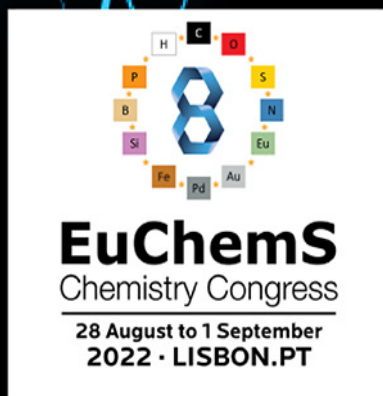


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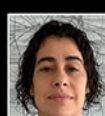
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Acid and Base Water Coexists in a Micro-Structured Ionic Liquid and Catalyzes Organic Reactions in One-Pot

Antonio Leyva-Pérez,^{*[a]} Cristina Bilanin,^[a] Matea Bacic,^[a] and Rossella Greco^[a]

The most paradigmatic example of antagonist chemical species are protons and hydroxyls, and their coexistence in a liquid system is of high interest. Here we show that commercial ionic liquids stabilize microdroplets of water with $\text{pH} < 0$ and

$\text{pH} > 14$, concomitantly and without any additive, and that this micro-structured liquid medium catalyzes organic reactions in one-pot.

Introduction

The coexistence of antagonist chemical species is often achieved in solid systems, where chemical mobility is restricted and immobilization avoids annihilation.^[1] In contrast, liquid systems cannot bear such a strategy, and compartmentalization is required to get opposite species working at the same location.^[2] Nature provides prominent examples, with a sort of complex membranes recurrently used to separate contrary chemical species, which otherwise would react and decompose if they find each other.^[3] This functional spatial separation in biological systems has been mimicked for years, with more or less degree of complexity, by synthetic chemical systems, however, these systems require the use of surfactants, polymers or any other chemical intermediate able to separate and, at the same time, manifold the traffic of chemical species through the compartment barrier.^[4]

Ionic liquids are typically constituted by ionically bonded organic molecules of high polarity, immiscible in water and with some acidity.^[5] It has been recently reported that the addition of small amounts of water, up to 5 wt%, spontaneously generate homogeneous microdroplets of $\sim 1 \mu\text{m}$, without any additive required.^[6] Thus, we envisioned here that acid and basic water microdroplets could coexist in the ionic liquid. We report here that this phenomenon indeed occurs, and that the so-formed microdroplets are indefinitely stable. The micro-structured acid/base liquid medium can be used as a catalyst and solvent for cascade organic reactions where acid and bases are required along the different synthetic steps.^[7]

Results and Discussion

Figure 1 shows that when a 5 wt% of acid water is added to a conventional ionic liquid such as 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF₄]), with a simple pipette, water microdroplets of $\sim 1 \mu\text{m}$ are spontaneously generated at room temperature. The same effect occurs when basic water is added, and also when both acid and base water are sequentially introduced. The microdroplets are formed without mixing, as visualized by the addition of phenol red in the base solution, since Figure 1 also shows that the base water microdroplets containing phenol red (red circles) are separated from the uncolored acid microdroplets (blue circles). The corresponding histograms and average particle size values of the different samples also support the independent formation of the acid and base water droplets in the mixture, since the histogram and particle diameter of the latter is precisely the average of the single acid and base microdroplet solutions. These droplets are stable for months and can be heated up to 100 °C without apparent coalescence,^[6b,8] and the order of addition of the acid and the base can be inverted without apparent change in the final micro-structured ionic liquid. A clear visualization of the acid/base coexistence in the ionic liquid is also obtained after mixing acetic acid CH₃COOH and Na₂CO₃ solutions in water, ethanol, *n*-hexane and [bmim][BF₄] (video S1 in the Supporting Information). While, as expected, CO₂ bubbles are immediately formed in the conventional solvents, gas evolution is not observed in [bmim][BF₄], even after heating. Thus, it seems that the aqueous protonic and carbonate solutions preserve their integrity within the ionic liquid even under heating conditions.

Figure 2 shows an amplification of the ¹H nuclear magnetic resonance (¹H NMR) spectrum of the ionic liquid [bmim][BF₄] after adding a solution of triethylamine (Et₃N, 0.1 mmol) in 12 N HCl_{aq}, and, then, a second solution of pyridine (Py, 0.1 mmol) in concentrated 10 M KOH_{aq}, and stirring for 15 min at room temperature (Figure S1 for the whole spectrum). The methylene signals (A) for protonated Et₃N (Et₃N·HCl) and the aromatic signals (A and C) for free Py can be clearly seen in the expected position and with the expected multiplicity after the addition procedure, untouched and not scrambled. In accordance, free Et₃N and protonated Py are marginally present and completely absent, respectively. The corresponding ¹³C NMR spectrum

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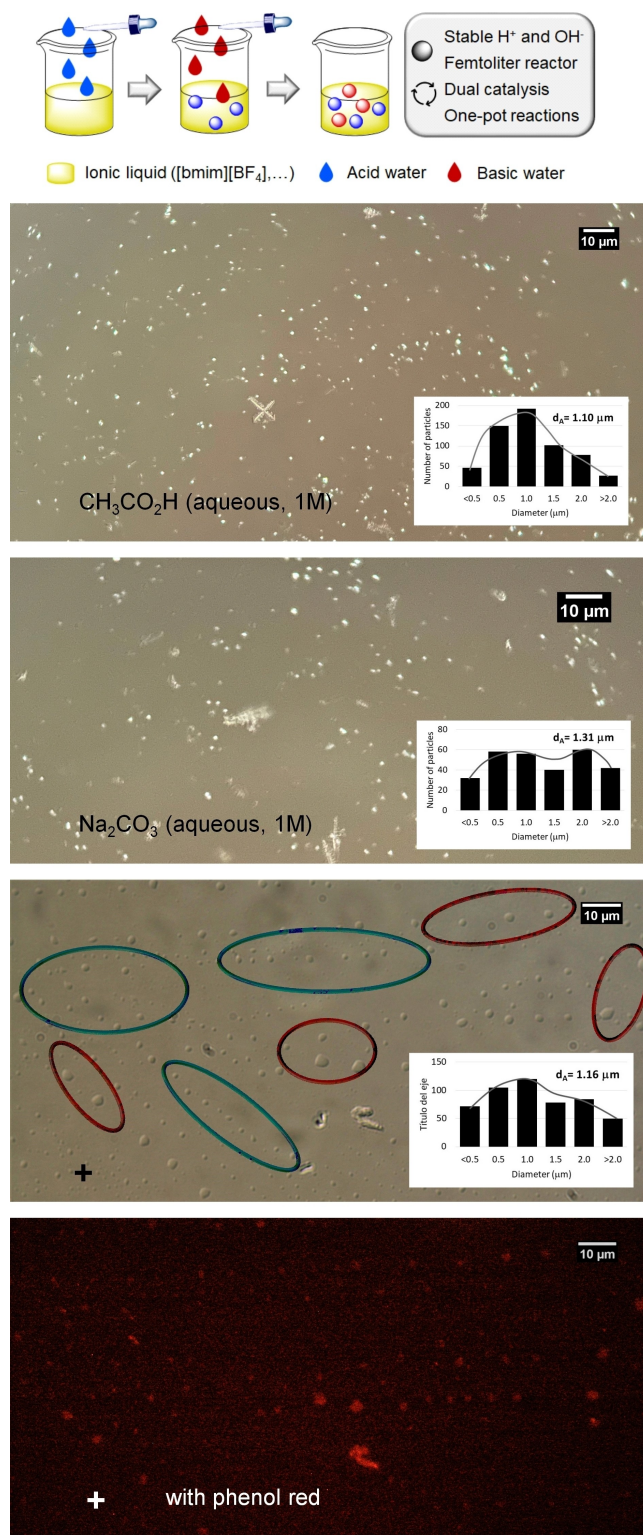


Figure 1. Top: Illustration of the generation in ionic liquids of acid and base water droplets, and potential catalytic applications. From middle to bottom: Representative microphotographs of the ionic liquid [bmim][BF₄] after adding a 5 wt% of 1 M water solutions of acetic acid, sodium carbonate, both together and both together with phenol red added in the basic water solution. Blue and red circles represent acid and base microdroplets, respectively, coexisting in [bmim][BF₄]. The insets show the corresponding histograms with the average microdroplet diameter (d_n).

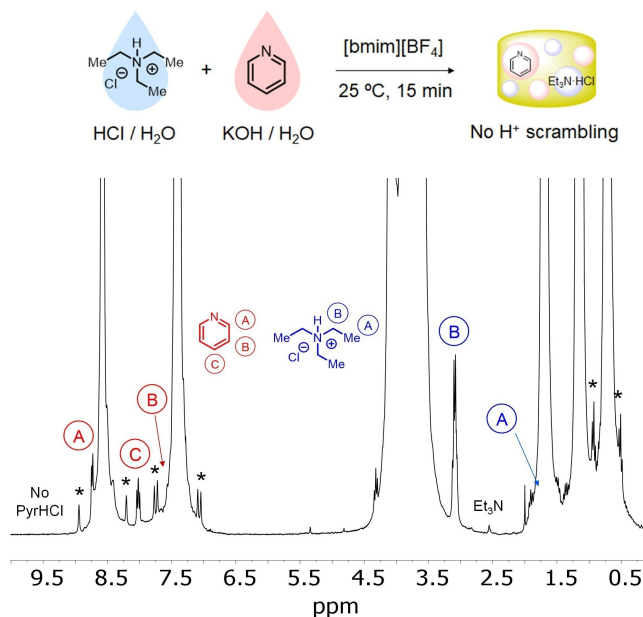


Figure 2. ¹H nuclear magnetic resonance (¹H NMR) spectrum of [bmim][BF₄] containing a 5 wt% solution of 0.1 mmol of Et₃N in HCl_{aq} (12 M) and a 5 wt% solution of 0.1 mmol of Py in KOH_{aq} (10 M). The spectrum was recorded in a capillary NMR tube containing separate CDCl₃ as a reference. Asterisks indicate resonance of the ionic liquid signals.

confirms these assignments (Figure S1). The lack of proton scrambling between Et₃N·HCl in HCl_{aq} and Py in KOH_{aq}, strongly supports that the microdroplets do not find each other after the sequential addition to [bmim][BF₄], keeping the corresponding pH values (<0 and >14, respectively). It is worth commenting here that the signals corresponding to the [bmim] carbene or carbene dimer are not visualized in the NMR spectrum, which indicates that the strong base KOH does not deprotonate the [bmim] cation up to 5 wt% water addition, and further supports the co-stability of the ionic liquid and the base water solution.^[9] Indeed, the characteristic green color of bmim carbenes and dimers is not observed.^[10]

The micro-structured acid/base liquid system was then tested as a catalytic/solvent system for organic reactions in one pot. Figure 3 shows the first reaction tested, i.e. the rearrangement of stilbene oxide **1**. This reaction was originally reported in strong acid media,^[11a,b] however, recent findings indicate that a dual acid/base system is beneficial for the rate and selectivity of the reaction,^[11c] in accordance with the accepted mechanism shown in Figure 3 (top). In our case, the micro-structured liquid system was a successful catalytic system when butyl iodide (BuI) was used as a co-catalyst (see Table S1 for optimization results), to give a 71% of the rearranged aldehyde product **2a** plus 20% of 1,2-diphenylethanone **2b** and 9% of styrene **2c** (complete conversion, Figure S2).^[11b] The use of either *trans* or *cis* epoxide **1** as the starting material does not have any significant influence in the reaction outcome (Figure S2) and 1-butyl-3-methylimidazolium hexafluorophosphate [bmim][PF₆] can also be used as the ionic liquid (entry 7, Table S1). Different acid/base amounts were tested and the results showed that the

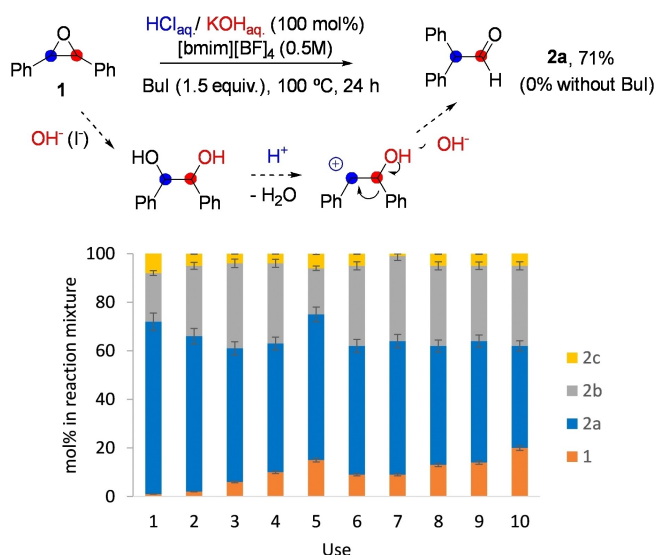


Figure 3. Rearrangement of stilbene oxide **1** catalyzed by the micro-structured acid/base liquid system (top) and the corresponding reuses (bottom, 1 equivalent of Bul respect to reagent **1** is added in each reuse). Error bars account for 5% uncertainty.

selectivity does not change but the yield does, and only for >0.5 equivalents (50 mol%) of HCl, the reaction works well (Table S1, entries 8–10). Bul apparently acts as a source of catalytically active iodides (I^-), since decreasing the amount of Bul still leads to high conversions of **1** and good yields of **2a**, however, at the expense of forming more by-product **2b** (Table S2). A kinetic analysis shows that by-products **2b** and **2c** are formed only at intermediate conversions, when significant amounts of both free OH^- and starting material **1** still exist in solution (Figure S3). When the reaction starts from isolated **2a**, by-products **2b** and **2c** are formed, which indicates that these by-products could come from **2a** (Figure S4). These results indicate that Bul is quenching the nucleophilic action of OH^- anions, which is confirmed by the quantitative formation of BuOH with time (not shown). Besides, other sources of iodide such as Bu_4NI , KI and iodobenzene can also be used as co-catalysts to give product **2a**, and the use of $[bmim][I]$ as both an iodide source and solvent, is also possible, but with lower yields (Table S2, entries 5–10). The moderate selectivity obtained for **2a** is compatible with previous findings in the literature,^[11] including reusable solid catalysts^[11d–e] (Table S3). With these results in hand, the liquid catalytic system could be used up to 10 times without any further addition of acid or base after adding 1 equivalent of Bul, giving a high conversion of **1** in all cases and just a slight decrease in selectivity through the reuses, as shown in Figure 3 (bottom).

Microscopic analysis shows that the acid/base microdroplets remain in the ionic liquid after the tenth use (Figure S5). The reuse of catalytic HCl_{aq} or KOH_{aq} for organic reactions in solution, even separately, is extremely difficult to find in the literature, moreover when both antagonist H^+ and OH^- catalysts are present at the same time in reaction. Therefore, the micro-structured catalytic system shown here opens the

door to use and recover H^+ and OH^- catalysts in a single reaction vessel in a very simple manner.

The second reaction tested was the one-pot ketal hydrolysis/Knoevenagel condensation, a cascade reaction previously performed with solid catalysts.^[11] Figure 4 (top) shows that the reaction between protected benzaldehyde **3** and malononitrile **4** proceeds in 89% yield of coupled product **5** with the acid/base ionic liquid system, in this case with ethanol rather than water as a microdroplet solvent (ethanol and methanol also generate the microdroplets, Figure S6). A kinetic analysis shows the appearance of benzaldehyde as a primary product of the reaction, after acid-catalyzed deprotection of **3**, and the progressive disappearance of intermediate benzaldehyde after reacting with **4** (Figure S7). However, when the reaction is performed directly from benzaldehyde, the yield is much lower (Figure S8). This result might be related to a higher propensity of benzaldehyde to suffer undesired by-reactions when present in higher amounts, instead of being dosed by the progressive in-situ deprotection of **3**. The necessary minimization of the water amount for the condensation reaction makes sense, considering that the base-catalyzed Knoevenagel reaction is an equilibrium which requires the removal of water, thus an excessive amount of water quenches the reaction. In contrast, ethanol does not hamper the condensation and provides enough amount of water for the first acid-catalyzed hydrolysis step. Optimization tests showed that the strong acid HCl is required for the hydrolysis, since acetic acid (CH_3COOH) does not catalyze the reaction (Table S4).

The only by-product formed to complete the mass balance is ester **6**, which comes from the rearrangement of ketal **3** triggered by the $[bmim]$ carbene formed after deprotonation of the ionic liquid under the reaction conditions (Figure S9).^[10] In

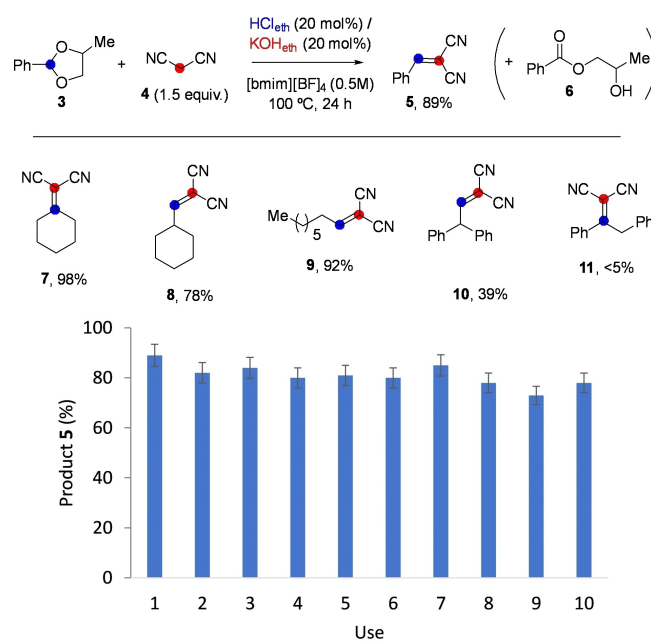


Figure 4. One-pot ketal hydrolysis/Knoevenagel condensation catalyzed by the micro-structured basic/acid liquid system (top) and reuses. Error bars account for 5% uncertainty.

agreement with this hypothesis, both products **5** and **6** are also found in [bmim][PF₆] but the only product found in 1-butyl-2-methyl-3-methylimidazolium hexafluorophosphate [bmmim][PF₆] as the ionic liquid, in which carbene formation is blocked, is **5** (Table S4). Since carbene dimers are not observed in the NMR (see Figure 2 above), it can be assumed that the deprotonation of [bmim] is undetected, possibly occurring very rapidly nearby the base microdroplets, and that the neighboring acid microdroplets re-protonate the [bmim] cation and avoid ionic liquid degradation (Figure S9). Figure 4 also shows that the one-pot ketal hydrolysis/Knoevenagel condensation in the acid/base ionic liquid can be extended to cyclic and acyclic ketals (products **7–9**), however, the presence of flanking aromatic groups around the ketal hampers the reaction, possibly due to steric hindrance (products **10–11**). Besides, the acid/base liquid catalytic system can be reused up to 10 times without any depletion in catalytic activity, although the acid and base had to be replenished in this case since the alcohol solution is significantly extracted after ethyl ether washings.

Ionic liquids are also good stabilizers of catalytic metal complexes and aggregates,^[12] and our strategy here also allows to use the water microdroplets as femtoliter reactors for soluble metal catalysts.^[13] Figure 5 shows the one-pot Pd/Cu-catalyzed Sonogashira coupling/silane deprotection/Au-catalyzed alkyne hydration, where methanol and water are necessary reagents along the different steps.^[14] First, the Sonogashira coupling between *p*-fluoriodobenzene **12a** and trimethylsilane (TMS)-protected acetylene **13** occurs under basic conditions in [bmim][BF₄], to in-situ generate product **14a**. Then, K₂CO₃ in methanol/water is added to the hot reaction mixture, to give the intermediate alkyne product **15a** after 3 h reaction time. Finally, a solution of AuCl in 3 M HCl is added, to trigger the hydration reaction and produce the final ketone product **16a** in 55% yield over three steps, without any isolation of intermediates and without any quenching treatment. The results for each individual step are also shown in Figure 5. Notice that the final acid-catalyzed hydration reaction of **15a** occurs in the presence of aqueous base, which supports the effectiveness of the ionic liquid in keeping separated the acid and base aqueous solutions during the one-pot reactions. Other aromatic iodides (**12b–d**) were tested, to give often good yields, although it was

necessary to clean the reaction after the second step to get products **16b–d**.

The use of AuCl as a source of Au is key for the reaction to proceed, since if the reaction is performed with HAuCl₄, [PPh₃Au]⁺ and [Au(NHC)]⁺ (the last two generated from the corresponding chloride salts + AgOTf in MeOH solvent and then added to the reaction medium), the yield of **16a** is < 5% yield in all cases, either under acid conditions or not. It is difficult to rationalize at this point the significant higher catalytic activity of AuCl with respect to the other Au counterpart catalysts, which are of course well-known catalysts for the hydration reaction.^[15] However, it can be argued not only a better stability of AuCl under the micro-structured reaction conditions but also to the different reagents accumulated in the reaction medium during the successive previous reactions, which include the Pd and Cu catalyst, triethylamine, and TMS derivatives, among others.

Conclusion

In summary, the synthesis of homogeneously distributed acid and base water microdroplets in an ionic liquid media, coexisting, has been achieved. The liquid system allows to perform acid/base catalyzed cascade reactions in water^[16] with the simplest acid and bases, i.e. HCl and KOH, and others. The additive-free formation of pH tunable water microdroplets can have further applications not only in catalysis but also in fundamental biological^[17] and physicochemical^[18] studies, including for instance nanofabrication^[19] and optics.^[20]

Experimental Section

Nuclear magnetic resonance (NMR) experiment with Et₃N and pyridine as acid/base probes. 1-Butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF₄], 400 μl) was placed in a 2 ml vial equipped with a magnetic stirrer. Then, 20 μl of conc. HCl containing 0.1 mmol of Et₃N was added and the mixture stirred for 5 min. After that, 20 μl of a 10 M KOH solution in water containing 0.1 mmol of pyridine was added, and the mixture was stirred for 15 min. Then, the liquid was transferred to a capillary NMR tube containing CDCl₃ in the capillary part, and the corresponding ¹H and ¹³C NMRs recorded at room temperature.

Reaction analysis. Reactions were performed in 2.0 ml vials equipped with a magnetic stirrer and closed with a steel cap having a rubber septum part to sample out. The reaction mixture was extracted with diethyl ether (2×2 ml) after reaction, and analyzed by GC, GC-MS and NMR in order to identify and quantify the products, using *n*-dodecane as an external standard. For kinetics, each point was taken from an individual reaction. Products were characterized by GC-MS, ¹H- and ¹³C-NMR, and DEPT, and compared with the given literature.

Reaction procedure for the rearrangement of epoxide **1.** 1-Butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF₄]) or hexafluorophosphate ([bmim][PF₆], 200 μl) was placed in a 2 ml vial equipped with a magnetic stirrer. Then, typically 10 μl of conc. HCl (1.0 equivalents respect to **1**, 100 mol%) was added and the mixture stirred for 5 min. After that, typically 10 μl of 10 M KOH (1.0 equivalents respect to **1**, 100 mol%) in water, the correspond-

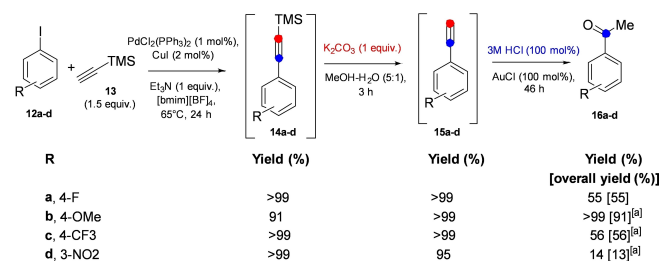


Figure 5. One-pot Sonogashira coupling/silane deprotection/alkyne hydration catalyzed by the micro-structured basic/acid liquid system containing different catalytic metals and different aqueous stoichiometric bases and acids. Overall yield refers to the three-step sequence. [a] The third step was performed from the isolated alkyne, in order to remove the accumulated impurities.

ing epoxide **1** (*cis* or *trans*, 0.1 mmol) and Bul (0.1 mmol, 1 equivalent respect to the reagent) were added, the vial was capped, and the mixture was stirred at 500 rpm in a pre-heated oil bath at 100 °C for 24 h. After cooling, the reaction mixture was analyzed as described above.

Reuses for the rearrangement of epoxide 1. The reuses of ionic liquid were performed recovering the ionic liquid reaction mixture at the end of the reaction and washing with diethyl ether (2×2 ml). Subsequently, the ionic liquid was dried under vacuum for 2–3 min in order to remove the remaining diethyl ether but not the acid/base water microdroplets. Then, the corresponding epoxide **1** (*cis* or *trans*, 0.1 mmol) and Bul (0.1 mmol, 1 equivalent respect to the reagent) were added and the reaction performed and analyzed as indicated above.

General reaction procedure for the acetal deprotection/Knoevenagel condensation reactions. 1-Butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF₄]) or hexafluorophosphate ([bmim][PF₆], 200 μl) was placed in a 2 ml vial equipped with a magnetic stirrer. Then, 2 μl of a 10 M KOH solution in ethanol (previously dissolved at 70 °C, 0.2 equivalents respect to the limiting reagent, 20 mol%), the corresponding reactants (0.1 mmol of the limiting reagent) and, finally, 2 μl of conc. HCl in ethanol (0.2 equivalents respect to the limiting reagent, 20 mol%) were sequentially added, under magnetic stirring. The vial was capped and the mixture was stirred at 500 rpm in a pre-heated oil bath at 100 °C for 24 h. After cooling, the reaction mixture was analyzed as described above.

Reuses for the acetal deprotection/Knoevenagel condensation reactions. The reuses of ionic liquid were performed recovering the ionic liquid reaction mixture at the end of the reaction and washing with diethyl ether (2×2 ml). Subsequently, the ionic liquid was dried under vacuum and used directly in the following reaction, after adding all the catalysts and reagents needed (as above indicated), including fresh ethanolic solutions of HCl and KOH. The reactions were performed and analyzed as indicated above.

Representative reaction procedure for the one-pot Sonogashira coupling/silane deprotection/alkyne hydration reaction. PdCl₂(PPh₃)₂ (0.0114 mmol) and CuI (0.0231 mmol) were placed in a 2 mL vial equipped with a magnetic stirrer. Then, [bmim][BF₄] (1 mL), Et₃N (1 mmol), *p*-fluoroiodobenzene **12a** (1 mmol) and trimethylsilane-protected acetylene **13** (1.5 mmol) were added, the vial was capped and the mixture was placed in an oil bath at 65 °C under magnetic stirring for 24 h. After this time, K₂CO₃ (1 mmol) in methanol/water (5:1 v:v) was added and the mixture kept at 65 °C for additional 3 h, when a solution of AuCl (1 mmol) in 3 M HCl (200 μL) was added and the reaction mixture kept reacting for another additional 46 h. For tests with [AuPPh₃]⁺ and [Au(NHC)]⁺ as catalysts, the cations were generated from the corresponding chloride salts + AgOTf (1 equivalent) in MeOH solvent and then added to the reaction medium. After cooling, the reaction mixture was analyzed as described above.

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

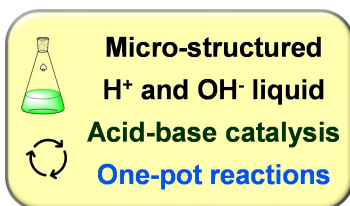
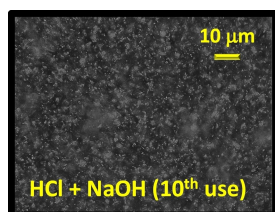
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: micro-structured liquid · water · ionic liquids · acid/base catalysis · one-pot reactions

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1 – 7

Acid and Base Water Coexists in a Micro-Structured Ionic Liquid and Catalyzes Organic Reactions in One-Pot



Domino reactions: The simple addition of acid ($\text{pH} < 0$) and base ($\text{pH} > 14$) water solutions to conventional ionic liquids generate independent acid and base microdroplets,

ready to catalyze, in one-pot, different organic reactions where both acid and base are required. The liquid system is fully recyclable.
