

## 1-Butyl-3-Methyl Imidazolium Hydrogen Sulphate Promoted One-Pot Three-Component Synthesis of Amidoalkyl Naphthols

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Received July 10, 2009, Accepted August 22, 2009

An efficient and easy method for one-pot three-component synthesis of amidoalkyl naphthols by the condensation of aromatic/heteroaromatic/aliphatic aldehydes, 2-naphthol and amides or urea under thermal condition at 60 °C in the presence of acidic ionic liquid 1-butyl-3-methylimidazolium hydrogen sulphate ([bmim]HSO<sub>4</sub>) has been described.

**Key Words:** Amidoalkyl naphthols, Ionic liquid, Operational simplicity, Three-component

### Introduction

Compounds bearing 1,3-amido oxygenated functional groups are ubiquitous to a variety of biologically important natural products and potent drugs including a number of nucleoside antibiotics and HIV protease inhibitors such as ritonavir, lipinavir, and the hypotensive and bradycardiac effects of these compounds have been evaluated.<sup>1,2</sup> It is noteworthy that 1-amidoalkyl-2-naphthols can convert into important biological active 1-aminoalkyl-2-naphthol derivatives by hydrolysis reaction.<sup>2,3</sup> The importance of amidoalkyl naphthols for their synthesis has attracted renewed attention and various improved procedures have been reported. Many of these reported methods employ catalysts, such as *p*-TSA,<sup>4</sup> iodine,<sup>5</sup> sulphamic acid,<sup>6</sup> montmorillonite K-10 clay,<sup>7</sup> Ce(SO<sub>4</sub>)<sub>2</sub>,<sup>8</sup> cation-exchanged resin,<sup>9</sup> zirconyl (IV) chloride,<sup>10</sup> PPA-SiO<sub>2</sub>,<sup>11</sup> H<sub>3</sub>PW<sub>12</sub>O<sub>40</sub>,<sup>12</sup> NaHSO<sub>4</sub>-SiO<sub>2</sub>,<sup>13</sup> and silica sulfuric acid.<sup>14</sup> These methods have various drawbacks such as prolonged reaction time, low yields, toxicity, low recovery and reusability of the catalyst (Table 1). Therefore, introduction of clean procedures and utilizing ecofriendly green catalyst can be simply recycled at the end of reaction have attracted more attention.

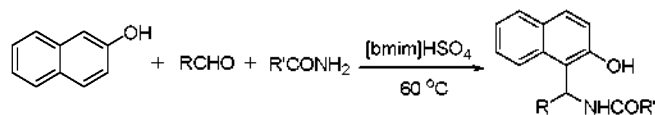
Multicomponent condensations constitutes an especially attractive synthetic strategy for rapid and efficient library generation due to the fact that the products are formed in a single step and the diversity can be achieved simply by varying the reacting components.<sup>15</sup> Very recently, we have reported the convenient synthesis of polyhydroquinolines and 2,4,5-triarylimidazole

derivatives *via* multicomponent condensation reaction.<sup>16,17</sup>

Due to the environmental concerns, the use of benign solvents as an alternative to volatile organic solvents and are of much interest to organic chemist. The use of ionic liquid as a reaction media and catalyst can offer a solution to solvent emission and catalyst recycle problems.<sup>18,19</sup> Ionic liquid posses the advantages like negligible vapour pressure, thermal stability, recyclability and dissolve many organic substrates.<sup>20</sup> In view of the emerging importance of imidazolium based ionic liquids as a novel reaction media herein, we wish to explore the use of ionic liquids as promoters and recyclable solvent systems for an one-pot three-component synthesis of amidoalkyl naphthol derivatives under mild conditions (Scheme 1).

In continuation of our interest in finding new environmentally benign methods for the synthesis of various compounds<sup>21,24</sup> and use of various ionic liquids for organic transformations.<sup>25</sup> Herein we want to report for first time, the rapid and selective synthesis of amidoalkyl naphthols in the presence of [bmim]HSO<sub>4</sub> ionic liquid as a Bronsted acidic ionic liquid.

Singh and coworkers reported the synthesis of [bmim]HSO<sub>4</sub> ionic liquid and its application for the synthesis of coumarins.<sup>26</sup> Ionic liquid technology, when used in place of chemical organic



Scheme 1

**Table 1.** Comparison results for the condensation of benzaldehyde, 2-naphthol and acetamide in the presence of ionic liquid with literature.

Entry	Catalyst	Amount of catalyst	Time (min)	Yield (%)	Condition	Reference
1	<i>p</i> -TSA	0.1 mmol	720	90	RT	4
		0.1 mmol	300	88	125 °C	
2	I <sub>2</sub>	5 mol%	720	91	RT	5
3	-	-	270	87	125 °C	5
4	ZrOCl <sub>2</sub>	0.1 mmol	840	86	RT	10
5	H <sub>3</sub> PW <sub>12</sub> O <sub>40</sub>	2 mol%	80	90	100 °C	12
6	Silica sulfuric acid	20 mg	120	85	RT	14
7	[bmim]HSO <sub>4</sub>	5 mol%	30	96	60 °C	Present work

**Table 2.** Effect of different ionic liquids in the reaction of benzaldehyde, 2-naphthol and acetamide.

Entry	Ionic liquid	Time (h)	Yield (%) <sup>a</sup>
1	[bmim]BF <sub>4</sub>	2	45
2	[bmim]PF <sub>6</sub>	2	40
3	[bmmim]Cl	2	55
4	[bmim]Cl	2	55
5	[bmim]HSO <sub>4</sub>	30 min	96
6	-	5	30

<sup>a</sup>Isolated yield.**Table 3.** Synthesis of amidoalkyl naphthols.<sup>a</sup>

Entry	R	R'	Time (min)	Yield (%)	M.P. (°C) <sup>Ref</sup>
1	C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>	30	96 (96, 94, 95) <sup>b</sup>	228 ~ 230 <sup>5</sup>
2	3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	55	92	237 ~ 239 <sup>10</sup>
3	4-ClC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	35	93	231 ~ 133 <sup>10</sup>
4	2-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	40	90	201 ~ 203 <sup>5</sup>
5	2-ClC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	40	89	197 ~ 199 <sup>5</sup>
6	4-FC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	35	92	204 ~ 206 <sup>11</sup>
7	3,4-OCH <sub>3</sub> C <sub>6</sub> H <sub>3</sub>	CH <sub>3</sub>	45	90	234 ~ 236 <sup>10</sup>
8	4-(CH <sub>3</sub> ) <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	45	94	125 ~ 127 <sup>11</sup>
9	C <sub>3</sub> H <sub>5</sub>	CH <sub>3</sub>	50	84	173 ~ 175 <sup>10</sup>
10	(CH <sub>3</sub> ) <sub>2</sub> CH	CH <sub>3</sub>	47	82	181 ~ 183 <sup>14</sup>
11	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub>	47	80	190 ~ 192 <sup>14</sup>
12	2-Furyl	CH <sub>3</sub>	45	90	218 ~ 220 <sup>5</sup>
13	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	45	90	235 ~ 237 <sup>10</sup>
14	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub>	45	88	190 ~ 192 <sup>8</sup>
15	4-FC <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub>	40	91	193 ~ 195 <sup>8</sup>
16	C <sub>6</sub> H <sub>5</sub>	NH <sub>2</sub>	35	92	174 ~ 176 <sup>8</sup>
17	4-ClC <sub>6</sub> H <sub>4</sub>	NH <sub>2</sub>	35	90	169 ~ 170 <sup>5</sup>
18	2-Thienyl	NH <sub>2</sub>	45	90	160 ~ 162 <sup>13</sup>
19	2-Pyridyl	NH <sub>2</sub>	45	88	153 ~ 155 <sup>13</sup>
20	(CH <sub>3</sub> ) <sub>2</sub> CHCH <sub>2</sub>	NH <sub>2</sub>	47	80	186 ~ 188 <sup>4</sup>

<sup>a</sup>Yield refer to isolated pure products. All known products have been reported previously in the literature and were characterized by comparison of <sup>1</sup>H NMR and MS spectra with authentic sample. <sup>b</sup>Yields after recovery of [bmim]HSO<sub>4</sub>.

solvents, may offer an environmentally benign approach toward modern synthetic chemistry.<sup>27</sup>

### Experimental

1-Butyl-3-methylimidazolium hydrogen sulphate ([bmim]HSO<sub>4</sub>) was prepared according to literature procedure.<sup>26</sup> All the melting points were taken in an open capillary and are uncorrected. The progress of the reactions was monitored by thin layer chromatography (TLC). IR spectra were recorded on Perkin-Elmer FT-IR spectrophotometer in KBr disc. <sup>1</sup>H NMR spectra were recorded on mercury plus Varian spectrometer at 400 MHz in CDCl<sub>3</sub> as a solvent and chemical shift values are recorded in units δ (ppm) relative to tetramethylsilane (Me<sub>4</sub>Si) as an internal standard.

#### Experimental procedure for the synthesis of amidoalkyl na-

phthols. A mixture of aldehydes (1 mmol), 2-naphthol (1 mmol) and amide or urea (1.1 mmol) in [bmim]HSO<sub>4</sub> (5 mol%) at 60 °C was stirred for the time as shown in Table 3. The progress of reaction was monitored by TLC. On completion, the reaction mixture was cooled at room temperature. Then it was extracted with ethyl acetate (2 × 20 mL) leaving behind [bmim]HSO<sub>4</sub>, organic layer washed by brine (2 × 10 mL) solution and dried over sodium sulphate. The organic layer was evaporated under reduced pressure. The solid obtained was crystallized from ethanol to get pure product.

### Results and Discussion

Our initial investigation focused on the use of ionic liquid as solvent as well as catalyst for the synthesis of amidoalkyl naphthols. In search of an efficient ionic liquid and the best experimental condition, the reaction of benzaldehyde, 2-naphthol and acetamide (Table 3, entry 1) at 60 °C in the presence of ionic liquid has been considered as the model reaction (Scheme 1).

In order to optimizing the reaction condition, it was found that the best results were obtained with 5 mol% of [bmim]HSO<sub>4</sub> ionic liquid at 60 °C. The reaction was completed within 30 minutes and the expected product (Table 3, entry 1) was obtained in 96% yield (Scheme 1). A variety of ionic liquids were employed for this synthesis. After successful screening of different ionic liquids such as 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF<sub>4</sub>), 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF<sub>6</sub>), 1-butyl-3-dimethylimidazolium chloride ([bmim]Cl), 1-benzyl-3-methylimidazolium chloride ([bmmim]Cl) and 1-butyl-3-methylimidazolium hydrogen sulphate ([bmim]HSO<sub>4</sub>) for the model reaction and found that, [bmim]HSO<sub>4</sub> was the best promoter for this reaction. These results are listed in Table 2.

The data collected in Table 2 indicates that, in the absence of ionic liquid the reaction occur at longer time with low yield of product. (Table 2, entry 6). To determine the appropriate condition of temperature, we have investigated the model reaction of 2-naphthol, benzaldehyde and acetamide in the presence of [bmim]HSO<sub>4</sub> for 30 minute at different temperature of 50, 60 and 70 °C. We found the formation of product in 75, 96 and 96% yields respectively. This indicates that the temperature 60 °C is sufficient for the best results of reaction by considering the yield of products. Encouraged by this protocol, we extended this reaction on substituted aromatic/heteroaromatic/aliphatic aldehydes, 2-naphthol and amides or urea under similar conditions, furnishing the respective amidoalkyl naphthols in excellent yields (80 ~ 96%). But the same model reaction in the presence of [bmim]HSO<sub>4</sub> catalyst performed with 1-naphthol afford the mixture of 2-substituted and 4-substituted amidoalkyl naphthol that required chromatographic separation techniques.

Also we have investigated the reusability of [bmim]HSO<sub>4</sub> and observed that the ionic liquid was successfully reused for four cycles without significant loss of activity (Table 3, entry 1). The aromatic and heteroaromatic aldehydes underwent smoothly and gave in higher yields but aliphatic aldehyde (Table 3, entries 9, 10, 11, 20) afforded comparatively low yield of product (80 ~ 84%). Aromatic aldehydes containing both electron-withdrawing and electron-donating groups afforded the desired pro-

ducts and are summarized in Table 3. The formations of products were confirmed by physical and spectroscopic data and are in good agreement with reported one. The simple experimental and product isolation procedure combined with ease of recovery and reusability of ionic liquid is expected to the development of green strategy for the synthesis of amidoalkyl naphthols.

### Conclusion

In conclusion, we have developed very simple and efficient methodology for the high yielding synthesis of amidoalkyl naphthols by the straight forward one-pot three-component condensation of aromatic/heteroaromatic/aliphatic aldehydes, 2-naphthol and amides or urea at mild (60 °C) condition in acidic ionic liquid. The operational simplicity of the procedure, shorter reaction time, simple workup procedure, cost effective recovery and reusability of ionic liquid make this method much attractive.

**Acknowledgments.** We gratefully acknowledge the financial support received for this research work from the University Grants Commission (UGC), New Delhi.

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