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# Task-oriented use of ionic liquids: efficient acetylation of alcohols and phenols

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# ABSTRACT

The ionic liquid 1-butyl-3-methylimidazolium acetate proves to be an excellent reaction medium for the acetylation of alcohols and phenols, providing better conditions than the acidic 1-butyl-3-methylimidazolium bisulfate. Reactions were carried at room temperature, with only a 10% excess of acylating agent and with no other solvent or catalyst added.

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The acetylation reaction of hydroxyl groups in alcohols and phenols constitutes an important synthetic procedure that is widely employed for protection in multi-step synthesis due to its easy reversibility. Protection reactions have to proceed rapidly, readily, quantitatively and keeping costs to a minimum. Typically, the acetylation of hydroxyl groups is performed with an excess of acetic anhydride under basic or acidic catalysis; in some cases acetyl halides have been used.<sup>1.2</sup> In the light of the 12 principles of Green Chemistry,<sup>3</sup> protection/deprotection reactions are intrinsically not-green, and better avoided whenever possible.

Ionic liquids, in particular, have received remarkable attention in the last decade or so as reaction media and/or catalysts in organic synthesis. They have also been employed in the acylation of hydroxyl groups. Thus, Brönsted acidic 1-H-3-methylimidazolium bisulfate has been used as the catalyst in the acetylation of alcohols and phenols;<sup>4</sup> as well as trimethylammoniumbutanesulfonate bisulfate,<sup>2</sup> and Lewis acidic ionic liquids have been used as well.<sup>5,6</sup> In other cases, the ionic liquid is used as the immobiliser for Lewis acidic rare-earth based catalysts.<sup>7,8</sup> Basic catalytic activity by an ionic liquid has been reported in the acetylation of alcohols and carbohydrates.<sup>9,10</sup> The use of enzymes and ionic liquids in the acylation of levoglucosan,<sup>11</sup> and glucosides has also been reported.<sup>12</sup> One imidazolium bromide ionic liquid has been employed as the medium for the ultrasonic activation of alcohols with acetic anhydride.<sup>13</sup> Moreover, acylimidazolium derivatives have been used as acylating agents in protection of alcohols.<sup>14–19</sup>

\* Corresponding author. *E-mail address:* iglomar@unex.es (I. López). In order to take advantage of beneficial ionic liquid features, such as nonvolatility, 'greenness' and wide solvent ability, a purpose-oriented selection of the melt is essential.<sup>20</sup> For instance, the widely used 1-butyl-3-methylimidazolium hexafluorophosphate or 1-butyl-3-methylimidazolium tetrafluoroborate employed as solvents for the acetylation of glucose yielded no product.<sup>10</sup> On the other hand, benzoate imidazoliums showed catalytic activity in this reaction, yet the acetate product formed complicated the recovery of products.<sup>10</sup> Depending on cation/anion combinations, the physico–chemical properties of ILs can be tuned for a particular application, in search of novel functional compounds termed as Task-Specific Ionic Liquids (TSILs).<sup>21</sup>

In our group, we have been testing the use of ionic liquids as reaction media in organic reactions. Thus, new methodologies involving ionic liquids and Lewis acid catalysts,<sup>22</sup> ultrasounds,<sup>23</sup> and mineral catalysts and microwaves have been studied.<sup>24</sup> In further pursuing these investigations, we have now studied the use of two simple ionic liquids, the acidic 1-butyl-3-methylimidazolium bisulfate [bmim][HSO<sub>4</sub>], and the mildly basic 1-butyl-3-methylimidazolium acetate, [bmim][OAc]. This choice is based on their distinctive Brönsted acid-base characteristics. Accordingly, the former could act as an acid catalyst, while the latter might show basic catalysis. Furthermore, these two ionic liquids are easy to synthesise and commercially available at a lower cost than analogous melts such as dicyanamides, which have proven to be excellent reaction media for acetylation of hydroxyl groups.<sup>9</sup> The acetate melt encompasses some other desirable features, the nontoxic nature of its anion, and the fact that it is a common ion involved in these processes.

We report herein that both [bmim][HSO<sub>4</sub>], and [bmim][OAc] are efficient reaction media for a wide variety of alcohols, including

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Table 1				
Acetylation	reactions	in	ionic	liquids

Entry	Substrate	Product	Solvent				
			[bmim][HSO <sub>4</sub> ]		[bmin	[bmim][OAc]	
			Time <sup>a</sup>	Yield <sup>b</sup>	Time <sup>a</sup>	Yield <sup>b</sup>	
1 <sup>c</sup>	ОН	OAc	10	90	5	94	
2 <sup>c</sup>	ОН	OAc	20	85	5	90	
3°	ДОН	OAc	20	88	5	91	
4 <sup>c</sup>	OH	∠OAc	60 <sup>f</sup>	40	5	95	
5 <sup>d</sup>	HOOH	AcOOAc	25	90	5	92	
6 <sup>c</sup>	<i>_</i> OH	OAc	60 <sup>f</sup>	g	5	89	
7 <sup>c</sup>	OH	OAc	10	89	<1	91	
8 <sup>c</sup>	OH	OAc	10	83	5	92	
9 <sup>e</sup>	HO OH HO OH OH	AcO AcO OAc	No reaction	-	15	90	

<sup>a</sup> Time (min) for 100% conversion by tlc monitoring.

<sup>b</sup> Isolated yield.

<sup>c</sup> 11 mmol of Ac<sub>2</sub>O added.

<sup>d</sup> 22 mmol of Ac<sub>2</sub>O added.

<sup>e</sup> 55 mmol of Ac<sub>2</sub>O added.

<sup>f</sup> Reaction not completed.

<sup>g</sup> Not isolated.

phenols and glucose, showing not only good solvent ability, but also catalytic activity and reusability. All products were identified by <sup>1</sup>H NMR.

In a typical experiment, 10 mmol of the alcohol was dissolved, under stirring, in 10 mmol (ca. 2 mL) of the corresponding ionic liquid at room temperature. Then 1.10 equiv of acetic anhydride per hydroxyl group was added to the medium and the reaction was monitored by tlc. Products were isolated either by extraction with ether and/or petroleum ether, washed with aqueous bicarbonate or by distillation under reduced pressure. Table 1 summarises results obtained for both ionic liquids and a variety of alcohols.

In [bmim][HSO<sub>4</sub>] all hydroxyl groups were transformed into their corresponding acetyl esters, except those for  $\beta$ -D-glucopyranose. It is important to note that while all other substrates are soluble in the ionic liquid or the solvent system formed by the ionic liquid and acetic anhydride, glucose is not, this, probably being the reason for its nonreactivity. Primary, benzylic and aromatic alcohols reacted quantitatively in short reaction times at room temperature, yielding the acetylated derivatives in solution. Remarkably, only a slight excess of acetic anhydride per hydroxyl group (1.1 mol/1.0 mol), in an equimolar amount of ionic liquid is needed.

Moreover, all the reactions carried out in [bmim][OAc] proceeded better than in [bmim][HSO<sub>4</sub>], under the same conditions. Per-O-acetylation of glucose, and acetylation of secondary, and allylic alcohols were successful in 5–15 min. It is worth mentioning the higher solubility of the glucose, compared to the other ionic liquid. Again, all the products were soluble in the reaction medium. These results show that there must be a significant catalytic effect of the acetate anion. Moreover, this anion and the acetic acid formed buffer the solution, keeping a stable pH.

It is important to check whether these reaction media can be reused. For that reason, several experiments were run after extraction of the products.  $\beta$ -Naphthol was used as a model substrate because the solid product formed can be readily weighed for yield

#### Table 2

Recycle experiments. Acetylation of β-naphthol

Run		Solvent				
	[bmim	[bmim][HSO <sub>4</sub> ]		n][OAc]		
	Time <sup>a</sup>	Yield <sup>b</sup>	Time <sup>a</sup>	Yield <sup>b</sup>		
1	20	85	10	95		
2	20	77	10	88		
3	20	73	10	91		
4	20	85	10	87		
5	20	80	10	76		

<sup>a</sup> At this unoptimised time 100% conversion, by tlc monitoring, was achieved in all cases.

<sup>b</sup> Isolated yield.

calculation. The procedure was the same as before. Results gathered in Table 2 show the feasibility of re-using these ionic liquids for five cycles with only a slight loss of activity.

Summing up, a rapid, clean, and efficient method for the acetylation of hydroxyl groups at room temperature with only a 10% excess of acetylating agent is reported. Quantitative transformation is achieved in very short reaction time. The ionic liquids perform a catalytic activity, as well as acting as the solvent. The results obtained show that the acetate ionic liquid outperforms the acidic bisulfate one. It is important to note that the acetate anion is safer and cheaper and, furthermore, due to its common nature with the by-product, acetic acid, spares all the work-up hassle arising from the presence of another species in the reaction medium. Products can be isolated by simple extraction, or distillation when suitable, and the reaction medium can be re-used at least for five times with nearly no loss of activity.

In conclusion, this protocol constitutes an improved, efficient methodology compared to others based on acid/base catalysis and/or ionic liquids. To extend its scope and limitations, and to gain insight into mechanistic details involved, further experimental and theoretical studies are under way.

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