[Bmim]OH mediated Cu-catalyzed azide–alkyne cycloaddition reaction: A potential green route to 1,4-disubstituted 1,2,3-triazoles

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Abstract

In this work, a task-specific ionic liquid 1-methyl-3-butylimidazolium hydroxide [Bmim]OH has been used as a potential greener solvent for Cu-catalyzed azide–alkyne cycloaddition reaction (CuAAC) and provides a simple way to access 1,4-disubstituted 1,2,3-triazoles regioselectively with excellent yields, without requiring bases, reducing agents, ligands or inert atmosphere. Moreover, a one-pot three component CuAAC reaction was developed using alkyl bromide, sodium azide, and terminal alkyne affording 1,2,3-triazoles in high yields.

Introduction

Nowadays, environmental consciousness is one of the most significant topics across the academia and the industry. Following the 12 principles of green chemistry the development of sustainable and efficient processes to convert molecules into products of interest, by using clean methodology is a global effort. Much attention has been paid to replace harmful organic solvents by environmentally benign reaction media, especially by water, ionic-liquids, supercritical fluids, solventless processes, and fluorous techniques. In this context ionic liquids (ILs) have gained a great deal of interest, extensively used in material science, electrochemistry, and organic synthesis due to their unique properties, such as negligible vapor pressure, nonvolatility, nonflammability, electrochemical and thermal stability and high conductivity. Additionally, ILs enjoy physicochemical properties that make them superior media able to increase reactivity, selectivity, catalyst recyclability, and so on.

Nevertheless, to exploit the advantages from using these new solvents, functionalized ILs (usually, defined task-specific ILs, TSILs) have been developed and characterized by the presence of functional groups able to impart a particular reactivity, enhancing the capability for inter action with specific solutes (acids, bases, metals, nanoparticles etc.). TSILs have shown improved performance with respect to molecular solvents used in well known reactions. Especially, basic ionic liquids have attracted unprecedented interest because they exhibit more advantages such as catalytic efficiency and recycling of the ionic liquid than the combination of inorganic base and ionic liquid for some base-catalyzed processes. A basic ionic liquid [Bmim]OH first reported by Ranu and coworkers in 2005 has been successfully applied to catalyze Michael addition, transesterification, Markovnikov Addition, amidation of azides and aldehydes, Gewald Reaction, Heterocyclization, Henry Reaction, synthesis of spiroxindole derivatives, Alkaline electrolyte membrane, Cycloaddition of Carbon Dioxide, synthesis of oximes, multi-component reaction, Mannich-type reaction, and Knoevenagel Condensation.

1,2,3-Triazoles are important structural motifs increasingly found in a wide array of applications including medicinal chemistry, chemical biology and materials science. As a result, there is extensive interest in developing synthetic methods for their facile construction. The conventional way to synthesize 1,2,3-triazole is the Huisgen 1,3-dipolar cycloaddition of alkynes with organic azides. However, due to the high activation energy, these cycloadditions normally require elevated temperature and long reaction times and typically afford a mixture of the 1,4- and 1,5-regioisomers. One of the most popular “click chemistry” reactions, the copper-catalyzed cycloaddition of azides with terminal alkynes (CuAAC), developed by Sharpless and co-workers and independently by Meldal and co-workers is a powerful method for the synthesis of 1,2,3-triazoles. This transformation leads to the enormously efficient formation of the corresponding 1,4-disubstituted

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Table 1
Optimization of reaction conditions.\textsuperscript{a}

\[
\begin{align*}
\text{Entry} & \quad \text{[Cu]} & \quad \text{Ionic liquid} & \quad \text{Yield} \quad \% \\
1 & \quad - & \quad [\text{Bmim}]\text{OH} & \quad 0 \\
2 & \quad \text{CuI} & \quad [\text{Bmim}]\text{OH} & \quad 99 \\
3 & \quad \text{CuI} & \quad [\text{Emim}]\text{OH} & \quad 85 \\
4 & \quad \text{CuI} & \quad [\text{Omim}]\text{OH} & \quad 90 \\
5 & \quad \text{CuBr} & \quad [\text{Bmim}]\text{OH} & \quad 90 \\
6 & \quad \text{CuCl} & \quad [\text{Bmim}]\text{OH} & \quad 86 \\
7 & \quad \text{Cu(II)} & \quad [\text{Bmim}]\text{OH} & \quad 88 \\
8 & \quad \text{CuSO}_4 & \quad [\text{Bmim}]\text{OH} & \quad 90 \\
9 & \quad \text{CuI} & \quad [\text{Bmim}]\text{OH} & \quad 75 \\
10 & \quad \text{CuI} & \quad [\text{Bmim}]\text{OH} & \quad 55 \\
11 & \quad \text{CuI} & \quad [\text{Bmim}]\text{Br} & \quad 40 \\
12 & \quad \text{CuI} & \quad [\text{Bmim}]\text{OAc} & \quad 42 \\
13 & \quad \text{CuI} & \quad [\text{Bmim}]\text{PF}_6 & \quad 40 \\
\end{align*}
\]

\textsuperscript{a} Reaction conditions: Benzyl azide 1a (1 mmol), phenyl acetylene 2a (1.2 mmol), IL (2 ml) in the presence of 1 mol% of [Cu].

\textsuperscript{b} Isolated yield of pure product based on 1a.

\textsuperscript{c} [Emim]OH, 1-methyl-3-ethylimidazolium hydroxide.

\textsuperscript{d} [Omim]OH, 1-methyl-3-octylimidazolium hydroxide.

\textsuperscript{e} 5 mol% Na ascorbate.

\textsuperscript{f} 0.5 mol% CuI.

\textsuperscript{g} 0.1 mol% CuI.

\textsuperscript{h} [Bmim]Br, 1-Butyl-3-methylimidazolium bromide.

\textsuperscript{i} [Bmim]OAc, 1-Butyl-3-methylimidazolium acetate.

\textsuperscript{j} [Bmim]PF\textsubscript{6}, 1-Butyl-3-methylimidazolium hexafluorophosphate.

Table 2
Substrate scope of the CuAAC reaction to form 1,4-disubstituted 1,2,3-triazoles in [Bmim]OH.\textsuperscript{a,b}

\[
\begin{align*}
\text{Entry} & \quad \text{Azide} & \quad \text{Alkyne} & \quad \text{Product} & \quad \text{Time} & \quad \text{Yield} \quad \% \\
1 & \quad & \quad & \quad & \quad 1 \text{ h} & \quad 99 \\
2 & \quad & \quad & \quad & \quad 1 \text{ h} & \quad 95 \\
3 & \quad & \quad & \quad & \quad 1 \text{ h} & \quad 92 \\
4 & \quad & \quad & \quad & \quad 1 \text{ h} & \quad 94 \\
5 & \quad & \quad & \quad & \quad 1 \text{ h} & \quad 96 \\
6 & \quad & \quad & \quad & \quad 1 \text{ h} & \quad 93 \\
\end{align*}
\]

\textsuperscript{a} Reaction conditions: Benzyl azide 1a (1 mmol), phenyl acetylene 2a (1.2 mmol), IL (2 ml) in the presence of 1 mol% of [Cu].

\textsuperscript{b} Isolated yield of pure product based on 1a.
1,2,3-triazoles as a sole regioisomer. Furthermore, numerous successful examples have been reported in the literature for the preparation of 1,2,3-triazoles regarding the green aspect of the method including water as a green solvent. The limited solubility of the less polar reactants can create a serious complication in a reaction step. In contrast, less attention has been paid to investigate the cycloaddition reactions of azides with alkynes in ionic liquids. Therefore, to go even further and also ensure high catalytic activity and stability, the development new synthetic strategy in ionic liquids is one of the most interesting topics in the field of organic synthesis.

**Table 2** (continued)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Azide</th>
<th>Alkyne</th>
<th>Product</th>
<th>Time</th>
<th>Yield (%)</th>
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<tr>
<td>7</td>
<td>N3</td>
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<td>N3</td>
<td>N</td>
<td><img src="image" alt="Product 8" /></td>
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<tr>
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<tr>
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<td>CN</td>
<td><img src="image" alt="Product 11" /></td>
<td>1 h</td>
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</tr>
<tr>
<td>12</td>
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<td>7</td>
<td><img src="image" alt="Product 12" /></td>
<td>3 h</td>
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</tr>
<tr>
<td>13</td>
<td>N3</td>
<td>N</td>
<td><img src="image" alt="Product 13" /></td>
<td>1 h</td>
<td>92</td>
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<tr>
<td>14</td>
<td>N3</td>
<td>OMe</td>
<td><img src="image" alt="Product 14" /></td>
<td>1 h</td>
<td>94</td>
</tr>
<tr>
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<td>N3</td>
<td>N</td>
<td><img src="image" alt="Product 15" /></td>
<td>3 h</td>
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<tr>
<td>16</td>
<td>N3</td>
<td>N</td>
<td><img src="image" alt="Product 16" /></td>
<td>3 h</td>
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<td>N3</td>
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<td>N</td>
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<td>19</td>
<td>N3</td>
<td>O</td>
<td><img src="image" alt="Product 19" /></td>
<td>0.5 h</td>
<td>95</td>
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*All reactions were carried out using azide (1 mmol), alkynes (1.2 mmol), CuI (1 mol%), in [Bmim]OH (2 mL) at room temperature.*

*Reported yields are for the isolated products.*
green chemistry. In continuation of our interest to develop straightforward, efficient and green methodology for the synthesis of 1,2,3-triazoles, herein we report that 1-methyl-3-butylimidazolium hydroxide [Bmim]OH could efficiently be used as a solvent in copper-catalyzed azide-alkyne cycloaddition reaction without need of bases, reducing agents, ligands or inert atmosphere, producing a series of 1,4-disubstituted 1,2,3-triazoles in excellent yields.

Results and discussion

We initiated our research on the model reaction of benzyl azide (1a) with phenyl acetylene (2a) under different reaction conditions (Table 1). This reaction did not proceed without catalyst (Table 1, entry 1). To our delight, the hydroxide-based ILs with different cations were effective for catalyzing this reaction (Table 1, entries 2–4). Especially, [Bmim]OH showed the best activity, affording the sole reaction product 1,4-disubstituted 1,2,3-triazole 3a in quantitative yields under the experimental conditions (Table 1, entry 2). Among the copper catalysts, CuI was found to be the most effective (Table 1, entry 2 vs. entries 5–8). Having [Bmim]OH as the best solvent for the reaction, we next investigated catalyst loading and we found that decreasing the catalyst loading lead to a significant drop in the conversion (Table 1, entries 9–10). Notably, under these optimized conditions, no undesirable by-product was detected. However replacing the anion of the ionic liquid [Bmim]OH showed no progress in product yield (Table 1, entries 11–13). The differences in the reactivity of the tested Bmim based ILs may result from the influences of their anions, suggesting that the anions of the ILs had effects on the reaction. The unique role of the [Bmim]OH in the reaction is to promote the formation of reactive Cu(I) acetylide complex by rapid deprotonation of the alkyne.

Using our optimized experimental conditions, the scope of the formation of 1,4-disubstituted 1,2,3-triazoles in [Bmim]OH was examined with a range of different azides and alkynes. The results are summarized in Table 2. It was worth noting that all the substrates could undergo the cycloaddition producing corresponding 1,2,3-triazoles in good to excellent yields. The reaction of benzyl azides with aromatic acetylene afforded 1,4-disubstituted 1,2,3-triazoles in excellent yields (Table 2, entries 1–4, 13–14). Reactions of phenyl azide with alkyne such as phenyl acetylene produced excellent yields of corresponding 1,4-disubstituted-1,2,3-triazole (Table 2, entry 18), respectively. Aliphatic azide such as octyl azide shows relatively slower reaction kinetics and the desired cycloaddition products were obtained in good yields when the time was increased from 1 h to 3 h (Table 2, entry 12). Interestingly, aryl azides which contain functional groups, such as, CN, halogen, and OMe, at different positions of the aromatic ring, delivered the expected product in excellent yields within 1 h (Table 2, entries 5–11). The reactions also worked on aliphatic amines, however, they showed less activity than the aromatic substrates (Table 2, entries 15–17). In addition, propargyl benzoate also reacted readily to give the desired triazole product in 95% yields within 0.5 h (Table 2, entry 19).

Besides, organic azides are generally safe and stable toward water and oxygen, those of low molecular weight can be mostly dangerous and difficult to handle. Notably, numerous methodologies can be found in the literature in order to avoid the handling and isolation of organic azides for CuAAC reaction. To demonstrate the generality of CuAAC reaction, a novel sequential one-pot procedure involving the formation of the organic azide in situ from the corresponding bromide with sodium azide was investigated. When carrying out the multicomponent model reaction of benzyl bromide, NaN₃, and phenylacetylene under the above-mentioned reaction conditions, we were delighted to notice that the desired triazole product formed in excellent yields within 1 h (Table 3, entry 1). Thus, 1,4-disubstituted-1,2,3-triazoles could be obtained directly from different bromides (Table 3, entries 2–4).

![Image of reaction equation]

Table 3
One-pot synthesis of 1,4-disubstituted 1,2,3-triazoles from bromides.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Bromide</th>
<th>Alkyne</th>
<th>Product</th>
<th>Time</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="1" alt="Image of bromide" /></td>
<td><img src="1" alt="Image of alkyne" /></td>
<td><img src="1" alt="Image of product" /></td>
<td>1 h</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td><img src="2" alt="Image of bromide" /></td>
<td><img src="2" alt="Image of alkyne" /></td>
<td><img src="2" alt="Image of product" /></td>
<td>1 h</td>
<td>92</td>
</tr>
<tr>
<td>3</td>
<td><img src="3" alt="Image of bromide" /></td>
<td><img src="3" alt="Image of alkyne" /></td>
<td><img src="3" alt="Image of product" /></td>
<td>1 h</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td><img src="4" alt="Image of bromide" /></td>
<td><img src="4" alt="Image of alkyne" /></td>
<td><img src="4" alt="Image of product" /></td>
<td>1 h</td>
<td>93</td>
</tr>
</tbody>
</table>

*All reactions were carried out using bromide (1 mmol), NaN₃ (1.2 mmol), alkynes (1.2 mmol), CuI (1 mol%), in [Bmim]OH (2 mL) at room temperature.

*Reported yields are for the isolated products.
Conclusion

In summary, a simple and practical method was developed for the generation of diverse 1,4-disubstituted 1,2,3-triazoles in excellent yields under very mild conditions. The CuAAC reactions of azides with various alkynes were performed well in the basic ionic liquid [Bmim]OH without using any bases, reducing agent and additives. Specifically, one-pot three-component cycloaddition process starting from bromide substrates, sodium azide, and alkynes was also effective in this facile and environmentally friendly alternative protocol.

Acknowledgements

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References

7. General procedure for the [3+2] cycloaddition of azides and terminal alkynes: A mixture of azide (1 mmol, 1 equiv.) and acetylene (2 mmol, 1 equiv.) in [Bmim]OH (2 mL), catalyst CuI (1 mol%) was consecutively added and the mixture was allowed to proceed at room temperature for the given time period as mentioned in Table 2. The progress of the reaction was monitored by TLC. After completion of the reaction it was extracted with EtOAc (2 × 20 mL), washed with brine, dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to give the crude product and purified through silica gel column chromatography (10–20% EtOAc/hexanes) to afford the desired product. The products are characterized by 1H and 13C NMR spectroscopic data.