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Graphical Abstract

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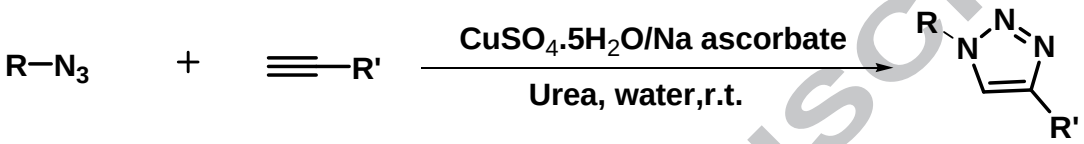

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ABSTRACT

Urea assisting easy and greener synthesis of 1,4-disubstituted 1,2,3-triazoles has been achieved using copper (I)-catalyzed azide–alkyne cycloaddition (CuAAC) reaction in water. The click reaction affords notable features, such as high efficiency and regioselectivity, mild reaction conditions, easy operation, and excellent yields with a broad spectrum of substrates.

Introduction

Of all the click reactions, the copper (I)-catalyzed version of Huisgen 1,3-dipolar azide–alkyne cycloaddition (CuAAC) reaction independently described by the groups of Sharpless and Meldal in 2002, is one of the most common and useful synthetic reactions in organic chemistry.[1-3] The CuAAC has become a prime example of click chemistry because of its reliability, specificity, and biocompatibility and has been widely used in different areas of science, such as organic synthesis, drug discovery, bioconjugation, polymer and supramolecular chemistry.[4-8]

Nevertheless, an increasing alertness of the need for more sustainable approach for synthetic chemistry across academic and industrial communities, numerous environmentally friendly strategies have been recognized: to carry out reactions in solvent free condition; to change the use of stoichiometric reagents with catalysts; to use biocatalytic processes, and finally to carry out reactions in aqueous media.[9] From the viewpoint of 'click chemistry' water is used as a solvent along with other water-miscible organic solvents such as DMSO, THF, and ^{t}BuOH in typical CuAAC reaction.[10] In particular, water is a cheap, nonflammable, nontoxic, and environmentally benign solvent.[11] Therefore, development of organic reactions in water over traditional solvents will contribute to the cleaner green chemistry process.

Very surprisingly, certain Cu-binding ligands play an important role in the rate acceleration of CuAAC over the ligand-free process with stabilization of copper (I) ions from oxidation and disproportionation.[12] In this regard, noteworthy examples include the commonly applied TBTA,[13] sulfide ligands,[14] histidine[15] and benzimidazole derivatives,[16] pyridine– phosphinimine,[17] bisoxazoline-pyridine (pybox) ligands,[18] phosphites,[19] phosphinite and phosphonite,[20] NHC carbenes,[21] THPTA,[22] oximinoalkylamines,[23] AMTC[24] and MBHTM.[25]

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However, these strategies have some inherent deficiencies, including relatively sluggish synthetic routes, high copper and ligand loading, high temperature, long reaction time and use of organic solvents. Most of the ligands are non polar and only a few reports are available for water soluble ligands such as THPTA[22] and AMTC[24]. Consequently, there is still a need for the development of new, efficient, highly economical, widely applicable, commercially feasible as well as environmentally sustainable way for the synthesis of 1,2,3-triazoles in order to meet their growing demand in various section.

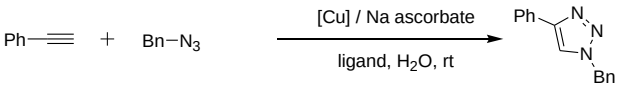
Urea is a cheap, remarkably stable, readily accessible, water soluble and non-toxic substance and nowadays the chemistry of urea based organic reactions has been developed rapidly because of interest in their geometrical structures and complexing ability.[26] We recently disclosed urea/$Pd(OAc)_2$ as efficient catalyst for phosphine-free Suzuki–Miyaura cross-coupling reactions.[27] In order to establish the utility of urea as a ligand we decided to extend its chemistry to CuAAC reaction and to the best of our knowledge this is one of the simplest green protocols for ligand promoted click reactions reported so far. To contribute our interest on click chemistry,[28] herein we describe a simple, reliable and synthetically straightforward approach for the preparation of diverse 1,2,3-triazoles under mild condition.

Results and discussion

We began to explore optimal parameters for the click reaction using benzyl azide as a coupling partner for phenyl acetylene in water using urea as a ligand under standard cycloaddition conditions (**Table 1, entry-1**). To our delight, the reaction undergoes near completion after only 60 min and excellent yields can be achieved. Further screening of different Cu salts indicated that $CuSO_4.5H_2O$/Na ascorbate showed superior reactivity over others in this reaction (**Table 1, entries 2-5**). Interestingly, using of thiourea or guanidine as a ligand led to slightly lower yield of the desired product (**Table 1, entries 6-7**). It was worth to note that in the absence of urea the product obtained was only 40%

after 60 min and the reaction was completed only after 6h highlighting the indispensable role of the ligand (**Table 1, entries 8-9**). Notably, it was found that all these reactions could be performed in air with no detectable evidence of side product formation. Throughout this work, the optimized reaction conditions comprise of 1 mol% $CuSO_4.5H_2O$ as catalyst, 5 mol% Na ascorbate as reducing agent and 2 mol% urea as the promoter ligand.

Table 1. Optimization of reaction conditions.[a]



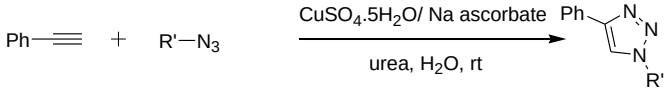
Entry	[Cu] 1 mol%	Na ascorbate	Ligand 2 mol%	time	Yield (%)[b]
1	$CuSO_4.5H_2O$	5mol%	Urea	1h	99
2	CuI	-	Urea	1h	90
3	$CuCl_2.2H_2O$	5mol%	Urea	1h	88
4	$Cu(OAc)_2.H_2O$	5mol%	Urea	1h	89
5	CuCl	-	Urea	1h	90
6	$CuSO_4.5H_2O$	5mol%	Thiourea	1h	78
7	$CuSO_4.5H_2O$	5mol%	Guanidine	1h	84
8	$CuSO_4.5H_2O$	5mol%	-	1h	40
9	$CuSO_4.5H_2O$	5mol%	-	6h	92
10	-	-	Urea	24h	-

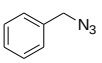
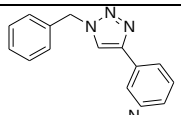
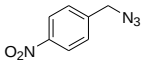
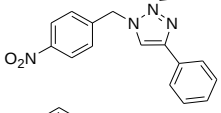
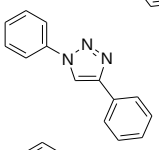
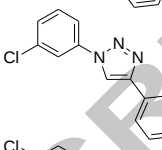
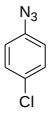
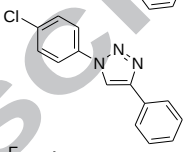
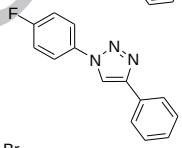
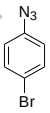
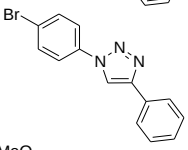
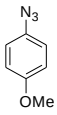
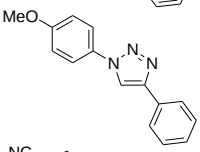
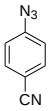
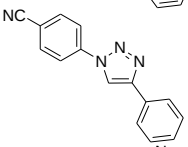
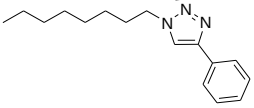
[a] 1 mmol of azide, 1.2 mmol of alkyne, 1.0 mol % of [Cu] and 5.0 mol % sodium ascorbate in the presence of 2 mol % of ligand in H_2O at room temperature.

[b] Isolated yields by column chromatography.

With the optimized reaction conditions established, exploration of the scope of the catalyst system was performed with structurally different azides and acetylenes. Phenylacetylene could react satisfactorily with diverse azides (**Table 2, Entries 1-10**) affording the corresponding products with high isolated yields. It is noteworthy that both the electron-rich and the electron deficient aryl azides showed an excellent reactivity and furnished the products in high yields in short reaction times (**Table 2, entries 3-9**) at room temperature. Halide substituents such as Br, F, and Cl were all tolerated in this transformation and resulting triazoles are primed for further functionalization. In the case of aliphatic azide also, good yields were observed under the standard reaction conditions (**Table 2, entry -10**). Obviously, cycloaddition with aromatic alkynes such as *p*-methylphenylacetylene, *p*-methoxyphenylacetylene proceeded smoothly to give the corresponding 1,2,3-triazoles in almost quantitative yields (**Table 3, Entries 1-3**). In addition, aliphatic alkynes were also effectively clicked with the benzyl azide to form the desired triazole products in excellent yields (94-99%) after 3h (**Table 3, entries 4-5**). Moreover the reaction appears to be quite tolerant of common functional groups including alcohols, esters and acids (**Table 3, entries 6-8**).

Table 2. Azide–alkyne cycloaddition of phenyl acetylene and different azides in water.[a]

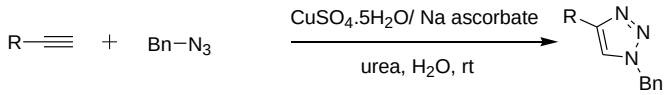


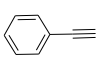
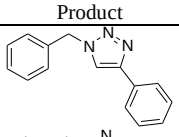
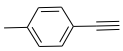
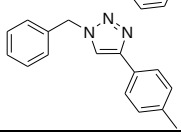
Entry	Azide	Product	Time	Yield[b]
1			1h	99
2			1h	96
3			1h	92
4			1h	96
5			1h	95
6			1h	96
7			1h	95
8			1h	97
9			1h	96
10			3h	90

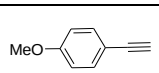
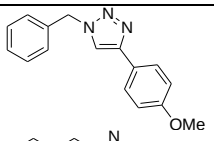
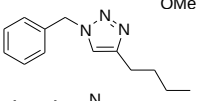
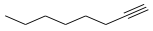
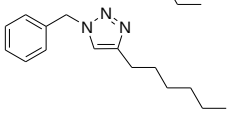
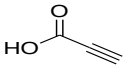
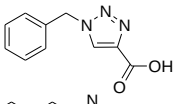
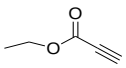
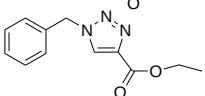
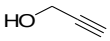
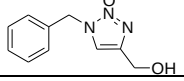
[a] 1 mmol of azide, 1.2 mmol of alkyne, 1.0 mol % of $CuSO_4.5H_2O$ and 5.0 mol % sodium ascorbate in the presence of 2 mol % of urea in H_2O at room temperature.

[b] Isolated yields by column chromatography.

Table 3. Azide–alkyne cycloaddition of benzyl azide and different alkynes in water.[a]



Entry	Alkyne	Product	Time	Yield[b]
1			1h	99
2			1h	94

3			1h	95
4			3h	90
5			3h	92
6			2h	90
7			2h	94
8			3h	92

[a] 1 mmol of benzyl azide, 1.2 mmol of alkyne, 1.0 mol % of $CuSO_4.5H_2O$ and 5.0 mol % sodium ascorbate in the presence of 2 mol % of urea in 2 ml of H_2O at room temperature.

[b] Isolated yields by column chromatography.

Conclusion

In summary, we have developed a simple and highly efficient methodology for copper-catalyzed azide alkyne cycloaddition reactions at room temperature. With the ease of procedure, mild reaction conditions, use of inexpensive reagents, and high generality of substrates, we believe that this greener and cost effective process creates a new avenue for scientific community.

Acknowledgement

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References and notes:

1. Huisgen, R. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, **1984**; pp 1-176.
2. Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2002,** 41, 2596.
3. Tornøe, C.W.; Christensen, C.; Meldal, M. *J. Org. Chem*. **2002**, 67, 3057.
4. (a) Chuprakov, S.; Kwok, S. W.; Fokin, V. V. *J. Am. Chem. Soc*. **2013**, 135, 4652. (b) Spangler, J. E.; Davies, H. M. L. *J. Am. Chem. Soc*. **2013**, 135, 6802.
5. Thirumurugan, P.; Matosiuk, D.; Jozwiak, K. *Chem. Rev*. **2013**, 113, 4905.
6. Lutz, J. F.; Zarafshani, Z. *Adv. Drug Delivery Rev*. **2008**, 60, 958.
7. (a) Golas, P. L.; Matyjaszewski, K. *Chem. Soc. Rev*. **2010**, 39, 1338. (b) Díaz, D. D. *Macromol. Symp*. **2015**, 358, 10.
8. Hua, Y.; Flood, A. H. *Chem. Soc. Rev*. **2010**, 39, 1262.
9. (a) Blackmond, D. G.; Armstrong, A.; Coombe, V.; Wells, A. *Angew. Chem. Int. Ed*. **2007**, 46, 3798. (b) Jessop, P. G. *Green Chem.* **2011**, 13, 1391.
10. (a) Wu, P.; Feldman, A. K.; Nugent, A. K.; Hawker, C. J.; Scheel, A.; Voit, B.; Pyun, J.; Fréchet, J. M. J.; Sharpless, K. B.; Fokin, V. V. *Angew. Chem., Int. Ed*. **2004**, 43, 3928. (b) Helms, B.; Mynar, J.; Hawker, C. J.; Fréchet, J. M. J. *J. Am. Chem. Soc*. **2004**, 126, 15020. (c) Rodionov, V.; Fokin, V. V.; Finn, M. G. *Angew. Chem., Int. Ed*. **2005**, 44, 2210.
11. Simon, M.-O.; Li, C.-J. *Chem. Soc. Rev.* **2012**, 41, 1415.
12. Presolski, S. I.; Hong, V.; Cho, S.H.; Finn, M.G. *J. Am. Chem. Soc*. **2010**, 132, 14570.
13. Chan, T. R.; Hilgraf, R.; Sharpless, K. B.; Fokin, V. V. *Org. Lett*. **2004**, 6, 2853.
14. Wang, F.; Fu, H.; Jiang, Y. Y.; Zhao, Y. F. *Green Chem.* **2008**, 10, 452.
15. Tanaka, K.; Kageyama, C.; Fukase, K. *Tetrahedron Lett.* **2007**, 48, 6475.
16. Rodionov, V. O.; Presolski, S. I.; Gardinier, S.; Lim, Y.-H.; Finn, M. G. *J. Am. Chem. Soc*. **2007**, 129, 12696.
17. Donnelloy, P. S.; Zanatta, S. D.; Zammit, S. C.; White, J. M.; Williams, S. J. *Chem. Commun*. **2008**, 2459.
18. Meng, J.-C.; Fokin, V. V.; Finn, M. G. *Tetrahedron Lett*. **2005**, 46, 4543.
19. Perez-Balderas, F.; Ortega-Munoz, M.; Morales-Sanfrutos, J.; Hemandez-Mateo, F.; Calvo-Flores, F. G.; Calvo-Asin, J. A.; Isac-Garcia, J.; Santoya-Gonzalez, F. *Org. Lett.* **2003**, 5, 1951.
20. Steven, L.; Jayne, M.; Andrew, J. P. W.; Silvia, D.-G. *Organometallics* **2011**, 30, 6225.
21. Silvia, D.-G.; Correa, A.; Cavallo, L.; Nolan, S. P. *Chem.-Eur. J.* **2006**, 12, 7559.
22. Hong, V.; Presolski, S. I.; Ma, C.; Finn, M. G. *Angew. Chem., Int. Ed*. **2009**, 48, 9879.
23. Semakin, A. N.; Agababyan, D. P.; Kim, S.; Lee, S.;Sukhorukov, A. Y.; Fedina, K. G.; Oh, J.; Ioffe, S. L. *Tetrahedron Lett*. **2015**, 56, 6335.
24. Szafranski, P. W.; Kasza, P.; Cegła, M. T. *Tetrahedron Lett.* **2015**, 56, 6244.
25. Tale, R. H.; Gopula, V. B.; Toradmal, G. K. *Tetrahedron Lett.* **2015**, 56, 5864.
26. (a) Puripat, M.; Ramozzi, R.; Hatanaka, M.; Parasuk, W.; Parasuk, V.; Morokuma, K. *J. Org. Chem*. **2015**, 80, 6959. (b) Hardman, A. M.; So, S. S.; Mattson, A.E. *Org. Biomol. Chem*. **2013**, 11, 5793. (c) Roberts, J. M.; Fini, B. M.; Sarjeant, A. A.; Farha, O. K.; Hupp, J. T.; Scheidt, K. A. *J. Am. Chem. Soc*. **2012**, 134, 3334. (d) Sarmah, M.; Dewan, A.; Thakur, A. J.; Bora, U. *Tetrahedron Lett*. **2016**, doi: http://dx.doi.org/10.1016/j.tetlet.2016.01.046.
27. Saikia, B.; Boruah, P. R.; Ali, A.A.; Sarma, D. *Tetrahedron Lett*. **2015**, 56, 633.
28. (a) Ali, A. A.; Chetia, M.; Saikia, P. J.; Sarma, D. *RSC Adv*. **2014**, 4, 64388. (b) Chetia, M.; Ali, A. A.; Bhuyan, D.; Saikia, L.; Sarma, D. *New J. Chem*. **2015**, 39, 5902. (c) Ali, A. A., Chetia, M., Saikia, B., Saikia, P.J., Sarma, D. *Tetrahedron Lett.* **2015**, 56, 5892.
29. In a typical experiment, a solution of $CuSO_4 \cdot 5H_2O$ (2.49 mg, 0.01 mmol), and sodium ascorbate (9.9 mg, 0.05 mmol) in H_2O (2.0 mL) was added a mixture of azide (1 mmol, 1 equiv.) and acetylene (1.2 mmol 1.2 equiv.) at room temperature. The resultant mixture was stirred continuously and after completion (monitored by TLC); the reaction mixture was extracted with ethyl acetate (10 mL x 3) and the combined organic layer was washed with brine (20 mL), dried over Na_2SO_4. Removal of the solvent yielded a residue, which was purified by a short chromatography (silica gel, EtOAc:n-Hexane = 1:3) to give the desired product. The products are characterized by ^1H, ^{13}C NMR and ESI-Mass spectroscopic data.

HIGHLIGHTS

- The method exploits commercially available and inexpensive urea as a ligand
- Economical and environmentally friendly water as the medium
- One of the simplest protocols for ligand promoted click reactions reported so far
- CuAAC reaction can be performed in water at room temperature