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COMMUNICATION

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Benedict's solution/ vitamin C: An alternative catalytic protocol for the synthesis of regioselective-1,4-disubstituted-*1H*-1,2,3-triazoles at room temperature

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A novel and highly efficient method for the synthesis of 1,4-disubstituted-*1H*-1,2,3-triazoles by copper-catalyzed azide-alkyne cycloaddition has been developed. This economic and sustainable protocol uses a readily available Benedict's solution/Vitamin C catalyst system affording a wide range of 1,4-disubstituted-*1H*-1,2,3-triazoles under mild conditions.

KEYWORDS
1,4-disubstituted-*1H*-1,2,3-triazole, azide-alkyne cycloaddition, Benedict's solution, vitamin C

1 | INTRODUCTION

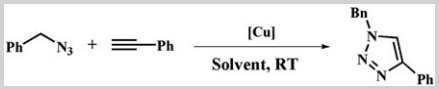
1,2,3-Triazoles are N-heterocyclic compounds that have been found in diverse applications ranging from materials to biological sciences.[1] Several synthetic methods have been developed for the preparation of 1,2,3-triazole derivatives. Among them, the copper-catalyzed azide-alkyne cycloaddition reaction (CuAAC), a premier example of 'click chemistry',[2] represents an easy and atom economical strategy to these heterocycles. The first CuAAC reaction discovered by Sharpless *et al*. preceded in presence of $CuSO_4$/ Na ascorbate mixture in water/^{t}-BuOH solvent affording triazoles in excellent yields.[2b,c] The click reaction is generally carried out in benign conditions[3] leading to drug innovation,[4] improvements for pharmaceutical and biological activities such as antifungal,[5,6] antimicrobial,[7] antitumor,[8] HIV inhibitor[9] bioconjugation,[10] triazole peptidomimetics[11] and organocatalysis.[12]

Recently, numerous greener approaches have been applied to the CuAAC reaction like synthesis in water,[13] the use of ultrasound,[14] microwave,[15] micro-flow technology,[16] etc. Several other techniques have also been developed including supported catalyst,[17–20] salts/additives or ligands,[21–33] nanotechnology,[34–39] photo catalysis[40] etc. for 1,2,3-triazole synthesis.

The Benedict's solution, an aqueous alkaline solution of copper(II) citrate, proved to be an important reagent in pharmaceutical and medicinal chemistry for the detection of presence of reducing sugars in urine,[41] determination of glucose in a solution.[42] In synthetic organic chemistry, Benedict's solution acts as a very good catalytic medium for reactions which are carried out in presence of copper source in aqueous solution.[13,43] Similarly, L-

Ascorbic acid or more commonly known as vitamin C is one of the most effective alternative reducing agents, which is environmentally friendly in nature.[44] The basic structure of L-ascorbic acid is the five-membered lactone sugar and due to this, it has some physiological activities towards organic synthesis.[45] More importantly, L-ascorbic acid is water soluble and hence it can be used in aqueous reaction generating metal ascorbate complexes through in-situ mechanism.[46] Herein we describe a cheap and readily available Benedict's solution (diluted up to 2 mol%)/ascorbic acid system as a homogeneous catalyst for the CuAAC reaction. The current strategy

TABLE 1 Optimization of the catalytic and solvent system[a]



Entry	[Cu]	Solvent	Time (h)	Yield[b](%)
1	Benedict solution +Na ascorbate	-	4	90
2	-	H_2O	12	-
3	Copper Citrate	H_2O	6	70
4	Benedict solution + Glucose	-	4	85
5	Copper Citrate	Ethylene glycol	8	70
6	Copper Citrate + Glucose	Ethylene glycol	3	70
7	Copper Citrate + Ascorbic acid	Ethylene glycol	3	85
8	Benedict solution[c]	-	5	50
9	Benedict solution[c] + Glucose	-	2	70
10	**Benedict solution[c] + Ascorbic acid**	**-**	**2**	**90**
11	Benedict solution[c]+ Na ascorbate	H_2O: ^{t}BuOH	3	88
12	$CuSO_4$+ Na ascorbate	H_2O: ^{t}BuOH	2	85

[a]Reaction condition: Benzyl azide (1 mmol), phenyl acetylene (1.2 mmol), catalyst (2 mol%), reducing agent (1 mmol), solvent (5 ml) at room temperature.

[b]Isolated yield.

[c]3 ml of Benedict solution (2 mol%) is added.

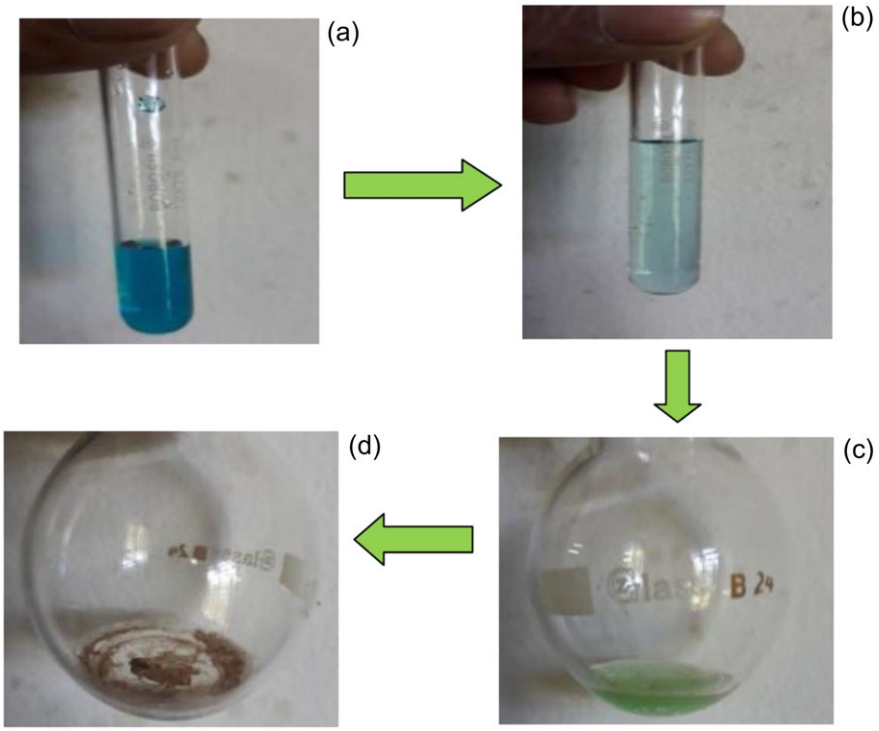


FIGURE 1 **a)** Benedict Reagent; **b)** Benedict solution (2 mol% copper loading); **c)** Optimized reaction in 2 mol% Bendict solution/ Ascorbic acid system through in-situ generated copper(II) complex; **d)** completion of reaction mixture and formation of copper(I) as colour changes from light blue to red

offers a wide range of corresponding 1,4-disubstituted-*1H*-1,2,3-triazoles in good to excellent yields at room temperature with very low loading of copper.

2 | EXPERIMENTAL

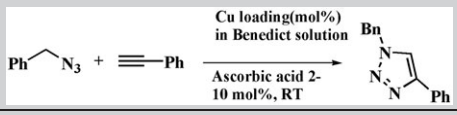
2.1 | General procedure for the synthesis of 1,4-disubstituted-*1H*-1,2,3-triazole

To a mixture of azide (1 mmol), acetylene (1.2 mmol) and Ascorbic acid (1 mmol) in 3 ml of Benedict's solution (2 mol%) was added. The mixture was stirred at room temperature for the given time period as mentioned in Table 3. The progress of the reaction was monitored by TLC. After completion of the reaction it was extracted with ethyl acetate (3 x 20 ml), washed with deionized water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The resulting residue was purified through silica gel column chromatography (15–20% EtOAc/hexane) to get the desired product and confirmed through ^{1}H & $^{13}CNMR$ analysis (details in Supporting Information).

3 | RESULTS AND DISCUSSION

To search out the optimized condition, we took the model reaction of benzyl azide and phenyl acetylene in various conditions as shown in Table 1 (Entries 1–10). From the study of the optimization conditions, it was seen that copper(II) source devoid of reducing agent slowed down the reaction kinetics whereas in presence of reducing agent it gave an enhanced product yield. Among the various reducing agents used (as mentioned in Table 1), ascorbic acid gave better results to Benedict's solution than the others and this is believed to be due to the enhanced activity of the enediol moiety present in ascorbic acid (Table 1, entry 10). Moreover, use of copper

TABLE 2 Optimization of the copper loading[a]

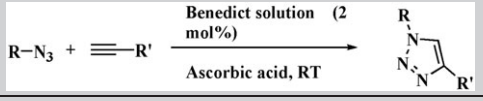


Entry	Copper loading (mol%)	Time (h)	Yield[b](%)
1	10	2	92
2	6	2	91
3	4	2	90
4	2	2	90
5	1	2	75

[a]Reaction condition: Benzyl azide (1 mmol), phenyl acetylene (1.2 mmol), reducing agent (1 mmol) with 3 ml of Benedict solution(1–10 mol%) at room temperature.

[b]Isolated yield.

TABLE 3 Substrate scope study[a]

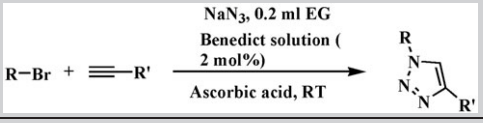


Entry	R	R/	Time (h)	Yield[b](%)
1	Bn	Ph	2	90
2	Ph	Ph	2	95
3	4-NO_2-Bn	Ph	2	60
4	$PhCH_2CH_2$	Ph	4	85
5	3-Cl-Ph	Ph	3	90
6	4-F-Ph	Ph	2	85
7	4-OCH_3-Ph	Ph	2	95
8	Bn	4-OCH_3-C_6H_4	2	93
9	2-CH_3-Ph	Ph	3	72
10	4-OCH_3-Ph	3-CH_3-C_6H_4	3	90
11	3-Cl-Ph	4-CH_3-C_6H_4	3	60
12	3-Cl-Ph	4-OCH_3-C_6H_4	4	88
13	Bn	-CH_2OOC-Ph	3	82
14	4-NO_2-Ph	-CH_2OOC-Ph	4	90
15	Bn	3-CH_3-C_6H_4	4	75
16	$PhCH_2CH_2$	4-OCH_3-C_6H_4	5	60
17	3-Cl-Ph	-CH_2OOC-Ph	2	92
18	$CH_3(CH_2)_7$-	-CH_2OOC-Ph	3.5	80
19	Ph	-$(CH_2)_3CH_3$	6	70
20	4-Br-Ph	-$(CH_2)_3CH_3$	6	78

[a]Reaction condition: azide (1 mmol), acetylene (1.2 mmol), Ascorbic acid (1 mmol), 3 ml Benedict solution (2 mol%) at room temperature.

[b]Isolated yield.

TABLE 4 One pot protocol for triazole synthesis[a]



Entry	R	R/	Time (h)	Yield[b](%)
1	Ph-CH_2	Ph	4	95
2	Ph-CH_2	-CH_2OOC-Ph	4	85
3	Ph-CH_2	3-CH_3-Ph	4	90
4	4-Br-Bn	Ph	4	88
5	4-NO_2-Bn	Ph	4	92

[a]Reaction Conditions: bromide (1 mmol), NaN_3 (1.2 mmol), alkynes (1.2 mmol), Ascorbic acid (1 mmol), 3 ml Benedict solution (2 mol%), 0.2 ml of Ethylene Glycol at room temperature.

[b]Isolated yield.

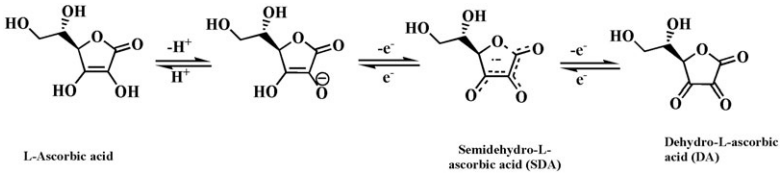


FIGURE 2 Redox reaction mechanism of L-ascorbic acid

citrate instead of Benedict solution also catalyzed the reaction to some extent but the reaction requires the presence of a solvent (Table 1, entries 5–7).

Benedict reagent is a commercially available alkaline solution containing copper sulphate, sodium carbonate and sodium citrate with very high amount of copper source (1 litre of Benedict solution contains 69 mmol of copper). We have minimized the copper loading in the Benedict solution by subsequent dilution method. For these, we made solutions of Benedict reagent that contains 1, 2, 4, 6 and 10 mol% of copper source and applied it in the model reaction of benzyl azide and phenyl acetylene (Figure 1 and Table 2). From the optimized condition of the catalyst loading, it is seen that the reactions containing 10, 6, 4, 2 mol% of Benedict solution gave almost identical yield of 92, 91, 90 and 90% respectively (Table 2, entries 1–4). Further reduction of copper loading to 1 mol%, the product yield reduced to 75% (Table 2, entry 5).

Various derivatives of both azide and acetylene were employed to investigate the scope of the formation of 1,4-disubstituted-*1H*-1,2,3-triazoles under optimized conditions (Table 3). Electron withdrawing as well as electron donating substituents were introduced on both substrates (azides and alkynes) to study the effects of the functional group on the click transformation (Table 3, entries 1–20). Irrespective of the electronic behaviour of the azide and alkyne, good to excellent results of the triazoles were obtained under this catalytic condition. The reaction rate decreased in the presence of ortho substituent in the aromatic azide owing to the steric effect of the functional group (Table 3, entry 9).

To avoid the handling and isolation of organic azides, a one-pot protocol for the synthesis of 1,2,3-triazoles is desirable. In this context, several methodologies have been developed for the simultaneous *in situ* generation of azides and [3 + 2] cycloaddition reaction with

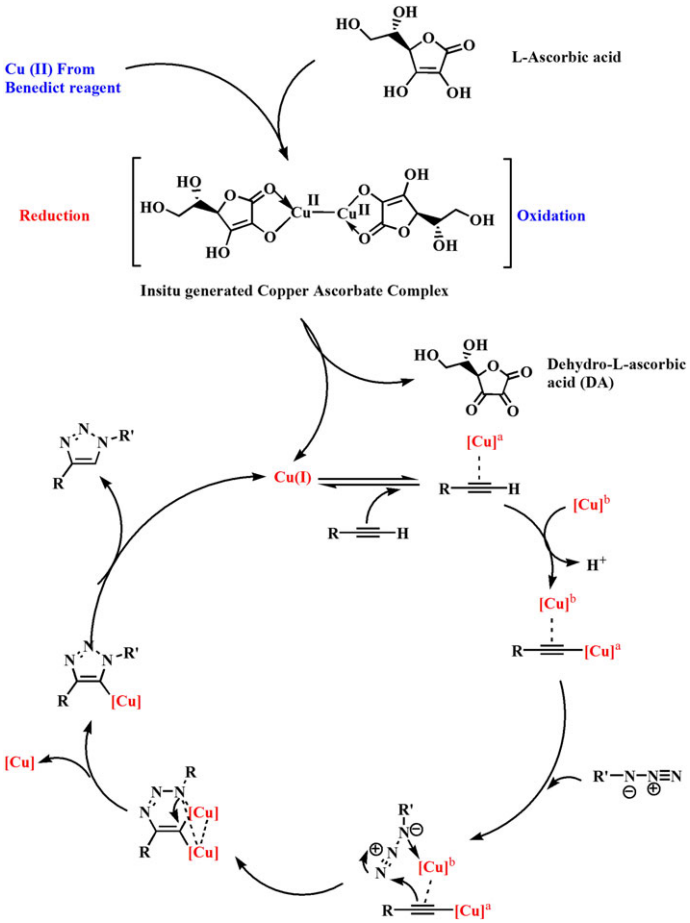


FIGURE 3 Plausible catalytic cycle

alkynes.[47] For the one-pot protocol, the reaction was carried out by the multicomponent reaction of benzyl bromide, sodium azide and phenyl acetylene under the above-mentioned reaction conditions using a little amount of ethylene glycol as a co-solvent, affording 95% of the desired triazoles in 4 h. Therefore, attempts were made to synthesize 1,2,3-triazoles from the benzyl bromide derivatives by this one pot protocol (Table 4, entries 1–5) affording desired products in good to excellent yields in relatively shorter time.

The Benedict's solution / Vitamin-C catalyzed AAC reaction is believed to proceed through an in-situ generated copper ascorbate complex (Figure 3). Vitamin C has very peculiar structure containing 2,3-enediol moiety, steric lactone ring, four hydroxyl groups with different reactivity and has hydrophilic character. The most significant 2,3-enediols moiety of vitamin C has the ability to reduce the oxidation state of a metal ion (Figure 2). In this regard, vitamin C is used along with the Benedict solution to reduce Cu^{2+} ion to Cu^{+} ion as insoluble copper(I) oxide which catalyzes the AAC reaction.

4 | CONCLUSIONS

In conclusion, an aqueous solution based copper salt as a catalytic medium has been reported for the synthesis of triazoles in presence of naturally available vitamin C as a reducing agent. Experimental ease, cheap, ready availability of reagents and simplicity of product isolation make this method very efficient for the synthesis of a variety of 1,4-disubstituted-1*H*-1,2,3-triazoles through both azide-alkyne cycloaddition and one pot protocol.

Supporting Information Summary.

The Supporting Information contains general information about the chemicals and instruments used, general experimental procedures for triazole synthesis and ^{1}H & ^{13}C NMR spectra of the compounds (see supporting information).

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