Electronic Supplementary Material (ESI) for Reaction Chemistry & Engineering.

Supporting Information

Carbonate Based Ionic Liquid Synthesis (CBILS®): Development of Continuous Flow Method for Preparation of Ultra-Pure Ionic Liquids

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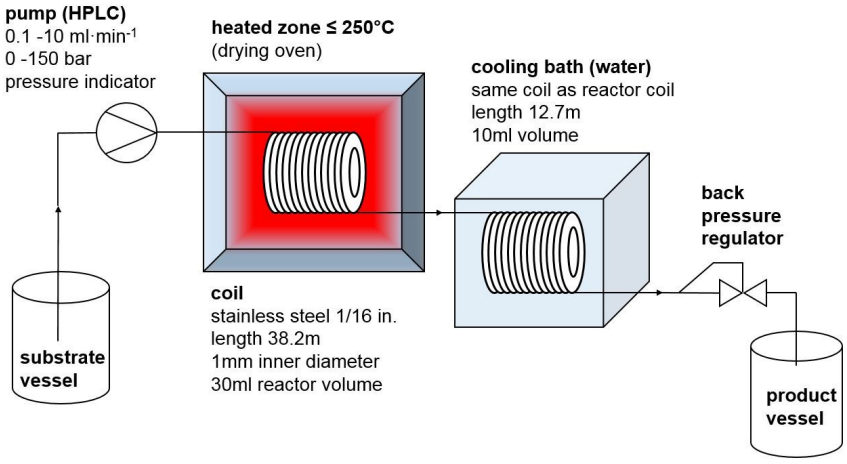
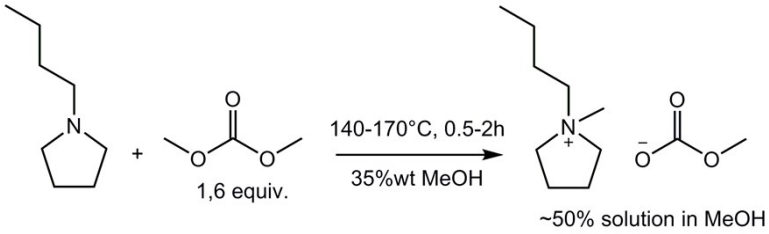
Setups for Batch and Continuous Flow Experiments

All chemicals were purchased from commercial sources with a purity >99%wt. 1-Butylpyrrolidine (BPyr) and 1-Ethylimidazole (EI) were freshly distilled under vacuum prior to use and dried over molecular sieve. Batch reactions were performed in 4 mL screw-capped vials equipped with a PTFE coated stir bar. The vessels were sealed with PTFE seals and PEEK screw caps to resist pressures up to 20 bar and temperatures up to 170°C. Heating occurred in a massive aluminum block, which was thermostated with an error of ± 1 K on a standard hotplate/stirrer. Continuous flow reactions were performed utilizing a simple setup consisting of a high-pressure HPLC pump with pressure indicator (flow rate 0.1-10 ml·min^{-1}), a 1/16 in. stainless steel coil with an inner diameter of 1mm and a length of 38.2m (30ml reactor volume) that was incorporated into a standard drying oven and thermostated with an accuracy of ± 1 K, and a cooling coil identical to the heating coil with a length of 12.7m (10ml cooling volume) that was submerged in a water reservoir. Since all substrate mixtures used were homogeneous, there was no need to use a microplate-mixer in our setup. The pressure inside the continuous flow setup was manually adjustable using a back pressure regulator (175 bar max. pressure).



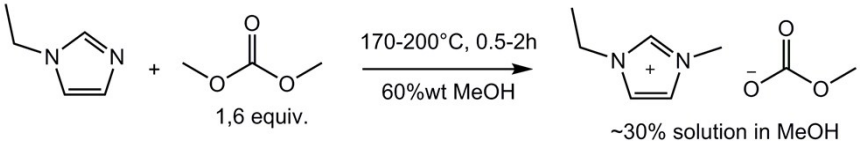
Scheme 1: Schematic of the continuous flow setup

Synthesis of 1-Butyl-1-methylpyrrolidinium methylcarbonate, BMPyr-MC (CAS 1223496-96-5)



For a standard batch reaction 10 mmol (1272 mg, 1562 µL) 1-Butylpyrrolidine (BPyr) were mixed with 16 mmol (1443 mg, 1347 µL, 1.6 equiv.) Dimethylcarbonate (DMC) and 1460 mg (1850 µL, 35 %wt) Methanol (MeOH). The 4 ml pressure vial was equipped with the PTFE coated stir bar and filled with the substrate mixture to a volume of 80%, leaving a gas phase of 20%. The aluminum block was preheated to the target temperature, the individual samples were thermostated for the desired time at the selected temperature and after cooling the reaction mixture was analyzed. For continuous flow experiments an analogue substrate mixture (~150 ml for each series of experiments) was prepared using 1.6 equiv. DMC and 35 %wt MeOH. The temperature of the heating oven was set to the desired temperature and the reaction time was controlled by the selected flow rate of the HPLC pump. For example, a flow rate of 1 ml·min^{-1} corresponded to a residence time of 30 min, since the volume of the stainless steel coil in the heated zone was 30 ml. The fractions were collected in septum-sealed vessels and analyzed.

Synthesis of 1-Ethyl-3-methylimidazolium methylcarbonate, EMIM-MC (CAS 251102-25-7)



Batch and continuous flow reactions were performed analogous to BMPyr-MC described above; 10 mmol (960 mg, 963 µL) 1-Ethylimidazole (EI), 16 mmol (1440 mg, 1347 µL) Dimethylcarbonate (DMC) and 3600 mg (4557 µL, 60 %wt) of MeOH were mixed. For continuous flow experiments ~150 ml of substrate mixture were prepared using 1.6 equiv. DMC and 60 %wt MeOH and the same procedure was utilized as described for the BMPyr-MC experiments. To investigate the influence of the applied pressure during the reaction the manually adjustable back pressure regulator was set to 20 bar, 50 bar, 100 bar and 150 bar, respectively.

Analytics

In general all analytical results are based on triple tests.

HPLC-UV-CAD analysis: Samples were prepared by dilution with HPLC eluent (60 %wt water containing 0.22 %wt trifluoroacetic acid, 40 %wt acetonitrile) to obtain a final concentration of 0.03 mg/ml. HPLC analysis was performed on a Dionex Ultimate 3000 system, combined with an Ultimate 3000 RS variable wavelength detector (UV) and a Corona Ultra RS charged aerosol detector (CAD). Measurements were carried out on a reversed-phase analytical column with embedded weak acidic ion-pairing groups (SIELC Primesep 200, 3.2 × 250 mm, particle

size 5 µm) using a mobile phase consisting of the eluent described above. Samples were analyzed applying isocratic elution, a flow rate of 0.5 mL/min, 25°C column temperature, injection volume 20 µL, 25 min per run. All chromatograms were integrated manually. Retention times and detection: 1-Ethylimidazole 10.3 min (UV 210nm), 1-Ethyl-3-methylimidazolium$^+$ cation 13.3 min (UV 210nm, CAD), 1-Butyl-1-methylpyrrolidinium$^+$ cation 20.6 min (CAD). Detection limit (undiluted sample) <0,1%wt. 1-Butylpyrrolidine is not detectable via HPLC-UV-CAD, therefore it was measured via titration (see below).

IC analysis: Samples were prepared by dilution with IC eluent (90 %wt water, 10 %wt acetonitrile) to stay within the linear range of the calibration curve (final sample concentration 10mg/ml for measurement of halides, 0.15mg/ml for acetate). IC analysis was conducted on a Dionex ICS-5000 system, combined with a Dionex ICS-3000 conductivity detector featuring a Thermo Scientific AMMS 300 micro membrane suppressor, regenerated with 50 mM sulfuric acid at flow rate of 0.4 mL/min. Measurements were carried out on an anion exchange column (Thermo Scientific Dionex IonPac AS20 RFIC, 4 × 250 mm, particle size 7.5 µm) applying the following elution program at a flow rate of 1 mL/min: 5 % 100 mM NaOH, 20 % acetonitrile from -7.5 min – 0 min (isocratic), 5 - 10 % 100 mM NaOH (gradient), 20 % acetonitrile from 0 min to 15 min, 10 - 60 % 100 mM NaOH (gradient), 20 % acetonitrile from 15 min to 35 min. Total run time: 42.5 min, 35 °C column temperature. All chromatograms were integrated manually. Retention times: Acetate 6.5 min, Fluoride 5.9 min, Chloride 9.0 min, Bromide 12.0 min, Iodide 13.8 min. Detection limit (undiluted sample) <5ppm.

Titration:

Total assay: Samples were prepared by diluting 0.5 – 0.7 g EMIM-MC or BMPyr-MC methanolic solution with approximately 50 mL deionized water and titrated against 1N HCl on a Metrohm Basic Titrino 794 equipped with a Metrohm Ecotrode Plus pH electrode. Titration curves were recorded and processed with tiamo 1.3 software. Total assay delivers the sum of methylcarbonate anion and unreacted starting material 1-ethylimidazole / 1-butylpyrrolidine. Detection limit <0,1%wt.

Free base (1-ethylimidazole, 1-butylpyrrolidine): During titration of the methylcarbonate with HCl the methylcarbonate anion is hydrolyzed to CO_2 and methanol; any free base is protonated. The samples were boiled for 15 minutes to liberate residual CO_2 and after cooling down back-titrated against 1N NaOH with a Metrohm 835 Titrando equipped with a Metrohm Ecotrode Plus pH electrode. Titration curves were recorded and processed with tiamo 1.3 software. Titration curves show two equivalent points, the first one (Ep.1) belonging to neutralization of excess 1N HCl, the second one belonging to deprotonation of protonated free base (Ep. 2). Free base is calculated via consumed volume of 1N NaOH between Ep1 and Ep2 ($V_{free\ base} = V_{Ep2}-V_{Ep1}$). Detection limit <0,1%wt. Measured results were in good accordance to corresponding HPLC-values. In case of 1-butylpyrrolidine, which is not detectable via HPLC, only titration values were used in Table 1 of the publication.

Methylcarbonate: Subtraction of *free base* from *total assay*. Detection limit <0,1%wt. Measured results for the methylcarbonate anion were in good accordance to corresponding HPLC-values of the 1-Ethyl-3-methylimidazolium$^+$ and 1-Butyl-1-methylpyrrolidinium$^+$ cation.

1-Ethyl-3-methylimidazolium acetate (EMIM-OAc) synthesis

To combine the optimized EMIM-MC synthesis with the second step of the CBILS® route - on the example of the ionic liquid 1-Ethyl-3-methylimidazolium acetate - EMIM-MC was mixed with acetic acid. First, EMIM-MC was synthesized under continuous flow conditions at 200°C using a residence time of 2 h and a pressure of 100 bar in the system. The resulting mixture of EMIM-MC in MeOH was analyzed by HPLC-UV-CAD, revealing that only 0.16 %wt of free base (1-Ethylimidazole) were left in the mixture and the content of EMIM-MC in MeOH was

32.83 %. The EMIM MC solution was mixed with exactly 1.000 equiv. of acetic acid (99.96 %) and stirred for 4 hours, the acetic acid was added portion-wise since a significant amount of carbon dioxide was generated especially during the initial phase of the reaction. After the transformation was finished, the excess of MeOH was removed under reduced pressure in a rotary evaporator (10 mbar, 40°C). Furthermore, a wiped thin film evaporator was used under molecular distillation conditions ($1 \cdot 10^{-2}$ mbar, 120 °C), to get rid of any remaining solvent molecules and other volatile compounds. The purity of the EMIM-OAc was checked by analytical methods described above. The water content was measured using a Metrohm Karl Fisher 652 Coulometer. The color was determined according to European Pharmacopoeia Method 2.2.2, *Degree of Coloration of Liquids*.

Calculation Conversion Rate and Space-Time Yield

The conversion rate (%) was calculated as the molar ratio of the product divided by the sum of methylcarbonate and residual free base multiplied by 100, which is applicable due to the absence of any other byproducts. In case of EMIM-MC, both values were obtained from HPLC measurements. With BMPyr-MC, the amount of product was identified via HPLC, while the content of the free base BPyr was determined by titration.

The space-time yield was calculated as described in the following: initially the productivity [$kg \cdot h^{-1}$] was calculated as the ratio of the amount of the processed reaction mixture divided by the reaction time (including heating and cooling period). The productivity values were then divided by the reactor volume (L) of the utilized reactor to obtain the capability of the individual reactors regarding the processability of reaction mixture [kg reaction mixture$\cdot L^{-1} \cdot h^{-1}$]. These calculated values were finally multiplied with the measured product content (EMIM MC and BMPyr MC) in the corresponding reaction mixtures to obtain the space-time yield [kg product$\cdot L^{-1} \cdot h^{-1}$].

The CBILS® Process (overview):

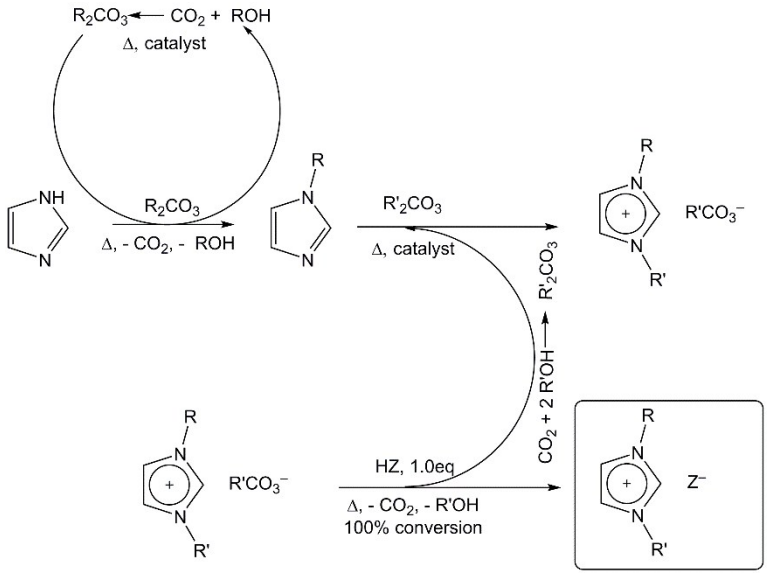


Figure 1: General concept of the Carbonate Based Ionic Liquid Synthesis (CBILS®) route on the example of 1,3-Dialkylimidazolium ionic liquids; for details see R. S. Kalb, E. N. Stepurko, V. N. Emel'yanenko and S. P. Verevkin, *Phys. Chem. Chem. Phys.,* 2016, **18**, 31904-31913