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Short Communication

Nanoscrystalline CuO: Synthesis and application as an efficient catalyst for the preparation of 1,2,3-triazole acyclic nucleosides via 1,3-dipolar cycloaddition

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ABSTRACT

Nanowire CuO particles with an average diameter range of 2.5–3.7 nm were examined as catalysts for the 1,3-dipolar cycloadditions of organic azides to terminal alkynes. The material was successfully synthesized at room temperature from metallic copper powder by a facile solution-phase method in the presence of nitric acid, sodium hydroxide (NaOH) and ethylene glycol (EG) as growth-directing agent. The crystallinity, purity, morphology, specific surface areas and structural features of the as-prepared nanowires were characterized by powder X-ray diffraction, Brunauer–Emmett–Teller (BET) method and high-Transmission Electron Microscopy. Under mild reaction conditions, the addition of organic azides to terminal alkynes gives 1,4-disubstituted 1,2,3-triazole as a single regioisomer in good yields with reusability of the catalyst. The present click reaction protocol of terminal alkynes, via 1,3-dipolar cycloaddition with various organic azides allows the regioselective synthesis of 1,2,3-triazole acyclic nucleosides in good yields. We have then initiated the one-pot tandem [3 + 2] cycloaddition where benzylchloride was reacted with propargyl derivatives and sodium azide in the presence of CuO nanoparticles as catalyst.

1. Introduction

Modern drug discovery requires the identification and the optimization of synthetic routes to biological active molecules. Simple methods that can quickly and easily generate a variety of molecules have become more and more used. The enormous attention recently gained by the click reaction began with the pivotal discovery by the groups of Meldal [1] and Sharpless [2–4], in which copper(I) catalysis was found to dramatically accelerate the reaction under mild conditions. At the same time, a high regioselectivity was achieved toward the 1,4-regioisomer of the triazole product. Consequently, this protocol has found increasing application in a variety of disciplines such as organic chemistry [5] drug discovery and medicinal chemistry [6] and bioconjugation [7]. A large number of protocols have been developed for the click reaction with the use of copper-zeolites [8], Cu on charcoal [9], Cu nano-powder [10], copper sulfate/sodium ascorbate system, [11] silica supported copper catalyst, [12] and recently copper nanoparticles [13]. The results obtained by any of these methods are, in general, excellent. But, since the discovery that nanostructured copper oxide has shown a general beneficial effect in the cycloaddition of alkynes and azides many groups have used it [14]. More recently, CuO hollow nanospheres on acetylene black (CuO/AB) have been used for the catalytic [3 + 2] cycloaddition of azides with terminal alkynes without solvent under microwave irradiation [15].

As a consequence of our interest in the synthesis of 1,2,3-triazole acyclic nucleosides [16–21], we have identified that CuO nanoparticle catalyzes efficiently the preparation of 1,4-disubstituted 1,2,3-triazole by cycloaddition of alkynes to azides. The catalytic system which is composed of recyclable CuO nanoparticles, in dioxane/water allows the synthesis of 1,2,3-triazole acyclic nucleosides.

2. Experimental

2.1. Preparation of the CuO nanowire catalyst

Metallic cupper powder, nitric acid, sodium hydroxide (NaOH) and ethylene glycol (EG) were purchased from Aldrich and used as received. For a typical CuO nanowire synthesis, 1.0 g (0.0157 mol) of metallic Cu was dissolved in 80 mL HNO_3 solution (0.86 M). 20 mL of EG was poured into the aqueous solution. After the EG was uniformly dispersed in the solution, 6.0 g (0.15 mol) of NaOH pellets was added. After stirring for a few minutes, a blue suspension was formed and left under stirring, at room temperature, for several more hours until the blue suspension totally transformed to a black suspension. The final black suspension was filtered and washed several times with water and finally with ethanol. Finally, the product was dried in air at 100 °C for 24 h. This process can be simply scaled up for mass production.

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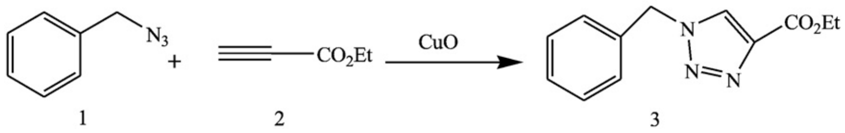
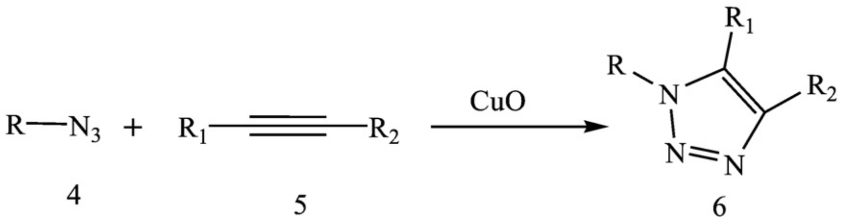
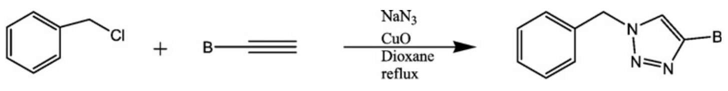


Scheme 1.



Scheme 2.



B= Uracil, 6-Azauracil, CO_2Et

Scheme 3.

2.2. General procedure for synthesis of 1,4-disubstituted 1,2,3-triazole

A suspension of nanostructured CuO (0.05 mmol, 5 mol %) was added to a mixture of alkyne **2** (1 mmol), and azide **1** (1.1 mmol) in 3 mL of dioxane/water (2/1, v/v). The solution was stirred at reflux (90 °C) for 2 h. Then, the solution was evaporated, and the residue was applied to flash column (silica gel).

All the spectroscopic data of the reaction products were compared with those reported in the literature [16–21].

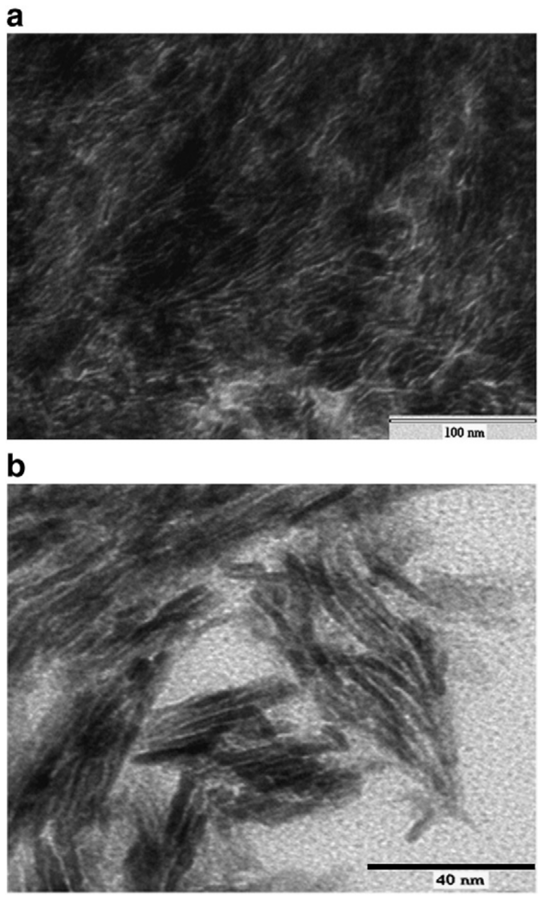


Fig. 1. TEM images of synthesized CuO nanowires.

2.3. General procedure for one-pot reaction

Propargyl derivatives (1 mmol), benzylchloride (1.1 mmol), and sodium azide (1.1 mmol) in the presence of CuO nanoparticles (0.05 mmol, 5 mol %) as catalyst were mixed in dioxane (3 mL) as solvent. The reaction mixture was refluxed for 3 h. The products were isolated by simple purification using flash column chromatography.

All the spectroscopic data of the reaction products were compared with those reported in the literature [16–21].

2.4. Characterizations

X-ray diffraction patterns (XRD) were obtained with a Philips X'Pert MPD diffractometer using Cu Kα radiation (λ = 1.54178 Å). Transmission Electron Microscopy (TEM) observations were carried out at 100 kV (JEOL 1200 EXII). Samples for TEM measurements were prepared by embedding the hybrid material in AGAR 100 resin, followed by ultramicrotomy techniques and deposition on

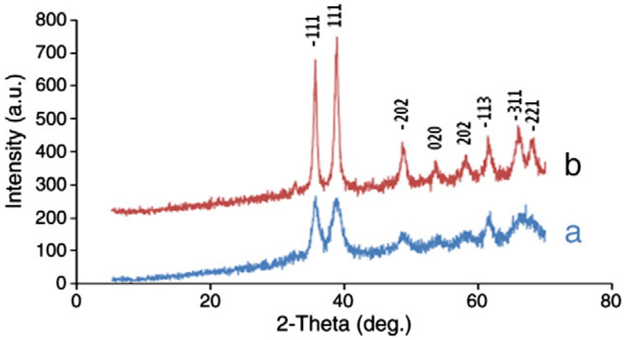


Fig. 2. (a) XRD pattern of prepared CuO, (b) after the fourth cycle of the CuO.

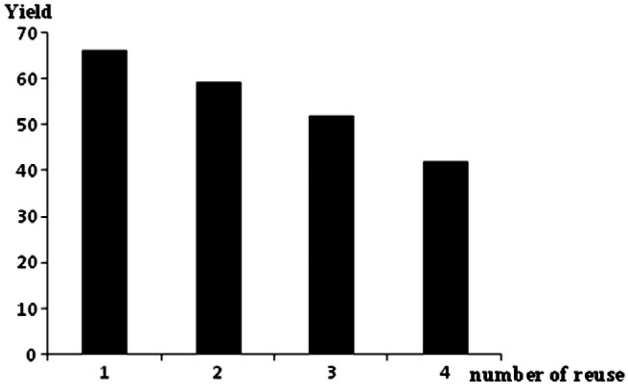


Fig. 3. The comparison of efficiency of catalysts' repeated use. Conditions: azide **1** (1, 1 mmol), alkynes **2** (1 mmol), CuO (0.05 mmol, 5 mol %), 60 °C, solvent: (3 mL) dioxane/H_20 (2/1), 2 h.

copper grids. The specific surface areas were obtained by BET on a Micromeritics Tristar 3000 after one night vacuum (10^{-2} mbar) at 120 °C. The average pore diameter and pore volume were calculated by the BJH method. The NMR spectra were recorded on a Bruker spectrometer (AC 300 MHz). Chemical shifts are reported as δ values (ppm) relative to TMS as a standard and the coupling constants J values are given in Hz. FAB mass spectra were recorded on a Varian MAT 311A spectrometer. TLC was performed on 60 F254 precoated plastic plate silica gel (Merck). Column chromatography was performed on silica gel (30–60 μm). All solvents were distilled and dried before using. All the spectroscopic data of the reaction products were compared with those reported in the literature [16–21].

3. Results and discussion

Morphology of the sample was studied by TEM. Fig. 1 shows a panoramic image of the product obtained. Interestingly, the product consisted of ultrafine crystallites. Closer observation revealed that these ultrafine nanostructure materials were composed of nanowires. Most of the nanowires are densely packed and align well so as to form compact nanowire arrays (Fig. 1). TEM image (Fig. 1b) further depicts the characterization of well-aligned nanowire arrays. Careful scaling of CuO nanowires reveals that they are 2.5–3.7 nm in diameter and about 20 nm in length.

XRD was used to examine the phase composition of the product. Fig. 2 presents a typical XRD pattern of CuO nanowire. All diffraction peaks are indexed to monoclinic CuO [JCPDS 41-0254]. No other diffraction peaks arising from possible impurities such as $Cu(OH)_2$, $CuNO_3$, Cu_2O or Cu are detected, indicating the preparation of pure phase CuO under the experimental conditions.

Average size of the obtained CuO particle shown in Fig. 1 is in the range of 2.5–3.7 nm. The crystallite size was also calculated by X-ray line broadening analysis using the Debye–Scherrer formula [22]. From XRD spectral in Fig. 2a, we found that the average CuO crystallite size was ~4.0 nm, in good agreement with the results of TEM image (Fig. 1b). The mean value of surface area of CuO catalyst was 52 m^2/g from BET analysis. After the fourth cycle of the CuO catalyst (Fig. 2b), the average crystallite size increases and reaches the value of ~14 nm.

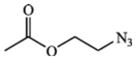
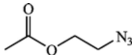
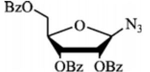
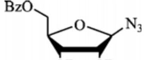
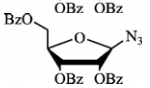
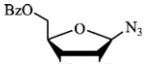
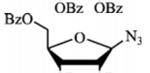
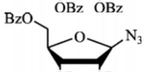
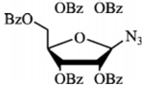
Preliminary investigation of the reaction of benzyl azide with ethyl propiolate in the presence of CuO nanoparticle revealed that the expected adduct was obtained as a single regioisomer. Next, the 1,3-dipolar cycloaddition of **1** to **2** (Scheme 1) was carried out in various solvents. The 1,3-dipolar cycloaddition reactions did not proceed in the absence of catalyst (Table 1, entry 1). Among the solvents tested, polar protic solvents such as water or mixed solvents such as dioxane/MeOH, CH_3CN/H_2O and toluene/H_2O (Table 1, entries 8, 9, 12, 13) the corresponding triazole **3** was not formed. In dioxane, dioxane/IL or THF/H_2O as solvent, the yield does not exceed 37% (Table 1, entries 7, 10, 11). In contrast, when the reaction was carried out in dioxane/H_2O (2/1,v/v), 1,2,3-triazole **3** was obtained in a good yield (Table 1, entry 3). However, the combination dioxane/H_2O (1/1,v/v) leads to a moderate yield (Table 1, entry 6). Furthermore, the ratio

Table 1
Synthesis of 1,4-disubstituted 1,2,3-triazole in different solvents.

Entry	CuO (mol%)	Solvent	Time (h)	Yield[a] %
1	0	Dioxane/H_2O	2	0
2	2.5	Dioxane/H_2O	2	18
3	5	Dioxane/H_2O	2	66
4	7.5	Dioxane/H_2O	2	45
5	10	Dioxane/H_2O	2	17
6	5	Dioxane/H_2O[b]	2	42
7	5	Dioxane	2	37
8	5	H_2O	12	0
9	5	Dioxane/MeOH	2	0
10	5	Dioxane/IL[c]	2	26
11	5	THF/H_2O	2	25
12	5	CH_3CN/H_2O	2	0
13	5	Toluene/H_2O	2	0

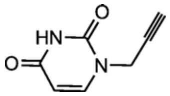
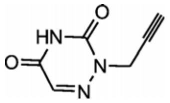
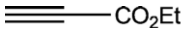
Conditions: azide (1, 1 eq), alkynes (1 eq), 60 °C.
All the spectroscopic data of the reaction products were compared with those reported in the literature [16–21].
[a] Isolated yield.
[b] Dioxane/H_2O (1/1).
[c] IL: ionic liquid (1-butyl-3methyl imidazolium chloride).

Table 2
Synthesis of 1,4-disubstituted 1,2,3-triazole with different alkynes and azides.

Entry	4	5		Yield %[a] 6
		R1	R2	
14	Ph-CH_2-N_3	CO_2Et	CO_2Et	66
3	Ph-CH_2-N_3	H	CO_2Et	68
15	Ph-CH_2-N_3	H	CH_2-PO(OEt)$_2$	75
16		CO_2Et	CO_2Et	70
17		H	CO_2Et	70
18		H	CH_2-PO(OEt)$_2$	78
19		CO_2Et	CO_2Et	71
20		H	CO_2Et	74
21	Ph-CH_2-N_3	H	CH_2-Ur[b]	70
22	Ph-CH_2-N_3	H	CH_2-Th[b]	68
23	Ph-CH_2-N_3	H	CH_2-Ad[b]	70
24	Ph-CH_2-N_3	H	CH_2-AzUr[b]	62
25		H	CH_2-Ur	72
26		H	CH_2-Th	68
27		H	CH_2-Ad	70
28		H	CH_2-AzUr	64

Conditions: azide **4** (1, 1 mmol), alkynes **5** (1 mmol), CuO (0,05 mmol), 60 °C, solvent: (3 mL) dioxane/H_20 (2/1), 2 h.
All the spectroscopic data of the obtained products were compared with those reported in the literature [16–21].
[a] Isolated yield.
[b] Ur: uracil, Th: thymine, AzUr: 6-Azauracil, Ad: adenine.

Table 3
Results for one-pot tandem reactions.

Entry	Alkyne	Yield %[a]
29		61
30		55
31		58

Conditions: azide (1, 1 mmol), alkynes (1 mmol), CuO (0,05 mmol), solvent: Dioxane (3 mL), 90 °C, 3 h.

[a] Isolated yield.

of the catalyst CuO nano was also examined. The result showed that 5% of CuO nano was the optimum amount of the catalyst (Table 1, entry 3).

Under the present reaction conditions, CuO (Scheme 2) nanoparticle catalyst was also found to be reusable, although gradual decline of activity was observed. The catalyst was separated by filtration, washed with water, ethanol and acetone and dried at 100 °C overnight before reuse. Such a procedure when applied for the 1,3-dipolar cycloaddition of **1** to **2** gave the product in 59% yield in the second run. The comparison of efficiency of catalyst on repeated use is reported in Fig. 3. The gradual decrease of catalytic activity is probably due to the agglomeration of nanoparticles in the reaction medium, acting negatively on the substrate–catalyst contact surface. This is visualized by the increase of crystallite size from 4 nm to 14 nm after the fourth cycle of the catalyst.

X-ray fluorescence study of aqueous reaction mixture after filtration shows that there were any traces of copper found in the solution. This result confirms that the reaction was heterogeneous and occurring in the surface of nanoparticle and there was no leaching of metal species involved during the reaction.

The scope of the present CuO nanocatalyst promoted 1,3-dipolar cycloaddition is summarized in Table 2. Various combination of substrates (three organic azides and seven terminal alkynes) were investigated and all the reactions efficiently proceed to give the corresponding 1,4-disubstituted 1,2,3-triazole derivatives in good isolated yield without any additives such as reducing agents, base, and stabilizing ligands.

In order to prove the applicability of the reaction conditions for synthesis of various 1,2,3-triazoles bearing pyrimidine heterocycle [16–21], we tested the methodology on a set of 1-propargylpyrimidine. The 1,3-dipolar cycloaddition coupling of sugar azide and 1-propargylpyrimidine took place with the same efficiency like in the case of benzyl azide under the applied conditions within 2 h.

Next, we studied the one-pot tandem [3 + 2] cycloaddition where benzylchloride was reacted with propargyl derivatives and sodium azide in the presence of CuO nanoparticles as catalyst in dioxane as solvent (Scheme 3). The reaction mixture was refluxed for 3 h and the products were isolated by simple purification using flash column chromatography. As shown in Table 3, the one-pot reaction proceeded efficiently to provide the desired products in good yields. These results indicate that the three-component reaction constitutes a powerful tool in 1,3-dipolar cycloaddition reactions.

4. Conclusion

In conclusion, the CuO nano acts as an efficient and recyclable catalyst for the 1,3-dipolar cycloaddition of organic and sugar azides with terminal alkynes and propargyl nucleobases, and allows the synthesis of 1,2,3-triazole acyclic nucleosides. The one-pot reaction has been performed efficiently to provide the desired products in good yields.

The simple experimental procedure, mild reaction conditions, inexpensive and recyclable catalyst, short reaction times and good yields are the advantages of the procedure.

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