



Light-induced copper(I)-catalyzed click chemistry

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ABSTRACT

Light can be used as an activator for the in situ generated copper(I)-catalyzed click reaction between azides and alkynes without adding reducing agents. The accumulation of sufficient concentration of copper(I) throughout the reaction can successfully be achieved by UV irradiation, in the presence of air.

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Light drives many important processes of life, such as photosynthesis, ozone production in the atmosphere, and warming the Earth system.^{1–3} Light-induced chemical reactions involve the absorption of light to create highly reactive excited molecules which can undergo chemical changes. For example, unimolecular reactions, such as ionization, dissociation, and isomerization, and bimolecular reactions involving a second molecule or atom to form a new compound, can be activated by light.

An extensively studied reaction is the copper(I)-catalyzed Huisgen 1,3-dipolar cycloaddition (CuAAC) reaction between azides and terminal alkynes, which is the most prominent example of ‘click’ chemistry, developed by the groups of Sharpless⁴ and Meldal.⁵ Since its extraordinary success under different reaction conditions with highly diverse building blocks, high yields, and with no (or conveniently separated) by-products, the click reaction has been applied widely in organic chemistry,^{5–7} supramolecular chemistry,^{8,9} drug discovery,¹⁰ bioconjugation^{11,12}, and materials science.^{13–18}

The required Cu(I) catalyst for the click reaction can be generated by several approaches including: (1) in situ reduction of Cu(II) to Cu(I) by various reducing agents,³ (2) addition of Cu(I) salts² directly or as carbene complexes,¹⁹ (3) electrochemically generated Cu(I),²⁰ (4) Cu(I) on immobile phases,^{21,22} and (5) copper-containing nanoparticles.^{23,24} Although, in situ generated Cu(I) using a reducing agent is generally used in click reactions,^{25,26} it has some drawbacks, especially in bioconjugation applications. For example, sodium ascorbate and derivatives, which are the most commonly

used reducing agents, can react with protein side chains²⁷ and lead to degradation of DNA.²⁸

Many Cu(II) complexes are known to be light-sensitive and undergo redox reactions during UV-irradiation.²⁹ Previous spectroscopic studies on Cu(II) complexes have shown that the strong absorption at 300 nm corresponding to the ligand-to-metal-charge transfer transition is responsible for the photoreduction of Cu(II) to Cu(I).³⁰ Recently, our group has developed the in situ generation of Cu(I) from a Cu(II) complex with light, which can be used as an activator in atom transfer radical polymerization (ATRP) without using any reducing agent at room temperature.^{31,32} A natural extension would be to consider employing the same catalytic complex for the CuAAC click chemistry. As shown later, the process offers the possibility to adjust the copper concentration of the system and consequently, coupling efficiency by choosing appropriate light intensities. The goal of this study was to use light as an activator for the CuAAC click reaction and to investigate its scope.

We selected benzyl azide and phenyl acetylene as simple model click components so as to eliminate the substituent effect on the click reaction. The reactions were performed in the presence of air and monitored by means of ¹H NMR spectroscopy. Conversions were determined by integration of a particular signal from a proton in one of the starting molecules and the corresponding proton in the product (e.g., protons **a** and **d**, Fig. 1).

The photo-induced click reaction followed second order kinetics with respect to the different catalyst concentration in agreement with the conventional click reaction.^{33,34} The reaction slows significantly as the relative concentration of catalyst decreases. Notably, the coupling yield with an azide/Cu(II)Cl₂ ratio of 1:0.05 was dramatically lower than those of 1:0.1 and 1:0.2 (Fig. 2). This behavior

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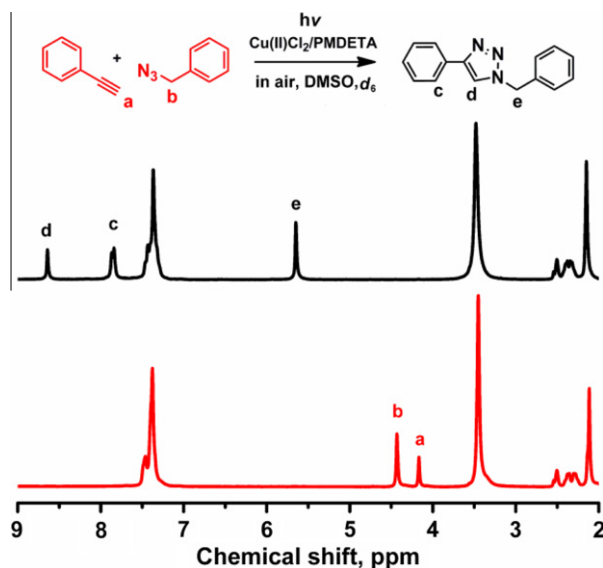


Figure 1. Hydrogen atoms used for ^1H NMR analysis. ^1H NMR spectra of the benzyl azide and phenyl acetylene mixture and the click product after 3 h UV irradiation in $\text{DMSO}-d_6$ using $\text{Cu}(\text{II})\text{Cl}_2/\text{PMDETA}$ as catalyst.

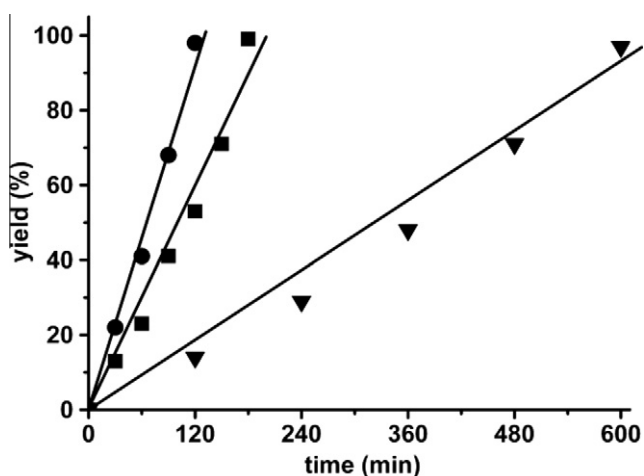


Figure 2. Light-induced click coupling reaction of benzyl azide and phenyl acetylene as a function of time using $\text{Cu}(\text{II})\text{Cl}_2/\text{PMDETA}$ as the catalyst system. Alkyne/azide ratio: 1; azide/ $\text{Cu}(\text{II})\text{Cl}_2$ ratio: 1:0.2 (●), 1:0.1 (■), and 1:0.05 (▼). Yield determined by ^1H NMR spectroscopy.

is due to the fact that a longer time was needed for the formation of sufficient catalyst concentration by light.

Table 1 lists the yields of the click reactions of benzyl azide with various alkynes catalyzed by the in situ generated $\text{Cu}(\text{I})$ catalyst from higher oxidation state species, without using any reducing agent at room temperature. As can be seen, no significant triazole formation occurred in the absence of the $\text{Cu}(\text{II})$ catalyst or in the dark (entries 1 and 2). With in situ generated $\text{Cu}(\text{I})$, benzyl azide reacted with phenyl acetylene and also with other simple alkynes, such as propargyl acrylate, propargyl alcohol, and propargyl bromide to give the corresponding triazoles in excellent yields (entries 3–6).

Care needs to be taken in interpreting these results as the reaction may be affected by side reactions with certain reactants. For example, propargyl alcohol can itself reduce $\text{Cu}(\text{II})$ to $\text{Cu}(\text{I})$. Thus the light-induced click reaction would be accelerated with the contribution of this additional redox process (entry 5).^{32,35} In contrast, prolonged irradiation times are needed for the click reaction using

Table 1
Light-induced CuAAC reaction^a between benzyl azide and various alkynes

Entry	Alkyne	Light	Catalyst	Time (min)	Yield ^b (%)
1		+	–	180	<1
2		–	+	180	<1
3		+	+	180	99
4		+	+	180	96
5		+	+	120	93
6		+	+	600	95

^a All reactions were carried out under irradiation at 350 nm with a light intensity of 3.0 mW cm^{-2} at room temperature in $\text{DMSO}-d_6$. The initial concentrations of azide, alkyne, $\text{Cu}(\text{II})\text{Cl}_2$ and PMDETA were 0.2 mM.

^b Yield determined by ^1H NMR spectroscopy.

propargyl bromide (entry 6). In this case, activation of bromide with the copper catalyst resulted in the concomitant formation of a 5-bromo-substituted triazole.³³

In summary, the photochemical protocol described here represents an efficient and simple method to catalyze the CuAAC reaction between azides and alkynes without the need for reducing agents. Thus, the problems associated with the use of reducing agents in click reactions, particularly in bioconjugation applications can be overcome. As stated previously, the oxidized products of certain reducing agents are potentially reactive toward biomacromolecules. It was also demonstrated that the light-induced CuAAC reaction is influenced by a number of parameters, including copper concentration and the structure of the azide and alkyne. The accumulation of a sufficient concentration of $\text{Cu}(\text{I})$ throughout the reaction can be achieved successfully with light in the presence of air. This synthetic approach opens new pathways for the direct fabrication of photo-patterned, imprinted nanostructures, and bioconjugation applications. Further studies in this direction are underway.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.10.166.

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