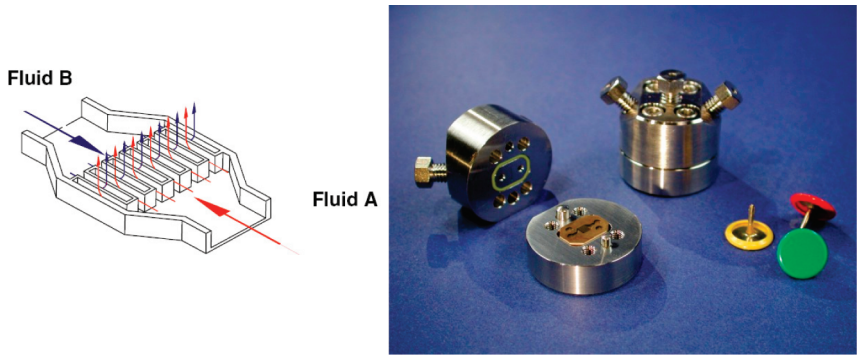


Figure 1. **Mixing principle and setup of the slit-interdigital mixer. The inner volume of the micromixer is 8 μL. Mixing takes place by very fast diffusion between the thin reactant layers formed by the parallel microchannel alignment.**

DSC curves were recorded on a Perkin-Elmer DSC 7 and a Perkin-Elmer Thermal Analysis Controller TAC 7/DX.

X-ray structure determination was collected on a Bruker AXS Smart CCD diffractometer with graphite monochromated Mo Kα radiation (λ = 0.710 69 Å).

Synthesis of Ionic Liquids in Batch. In a typical experiment, a 100 mL two-necked glass flask equipped with a mechanical stirrer was charged with 17.78 mL (20.8 g, 0.126 mol) of 1-bromohexane and 10 mL (10.35 g, 0.126 mol) of 1-methylimidazole and immediately immersed into an oil bath pretempered to the desired temperature. After stirring for 10 min, small samples were removed, cooled down to 0 °C, and dissolved in DMSO-d_6 for NMR characterization.

Synthesis of Ionic Liquids in Continuous Flow. All reactions were carried out in a continuous flow reaction setup provided by the Institut für Mikrotechnik Mainz (IMM). It consists of a tempered oil bath hosting the micromixing device (stainless steel interdigital SIMM-V2 mixer with an internal volume of 8 μL and channel widths of 45 μm) that is equipped with two reactant inlets and one outlet. In a typical experiment, alkyl bromide and imidazole were separately pumped into the mixing chamber. After mixing, the reaction mixture is directly guided into the respective capillary residence tube with a diameter of 500 μm (Volume = 10 or 30 mL). The rear end of the tubular delay tube leads to the reactor outlet. Flow rates are controlled via HPLC pumps (Knauer WellChrom K-501, inert 10 mL pump heads with ceramic inlays).

Results and Discussion

All syntheses presented in this paper were carried out in a reactor equipped with a stainless steel slit-interdigital mixer provided by the *Institut für Mikrotechnik Mainz* (IMM). The layout of the micromixer allows mixing processes to take place within several milliseconds due to the combination of the regular flow pattern created by multilamination with geometric focusing (Figure 1).

Residence times are very short as the inner volume of the mixer is extremely small (~8 μL). High pressure stability of the setup (up to 100 bar) permits continuous flow at viscosities of up to 10 000 mPas. To determine the applicability of the continuous reactor setup for the intended synthesis of ionic liquids, a compound well established in conventional batch synthesis (3-hexyl-1-methylimidazolium bromide **IL-1**) was targeted. It can be obtained from alkylation of 1-methylimdidazole with 1-bromohexane and exhibits very low viscosity at elevated temperatures. Hence, it was considered a suitable reaction product for an initial test run of the applied setup, which included two HPLC pumps separately introducing the liquid reactants to the preheated micromixer. There, the fluids are combined to form a homogeneous solution that is passed through a residence tube of variable length before the reaction product is recovered at the outlet of the device (Figure 2).

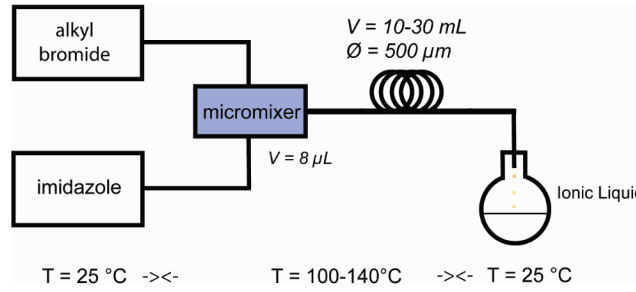


Figure 2. **Illustration of the experimental setup for the synthesis of ionic liquids in continuous flow.**

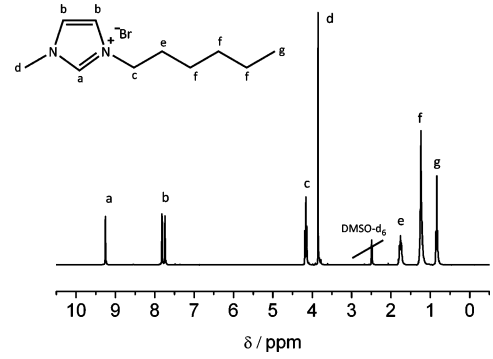
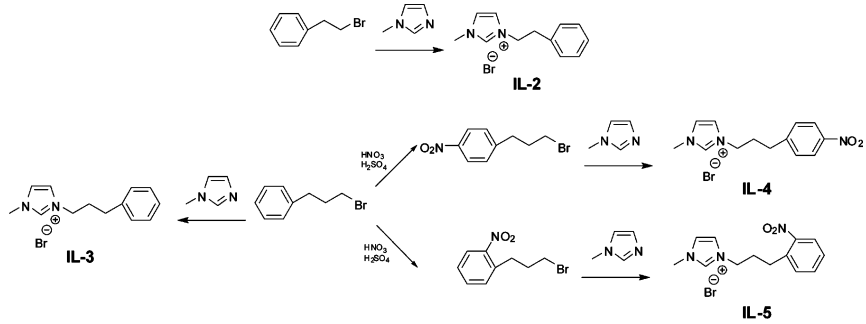


Figure 3. **^{1}H NMR spectrum of 3-hexyl-1-methylimidazolium bromide (IL-1).**

The reaction time can be varied by simply adjusting the flow rate and/or elongation or shortening of the residence tube. Compound **IL-1** was obtained as a slightly yellow liquid. The highly efficient mixing process permits working at a temperature of 140 °C without noticeable hotspot formation. These reaction conditions accounted for very short reaction times of 5−10 min, depending on the specific system and the flow rates. The ^{1}H NMR spectrum of **IL-1** is shown in Figure 3. It indicates a remarkably high quality of the crude ionic liquid recovered directly from the outlet of the microreactor setup without the necessity for further purification steps.

Scheme 1. **Synthesis of phenylalkyl imidazolium bromides**



In addition, analysis by HPLC showed less than 1% of impurities (mostly unreacted starting materials). In the conventional batch synthesis, the reaction proceeds explosively at temperatures higher than 100 °C and thus has to be carried out at milder conditions. Lower temperatures however involve the drawback of significantly slower kinetics. High conversions cannot be achieved within reaction times in a range comparable to the continuous flow approach. For instance, after 10 min at 60 °C, a conversion of only 5% was observed in the batch experiment, whereas the continuous flow setup permits working safely at high temperatures without thermal overrun and subsequent loss of control over the reaction. NMR spectra and conversion data for the samples obtained by the standard batch approach can be found in the Supporting Information. Encouraged by the promising initial results obtained by applying the continuous setup we directed our efforts towards the synthesis of entirely new ionic liquids that had not been reported previously. These were prepared by alkylation of alkylimidazoles with phenylalkyl bromides in the microstructured reactor. The novel compounds represented an interesting class of ILs for probing and establishing the versatility of our continuous flow process. Scheme 1 depicts the pathway to four different novel ionic liquids that we prepared in the microstructured reaction device described above.

All compounds were obtained as slightly yellow or orange liquids at high throughputs between 100 and 200 mL/h at analogous conditions to the preparation of **IL-1**. The respective ^{1}H NMR spectra of compounds **IL-2**−**IL-5**, measured directly after recovery from the continuous reaction device (see Figure 4 and Supporting Information), indicate complete reactant conversion as well as the absence of any undesired side products, which are frequently observed in conventional batch syntheses for ionic liquids.

It should be noted that compound **IL-2** differs from the ionic liquid **IL-3** by just one methylene group. However, **IL-2** does not remain liquid at room temperature but turns into a tough yellow solid after several hours that can be recrystallized from acetone to form colorless needles. The crystal structure of recrystallized **IL-2** was characterized by X-ray crystallography and is shown in Figure 5.

The additional methylene group incorporated into compound **IL-3** is sufficient to prevent formation of a highly ordered crystal lattice at room temperature. The ionic liquids possessing a nitro group on the phenyl subsituent remained liquid at room temperature for prolonged periods but started crystallizing after several weeks. Nitro groups introduce an additional polar moiety capable of intermolecular interaction that apparently promotes slow crystallization, a behaviour that is not observed for the nonsubsituted derivative **IL-3**. Thermal analysis (DSC) of the ionic liquids obtained from the microreactor showed generally low glass transition temperatures below 0 °C (Table 1) and a clear trend in the phenyl-substituted series **IL-2**−**IL-5**. The presence of an additional nitro group leads to a strong increase of the T_g. Compound **IL-1** exhibits the lowest transition temperature, attributed to the disorder associated with the flexible alkyl substituent. While **IL-3** is liquid at room temperature, all other species, exhibiting the typical characteristics of ionic liquids, should be employed at temperatures above 50 °C where they form viscous liquids.

Ionic liquids **IL-1**−**IL-5** represent typical examples for expedient, easily accessible ionic liquids that exhibit high dissolving power for polar organic compounds. Another interesting ionic liquid prepared within the scope of our initial investigations was a structure containing a vinyl instead of a methyl group (Scheme 2). This was achieved by reaction of vinyl imidazole with 1-bromohexane.

To prevent thermal polymerization of the vinyl function, this compound was prepared at a reduced temperature of 110 °C using a delay loop with an increased inner volume of 30 mL. Incorporation of a vinyl group into an ionic liquid offers great potential for structural diversification, as the respective com-

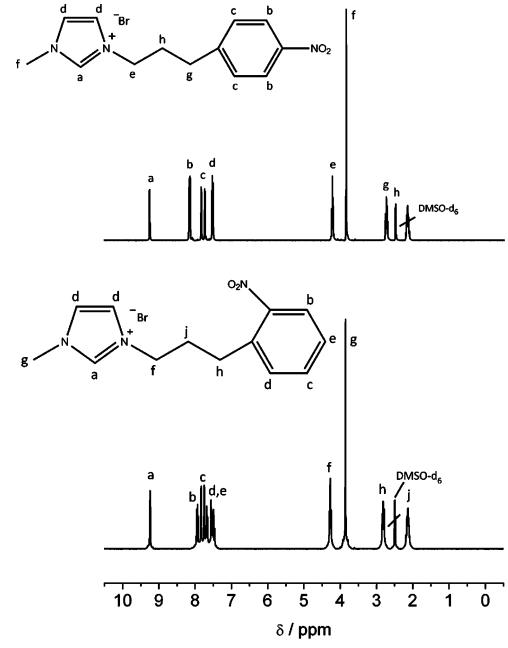


Figure 4. **^{1}H NMR spectra of novel nitrophenyl substituted ionic liquids IL-4 (top) and IL-5 (bottom).**

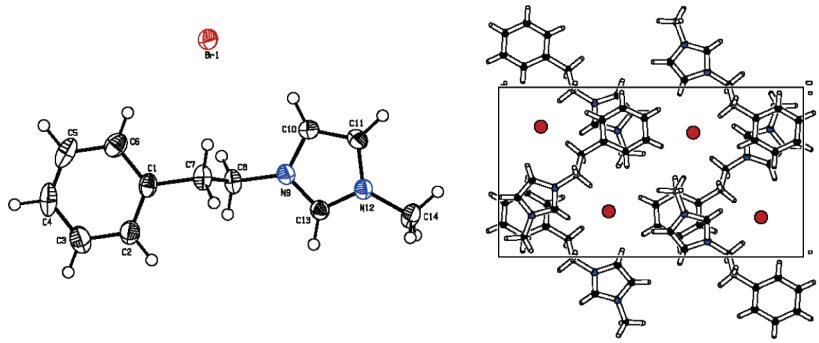
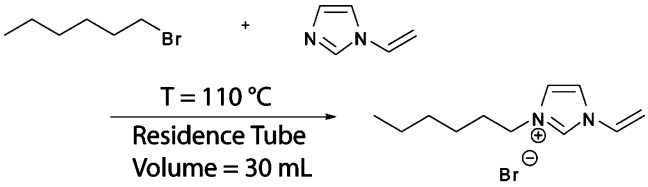


Figure 5. **Single crystal X-ray structure of 1-methyl-3-phenethyl-imidazolium bromide IL-2.**

Table 1. **Glass temperatures of ionic liquids synthesized in the microstructured reaction device**

ionic liquid	IL-1	IL-2	IL-3	IL-4	IL-5	IL-6
T_g/°C	−68.6	−47.3	−39.1	−8.9	−6.3	−65.6
crystallization at room temperature	no	yes	no	yes	yes	no

Scheme 2. **Synthesis of 3-hexyl-1-vinylimidazolium bromide**



pounds can be derivatized by subsequent reaction sequences such as olefin cross metathesis, radical polymerization, hydrosilylation, and other olefin addition reactions. It is important to point out the versatility of the process described. Reaction temperatures and residence times can be individually chosen without having to change the experimental setup. A crucial advantage of the described approach is the possibility to prepare large product amounts with little experimental effort. Scale-up can be achieved by simply operating several continuous flow reactors in parallel. While in a typical experiment using a single microstructured reactor, up to 200 mL of high purity ionic liquid can be prepared; the employment of additional similar devices and parallel operation provides convenient access to multikilogram per hour scales without having to resort to a more complex system.

Conclusion

In conclusion, we have developed a quick and facile continuous flow process for the synthesis of ionic liquids in a microstructured reactor. The remarkably versatile approach based on micromixing of the reactants permitted the first preparation of imidazolium-type ILs bearing additional aromatic units. A wide variety of further novel ionic liquids are conveniently accessible by this procedure under facile control of the reaction parameters. Our approach avoids time-consuming purification steps while meeting the strict demands for highly pure reaction products and simultaneously bearing the possibility to prepare large scales of the desired compounds "on demand". Further work will involve counterion variation as well as detailed kinetic studies. This will finally lead to the rapid synthesis of tailor-made products for a steadily growing demand for ionic liquids.

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Supporting Information Available

Additional NMR characterization data and illustrations of the experimental setup. This material is available free of charge via the Internet at http://pubs.acs.org.

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