Ionic Liquids—Advanced Reaction Media for Organic Synthesis

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Published online: 12 Jul 2011.

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IONIC LIQUIDS—ADVANCED REACTION MEDIA FOR ORGANIC SYNTHESIS

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Abstract *The advantages in the application of ionic liquids as reaction media in organic synthesis, i.e., in the preparation of chromane derivatives, substituted pyrazines, 4-aminofuran-2(5H)-ones, or in bromination of Levulinic acid or dehydration of alcohols, saccharides, and polysaccharides, have been demonstrated on several examples. Ionic liquids with Brønsted acidity have been shown to possess catalytic activity and provide access to convenient technologies for the preparation of various useful compounds.*

Keywords Ionic liquids; organic synthesis; reaction media

INTRODUCTION

Ionic liquids (ILs) or liquid salts are chemical substances that consist of an organic cation and organic or inorganic anion. They typically do not comprise neutral molecules and usually have melting points below 373 K. Ionic liquids that are liquid at room temperature, or room temperature ionic liquids (RTIL) are of major interest for their application in organic synthesis.

Intensive research dealing with the synthesis of new ionic liquids and their applications in different fields, e.g., electrochemistry, energy storage and conversion, organic chemistry, catalysis, chemical engineering, material science, etc., is currently in progress in all industrially developing countries. The reasons for this are the unique properties of this new class of chemical substances, e.g., negligible vapor pressure, liquid state over large temperature scale, nonflammability, electrical conductivity, and high electrochemical and thermal stability. Review articles on ionic liquids are, for example in Refs.[1–7] Several

books devoted to synthesis and practical applications of ionic liquids have been published recently; see for instance Refs.[8–10]

The properties of ionic liquids, for example melting point, thermal and electrochemical stability, and viscosity, are strongly influenced by the nature of the anion. The polarity and the hydrophilicity or lipophilicity of ionic liquids can be varied by a suitable choice of the cation/anion pair. The combination of available (known) anions and cations gives the possibility of constructing thousands of different ionic liquids with various properties, but it is still a challenge to synthesize ionic liquids having low viscosity and high thermal, electrochemical, and hydrolytic stability at the same time. For example, the tetrafluoroborate anion, $[BF_4]^-$, is one of the favored anions for the preparation of hydrophilic (water miscible) ionic liquids. The major disadvantages of tetrafluoroborate ionic liquids are their not perfect hydrolytic stability (in particular at raised temperature) and their relatively high viscosity. Recently, we have improved the properties of such ionic liquids by introducing the tetracyanoborate anion, $[B(CN)_4]^-$,[11] instead of the $[BF_4]^-$ anion. That greatly improves the hydrolytic stability and reduces the viscosity of the ionic liquid.

The typical example of hydrophobic (water immiscible) ILs are ionic liquids that bear, for example, the $[PF_6]^-$ anion. These ionic liquids are even less hydrolytically stable than ILs with the $[BF_4]^-$ anion. In contact with water (or with moisture), these ionic liquids can generate hydrogen fluoride (HF), which can not only influence the performed chemical reaction but create additional inconveniences related to the toxicity of HF. Recently, we have developed a new generation of hydrophobic ionic liquids with the $[(C_2F_5)_3PF_3]^-$ anion (FAP anion) having superior hydrolytic stability, low viscosity, and high thermal and electrochemical stability.[12] More information about new ionic liquids that are now available in commercial quantities from Merck KGaA, Darmstadt, Germany, can be found on the following Web site: http://www.ionicliquids-merck.de

RESULTS AND DISCUSSION

Ionic liquids can be used as inert reaction media for organic synthesis to replace volatile organic solvents or additionally as reactive substances to catalyze chemical reactions.

We have found that volatile Brønsted acids dissolved in ionic liquid with the same counter anion stay in the mixture, even at temperatures well above the boiling point of the pure Brønsted acid. For example, trifluoroacetic acid (bp 72°C) dissolved in 1-butyl-3-methylimidazolium trifluoroacetate [BMIM][TFA], (concentration 20%) does not evaporate from this mixture up to the temperature of about 120°C (see Figure 1).

It is most likely that a high concentration of trifluoroacetate anions in the mixture of [BMIM][ATF]/CF$_3$COOH leads to a solvation of the proton by many trifluoroacetate anions (cluster formation), which dramatically reduces the volatility of the dissolved trifluoroacetic acid in the ionic liquid. This phenomenon is observed for various combinations of ionic liquids and Brønsted acids, namely 1,3-dialkylimidazolium triflate + triflic acid; 1,1-dialkylpyrrolidinium triflate + triflic acid, and 1,3-dialkylimidazolium hydrogensulfate ($[HSO_4]^-$) + sulfuric acid. The hydrogensulfate ionic liquids themselves possess certain Brønsted acidity by means of proton activity in the hydrogensulfate anion, but the addition of sulfuric acid to the ionic liquid allows for smooth tuning of the acidity of this catalytic system. In many cases, the acidity of hydrogensulfate ionic liquids themselves is sufficient enough to *f.e.* dehydrate secondary alcohols (Scheme 1).[13]
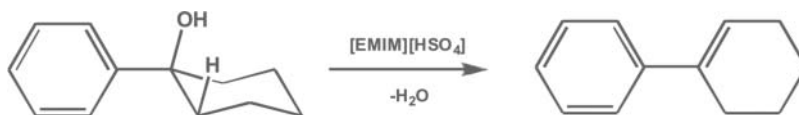
Scheme 1 Synthesis of 1-phenylcyclohex-1-en in ionic liquid.

The application of 1-ethyl-3-methyl-imidazolium hydrogensulfate, [EMIM][HSO$_4$], provides a convenient synthesis of 1-phenylcyclohex-1-ene in very high yield. The ionic liquid can be reused several times without losing its activity in the dehydration of 1-phenyl-1-cyclohexanol (see Table 1).

The 1-phenyl-cyclohexan-1-ol possesses a good solubility in ionic liquid. But, after conducting the reaction (80–90°C, 1 h) and cooling the reaction mixture to room temperature, the product, 1-phenylcyclohex-1-ene, forms an upper phase and can be easily separated by means of decantation. This procedure can be repeated several times (see Table 1) without treatment of the recycled ionic liquid. It appears as though the water formed is solubilized in the ionic liquid's medium and does not influence the dehydration process to disrupt it. Only after converting four or five recharges of reactant should the ionic liquid be dried in vacuum to remove the formed water (see Table 1, note *b*).
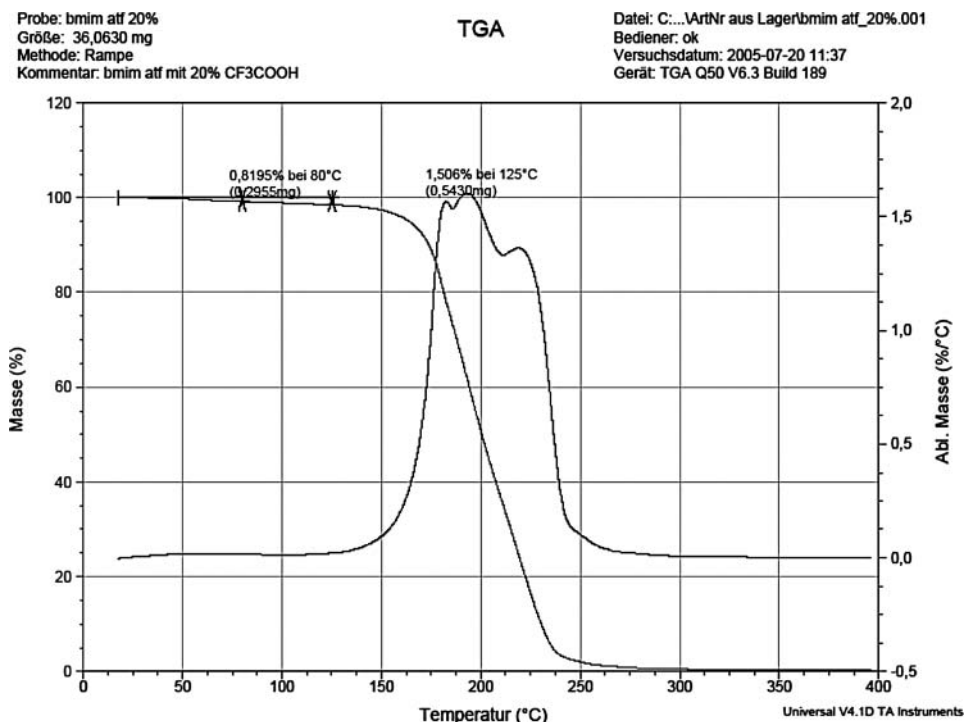

Figure 1 Thermogravimetric analysis (TGA) of the mixture containing 20% of CF$_3$COOH dissolved in 1-butyl-3-methylimidazolium trifluoroacetate.
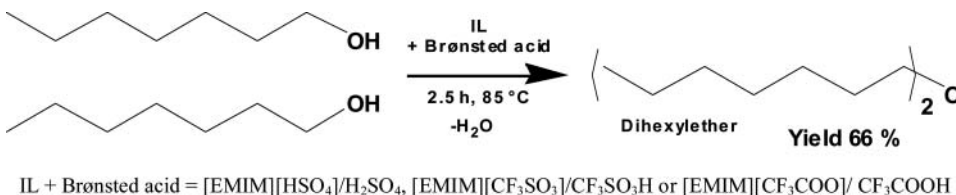
Table 1 Dehydration of 1-phenyl-cyclohexanol in 1-ethyl-3-methyl-imidazolium hydrogensulfate, [EMIM][HSO$_4$]

| Experiment no.	Loading of phenyl cyclohexanol [g]	Yield [g]	Yield [%]
1	10.27	7.85	85
2	6.17	5.89	106[a]
3	8.86	8.30	104[a]
4	6.92	6.35	102[a]
IL drying[b]			
5	6.55	4.65	79
6	4.29	3.95	102[a]
7	7.56	6.16	91
8	7.25	5.85	90
9	5.20	4.73	101[a]
IL drying[b]			Total yield: 97%

[a]Additional quantity of product comes from previous charges and is therefore above 100%.
[b]Drying the IL for 2 h in vacuum (10^{-3} mbar) at 150°C.

The dehydration of primary alcohols required stronger acidic conditions. It can be successfully carried out in the following mixture: ionic liquid + Brønsted acid; for example in the system 1-ethyl-3-methylimidazolium hydrogensulfate, [EMIM][HSO$_4$] + concentrated sulfuric acid (see Scheme 2).[13]

IL + Brønsted acid = [EMIM][HSO$_3$]/H$_2$SO$_4$, [EMIM][CF$_3$SO$_3$]/CF$_3$SO$_3$H or [EMIM][CF$_3$COO]/ CF$_3$COOH

Scheme 2 Dehydration of 1-heptanol in the system ionic liquid + Brønsted acid.

This catalytic system can also be successfully applied for dehydration of secondary alcohols, for example cyclohexanol, and tertiary alcohols, for instance *tert*-butanol (see Scheme 3).[13]
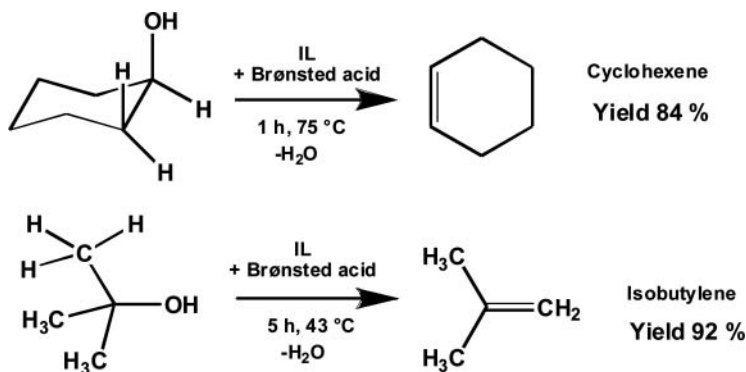
Scheme 3 Dehydration of secondary and tertiary alcohols in the catalytic system ionic liquid + Brønsted acid.

The dehydration of *tert*-butanol to isobutylene proceeds very efficiently in acidic ionic liquids. This process does not require high temperatures and can be easily performed continuously because of the low boiling point of isobutylene ($-7°C$), which can constantly be removed from the reaction mixture.

The technology described can also be applied for the preparation of basic chemicals out of natural products. For example, acidic ionic liquids are suitable reaction media for the conversion of mono-, di-, and poly-saccharides into furan derivatives (see Schemes 4, 5, and 6)[13,14]—important building blocks for fine chemistry.
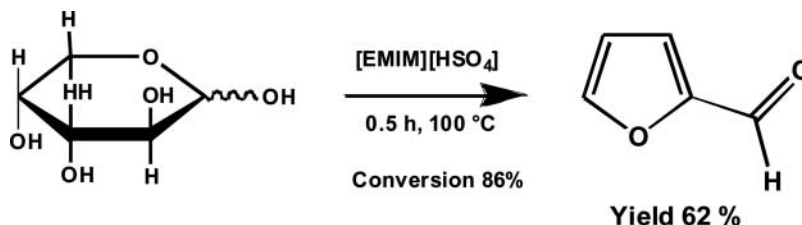
Scheme 4 Conversion of xylose (pentose) to furfural in [EMIM][HSO$_4$].

The xylose is converted very efficiently to furfural (see Scheme 4). The yield of furfural has been improved up to 84% by use of a two-phase system of [EMIM][HSO$_4$]/toluene and longer reaction time (6 h). The ionic liquid, [EMIM][HSO$_4$], can be effectively recycled and used several times in the conversion of xylose to furfural.

Hexoses, for instance fructose, can be converted to 5-(hydroxymethyl)-2-furaldehyde (HMF) by use of the two phase system of [EMIM][HSO$_4$]/methyl isobutyl ketone (Scheme 5).[14]
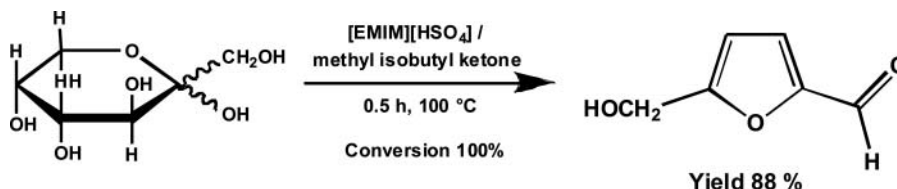
Scheme 5 Conversion of fructose (hexose) to 5-(hydroxymethyl)-2-furaldehyde (HMF) in [EMIM][HSO$_4$].

Dehydration of glucose in the biphasic system [EMIM][HSO4]/toluene gives 95% conversion but only 9% HMF yield at 100°C within 4 h.[14] The rather low HMF yield may be due to the lack of selectivity in the dehydration of glucose units in this system. To improve the yield of HMF from glucose, the isomerization of glucose into fructose is required to increase the selectivity of this process. It can be achieved with the application of Lewis acid catalysts, for example in the system CrCl$_2$/[BMIM][Cl] reported by Zhang and co-workers.[15] More stable and readily available CrCl$_3$ can be effectively used instead of CrCl$_2$. The HMF can be obtained in 81% yield from glucose in the system [BMIM][Cl]/CrCl$_3$ (i.e., no co-solvent) within 4 h at 100°C.[14] Application of the biphasic system [BMIM][Cl]/CrCl$_3$/toluene further improves the yield of HMF to 91%.[14]

Not only mono- or disaccharides can be converted into 5-(hydroxymethyl)-2-furaldehyde and also some polysaccharides, for instance inulin, which undergoes conversion to HMF in acidic ionic liquids (see Scheme 6).[14]
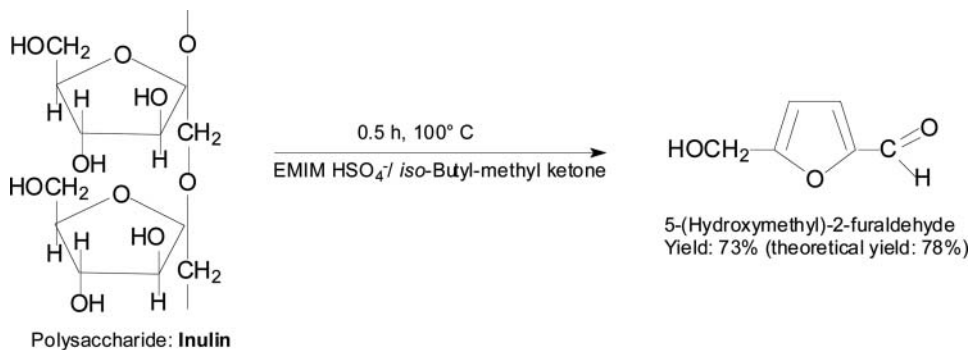
Scheme 6 Conversion of the polysaccharide inulin to 5-(hydroxymethyl)-2-furaldehyde (HMF) in [EMIM][HSO$_4$].

HMF is a useful substance for multipurpose applications.[16] It can be used for example as starting material for production of bio-fuel or fuel additives.

The catalytic system of ionic liquid and Brønsted acid can not only be used for dehydration processes, but it also allows for combination of the alkylation and ring closure reaction by means of water abstraction, for example in the synthesis of chromane derivatives (see Scheme 7).[17]
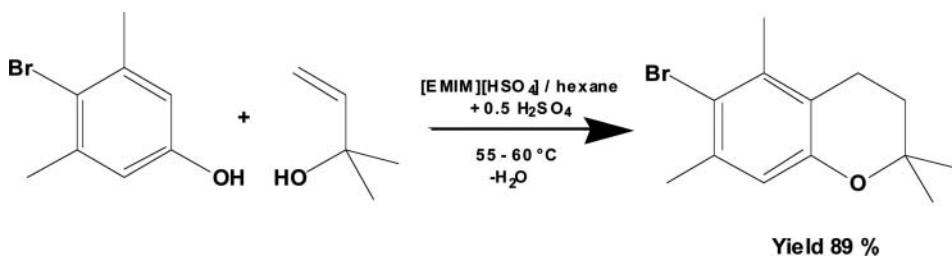
Scheme 7 Synthesis of the 6-bromo-2,2,5,7-tetramethylchromane in two-phase system ionic liquid with Brønsted acid and hexane.

Reaction of 4-brom-3,5-dimethyl-phenol and buten-2-ol proceeds in a two-phase system at relatively low temperature (55–60°C) and results in the formation of the desired product in a very short time (15 min) in good yield (89%).

The same system can be applied for the synthesis of vitamin E (D,L-α-tocopherole)—an industrial product with multi-ton production per year. Typical technology is based on the application of special catalyst (strong Brønsted acid) to induce the condensation of 2,3,5-trimethyl hydroquinone with isophytol. Application of acidic ionic liquids as reaction media and catalyst simplifies the process and provides the possibility to reduce the costs (see Scheme 8). The synthesis was optimized by use of a two-phase system: ionic liquid/hexane. The ionic liquid can be recycled several times.[17]
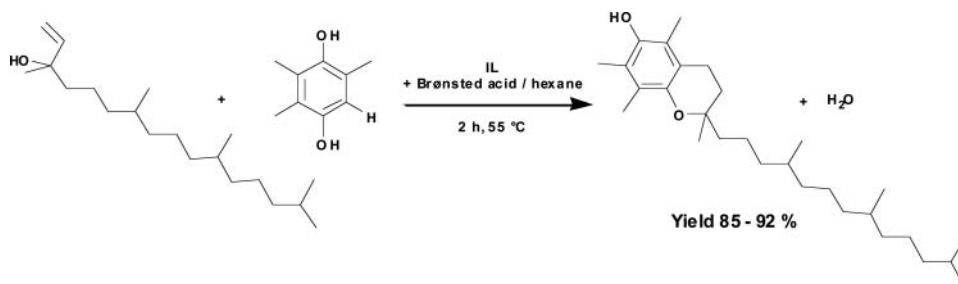
Scheme 8 Synthesis of vitamin E in the two phase system ionic liquid and Brønsted acid.

The last two examples clearly demonstrate that ionic liquids are advanced media for multistep reactions (cascade reactions), which can be combined in one-pot synthesis. It is not always necessarily to apply an acidic medium to such kind reactions. For example, aza-Michael addition of NH-acids to functionalized alkynes proceeded very effectively in "neutral" ionic liquids, such as in 1-butyl-3-methylimidazolium tetrafluoroborate, [BMIM][BF$_4$] (see Scheme 9).[18,19]
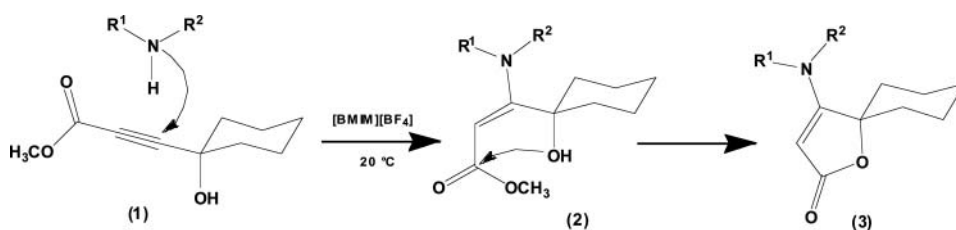
Scheme 9 Synthesis of 4-aminofuran-2(5H)-ones (**3**) from 3-(hydroxyalkyl) propargylic ester (**1**) and amines in [BMIM][BF$_4$].

The one-pot synthesis of 4-aminofuran-2(5H)-ones (**3**) from 3-(hydroxyalkyl) propargylic ester (**1**) and amines is significantly accelerated in ionic liquids when compared to traditional organic solvents (see Table 2). Ionic liquids can be reused many times without decrease in the reaction rate and yield.

Table 2 Aza-Michael addition of NH-acids to functionalized alkynes in organic solvents and ionic liquid [BMIM][BF$_4$]

Entry	Amine	Reaction time, h (solvent, temp°C)	Reaction time, h (IL, 20°C)	Yield in organic solvent (%)	Yield in IL (%)
1	Piperidine	140 (Et$_2$O, 20)	1	67 (Et$_2$O)	85
2	Morpholine	140 (Et$_2$O, 20)	1	72 (Et$_2$O)	85
3	2-Methylpiperidine	250 (Et$_2$O, 20)	2	82 (Et$_2$O)	87
4	Dibenzylamine	250 (Et$_2$O, 20)	4	78 (Et$_2$O)	82
5	Anabazine	20 (MeOH, reflux)	6	62 (MeOH)	99

It seems to be a general tendency that ionic liquids accelerate the ring-closing reactions based on the water or alcohol splitting in the intermediate state. This phenomenon can relate to the ability of ionic liquids to solubilize these small polar molecules, resulting in a decrease of their activity in side or back reactions.

Another example of such type of reaction is the formation of pyrazine ring by the interaction of α-diketones with diamines (see Scheme 10).[20]
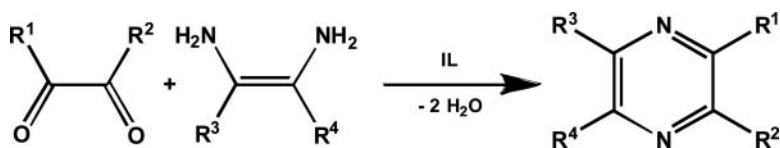
Scheme 10 Synthesis of pyrazines in ionic liquids.

The typical synthesis of pyrazine derivatives is based on the condensation of 1,2-diamines (mostly aryl-1,2-diamines) with 1,2-dicarbonyl compounds in alcohol or in acetic acid medium under reflux. The reaction proceeds very slowly and requires heating of the reaction mixture for many hours.[21–23]

Surprisingly, the same reaction proceeds in ionic liquids much faster, even at room temperature and gives the products in a good yield (see Table 3).

The product isolation procedure is very simple. The reaction mixture can be diluted with water (in the case of ionic liquids A, B, C, D, E), and the product is filtered off or the product can be extracted from ionic liquid (in the case F and G) with hexane. In both cases, the ionic liquid can be regenerated and reused several times.[20]
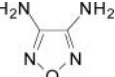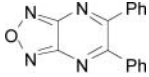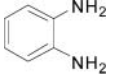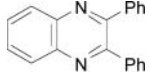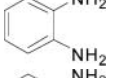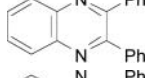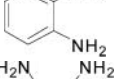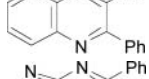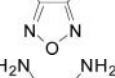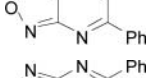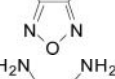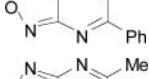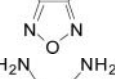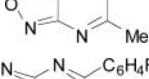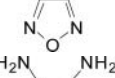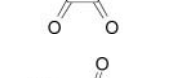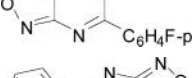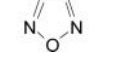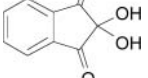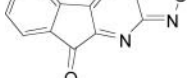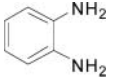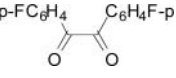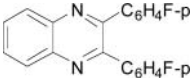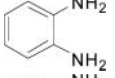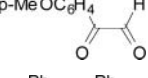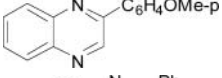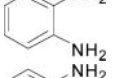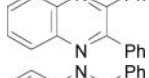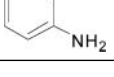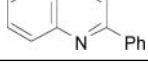
Ionic liquid as reaction medium can influence not only the kinetic of chemical reactions but also the regioselectivity in the synthesis of chemical substances, for example in the bromination of levulinic acid (Scheme 11).[24]

R = H (a), n-C$_4$H$_9$ (b) or CH$_3$ (c)
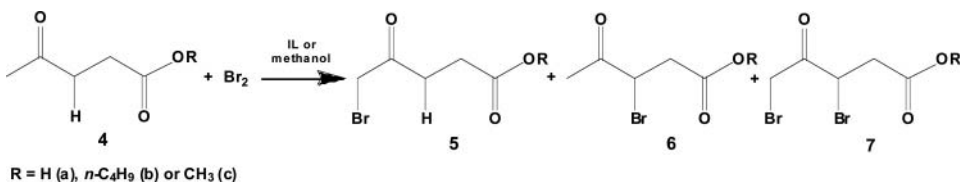
Scheme 11 Bromination of levulinic acid in ionic liquids.[24]

If the bromination of levulinic acid (**4**) proceeds in methanol, the major product in the reaction mixture is the mono-bromo compound (**5**). Replacement of methanol as reaction medium with an ionic liquid not only accelerates the bromination process but also results in the inversion in the regioselectivity. The major product that is formed in ionic liquid medium is the mono-bromo compound (**6**) (see Table 4), which is of interest for further derivatization. After separation of the brominated adducts, the ionic liquid can easily be recovered and reused for the next charge.[24]

Table 3 Synthesis of diazines in ionic liquids[20]

	Diamin	1,2-Dicarbonyl	Ionic liquid*	Temp. °C	Time h	Product	Yield %	Mp, °C
1	H2N—NH2 (furazan)	Ph—Ph (dione)	A	70	8,5		72	200–201
2	o-phenylenediamine	Ph—Ph (dione)	A	30	1		85	123–125
3	o-phenylenediamine	Ph—Ph (dione)	B	30	1		92	123–125
4	o-phenylenediamine	Ph—Ph (dione)	C	30	1		93	123–125
5	H2N—NH2 (furazan)	Ph—Ph (dione)	D	70	1		55	200–201
6	H2N—NH2 (furazan)	Ph—Ph (dione)	B	70	10,5		70	200–201
7	H2N—NH2 (furazan)	Me—Me (dione)	E	20	1		60	106–107
8	H2N—NH2 (furazan)	p-FC6H4—C6H4F-p (dione)	E	80	9		65	169–170
9	H2N—NH2 (furazan)	indane-dione diol	E	20	5		60	302–303
10	o-phenylenediamine	p-FC6H4—C6H4F-p (dione)	E	30	2		84	135–137
11	o-phenylenediamine	p-MeOC6H4—H (glyoxal)	B	80	0,25		100	99–100
1	o-phenylenediamine	Ph—Ph (dione)	F	30	1		75	125–126
2	o-phenylenediamine	Ph—Ph (dione)	G	30	1		77	125–126

*Ionic liquid: A 1-Ethyl-3-methylimidazolium (**EMIM**) tetrafluoroborat.

B N-Butyl-N-methylpyrrolidinium (**BMPL**) triflat.

C 1-Butyl-3-methylimidazolium (**BMIM**) methylsulfonat.

D 1-Ethyl-3-methylimidazolium (**EMIM**) hydrogensulfat.

E 1-Ethyl-3-methylimidazolium (**EMIM**) triflat.

F N-Butyl-N-methylpyrrolidinium (**BMPL**) bis(trifluoromethylsulfonyl)imide.

G Trihexyl(tetradecyl)phosphonium tris(pentafluoroethyl)trifluorophosphat.

Table 4 Bromination of levulinic acid

| R	Solvent	Temp. (°C)	Reaction time (h)	Ratio 5–7		
				5	**6**	**7**
b	CH_3OH	20	21	3.0	1.0	Nd
A	$CH_3OH^{(d)}$	65	3.5	3.0	1.0	Nd
A	[BMIM]Br	20	0.33	1.0	3.4	0.6
A	[OMIM]Br	50	0.25	1.0	5.0	0.4
A	[EMIM][HSO_4]	20	0.42	1.0	6.0	2.0
A	[BMPL][$N(CF_3SO_2)_2$]	20	0.75	1.0	6.0	2.6
C	[BMIM]Br	20	0.33	1.0	4.5	0.7
C	[EMIM][HSO_4]	20	0.05	1.0	4.2	1.8

The products **5–7** have been isolated as methyl esters, which are formed with the participation of the solvent (methanol).

Presumably, ionic liquids support the enolization of γ-diketones [for example levulinic acid (**4**)] resulting in the formation of internal enol (**4a**), which undergoes fast bromination into position 3 (Scheme 12).[24]
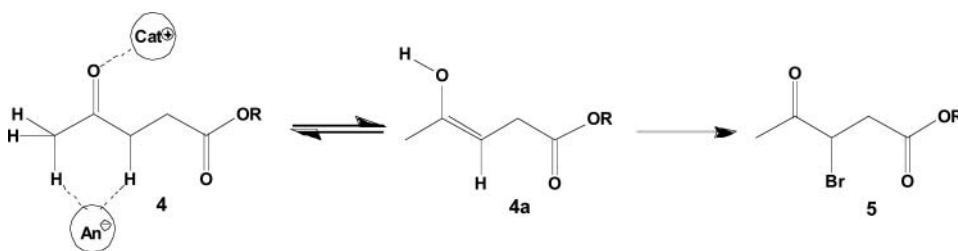
Scheme 12 Influence of ionic liquids on the bromination of levulinic acid.

CONCLUSION

Ionic liquids are new advanced media for organic synthesis. They are commercially available from several companies around the world, including Merck KGaA, Darmstadt, Germany.

Hydrogensulfate ionic liquids possess catalytic activity and provide access to convenient technologies for the preparation of various useful compounds.

EXPERIMENTAL

Chemicals

Ionic liquids were prepared as described in the citations related to the patents or patents applications or publications referred below. Other chemicals were purchased from the companies or suppliers of chemical reagents and used without further purification unless stated otherwise.

Analytical Procedures

NMR samples were measured in a 5-mm precision glass NMR tube (Wilmad 507 or 528 PPT) at 24°C. Ambient and low-temperature NMR spectra were recorded in the deuterium-locked mode on a Bruker Avance II (300 MHz) or Avance III (400 MHz) spectrometer.

The ^{1}H NMR chemical shifts were referenced with respect to tetramethylsilane (TMS) using the chemical shifts for the solvents CH_2Cl_2 (5.32 ppm) and CH_3CN (1.95 ppm). The ^{13}C NMR chemical shifts were referenced with respect to TMS using the chemical shifts for the solvents CH_2Cl_2 (53.5 ppm) and CH_3CN (118.7 ppm). The ^{19}F NMR spectra were referenced with respect to $CFCl_3$ using either the internal standards C_6F_6 (-162.9 ppm) or $C_6H_5CF_3$ (-63.9 ppm), or externally to a neat $CFCl_3$ reference sample at 25°C. The ^{31}P NMR chemical shifts were referenced with respect to 85% H_3PO_4 in D_2O.

The purity (quality) of ionic liquids was controlled by measuring the residual water (Karl-Fischer titration; 831 KF-Coulometer, Metrohm) and halides (ion-chromotography, Metrohm Advanced IC System; stationary phase: Metrosep A SUPP4 – 150).

The Synthesis Procedure

The syntheses of the compounds described here are given in the patents/patents application or publications and literature cited therein.

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