



Facile route for the regioselective synthesis of 1,4-disubstituted 1,2,3-triazole using copper nanoparticles supported on nanocellulose as recyclable heterogeneous catalyst

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Abstract. In this work, a green and efficient methodology has been developed for the synthesis of 1,2,3-triazoles by 'copper nanoparticles supported on nanocellulose (CuNPs/NC)-catalyzed azide-alkyne cycloaddition reaction in glycerol, an environmentally benign solvent, with excellent yields. The present catalyst was characterized by TEM, XRD, SEM-EDX and FT-IR spectroscopy. The reusability of the prepared nanocatalyst was examined up to five times without significant loss of catalytic activity.

Keywords. Heterogeneous catalysis; cycloaddition; regioselectivity; click reaction; copper nanoparticles.

1. Introduction

1,2,3-Triazoles are an important and most useful class of five-membered heterocycles which have plethora of applications starting from industrial fields to pharmaceutical compounds.¹⁻⁴ Many 1,2,3-triazole containing compounds have been found possessing important biological activities such as anti-viral, anti-epileptic, anti-allergic, anti-microbial as well as anti-cancer and anti-HIV activities.⁵⁻⁸ The 1,2,3-triazoles are generally formed by the 1,3-dipolar cycloaddition of azides and alkynes which were first introduced by Michael in 1893. Later, it was thoroughly developed by the German Chemist R. Huisgen⁹ and it is the most convenient and straightforward approach for the synthesis of 1,2,3-triazoles. But this classical method produces both the 1,4- and 1,5-regioisomers and the reaction requires elevated temperature. Overcoming these problems, in 2002, Sharpless *et al.*,¹⁰ and Meldal *et al.*,¹¹ independently published their pioneering work on Cu-catalyzed azide-alkyne cycloaddition (CuAAC) reactions, leading to a mild and efficient regioselective synthesis of 1,4-disubstituted 1,2,3-triazoles. Considering the important

applications of 1,2,3-triazoles, many works have been done on azide-alkyne cycloaddition for the synthesis of 1,4-disubstituted 1,2,3-triazoles. Most of the CuAAC reactions use homogeneous Cu (I) source – either by direct addition of a Cu(I) salt in presence of stabilizing ligands, or by *in situ* reduction of Cu(II) by sodium ascorbate or other reducing agents.¹² However, the complexity of separating the catalyst as well as the requirement for reducing agents and stabilizing ligands cause tricky problems. Therefore, the search for new competent methods offering high yield, mild conditions, recyclability and waste avoidance are highly desirable from an environmental point of view. In this context, heterogeneous catalysis has attracted much attention in developing environmentally benign chemical processes. Moreover, it brings significant advantages, particularly in the removal of the catalyst from the reaction media, which can be done by simple filtration.¹³ In an effort to find heterogeneous copper catalysts, Cu(0) on charcoal,¹⁴ Cu(0) nanoparticles,¹⁵ or nanoporous Cu(0),¹⁶ CuO–CeO₂ nanocomposite,¹⁷ porous Cu¹⁸ as well as microwave irradiated Cu turnings¹⁹ have also successfully established activity for CuAAC reaction.

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Cellulose is Earth's most abundant and ubiquitous natural biopolymer and serves as a bio-compatible support for the catalysts. Thus, it is an excellent starting material for developing new, more sustainable materials from renewable resources.^{20,21} Cellulose nanocrystallites are particularly more important and appealing derivative of cellulose as they possess unique properties of high crystalline order, well defined size and morphology, a controlled surface chemistry, and superior mechanical strength.²² In recent years, nano-catalysis has come out as a sustainable alternative to conventional catalysis due to unique properties of the metal nanoparticles like a high surface-to-volume ratio, which enhances their activity and selectivity, while at the same time maintaining the intrinsic features of a heterogeneous catalyst.²³ Cellulose-supported cuprous iodide nanoparticles (Cell-CuI NPs) have been used for one pot synthesis of 1,4-disubstituted 1,2,3-triazoles.²⁴ The long and tedious procedures were normally required for the heterogenization of copper and hence, there is still demand to develop easy-to-prepare and versatile heterogeneous copper catalysts that easily facilitate the synthesis of triazoles. Owing to our dedication to study 'click reaction',^{25–31} herein we report a facile synthesis of 1,2,3-triazoles by copper nanoparticles supported on nanocellulose (CuNPs/NC) as a highly efficient and recyclable heterogeneous catalyst in glycerol at room temperature.

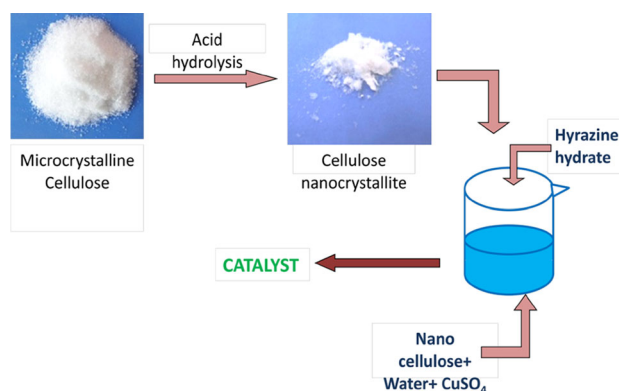
2. Experimental

2.1 Materials and methods

Reagents and solvents were purchased from Spectrochem, Merck and Sigma Aldrich and used without further purification. All reactions were carried out in oven-dried glassware. All reactions were monitored by thin layer chromatography on aluminium sheets pre-coated with silica gel 60F₂₅₄ (Merck) and was visualized under 254 nm UV light. Melting points (M.p.) were obtained on a BÜCHI Melting Point B-540. ¹H NMR (400 MHz), ¹³C NMR (100 MHz) spectra were measured on a Bruker Avance 400 MHz spectrometer. Chemical shifts are reported in parts per million (ppm, δ) downfield from residual solvent peaks and coupling constants are reported as Hertz (Hz). Splitting patterns are designated as singlet (s), doublet (d), triplet (t). Splitting patterns that could not be interpreted is designated as multiplet (m).

2.2 Catalyst preparation

The first step in the accomplishment of the goal for the synthesis of CuNPs/NC was the synthesis of nanocellulose



Scheme 1. Preparation of the catalyst.

which is prepared by acid hydrolysis procedure reported elsewhere. Briefly, the microcrystalline cellulose was acid hydrolysed with sulphuric acid concentration of 63 wt% at 45°C for 105 min to remove the amorphous regions and were neutralized using a series of centrifugation cycles, and thereafter sonicated to individualise the nanocrystals (Scheme 1).^{32,33}

To prepare Cu nanoparticles over nanocellulose, nanocellulose suspension was dispersed with $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (0.5 g) in water (500 mL) at room temperature for 30 min. Then, hydrazine hydrate (50%, 10 mL) was added drop wise for 30 min and the reaction mixture was stirred at room temperature for 2 h. The obtained solid was centrifuged and washed with distilled water and acetone, to remove un-reacted reagents. The product was dried at 100°C for 10 h and stored in desiccators. The resultant product was characterized by FT-IR, XRD, SEM-EDX, and TEM analysis.

2.3 Catalyst characterisation

The copper nanoparticles supported on nanocellulose (CuNPs/NC) catalyst was fully characterised in order to determine their nature and morphology. The weight percentage of copper was found to be 3.31 wt% by inductively coupled plasma-atomic emission spectroscopy (ICP-AES) analysis. Transmission electron microscopy (TEM) revealed the presence of well-dispersed nanoparticles with an average size of 6–7 nm (Figure 1). The EDX pattern determined the elemental compositions of different elements in the Cell-Cu sample (Figure 2). The characteristic peaks of C, O and Cu confirmed that the Cell-Cu sample is composed of C, O and Cu elements. The infrared spectrum of catalyst in the range of 500–4000 cm^{-1} is presented in Figure 3(a). The significant feature in the FT-IR spectrum is the appearance of peak at 806.61 cm^{-1} for Cu–O stretching vibration. Bands of 1050–1650 cm^{-1} due to C–OH groups and that of 2700–3500 cm^{-1} due to O–H and C–H groups were observed concerning to nanocellulose. The XRD pattern shows characteristic peaks of copper(I) nanoparticles, presenting all the phases of Cu_2O (JCPDS card no -78-2076) as shown in Figure 3(b).

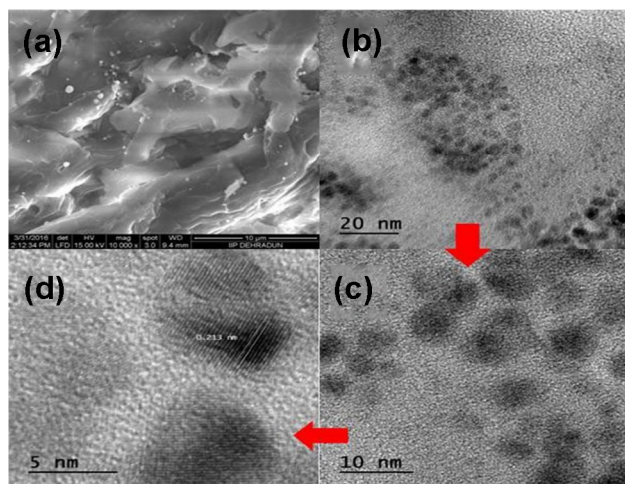


Figure 1. (a) SEM image of the CuNPs/NC, the surface morphology of nanocellulose support is observed to be very smooth. (b), (c) and (d) show the HRTEM images of the prepared catalyst. The HRTEM images evidence the presence of well dispersed nanoparticles in the support. The average particle size is found to be 6–7 nm.

2.4 General procedure for the synthesis of 1,4-disubstituted-1H-1,2,3-triazole

To a mixture of azide 1 (1 mmol, 1 equiv.) and acetylene 2 (1.1 mmol, 1.1 equiv.) in glycerol (2 mL) was added the catalyst (20 mg, 3.31 wt%, 1.05 mol%). The mixture was stirred at room temperature for an appropriate time. The progress of the reaction was monitored by TLC. After completion of the reaction it was extracted with EtOAc (2x20 mL), washed with brine, dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to give the crude product and purified through silica gel column chromatography (10–20% EtOAc/hexanes) to get the desired product. The products were characterized by ^1H and ^{13}C NMR spectroscopy.

3. Results and Discussion

The experiments began with the aim of optimizing the reaction conditions for CuAAC reaction of benzyl

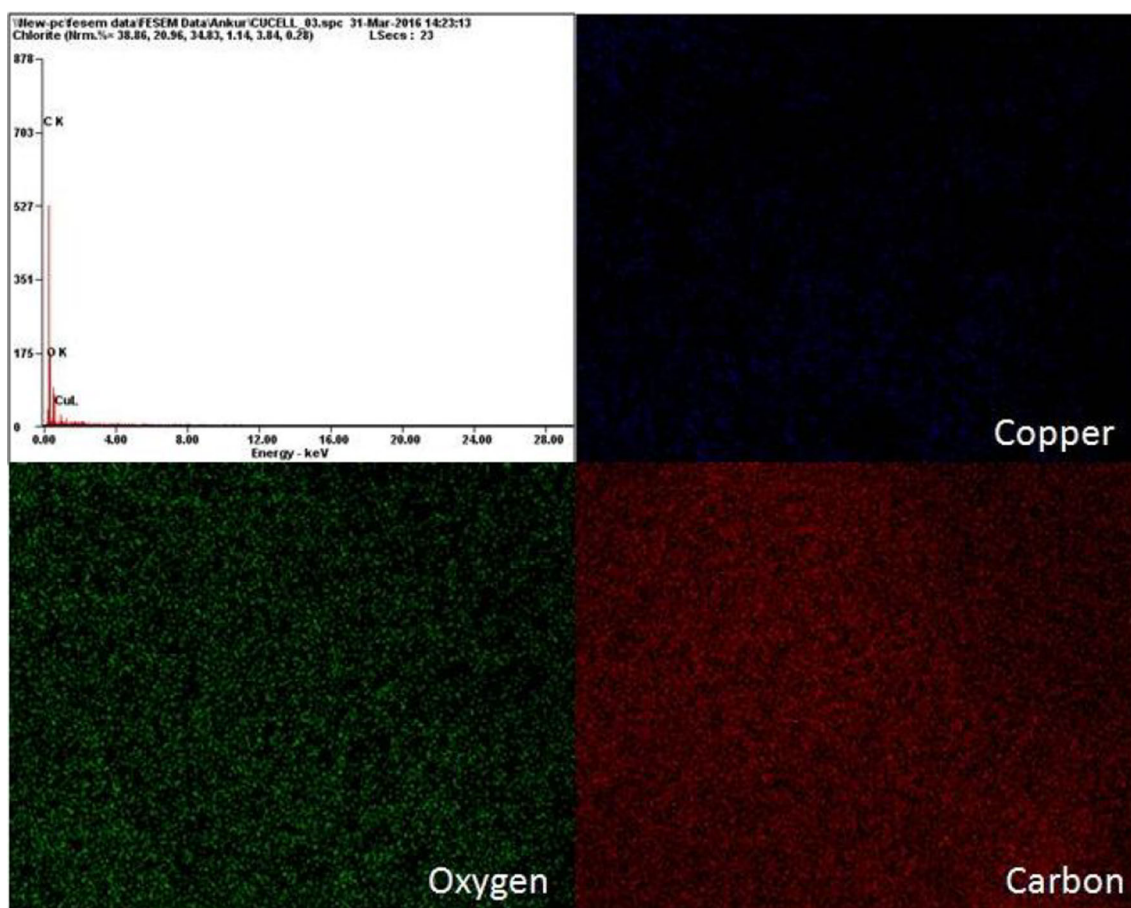


Figure 2. EDX pattern of the catalyst.

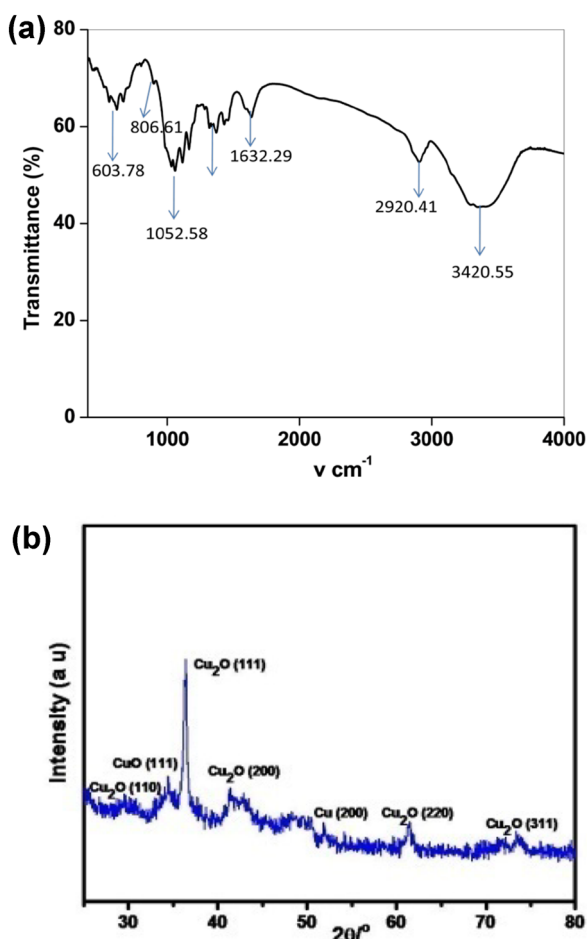


Figure 3. (a) FTIR spectrum and (b) XRD pattern of the catalyst.

azide and phenylacetylene. At the first step, the reaction between benzyl azide and phenyl acetylene was allowed to run without solvent, adding 20 mg of the catalyst. But no noticeable progress of the reaction was observed. Then the model reaction was performed with different solvents and among them glycerol was found superior than others (Table 1).

Having identified glycerol as the best solvent for the reaction, we then investigated catalyst loading for the reaction. However, upon lowering the catalyst concentration to 5 mg the reaction still proceeded but afforded only 55% yield (Table 1, entry 11). Therefore a catalyst loading of 20 mg appeared to be optimal with respect to yield and reaction time (Table 1, entry 7).

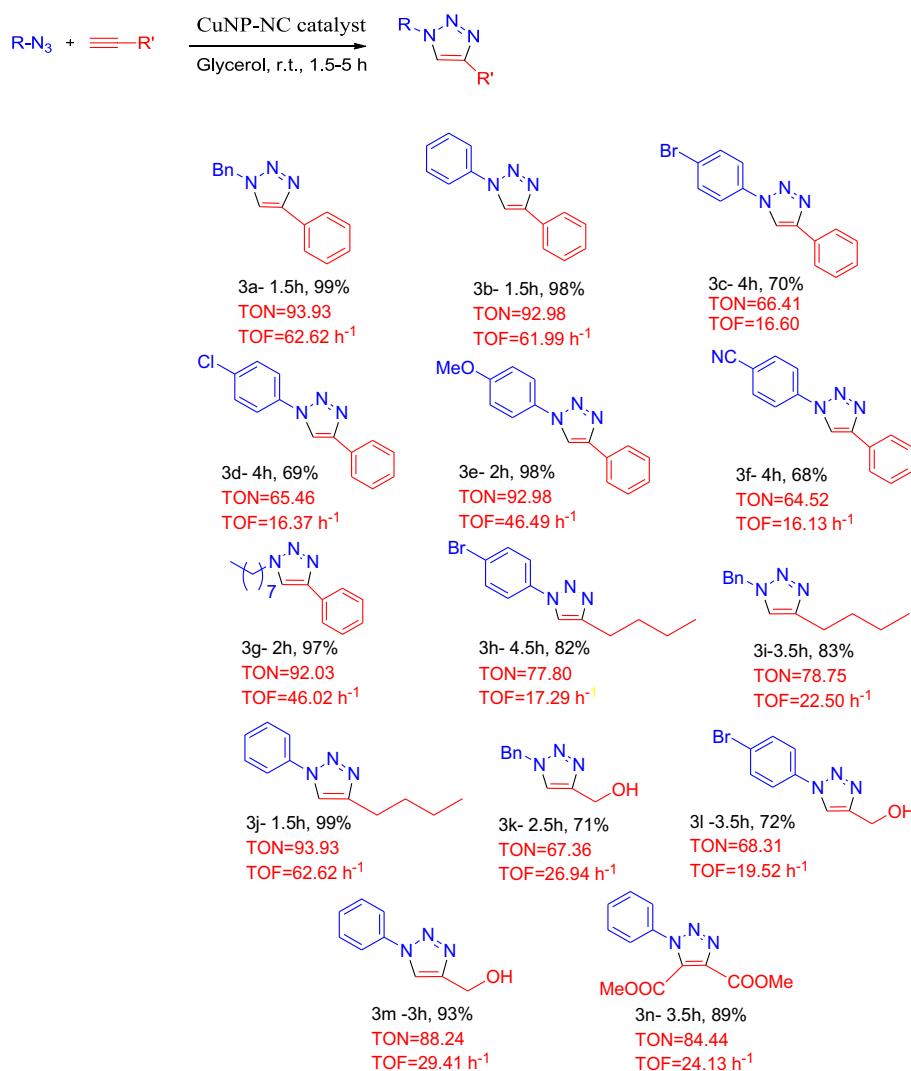
Taking the optimized reaction conditions in hand, the scope of the cycloaddition reaction using CuNPs/NC was investigated with various alkynes and azides at room temperature. The results are summarized in Table 2. Both aromatic and aliphatic terminal alkynes readily reacted with the diverse azides to give the corresponding 1,2,3-triazoles in good to excellent yields in most of the tested reactions.

We then examined the possibility of recycling the catalyst. The recyclability of CuNPs/NC was tested in the cycloaddition of phenylacetylene and benzyl azide (Figure 4). After each cycle the catalyst was recovered by simple filtration and reused after washing with ethyl acetate and drying in the air. The activity of the catalyst was found to decrease to a minor extent in the reuse; about 90% of the original activity was obtained even after the fifth run. Moreover, there was no sig-

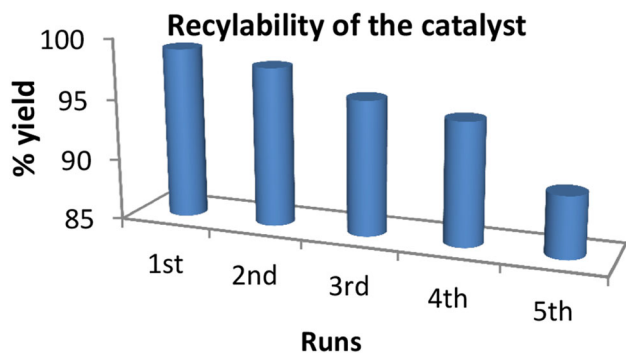
Table 1. Solvent optimization study^a.

Entry	Solvent	Catalyst loading (mg)	Yield (%) ^b
1	—	20	Trace
2	H ₂ O/t-BuOH (1:1)	20	60
3	H ₂ O	20	89
4	THF	20	48
5	THF/H ₂ O	20	60
6	Acetonitrile	20	65
7	Glycerol	20	99
8	DMF	20	10
9	DMSO	20	45
10	Glycerol	10	65
11	Glycerol	5	55

^aReagents and reaction conditions: benzyl azide (1 mmol), phenyl acetylene (1.1 mmol), catalyst (20 mg, 1.05 mol%) in the given solvent (2 mL) was stirred at room temperature for 4 h in open air. ^bIsolated yields.

Table 2. Scope of cycloaddition reaction of different azides and alkynes^a.

^aReagents and reaction conditions: azide (1 mmol), alkyne (1.1 mmol) and catalyst (20 mg, 3.31 wt%, 0.0105 mmol, 1.05 mol%) in 2 mL glycerol at room temperature. Yields were isolated yields.

**Figure 4.** Recyclability of the catalyst.

nificant leaching of copper species from our catalyst during the recycling test which was confirmed by ICP analysis.

4. Conclusions

In conclusion, we have reported here a highly efficient and versatile method for the cycloaddition of various azides and alkynes using an easily prepared heterogeneous catalyst. Use of benign solvent, high yield, short reaction time, and room temperature reaction system make this protocol more advantageous in the synthesis of 1,4-disubstituted 1,2,3-triazoles. This work can be considered as a very good step towards the emerging trend of heterogeneous and environmental friendly synthesis of organic compounds.

Supplementary Information (SI)

General Information, Experimental and Analytical data, ¹H and ¹³C NMR spectra and characterisation data of all the

synthesised compounds are available as Supplementary Information at www.ias.ac.in/chemsci.

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