Nanocrystalline Copper Oxide(II)-Catalyzed Alkyne-Azide Cycloadditions

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Although the use of Cu(II) salts as catalysts without reductants is limited in the cycloaddition of acetylenes with azides, the catalytic system employing average 10 nm CuO(II) nanoparticles in the absence of reductants shows good catalytic activity to form 1,4-disubstituted 1,2,3-triazoles even in wet THF as well as water. It is also noticeable that CuO(II) nanoparticle catalysts can be recycled with consistent activity. A range of alkynes and azides were subject to the optimized CuO(II) nanoparticle-catalyzed cycloaddition reaction conditions to afford the desired products in good yields.

Key Words : Click chemistry, Copper oxide nanoparticles, Cycloaddition, Heterogeneous catalysis

Introduction

The copper catalyzed Huisgen 1,3-dipolar cycloaddition reaction of azides and terminal alkynes, as a representative example of click chemistry, has made a great impact on biological, industrial and synthetic applications.[1,2] This reaction provides synthetically and biologically useful 1,2,3-triazole type products with high regioselectivity and is also tolerant to a wide range of functional groups and reaction conditions involving air and water.

To perform this transformation, commercially available Cu(I) salts and Cu(I) species, generated in situ from Cu(II) salts in the presence of sodium ascorbate, have been widely used assuming that copper (I) species are catalytically competent in the homogeneous reactions.[1c,3] Alternatively, heterogeneous Cu catalysts *e.g.* Cu/Cu_2O nanoparticles, Cu in charcoal, and Cu nanoclusters are also reported.[4] In addition to Cu(I) catalysts and heterogeneous Cu catalysts, $Cu(OAc)_2$ was reported as a catalyst for the cycloaddition of azides and acetylenes in the absence of sodium ascorbate. However, drawbacks of this catalytic system are high catalyst loadings (20 mol%) and low yield compared to that of Cu(I) catalyzed reactions.[5] Accordingly, we are encouraged to explore low-cost, highly efficient, and environmental friendly cycloaddition protocols using Cu(II) nanoparticles.

The objectives of catalysis involving nanoparticles are not only to achieve high activities and selectivities resulting from the enlarged surface area but also take advantage of the recyclability of them.[6] Together with the studies pertaining to novel chemical properties of nanoparticles, the development of new nano-catalysts with an excellent level of performance over a wide range of chemical transformations has been an on-going theme in the catalysis area. As a result, many other metal and metal oxide nanoparticles (*e.g.*, Pd, Au, Cu, Co, Rh, ZnO, MgO) have been utilized as catalysts in various organic reactions.[6,7] Among them, the use of CuO(II) nanoparticles is limited to industrial and environmental chemistry involving decomposition, reduction and oxidation reactions and a few recent coupling reactions.[8,9]

In the present work, we have demonstrated the excellent catalytic activity of CuO(II) nanoparticles in the Huisgen cycloaddition reaction of azides and acetylenes. It is noteworthy that the catalytic activity of Cu(II) species is remarkably improved by controlling the particle size, resulting in no use of reductants and the good chemical yield over other Cu(II) salts catalyzed reactions. Indeed, the use of cheap, stable and recyclable heterogeneous CuO(II) nanoparticles allows this reaction to be a clean and economical catalytic process.

Results and Discussion

The CuO(II) nanoparticles were prepared by the precipitation method[10] and characterized by powder X-ray diffraction spectroscopy (XRPD), transmission electron microscopy (TEM) and thermogravimetric analysis. The XRPD pattern, shown in Figure 1, displays that CuO(II) nanoparticles are composed of the single-phase CuO(II) with monoclinic structure (JCPDS# 45-0937) without any contamination of Cu_2O.[11] The CuO(II) particles have a spherical shape with the average size of 10 nm as shown in the TEM image (Fig. 2a). The phase purity of CuO(II)

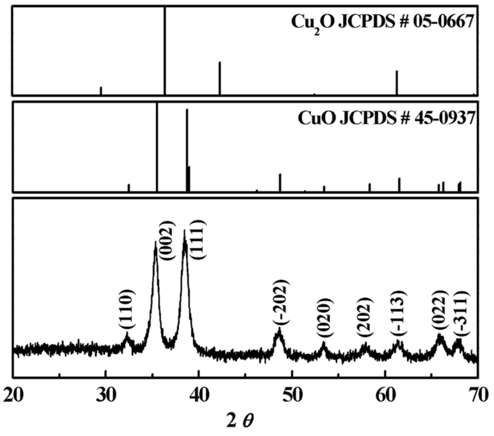


Figure 1. The XRPD pattern of CuO(II) nanoparticles.

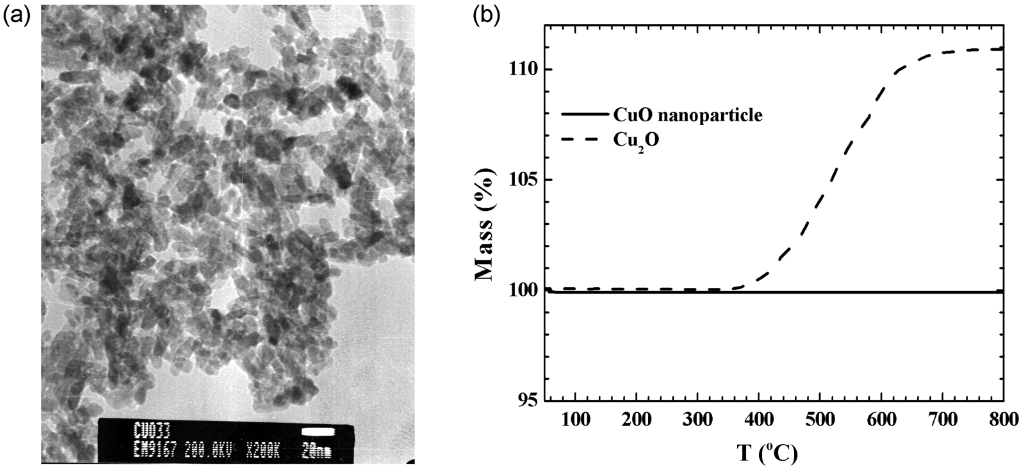


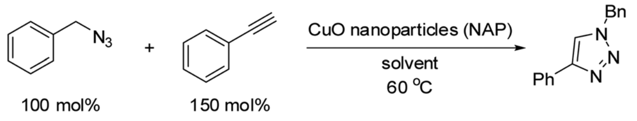
Figure 2. The TEM image (a) and the thermogravimetric (TG) analysis of CuO(II) nanoparticles under ambient atmosphere (b). For comparison, the TG curve for commercial Cu_2O powder (Adrich) is also represented.

nanoparticles was confirmed with thermogravimetric analysis. No change of the sample weight over the range of temperature from 50 °C to 800 °C indicates that CuO(II) nanoparticles do not contain any secondary phase such as Cu_2O (Fig. 2b).

In the context of utilizing CuO(II) nanoparticle-catalysts without reductants for the Huisgen cycloaddition and expanding the solvent scope of the Huisgen cycloaddition other than water, the following reaction conditions were examined. As indicated in Table 1, to improve the dispersion of nanoparticles in the solvent, the reaction mixture was sonicated for 10 minutes prior to raising the temperature to 60 °C. The cycloaddition reaction of benzyl azide (1 mmol, 100 mol%) and phenylacetylene (1.5 mmol, 150 mol%) with CuO(II) nanoparticles (0.05 mmol, 5 mol%) in THF from the shelf afforded 1,4-disubstituted 1,2,3-triazoles as a single regioisomer (63% yield). Considering the hygroscopic property of THF, it is expected that the reaction conditions need to be optimized by controlling the amount of water (Table 1). Initially, the optimization was carried out in anhydrous THF (2.5 mL, 0.4 M) purchased from Aldrich to afford the product in 41% yield (entry 1, Table 1). This result led us to consider that the anhydrous reaction conditions might diminish the catalytic activity of CuO(II) nanoparticles. To prove this hypothesis, 0.1 mL of water (v/v 4%) was used as an additive. Under reaction conditions involving a small amount of water (v/v 4%), the yield was increased to 95% (entry 2, Table 1). However, adding more water (v/v 20%) induced the lower yield (entry 3, Table 1). Based on the water effect in THF, other organic solvents were screened with water and without water. Unfortunately, both toluene and dioxane appeared to be less effective than THF, yet water additives improved the yield compared to the anhydrous reaction conditions (entry 4-7, Table 1). In addition to organic solvents, water as a generally applied solvent in this transformation was tested. The cycloaddition reaction in water provided the desired product in 76% yield (entry 8, Table 1).

Another advantage of using heterogeneous nanoparticles is the recyclability. To test the recyclability of this system, recovered CuO(II) catalysts were exposed to the standard reaction conditions, exhibiting an excellent reactivity (entry 9, Table 1). The XRPD pattern of the recovered catalyst shows the structure of CuO(II) nanoaprticles has not been changed by water and other reactants during the catalytic process. Regarding the amount of catalysts, it was found that reduced catalyst loadings (3 mol%) did not affect the yield of the reaction (entry 10, Table 1). Next, the catalytic activity of commercial CuO(II) powder purchased from Aldrich (ACS reagent 99.0%, particle size < 5 micrometer) was tested resulting in 7% isolated yield, while under similar conditions CuO(II) nanoparticle-catalyzed the reaction provided 95% of the product (entry 11, Table 1). Presumably, this difference is attributed to the larger contact area of CuO(II) nanoparticles, eventually accelerating the

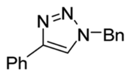
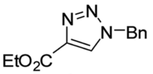
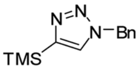
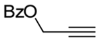
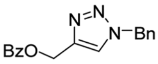
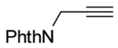
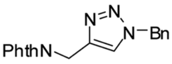
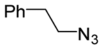
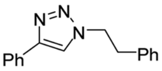
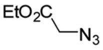
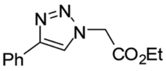
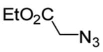
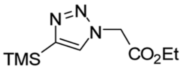
Table 1. Optimization of cycloaddition catalyzed by CuO(II) nanoparticles



Entry	Catalyst	time	Solvent	Yield
1	CuO(NAP)(5 mol%)	24 h	THF (0.4 M)	41%
2	**CuO(NAP)(5 mol%)**	**24 h**	**THF:H_2O 24:1 (0.4 M)**	**95%**
3	CuO(NAP)(5 mol%)	24 h	THF:H_2O 20:5 (0.4 M)	47%
4	CuO(NAP)(5 mol%)	24 h	toluene (0.4 M)	33%
5	CuO(NAP)(5 mol%)	24 h	toluene:H_2O 24:1 (0.4 M)	54%
6	CuO(NAP)(5 mol%)	24 h	dioxane (0.4 M)	14%
7	CuO(NAP)(5 mol%)	24 h	dioxane:H_2O 24:1 (0.4 M)	30%
8	CuO(NAP)(5 mol%)	24 h	H_2O (0.4 M)	76%
9	CuO(NAP)(5 mol%)[a]	24 h	THF:H_2O 24:1 (0.4 M)	97%
10	CuO(NAP)(3 mol%)	24 h	THF:H_2O 24:1 (0.4 M)	95%
11	CuO(powder)(5 mol%)	24 h	THF:H_2O 24:1 (0.4 M)	7%
12	No catalyst	24 h	THF:H_2O 24:1 (0.4 M)	2%

The reaction was sonicated for 10 minutes prior to increasing the temperature. The cyclized products of all entries were obtained as single regioisomer. [a]Recycled CuO nanoparticle catalysts were used.

Table 2. The scope of substrates

Entry	Alkyne	Azide	Product	Yield
1	Ph—≡ **1a**	Bn—N_3 **1b**	 **1c**	95%
2	EtO_2C—≡ **2a**	Bn—N_3 **1b**	 **2c**	88%
3	TMS—≡ **3a**	Bn—N_3 **1b**	 **3c**	25%
4	 **4a**	Bn—N_3 **1b**	 **4c**	88%
5	 **5a**	Bn—N_3 **1b**	 **5c**	43%
6	Ph—≡ **1a**	 **6b**	 **6c**	94%
7	Ph—≡ **1a**	 **7b**	 **7c**	67%
8	TMS—≡ **1a**	 **7b**	 **8c**	21%

desired cycloaddition process. In the absence of the catalyst, this reaction does not appear to occur efficiently (entry 12, Table 1). Throughout the optimization, the reaction conditions involving 5 mol% of CuO(II) nanoparticle-catalysts using wet THF were chosen as standard conditions for further reactions (entry 2, Table 1).

To explore the scope of the substrates, various alkynes and azides were subject to the standard CuO(II) nanoparticles-catalyzed cycloaddition conditions. Since the functional groups on the substrates are known to play a significant role in terms of the yield and selectivity, initially, alkynes possessing different groups were examined (Table 2).[12] Ethyl propiolate **2a** whose alkyne is adjacent to electron withdrawing group (ester) underwent the cycloaddition reaction with benzyl azide **1b** to afford the product **2c** in 88%; however, ethynyltrimethylsilane **3a** possessing silicon next to the acetylene reacted with benzyl azide **1b** to provide the desired product **3c** in 25% yield under the same reaction conditions. Prop-2-ynyl benzoate **4a** containing benzoyl protected alcohol participated in this transformation to provide the product **4c** in 88%. *N*-propargylphthalimide **5a** showed somewhat lower reactivity although the structure of substrate **5a** seems similar to substrate **4a** possessing a heteroatom at the propargylic position.

Subsequent to the screen of acetylenes, different azides possessing different functional groups were used (Table 2). (2-Azidoethyl)benzene **6b** reacted with phenyl acetylene to show the comparable yield (94%) with respect to the reaction of benzyl azide **1b** and phenylacetylene (95%). Ethyl 2-azidoacetate **7b** having ethyl acetate was exposed to the standard conditions to provide the product in 67% yield. The diminished reactivity of ethyl 2-azidoacetate was not improved by changing the acetylene partner to ethynyl trimethyl silane. In view of these results, most cycloaddition reactions involving different acetylenes and azides show moderate to good yields except for the reaction using ethynyltrimethylsilane.

Conclusions

In summation, CuO(II) nanoparticles have been used for the catalytic cycloaddition reaction of azides and acetylenes to provide the cyclized products in good yields with high regioselectivity. By employing nanocrystalline catalysts, the catalyst activity was remarkably improved compared to micro size CuO(II). In addition, CuO(II) nanoparticle-catalysts were recycled to catalyze the cycloaddition with the consistent reactivity under standard reaction conditions.

Experimental Section

Anhydrous THF (99.9% inhibited with 0.025% BHT) was purchased from Aldrich and used without extra purification. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded with a Varian Mercury plus (400 MHz) spectrometer. Chemical shifts are reported in delta (δ) units, part per million (ppm) downfield from trimethylsilane. Coupling constants are reported in Hertz (Hz). Carbon-13 nuclear magnetic resonance (^{13}C NMR) spetra were recorded with a Varian Mercury plus (100 MHz) spectrometer. Chemical shifts are reported in delta (δ) units, part per million (ppm) relative to the center of the triplet at 77.00 ppm for deuteriochloroform. Infrared spectra were recorded on a MAGNA-IR560. High-resolution mass spectra (HRMS) are obtained on a JMS700 spectrometer (Korean basis science institute). CuO(II) nanoparticles were characterized by XRPD (Rigaku DMAX-2200PC diffractometer using CuK radiation), TEM (JEOL-2000EXII) and thermogravimetric analysis (MAC TG-DTA 2010). Substrates **4a**, **5a**, **1b**, **6b**, and **7b** were prepared according to the previously reported procedures.[13] Products **1c**-**3c** and **5c**-**7c** exhibited spectral properties consistent with previous literature reports.[14]

Synthesis of CuO(II) nanoparticles. Copper acetate (1.0 g) and acetic acid (1.0 ml) were dissolved in 250 mL of distilled water. The solution was heated to 100 °C before a rapid introduction of 0.8 g of NaOH flakes with vigorous stirring. After being cooled to room temperature, black powders precipitated were separated by centrifugation at 10000 rpm for 10 min, then washed several times with distilled water and ethanol, and dried at 130 °C for 12 h.

The representative procedure for the cycloaddition

reaction. To a solution of phenyl acetylene (133 mg, 1.5 mmol, 150 mol%) and benzyl azide (153 mg, 1 mmol, 100 mol%) in THF (2.4 mL) at ambient temperature was added CuO(II) nanoparticles (3.97 mg, 0.05 mmol, 5 mol%) and water (0.1 mL). The system was purged with nitrogen gas and the reaction was allowed to stir at 60 ºC for 24 hours, then the reaction mixture was evaporated onto silica gel and the product purified *via* silica gel chromatography.

The recovery procedure of CuO(II) nanoparticles. Upon the completion of the reaction, the solution containing the product was decanted. Subsequently, fresh THF was added into CuO(II) nanoparticles and the resulting solution was stirred for 10 minutes with sonication. Then, the THF layer was decanted. This washing process was repeated twice. After drying the CuO(II) nanoparticles under vacuum for 10 minutes, the cycloaddition reaction was performed with the recovered CuO(II) nanoparticles.

1-Benzyl-1H-1,2,3-triazol-4-yl)methyl benzoate (4c). ^{1}H NMR (CDCl$_3$): δ = 8.01 (d, J = 7.2 Hz, 2H), 7.60 (s, 1H), 7.45 (m, 3H), 7.31 (m, 5H), 5.51 (s, 2H), 5.43 (s, 2H) ppm. ^{13}C NMR (CDCl$_3$): δ = 166.5, 143.5, 134.5, 133.4, 129.9, 129.3, 129.0, 128.5, 128.3, 124.0, 58.4, 54.6, HRMS [M]$^+$ calcd: 293.12, obsd: 293.12, IR: 3060, 2360, 1710, 1270, 1100 cm^{-1}.

Ethyl 2-(4-(trimethylsilyl)-1H-1,2,3-triazol-1-yl)acetate (8c). ^{1}H NMR (CDCl$_3$): δ = 7.65 (s, 1H), 5.12 (s, 2H), 4.25 (q, J = 6.8 Hz, 2H), 1.30 (t, J = 6.8 Hz, 3H), 0.33 (s, 9H) ppm. ^{13}C NMR (CDCl$_3$): δ = 166.6, 130.4, 128.9, 62.6, 50.6, 14.5, 0.7, HRMS [M+H]$^+$ calcd: 228.12, obsd: 228.12, IR: 2960, 2360, 1750, 1650, 1210 cm^{-1}.

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