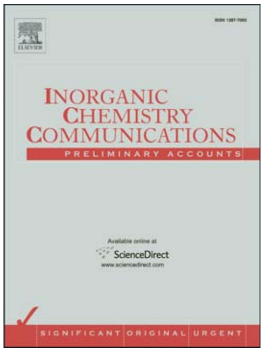

A copper-based ionic liquid as inexpensive and efficient catalyst for the [3+2] cycloaddition of azides and terminal alkynes

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A copper-based ionic liquid as inexpensive and efficient catalyst for the [3+2] cycloaddition of azides and terminal alkynes

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Abstract

A fast and single-step synthesis of the octahedral $Cu[(OHCH_2CH_2)_2NH]_6[CF_3SO_3]_2$ ionic liquid is presented for use in click chemistry. The ionic liquid effectively catalyzes the [3+2] cycloaddition of azides and terminal alkynes to give 1,4-disubstituted 1,2,3-triazoles regioselectively with high yields, without requiring bases, reducing agents, or inert atmospheres. The scope and catalytic activity of this ionic liquid are described herein for the first time. In addition, the present cost effective catalytic system is impressive even under stirring free conditions.

Key Words: Alkynes; Copper; Cycloaddition; Homogeneous catalysis; Ionic Liquid.

The term “click chemistry” was coined by Sharpless [1] in 2001. Click chemistry refers to the synthesis of complex compounds from a small set of modular building blocks and reactions and has applications in various fields [2]. For example, the copper(I)-catalyzed azide–alkyne cycloaddition regioselectively produces 1,2,3-triazoles with high yields. This cycloaddition is generally achieved by in situ reduction of cupric salts [3], direct usage of cuprous salts with phosphane [4] or polytriazoles [5] as ligands, N-heterocyclic carbene complexes [6] or comproportionation of Cu^0/Cu^{II} couples [7]. Recently, many heterogeneous catalysts [8] such as Cu^I species immobilized on solid supports like silica, activated charcoal, dendrimers, and zeolites were reported. Nevertheless, these heterogeneous catalytic systems often suffer from aerial oxidation of Cu^I to Cu^{II}. Hence, these catalysts require an inert atmosphere and anhydrous conditions to remain active, be recyclable, and give high yields of 1,4-regioisomers.

Furthermore, there are some reports of click chemistry catalyzed by Cu^{II} supported on heterogeneous systems [9], which usually requires high temperatures, long reaction times, an inert atmosphere, and pretreatment of the catalysts. In contrast, homogeneous catalysts [10] have also been employed, which generally demand microwave irradiation, mixture of solvents, prolonged maintenance, reducing agents, additives, etc. In view of these drawbacks, the use of metal nanoparticles has been increasingly explored to reduce both catalyst quantity and reaction time. Regardless of the fascinating properties associated with copper nanoparticles (CuNPs) [11], there are some drawbacks preventing their application, scope, competitiveness, and general acceptance that need to be overcome. For instance, most of the methods to synthesize CuNPs require a long reaction time, base, high temperature, and an inert atmosphere. In addition, the presence of stabilizing agents or surfactants is essential to circumvent the agglomeration of NPs and the oxidation of Cu^I to Cu^{II} in most of the cases.

Metal nanoparticles immobilized on ionic liquids have been used as catalysts in various organic transformations. For instance, Salunkhe et al. showed that CuNPs [12] immobilized in imidazolium ionic liquids were active catalysts for the effective synthesis of triazoles under mild conditions. Although this catalyst is very active, it requires an excess of reducing agents and two steps for the click reaction: synthesis of CuNPs protected by PVP (Polyvinylpyrrolidone), followed by immobilization of CuNPs in imidazolium ionic liquids.

To our knowledge, copper-based ionic liquids have not extensively been studied as catalysts [13] in organic synthesis in the context of click chemistry, as opposed to in the context of immobilized ionic liquids [14]. Anderson etal. [15] reported the simple synthesis of copper-, manganese-, iron-, and zinc-based ionic liquids well characterized by various techniques, including IR, CV, TGA, and magnetic susceptibility measurements. Among these, we have chosen the copper-based ionic liquid to study its catalytic activity in cycloadditions of azides and terminal alkynes. Remarkably, this ionic liquid shows excellent catalytic activity with fast and complete consumption of azides under very mild conditions in the absence of additives, stabilizers, and reducing agents. Thus, based on the above report, [15]we synthesized the copper ionic liquid by mixing copper trifluoromethanesulfonate and diethanolamine (DEA) at elevated temperature and employed it as the catalyst for the azide–alkyne cycloaddition under aerobic conditions. Our results demonstrate that this copper ionic liquid is an indispensable, environmentally friendly homogeneous catalytic system that can convert both activated and non-activated substrates into the corresponding 1,4-disubstituted 1,2,3-triazoles with excellent yields.

Reagents were purchased from Aldrich Chemical Co., TCI and Strem Chemical Co. and used as received. Reaction products were analyzed by ^{1}H and ^{13}C-NMR (Varian Mercury Plus, 300 MHz). Chemical shift values were recorded as parts per million relative to tetramethylsilane as an internal standard, unless otherwise indicated, and coupling constants in Hertz. Reaction products were assigned by comparison with the literature value of known compounds. A copper-based ionic liquid [Cu-IL] catalyst was synthesised [see Supplementary data] from Anderson’s procedure [15]. All substituted triazoles (Table 2, entries 1-10) are synthesized at the reaction temperature of 50℃ in order to get good
yields.

A 25mL Schlenk tube was flame dried under vacuum and cooled to room temperature. The flask was charged with Cu-IL(10mol%), azide (200mg,1.503mmol), acetylene (184mg, 1.803mmol) were charged along with 2mL of DMF and kept it in a preheated 50°C water bath under vigorous stirring. Reaction progress was monitored by TLC (10% Ethyl Acetate : Hexane) from the consumption of azide. After the complete consumption of azide, reaction mass was cooled to RT and poured into a beaker contains 10mL of water, stirred well and extracted with dichloromethane or diethyl ether. Combined organic layers were separated and washed with water until complete copper ionic liquid goes off into aqueous layer. The separated organic layer was dried with anhydrous sodium sulfate, filtered and concentrated in a rotary evaporator until to remove solvent completely. The crude solid product was analyzed by ^{1}H & ^{13}C – NMR.

First, the cycloaddition of benzyl azide and phenylacetylene was carried out under various experimental conditions (see Table 1). The solvent screening revealed that dimethylformamide (DMF) gave excellent yield within a short time (Table 1, entry 10) under very mild conditions. Other solvents such as t-butanol and t-butanol:water (Table 1, entries 3 and 4) also gave quantitative yields of **3aa** at slightly higher temperatures. Moderate yields were obtained with water, toluene, and tetrahydrofuran (THF) (Table 1, entries 1, 2, 5, and 7). The reactions were also performed with copper triflate alone and copper triflate combined with diethanolamine (Table 1, entries 13, 11, and 12). The former isolates only the starting materials, whereas the latter exhibits low conversions due to incomplete ionic-liquid formation at low temperature. Furthermore, the reaction in acetonitrile and without solvent (Table 1, entries 6 and 8) took a long time.

Because the catalytic system is homogeneous, we compared its catalytic activity with and without stirring. Surprisingly, the present catalytic system showed outstanding consumption of benzyl azide within 2 h (Scheme 1) under mild conditions without stirring. We examined the catalytic activity of other copper (I) sources such as CuI, $[Cu(OTf)_2].C_6H_6$, $[Cu(NCCH_3)_4][PF_6]$ shows 39, 83, 99% yields respectively. Among above, expensive $[Cu(NCCH_3)_4][PF_6]$ claims highest yield and almost equal to our copper (II) coordinated ionic liquid. We also investigated whether Glaser homocoupling occurred in the absence of azides. Surprisingly, the catalytic system showed no homocoupling products even under long-time stirring and heating (Scheme 2).

The scope of the present 1,3-dipolar cycloaddition of azides and terminal alkynes catalyzed by a copper ionic liquid is rather broad, as illustrated in Table 2. All reactions showed excellent yields of 1,4-disubstituted 1,2,3-triazole derivatives in the presence of air and in the absence of additives, bases, reducing agents, and expensive ligands. NMR analyses revealed that the obtained products are exclusively 1,4-regioisomers (Table 2, entries 1–10).

In conclusion, the reported copper ionic liquid could act as an efficient, inexpensive homogeneous catalyst for the 1,3-dipolar cycloaddition of azides and terminal alkynes. To improve the stability and recyclability of the catalyst, work focusing on immobilizing the copper ionic liquid on a supporting material is underway.

Acknowledgments

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References

[1] (a) V.V. Rostovtsev, L.G. Green, V.V. Fokin, K.B. Sharpless, Angew. Chem. 41 (2002) 2596-2599.
(b) V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, Angew. Chem. Int. Ed. 114 (2002) 2708-2711.

[2] For example,
(a) R. Luxenhofer, R. Jordan, Macromolecules. 39 (2006) 3509-3516.
(b) V. Ladmiral, G. Mantovani, G.J. Clarkson, S. Cauet, J.A. Irwin, D.M. Haddleton, J. Am. Chem. Soc. 128 (2006) 6564-6565.
(c) P. Kocalka, N.K. Andersen, F. Jensen, P. Nielsen, ChemBioChem. 8 (2007) 2106-2116.
(d) C. Ornelas, J. R. Aranzaes, L. Salmon, D. Astruc, Chem. Eur. J. 14 (2008) 50-64.
(e) R. A. Evans, Aust. J. Chem. 60 (2007) 384-395.
(f) T. Lummerstorfer, H. Hoffmann, J. Phys. Chem. B. 108 (2004) 3963-3966.
(g) S. Lcber, H. Hubner, P. Gmeiner, J. Comb. Chem. 8 (2006) 252-261.
(h) D.Bonnet, B. Ilien, J.-L. Galzi, S. Riche, C. Antheaune, M. Hibert, Bioconjugate Chem. 17 (2006) 1618-1623.
(i) W. R. Dichtel, O. S. Miljanic, J. M. Spruell, J. R. Health, J. F. Stoddart, J. Am. Chem. Soc. 128 (2006) 10388-10390.

[3] A. K. Feldman, B. Colasson, V. V. Fokin, Org. Lett. 6 (2004) 3897-3899.

[4] (a) D. Wang, N. Li, M.M. Zhao, W. L. Shi, C.W. Ma, B. H. Chen, Green Chem. 12 (2010) 2120-2123.
(b) D. Wang, M. Zhao, X. Liu, Y. Chen, N. Li, B. Chen, Org. Biomol. Chem. 10 (2012) 229-231.
(c) S. Lal, S. D-González, J. Org. Chem. 76 (2011) 2367-2373.

[5] T. R. Chan, R. Hilgraf, K. B. Sharpless, V. V. Fokin, Org. Lett. 16 (2006) 2853-2855.

[6] S. D-Gonzalez, E. D. Stevens, S. P. Nolan, Chem. Commun. (2008) 4747-4749.

[7] J. Broggi, S. D-Gonzlez, J. L. Petersen, S. B. Raboin, S. P. Nolan, L.A. Agrofoglio, Synthesis. (2008) 141-148.

[8] (a) T. Miaoa, L. Wang, Synthesis. (2008) 363-368.
(b) B. H. Lipshutz, B. R. Taft, Angew. Chem. Int. Ed. 45 (2006) 8235-8238.
(c) E. Moore, S. J. McInnes, A. Vogt, N.H. Voelcker, Tetrahedron Lett. 52 (2011) 2327-2329;
(d) S. Chassaing, A.S.S. Sido, A. Alix, M. Kumarraja, P. Pale, J. Sommer, Chem. Eur. J. 14 (2008) 6713–6721.

[9] (a) T. Katayama, K. Kamata, K. Yamaguchi, N. Mizuno, ChemSusChem 2 (2009) 59-62.
(b) K. Namitharan, M. Kumarraja, K. Pitchumani, Chem. Eur. J. 15 (2009) 2755 – 2758.
(c) K. Yamaguchi, T. Oishi, T. Katayama, N. Mizuno, Chem. Eur. J. 15 (2009)10464 – 10472.

[10] (a) P. Appukkuttan, W. Dehaen, V.V. Fokin, E.V.D. Eycken, Org. Lett. 6 (2004) 4223-4225.
(b) H. S. G. Beckmann, V. Wittmann, Org. Lett. 9 (2007) 1-4.
(c) B. Gerard, J. Ryan, A. B. Beeler, J.A. Porco Jr, Tetrahedron. 62 (2006) 6405-6411.
(d)Y.B. Zhao, Z.Y. Yan, Y.M. Liang, Tetrahedron Letters. 47 (2006) 1545-1547.

[11] (a) J.Y. Kim, J.C. Park, H. Kang, H. Song, Chem. Commun. 46 (2010) 439-441.
(b) F. Alonso, Y. Moglie, G. Radivoy, M. Yus, Eur. J. Org. Chem. (2010) 1875–1884.
(c) J. Kim, S.W. Kang, S.H. Myun, Y.S. Kang, Ind. Eng. Chem. Res. 48 (2009) 7437–7441;
(d) P. Arquilliere, P.H. Haumesser, C.C. Santini, Micro. Elect. Engg. 92 (2012)149-151.

[12] D. Raut, K. Wankhede, V. Vaidya, S. Bhilare, N. Darwatkar, A. Deorukhkhar, G. Trivedi, M. Salunkhe, Catal. Commun. 10 (2009) 1240-1243.

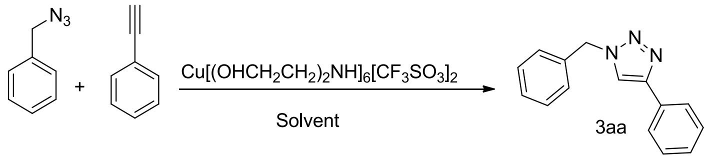
[13] (a) Y. Wang, J. Liu, C. Xia, Adv. Synth. Catal. 353 (2011) 1534-1542.
(b) S. Doherty, P.Goodrich, C. Hardacre, V. Parvulescu, C. Paun, Adv. Synth. Catal. 358 (2008) 295-302.

[14] (a) M.L. Kantam, V. Neeraja, B. Kavita, B. Neelima, M.K. Chaudhuri, S. Hussain, Adv. Synth. Catal. 347 (2005) 763-766.

(b) M.H. Valkenberg, C. deCastro, W.F. Holderich, Green Chemistry. 2002, 4, 88-93; c) P. Wasserscheid, W. Keim, Angew. Chem. Int. Ed. 39 (2000) 3772-3789.

[15] H.D. Pratt III, A. J. Rose, C. L. Staiger, D. Ingersoll, T. M. Anderson, Dalton Trans. 40 (2011) 11396-11401.

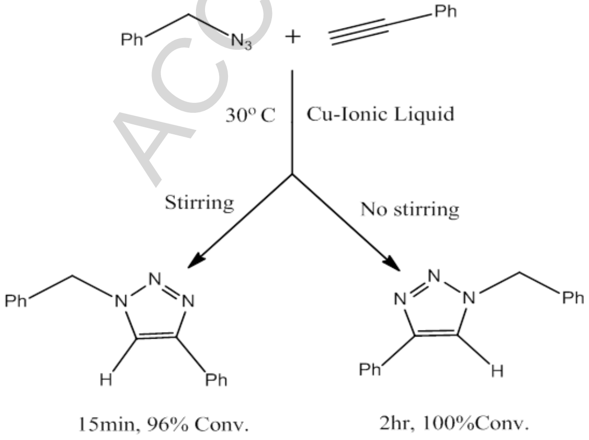
Table 1. Click reaction under various experimental conditions



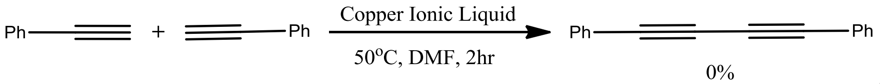
Entry	Catalyst	Time	T (°C)	Conv.(%)[a]	Solvent
1	10 mol%	30mts	50	46	H_2O
2	10 mol%	1hr	50	100	H_2O
3	10 mol%	30mts	50	96	t-BuOH:H_2O (1:1)
4	10 mol%	30mts	50	100	t-BuOH
5	10 mol%	30mts	50	71	Toluene
6	10 mol%	30mts	50	32	Acetonitrile
7	10 mol%	30mts	50	72	THF
8	10 mol%	30mts	50	53	Neat
9	10 mol%	30mts	30	67	t-BuOH
10	10 mol%	15mts	30	96	DMF
11	$Cu(OTf)_2$ + DEA	30mts	50	23	t-BuOH
12	$Cu(OTf)_2$ + DEA	30mts	50	37	DMF
13	$Cu(OTf)_2$	30mts	50	0	DMF

[a]Determined by ^1H NMR from the amount of benzyl azide used.

Scheme 1. Catalytic activity of copper ionic liquid with and without stirring conditions

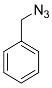
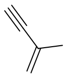
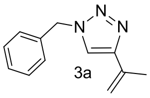
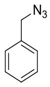
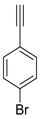
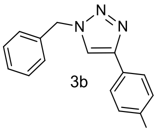
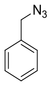
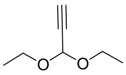
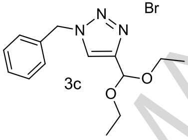
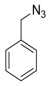
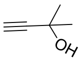
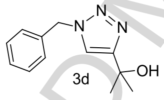
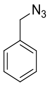
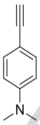
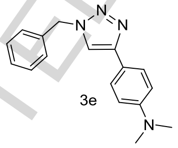
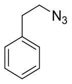
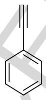
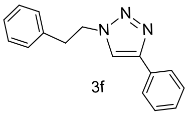
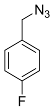
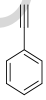
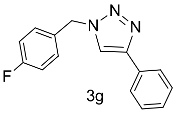
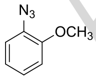
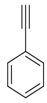
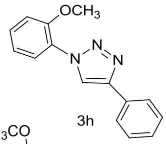
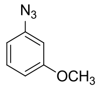
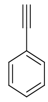
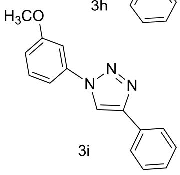
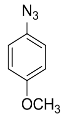
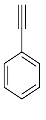
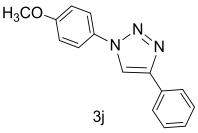


Scheme 2. An inert catalytic system for Glaser homo coupling reaction



0%

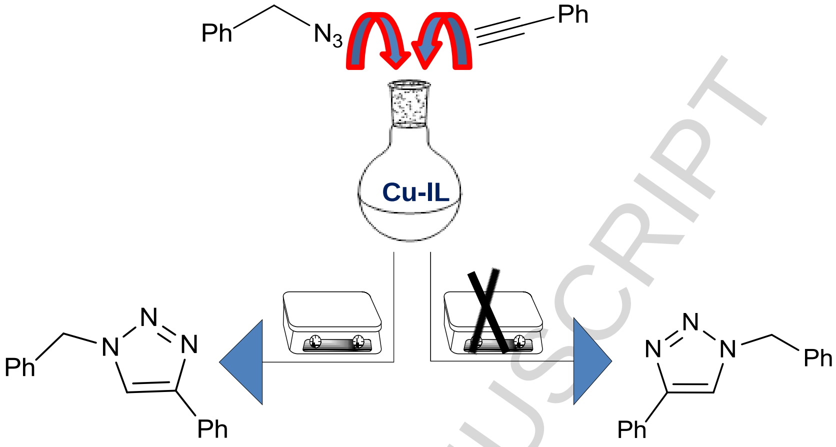
Table 2. Copper ionic liquid assisted 1,3-dipolar cycloaddition

Entry	Azide	Alkyne	Product	Time(min)	Conv.(%)[a]
1			 3a	120	100 (100)
2			 3b	60	100 (100)
3			 3c	30	100 (100)
4			 3d	30	100 (100)
5			 3e	60	100 (100)
6			 3f	45	100 (100)
7			 3g	30	100 (100)
8			 3h	120	100 (98)
9			 3i	60	99 (100)
10			 3j	30	91 (100)

[a] Determined by ^{1}H & ^{13}C NMR spectra.

Yield in parenthesis determined by GC-MS.

Graphical Abstract



A fast single-step synthesis of the octahedral Cu[(OHCH$_2$CH$_2$)$_2$NH]$_6$[CF$_3$SO$_3$]$_2$ ionic liquid is presented for use in click chemistry. The ionic liquid effectively catalyzes the [3+2] cycloaddition of azides and terminal alkynes to give1,4-disubstituted 1,2,3-triazoles regioselectively with high yields, without requiring bases, reducing agents, or inert atmospheres.

Highlights

- A fast and Single step synthesis of copper-based ionic liquid
- The catalytic activity of copper coordinated ionic liquid to synthesize triazoles through click chemistry
- High regioselectivity with various substituted triazoles were reported
- Stirring free conditions and no side products