Copper(II)-Promoted Regioselective Synthesis of 1,4-Disubstituted 1,2,3-Triazoles in Water

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Received 17 October 2005

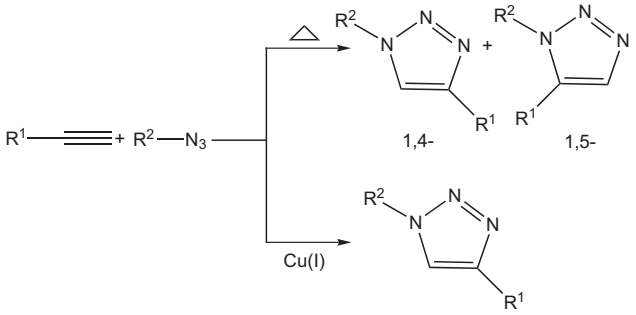
Abstract: A high-yielding synthesis of 1,2,3-triazole with cheaply available $Cu(OAc)_2$ without any additional reducing agents is explored, which provides an exclusive 1,4-regioselectivity at ambient conditions in an environmentally benign solvent – water.

Key words: Cu(II) catalyst, regioselective, 1,2,3-triazole, water

Replacement of volatile organic solvents with environmentally benign solvents has received considerable attention in organic synthesis due to increased environmental regulations.[1] Several solvent systems, including water,[2] supercritical fluids,[3] ionic liquids,[4] soluble polymers,[5] and fluorous liquids,[6] have been exploited over the last several years as alternative media for organic synthesis. In recent years significant progress has been made in the field of organic chemistry in water/aqueous media, and several organic transformations, e.g. aldol, allylation, Diels–Alder, Michael, Heck and Suzuki reactions, have been performed efficiently in water.[7]

1,3-Dipolar cycloaddition of azides with alkynes investigated by Huisgen et al. is an important organic transformation[8] and the resulting five-membered 1,2,3-triazoles have a wide range of industrial applications in agrochemicals, corrosion inhibitors, dyes, optical brighteners and pharmaceuticals.[9] The traditional method for the synthesis of triazoles requires elevated temperatures and this non-catalyzed reaction is poorly regioselective, which gives a mixture of 1,4- and 1,5-disubstituted triazoles (Scheme 1).

Recently, Sharpless and co-workers have reported a high yielding synthesis of triazoles using a Cu(I) catalyst with an excellent 1,4-regioselectivity.[10] The reaction tolerates a variety of functional groups and, being insensitive to water and oxygen, makes it a candidate for use in click chemistry.[11] It is postulated that the reaction proceeds via a copper acetylide intermediate, generated from Cu(I) and the terminal alkyne, which then participates in a cycloaddition process with the coordinated azide.[12] The active Cu(I) catalysts are introduced directly in the form of different copper(I) salts, generated in situ from Cu(II) salts with reducing agents or by the in situ oxidation of copper metal turnings. Herein we wish to report on the direct Cu(II)-catalyzed regioselective synthesis of 1,4-triazole derivatives in high yields under ambient conditions in water without any additional reducing/oxidizing agents.



Scheme 1 Synthesis of 1,4-disubstituted 1,2,3-triazole

Initially, we evaluated the reaction between benzyl azide and phenylacetylene (Table 1) with 20 mol% of the copper catalyst. As expected, Cu(I) salts provided exclusive 1,4-regioselectivity irrespective of the source of copper. On the other hand, a large difference in activity was observed for different Cu(II) salts. Among several Cu(II) salts, $Cu(OAc)_2 \cdot H_2O$ was found to be the best in terms of activity and selectivity and all further experiments were carried out with this catalyst.

The results of the Cu(II)-catalyzed [3+2] cycloaddition of various terminal alkynes with benzyl azide are summarized in Table 2 and compared further with the blank as well as Cu(I)-catalyzed reactions. The reaction of phenylacetylene and benzyl azide in water with 20 mol% of the catalyst resulted in 77% of product, while under similar conditions a blank experiment provided only 20% of the product (Table 2, entry 1). Slightly lower conversion (71%) is observed for *p*-methylphenylacetylene and benzyl azide reaction (Table 2, entry 2). On the other hand, *m*-methoxyphenylacetylene having an electron-donating group underwent quantitative conversion (Table 2, entry 3). In the case of aliphatic alkynes, propargyl alcohol gave quantitative conversion (Table 2, entry 4); whereas substituted derivatives resulted in lower yields (Table 2, entries 5 and 6), which might be due to steric factors. Irrespective of the nature of alkynes, complete 1,4-regioselectivity is observed in all the experiments with the present catalyst. Higher conversions are observed compared with the blank experiments, which clearly indicates that the activity is associated with the Cu(II) catalyst.

SYNLETT 2006, No. 6, pp 0957–0959
Advanced online publication: 21.02.2006
DOI: 10.1055/s-2006-933134; Art ID: D31805ST

Table 1 Synthesis of 1,2,3-Triazole from Phenylacetylene and Benzyl Azide with Different Copper Sources in Water[a]

Entry	Copper source	Yield (%)[b]	Ratio of 1,4-:1,5-isomers
1	None (control)	20	91:9
2	CuI	100	100:0
3	CuBr	100	100:0
4	$CuCl_2$	5	28:72
5	$Cu(NO_3)_2 \cdot 3H_2O$	13	100:0
6	$Cu(OAc)_2 \cdot H_2O$	77	100:0

[a] Reaction conditions: phenylacetylene (1.2 mmol), benzyl azide (1 mmol), Catalyst (20 mol%), H_2O (3 mL).
[b] NMR yields based on benzyl azide starting material.

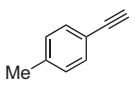
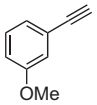
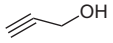
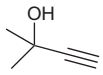
In the majority of reported procedures, activation of terminal alkynes is achieved by the formation of Cu-acetylide with the main catalyst precursor as a Cu(I) salt. However, there is some precedent in the literature where the nature of the Cu(II) salts do effect the activation of terminal alkynes. For example, Yamamoto and co-workers recently reported that the activity of $CuBr_2$ and $CuCl_2$ are comparable to CuBr in the synthesis of glycinate-tethered α,ω-enynes, whereas, $Cu(OAc)_2$ and CuI proved to be ineffective.[13] Similarly, simple $Cu(ClO_4)_2$ and oxazoline ligand combination is utilized for the coupling of terminal alkynes with nitrones.[14]

Recently, Alper and co-workers also observed slightly lower activity of $Cu(OAc)_2$ with respect to Cu(I) salts for the synthesis of propargylamines in ionic liquids.[15] However, in all the above cases utilization of Cu(II) salts for the activation of terminal alkynes is not fully focused. To probe further on the nature of the metal ion in solution, we have recorded the electronic spectra before and after the reaction and the spectral features clearly indicate no change in formal oxidation state of the metal ion.

Moreover, the aqueous phase after extraction with ethyl acetate is still active for further recycling experiments. We observed no loss in activity even after two cycles. These results clearly indicate that the activity is associated with $Cu(OAc)_2$. Further studies on the influence of counter ions on the activation of alkynes are under investigation.

In conclusion, we have shown a simple protocol for the synthesis of 1,4-disubstituted 1,2,3-triazoles in an environmentally benign solvent with copper(II) acetate under ambient conditions in high yields.

Table 2 Formation of Triazoles from Different Alkynes in Water[a]

Entry	Alkyne	Product	Control Yield (%)[b,c]	CuI Yield (%)[b,c]	$Cu(OAc)_2$ Yield (%)[b,c]
1		**1a**	20 (91:9)	100 (100:0)	77 (100:0)
2		**2a**	2 (100:0)	100 (100:0)	71 (100:0)
3		**3a**	10 (100:0)	100 (100:0)	100 (100:0)
4		**4a**	0	87 (100:0)	100 (100:0)
5		**5a**	0	100 (100:0)	83 (100:0)
6		**6a**	0	91 (100:0)	77 (100:0)

[a] Reagents: alkyne (1.2 mmol), benzyl azide (1 mmol), catalyst (20 mol%), H_2O (3 mL).[16]
[b] NMR yields based on benzyl azide starting material.
[c] The 1,4- vs. 1,5-regioselectivities are shown in parenthesis.

Acknowledgment

We wish to thank the CSIR for financial support under the Task Force Project CMM-0005 and K.R thanks UGC for a Junior Research Fellowship.

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(16) **Typical Procedure for the Synthesis of 1,2,3-Triazoles**
To the stirred solution of alkyne (1.2 mmol) and copper catalyst (20 mol%) in H_2O (3 mL), was added alkyl azide (1.0 mmol) in one portion at r.t. After 20 h of stirring, the precipitated product was extracted with EtOAc (3 × 5 mL) and the organic extract was dried. The crude product was subjected to column chromatography to yield the desired product. The products were characterized by ^{1}H NMR. Compound **1a**: ^{1}H NMR ($CDCl_3$): δ = 5.55 (s, 2 H), 7.25–7.37 (m, 8 H), 7.58 (s, 1 H), 7.75 (d, 2 H, *J* = 8.30 Hz). Compound **2a**: ^{1}H NMR ($CDCl_3$): δ = 2.36 (s, 3 H), 5.55 (s, 2 H), 7.14–7.37 (m, 7 H), 7.55 (s, 1 H), 7.64 (d, 2 H, *J* = 8.3 Hz). Compound **3a**: ^{1}H NMR ($CDCl_3$): δ = 3.83 (s, 3 H), 5.52 (s, 2 H), 6.69 (m, 1 H), 7.19–7.38 (m, 8 H), 7.58 (s, 1 H). Compound **4a**: ^{1}H NMR ($CDCl_3$): δ = 3.12 (br, 1 H), 4.69 (s, 2 H), 5.48 (s, 2 H), 7.18–7.38 (m, 6 H). Compound **5a**: ^{1}H NMR ($CDCl_3$): δ = 1.52 (s, 6 H), 4.20 (br, 1 H), 5.39 (s, 2 H), 7.21–7.36 (m, 6 H). Compound **6a**: ^{1}H NMR ($CDCl_3$): δ = 1.90 (s, 3 H), 2.93 (br, 1 H), 5.43 (s, 2 H), 7.15–7.42 (m, 11 H).