Simple preparation of cuprous oxide nanoparticles for catalysis of azide–alkyne cycloaddition

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Cuprous oxide (Cu_2O) nanoparticles were prepared by two simple methods and their structural, morphological and electronic properties were investigated by X-ray diffraction analysis, X-ray absorption near-edge structure, energy dispersive X-ray analysis and scanning electron microscopy. Cuprous oxide nanoparticles efficiently catalyse 1,3-dipolar cycloaddition of a variety terminal alkynes and organic azides producing the corresponding 1,2,3-triazole derivatives in excellent yields without use of any additives. Phenylacetylene and benzyl chloride were chosen as model starting compounds for the optimisation of the reaction conditions, such as effect of solvent, reaction temperature and time of reaction in the presence of a-Cu_2O nanoparticles as a catalyst. The results showed that using cuprous oxide nanoparticles (0.035 mmol) and heating at 70 °C in water, the reaction of phenylacetylene with benzyl chloride and sodium azide gave 1-benzyl-4-phenyl-1*H*-1,2,3-triazole almost quantitatively in 6 h of reaction time. A study of the recyclability and reusability of the catalyst revealed that a-Cu_2O could be reused at least five times without significant loss of yield.

Keywords: nanoparticles, cuprous oxide, azide–alkyne cycloaddition

1,3-Cycloaddition reactions of azides with olefins provide direct access to a wide range of 1,2,3-triazoles as useful heterocyclic systems and a rich source of various biologically and pharmacologically active molecules.[1–5] The copper-catalysed azide–alkyne cycloaddition is one of the most attractive and fundamental reactions in synthetic organic chemistry.[6–10]

Cuprous oxide (Cu_2O), a *p*-type semiconductor, is considered to be one of the most attractive and promising inorganic materials and an excellent candidate for catalytic activity, sensing, fuel cells and solar cells.[11–14] Owing to its good stability, non-toxicity and low cost, catalytic applications of Cu_2O have been reported and applied in various fields.[15–20]

Therefore, in this study, cuprous oxide nanoparticles were prepared by two simple methods and their structural, morphological and electronic properties were investigated by X-ray diffraction analysis (XRD), X-ray absorption near-edge structure (XANES), energy dispersive X-ray analysis (EDX) and scanning electron microscopy (SEM). The catalytic activity of Cu_2O nanoparticles in the 1,3-dipolar cycloaddition of organic azides and alkynes were investigated under air.

Results and discussion

Catalyst characterisation

The indexed XRD peaks of the cuprous oxide nanoparticles are shown in Fig. 1a to demonstrate the structures and phase purities of Cu_2O. The XRD peaks of the samples were found to match with cubic bulk Cu_2O (JC-PDS file no. 78–2076).[21] The absence of any peaks corresponding to $Cu(OH)_2$, Cu_2O or Cu confirmed the purity of the Cu_2O phase in the two samples. The sharp diffraction peaks clearly indicate high crystallinity of sample **2**. To probe the 3*d* character of Cu in the Cu_2O samples, the Cu L-edge XANES spectra were collected from cuprous oxide nanoparticles. According to Fig. 1b, the two distinct peaks at ~936.4 eV and ~956.5 eV, which are assigned to the transitions of $Cu2p_{3/2}$ (L_3) and $2p_{1/2}$ (L_2) electrons into the empty *d*-states, respectively, signify the formation of the Cu_2O phase in these two samples.[22] The energy separation between the L_3 and L_2 edges, which is dependent on the copper oxidation state, are consistent with reported values and thus signify the formation of the Cu_2O phase in the nanoparticles.[22] Also the EDX spectrum confirms the presence of copper and oxygen in the cuprous oxide nanoparticles (Fig. 1c).

The morphological properties and structural information about the cuprous oxide nanoparticles were investigated by SEM, and the results are shown in Fig. 2. SEM images showed a uniform size distribution of the cuprous oxide nanoparticles.

Catalytic effects

Phenylactelylene and benzyl chloride were chosen as model starting compounds for the optimisation of the reaction conditions in the presence of nanoparticles **1** as a catalyst. Interestingly, from the different solvents tested, water was found to be the most effective for this reaction (Table 1, entries 1–6). A significant improvement in the product yield was observed at higher temperatures than room temperature (Table 1, entries 7–9). The optimisation of the reaction time showed that when using cuprous oxide nanoparticles (0.035 mmol) and

Table 1 Effect of various reaction conditions on the azide–alkyne cycloaddition

Entry	Catalyst	Solvent	Temperature (°C)	Time (h)	Yield (%)[a]
1	1	H_2O	70	6	94
2	1	CH_3OH	70	6	69
3	1	2-PrOH	70	6	19
4	1	CH_3CN	70	6	35
5	1	Toluene	70	6	25
6	1	DMSO	70	6	23
7	1	H_2O	r.t.	6	18
8	1	H_2O	40	6	49
9	1	H_2O	60	6	77
10	1	H_2O	70	2	65
11	1	H_2O	70	4	88
12	2	H_2O	70	6	87
13	–	H_2O	70	6	0

[a] Isolated yield

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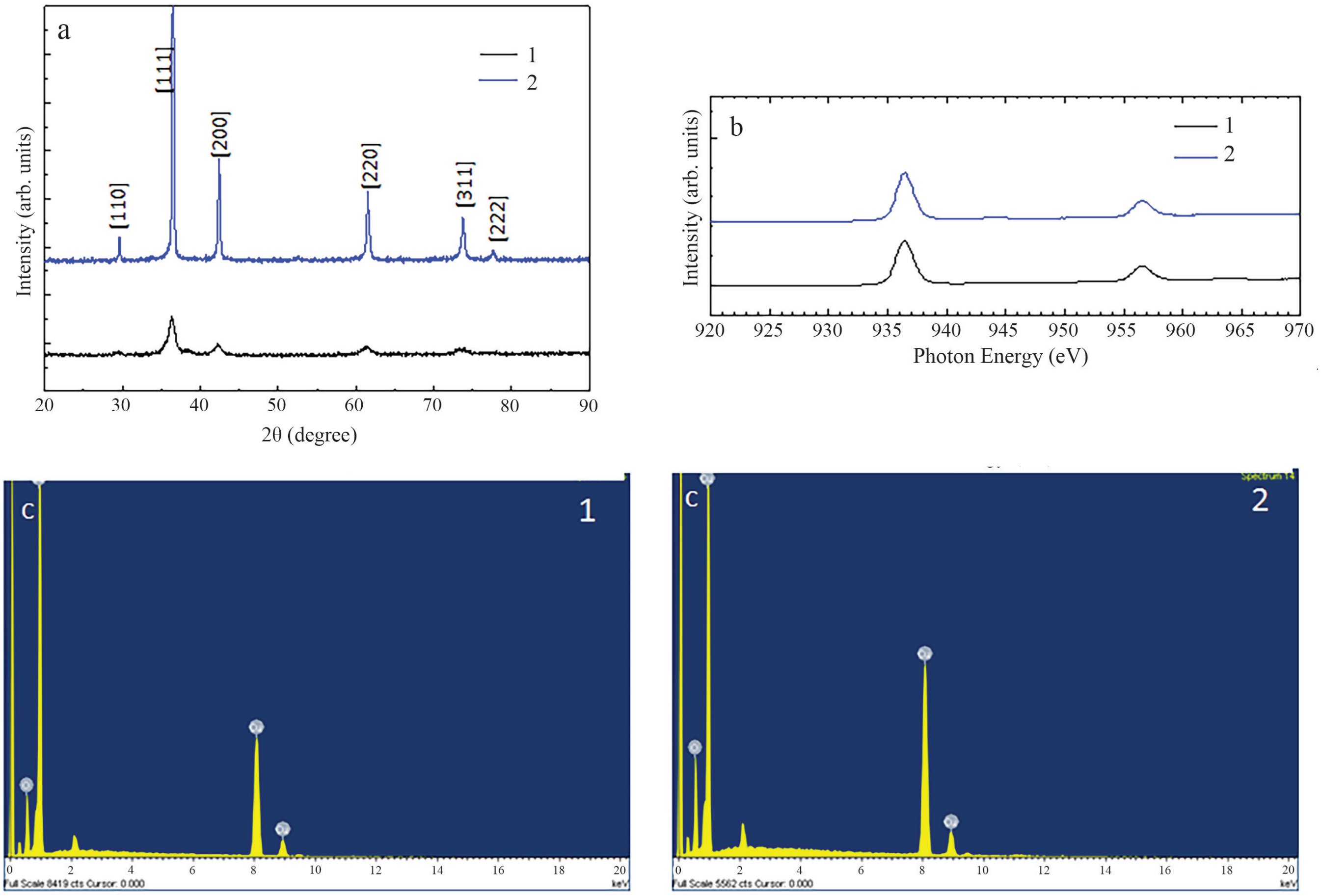


Fig. 1 (a) XRD spectra, (b) copper L-edge XANES spectra and (c) EDX analysis of the cuprous oxide nanoparticles.

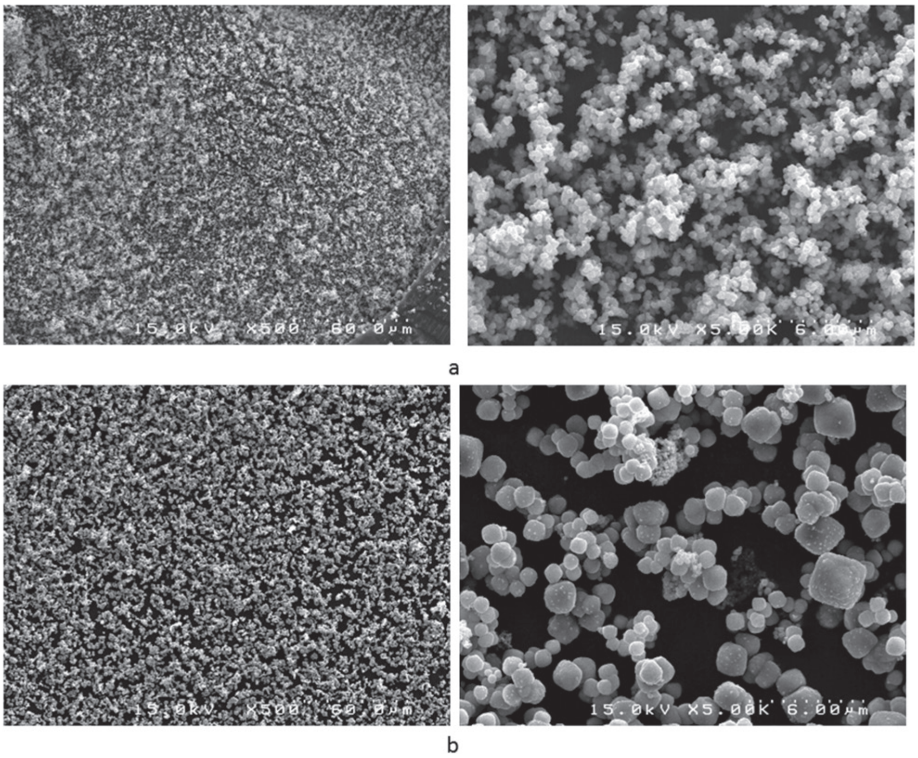
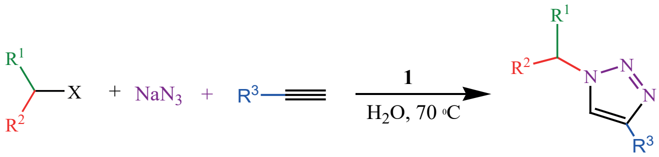


Fig. 2 SEM images of the cuprous oxide nanoparticles: (a) **1** and (b) **2**.

heating at 70 °C in water, the reaction of phenylacetylene with benzyl chloride and sodium azide gave 1-benzyl-4-phenyl-1*H*-1,2,3-triazole almost quantitatively in 6 h of reaction time, but for catalyst **2**, 87% product was obtained (Table 1, entries 1 and 10–12). The Cu-catalysed 1,3-dipolar cycloaddition reaction did not work in the absence of catalyst (Table 1, entry 13).

From these results, nanoparticles **1** were demonstrated to be a very efficient catalyst in the multicomponent 1,3-dipolar cycloaddition of terminal alkynes and organic azides generated *in situ* from sodium azide and different organic halides. The same methodology was successfully applied for the reaction of various alkynes and alkyl halides (Table 2). Cycloaddition of phenyl acetylenes with benzyl halides bearing both electron-withdrawing and electron-releasing groups attached to the aromatic ring, and also steric hindrance of the *ortho* substituents on the benzyl chloride, do not greatly affect the yield of cycloaddition products (Table 2, entries 1–17). Owing to the weak C–Br bond compared with C–Cl, replacement of benzyl chloride with benzyl bromide facilitated the reaction under the same conditions (Table 2, entries 9–12). In the presence of aliphatic alkynes (Table 2, entries 7, 8, 16 and 17) and aliphatic halides (Table 2, entries 13–15), a decrease in the yield of cycloaddition products was observed.

Table 2 Cycloaddition of benzyl halides with terminal alkynes in the presence of cuprous oxide nanoparticles



Entry	R¹	R²	X	R³	Yield (%)[a]
1	Ph	H	Cl	Ph	94
2	4-Me-Ph	H	Cl	Ph	96
3	2-Me-Ph	H	Cl	Ph	85
4	4-NO$_2$-Ph	H	Cl	Ph	94
5	Ph	H	Cl	4-MeO-Ph	94
6	Ph	H	Cl	4-Me-Ph	93
7	Ph	H	Cl	(HO)CH$_2$	78
8	Ph	H	Cl	(HO)(H$_3$C)$_2$CH$_2$	65
9	Ph	H	Br	Ph	97
10	Ph	H	Br	4-MeO-Ph	97
11	Ph	H	Br	4-Me-Ph	97
12	Ph	Ph	Br	Ph	92
13	CH$_3$(CH$_2$)$_3$	H	Br	Ph	71
14	CH$_3$(CH$_2$)$_3$	H	Br	4-MeO-Ph	74
15	CH$_3$(CH$_2$)$_3$	H	Br	4-Me-Ph	75
16	Ph	H	Br	(HO)CH$_2$	85
17	Ph	H	Br	(HO)(H$_3$C)$_2$CH$_2$	79

[a]Isolated yield.

The recyclability of a catalyst is an important and critical topic in the field of heterogeneous catalysis. In a final set of experiments, the recyclability of **1** as a catalyst was surveyed (Fig. 3). After completing one run of the reaction, the reaction mixture was centrifuged and washed with water and ethanol and, after drying, another cycle of the reaction was carried out using the same particles. The results revealed that **1** could be reused at least five times without significant loss of yield.

Based on the nature of the product and analogous mechanisms in previous reports,[23,24] a reaction mechanism for the Cu$_2$O-catalysed 1,3-dipolar cycloaddition reactions was proposed, as shown in Scheme 1. After formation of a Cu–acetylide complex *via* addition of Cu$_2$O to the phenylacetylene, subsequently, the azide coordinates to the copper acetylide to form a six-membered copper metallacycle, which, with protonolysis of the copper triazole complex in the final step, creates the triazole product and regenerates the Cu$_2$O catalyst. To confirm that the rate-limiting process is the formation of the benzyl azide or the Cu$_2$O-catalysed cycloaddition reaction, the reaction of phenylacetylene and benzyl azide was studied in water with 0.035 mmol of **1** and the corresponding product was obtained

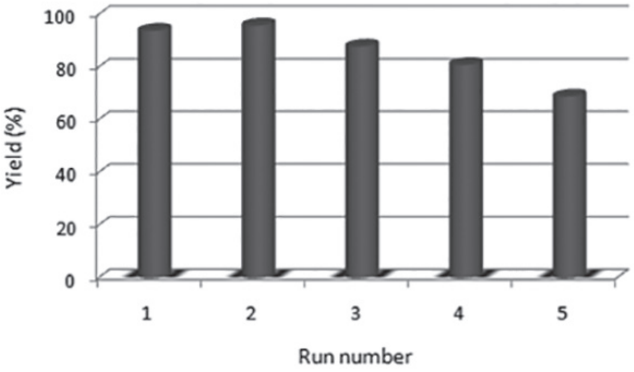
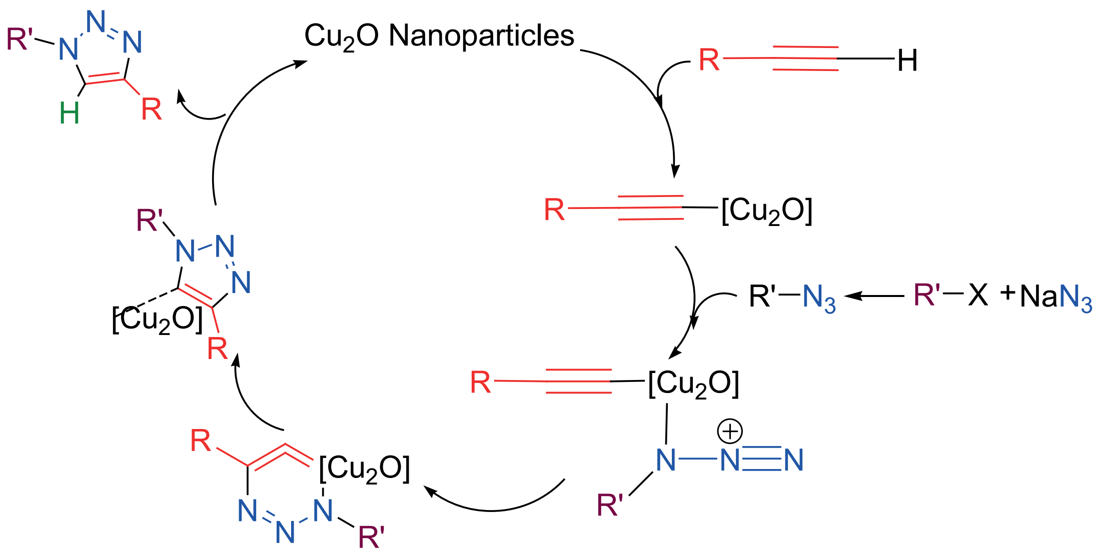


Fig. 3 Recycling study of catalyst **1** in the azide–alkyne cycloaddition.



Scheme 1 Proposed mechanism of cuprous oxide catalytic cycle for the formation of 1,2,3-triazoles.

in 96% yield in 6 h, while under similar conditions, a blank experiment provided only 3% of the product; therefore, the rate-limiting process is the Cu-catalysed cycloaddition reaction.

Conclusions

We have developed a simple and efficient protocol for the synthesis of the corresponding 1,2,3-triazoles in excellent yields through 1,3-dipolar cycloaddition of terminal alkynes with organic azides generated *in situ* from sodium azide and different organic halides using cuprous oxide nanoparticles as an efficient and recyclable catalyst.

Experimental

Chemicals and solvents were purchased from Merck and Fluka and were used without further purification.

Synthesis of Cu_2O nanoparticles (**1**)

$Cu(NO_3)_2{\cdot}3H_2O$ (4.0 mmol) was mixed in a transparent solution of poly(ethylene glycol) (PEG) 1000 (0.5 g) and a 1:1 mixture of H_2O/ethanol (30 mL) with constant stirring at 50 °C for 30 min. Then hydrazinehydrate (3.0 mol) was added. After continuous stirring for 2 h, the red precipitate was filtered, washed with water and ethanol several times, and dried under air at room temperature.

CAUTION: This procedure uses hydrazine, which is highly toxic and should be handled carefully in an efficient fume cupboard.

Synthesis of Cu_2O nanoparticles (**2**)

In a typical method, a 1:1 mixture of distilled water and ethanol (30 mL) was mixed with $Cu(NO_3)_2{\cdot}3H_2O$ (4.0 mmol) and PEG 1000 (0.5 g) and stirred vigorously until it dissolved completely. Then a solution of NaOH (35 mmol, 10 mL) and glucose (1.2 g) was slowly added dropwise under vigorous stirring to the solution. The solution was stirred for 20 min, and the dark red solid obtained was filtered, washed with water and ethanol several times, and dried under air at room temperature.

General procedure for the azide–alkyne cycloaddition

Alkyne (0.5 mmol), organic halide (0.55 mmol) and NaN_3 (0.55 mmol) were added to a suspension of Cu_2O nanoparticles (0.035 mmol) in H_2O (2 mL). The reaction mixture was warmed to 70 °C and stirred for 6 h. Then water (5 mL) was added to the resulting mixture and the product was extracted with EtOAc (2 × 10 mL). The collected organic phases were dried with anhydrous Na_2SO_4 and the solvent was removed under reduced pressure to give the corresponding triazoles, which did not require any further purification. The purity of the compounds was checked by ^{1}H NMR and elemental analysis (C, H and N).

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