Comparing Copper Catalysts in the Synthesis of 1,2,3-Triazoles via Click Chemistry

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ABSTRACT

Copper-catalyzed azide-alkyne cycloadditions (CuAAC) produce 1,4-disubstituted 1,2,3-triazoles, molecules that have many applications in pharmaceuticals. Click reactions are atom-efficient and produce 1,4-disubstituted triazoles selectively with high yields at room temperature. Byproducts are rarely observed, and the product is easily separated by washing, eliminating the need for purification measures such as column chromatography. We tested various copper complexes for ease of use as homogeneous catalysts at various conditions. The 1,4-disubstituted triazole products were obtained in moderate to excellent yields. The progress of reaction was determined using TLC and IR spectroscopy, and products were characterized by GC-MS and NMR spectroscopy. We found that there is little that changes the outcome of the reaction upon variations in solvent and temperature conditions. However, preliminary results show that the anion of the copper salt used in preparing the copper complexes affects the kinetics of the triazole formation. A significant finding was that copper(II)-catalyzed reactions appear to form product even in the absence of a reducing agent.

Keywords: click chemistry, copper, catalysts, azide-alkyne cycloadditions, triazole synthesis, CuAAC, Huisgen reaction

INTRODUCTION

1,2,3-triazoles have wide applications in medicinal chemistry, including antiallergic, antiepileptic, antibacterial, and antiviral properties (Wu et al., 2013). These molecules can be easily synthesized through click chemistry. The usefulness of these molecules extends beyond pharmaceuticals, as click chemistry and triazoles can be used in fluorescent staining of tissues for the monitoring of DNA (Salic and Mitchison, 2007), cell surface engineering (Link and Tirrell, 2003), dendrimer synthesis (Wu et al., 2004), nanotechnology (Choudhury et al., 2022), among others (Sharpless and Manetsch, 2006). Copper-catalyzed azide-alkyne cycloadditions produce 1,4-disubstituted 1,2,3-triazoles with virtually no isomers or side products (Sharpless et al., 2001).

Previous click reactions have used heavy metals catalysts such as platinum, palladium, and ruthenium. While successful, these reactions are expensive and harmful to the environment as heavy metals such as these are toxic and costly to obtain. The discovery of copper as a catalyst in Huisgen reactions eliminated the need for the use of heavy metals. The goal of this research was to investigate common and commercially available copper complexes as catalysts for benzyl azide and terminal alkyne cycloaddition (Scheme 1), with the available resources and instrumentation. Copper is cheaper and more benign than heavy metals while still providing the benefits of being a transition metal.

We began this project with some limited instrumentation, having no NMR instrument in our facilities. We screened for various alkynes that provided distinguishable IR peaks for easy monitoring of reaction progress. Alkynes used were phenylacetylene; 2-phenyl-3-butyn-2-ol; phenyl propargyl ether; and 1,3-diethynylbenzene. Out of these, phenylacetylene and phenyl propargyl ether were selected. For all reactions, the azide was benzyl azide (Schemes 2 and 3).
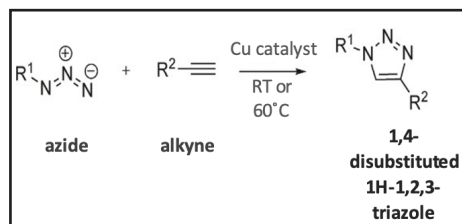
Scheme 1. Copper-catalyzed Huisgen Dipolar Cycloaddition of Azides and Alkynes.
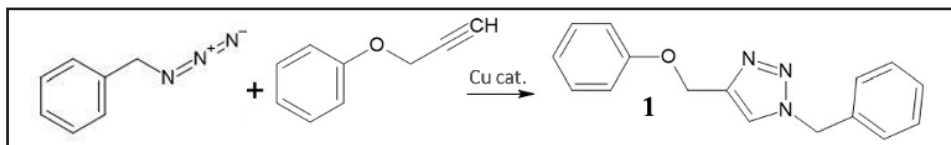
Scheme 2. Cu-catalyzed click reaction of benzyl azide and phenyl propargyl ether to produce 1- benzyl-4-(phenoxymethyl)-1H-1,2,3-triazole (product **1**).
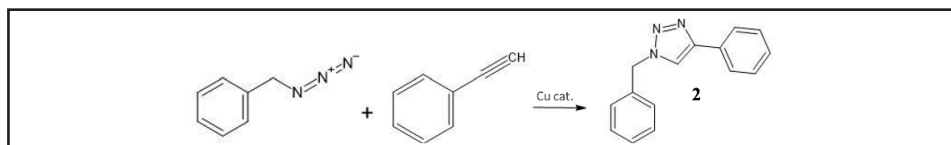
Scheme 3. Cu-catalyzed click reaction of benzyl azide and phenylacetylene to produce 1-benzyl-4-phenyl-1H-1,2,3-triazole (product **2**).

Comparing Copper Catalysts in the Synthesis of 1,2,3-Triazoles via Click Chemistry
Emma E. Green, Ethan A. Leitschuh, and Jocelyn P. Lanorio

32

After finding reactions that allowed monitoring, we began examining the copper complexes as catalysts, the goal being to search for differences between Cu(I) and Cu(II). Sodium ascorbate reduces Cu(II) to Cu(I), the proposed active catalyst in this reaction (Rostovtsev et al., 2002). This theory was tested by using Cu(II) complexes and omitting the use of the reducing agent. This will give insight to the active form of copper as a catalyst.

MATERIALS AND METHODS

The reaction between benzyl azide and common terminal alkynes was utilized to produce the corresponding triazoles (Schemes 2 and 3). All reagents were commercially purchased from Sigma Aldrich, except for the Cu(I)-NHC (NHC = N-heterocyclic carbenes) complex, [Cu(IPr)Cl] where IPr = 1,3-bis (diisopropylphenyl)imidazol-2-ylidene (Figure 1). Four readily and commercially available copper complexes were examined as catalysts including $CuSO_4$, CuCl, $CuCl_2 \cdot 2H_2O$, and CuI. A 1M aqueous solution of $CuSO_4 \cdot 5H_2O$ was also prepared. The 14-electron copper-NHC complex, [Cu(IPr)Cl], was synthesized as reported in the literature (Citadelle et al., 2010). All solid copper complexes were used as received with the exception of the prepared solution of $CuSO_4 \cdot 5H_2O$ (1M).
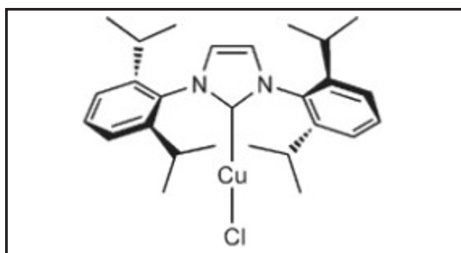

Figure 1. Structure of the [Cu(IPr)Cl] complex.

Deuterated chloroform (NMR solvent) was purchased from Sigma Aldrich and used as received. ^1H NMR spectra were recorded on an Etf-60 MHz Anasazi NMR, which was acquired the following semester (Fall 2021). Chemical shifts are given in δ values (ppm) at room temperature and referenced using tetramethylsilane (TMS) and $CDCl_3$ solvent peaks. The NMR data processing software used is MNova 11.0.

Solid state IR spectra were recorded on an Agilent Cary 630 FT-IR spectrometer. The solid samples were pressed against the diamond crystal using the attached pressure clamp.

GC-MS spectra were obtained using a Buck Scientific model 910 gas chromatography-mass spectrometer. All measurements were repeated at least five times to ensure reproducibility.

Experimental conditions include 5 mol% of copper catalyst, 1 mmol of the azide, and 1 mmol of the corresponding alkyne. The general procedure for the neat reactions was to add the liquid reagents to an 8-dram scintillation vial/test tube (no cap) with a magnetic stir bar, then to add the copper solid, and mix until completion. The product was then filtered and rinsed with hexanes. All reactions were monitored by TLC (hexanes:ethyl acetate 2:1) and IR spectroscopy. For reactions using solvent, 1 mmol of benzyl azide and 1 mmol of terminal alkyne were stirred in 3 mL of t-BuOH/water solution in an 8-dram scintillation vial (Díez-Gonzalez, 2006). Sodium ascorbate (10 mol%) and 5 mol% copper catalyst were added sequentially, and the mixture was stirred for 3-4 hours until completion, monitored by TLC (hexanes:ethyl acetate 2:1). The reaction mixture was diluted with 10 mL ice water, followed by the addition of 2 mL of 10 % aqueous ammonia. After stirring for a few more minutes, the solid precipitate was collected with a Buchner funnel and vacuum-dried overnight. The neat and solvent versions of reactions were examined under heated (oil bath at 60 °C) and room temperature conditions. All products were placed under vacuum for at least 24 hours in order to remove volatiles.

Reaction time varied by catalyst and solvent presence. It was observed that for neat reactions, reaction completion was accompanied by solidification of the reaction mixture (see Figure 2 for reaction progression). Solvent reac-
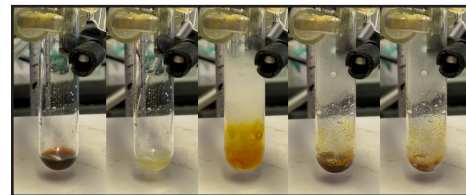

Figure 2. Reaction progress of benzyl azide and phenyl propargyl ether. The liquid starting materials solidified, accompanied by evolution of heat (exothermic reaction).

tions were stirred for 3 hours to ensure completion as no solidification occurs. For all remaining reaction trials, the corresponding neat or solvent procedure was followed regardless of the determined length of reaction from monitoring. The product was then purified and isolated by dissolving the crude product in a small amount of dichloromethane (≤ 1 mL). The product was precipitated from hexanes (ca. 6-8 mL). Suction filtration was conducted to collect the solids. Chromatographic purification was not needed as indicated by the characterization results.

After obtaining the product, characterization tests were run. Thin Layer Chromatography (TLC) was used as an early indicator of the presence of any starting material. The alkyne, the azide, and the product (using dichloromethane to dissolve) were spotted onto the TLC plate and placed in a chamber containing 2:1 hexanes:ethyl acetate. IR spectra of starting materials and products were obtained. As the solid products had sharp melting points, no extraction with an organic solvent–such as dichloromethane–was needed. Gas Chromatography Mass Spectrometry (GC-MS) technique was utilized to confirm the completion of reactions and to detect the presence of the starting materials and product via molecular weight. Melting point and NMR spectroscopy were used to further determine product purity.

Some product proved to precipitate in the wash of the vacuum filtration process. Recollection of the newly precipitated product in the wash was found to be less pure and abundant than the original product collected in the fun-

Comparing Copper Catalysts in the Synthesis of 1,2,3-Triazoles via Click Chemistry
Emma E. Green, Ethan A. Leitschuh, and Jocelyn P. Lanorio

33

nel, and rewashing did not improve recollection.

Typical safety standards and protocols such as wearing a lab coat, gloves, goggles, and using a fume hood were followed. Benzyl azide, phenylacetylene, and phenyl propargyl ether were stored at 8 °C and kept away from intense light to prevent decomposition.

RESULTS AND DISCUSSION

The neat reaction time varied between catalysts. Reactions with $CuSO_4$ and CuI solidified within 10 minutes. The [Cu(IPr)Cl], CuCl, $CuCl_2$ catalyzed reactions were completed in under 2 hours when heated, while at room temperature they took ≥24 hours. Surprisingly, our results indicated that there is no significant difference in the yield and rate of reaction with both Cu(I)- and Cu(II)-catalyzed reactions. This is what led us to run Cu(II)-catalyzed reactions in the absence of sodium ascorbate as control reactions. We found that Cu(II)-catalyzed reactions, even in the absence of sodium ascorbate, ran at similar rates as Cu(I)-catalyzed reactions. This indicates that something else in reaction mixture may be acting as the reducing agent.

The color of the products was commonly light green, rust, tan, or white as seen in Figures 3 and 4. Most resulting materials were fine and powdery, although crystals and clay-like textures were also observed. This variable consistency can be attributed to the speed of addition and ratio of hexanes to CH_2Cl_2 administered during product recrystallization/precipitation. Slowly adding a larger amount of hexanes relative to dichloromethane proved to result in a more powder-like consistency.
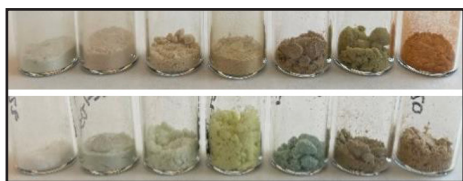
The best catalysts appeared to be $CuSO_4 \bullet 5H_2O$, $CuSO_4$, and CuI (based on all factors). The data showed no differences between Cu(I) and Cu(II) reactions, even without the presence of a reducing agent. One catalyst proved to be much less effective than others based on the amount of product obtained. Reactions utilizing the NHC ligand ([Cu(IPr)Cl]) had percent yields averaging around 20%. This could possibly be attributed to the sterics around the Cu metal center for [Cu(IPr)Cl] (see Figure 1). In addition, the melting points for products from this reaction were lower than expected. For the solvent reactions for product **2**, the melting point was broader than normal, indicating trapped solvent. This explains the high yield for product **2**.

All reactions exhibit moderate to excellent yields of *ca*. 70 - 90% (Table 1). TLC of the isolated product revealed only one spot different from that of the starting material. For reactions with phenylacetylene, the R_f value of **1** was near 0.6. For reactions with phenyl propargyl ether, the R_f value of **2** was at around 0.4-0.5. The melting points varied with reaction conditions, with those using aqueous solvent having lower melting point and wider temperature range. This can be attributed to the difficulty of removing the water solvent. The melting points of **1** and **2** are 120-122 °C and 126-128 °C, respectively.

The products were also characterized by IR spectroscopy. For both reactions, disappearance of the starting materials' triple bonds was observed (Figures

	Product **1**	Product **2**
$CuSO_4 \bullet 5H_2O$	79%	89%
$CuSO_4$ (s)	83%	91%
CuCl	75%	75%
$CuCl_2 \bullet 2H_2O$	87%	82%
CuI	80%	81%
[Cu(IPr)Cl]	18%	19% neat 76% solvent
Control (no catalyst)	0%	0%

Table 1. Percent yield in cycloaddition reactions of products **1** and **2**, based on the highest yields from neat and solvent reactions.

5 and 6). Figure 5 shows the IR spectrum of phenyl propargyl ether. The carbon-carbon triple bonds of phenyl propargyl ether show up at 2100 cm^{-1}. The disappearance of these peaks indicated completion of reaction. The triazole product **1** from phenyl propargyl ether reactions does not have characteristic IR peaks, as the C=N stretching peaks overlap with the C=C peaks.

Figure 6 shows the stacked IR spectra of benzyl azide, phenylacetylene, and product **2**. Benzyl azide has a strong intensity peak at 2160-2120 cm^{-1} attributed to the azide N=N=N stretching. Phenylacetylene has peaks at 2100 cm^{-1} for carbon-carbon triple bonds and 3300 cm^{-1}, characteristic of a terminal alkyne. The IR spectrum of product **2** displays the appearance of more C-H stretching peaks compared to that of the benzyl azide and phenylacetylene starting materials.

GC-MS provided further confirmation of the purity of each reaction run. There is only one component separated by GC with the mass spectrum indicating the product's molecular weight. The GC-MS data indicated that the experimental isotope pattern of the products matches the theoretical isotope patterns obtained from https://www.sisweb.com/mstools/isotope.htm. (Figure 7).

^{1}H NMR spectra revealed that the products are pure. As shown in Figure 8, for product **1**, the aromatic protons show up at 7.53 ppm (singlet), and 7.44-6.76 ppm (multiplet), which integrate for 11 protons. The methylene protons show up at 5.52 ppm for $-CH_2$-O (integral of 2 protons), and 5.19 ppm for $-CH_2$-N (integral of 2 protons). TMS peak is at 0 ppm and $CDCl_3$ peak is at 7.26 ppm.

Purity seems to have a direct correlation to the color of the product. The closer to white, the purer the product appeared to be according to characterization. Products that were green, tan, or rust colored may have retained some copper catalyst. Additional washing with CH_2Cl_2 and hexanes improved the color slightly. Product extraction using a separatory funnel with water and CH_2Cl_2 did not significantly change the
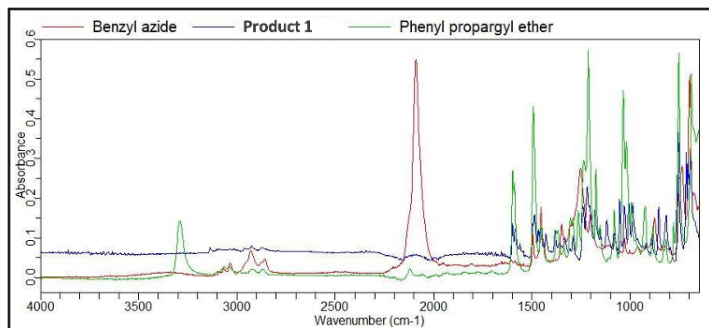

Figures 3 & 4. Various colors and textures of products obtained. Top image is product **1**; bottom image is product **2**.

Comparing Copper Catalysts in the Synthesis of 1,2,3-Triazoles via Click Chemistry
Emma E. Green, Ethan A. Leitschuh, and Jocelyn P. Lanorio

34

Figure 5. Stacked IR spectra of benzyl azide, phenyl propargyl ether, and product **1**.
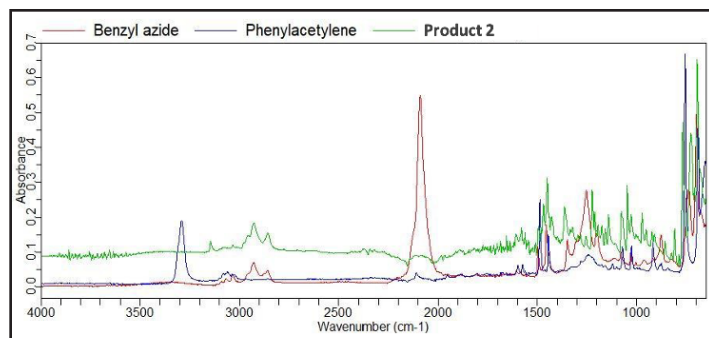

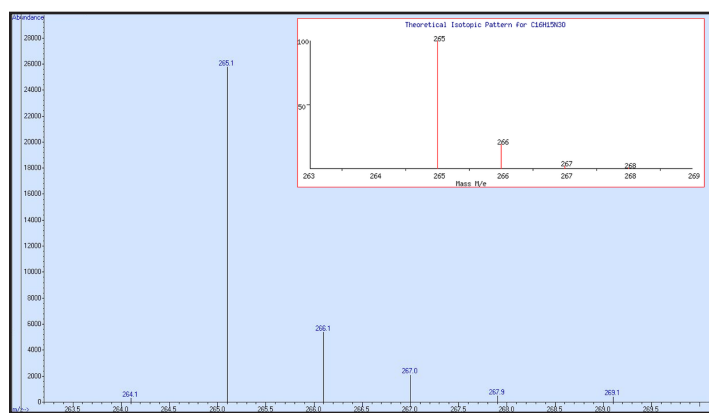**Figure 6.** Stacked IR spectra of benzyl azide, phenylacetylene, and product **2**.

Figure 7. MS spectrum of **1**. Inset shows computer generated spectrum of product **1**.
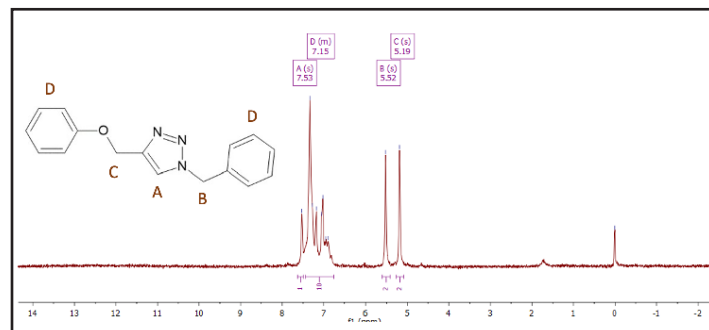

**Figure 8.** ^{1}H NMR spectrum for 1-benzyl-4-(phenoxymethyl)-1H-1,2,3-triazole (product **1**).

appearance of the product.

The texture of the final product is also noteworthy. Products that were fine powders were the most desirable, while clay-like products that were sometimes produced contained trapped solvents. This poor texture occurred most frequently in aqueous reactions. The clay-like products were difficult to load into the melting point tubes and had broader melting ranges. Placing these products under vacuum did not seem to improve the texture a considerable amount.

Although the reactions work in heat and with solvent, it is not necessary to run them under these conditions. Ample pure product is produced from neat, room temperature reactions. Heated reactions yielded slightly more product but did not seem to differ from room temperature reactions in terms of purity. In the case of the catalysts we deemed poor, the heated reactions

were faster than the room temperature reactions. However, for the better catalysts the difference was not large enough to explicitly state that heat application is better. For several reactions, solidification occurred rapidly and exothermically. It is recommended that the reaction container remain open to air to prevent glass shattering.

The catalyst with NHC as a ligand ([Cu(IPr)Cl]) performed poorly with phenyl propargyl ether. This indicates that the sterics around the metal center is important. Its large size may be hindering its ability to interact with the azide and alkyne. As the proposed catalytic cycle indicates (Scheme 4), the copper metal center should be accessible.
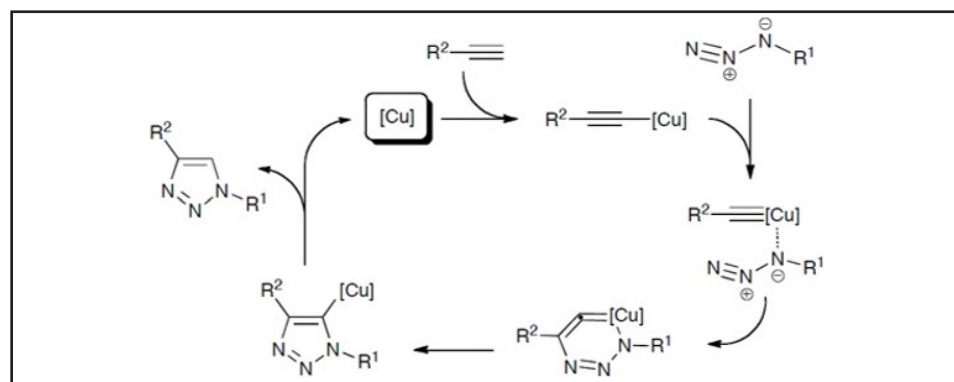
Scheme 4. Early mechanism proposal for copper-catalyzed azide-alkyne Huisgen cycloaddition (Rostovtsev et al., 2002).

Comparing Copper Catalysts in the Synthesis of 1,2,3-Triazoles via Click Chemistry
Emma E. Green, Ethan A. Leitschuh, and Jocelyn P. Lanorio

35

The copper chloride compounds, prior to use, both appeared to have decomposed in their containers due to air exposure. The top layer of powder was scraped away in an attempt to reach better catalyst. We limited air exposure during transfer for all catalysts as a precaution.

Based on the yield and the reaction time, it is suspected that stable anion/leaving groups such as I$^-$ of the CuI complex favor the triazole formation. This is also coinciding with our sterics theory. The anions that performed best were smaller in size. The chloride compounds likely would have been better based on this, if only the catalyst condition had been better.

Control reactions were run for both alkynes. The same procedure for all reactions was followed with the exception of omitting the copper catalyst. Additional time did not yield product, nor did heat. We confidently state that azides and alkynes will not produce product without the addition of a catalyst. This shows that the catalyst is imperative for the reaction to occur.

Future investigations could involve screening more catalysts or exploring more reaction conditions. Sterics of the ligand seem to play a role in the success of these click reactions. For solvent reactions, the solubility of the counter ion may also affect the results. We encourage further testing of Cu(II)-catalyzed reactions in the absence of a reducing agent. Further studies on use of spectator ions with no ability to act as reducing agents are recommended.

ACKNOWLEDGEMENTS

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