

Azide-alkyne cycloaddition by recyclable heterogeneous Cu catalysts on reverse phase silica gel

Y. Jang*, H. Kim*, M. Lim* and H. Rhee*

*Department of Bionanotechnology, Hanyang University, 55 Hanyangdaehak-ro, Sangnok-gu, Ansan, Gyeonggi-do, 15588, South Korea

ABSTRACT

Functionalized reverse phase silica gel was synthesized as heterogeneous catalysts support. Cu(I) and Cu(II) catalysts immobilized onto two types of supports were prepared and characterized. The copper catalyzed azide-alkyne cycloaddition was performed in water via a one-pot reaction and yielded good results. And these catalysts were applied to azide-alkyne cycloaddition reaction of glycidyl azide polymer in DMSO. These catalysts are air stable and reusable over multiple uses.

Keywords: Azide-alkyne cycloaddition, heterogeneous Cu catalyst, GAP copolymer

1 INTRODUCTION

Triazole is a very useful motif within the fields of medicinal chemistry, [1] carbohydrate chemistry,[2] and materials science.[3] Triazole has also been studied as a strong ligand for metal coordination with wide applicability.[4] The thermal Huisgen 1,3-dipolar cycloaddition of organoazides and alkynes is a classic method for the synthesis of triazole.[5] However, this method is slow even at high temperatures, producing a mixture of 1,4- and 1,5-disubstituted triazoles. Numerous synthetic methods using metal catalysts have been reported.[6] Copper has been shown to especially accelerate the reaction. The copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) reaction is considered to be a powerful pathway with a high regioselectivity and yield.[7] However, copper catalyzed methods also possess drawbacks due to limited catalyst recyclability and the use of relatively expensive copper complexes that are difficult to remove.[8] Therefore, the development of copper immobilized heterogeneous catalysts has attracted attention due to its reusability and ease of catalyst separation.[9] A variety of solid supports have been applied including zeolites,[10] charcoal,[11] silica,[12] and polysaccharides.[13] Additionally, the use of water as a solvent is a promising approach with regard to green chemistry.[14]

Previously, we developed an aminopropyl-functionalized reverse phase silica gel, which is end capped with a hydrophobic alkyl group. These properties make it possible to use water as a solvent for organic reactions.

On the basis of previous results[15], we applied Cu(I) catalyst to the polymeric binder in solid propellant, such as glycidyl azide polymer (GAP). GAP contains azide groups as energetic pendant groups that release heat by exothermic decomposition.[16] Also, It has many advantages such as a high positive heat of formation (+957 kJ kg⁻¹), low sensitivity and high energy.[17] However, bulky and polar azide groups in GAP cause low flexibility of backbone by hindrance of motion in molecular chain. Therefore, GAP has poor low temperature characteristics and low thermal stability due to azide group.[18,19] To solve these problems, GAP copolymers such as fluorinated GAP copolymer, GAP-THF copolymer and GAP-PEG copolymer have been synthesized.[20-22] These GAP copolymers have better mechanical properties than GAP by introducing different monomers or polymers.

In this work, Cu(I) and Cu(II) catalysts immobilized onto two support types were synthesized and characterized. The copper catalyzed azide-alkyne cycloaddition was performed in water. Additionally, we have focused on improvement of mechanical properties of GAP by introducing 1,4- triazole as a part of application of Cu(I) catalyst.

2 RESULT AND DISCUSSION

2.1 Synthesis and characterization of copper catalysts immobilized onto reverse phase silica gel

Cu(I) and Cu(II) catalysts immobilized onto reverse phase silica gel were synthesized; First, the 2-pyridinecarboxaldehyde ligand was anchored to a commercially available reverse phase 3-aminopropyl-functionalized silica gel (APSi).

Table 1 Optimization of the azide-alkyne cycloaddition^a

Entry	Catalyst	Mol%	Temp. (°C)	Time (h)	Yield (%) ^b	TON (mol/mol) ^c	TOF (h ⁻¹) ^d
1	Cu(I)@IPSi	5	r.t.	24	94	18.8	0.78
2	Cu(I)@IPSi	5	60	2	92	18.4	9.2
3	Cu(I)@IPSi	5	80	2	89	17.8	8.9
4	Cu(I)@IPSi	2.5	60	2	92	36.8	18.4
5	Cu(I)@APSi	2.5	60	2	84	35.2	17.6
6	Cu(II)@IPSi	5	r.t.	24	94	18.8	0.78
7	Cu(II)@IPSi	5	60	2	93	18.6	9.3
8	Cu(II)@IPSi	5	80	2	87	17.4	8.7
9	Cu(II)@IPSi	2.5	60	2	87	34.8	17.4
10	Cu(II)@APSi	5	60	2	78	15.6	7.8

^a Reaction conditions: benzyl bromide (1.0 mmol), phenyl acetylene (1.0 mmol), sodium azide (1.0 mmol), H₂O (2 mL). ^b Isolated yield. ^c TON (turnover number): reactant moles converted/catalyst moles. ^d TOF (turnover frequency): TON/reaction time.

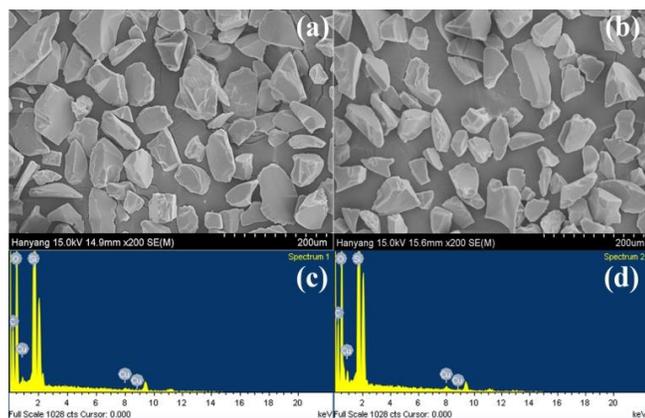


Figure 1 Scanning electron microscope (SEM) image and energy dispersive X-ray analysis (EDXA) of Cu(I)@IPSi(a,c) and Cu(II)@IPSi(b,d).

The complexation of [Cu(CH₃CN)₄]PF₆ and CuSO₄ with the resulting iminopropyl-functionalized silica gel (IPSi) subsequently followed, yielding Cu(I)@IPSi and Cu(II)@IPSi. Introduction of the 2-pyridinecarboxaldehyde ligand to the starting silica gel was confirmed via solid-state ¹³C NMR (ESI). The copper catalysts possessed an irregular shape based on scanning electron microscopy (SEM) images acquired primarily from the shape of the starting silica gel. Energy dispersive X-ray analysis (EDXA) further confirmed that Cu was indeed present (Figure 1). Copper loading values on the catalysts were determined via inductively coupled plasma (ICP); the results showed the loading values to be 0.498 mmol/g of Cu(I)@IPSi and 0.319 mmol/g of Cu(II)@IPSi. As a result of the Brunauer-Emmet-Teller (BET) method, the catalysts possessed pore sizes of 6–8 nm similar to the starting silica gel and pore volumes of 0.332 cm³/g and 0.416 cm³/g for Cu(I)@IPSi and Cu(II)@Si,

respectively (ESI). The oxidation number of copper supported on the catalyst was confirmed by X-ray photoelectron spectroscopy (XPS) (ESI).

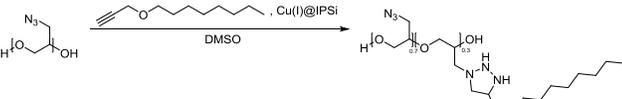
The reverse phase silica gel possessed an end capped alkyl group yielding hydrophobicity. We anticipated that transport of the hydrophobic substrate towards the hydrophobic surface would enhanced reactivity by bringing the substrate and catalyst in close proximity. This property would also enable the azide-alkyne cycloaddition reaction in water.

2.2 Azide-alkyne cycloaddition

Azide-alkyne cycloaddition reactions were performed to explore the catalytic activity of the prepared catalysts. The reaction was performed via the one-pot reaction of benzyl bromide, sodium azide, and phenylacetylene. First, the reaction of benzyl bromide with sodium azide generated benzyl azide in situ. Then, benzyl azide reacted with phenylacetylene to form the triazole product. Optimization of the reaction has been assessed as shown in Table 1. The turnover number (TON) and turnover frequency (TOF) values were compared. Initially, the reaction was performed at room temperature using 5 mol% of catalyst with excellent yields (94%) by the Cu(I)@IPSi and Cu(II)@IPSi catalysts (Table 1, entries 1&6). The reaction temperature was varied to reduce the reaction time and the amount of catalyst was reduced to improve the TON and TOF values. The reactivity of the copper catalyst immobilized on the starting silica gel (Cu@APSi) was also compared to countercheck effects of the ligand (Table 1, entries 4&5, 7&10).

Both catalysts were effective and Cu(I)@IPSi was more reactive than Cu(II)@IPSi. Therefore, we choose Cu(I)@IPSi as a catalyst of azide-alkyne cycloaddition in GAP due to higher reactivity as can be seen in Table 1. The azide-alkyne cycloaddition was performed under the established reaction conditions of two temperatures and various amount of catalysts (Table 2). The more catalyst was added in the same reaction time, the faster the rate of reaction. So, reaction was complete in case of using 20 mol% of Cu(I)@IPSi. In addition, the rate of reaction was faster at the higher temperature.

Table 2 The azide-alkyne cycloaddition of GAP



Entry	Mol%	Temp. (°C)	Time (h)	Yield (%)	Composite [azide] : [Triazole] ^a
1	2.5	80	26	84	0.87 : 0.13
2	5	80	26	87	0.80 : 0.20
3	10	80	26	89	0.76 : 0.24
4	20	80	26	93	0.71 : 0.29
5	2.5	95	5	84	0.80 : 0.20
6	5	95	5	91	0.75 : 0.25
7	10	95	5	91	0.72 : 0.28
8	20	95	5	93	0.72 : 0.28

^a Analyzed by inverse gated decoupling ¹³C NMR

3 EXPERIMENTAL

3.1 Material and Characterization

All chemicals were purchased from commercial sources (Sigma Aldrich, TCI and Alfa Aesar) and were used without further purification unless specifically mentioned. 2-Pyridinecarboxaldehyde was distilled under reduced pressure prior to use. The silica gel support used to prepare the catalysts was commercially available 9% functionalized aminopropyl silica gel with 1 mmol NH₂/gram (particle size 40-63 μm; pore size 60 Å; surface area 550 m²/g). The copper catalyst loading on the silica support and the azide-alkyne cycloaddition reaction were performed using a shaker (Eyela, Mixer CM-1000) at 12 x 10³ rpm. Scanning electron microscopy (SEM) and energy dispersive X-ray analysis (EDXA) were performed on a HRTEM JEOL electron microscope at an acceleration voltage of 300 kV. The copper catalyst loading values were estimated via inductively coupled plasma (ICP) analysis with a JY Ultima2C. ICP analysis was also used to check for Cu leaching after the recycle test. X-ray photoelectron spectroscopy (XPS) analysis was performed on a VG SCIENTA R3000 to show

the electronic state of copper. ¹H and ¹³C NMR spectra were obtained in CDCl₃ and DMSO with a Bruker NMR at 400 MHz for ¹H and at 100 MHz for ¹³C with TMS as an internal standard. For solid-state NMR experiments, 1D ¹³C spectra were measured via a cross polarization (CP) pulse sequence (contact time: 2 ms) on a Bruker 400 MHz NMR spectrometer equipped with a 4-mm magic angle spinning (MAS) probe (Bruker Biospin, Billerica, MA) operating at a 10-kHz spinning rate. Low temperature nitrogen adsorption-desorption isotherms were measured at -196 °C on an absorption volumetric analyzer BEL MINI manufactured by BEL, Inc. (Japan). Specific surface areas were determined using the Brunauer-Emmet-Teller (BET) method from nitrogen adsorption isotherms of gas adsorbed at the relative pressure P/P₀ = 0.99. Infrared spectra were recorded on a Bruker Alpha FT-IR spectrometer. Melting points were determined with a Sanyo Gallenkamp melting point apparatus. Analytical thin layer chromatography (TLC) was performed with E. Merck 60 F254 aluminum-backed silica gel plates (0.2 mm) containing a fluorescent indicator.

3.2 Synthesis of Cu(I)IPSi and Cu(II)@IPSi

3-Aminopropyl functionalized silica gel (3 mmol NH₂ unit, 1.0 equiv., 3 g) was added to a jacketed vial containing a solution of 2-pyridinecarboxaldehyde (1.1 equiv., 0.34 mL) in 15 mL of distilled CH₂Cl₂. After 3 hours of vigorous stirring, the reaction mixture was filtered, washed with CH₂Cl₂, and dried under vacuum at 40 °C. To coordinate Cu(I) with silica, imine functionalized silica gel (IPSi, 1.0 equiv., 1.1 g) and [Cu(CH₃CN)₄]PF₆ (1.1 equiv., 0.21 g) were added to 25 mL of methanol. The reaction mixture was shaken at room temperature for 12 hours, followed by filtration, washing with methanol, and drying under vacuum at 40 °C. The loading value of Cu(I)@IPSi was 0.498 mmol/g. For the preparation of Cu(II)@IPSi, imine functionalized silica gel (1.0 equiv., 1.1 g) was added to a jacketed vial containing CuSO₄·5H₂O (1.1 equiv., 0.27 g) dissolved in 25 mL of H₂O. The mixture was stirred for 12 hours at room temperature, followed by filtration, washing with H₂O, and drying under vacuum at 40 °C. The loading value of Cu(II)@IPSi was 0.319 mmol/g.

3.3 Synthesis of 1-Benzyl-4-phenyl-1H-1,2,3-triazole

For a synthesis experiment, benzylbromide (1.0 mmol), sodium azide (1.0 mmol), phenylacetylene (1.0 mmol), and catalysts were added to a 20 mL of jacketed vial containing 2 mL of H₂O. After the addition of the Cu(I)@IPSi catalyst (2.5 mol%), Cu(II)@IPSi catalyst (5.0 mol%), the reaction mixture was stirred at 60 °C. The reaction was monitored via thin layer chromatography (TLC). After completion, the reaction mixture was cooled and 6 mL of CH₂Cl₂ was added, followed by filtration, and washing with CH₂Cl₂ and H₂O.

The reaction mixture was filtered through a pad of celite and dried in vacuo. The product was purified by silica gel column chromatography with hexane/ethyl acetate and analyzed by ^1H and ^{13}C NMR spectroscopy.

3.4 Synthesis of Poly(GA-triazole)

GAP (3 mmol, 1.0 equiv.) was dissolved in DMSO (15 mL) in jacketed vial at $60\text{ }^\circ\text{C}$. Cu(I)@IPSi (2.5 mol%) and octyl propargyl ether (0.3 equiv.) were added to the reaction mixture and stirred at $95\text{ }^\circ\text{C}$ for 5 h or $80\text{ }^\circ\text{C}$ for 26 h. After the completion, the reaction mixture was cooled and 6 mL of CH_2Cl_2 was added, followed by filtration, and washing with CH_2Cl_2 and H_2O . The reaction mixture was filtered through a pad of celite and dried in vacuo. The product was analyzed by ^1H and ^{13}C NMR spectroscopy.

4 CONCLUSION

The solid support was synthesized for the preparation of heterogeneous catalysts. That was aminopropyl-functionalized reverse phase silica gel, which possessed an end capped hydrophobic alkyl group. These catalyst properties enabled one-pot azide-alkyne cycloaddition reactions in water. A series of 1,4-disubstituted-1,2,3-triazoles were synthesized with good results and the catalysts could be reused multiple times. Furthermore, we applied these catalysts to azide-alkyne cycloaddition reaction of glycidyl azide polymer (GAP). Contrary to expectations, GAP was not reacted in water. However, we could obtain poly(GA-triazole) in DMSO with good yields. Therefore, we will analyse the mechanical properties of poly(GA-triazole) later.

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