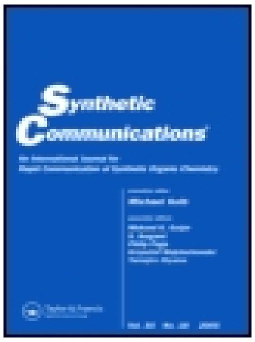

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CTAB promoted CuI catalyzed green and economical synthesis of 1,4-disubstituted-1,2,3-triazoles

Abdul Aziz Ali[a], Rahul Sharma[a], Prakash J. Saikia[b], and Diganta Sarma[a]

[a]Department of Chemistry, Dibrugarh University, Dibrugarh, Assam, India; [b]Analytical Chemistry Division, CSIR-North East Institute of Science & Technology, Jorhat, Assam, India

ABSTRACT
A practical, straightforward, and highly efficient CuI mediated green protocol for the regioselective synthesis of 1,4-disubstituted-1,2,3-triazole was developed using cetyltrimethylammonium bromide as a cheap additive in good to excellent yields. Low catalyst loadings, environmentally friendly solvent, wide substrate scope and short reaction times at room temperature make this strategy more accessible and safe.

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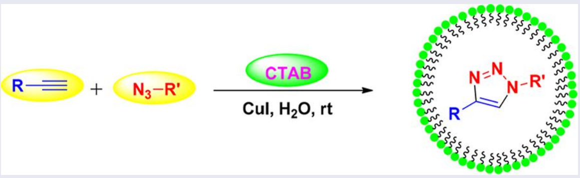
KEYWORDS
1,2,3-Triazoles; CTAB; CuAAC; phase transfer catalyst; water

GRAPHICAL ABSTRACT



Introduction

1,2,3-Triazoles are nitrogen-containing five-membered heterocycles, and an important structural motif owing to its significant applications in medicinal chemistry.[1] As an important amide isostere, the 1,2,3-triazole core demonstrates a broad spectrum of biological activities such as antibacterial, antifungal, antiviral, antiallergic, anti-HIV, and antituberculosis activities and some of them are available in the market as drugs.[2] Furthermore, the application of 1,2,3-triazoles is also extended to other areas such as organic synthesis, chemical biology, polymer, and materials science.[3] The 1,2,3-triazole moiety has also exhibited as a versatile ligand for metal coordination, directing groups for transition-metal-catalyzed C–H activation as well as industrial applications, such as photostabilizers, lubricants, dyes, and corrosion inhibitor.[4] Numerous methodologies have been developed for the synthesis of 1,2,3-triazoles so far, but the Cu(I)-catalyzed version of Huisgen 1,3-dipolar cycloaddition reaction is undoubtedly the most powerful tool to furnish 1,2,3-triazole scaffolds.[5] The Cu-catalyzed alkyne-azide cycloaddition is an elegant and powerful protocol for the synthesis of 1,4-disubstituted 1,2,3-triazoles owing

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CONTACT Diganta Sarma ✉ dsarma22@gmail.com; dsarma22@dibru.ac.in Department of Chemistry, Dibrugarh University, Dibrugarh 786 004, Assam, India.
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Supplemental data (full experimental details, ^{1}H and ^{13}C NMR spectra) can be accessed on the publisher's website.

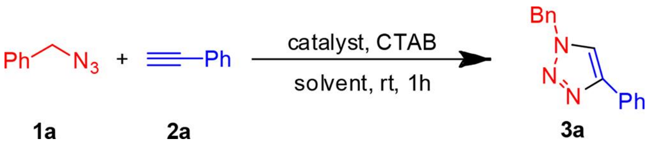
to its ample applicability and efficiency.[6] The typical Cu(I) catalyst was usually generated from the cheap and easily available mixture of $CuSO_4$ and sodium ascorbate and stabilized by either amine base or ligand.[7]

In recent years, many new catalyst systems have been reported involving homogeneous as well as heterogeneous Cu catalyst.[8] Lim et al.[9] developed a mild methodology using β-cyclodextrin as a phase transfer catalyst. Similarly, the Scarso group reported miceller (sodium lauryl sulfosuccinate and TPGS-750-M) promoted simple, and efficient synthesis of 1,2,3-triazoles in the presence of [Cu(IMes)Cl] catalyst at room temperature.[10] Recently, Doris et al.[11] developed an efficient nano Cu-catalyst in polydiacetylene micelles for Huisgen cycloaddition reaction. Despite these remarkable advances, most of the systems often used expensive additive, organic solvents, high catalyst loading, multistep Cu-complex synthesis, long reaction time and harsh reaction conditions which limited their practical applications. Therefore, the development of a convenient, green and efficient method to access 1,4-disubstituted-1,2,3-triazoles is of great significance. In continuation of our work on 1,2,3-triazoles[12] herein, we wish to report a straightforward, rapid, and economical protocol for the synthesis of 1,4-disubstituted 1,2,3-triazoles at room temperature under environmentally friendly condition using cetyltrimethylammonium bromide (CTAB) as an additive.

Results and discussion

We initialized the copper-catalyzed optimum cycloaddition conditions using benzyl azide with phenylacetylene as the model substrates, as shown in Table 1. In this preliminary experiment, the Huisgen cycloaddition reaction was performed in standard cycloaddition conditions (t-BuOH/H_2O) with various Cu sources (1 mol%) as a catalyst, CTAB as an additive in the air at room temperature for 1 h. We were delighted to see that the reaction proceeded well to give in 90% yields of the desired product **3a** (Table 1, entry 1). Encouraged by this result, we have decided to screen different commercial Cu catalysts in the cycloaddition reaction. It was revealed that CuI displayed high catalytic activities resulting 75% conversion to the 1,4-disubstituted-1,2,3-triazole (Table 1, entry 2). It is noteworthy that water as a solvent lead superior activity than organic solvents (Table 1, entry 8). Developing an economic and environmentally friendly reaction using water as solvent is undoubtedly the most favorable condition. Increasing the catalyst loading had the expected effect of enhancing the rate of the reaction. From 1 to 10 mol%, it was possible to notably decrease the reaction time to accomplish full conversion within 30 min (Table 1, entry 13).When the reaction was performed in the presence of 10 mol% of CuI without adding CTAB, the reaction did not give satisfactory result and only 45% yield of the triazole was obtained (Table 1, entry 14). Nevertheless, 1 mol% copper catalyst affords sufficiently rapid reaction times, making it unnecessary to rely on higher catalyst loadings to get the desired rates. However, it is evident that no product was obtained in the absence of a catalyst under this identical condition (Table 1, entry 16). Similarly, no byproduct was detected under this conditions, and interestingly, 40% yield of the desired adduct was obtained without using CTAB highlighting the role of the additive (Table 1, entry 15). It is noteworthy that, in the presence of other surfactants such as SDS (anionic surfactant) and Tween-80 (nonionic), the reaction led to a negligible yield of the desired triazole (Table 1, entries 17 and 18).

Table 1. The azide-alkyne cycloaddition with different catalysts in various solvent system[a].



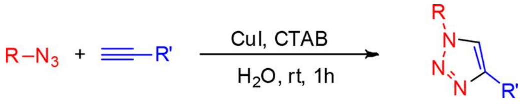
Entry	Catalyst	Solvent	Yield (%)[b]
1	$CuSO_4 \cdot 5H_2O$/Na ascorbate	t-BuOH/H_2O	70
2	CuI	t-BuOH/H_2O	75
3	CuBr	t-BuOH/H_2O	70
4	$Cu(OAc)_2 \cdot 2H_2O$	t-BuOH/H_2O	60
5	$Cu(NO_3)_2$/Na ascorbate	t-BuOH/H_2O	40
6	$CuCl_2 \cdot H_2O$/Na ascorbate	t-BuOH/H_2O	60
7	CuO	t-BuOH/H_2O	No reaction
8	CuI	H_2O	95
9	CuI	DMSO	75
10	CuI	DMF	70
11	CuI	THF	70
12	CuI	Toluene	50
13	CuI	H_2O	96[c]
14	CuI	H_2O	45[d]
15	CuI	H_2O	40[e]
16	–	H_2O	No reaction
17	CuI	H_2O	30[f]
18	CuI	H_2O	35[g]

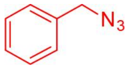
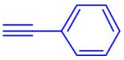
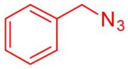
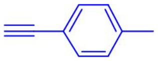
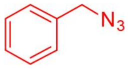
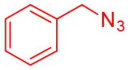
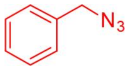
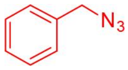
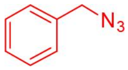
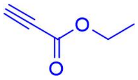
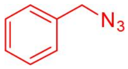
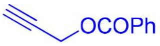
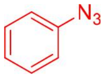
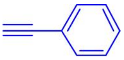
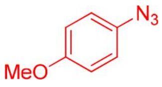
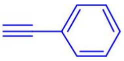
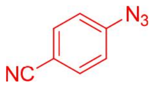
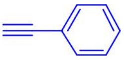
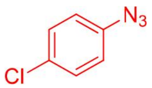
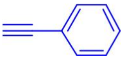
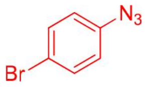
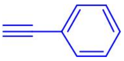
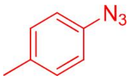
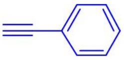
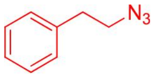
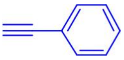
[a] Reaction condition: benzyl azide (1 mmol), phenyl acetylene (1.2 mmol), catalyst (1 mol%), CTAB (1 mol%), solvent (2 mL) at room temperature.
[b] Isolated yields.
[c] CuI (10 mol%).
[d] CuI (10 mol%) without adding CTAB.
[e] In the absence of CTAB.
[f] Instead of CTAB, SDS is used.
[g] Instead of CTAB, tween-80 is used.

With the optimal conditions established, we then explored the scope of the reaction and the results are presented in Table 2. For all the examined substrates, experiments were performed efficiently to completion in short reaction times and the corresponding triazoles were obtained in good to excellent yields. As expected, aromatic acetylenes reacted readily with benzyl azide to form the desired triazole products in excellent yields (Table 2, entries 1–3). Cycloaddition of phenylacetylene with functionalized benzyl azides afforded excellent yields of 1,4-disubstituted-1,2,3-triazoles, respectively. The utility of this reaction is further proved in aliphatic alkynes and found that they also worked well and afforded the desired products in good yields (Table 2, entries 4 and 5). The reaction of phenethyl azide with phenylacetylene also furnished the appropriate products with high yields (Table 2, entry 15). In the case of aromatic azides, phenylazides with both electron-withdrawing groups (such as halogen and CN) and electron-donating groups (such as CH_3 and OMe) were feasible substrates for this reaction affording the triazole products in excellent yields (Table 2, entries 9–14). The extension of this protocol to a variety of reactive functional groups such as alcohol and ester also resulted in the formation of corresponding 1,4-disubstituted-1,2,3-triazoles in good yields (Table 2, entries 6–8).

The acceleration of copper-catalyzed azide-alkyne cycloaddition reactions by cationic surfactant CTAB is believed to be due to the micelle formation of CTAB in water and this micelle acts as a phase transfer catalyst. Micellar media have been broadly used to influence the rate of various organic and inorganic reactions. The promoting effect of CTAB can be

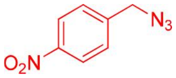
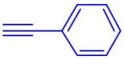
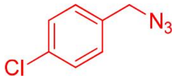
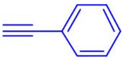
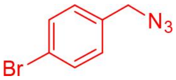
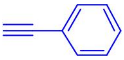
Table 2. Cycloaddition of various azides and alkynes catalyzed by copper iodide in water and CTAB as additive[a].



Entry	Azide	Alkyne	Product	Yield (%)[b]
1			**3a**	92
2			**3b**	90
3			**3c**	90
4			**3d**	85
5			**3e**	80
6			**3f**	65
7			**3g**	80
8			**3h**	90
9			**3i**	85
10			**3j**	88
11			**3k**	85
12			**3l**	90
13			**3m**	90
14			**3n**	88
15			**3o**	80

(*Continued*)

Table 2. Continued.

Entry	Azide	Alkyne	Product	Yield (%)[b]
16			**3p**	85
17			**3q**	88
18			**3r**	90

[a] Reaction condition: azide (1 mmol), alkyne (1.2 mmol), CuI (1 mol%), CTAB (1 mol%), H_2O (2 mL) at room temperature.
[b] Isolated yield.

explained by considering both electrostatic and hydrophobic interactions of CTAB with the reactants which work simultaneously.[13] The CTAB micellar system has positively charged head groups at the periphery and non-polar hydrocarbon chains in its core. It allows the apolar organic substrates to enter the same phase and bring the substrates close to one another to drive the reaction forward. On the basis of the recent experimental mechanistic study by Fokin's group,[14] we have proposed a plausible mechanism for this reaction (Fig. 1).

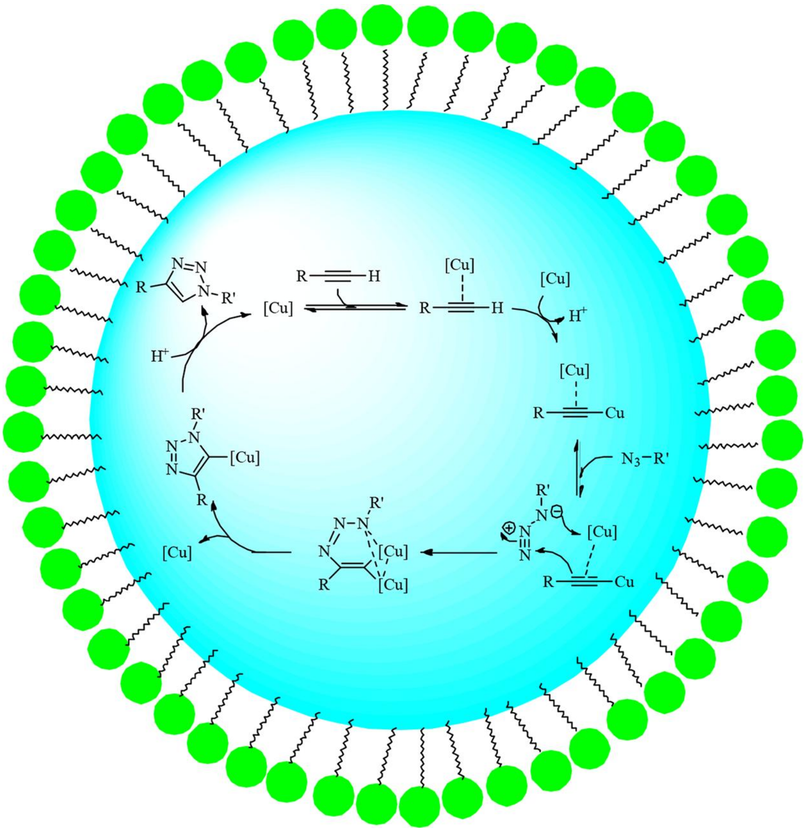


Figure 1. Plausible reaction mechanism.

Conclusion

In conclusion, we have developed a highly efficient and straightforward protocol of surfactant CTAB promoted CuI catalyzed regioselective synthesis of 1,4-disubstituted-1,2,3-triazoles in good to excellent yields from terminal alkyne and organic azides under environmentally benign conditions. Cheap and readily available materials and mild reaction conditions make this green strategy more attractive toward the application in different fields of chemistry.

Experimental

General information

Reagents and solvents were purchased from different commercial sources and used without further purification unless otherwise is noted. Purifications of products were performed by column chromatography using silica gel (200–300 mesh). Analytical thin-layer chromatography was performed using silica gel $60F_{254}$ plates and visualized with UV light. ^{1}H NMR (500 MHz), ^{13}C NMR (125 MHz) were recorded on a Bruker Avance 500 MHz spectrometer using TMS as an internal standard. Chemical shifts are reported in parts per million (ppm, d) downfield from residual solvents peaks and coupling constants are reported as Hertz (Hz). Splitting patterns are designated as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, etc. Melting points were determined on a Büchi B-540 melting point apparatus.

*Typical procedure for the synthesis of 1,4-disubstituted-1*H*-1,2,3-triazole*

To a mixture of CuI (1 mol%) and CTAB (1 mol%) was added acetylene (1.2 mmol) and azide (1 mmol) in water (2 mL) and stirred at room temperature for 1 h. After completion of the reaction it was extracted with ethyl acetate (2 × 20 mL), washed with brine, dried over anhydrous sodium sulfate and concentrated under vacuum, which on column chromatography (ethyl acetate:hexanes) afforded the desired product.

*1-Benzyl-4-phenyl-1*H*-1,2,3-triazole (3a)*

White solid, mp 128–130 °C, 92% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79 (d, $J = 5.5$ Hz, 2H), 7.66 (s, 1H), 7.41–7.29 (m, 5H), 5.57 (s, 2H), ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.9, 134.1, 130.5, 129.0, 128.7, 128.6, 128.0, 127.9, 125.6, 119.5, and 54.3.

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