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Efficient Synthesis of 1,3-Dialkylimidazolium-Based Ionic Liquids: The Modified Continuous Radziszewski Reaction in a Microreactor Setup

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Abstract:

By making use of a modified Radziszewski reaction, it is demonstrated that water-soluble 1,3-dialkylimidazolium-based ionic liquids can be produced in good yields (70−90%) and purities (>95%) starting from readily available, cost-effective monoalkylamines, glyoxal, formaldehyde, and mineral or organic acids. The homosubstituted 1,3-dialkylimidazolium salts feature high thermal stabilities similar to those of their heterosubstituted counterparts, and relatively low viscosities, thus fulfilling the requirements for solvent application. The effect of various parameters has been studied with the goal of improving yields for both the batchwise and continuous synthesis (making use of a microreactor setup), allowing for the production of a wide variety of ionic liquids and the introduction of functionalities. The applicability of these ionic liquids is demonstrated on the example of cellulose dissolution and the dehydration of fructose to 5-hydroxymethylfurfural.

Introduction

The synthesis of ionic liquids is most often carried out by alkylation of an organic base, e.g., 1-methylimidazole, with an alkylating agent. Unless this alkylating agent contains the desired ionic liquid anion (as it may be the case when using, for example, dialkyl sulfate, dialkyl carbonate, or alkyl trifluoromethylsulfonate, to yield the respective ethylsulfate, alkylcarbonate or trifluoromethylsulfonate), a haloalkane is used for alkylation, and a subsequent ion-exchange step is required to obtain the final ionic liquid (Scheme 1).[1,2]

A review of the literature[3] reveals that very little chemical engineering data is available on the synthesis of 1,3-dialkylimidazolium-based ionic liquids for large-scale production, with the exception of the work of Große Böwing et al. who investigated the production of 1-butyl-3-methylimidazolium chloride ([C_4MIM]Cl) from 1-methylimidazole and butylchloride in a continuous tube reactor.[4] A continuously operated tank reactor for similar alkylations has been proposed.[5] Interestingly, in the past years, a series of reports has appeared that demonstrate the applicability of microreaction technology for the first step of the conventional ionic liquid synthesis (Scheme 1).[6−11]

For example, the solvent-free continuous synthesis of 1,3-dialkylimidazolium-based ionic liquids was performed in a spinning tube-in-tube reactor,[6] which is known to increase the mixing efficiency by quickly rotating (12000 rpm) a cylinder inside a stationary shell. Heat transfer is achieved by thermostatting both the rotor and stator. Using equimolar amounts of 1-methylimidazole and various alkylating agents at temperatures between 70 and 180 °C (depending on the reactivity of the alkylating agent), up to 18.7 kg d^{-1} of ionic liquid can be produced at a conversion of 99%. Waterkamp et al. reported the solvent-free synthesis of [C_4MIM]Br at 85 °C in a microreactor system equipped with a vortex mixer. The excellent heat removal during the exothermic reaction allows for running the reaction isothermally at a much higher temperature than the maximum temperature (48 °C) of the batch setup. Under optimized conditions (85 °C, flow rate: 8 mL min^{-1}, molar ratio of butyl bromide:1-methylimidazole, 1:1), a 24-fold increase in space-time yield is obtained (1.27 kg L^{-1} h^{-1} vs 0.05 kg L^{-1} h^{-1} in a 4-L reactor), with the potential for further optimization by applying even higher temperatures. This translates into a production rate of 9.3 kg [C_4MIM]Br per day in >99% purity.[7,8]

Renken et al. described the use of a microstructured reactor for the production of 1-ethyl-3-methylimidazolium ethylsulfate ([C_2MIM][$EtSO_4$]), with a reactor performance of 15.84 kg L^{-1} h^{-1},[9] which can be followed by ATR-IR online spectroscopy.[10] In a similar fashion, the synthesis of [C_2MIM][$EtSO_4$] in a tubular reactor has been mentioned.[11]

A summary of the technical setups, optimum temperatures, and space-time yields (STY) and capacities of these reports is given in Table 1. Although continuous alkylation methods have thus been described, this most often employed synthetic strategy requires the following:

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Scheme 1. **Conventional method of ionic liquid preparation**

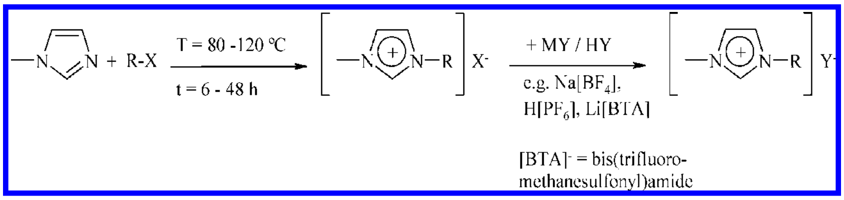

Table 1. **Reported technical setups, process conditions, and performance of continuous ionic liquid synthesis strategies**

ionic liquid	technical setup	T [°C]	STY [kg L^{-1} h^{-1}]	capacity [kg d^{-1}]	ref
$[C_4MIM]Cl$	continuous tube reactor (6 m × 3 mm)	75	0.02	10.0	4
$[C_6\ MIM]Cl$	continuous batch reactor (700 mL)	130	0.17	2.9	5
various, e.g. $[C_4MIM]Br$	spinning tube-in-tube microreactor (gap: 0.25 − 0.44 mm)	112	4.90	3.2	6
$[C_4MIM]Br$	vortex micromixer (450 μm channel width)	85	1.27	9.3	7, 8
$[C_2MIM][EtSO_4]$	caterpillar micromixer (600 μm × 600 μm)	95	15.84	11.9	9

(i) high temperatures and reaction times for the alkylation, especially if a chloroalkane is used, leading to high energy consumption;[12,13]

(ii) two extraction steps to remove unreacted starting materials: the first after the alkylation, and the second after the ion exchange, leading to a high solvent consumption.

Besides the impact on the environment resulting from energy and solvent consumption,[12,13] this synthesis makes use of the rather costly precursor 1-methylimidazole, leading to prohibitively high ionic liquid prices for technical solvent applications.

Furthermore, it can be noted that the synthetic strategy depicted in Scheme 1 does not allow for the technical-scale manufacture of halide-free, water-soluble ionic liquids, since these ionic liquids cannot be easily purified by aqueous extraction.

More than 100 years ago, Radziszewski described the synthesis of lophine from the condensation of benzil, benzaldehyde, and ammonia. Lophine is nowadays known as 2,4,5-triphenyl-1*H*-imidazole.[14] This reaction was revived and modified by organometallic chemists, in particular in the group of Arduengo III, who sought after a method to produce 1,3-disubstituted imidazolium salts as carbene precursors (Scheme 2).[15−17]

Although the method, which allows for the introduction of alkyl-, aryl-, and other functionalized moieties, was patented, a systematic optimization to use this strategy for the technical production of structurally related ionic liquids has not been published to the best of our knowledge. The obvious difference between Arduengo's carbene precursors and conventionally used ionic liquids is the substitution pattern on the nitrogen atoms. While the carbene precursors are homosubstituted (i.e., bearing the same substituent on both nitrogen atoms), ionic liquids are in general heterosubstituted (1-alkyl-3-methylimidazolium derivatives, where alkyl > CH_3). The influence of this heterosubstitution has been the focus of many studies, resulting in the general understanding that asymmetric cations lead to salts of lower melting points and viscosities.[18−20] On the one hand, it was shown[21] that heterosubstituted 1,3-dialkylimidazolium salts cannot be selectively obtained using two different amines (e.g. methylamine and *n*-butylamine) in the modified Radziszewski reaction, but a statistic mixture results. On the other hand, relatively little is known to date about the physicochemical properties[22−26] and the potential application of homosubstituted 1,3-dialkylimidazolium salts.

Hence, it is the goal of this contribution to demonstrate that

(i) water-soluble 1,3-dialkylimidazolium-based salts can be produced in good yields and purities starting from readily available starting materials;

(ii) the properties of the 1,3-dialkylimidazolium salts indeed allow for their classification as ionic liquids (i.e. melting points below 100 °C);

(iii) the novel ionic liquids can be used in a variety of applications (cellulose dissolution, dehydration of fructose to 5-hydroxymethylfurfural); and

(iv) the technical production is feasible in continuous mode using a microreaction setup.

Experimental Section

Chemicals. All chemicals (from Sigma-Aldrich: methylamine (40% aq sol.), *n*-propylamine (>99%), *n*-butylamine (>99.9%), nitric acid (70% aq sol.), acetic acid (>99.7%), tetrafluoroboronic acid (50% aq sol.), formic acid (98%), glyoxal (40% aq sol.), formaldehyde (36% aq sol., stabilized with 10% methanol), Avicel (PH-101), fructose (>99%); sulfuric acid (64% aq sol.) and HCl (Merck, 32% and 37% aq sol.))

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Scheme 2. **Modified Radziszewski reaction**

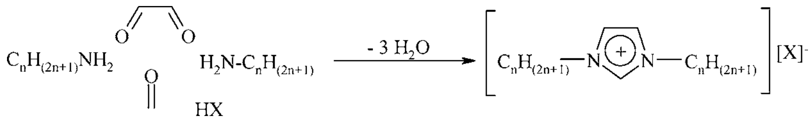

Table 2. **Variation of reaction times (addition sequence I, *n*-butylamine/glyoxal/formaldehyde/tetrafluoroboronic acid = 2:1:1:1, $T_1 = T_2 < 10$ °C, $T_3 = 20$ °C) in the batch synthesis of 1,3-dibutylimidazolium tetrafluoroborate**

entry	t_1 [min]	t_2 [min]	t_3 [h]	yield [%]
1	15	30	6	43
2	30	30	6	46
3	60	30	6	40
4	120	30	6	37
5	30	15	6	44
6	30	60	6	39
7	30	120	6	38
8	30	30	1	25
9	30	30	2	32
10	30	30	3	34
11	30	30	4	38
12	30	30	5	40
13	30	30	6	46
14	30	30	20	59

Table 3. **Variation of reactant ratios (addition sequence I, $t_1 = t_2 = 30$ min, $t_3 = 6$ h, $T_1 = T_2 < 10$ °C, $T_3 = 20$ °C) in the batch synthesis of 1,3-dibutylimidazolium tetrafluoroborate**

entry	$C_4H_9NH_2$	HCHO	$C_4H_9NH_2$	HBF_4	glyoxal	yield [%]
1	1	1	1	1	1	46
2	1	1	1	1.2	1	59
3	1	1	1	1.4	1	61
4	1	1.2	1	1	1	48
5	1	1	1	1	1.2	47
6	1.2	1	1.2	1	1	20

have been used as received. The content of formaldehyde was determined following standardized procedures.[27]

Batch Experiments. Batch experiments were conducted on a 0.05 molar scale in 250-mL, three-necked, round-bottomed flasks equipped with a dropping funnel, thermometer, reflux condenser, and a magnetic stirrer bar. Exothermic reactions were controlled by immersing the flask in a stirred ice bath while adding each reactant dropwise. The respective reaction times, reactant ratios, temperatures, and addition sequences are detailed in Tables 2−4.

The workup of the products was achieved by extraction with diethyl ether until the extractant phase was colorless. The water of the aqueous phase was removed on a rotary evaporator and the product further dried *in vacuo* (80 °C, 12 h, 5 mbar). The product purity was determined by ^{1}H NMR and/or HPLC[28] (*vide infra*), which was >70% in all cases.

Continuous Experiments. The multipurpose microreaction setup (Figure 1), designed and built at the TU Ilmenau (Prof. Köhler/Dr. Groß) has been used for the continuous experiments. This LABVIEW-controlled setup features a Cetoni syringe pump with six independent axes (Cetoni GmbH, Korbussen, Germany), PT-1000 temperature sensors (Umweltsensortechnik, Geschwenda, Germany), and pressure sensors (Profimess, Bremerhaven, Germany, PU-02), for timely detection of clogging. The components are connected *via* 1/16 in. PFA tubing (i.d. 1.016 mm). For mixing units, a glass X-mixer (MR-Lab, Little Things Factory)[29] was used. The residence time units (RTUs) and flow rates were altered as summarized in Table 5.

Table 4. **Yields obtained by variation of acids (addition sequences I, II, III: $t_1 = t_2 = 30$ min, $t_3 = 6$ h, $T_1 = T_2 < 10$ °C, $T_3 = 20$ °C, addition sequence IV: $t_1 = 30$ min, $t_2 = 6$ h, $T_1 < 10$ °C, $T_2 = 20$ °C; *n*-butylamine/glyoxal/formaldehyde/acid = 2:1:1:1.2) in the batch synthesis of 1,3-dibutylimidazolium-based ionic liquids**

	addition sequence			
acid	I	II	III	IV
HBF_4	59	53	65	60
HCl	60	72	67[a]	63[a]
HOAc	79	80	81	86

[a] The solution of HCl and formaldehyde should be freshly prepared and handled in a fume-hood, as bis(chloromethyl)ether may form, which is carcinogenic.

For HPLC analysis, samples were drawn at the exit of the setup (0.25 mL, diluted to 25 mL with eluent) at the times indicated (Table 5), and analyzed (*vide infra*). For ^{1}H NMR analysis, the product was extracted with ethyl acetate until the extractant phase was colorless. Volatiles were removed on a rotary evaporator, and the product was further dried *in vacuo* (80 °C, 12 h, 5 mbar).

The product purity was determined by ^{1}H NMR and/or HPLC (*vide infra*),[28] which was >95% in all cases.

Analytics. Yields were determined using a $[C_4C_4IM]Br$ standard made by conventional synthesis (alkylation of 1-butylimidazole) on a Jasco HPLC equipped with a Prontosil NC-04 (250 mm × 4 mm), 120-5-C18H 5 μm column from Bischoff Chromatography, using isocratic 70% aqueous Na_2HPO_4 (0.065 M, pH = 5)/30% acetonitrile as eluent. Detection was achieved with an UV-diode array detector at 208 nm.

^{1}H NMR spectra were recorded on a Bruker 200 MHz at room-temperature using deuterated DMSO as solvent. Yields were obtained by addition of a standard of approximately equimolar amounts of toluene to which peak integrals were related.

Yields determined by HPLC and ^{1}H NMR agreed within 5%. Residual traces of water were analyzed with a Karl Fischer Mettler DL37 Coulometer, using Hydranal-Coulomat A and C (both from Riedel-de Haën). The measurements were performed in duplicate and agreed within 5%.

As a further indication of the purity, the pH values in 0.1 M aqueous solution were measured. These pH values ranged between 5.2−5.3, 2.2−2.9, and 4.5−5.7 for the acetate, chloride,

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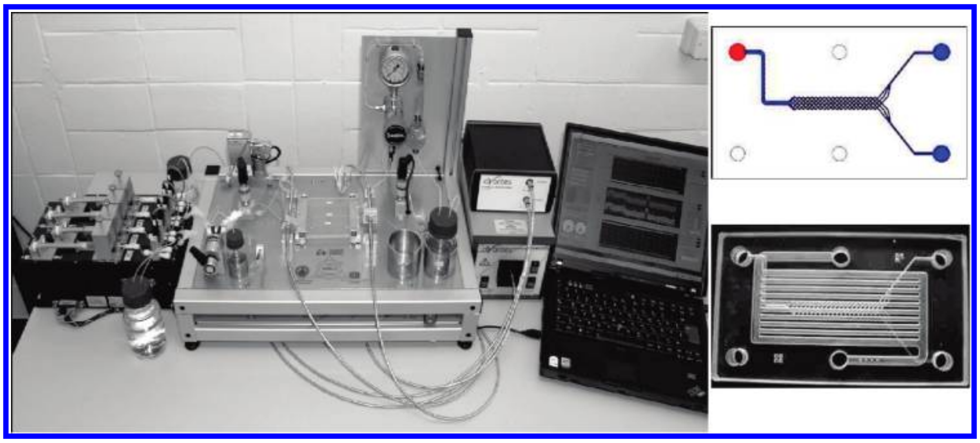


Figure 1. **Multipurpose microreaction setup used in the present study, and the X-mixer from the Little Things Factory.**[29]

Table 5. **Reaction parameters**[a] **for the continuous synthesis of [C_4C_4IM]Cl (entries 1−6)**[b] **and [C_4C_4IM][OAc] (entries 7−9)**

	RTU [m]		flow rate [mL min^{-1}]				residence time [min]				
entry	L_1	L_2	$C_4H_9NH_2$	HCHO + HCl	glyoxal	total	τ_1	τ_{total}	yield [%][c]	capacity [kg d^{-1}]	STY [kg L^{-1} h^{-1}]
1	2.5	7.0	0.20	0.20	0.12	0.51	5.07	15.10	5	0.01	0.08
2	2.5	7.0	0.40	0.39	0.23	1.02	2.57	7.55	10	0.06	0.31
3	2.5	7.0	1.00	0.98	0.58	2.56	1.02	3.01	12	0.17	0.92
4	7.0	30.0	0.34	0.30	0.20	0.84	8.87	35.71	45	0.22	0.30
5	7.0	30.0	0.17	0.15	0.10	0.42	17.73	71.42	55	0.13	0.18
6	7.0	30.0	0.09	0.08	0.05	0.22	33.38	136.35	69	0.09	0.12
			$C_4H_9NH_2$	HCHO + HOAc	glyoxal	total					
7	5.0	15.0	0.35	0.25	0.20	0.80	6.76	20.27	50	0.27	0.70
8	7.0	30.0	0.35	0.25	0.20	0.80	9.46	37.50	74	0.40	0.56
9	7.0	30.0	0.18	0.13	0.10	0.41	18.31	73.16	91	0.25	0.35

[a] $c(C_4H_9NH_2)$ = 10.08 mol L^{-1}, c(HCHO, 37% aq sol.) = 13.34 mol L^{-1}, for entries 1−3; (HCl, 32% aq sol.) = 10.18 mol L^{-1}, for entries 4−6: (HCl, 37% aq sol.) = 12.03 mol L^{-1}, c(HOAc, > 99%) = 17.49 mol L^{-1}, c(glyoxal, 40% aq sol.) = 8.75 mol L^{-1}. [b] The solution of HCl and formaldehyde should be freshly prepared and handled in a fume-hood, as bis(chloromethyl)ether may form, which is carcinogenic. [c] Except for entries 6 and 9, yields increased with time by further reaction in the collecting vessel.

and formate samples, respectively, indicating that traces of acid are present in all cases.

Ionic Liquid Specifications. *Physicochemical Properties.* Thermogravimetric analyses were conducted on a DTG-60 from Shimadzu Corporation, using a platinum pan under inert conditions (nitrogen), at a heating rate of 10 °C min^{-1}. As reference, α-alumina Al_2O_3 was used. The midpoint was obtained by integration of the decomposition curve.

Kinematic viscosities were measured using an Ubbelohde viscometer ($K = 0.5007$) connected to drying tubes filled with anhydrous calcium sulfate to exclude moisture, equipped with a pump and a cryostat to control temperature.

The purities of the materials investigated by TGA and viscometry are given in Table 6 and in the Supporting Information.

Cellulose Dissolution. Avicel was dissolved by incremental addition in the ionic liquid at 100 °C while stirring, until further addition of cellulose rendered the solution visually opaque.

Dehydration of Fructose. Fructose (8.6 wt %) was dissolved in either 3.0 g of [C_4MIM][CH_3SO_3] or [C_4C_4IM]Cl. The reaction (80 °C) was followed by taking samples at the appropriate times and analyzing after dilution with acetonitrile/water (80:20). HPLC was used for analysis (5-hydroxymethylfurfural: UV-DAD, 283 nm, fructose: light scattering detector) equipped with a Prontosil 120-5-Amino 0.5 μm column from Bischoff Chromatography using an isocratic acetonitrile/water eluent (80:20).

Results and Discussion

Initial experiments showed that water-insoluble 1,3-dibutylimidazolium tetrafluoroborate ([C_4C_4IM][BF_4]) can be obtained by reacting stoichiometric amounts of *n*-butylamine, glyoxal, formaldehyde, and tetrafluoroboronic acid. Although water-insoluble ionic liquids were not the primary goal of the study, this example was initially chosen as it allows for aqueous extraction, and hence a larger variability of the process parameters in the optimization experiments. In order to elucidate the effect of the relative reactant ratios, various experiments were carried out using addition sequence I (Scheme 3), in which in reaction step 1, equimolar amounts of *n*-butylamine and formaldehyde are allowed to react at temperature T_1 for a reaction time t_1, before a premixed solution of equimolar amounts of *n*-butylamine and HBF_4 is added in reaction step 2. The resulting mixture is allowed to react at temperature T_2 for a reaction time t_2. Finally, glyoxal is added and the mixture reacted (T_3, t_3) in reaction step 3.

Preliminary experiments indicated that reaction steps 1 and 2 were very sensitive to heating (both are exothermic reactions), with low selectivities at higher temperatures. Hence, these two steps were kept <10 °C throughout the study, while the less sensitive step 3 was run isothermally at room-temperature.

Reaction Times. First, the influence of the reaction times was investigated in batch experiments on a 0.05 molar scale.

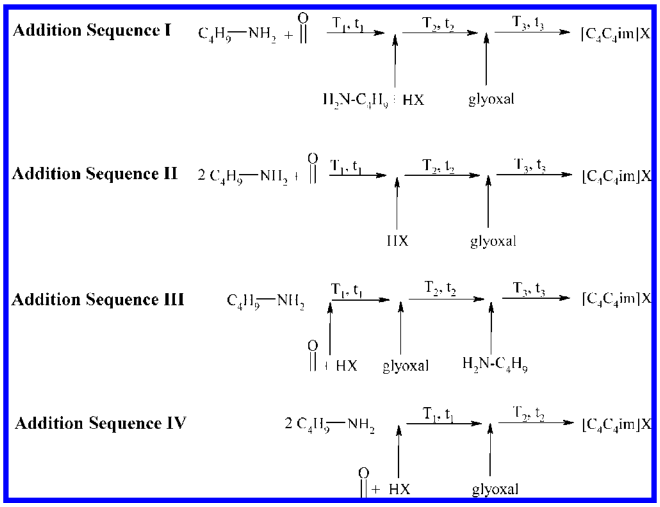
The successive variation of the reaction times showed that an extension of t_1 and t_2 beyond 30 min does not improve yields,

Table 6. **Yields, purities, decomposition temperatures at midpoint, kinematic viscosities, and water content of some homosubstituted 1,3-dialkylimidazolium salts prepared by the modified Radziszewski reaction**

				kinetic viscosity $\ln(\nu)$ [$mm^2\ s^{-1}$]^c			
ionic liquid	yield^a [%]	purity [%]	dec. temp. [°C]^{b,c}	25 °C	50 °C	80 °C	water content^d [wt %]
$[C_1C_1IM][OAc]$	85	95	271.5	nd	nd	nd	1.46
$[C_3C_3IM][OAc]$	84	98	273.6	6.12	4.55	3.27	1.17
$[C_4C_4IM][OAc]$	86	>95	275.2	6.53	4.95	3.62	0.75
$[C_1C_1IM][NO_3]$	85	95	321.9	nd	nd	nd	0.37
$[C_3C_3IM][NO_3]$	78	>95	313.3	6.37	4.92	3.68	0.32
$[C_4C_4IM][NO_3]$	79	95	321.5	6.74	5.13	3.80	0.22
$[C_1C_1IM][HCO_2]$	95	93	250.8	nd	nd	nd	0.90
$[C_3C_3IM][HCO_2]$	91	93	253.1	5.41	4.07	3.00	1.30
$[C_4C_4IM][HCO_2]$	94	>95	254.1	5.58	4.30	3.21	1.09
$[C_1C_1IM][HSO_4]$	70	>95	383.8	nd	nd	nd	1.00
$[C_3C_3IM][HSO_4]$	75	94	387.5	nd	6.95	5.32	0.32
$[C_4C_4IM][HSO_4]$	73	>95	384.0	nd	7.29	5.59	0.22
$[C_4C_4IM]Br$	76	79	310.1	nd	nd	nd	1.95
$[C_4C_4IM]Cl$	63	78	280.3	nd	nd	nd	1.30
$[C_4C_4IM][BF_4]$	65	>95	440.7	nd	nd	nd	0.87
$[C_4MIM][BF_4]^e$	nd	>98	nd	4.52	3.41	2.42	0.11
$[C_6MIM][BF_4]^e$	nd	>98	nd	5.17	3.94	2.88	0.05
$[C_8MIM][BF_4]^e$	nd	>98	nd	5.64	4.35	3.22	0.08

[a] Isolated yield. [b] Midpoint decomposition temperature determined by TGA, Pt cup, N_2, rate: 10 °C min^{-1}. [c] For graphic presentation of the decomposition temperatures and kinematic viscosities, see Supporting Information. [d] Determined by automated Karl Fischer titration. [e] Prepared by conventional alkylation.[22] nd = not determined.

Scheme 3. **Sequence of addition of reactants**



and for t_3, 6 h is sufficient, although this part of the reaction is most sluggish (Table 2). It should be noted here that it is not possible to reduce t_1 and t_2 < 15 min in batch mode on this scale with T < 10 °C, due to the exothermic nature of these reactions.

Relative Reactant Ratios. Second, the relative ratio of reactants was investigated. As displayed in Table 3, under constant reaction conditions, stoichiometric amounts of the reactants gives a yield of 46%. An increase of the acid ratio to 1.2 leads to an enhancement of the yield to 59%. Further increasing the acid ratio did not improve the yield further (entry 3).

Increasing the ratio of either the formaldehyde, glyoxal, or *n*-butylamine did not further the yield (entries 4−6). Hence, for the remainder of the study, a stoichiometric composition with a 1.2-fold excess of the acid was adapted.

Variation of Acid. Third, the reaction conditions giving highest yields were transposed to the synthesis of the corresponding chloride and acetate, since these water-soluble ionic liquids were the goal of the study.

Surprisingly, a tremendous increase in yield to 80% resulted if acetic acid was used instead of tetrafluoroboronic acid employing addition sequence I, while the same yield (60%) was obtained with HCl (Scheme 3 and Table 4).

Sequence of Reactant Addition. Finally, the effect of the sequence of reactant addition was investigated for the three acids (Table 4). Addition sequence II is the one described for the preparation of carbene precursors.[15−17,30,31]

Interestingly, this sequence gives slightly lower yields for the tetrafluoroborate analogue, while the yield of the chloride improves to about 70%, and that of the acetate remains the same when compared to addition sequence I. Addition sequence III improves the yields slightly for the tetrafluoroborate and the chloride, but not for the acetate. Addition sequence IV was investigated as it reduces the number of addition steps to two, which would facilitate the handling of chemicals (number of pumps) in a continuous setup. This method provides yields for the tetrafluoroborate and chloride comparable to those of Addition Sequence I, and slightly higher for the acetate. Addition Sequence IV was thus adapted for the continuous synthesis using a microreactor setup.

Variation of Reactants. The synthesis was carried out using various primary amines, and mineral or organic acids, with glyoxal and formaldehyde, clearly showing the applicability of the method (see Supporting Information). Yields vary between 60 to 95%. Although a clear trend can not be derived, it appears as if the acidity of the acid played a role with regard to the yields, with less acidic ones giving higher yields. This may be due to the protonation of the amine in the case of strong acids, leading to unproductive ammonium-based intermediates during the reaction.

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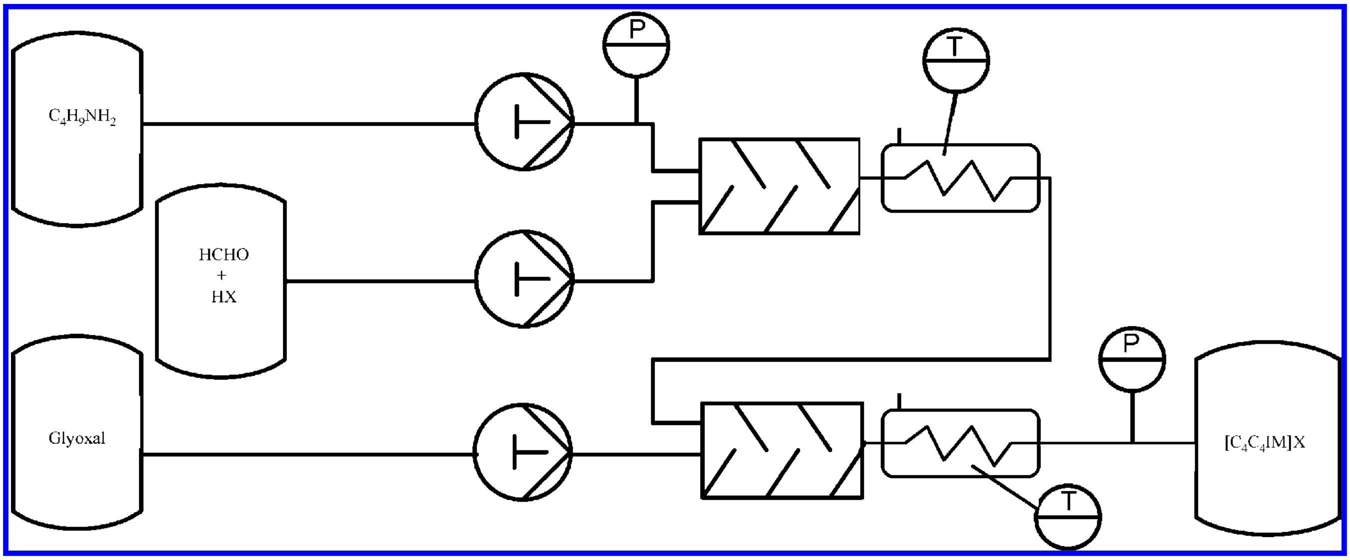

Figure 2. **Flow scheme of the microreaction setup.**

Transfer to Continuous Production in a Microreactor Setup. Water-soluble ionic liquids ($[C_4C_4IM][OAc]$ and $[C_4C_4IM]Cl$) were synthesized with the modified Radziszewski reaction in a continuous procedure in a multipurpose microreaction device (Figure 1) applying addition sequence IV.

Different total flow rates of reactants from 0.2−2.6 mL min^{-1} were chosen to ascertain the reaction stoichiometry of sequence IV, and total lengths of residence time units (RTUs) from 9.5 to 37 m were applied to determine the conditions giving highest yields.

Due to the exotherms occurring during reaction step 1, the microreactor, mounted in a special metal frame construction (Figure 1), was cooled in a water bath at 10 °C. It was found that heating of the second RTU to 40 °C had no significant influence on product yield and purity. Hence, the reaction step 2 was carried out at ambient temperatures. Figure 2 shows the flow scheme of the microreaction setup:

First, *n*-butylamine is reacted with a premixed solution of formaldehyde and acid (HX = HCl, HOAc) for selected residence times τ_1. After the pass through an X-mixer (MRLab, LTF)[29] and a RTU of length L_1 the reaction mixture is brought in contact with glyoxal in a second X-mixer and reacted in a second RTU (L_2) for τ_2. The pressure at the beginning and the end of the device is monitored with the pressure senors P1 and P2. The temperature in the RTUs is measured with the temperature sensors T1 and T2.

Table 5 shows the reaction parameters as well as residence times and space-time yields for the ionic liquids $[C_4C_4IM]Cl$ and $[C_4C_4IM][OAc]$.

Initially, the synthesis of $[C_4C_4IM]Cl$ was carried out using short RTUs (9.5 m in total) and different flow rates to determine suitable residence times for the reaction. Here, the residence time τ_{hydr} was not sufficient to give high yields of the desired reaction product (entries 1−3, Table 5).

$$\tau_{hydr} = \frac{V}{\vec{V}} \tag{1}$$

where $\vec{V}$ is the reactants' flow rate [mL min^{-1}] and V is the inner volume of the device of length L with diameter = 1.016 × 10^{-3} m. Considering the minimum reaction time t_3 of 6 h in the batch reaction, a minimum length of the RTU L_2 of 222 m, 444 m, and 1110 m at the flow rates applied in entries 1−3 would be required (eq 1). Therefore, longer RTUs of 37 m in total and decreased total flow rates of 0.8, 0.4, and 0.2 mL min^{-1} were operated (entries 4−6).

In the case of the synthesis of $[C_4C_4IM]Cl$, an increase in yield up to 70% was achieved (Table 5, entry 6), resulting in a STY of 0.12 kg L^{-1} h^{-1} and a capacity of 0.09 kg d^{-1}.

The reaction parameters were adapted for the synthesis of 1,3-dibutylimidazolium acetate. Interestingly, a tremendous increase to 91% yield within a residence time of only 73 min was obtained, resulting in a STY of 0.35 kg L^{-1} h^{-1} and a capacity of 0.25 kg d^{-1} (Table 5, entry 9).

In comparison to the modified Radziszewski reaction in batch mode, the results clearly show the potential of microreaction technology in terms of process intensification:[32,33] the reaction times are reduced by factor 3 and 6 for chloride- and acetate-based ionic liquids, respectively, while the yields increase slightly (compare Tables 4 and 5). Both improvements are a result of improved mixing and heat transfer in micromixers, which allows for faster reactant combination in exothermic reactions, while reducing side-product formation.

Direct comparison to the conventional synthesis (Table 1) is not possible owing to both, unlike reactivities of the systems and the fact that the products are different (homo- vs. hetero-substituted cations). However, in general the performance of the combination of the Radziszewski reaction with microreaction technology in terms of STY lies between conventional and microreaction processing strategies by the conventional synthesis route.

Physicochemical Properties of Homosubstituted 1,3-Dialkylimidazolium Salts. Series of homologues of homosubstituted 1,3-dialkylimidazolium salts have been prepared (see Supporting Information) and their physicochemical properties investigated. It was found that all 1,3-dimethylimidazolium-based salts (hydrogensulfate, nitrate, acetate, formate, tetrafluo-

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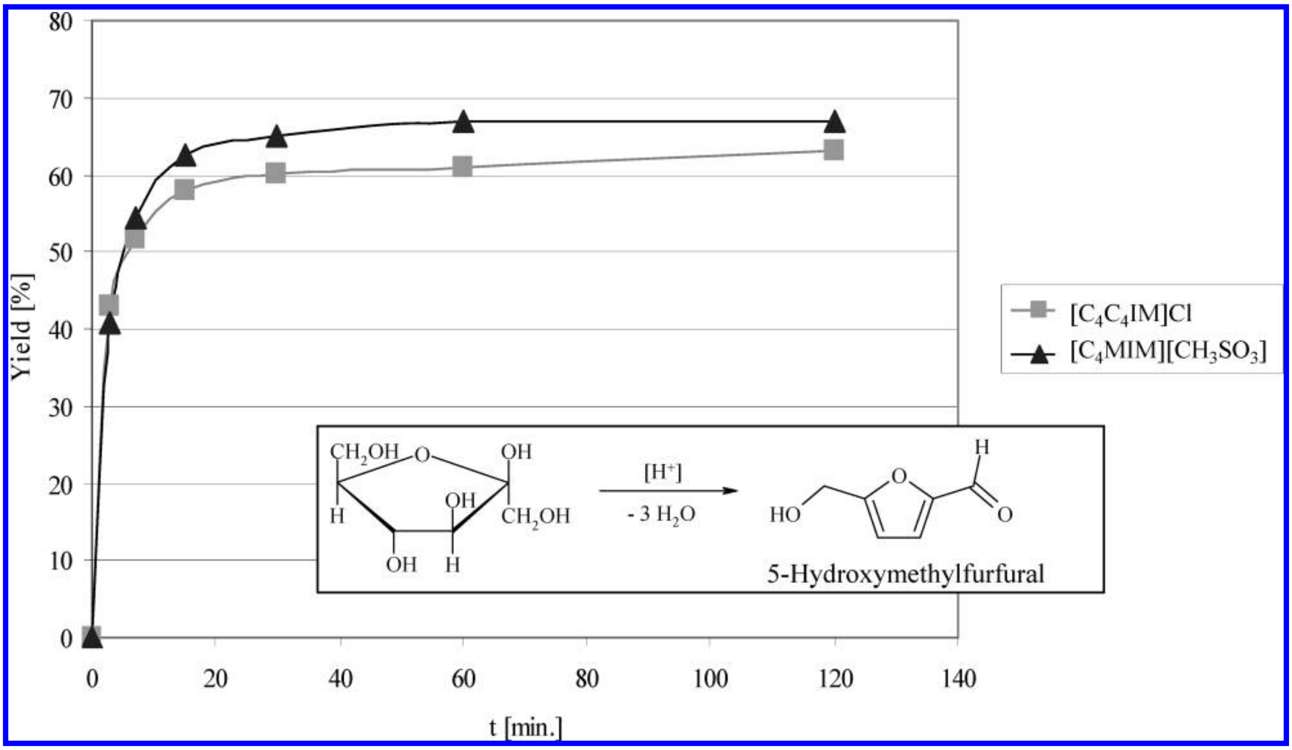

Figure 3. **Comparison of performance of $[C_4MIM][CH_3SO_3]$ and $[C_4C_4IM]Cl$ in the synthesis of 5-hydroxymethylfurfural from fructose (8.6 wt %) as function of time, at 80 °C, under otherwise identical conditions.**

roborate, chloride) were solid at room-temperature. Increasing the alkyl chain length to *n*-propyl or *n*-butyl gave room-temperature liquids.

The viscosity (Table 6) decreases with increasing temperature, as is the case for heterosubstituted salts.[34] Furthermore, *n*-propyl derivatives have lower viscosities than *n*-butyl derivatives, independent of the anion chosen. With regard to the influence of the anion, the viscosity decreases according to $[HSO_4]^- > [NO_3]^- > [OAc]^- > [CHO_2]^-$. In comparison to the three heterosubstituted (conventional) ionic liquids presented in Table 6, the novel ionic liquids feature surprisingly low viscosities, even if they comprise highly coordinating anions (compare e.g. tetrafluoroborate vs formate).

The thermal stability of the materials was investigated by thermogravimetric analysis (Table 6). Interestingly, the decomposition temperature is independent of the alkyl chain length of the cation but decreases with increasing nucleophilicity of the anion. This clearly indicates that the decomposition mechanism involves nucleophilic attack of the anion on the alkyl substituent, known as Hofmann degradation or reversed Menschutkin reaction,[35] as previously observed for 1-alkylpyridinium[36] and tetraalkylammonium salts.[37,38]

Furthermore, the consistency of decomposition temperatures is a reflection of the purity of the materials obtained. In general, these homosubstituted 1,3-dialkylimidazolium salts feature similar thermal stabilities as their heterosubstituted counterparts.[39] Although conclusions about long-term stability should only be drawn from isothermal measurements, their relatively high thermal stability renders these ionic liquids applicable as solvents for organic reactions.

Application as Solvents. 1,3-Dibutylimidazolium acetate was tested in cellulose dissolution, a process of wide recent interest.[40−42] The solubility of the microcrystalline cellulose Avicel (DP = approximately 300) was about 9 wt %, which is in good agreement with conventional ionic liquids,[40−42] thus indicating the potential of these ionic liquids in cellulose processing.

The dehydration of fructose to 5-hydroxymethylfurfural (a compound presently promoted as platform chemical from renewable resources) is well-known to proceed efficiently in ionic liquids.[43−48] Figure 3 shows that the performances of both heterosubstituted 1-butyl-3-methylimidazolium methanosulfonate ($[C_4MIM][CH_3SO_3]$) and the homosubstituted $[C_4C_4IM]Cl$ in the conversion of fructose (8.6 wt %, 80 °C) to 5-hydroxymethylfurfural are identical under otherwise similar conditions. These preliminary findings show the potential of homosubstituted ionic liquids to substitute for the more expensive heterosubstituted ones, e.g. in the processing and conversion of renewable resources.

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Conclusions

This study has demonstrated that homosubstituted 1,3-dialkylimidazolium-based ionic liquids can be prepared continuously in high yields (70−90%) using readily available starting materials. The purities (>95%) compare well with many ionic liquid products commercially available presently and may be improved further in future. Therefore, the continuous process shows potential for further scale-up. Additionally, the modified Radziszewski reaction is atom-efficient, with water being the only byproduct.

It appears reasonable to argue that this synthetic strategy reduces the energy and solvent requirement of the preparation of 1,3-dialkylimidazolium-based ionic liquids compared to those prepared by the conventional method,[1,2,12,13] and detailed energy measurements will be reported in due course.

This synthetic strategy allows for the cost-efficient technical production of water-soluble ionic liquids. The chemical costs (Germany, Sigma-Aldrich catalogue, July 2009, 1 kg-scale) amount to between 75 and 85 € kg^{-1} for the [C_4C_4IM]-based ionic liquids presented herein. On the same scale and at 95% yield, the chemical cost for 1 kg of [C_4mim]Cl is about the same (83 € kg^{-1}). Although this appears to be similar, several aspects need to be considered; first, bulk chemicals (as required in the Radziszewski reaction) are proportionally cheaper on large scale than the more highly specialized ones (e.g., 1-methylimidazole), and thus the chemical costs will deviate considerably on ton scale. Second, [C_4mim]Cl is only an intermediate in the conventional synthesis, and further costs will have to be added for ion exchange. Contrary to this, with the Radziszewski reaction, the acid component can be simply varied, and the ionic liquid with the desired anion is directly produced. Finally, as pointed out above, energy savings can be expected.

Using this approach, it is also possible to produce halide-free ionic liquids, an aspect relevant to catalysis and reactor corrosion.

The applicability of homosubstituted 1,3-dialkylimidazolium-based ionic liquids as solvents has been demonstrated on two presently heavily investigated processes: the dissolution of cellulose and the dehydration of fructose to 5-hydroxmethylfurfural. In such applications, the ionic liquid solvent cost is paramount for the transferral of novel technologies to industrial production.

Furthermore, by structural alteration of the starting material, especially the amines (amino acids), chiral centers and other functionalities can be introduced, further enhancing the possibility of using ionic liquids as designer solvents on technical scale.

From a technical perspective, the application of a microreaction setup allows for a quick changeover to other ionic liquid products, resulting in a reduction of setup time and enabling on-demand synthesis of various products in the same apparatus.

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Supporting Information Available

Data of various other ionic liquids prepared by the modified Radziszewski reaction, graphic presentation of the decomposition temperatures and kinematic viscosities. This information is available free of charge via the Internet at http://pubs.acs.org/.

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