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catalyst investigation by electrospray (tandem) mass spectrometry Haline G. O. Alvim,^a Heibbe C. B. de Oliveira,^a Giovana A. Bataglion,^b Marcos N. Eberlin,^b Luciana

Synthesis of 2-arylbenzimidazoles under mild conditions catalyzed by a heteropolyacid-containing task-specific ionic liquid and

A task-specific ionic liquid constituted by a Bronsted acid (1-(3-sulfopropyl)-3-methyl-imidazolium hydrogen sulfate as the cation, namely MSI, and by $[PW_{12}O_{40}]^{3-}$ as the triply charged counteranion, namely PW (a heteropolyacid derivative), was used as an efficient catalyst for the condensation reaction between aldehydes and o-phenylenediamines.

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There is growing interest in the synthesis of benzimidazole derivatives mostly because of their potential as antitumoral agents.¹ The similarity between purine bases and benzimidazolebased structures renders benzimidazoles the status of "privileged scaffolds".² The interest in benzimidazole derivatives is also based on their vast and frequent therapeutic potential, which includes their action as antihypertensive, anti-inflammatory, antimicrobial, antiviral, psychoactive, antioxidant, anticoagulants, and antidiabetic agents.³ This large spectrum of biological activities shown by a plethora of benzimidazole-based molecules has boosted the development of several synthetic methodologies.⁴ Most of those methodologies require, however, toxic solvents, high temperatures, aryl acid chlorides, reagents excesses, large catalysts amounts or other undesired conditions (environmentally maleficent).⁵ The development of new catalytic and green chemistry methodologies using eco-friendly and sustainable conditions aiming at better yields, selectivities, and atom economy are therefore highly desired features.

A very promising strategy to overcome these aforementioned shortcomings is the use of ionic liquids (ILs) as the reaction media, mostly because they are regarded as "a pathway to environmental acceptability", ⁶ particularly when imidazolium-based ILs are used.⁷

a Laboratory of Bioactive Compounds Synthesis N.T.S, University of Brasilia (IQ-UnB). Campus Universitário Darcy Ribeiro, CEP 70904970, P.O.Box 4478, Brasília-DF, Brazil. Environmentally-friend reactions may be achieved by a proper combination of a catalyst and an IL,⁸ with a distinct attention for imidazolium ILs, which proved to be excellent solvents for synthesis and catalysis.⁹⁻¹³ Functionalized ILs, also known as task-specific ionic liquids (TSILs), with these ideas in mind, we have successfully supported transition metals in imidazolium ILs for an improved Biginelli multicomponent reaction.¹⁴ We have also used ionophilic ligands and complexes for iron-catalyzed oxidations in ILs.¹⁵.More recently, we evaluated the incorporation of the anionic heteropolyacid derivative $[PW_{12}O_{40}]^{3-}$ (phosphotungstic acid derivative, namely PW) as the counterion for a Bronsted-acid imidazolium-based cation (1-(3-sulfopropyl)-3-methyl-imidazolium hydrogen sulfate, namely MSI, Figure 1) applied for a multicomponent reaction in imidazolium-based ILs.¹⁶



Figure 1. Imidazolium-based ionic liquids commonly used as supports for catalyzed reactions (top). Bronsted-acid task-specific ionic liquid incorporating an anionic heteropolyacid derivative, namely MSI₃PW (bottom).

Initially, the condensation reaction to afford 2-arylbenzimidazole derivatives (Scheme 1) was tested using benzaldehyde and ophenylenediamine as the substrates. Upon increasing the temperature the system was noted to turn dark, especially for temperatures above 100 °C. Reactions carried out at 60 °C afforded the desired product in 83% whereas 67% was obtained at 90 °C. Aiming at more amenable conditions, we tested all reactions close to room temperature (40 °C) with no reagent excess and using 5 mol% of the catalyst MSI_3PW . The reaction time was set for 10 h in order to pursue maxima yields. Most reactions were however completed after 4 h.

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Scheme 1. Condensation reactions catalyzed by MSI_3PW (5 mol%) in BMI.NTf_2 (0.5 mL) at 40 °C using 1.00 mmol of each reagent for 10 h.

Table 1 summarizes the results for the synthesis of the 2arylbenzimidazoles. All products were obtained in excellent yields under very mild conditions, except for the chlorinecontaining derivative (Table 1, Entry 3), for which the yield of the isolated product was good (73%).

Table 1. Synthesized 2-arylbenzimidazoles using MSI_3PW (5 mol%) in $BMI.NTf_2$ at 40 $^{\circ}C$ for 10 h.



The inherent ionic nature of both the TSIL (catalyst) and the used IL (BMI.NTf₂) and, therefore, their facile transfer from solution to the gas phase by ESI, allowed an investigation on the acid strength behavior of MSI₃PW in the presence and in the absence of the IL by ESI-MS(/MS). Indeed, ESI-MS has been shown to be an unsurpassed proper tool for the investigation of ILs/TSILs properties, effects and mechanisms.¹⁷ It is also known that Bronsted acids may behave as superacids when supported (or embedded) in ILs.^{18,19}

Initially, a methanolic solution (50 μ M) of the catalyst (MSI₃PW) was monitored online²⁰ by ESI-MS in both the positive (Figure 2) and negative (Figure 3) ion modes. The ESI(+)-MS detected a single ion of m/z 205 (attributed to the MSI cation) which had its ESI(+)-MS/MS acquired (Figure 2). The tandem mass spectrum of MSI.PW solution shows that the gaseous cation of the TSIL (MSI, m/z 205) dissociates to afford fragments in full accordance with the proposed structure (Figure 2).





The ESI(-)-MS of the same solution (Figure 3) detected mainly the triply charged PW anion of m/z 958. The doubly charged $[PW + H]^{2-}$ anion of m/z 1439 could also be detected as the second most abundant ion. A supramolecular assembly $[MSI + PW]^{2-}$ was also detected as a doubly charged anion of m/z 1541 (show as the inset in Figure 3).



Figure 3. ESI(-)-MS of the catalyst MSI₃PW acquired from a 50 μ M methanolic solution. The inset shows the doubly charged anion [MSI.PW]^S of m/z 1541 corresponding to the supramolecular assembly of a MSI cation and one triply charged PW (PW₁₂O₄₀⁻) anion.

Next, the increase of the acidic strength of the catalyst was investigated in the presence of BMI.NTf₂ (Figure 4). Interestingly, the ion of m/z 1439 ($[PW + H]^{2}$, also detected in Figure 3) had its abundance considerably decreased, whereas the abundance of the triply charged anion PW increased. This trend shows therefore that the dissociation of the acid was even at a larger extent, in accordance with the expected acidic strength increase in the presence of the IL BMI.NTf₂. This feature is directly related with the catalyst efficiency in the IL media. When the concentration of BMI.NTf₂ was increased from 50 μ M to 100 μ M, the supramolecular [BMI(NTf₂)₂]⁻ anion of m/z 698.9 was therefore detected (Figure 4). Note that this type of supramolecular aggregate is commonly noted for imidazolium-based ILS.²¹ Other interesting ion detected in the ESI(-)-MS of Figure 4 is the supramolecular doubly charged anions [BMI + PW]²⁻ of m/z 1507.5.

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Figure 4. ESI(-)-MS of the catalyst MSI₃PW acquired from a 50 μ M methanolic solution in the presence of BMI.NTf₂. The supramolecular anion of m/z 698.9 was detected from a 100 μ M methanolic solution (BMI.NTf₂) whereas from the 50 μ M methanolic solution of BMI.NTf₂ only the anion of m/z 279.9 (NTf₂) could be detected.

Based on the ESI-MS(/MS) data, a plausible catalytic cycle could be proposed to explain the transformation (Scheme 2). In the presence of BMI.NTf₂, the acid strength of the catalyst increases and the aldehyde is protonated. The amine is protonated as well, but the equilibrium has been omitted for clarity. The protonated aldehyde then undergoes the amine addition followed by water elimination. The processes takes place again in its intramolecular version releasing the condensation product and restoring the acidic hydrogen. Note that the NTf₂⁻ anion is available to form ion-pairs with the protonated (cationic) structures therefore stabilizing them through ion-pairing (ionic liquid effect).

Finally, theoretical calculations were performed to gain insights on the acid strength increase of the catalyst in the presence of the IL BMI.NTf₂. We had as the bases the formation of a supramolecular structure as a consequence of the association between the BMI cation and PW anion, which allows the cation MSI to be more prone to promote the reaction. ESI-MS data (from Figures 3 and 4) showed that in the presence of the IL (BMI.NTf₂), the cation MSI is more available (and more acidic) in the reaction medium to catalyze the reaction as a consequence of the cation exchange. The cation exchange affords BMI_3PW structures and releases the MSI cation (Scheme 2). All calculations were performed at M062X/6-31G(d,p)/LAN2LDZ//PM6 level of theory and the results are summarized in Figure 5.



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Scheme 2. Plausible catalytic cycle proposed for the synthesis of 2-arylbenzimidazole derivatives promoted by MSI₂PW in BMI.NTf₂. Note that the cationic intermediates shown in the catalytic cycle may form ion-pairs with the NTf₂ anion therefore with stabilizing effects (ionic liquid effect).



Figure 5. Relative energies profile and stabilizing effects resulting from the BMI cation association with the triply charged PW anion (0.00 kcal mol-1) affording the supramolecular structure BMI_PW . Calculations performed at M062X/6-31G(d,p)/(LAN2L0Z/PM6 level of theory. Structures have been calculated considering PW anion (triply charged) with three non-coordinate BMI cations followed by consecutive associations affording [PW + BMI]², [PW + 2.BMI]² and [PW + 3.BMI], respectively.

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Figure 5 shows that the consecutive associations with BMI cation greatly improve the stability of the anionic (triply charged) heteropolyacid derivative therefore in accordance with the observed IL effect. This high stabilizing effect seems also to explain the origin of the superacid behavior observed for Bronsted acids in imidazolium-based ILs and the efficiency of the catalytic system described herein.

Conclusions

In summary, we have demonstrated the catalytic ability of MSI_3PW in the synthesis of 2-arylbenzimidazole derivatives performed in ILs under mild conditions.²² ESI-MS monitoring pointed to the origin of the superacid behavior and the high stabilization of the catalyst in ILs. Theoretical calculations²³ allowed a better understanding on the superacid behavior of the catalyst and its efficiency as a consequence of the pronounced ionic liquid effect.

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20 ESI-MS and ESI-MS/MS measurements were performed in both the positive and negative ion modes (m/z 50–2000 range) on a HDMS instrument. This instrument has a hybrid quadrupole/ion mobility/orthogonal acceleration time-of-flight (oa-TOF) geometry and was used in the TOF V+ mode. All samples were dissolved in methanol to form 50 μ M solutions and were directly infused into the ESI source at a flow rate of 10 μ L/min. ESI source conditions were as follows: capillary voltage 3.0 kV, sample cone 20 V, extraction cone 3 V.

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22 A sealed Schlenk tube containing 0.5 mL of BMI.NTf2,1.00 mmol of the aldehyde, 1.00 mmol of the diamine and MSI₃PW (5 mol %) was allowed to react at 40 °C for 10 h. Substrates were purified by chromatographic column eluted with mixtures of hexane/ethyl acetate. 2-phenyl-1H-benzo[d]imidazole (1). 1H NMR (300 MHz, DMSO-d6), δ : 7.55-7.60 (m, 2H), 7.72-7.78 (m, 2H), 7.86-7.91 (m, 2H), 8.45-8.51 (m, 2H). 13C NMR (75 MHz, DMSO-d6), δ : 113.9, 123.1, 125.8, 127.9, 129.5, 131.8, 133.2, 148.5.

23 Aiming to build up the complex of interest, we started from the crystallographic structure of HPW (with the acidic H removed) in which we included the three geometric structures of BMI. During the geometry optimization, the Cartesian coordinates of the PW triply charged anion were kept frozen and only the relative positions of the three BMI cations were optimized using the semiempirical parametric method (PM6). The optimized geometry were therefore used for the single point calculation at M06-2X/6-31G(d,p)/LANL2DZ level of theory (i.e. LANL2DZ pseudo potential for W and the 6-31G(2,p) splitvalence basis set for all other atoms). To avoid a basis-set superposition error (BSSE) the interaction energies were counter-poise corrected using the standard approach of Boys and Bernardi. All theoretical calculations were carried out using Gaussian 09 program suite.