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High Conversion, Solvent Free, Continuous Synthesis of Imidazolium Ionic Liquids In Spinning Tube-in-Tube Reactors

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Abstract:

A spinning tube-in-tube (STT) reactor has been used for the accelerated solvent-free synthesis of a number of 1-methylimidazole-based ionic liquids with excellent conversions (>99%) and high throughputs (tens of kg/day).

Introduction

Ionic liquids, salts with melting points near room temperature, are the subject of intense research as customizable replacements for the conventional organic solvents used in industry and academia. The market for ionic liquids is burgeoning; these compounds have been used as solvents for a wide variety of syntheses, from organic compounds to nanomaterials, and have even been suggested as a replacement for mercury in thermometers.[1]

Although the negligible vapor pressure, high polarity, and reusability of the ionic liquids make them attractive compounds, most large-scale uses are cost prohibitive. The typical synthesis, carried out in an inert solvent, is the reaction of 1-methylimidazole with an alkylating reagent. Incomplete conversion is common and requires solvent-intensive purification schemes, contrary to green chemistry principles. Batch synthesis typically requires long reaction times, reducing the space-time yield, and/or higher temperatures, often contaminating the product with thermal degradation products.[2] Large-scale, solvent-free synthesis using conventional glassware and heating is intriguing, but the product phase separates from the reactants due to inefficient mixing, reducing the yield.[3] Microwave and sonochemical processes have been demonstrated as alternative synthetic methods; however, the throughput is limited.[4] Microreactors have shown promise for bulk syntheses of selected compounds.[5] Cognizant of these synthetic methods, a rapid, high-conversion, high-purity process is needed to produce ionic liquids at price-points that encourage their use. The ideal process would use inexpensive equipment that is easy to troubleshoot and allow for quick change-over of product streams to maximize the customizable nature of ionic liquids.

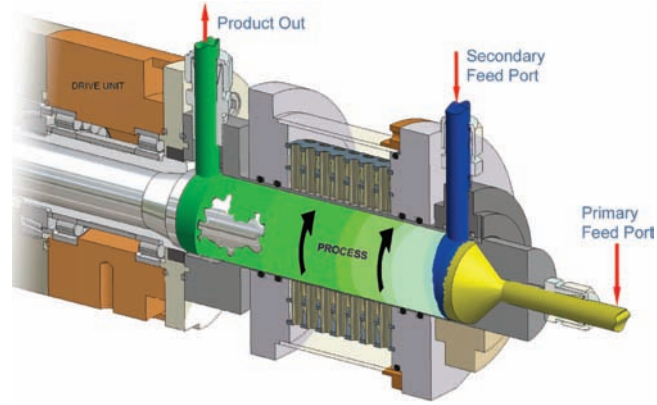

Figure 1. **Cross section of the STT reactor.**

Reaction rates in batch reactors are often mass-transfer limited. Mixing efficiency is increased by using a temperature-controlled, continuous-flow reactor called the Spinning Tube-in-Tube (STT) reactor manufactured by Kreido Biofuels.[6] The STT reactor (Figure 1) creates a thin film on the surface of a rotating cylinder (rotor) inside a stationary shell (stator). Introduced reactants flow into the gap between the rotor and the stator to produce a thin film of highly mixed fluid. The gap (0.25−0.44 mm) between the rotor and the stator and the high rotation rates (up to 12000 rpm, depending on model) facilitate creation of the thin film, which flows along the rotor surface to the exit port. Through judicious choice of reactants, flow rate, temperature, and rotation rate, desired chemical reactions occur within the thin film, and high-purity products flow continuously from the exit port.

The continuous-flow nature of the STT reactor also facilitates quick changeover of product streams simply by changing

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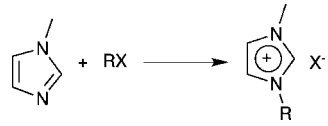
Table 1. **Temperature, production rates, and conversion of ionic liquids produced in the Innovator STT (27.1 mL working volume); the shear rate was 29 164 s^{-1} for each compound**



entry	alkylating reagent	equiv	*T* (°C)	production rate g/min	production rate kg/day	conversion (%)[a]
1	ethyl chloride	1.19	174	0.10[b]	1.4[b]	92
2	ethyl bromide	1.20	112	2.0	2.9	>99
3	ethyl iodide	1.06	83	11.5	16.6	>99
4	ethyl tosylate	1.25	102	5.6	8.1	>99
5	ethyl triflate	1.01	73	12.4	17.9	>99
6	isopropyl bromide	1.07	176	1.8[b]	2.6[b]	76
7	*tert*-butyl bromide[c]	1.06	106	2.0	2.9	>99
8	benzyl bromide	1.05	155	10.9	15.7	>99
9	butyl bromide	1.05	129	2.2	3.2	>99
10	hexyl bromide	1.05	131	12.7	18.3	>99
11	octyl bromide	1.05	142	5.8	8.4	>99
12	1,2-dibromobutane	0.48	158	3.5	5.0	>99

[a] Determined by ^{1}H NMR and based on 1-methylimidazole. [b] mL/min total reagent flow. [c] The only product obtained was 1-methylimidazole hydrogen bromide.

reactant feeds, reactor temperature, and/or rotor speed. With these advantages over conventional batch reactors, the STT reactor is well suited for the high-volume production of a variety of chemicals.

Results and Discussion

The reaction of an alkylating reagent with 1-methylimidazole in an Innovator 200 STT reactor proceeded expeditiously. Table 1 provides a summary of the ionic liquids produced, optimized reaction conditions, and production rates. ^{1}H NMR spectroscopy of the unpurified product was used to determine the conversion of the starting materials; the spectra for known compounds are consistent with reported spectral data.[7]

Optimization of reaction conditions for individual compounds was usually accomplished in less than 3 h. Ionic liquids synthesized were generally lightly colored upon exit from the reactor. Room temperature solids were white or very lightly colored after solidification; however, room temperature liquids were often more darkly colored. Reactivity followed the trends expected of an S_N2 reaction, i.e., higher temperatures and longer residence times are required with poorer leaving groups ($TfO^- < I^- < TsO^- < Br^- < Cl^-$) or for more highly hindered alkyl groups (1° < benzyl < 2°). Too short a residence time (the time spent in the reactor, which is equal to reactor volume divided by flow rate) resulted in higher residual concentrations of 1-methylimidazole in the product stream (i.e., lower reaction conversion).

Product flow rates obtained equate to potential yields of tens of kilograms per day, e.g., the reaction of ethyl iodide with 1-methylimidazole (entry 3) at a product flow rate of 5.0 g/min (equivalent to 16.5 kg/day) provides a product with an undetectable amount of 1-methylimidazole without any purification step. The use of ethyl chloride (entry 1) results in low conversions and in handling difficulties unless a cold (4 °C) mixture of ethyl chloride in 1-methylimidazole was fed into the reactor. All other alkylating reagents could be introduced as neat liquids. The reaction of 1-methylimidazole with ethyl chloride and with ethyl bromide required a slightly higher molar ratio of the ethyl halides compared to the higher-boiling alkylating reagents. Since the STT reactors used operate at atmospheric pressure, we were unable to determine if this was due to the low boiling points of the ethyl chloride and ethyl bromide or due to lower reaction rates.

The reaction between 1-methylimidazole and *tert*-butyl bromide (entry 7) resulted in the exclusive formation of 1-methylimidazole hydrobromide instead of 1-(*tert*-butyl)-3-methylimidazolium bromide due to the elimination of hydrogen bromide from the *tert*-butyl bromide.

The production of 1-ethyl-3-methylimidazolium tosylate (entry 4) and 1-ethyl-3-methylimidazolium triflate (entry 5) demonstrates that these compounds can be readily synthesized in high yields without resorting to anion exchange methods. Some difficulty in maintaining reagent stoichiometry was experienced during the course of the production of 1-ethyl-3-methylimidazolium tosylate as the melting point of ethyl tosylate (29−33 °C) required heating of the syringe pumps to 50 °C.

Scale-up in the STT reactor was anticipated to be straightforward since molecular velocity in the thin film should be proportional to shear rate (holding the mean free path of the molecules constant),[8] which is dependent on spin rate and gap size. Thus, to keep shear rate (and kinetic rate) comparable between two STT reactors with different working volumes, the gap size and spin rate must be set appropriately. To determine if this were true, the reaction of 1-methylimidazole with butyl bromide was run in two different reactors—the Innovator 200 STT reactor used above, and a smaller Magellan STT reactor (working volume is1.29 mL—21 times smaller). As can be seen in Figure 2, the percent conversion as a function of shear rate is remarkably similar for both reactors. It can also be seen in Figure 2 that, as the shear rate increases, the reaction rate levels off, implying that the kinetics of the reaction are governed by mixing at low shear rates.

Experimental Section

Reagents and NMR solvents ($CDCl_3$, C_6D_6) were purchased from Sigma-Aldrich and used as received; 1-methylimidazole purchased was 99% pure. NMR analyses were performed on a Bruker 300 MHz NMR spectrometer and were referenced to residual protiated solvent signals (^{1}H) or deuterated solvent signals (^{13}C). Conversions were determined by integration of the product and remaining 1-methylimidazole signals present in the collected product samples. NMR samples were prepared immediately following collection of a product sample and were analyzed within 10 min.

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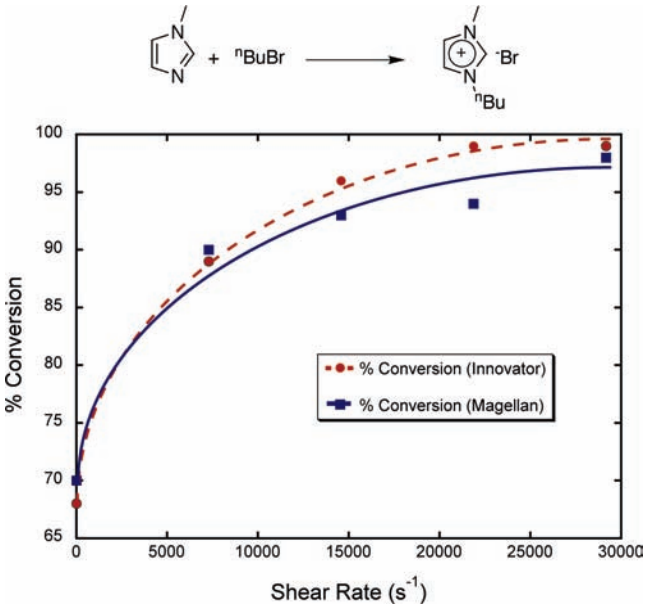

Figure 2. **Plot of percent conversion vs shear rate for the reaction of butyl bromide with 1-methylimidazole using two different STT reactors at the same temperature (135 °C) and residence time (14.0 min). The Innovator has a working volume of 27.1 mL, and the Magellan has a working volume of 1.29 mL.**

Reagents were fed into the STT reactor via ISCO 260D or 100D syringe pumps operating in constant flow mode, which were heated or cooled with Julabo chillers if needed to ensure that the reagents were liquid. The STT reactor temperature was controlled to within ±1 °C by a Mokon heating/cooling system (Innovator) or by a Julabo heater/chiller (Magellan) utilizing Paratherm NF heat transfer fluid. The design of the Innovator heat exchangers circulates the heat-transfer fluid over the outside surface of the stator and over the inside surface of the rotor, whereas only the outer stator surface temperature is controlled in the Magellan. Temperature variation versus rotor position has not been determined. Alteration of reagent flow rates, reactor temperature, or rotor speed was followed by allowing at least three full reactor (bed) volumes of reagents to flow through the STT reactor to allow the reaction to reach equilibrium conditions.

General Optimization Procedure for Syntheses. The reactor was set to a predetermined temperature, typically around 50 °C. The reagents were pumped into the reactor such that the flow rates created an equimolar ratio of the reagents in the reactor. Rotor rate was varied at these conditions until conversion was maximized. Reactor temperature was then varied to maximize conversion, and finally reagent flow was varied to maximize conversion (both molar ratio and total flow rate).

Synthesis of 1-Ethyl-3-methylimidazolium Bromide. 1-Methylimidazole was fed into the preheated STT reactor (112 °C) at a flow rate of 0.800 mL/min (1.17 g/min, 10.7 mmol/min), along with ethyl bromide at a flow rate of 0.900 mL/min (0.927 g/min, 11.3 mmol/min, 1.05 equiv). Six minutes after the reaction was started, the product stream was collected into a tared glass vial for a known period of time. The vial containing the sample was weighed, and ^{1}H and ^{13}C NMR spectra of the sample were recorded. The synthesis of the other ionic liquids was performed as described above after the optimum conditions were determined.

Conclusion

The STT reactor is capable of realizing large throughput rates (∼3−16 kg/day) of imidazole-based ionic liquids in a continuous fashion with minimal purification requirements (i.e., removal of excess alkylating reagent) and without the use of added reaction solvents. This continuous-flow process enables easy optimization of reaction conditions and lends itself to real-time, in-line analytical monitoring and rapid reactant switching. The reaction rate is dependent on shear rate, thereby enabling scale-up in larger reactors by setting the shear rate appropriately. The STT reactor exemplifies the concepts of "process intensification" with its adaptable, efficient, and novel design that addresses green chemistry concerns over solvent usage while simultaneously maximizing product throughput, conversion, and physical footprint.

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