DOI: 10.1002/cjoc.201100231

Copper Supported on the SiO_2 Nanoparticle in Click Chemistry: An Alternative Catalytic System for Regioselective and One-Pot Synthesis of 1,2,3-Triazoles and *β*-Hydroxytriazoles

Ciyabi Hashjin, Maryam* Ciyabi, Roghayeh Baharloui, Maryam
Hosseini, Ghaffar Tavakoli, Hamed

Department of Chemistry, Faculty of Science, Islamic Azad University, Karaj Branch, P.O. Box 31485-313, Karaj, Iran

In this work, readily prepared copper supported on the SiO_2 nanoparticles has been found to effectively catalyze the 1,3-dipolar cycloaddition of a variety of azides, alkynes, epoxides and sodium azide, furnishing the corresponding 1,2,3-triazoles and *β*-hydroxytriazoles. Click reaction proceeds in short reaction times and under mild reaction conditions, and the resulting products are obtained in good yields at ambient temperature.

Keywords nanoparticle, 1,3-dipolar cycloaddition, 1,2,3-triazole, *β*-hydroxytriazole

Introduction

Few reactions in organic chemistry have experienced the revival and great splendour achieved by the Huisgen 1,3-dipolar cycloaddition reaction of organic azides and alkynes[1] in the dawn of the 21st century. The enormous attention recently gained by this reaction began with the pivotal discovery by the groups of Meldal[2] and Sharpless,[3] in which copper(I) catalysis was found to dramatically accelerate the reaction under mild conditions at the same time a high regioselectivity was achieved towards the 1,4-regioisomer of the triazole product.[4] This powerful, highly reliable and selective reaction is the paradigm of a click reaction, as it meets the set of stringent criteria required in click chemistry as defined by Sharpless *et al*.[5] Consequently, this protocol has found increasing application in a variety of disciplines[4b,6] such as organic chemistry,[4] drug discovery and medicinal chemistry,[7] polymer and materials science,[8] or bioconjugation.[7a,9]

In spite of the fact that some copper-free azide-alkyne cycloaddition strategies have been recently reported, the kinetics is rather low and the regioselectivity unpredictable.[10] Therefore, the copper(I)-catalyzed process is still the preferred choice. The sources of copper(I) include: (a) copper(I) salts (normally in the presence of a base and/or a ligand), (b) *in-situ* reduction of copper(II) salts (*e.g.*, copper sulfate with sodium ascorbate) and (c) comproportionation of copper(0) and copper(II), generally limited to special applications (*e.g.*, biological systems).[4] The results obtained by any of these methods are, in general, excellent. There are, however, some issues that should be addressed in order to further improve the efficiency of the reaction and to fulfill the requirements of a truly click reaction. The addition of some copper complexes[11] or ligands[4,12] was found to enhance the reaction rate, but it was with the application of microwave chemistry (75—140 ℃) that reaction times were dramatically reduced to less than 1 h.[4a,13] New and interesting advances in the title reaction involve heterogeneous catalysis.[14] In recent times, our group developed new protocols using $SiO_2/CuSO_4$ as solid-supported catalyst to prepare 1,2,3-triazoles and *β*-hydroxytriazoles.[15]

Experimental

General experimental considerations

Melting points were measured on an Electrothermal 9100 apparatus and uncorrected. The chemicals used were purchased from Merck and Fluka Chemical Companies.

General procedure for the synthesis of 1,2,3-triazole 4a—4k

To a mixture of azides (1 mmol) and alkynes (1 mmol) was added 10 mg of $SiO_2/CuSO_4$ and ascorbic acid (10 mol%) in 2 mL of water and 2 mL of ethanol and the whole mixture was stirred at room temperature. After stirring for 3 h, ethyl acetate (10 mL) was added, and the organic solution was separated from $SiO_2/CuSO_4$ by filtration. The solvent was evaporated

* E-mail: mciyabi@gmail.com; Fax: 0098-21-22431661
Received August 13, 2011; accepted September 29, 2011.
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/cjoc.201100231 or from the author.

under reduced pressure, and the residue was purified by column chromatography over silica gel eluting with hexanes/AcOEt (V : V = 9 : 1) to give the 1,2,3-triazoles **4a**—**4k**.

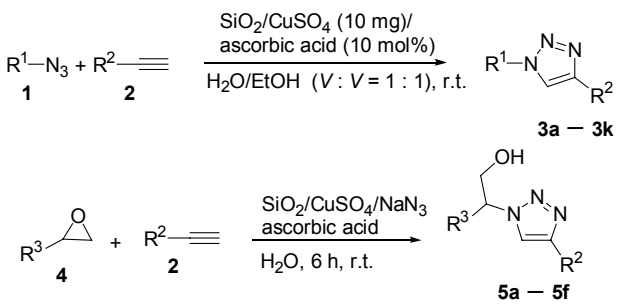
General procedure for the synthesis of β-hydroxytriazoles 5a—5f

To a suspension of epoxides (1.0 mmol) and sodium azide (1.2 mmol) in water (3.0 mL) were added $SiO_2/CuSO_4$ (10 mg) and sodium ascorbate (20 mol%). The resulting solution was stirred for 2 h at room temperature. After completion indicated by TLC, acetylenes (1 mmol) was added to the reaction mixture, and the solution was stirred for another 4 h. The reaction mixture was extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4, and concentrated in vacuum. The resulting residue was purified by column chromatography (hexane/EtOAc, V : V = 3 : 1) to give the β-hydroxytriazoles **5a**—**5f**.

Results and Discussion

As a continuation, we report herein the results of new and cleaner methods for classical synthesis of the 1,2,3-triazoles and β-hydroxytriazoles by a two-component one-pot condensation of an azides **1**, an alkynes **2** and a three-component one-pot condensation of alkynes **2**, epoxides **4**, sodium azide in the presence of a catalytic amounts of $SiO_2/CuSO_4$ and ascorbic acid at ambient temperature in good yields with rather short reaction times (Scheme 1).

Scheme 1 Synthesis of 1,2,3-triazoles **3a**—**3k** and and β-hydroxytriazoles **5a**—**5f**



First, we prepared $SiO_2/CuSO_4$ as a catalyst with Jacob's method.[15] To a 100 mL beaker was added nano-SiO_2 (Aerosil 200) which was supplied by Degussa Co., Germany, with an average size of 12 nm and a specific surface area of 200 m^2/g (5.0 g), $CuSO_4 \cdot 5H_2O$ (2.0 g) and water (4.0 mL). The suspension was stirred for 5 h at room temperature, dried at 80 ℃ for 12 h and for an additional 24 h at 150 ℃ in an oven and then cooled in a desiccator.

The effect of solvent on the reaction has been investigated. As indicated in Table 1, the reaction could be progressed very efficiently in H_2O/EtOH (V : V = 1 : 1). This solvent was chosen as a green solvent for the synthesis.

Table 1 Effects of solvents on the synthesis of **3a**[a]

Entry	Solvent	Time/h	Yield/%
1	$PhCH_3$	3	25
2	CH_2Cl_2	3	32
3	CH_3CN	3	25
4	EtOH	3	60
5	H_2O	3	60
6	H_2O/EtOH (V : V = 1 : 2)	3	80
7	H_2O/EtOH (V : V = 1 : 1)	3	85

[a] Benzyl azide (1 mmol), phenylacetylene (1 mmol) in the presence of $SiO_2/CuSO_4$ (10 mg) and ascorbic acid (10 mol%) under ambient temperature in the presence of different solvents.

To study the effect of amount of the catalyst on this reaction, the synthesis of 1,2,3-triazoles **3a** was selected as model reaction. To illustrate the need of catalyst for these reactions an experiment was conducted in the absence of catalyst and the yield in this case was trace after 3 h. Obviously, catalyst is an important component of the reaction. To determine the optimum amount of catalyst, the reaction was investigated using 10, 20, 30, 40 and 50 mg of $SiO_2/CuSO_4$. The results are shown in Table 2. It is clear that the yields depend on the amount of catalyst, and the optimum amount was 10 mg for all derivatives.

Table 2 Effects of amounts of $SiO_2/CuSO_4$ on the synthesis of **3a**[a]

Entry	Catalyst amount/mg	Time/h	Yield/%
1	10	3	85
2	20	3	86
3	30	3	85
4	40	3	84
5	50	3	85
6	—	3	Trace

[a] Benzyl azide (1 mmol), phenylacetylene (1 mmol) in the presence of $SiO_2/CuSO_4$ and ascorbic acid (10 mol%) under ambient temperature in H_2O/ EtOH (V : V = 1 : 1).

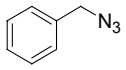
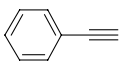
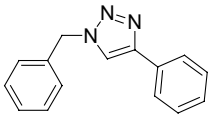
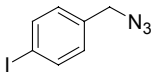
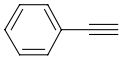
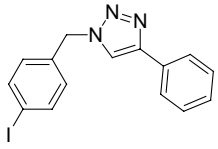
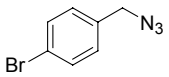
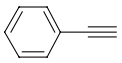
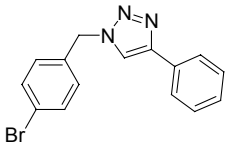
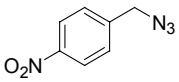
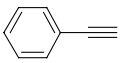
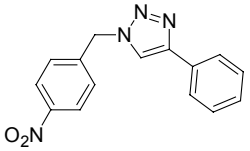
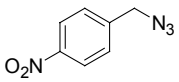
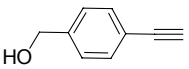
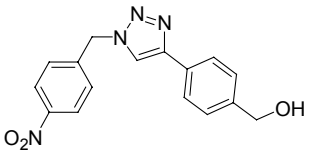
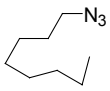
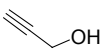
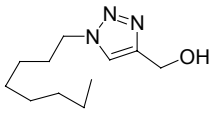
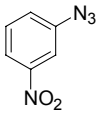
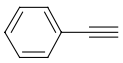
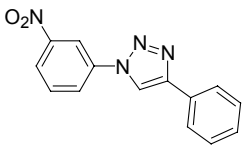
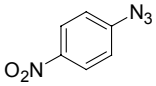
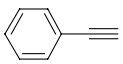
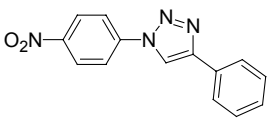
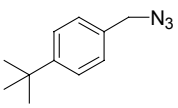
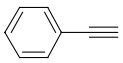
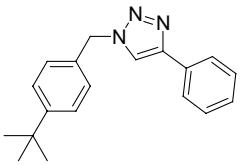
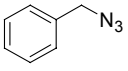
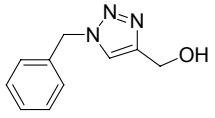
The catalyst is very active, stable to air and moisture, nontoxic and inexpensive. In addition, it can be quantitatively recovered by filtration and reused. In a pilot experiment, azides and alkynes were stirred in water and ethanol in the presence of catalytic amounts of $SiO_2/CuSO_4$ and ascorbic acid. The progress of the reaction was monitored by TLC. After completion of the reaction, an aqueous workup afforded 1,2,3-triazoles **3a**—**3k** in 80%—85% yields. To evaluate the use of this approach, several azides and alkynes were condensed under similar circumstances. The results shown in Table 3 clearly indicate the efficient scope and limitations of this reaction. This reaction proceeded very cleanly un-

CHINESE JOURNAL OF CHEMISTRY

der mild conditions at ambient temperature and no undesirable side reactions were observed.

Recyclability of the catalyst was examined too. For this reason, catalyst was recovered from reaction between benzyl azide and phenylacetylene by filtration; after drying the catalyst in oven (150 ℃, 24 h), it was used again. This procedure was carried out for four times. Results of these successive reactions are shown

Table 3 Synthesis of 1,2,3-triazoles **3a**—**3k**

Compd.	Azide	Alkyne	Time/h	Triazole	Yield[a]/%	m.p./℃	
						Found	Reported
3a			3		85	128—130	128—129[16c]
3b			3		82	155—157	154—156[16c]
3c			3.5		85	150—151	150—152[16c]
3d			3.5		83	141—143	140—142[16c]
3f			3		80	135—136	135—136[16e]
3g			4		80	46—48	46—49[16e]
3h			4		81	199—200	198—200[16b]
3j			3.5		85	236—238	236—238[16c]
3i			3		85	164—166	164—165[16e]
3k			3		84	75—77	76—77[16d]

[a] Isolated yield.

in Table 4. It is clear that by successive use of catalyst no decrease in reactivity or performance can be seen.

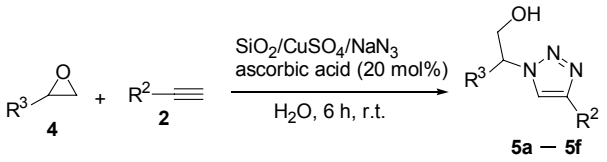
Table 4 Recycle of the catalyst[a]

Cycle	Amount of (SiO_2/$CuSO_4$)/mg	Yield/%
1	10	85
2	9	84
3	9	85
4	8	82

[a] Benzyl azide (1 mmol), phenylacetylene (1 mmol) in the presence of SiO_2/$CuSO_4$ and ascorbic acid (10 mol%) under ambient temperature in H_2O/EtOH (V∶V=1∶1).

To check the generality of this catalyst, we report an efficient approach for the one-pot synthesis of *β*-hydroxytriazoles from epoxides, sodium azide, and alkynes by way of a three-component reaction, proceeding via the formation of 2-azidoalcohols from epoxides and sodium azide in the presence of catalytic amounts of SiO_2/$CuSO_4$ and ascorbic acid. In a preliminary experiment, epoxides **4** were treated with sodium azide and acetylenes **2** in the presence of catalytic amounts of SiO_2/$CuSO_4$ and 20 mol% of sodium ascorbate in water. The reactions went to completion at ambient temperature and the products, *β*-hydroxytriazoles **5a—5f** were obtained in 70%—75% yields (Scheme 2).

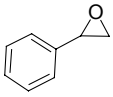
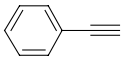
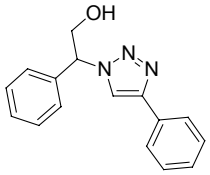
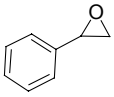
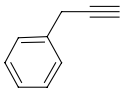
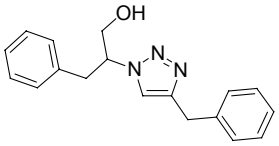
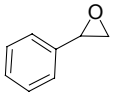
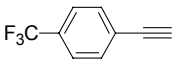
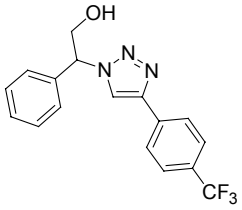
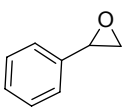
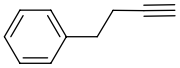
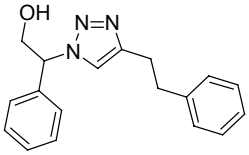
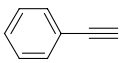
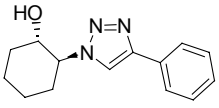
Scheme 2 Synthesis of *β*-hydroxytriazoles **5a—5f**



Various other alkynes reacted readily with various epoxides and sodium azide under these reaction conditions to produce *β*-hydroxytriazoles in good yields (Table 5).

In Table 6 we have compared the results of our investigations with previous report with $CuSO_4$•$5H_2O$. The results show that SiO_2/$CuSO_4$ is a best catalytic system in times, amount of catalyst and yields for synthesis of the 1,2,3-triazole **3a** and *β*-hydroxytriazole **5a**.

Table 5 One-pot synthesis of *β*-hydroxytriazoles from various epoxides, sodium azide and alkynes

Compd.	Epoxide	Alkyne	Time/h	Triazole	Yield[a]/%	m.p./℃	
						Found	Reported
5a			6		75	130	130—132[17]
5b			6		75	109—111	110—112[15d]
5c			6		74	108—110	108[18]
5d			6		70	65—66	64[18]
5f			6		70	180—182	182—184[17]

[a] Isolated yield

Table 6 Comparison of the results of $SiO_2/CuSO_4$ with $CuSO_4 \cdot 5H_2O$

Entry	Catalyst	Dosage of catalyst	Yield	Time	Ref.
3a	$CuSO_4 \cdot 5H_2O$	1 mol%	88%	30 h	[19]
5a	$CuSO_4 \cdot 5H_2O$	16 mg	92%	4 h	[17]
3a	$SiO_2/CuSO_4$	10 mg	85%	3 h	This work
5a	$SiO_2/CuSO_4$	10 mg	75%	6 h	This work

This results show that amount, time and recyclability of $SiO_2/CuSO_4$ in these reactions is good. For this reason, we believe that this is one of the fastest and better catalyst system procedures for synthesis of 1,2,3-triazoles and β-hydroxytriazoles in good yields.

Conclusions

In conclusion, we have introduced a catalytic system based on $SiO_2/CuSO_4$, can catalyze the 1,3-dipolar cycloaddition of azides and terminal alkynes. The $SiO_2/CuSO_4$ is quickly prepared from commercially available reagents under mild conditions. We believe that the herein described methodology fulfils the requirements of a true click reaction, namely: (a) wide scope, (b) simple reaction conditions, (c) readily available starting materials and reagents, (d) easily removed solvent and (e) simple removal of by-products and product isolation. In view of the results presented above, we also believe that this is one of the fastest procedures ever reported for the title reaction, but involving milder conditions and without the inherent limitations and at ambient temperature in good yields. Further research to extend the substrate scope and on the reaction mechanism is underway and will be reported in due course. The operational simplicity of this method makes it attractive for preparative applications as well as for the synthesis of screening libraries for drug discovery.

Acknowledgement

We gratefully acknowledge financial support from the Research Council of Islamic Azad University of Karaj.

References

[1] (a) Huisgen, R.; Knorr, R.; Moebius, L.; Szeimies, G. *Chem. Ber.* **1965**, *98*, 4014; (b) Huisgen, R. *Pure Appl. Chem.* **1989**, *61*, 613.

[2] Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057.

[3] Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596.

[4] (a) Bock, V. D.; Perciaccante, R.; Jansen, T. P.; Hiemstra, H.; Van Maarseveen, J. H. *Org. Lett.* **2006**, *8*, 919; (b) Meldal, M.; Tornøe, C. W. *Chem. Rev.* **2008**, *108*, 2952.

[5] Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004.

[6] (a) Gil, M. V.; Arévalo, M. J.; López, O. *Synthesis* **2007**, 1589; (b) Moses, J. E.; Moorhouse, A. D. *Chem. Soc. Rev.* **2007**, *36*, 1249; (c) Van der Eycken, E.; Sharpless, K. B. *QSAR Comb. Sci.* **2007**, *26*, 1115.

[7] (a) Kolb, H. C.; Sharpless, K. B. *Drug Discovery Today* **2003**, *8*, 1128; (b) Tron, G. C.; Pirali, T.; Billington, R. A.; Canonico, P. L.; Sorba, G.; Genazzani, A. A. *Med. Res. Rev.* **2008**, *28*, 278; (c) Moorhouse, A. D.; Moses, J. E. *Chem. Med. Chem.* **2008**, *3*, 715.

[8] (a) Nandivada, H.; Jiang, X.; Lahann, J. *Adv. Mater.* **2007**, *19*, 2197; (b) Lutz, J.-F. *Angew. Chem., Int. Ed.* **2007**, *46*, 1018.

[9] (a) Dondoni, A. *Chem. Asian. J.* **2007**, *2*, 700; (b) Lutz, J.-F.; Zarafshani, Z. *Adv. Drug Delivery Rev.* **2008**, *60*, 958.

[10] (a) Li, P.; Wang, L. *Lett. Org. Chem.* **2007**, *4*, 23; (b) Lutz, J.-F. *Angew. Chem., Int. Ed.* **2008**, *47*, 2182.

[11] (a) Díez-González, S.; Correa, A.; Cavallo, L.; Nolan, S. P. *Chem.-Eur. J.* **2006**, *12*, 7558; (b) Broggi, J.; Díez-González, S.; Petersen, J. L.; Berteina-Raboin, S.; Nolan, S. P.; Agrofolio, L. A. *Synthesis* **2008**, 141.

[12] (a) Chan, T. R.; Hilgraf, R.; Sharpless, K. B.; Fokin, V. V. *Org. Lett.* **2004**, *6*, 2853; (b) Gerard, B.; Ryan, J.; Beeler, A. B.; Porco, J. A. J. *Tetrahedron* **2006**, *62*, 6405.

[13] (a) Pérez-Balderas, F.; Ortega-Muñoz, M.; Morales-Sanfrutos, J.; Hernández-Mateo, F.; Calvo-Flores, F. G.; Calvo-Asín, J. A.; Isac-García, J.; Santoyo-González, F. *Org. Lett.* **2003**, *5*, 1951; (b) Appukkuttan, P.; Dehaen, W.; Fokin, V. V.; Van der Eycken, E. *Org. Lett.* **2004**, *6*, 4223; (c) Moorhouse, A. D.; Moses, J. E. *Synlett* **2008**, 2089.

[14] (a) Lipshutz, B. H.; Taft, B. R. *Angew. Chem., Int. Ed.* **2006**, *45*, 8235; (b) Chassaing, S.; Sido, A. S. S.; Alix, A.; Kumarraja, M.; Pale, P.; Sommer, J. *Chem.-Eur. J.* **2008**, *14*, 6713; (c) Alonso, F.; Moglie, Y.; Radivoy, G.; Yus, M. *Tetrahedron Lett.* **2009**, *50*, 2358.

[15] (a) Jacob, R. G.; Perin, G.; Loi, L. N.; Pinno, C. S.; Lenardão, E. J. *Tetrahedron Lett.* **2003**, *44*, 3605; (b) Jacob, R. G.; Perin, G.; Botteselle, G. V.; Lenardão, E. J. C. *Tetrahedron Lett.* **2003**, *44*, 6809; (c) Lenardão, E. J.; Mendes, S. R.; Ferreira, P. C.; Perin, G.; Silveira, C. C.; Jacob, R. G. *Tetrahedron Lett.* **2006**, *47*, 7439; (d) Jacob, R. G.; Dutra, L. G.; Radatz, C. S.; Mendes, S. R.; Perin, G.; Lenardão, E. J. *Tetrahedron Lett.* **2009**, *50*, 1495.

[16] (a) Gonda, Z.; Novak, Z. *Dalton Trans.* **2010**, *39*, 726; (b) Wang, D.; Li, N.; Zhao, M.; Shi, W.; Maa, C.; Chen, B. *Green Chem.* **2010**, *12*, 2120; (c) Durugkar, K. A.; Gonnade, R. G.; Ramana, C. V. *Tetrahedron* **2009**, *65*, 3974; (d) Girard, C.; Onen, E.; Aufort, M.; Beauviere, S.; Samson, E.; Herscovici, J. *Org. Lett.* **2006**, *8*, 1689; (e) Ozcubukcu, S.; Ozkal, E.; Jimeno, C.; Pericas, M. A. *Org. Lett.* **2009**, *11*, 4680.

[17] Yadav, J. S.; Reddy, B. V. S.; Reddy, G. M.; Chary, D. N. *Tetrahedron Lett.* **2007**, *48*, 8773.

[18] Boningari, T.; Olmos, A.; Reddy, B. M.; Sommer, J.; Pale, P. *Eur. J. Org. Chem.* **2010**, 6338.

[19] Campbell-Verduyn, L. S.; Mirfeizi, L.; Dierckx, R. A.; Elsinga, P. H.; Feringa, B. L. *Chem. Commun.* **2009**, 2139.

(Zhao, C.)

