An Efficient One-pot Three-component Reaction to Produce 1,4-Disubstituted-1,2,3-triazoles Catalyzed by a Dicopper-substituted Silicotungstate

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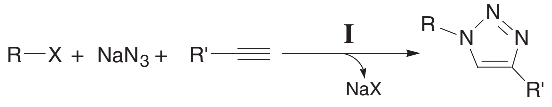
The dicopper-substituted γ-Keggin silicotungstate with bis-μ-1,1-azido ligands $TBA_4H_2[\gamma\text{-}SiW_{10}O_{36}Cu_2(\mu\text{-}1,1\text{-}N_3)_2]$ (TBA = tetrabutylammonium) could act as an effective homogeneous precatalyst for the one-pot synthesis of various kinds of 1,4-disubstituted-1,2,3-triazole derivatives from organic halides, NaN_3, and alkynes.

Triazole derivatives are very important five-membered nitrogen heterocycles and have a wide range of applications including biochemicals, agrochemicals, dyes, photostabilizers, and corrosion inhibitors.[1] The Huisgen 1,3-dipolar cycloaddition of organic azides to alkynes is one of the most powerful synthetic routes to triazole derivatives and shows high chemoselectivity because many functional groups do not react with organic azides or alkynes.[2] However, this transformation is not regioselective and gives a ca. 1:1 mixture of 1,4- and 1,5-regioisomers.[2] The groups of Sharpless et al.[3a] and Meldal et al.[3b] have independently reported that copper salts dramatically accelerate the reaction and make it totally regioselective to the 1,4-regioisomers. Now, the copper-mediated regioselective 1,3-dipolar cycloaddition has been used for the tailor-made syntheses of triazole derivatives with various functional groups because of the exclusive 1,4-regioselectivity and wide synthetic scope.[3] Recently, the one-pot synthesis of 1,4-disubstituted-1,2,3-triazole derivatives from organic halides, NaN_3, and alkynes has received much attention.[4]

The interests in the catalysis of partially metal-substituted polyoxometalates, which are synthesized by the substitution of metal cations into the vacant site(s) of lacunary polyoxometalates as structural motifs, have been growing because of the rich diversity of lacunary polyoxometalates.[5] To date, various kinds of metal-substituted polyoxometalates have been synthesized and used as catalysts for various functional group transformations.[5] Very recently, we have reported that dicopper-substituted γ-Keggin silicotungstate with bis-μ-1,1-azido ligands $TBA_4H_2[\gamma\text{-}SiW_{10}O_{36}Cu_2(\mu\text{-}1,1\text{-}N_3)_2]$ (denoted as **I**, Figure S1) showed high catalytic activity for the oxidative alkyne–alkyne homocoupling[6a,6b] and 1,3-dipolar cycloaddition of organic azides to alkynes.[6c] In this paper, the application of **I** to the one-pot three-component reaction of organic halides, NaN_3, and alkynes to produce 1,4-disubstituted-1,2,3-triazole derivatives is described (eq 1).



(1)

First, we examined the reactivity of organic halides with NaN_3 prior to the development of a one-pot sequential synthesis of 1,4-disubstituted-1,2,3-triazole derivatives (Table S1). The reaction smoothly proceeded in polar organic solvents such as acetonitrile, methanol, and *N*,*N*-dimethylformamide. After the reaction was completed, the pure organic azides were obtained in >90% isolated yields by Kugelrohr distillation.

Using the benzyl azide obtained, the **I**-mediated 1,3-dipolar cycloaddition of benzyl azide to phenylacetylene was next carried out in order to optimize the reaction conditions (Table S2). Among the solvents tested, polar organic solvents such as acetonitrile, methanol, and *N*,*N*-dimethylformamide gave the corresponding 1,4-disubstituted-1,2,3-triazole of 1-benzyl-4-phenyl-1*H*-1,2,3-triazole in high yields, while non-polar toluene, heptane, and 1,2-dichloroethane were poor solvents. In polar organic solvents, the reactions efficiently proceeded *without any additives such as reducing agents and nitrogen bases*. It is noted that *no precautions to exclude oxygen were necessary* in all **I**-mediated reactions. Under the optimized conditions, various combinations of organic azides and alkynes were efficiently converted into the corresponding 1,4-disubstituted-1,2,3-triazole derivatives in excellent yields (14 examples, Table S3).

Under the conditions described in Table S2, the 1,3-dipolar cycloaddition did not proceed at all in the absence of the catalyst or in the presence of copper(I) and copper(II) salts such as $[Cu(OTf)]_2{\cdot}C_6H_6$, $[Cu(CH_3CN)_4]PF_6$, $[Cu(CH_3CN)_4]ClO_4$, $Cu(ClO_4)_2{\cdot}6H_2O$, $CuCl_2$, and $CuSO_4{\cdot}5H_2O$. The monocopper-substituted silicotungstate $TBA_4[\alpha\text{-}H_2SiW_{11}CuO_{39}]$, the non-copper-substituted silicotungstate $TBA_4[\gamma\text{-}SiW_{12}O_{40}]$, and a mixture of $TBA_4[\gamma\text{-}SiW_{10}O_{34}(H_2O)_2]$ and $CuCl_2$ were almost inactive. Therefore, the diazido-bridged dicopper core $\{Cu_2(\mu\text{-}1,1\text{-}N_3)_2\}$ in **I** plays an important role in the present 1,3-dipolar cycloaddition. We have very recently proposed that the **I**-promoted alkyne–alkyne homocoupling proceeds via the dicopper(II) alkynyl intermediate of $\{Cu_2(\mu\text{-}C{\equiv}CR)_2\}$ followed by the elimination of the corresponding 1,3-diyne with the formation of reduced dicopper(I) species.[6a,6b] Under the present transformations, the corresponding 1,3-diynes could be detected as by-products albeit in small amounts in most substrates tested (<1% yield), suggesting the formation of the dicopper(I) species. Thus, it is likely that the copper(I) acetylide species would be formed by the reaction of the dicopper(I) species in **I** with an alkyne followed by the reaction with an azide to form the corresponding triazole.

Finally, we turn our attention to the one-pot three component synthesis of 1,4-disubstituted-1,2,3-triazole derivatives from the corresponding organic halides, NaN_3, and alkynes (12 examples, Table 1).[4,7,8] The overall conversion of organic halides to 1,4-disubstituted-1,2,3-triazole derivatives was accomplished as a one-pot procedure by simply adding alkynes to the reaction solution after the S_N2 displacement of organic

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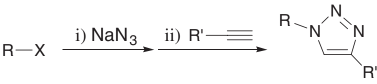
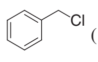
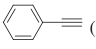
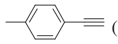
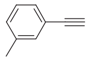
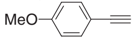
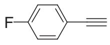
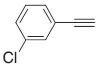
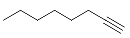
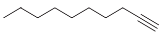
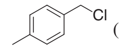
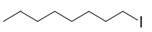
Table 1. One-pot syntheses of 1,4-disubstituted-1,2,3-triazole derivatives from organic halides, NaN_3, and alkynes catalyzed by **I**[a]



Entry	Halide	Alkyne	Time[b] /h	Yield[c] /%
1	 **(1a)**	 **(2a)**	31	81
2	**1a**	 **(2b)**	48	89
3	**1a**	 **(2c)**	48	90
4	**1a**	 **(2b)**	31	94
5	**1a**	 **(2b)**	31	88[d]
6	**1a**	 **(2f)**	31	91[d]
7	**1a**	 **(2g)**	72	94[d]
8	**1a**	 **(2h)**	72	71
9	 **(1b)**	**2a**	50	92
10	**1b**	**2b**	53	87[d]
11	 **(1c)**	**2a**	26	79
12	**1c**	**2f**	55	65

[a]Reaction conditions: (i) **I** (2 mol % with respect to halides), halide (0.5 mmol), NaN_3 (0.525 mmol), CH_3CN/CH_3OH (2 mL, 1/1 v/v), 60 °C under an air atmosphere for 7 h, (ii) followed by addition of an alkyne (1 mmol), 60 °C, under an air atmosphere. [b]Total reaction time. [c]Isolated yields. [d]GC yields.

halides with NaN_3 was completed. The procedures are as follows: Into a glass vial were successively placed **I** (2 mol %), an organic halide (0.5 mmol), NaN_3 (0.525 mmol, 1.05 equiv with respect to halides), and acetonitrile/methanol (2 mL, 1/1 v/v). The reaction mixture was stirred at 60 °C. After 7 h, an alkyne (1 mmol, 2 equiv with respect to halides) was added to the mixture and the reaction was carried out at 60 °C for an appropriate time. Although it took longer reaction times to attain high yields of the corresponding 1,4-disubstituted-1,2,3-triazoles, the amounts of alkynes could be reduced: The reaction of **1a** with an equimolar amount of **2a** under the conditions in Table 1 gave the corresponding triazole in 74% yield for 53 h, for example. Isolation and purification of 1,4-disubstituted-1,2,3-triazoles were carried out by column chromatography on silica gel using a mixed solvent of hexane and diethyl ether as an eluent (5/1 v/v).

Benzyl halides as well as alkyl halides were successfully used and the reactions efficiently proceeded to give the corresponding 1,4-disubstituted-1,2,3-triazoles in excellent yields. For alkynes, electron-rich and -poor phenylacetylenes as well as aliphatic terminal alkynes worked well as reaction partners of organic halides. It was confirmed by X-ray crystallographic analyses and/or NOE experiments that the 1,4-disubstituted-1,2,3-triazole derivatives were formed in a completely regioselective manner without formation of 1,5-regioisomers in all cases.[8] In addition, no competitive formation of N–H triazoles due to the direct addition of N_3^- to alkynes was observed in any case.

In summary, the efficient one-pot synthesis of 1,4-disubstituted-1,2,3-triazole derivatives from organic halides, NaN_3, and alkynes was realized in the presence of **I**.

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References and Notes

1 a) R. Alvarez, S. Velazque, A. San-Felix, S. Aquaro, E. D. Clercq, C.-F. Perno, A. Karlsson, J. Balzarini, M. J. Camarasa, *J. Med. Chem.* **1994**, *37*, 4185. b) M. J. Genin, D. A. Allwine, D. J. Anderson, M. R. Barbachyn, D. E. Emmert, S. A. Garmon, D. R. Graber, K. C. Grega, J. B. Hester, D. K. Hutchinson, J. Morris, R. J. Reischer, C. W. Ford, G. E. Zurenko, J. C. Hamel, R. D. Schaadt, D. Stapert, B. H. Yagi, *J. Med. Chem.* **2000**, *43*, 953. c) A. Brik, Y. Lin, J. Elder, C. Wong, *Chem. Biol.* **2002**, *9*, 891.

2 R. Huisgen, in *1,3-Dipolar Cycloaddition Chemistry*, ed. by A. Padwa, Wiley, New York, **1984**, pp. 1–176.

3 a) V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem., Int. Ed.* **2002**, *41*, 2596. b) C. W. Tornøe, C. Christensen, M. Meldal, *J. Org. Chem.* **2002**, *67*, 3057. c) L. D. Pachón, J. H. van Maarseveen, G. Rothenberg, *Adv. Synth. Catal.* **2005**, *347*, 811. d) G. Molteni, C. L. Bianchi, G. Morinoni, N. Santo, A. Ponti, *New J. Chem.* **2006**, *30*, 1137. e) S. Díez-González, A. Correa, L. Cavallo, S. P. Nolan, *Chem.—Eur. J.* **2006**, *12*, 7558. f) B. H. Lipshutz, B. R. Taft, *Angew. Chem., Int. Ed.* **2006**, *45*, 8235. g) V. D. Bock, H. Hiemstra, J. H. Maarseveen, *Eur. J. Org. Chem.* **2006**, 51. h) F. Himo, T. Lovell, R. Hilgraf, V. V. Rostovtsev, L. Noodles, K. B. Sharpless, V. V. Fokin, *J. Am. Chem. Soc.* **2005**, *127*, 210. i) V. O. Rodionov, V. V. Fokin, M. G. Finn, *Angew. Chem., Int. Ed.* **2005**, *44*, 2210. j) S. S. Gupta, K. S. Raja, E. Kaltgrad, E. Strable, M. G. Finn, *Chem. Commun.* **2005**, 4315. k) V. Ladmiral, G. Mantovani, G. J. Clarkson, S. Cauet, J. L. Irwin, D. M. Haddleton, *J. Am. Chem. Soc.* **2006**, *128*, 4823. l) R. Srinivasan, M. Uttamchandani, S. Q. Yao, *Org. Lett.* **2006**, *8*, 713. m) D. D. Díaz, K. Rajagopal, E. Strable, J. Schneider, M. G. Finn, *J. Am. Chem. Soc.* **2006**, *128*, 6056. n) Y. L. Angell, K. Burgess, *Chem. Soc. Rev.* **2007**, *36*, 1674.

4 a) P. Appukkuttan, W. Dehaen, V. V. Fokin, E. van der Eycken, *Org. Lett.* **2004**, *6*, 4223. b) Y.-B. Zhao, Z.-Y. Yan, Y.-M. Liang, *Tetrahedron Lett.* **2006**, *47*, 1545. c) B. Saha, S. Sharma, D. Sawant, B. Kundu, *Synlett* **2007**, 1591.

5 a) N. Mizuno, K. Yamaguchi, K. Kamata, *Coord. Chem. Rev.* **2005**, *249*, 1944. b) I. V. Kozhevnikov, *Catalysis by Polyoxometalates*, John Wiley & Sons, Ltd, Chichester, England, **2002**. c) Thematic Issue on Polyoxometalates, ed. by C. L. Hill, *Chem. Rev.* **1998**, *98*, No. 1. d) R. Neumann, *Prog. Inorg. Chem.* **1998**, *47*, 317. e) T. Okuhara, N. Mizuno, M. Misono, *Adv. Catal.* **1996**, *41*, 113. f) M. T. Pope, *Heteropoly and Isopoly Oxometalates*, Springer-Verlag, Berlin, **1983**.

6 a) K. Kamata, S. Yamaguchi, M. Kotani, K. Yamaguchi, N. Mizuno, *Angew. Chem., Int. Ed.* **2008**, *47*, 2407. b) K. Yamaguchi, K. Kamata, S. Yamaguchi, M. Kotani, N. Mizuno, *J. Catal.* **2008**, *258*, 121. c) K. Kamata, Y. Nakagawa, K. Yamaguchi, N. Mizuno, *J. Am. Chem. Soc.*, in press.

7 The reaction rate for the cycloaddition of an azide to an alkyne decreased in the presence of NaN_3 and NaCl (Table S3), which is likely due to the competitive coordination of N_3^- or Cl^- to the active copper site. Although the present one-pot procedure needs longer time than the step-by-step synthesis, it completely avoids the isolation of an explosive organic azide. This is a very important advantage of the present one-pot procedure.

8 Supporting Information is also available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

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