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[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.[1] Much attention has been paid to replace harmful organic solvents by environmental benign reaction media, especially by water, ionic-liquids, supercritical fluids, solventless processes, and fluorous techniques.[2] In this context ionic liquids (ILs) have gained a great deal of interest, extensively used in material science,[3] electrochemistry,[4] and organic synthesis[5] due to their unique properties, such as negligible vapor pressure, nonvolatility, nonflammability, electrochemical and thermal stability and high conductivity.[6] Additionally, ILs enjoy physicochemical properties that make them superior media able to increase reactivity, selectivity, catalyst recyclability, and so on.[7]

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.).[8] TSILs have shown improved performance with respect to molecular solvents used in well known reactions.[9] 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.[10] A basic ionic liquid [Bmim]OH first reported by Ranu and coworkers[11] in 2005 has been successfully applied to catalyze Michael addition,[12] transesterification,[13] Markovnikov Addition,[14] amidation of azides and aldehydes,[15] Gewald Reaction,[16] Heterocyclization,[17] Henry Reaction,[18] synthesis of spirooxindole derivatives,[19] Alkaline electrolyte membrane,[20] Cycloaddition of Carbon Dioxide,[21] synthesis of oximes,[22] multi-component reaction,[23] Mannich-type reaction,[24] and Knoevenagel Condensation.[25]

1,2,3-Triazoles are important structural motifs increasingly found in a wide array of applications including medicinal chemistry, chemical biology and materials science.[26] 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.[27] 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,[28] and independently by Meldal and co-workers[29] 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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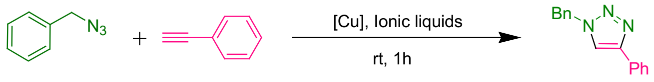
Table 1
Optimization of reaction conditions.[a]

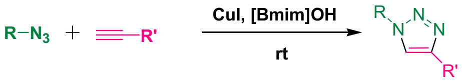


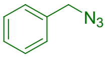
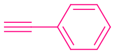
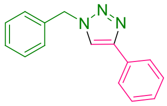
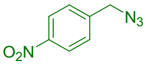
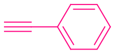
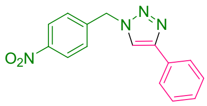
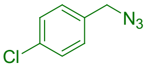
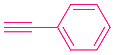
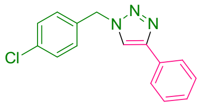
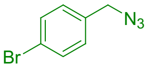
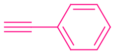
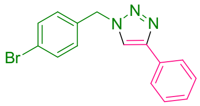
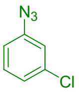
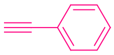
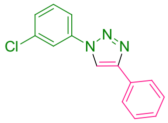
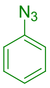
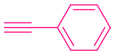
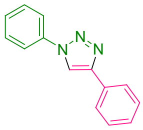
1a **2a** **3a**

Entry	[Cu]	Ionic liquid	Yield[b] (%)
1	–	[Bmim]OH	0
2	CuI	[Bmim]OH	99
3[c]	CuI	[Emim]OH	85
4[d]	CuI	[Omim]OH	90
5	CuBr	[Bmim]OH	90
6	CuCl	[Bmim]OH	86
7[e]	$Cu(OAc)_2 \cdot H_2O$ + Na ascorbate	[Bmim]OH	88
8[e]	$CuSO_4 \cdot 5H_2O$ + Na ascorbate	[Bmim]OH	90
9[f]	CuI	[Bmim]OH	75
10[g]	CuI	[Bmim]OH	55
11[h]	CuI	[Bmim]Br	40
12[i]	CuI	[Bmim]OAc	42
13[j]	CuI	$[Bmim]PF_6$	40

[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].
[b] Isolated yield of pure product based on 1a.
[c] [Emim]OH,1-methyl-3-ethylimidazolium hydroxide,
[d] [Omim]OH,1-methyl-3-octylimidazolium hydroxide,
[e] 5 mol% Na ascorbate.
[f] 0.5 mol% CuI.
[g] 0.1 mol% CuI.
[h] [Bmim]Br, 1-Butyl-3-methylimidazolium bromide.
[i] [Bmim]OAc, 1-Butyl-3-methylimidazolium acetate.
[j] $[Bmim]PF_6$, 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.[a]>



Entry	Azide	Alkyne	Product	Time	Yield[b] (%)
1				1 h	99
2				1 h	95
3				1 h	92
4				1 h	94
5				1 h	96
6				1 h	93