

Efficient synthesis of 1,4-disubstituted 1,2,3-triazoles in ionic liquid/water system

Ya-Bin Zhao, Ze-Yi Yan and Yong-Min Liang*

State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, PR China

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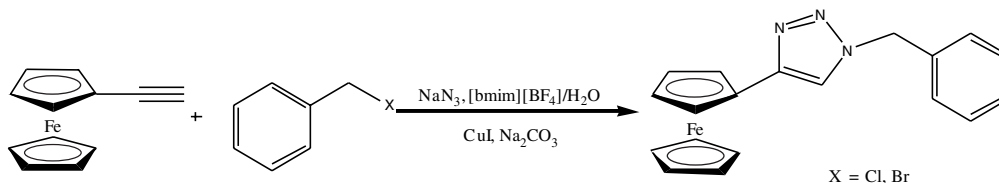
Abstract—A copper(I) catalyst in a mixture of the ionic liquid [bmim][BF₄] and water, can effect three-component reaction of halides, sodium azide and alkynes to form 1,4-disubstituted 1,2,3-triazoles in good to high yields. The method is efficient and environmentally friendly.

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1,2,3-Triazoles are important five-membered nitrogen heterocycles, involved in a wide range of industrial applications such as agrochemicals, corrosion inhibitors, dyes, optical brighteners and biologically active agents.¹ Earlier, the compounds are in general prepared through the coupling reaction between alkynes and azides to form a mixture of 1,4-substituted- and 1,5-substituted-1,2,3-triazoles at high temperature.² The recent important investigations led to the ‘click’ chemistry approach.³ Sequentially, the copper(I)-catalyzed Huisgen cycloaddition reaction of azides and terminal alkynes has emerged as a novel alternative, and received much attention since its discovery. The methodology has found applications in drug discovery, bioconjugations and materials science.⁴ Exclusive regioselectivity, wide substrate scope and mild reaction conditions have made it the method of choice for making permanent connections by means of 1,4-disubstituted 1,2,3-triazoles. For instance, in the last few years, the copper(I)-catalyzed Huisgen cycloaddition reaction has been widely used in multi-component reactions (MCRs) to prepare 1,2,3-triazoles with various functional groups.⁵

Room temperature ionic liquids are environmentally benign solvents due to their unique chemical and physical properties, and have proved to be especially useful in the case of catalytic reactions.⁶ Ionic liquid has also shown promising results, such as hydrogenations,⁷ Diels–Alder reaction,⁸ enantioselective allylation reactions⁹ enantioselective epoxidation of alkenes¹⁰ and enantioselective ring opening of epoxides.¹¹ Although coupling reactions of aryl halides with sodium azide was reported,¹² and Zhong and Guo developed a thermal 1,3-dipolar cycloaddition of alkynes to azides in ionic liquid,¹³ however, no attempt has been made for the use of ionic liquids in copper(I)-catalyzed Huisgen cycloaddition process. Herein, we reported an efficient and safe recyclable one-pot three-component reaction in ionic liquid to form 1,4-disubstituted 1,2,3-triazoles. Reaction of various halides, sodium azide with terminal alkynes in [bmim][BF₄]/H₂O afforded corresponding triazoles in good to excellent yields (Scheme 1).

Initially, we investigated the catalytic activity of various copper catalysts for the MCR of benzyl chloride,



Scheme 1.

* Corresponding author. Tel.: +86 931 8912596; fax: +86 931 8912582; e-mail: liangym@lzu.edu.cn

Table 1. Evaluation of catalysts in the reaction^a

Entry	Catalyst	Time (h)	Yield (%) ^b
1	CuCN	6	72
2	CuBr	6	65
3	CuCl	6	45
4	CuI	4	75
5	CuSO ₄ /Vc	8	63

^aAll reactions were carried out using 0.5 mmol benzyl chloride, 0.5 mmol phenylacetylene, 15 mol % copper salts catalyst, 0.6 mmol NaN₃ and 1 mmol Na₂CO₃ in 4 ml [bmim][BF₄] at room temperature.

^bIsolated yield.

Table 2. Evaluation of various solvents for the reaction

Entry	Solvent	Time (h)	Yield (%) ^a
1	DMSO	4	30
2	THF	4	35
3	[bmim][BF ₄]	4	75
4	[bmim][BF ₄]/H ₂ O 1:4	4	80
5	[bmim][BF ₄]/H ₂ O 1:1	4	94
6	DMSO/H ₂ O 1:4	24	90

^aIsolated yield.

sodium azide and phenylacetylene in ionic liquid. As expected, the cycloaddition reaction proceeded well in the presence of 15 mol % of copper salts (CuI, CuBr, CuCl, CuCN and Vc-CuSO₄ system) to give triazole in 45–75% yield (Table 1, entries 1–5). But, compared to 75% yield in [bmim][BF₄], only trace of the corresponding product was isolated by using CuI in water. Sole

Table 3. Recycle of [bmim][BF₄]/H₂O reaction medium

Entry	Cycle	Time (h)	Yield (%) ^a
1	0	4	94
2	1	3.5	91
3	2	4	92
4	3	5	93
5	4	4	92

^aIsolated yield.

copper(II) catalysts such as CuBr₂, CuCl₂ and CuSO₄ showed no catalytic effect. Although some workers reported that copper metal could catalyze the cycloaddition in low yield, in this study, no reaction occurred in the presence of copper(0) either copper powder or copper turning.¹⁴ Attempts to explore other metal catalysts such as AgCl, AgBr, AgI and ZnCl₂ failed. Although all Cu(I) species showed the good catalytic properties, the best effect was observed by using CuI (Table 1, entry 4).

We also evaluated the solvent effect in the three-component reaction. The results evaluating the merits of various solvents are presented in Table 2. It was shown that ionic liquid was a type of feasible reaction medium in Huisgen cycloaddition. In comparison with the reactions in organic solvent and water, it only took 4 h in ionic liquids to give moderate yield. To our surprise, using [bmim][BF₄]/H₂O 1:1 instead of [bmim][BF₄], the corresponding product was obtained in excellent yield (Table 2, entry 5). We presumed that water played a positive role in the present system due to good water solubility of sodium azide.¹⁵

Table 4. Reactions of halides, alkynes and NaN₃ to form corresponding triazoles

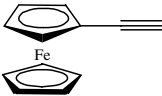
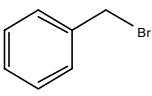
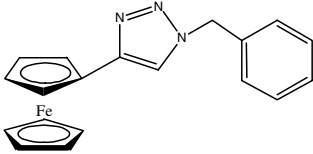
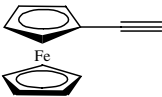
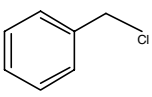
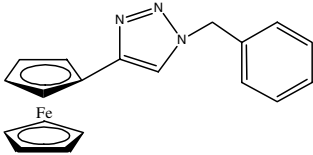
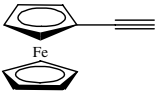
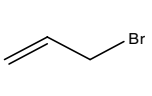
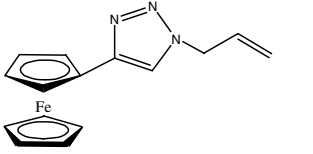
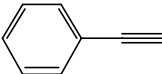
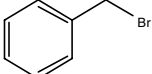
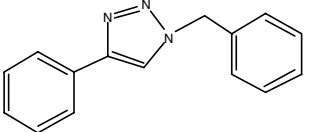
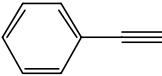
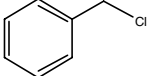
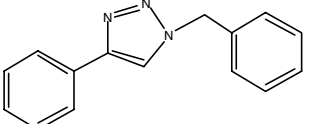
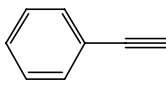
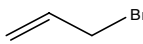
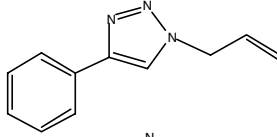
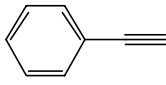
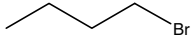
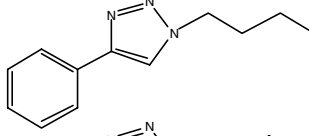
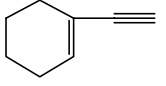
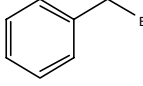
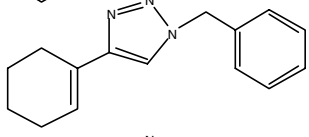
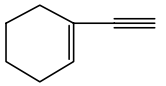
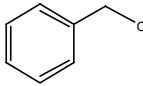
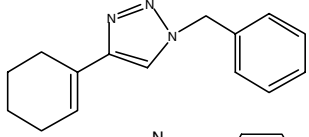
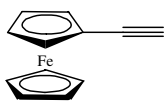
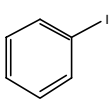
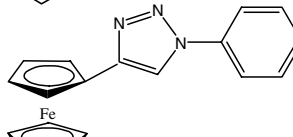
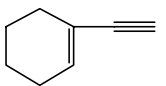
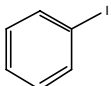
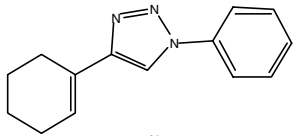
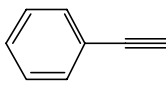
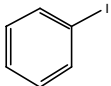
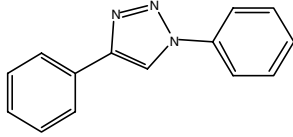
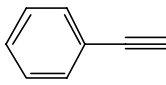
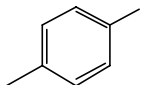
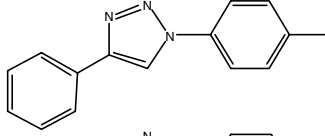
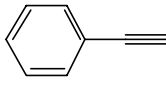
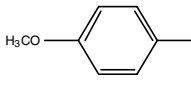
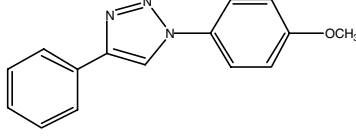
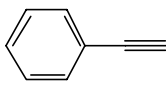
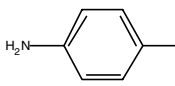
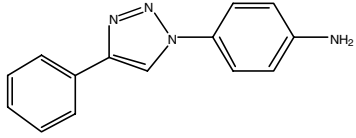
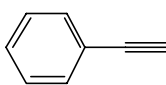
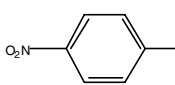
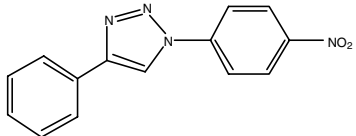
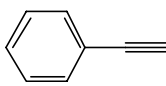
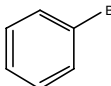
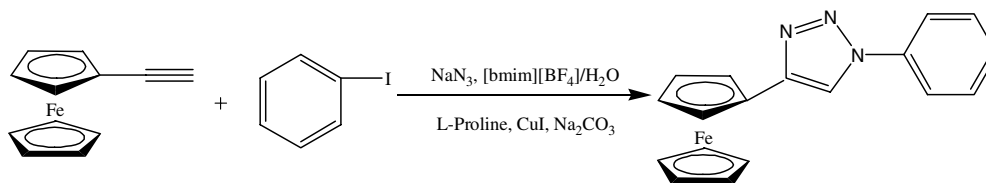
Entry	Alkyne	Halide	T (°C)	Time (h)	Product	Yield (%)
1			rt	8		99
2			rt	8		97
3			rt	10		75
4			rt	4		97
5			rt	4		94

Table 4 (continued)

Entry	Alkyne	Halide	T (°C)	Time (h)	Product	Yield (%)
6			rt	5		76
7			rt	5		90
8			rt	4		96
9			rt	4		95
10			65	8		80
11			65	7		72
12			65	6		83
13			65	8		70
14			65	8		75
15			75	10		72
16			80	12		68
17			100	20	No reaction	

Having optimized the reaction conditions, the recyclability of three-component reaction with copper(I) catalysts in [bmim][BF₄]/H₂O was examined (Table 3).

Similar high conversions were obtained, showing that the ionic liquid remained active. Furthermore, no significant loss of the ionic liquid was observed after five



Scheme 2.

cycles, which indicated that it could be recycled efficiently in this way.

Having established the recyclability and reuse of the ionic liquid, the scope and generality of this method was illustrated with respect to various triazoles (Table 4). It is important to stress that we explored the Huisgen reaction of ferrocenylacetylene because ferrocene-containing heterocyclic rings were reported to be useful materials in electrochemistry, biochemistry and material science.¹⁶ Up to now, although the Cu(I) catalyzed reaction of alkynes and azides have been widely reported, no attempt was carried out to synthesize triazoles including ferrocene segment. Herein, we were pleased to find that ferrocenylacetylene would be compatible with azide and copper catalyst.¹⁷

In order to understand more about the effect of the copper(I)-catalyzed Huisgen cycloaddition reaction in ionic liquids, we extended our study by using halides at sp^2 -hybridized carbon atoms (phenyl halides). At room temperature, it was failed to complete the reaction of phenyl halides. Thus, we had to explore new reaction system (Scheme 2). The reaction temperature and various auxiliary conditions were examined.¹⁸ We found that the reaction of iodobenzene, alkynes and sodium azide proceeded well in the presence of 20% L-proline at 65 °C, and gave the corresponding products in 68–83% conversion (Table 4, entries 10–16). An attempt to extend the reaction to bromobenzene was proved to be not effective. No expected product was isolated even elevating the temperature to 100 °C.

In conclusion, we found that the ionic liquid/ H_2O was a good reaction medium for the one-pot synthesis of 1,4-disubstituted 1,2,3-triazoles using either halides at sp^3 -hybridized carbon atoms or halides at sp^2 -hybridized carbon atoms in good yields. Better performance was obtained than that of conventional reaction condition. This procedure permits extensive recycling of the solvent without substantial loss in activity within five times. On the basis of the current efforts, it seems to be likely that a number of metal catalyzed transformations could be performed equally well or even more effectively in this ionic liquid. Studies to determine applicability to other catalytic reactions are currently underway in our lab.

Acknowledgements

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17. Representative procedure: benzyl chloride (64 mg, 0.5 mmol), phenylacetylene (52 mg, 0.5 mmol) and NaN_3 (39 mg, 0.6 mmol) were placed in a 10 ml round-bottomed flask. Sequentially, Na_2CO_3 (106 mg, 1 mmol) and CuI (15 mol %) were added, the reaction mixture was stirred in 4 ml $[\text{bmim}][\text{BF}_4]/\text{H}_2\text{O}$ 1:1 at room temperature for 4 h and then extracted with ether (3×10 ml). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 filtered and concentrated in vacuo. The residual crude product was purified via silica gel. Ionic liquid was recovered by extracting with dichloromethane and can be reused for the same reactions. 1-Benzyl-4-cyclohex-1-ene-1-*H*-[1,2,3]triazole: ^1H NMR (CDCl_3 , 300 MHz, δ ppm): 7.32 (s, 1H), 7.30–7.17 (m, 5H), 6.43 (t, H), 5.41 (s, 2H) 2.29 (t, 2H), 2.11 (t, 2H), 1.56–1.71 (m, 4H); ^{13}C NMR (CDCl_3 , 75 MHz, δ ppm): 150.3, 135.5, 129.4, 128.9, 128.3, 127.8, 125.3, 118.9, 118.8, 54.3, 26.8, 25.7, 22.9, 22.7; MS: $m/z = 239$ (M^+), 210, 182, 120, 91, 77. IR (KBr, cm^{-1}): 3103, 2927, 1454, 1431, 1215, 1070.
18. Procedure for the reaction of phenyl iodide: other reaction conditions are the same as benzyl chloride, reaction could proceed in the presence of L-proline (24 mg, 20 mol %) at 65 °C. 1-(4-Methylphenyl)-4-phenyl-1-*H*-[1,2,3]triazole: ^1H NMR (CDCl_3 , 300 MHz, δ ppm): 8.16 (s, 1H), 7.91 (d, $J = 8.1$, 2H), 7.60 (d, $J = 8.1$, 2H), 7.48–7.45 (m, 2H), 7.39–7.31 (m, 3H), 2.43 (s, 3H); ^{13}C NMR (CDCl_3 , 75 MHz, δ ppm): 148.2, 138.8, 134.7, 130.3, 130.2, 128.9, 128.3, 125.8, 120.4, 117.6, 21.1; MS: $m/z = 235$ (M^+), 206, 116, 91. IR (KBr, cm^{-1}): 3124, 1520, 1230, 1044.