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Visible-Light-Mediated Click Chemistry for Highly Regioselective Azide-Alkyne Cycloaddition *via* Photoredox Electron-Transfer Strategy

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Dedicated to the 100th anniversary of the School of Chemistry and Chemical Engineering, Nanjing University

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Abstract: "Click" chemistry is focused on the development of highly selective reactions utilizing simple precursors for the exquisite synthesis of molecules. Undisputedly, the Cu(I)-catalyzed azidealkyne cycloaddition (CuAAC) is one of the most valuable examples of click chemistry, but there are still some limitations as needing additional reducing agents and ligands as well as the toxicity of copper in cell or body. Here, we demonstrate a novel strategy of photoredox electron-transfer radical cation pattern for AAC reaction instead of traditional metal-catalyzed coordination process. This newlydeveloped photocatalyzed azide-alkyne cycloaddition (PcAAC) could be performed in mild conditions of room temperature, air and visible light with good functional group tolerance, excellent atom economy, high yield up to 99%, and absolute regioselectivity, affording variety of 1,4-disubstituted 1,2,3-triazole derivatives including bioactive molecules and pharmaceuticals. The use of a recyclable photocatalyst, solar energy and water makes this photocatalytic system sustainable and environmentally friendly. Moreover, the metal-free photocatalyzed AAC reaction with excellent regioselectivity was also implemented for the first time, representing an important development for click chemistry, which should find versatile applications in organic synthesis, chemical biology and materials science.

Introduction

Inventing new chemical reactions to promote the development of organic synthesis chemistry is a long-standing passion of chemists. Click chemistry as one of the most powerful paradigms in organic synthesis, drug chemistry, materials and biology science, have attracted an enormous amount of interest over the past decade.^[1] The term "click" chemistry proposed in 2001 by Sharpless *et al*, is addressing a set of powerful, highly reliable, and selective reactions for the rapid and exquisite synthesis of molecules. The required process is featured of high efficiency, excellent atom economy, readily available starting materials, mild reaction conditions and easy purification or isolation. Several reactions have been identified as good candidates for click chemistry,^[2] but without doubt the Cu(I)-catalyzed azide–alkyne cycloaddition (CuAAC) leading to 1,4-disubstituted 1,2,3-triazoles

has been established as one of the most useful and valuable examples of click chemistry.^{[2a,2b]}

Triazoles are not only the important structural motifs in biologically active compounds (Figure 1a),^[3] but also widely applied in a broad range of disciplines including biomolecular ligation, chemical sensors, supramolecular and polymeric materials.^[4] A pioneer work for the triazole synthesis is a thermal 1.3-diploar cycloaddition between azides and alkynes (Fig 1b), which was investigated by Huisgen in the 1960s.^[5] Due to the high activation barrier, the reaction yields are generally low and the regioselectivity is poor with a mixture of regioisomeric 1,4- and 1,5-disubstituted 1,2,3-triazoles. Ever since the groups of Meldal and Sharpless independently reported their pioneering works on CuAAC reaction for 1,4-disubstituted-1,2,3-triazole the regioisomer with excellent regioselectivity and high yields (Fig. 1b), which represents a powerful tool for preparing this class of heterocycles, the development and application of this reaction received enormous attention.^[6] In light of this, besides copper, click reactions involving other metals for AAC reaction have also been developed in full swing, including ruthenium (RuAAC),^[7] zinc (ZnAAC),^[8] silver (AgAAC),^[9] gold (AuAAC)^[10] and Raney-Ni (RaneyNiAAC)^[11] catalyzed AAC reactions.

As is known, the metal-catalyzed AAC reactions usually involve the formation of $\pi\text{-alkynyl}$ complex with metal at first. The next step is the complexation of the azide by metal of the π coordinated triple bond. After cyclization produces the metallacycle and then reductive elimination affords the respective 1,4-disubstituted 1,2,3-triazole (Fig. 1b). However, in this transformation, the metal acetylide complex and the intermediate metallacycle would lead some side reactions, such as oxidative coupling for formation of diacetylene, bistriazole and 5-alkynyl triazole.^[12] Additionally, most of these click reaction processes have their own necessities such as additional suitable bases, reducing agents like sodium ascorbate, different solvents, harsh reaction conditions, modified substrates, and catalysts.[13] Besides, due to the toxicity of copper in cell or body, the trials for achieving 'copper-free' click chemistry are in progress, which is highly attractive to biological or biomedical researchers.[14] Therefore, the development of efficient, selective, green, and sustainable method for triazole synthesis has always been a greatly significant work.

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Figure 1. Structures of 1,4-disubstituted 1,2,3-triazoles and their synthetic strategies. [a] Bioactive molecules and pharmaceuticals based on 1,4-triazole core; [b] The reported synthetic methods for 1,4-trizole and the mechanism for traditional metal-catalyzed AAC reaction; [c] Our designed strategy for AAC reaction through photoredox electron-transfer cyclization and its advantages and features, as well as the proposed mechanism.

In recent years, visible-light-induced photoredox catalysis for the synthesis of high value added chemicals has been a hot topic of research for chemists due to the inherent green character of light, high reactivity, and good functional group tolerance. Several recent studies have revealed that the some unsaturated compounds, including alkene, alkyne and imine, et al, could undergo a single electron transfer (SET) process to afford the corresponding radical, radical cation or radical anion by an oxidative or reductive quenching cycle of the excited state of the photocatalyst (PC).^[15] Inspired by this, we speculate that this AAC reaction would be realized through a photoredox electron-transfer radical strategy instead of traditional metal-catalyzed coordination with alkynes. The proposed mechanism is described in Fig 1c. A single electron-oxidation of alkyne generates radical cation A in the presence of the excited state of the PC.^[16] The intermediate A combines with the azide to form the intermediate B, which undergoes cycloaddition to afford intermediate C. Finally, a single-electron reduction of C by PC⁻ provides the desired 1,4disubstituted 1,2,3-triazole with the concurrent regeneration of the PC for the next cycle. Therefore, a new pathway employing the visible-light-induced AAC reaction via radical strategy is brought up.

Here, we present a visible light-mediated click reaction of azide and alkyne: the photocatalyzed AAC (PcAAC) reaction for formation of 1,4-disubstituted 1,2,3-triazole via photoredox electron-transfer strategy with excellent efficiency and regioselectivity, which is an important complementarity and development of click chemistry.

Results and Discussion

Firstly, we investigated the reaction of benzyl azide (1a) with phenylacetylene (2a) in the presence of various photocatalysts with very simple conditions under room temperature (r.t.), air and visible light irradiation. From Table 1 it can be found that the widelv used photocatalysts of $Ru(bpy)_{3}Cl_{2}GH_{2}O$, (dfppy)₂Ir(dtbpy)PF₆, Ir(ppy)₃, FIrpic and EosinY were explored for this reaction (Table 1, entries 1-7, the structures of photocatalysts are supplied in SI). Fortunately, the photocatalysts of (piq)₂Ir(acac) or TPPT-CI do indeed catalyze the formation of 1,4disubstituted 1,2,3-triazoles, and the resulting reaction product was then analyzed by NMR and XRD, illustrating absolutely regioselective 1, 4-triazole, without any 1,5-triazole isomer. Though the reaction efficiency and yield of this photocatalyzed click cycloaddition are low, the results confirm our hypothesis that the AAC reaction could be realized via a photoredox electrontransfer radical strategy with excellent regioselectivity.

Inspired by this, the further investigation of solvents effect was conducted, and the results demonstrated that DCM was the optimal choice with an enhanced yield of 83% (EtOH: 26%, Acetone: 75%, EA: 40%, THF: trace, Toluene: 62%) (Table 1, entries 8-13). When the reaction was performed under blue LED, the yield became lower due to the slight degradation of azide under high irradiation energy (Table 1, entry 14). Furthermore, with the increase of reaction time, the yield could be further improved to 98% (Table 1, entry 15). The control experiments demonstrated that no product was observed without photocatalyst

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or light (in the dark), thus supporting our proposed mechanism (Table 1, entries 16, 17). Besides, a radical inhibition experiment with 2 equiv of DMPO or BHT entirely stopped the reaction, therefore suggesting a radical pathway (Table 1, entries 18, 19). The optimization results demonstrate this PcAAC reaction can be performed under air, r.t. and visible light irradiation with high efficiency and absolute regioselectivity.



Entry	Catalyst	Solvent	Time/Atmosphere	Yield ^[b]
1	Ru(bpy) ₃ Cl ₂ 6H ₂ O	DMF	4h/r.t., Air, White LED	trace
2	(dfppy)₂Ir(dtbpy)PF ₆	DMF	4h/r.t., Air, White LED	NR
3	Ir(ppy) ₃	DMF	4h/r.t., Air, White LED	NR
4	(piq)₂lr(acac)	DMF	4h/r.t., Air, White LED	20%
5	FIrpic	DMF	4h/r.t., Air, White LED	trace
6	EosinY	DMF	4h/r.t., Air, White LED	NR
7	TPPT-CI	DMF	4h/r.t., Air, White LED	11%
8	(piq) ₂ Ir(acac)	EtOH	4h/r.t., Air, White LED	26%
9	(piq) ₂ Ir(acac)	Acetone	4h/r.t., Air, White LED	75%
10	(piq) ₂ Ir(acac)	EA	4h/r.t., Air, White LED	40%
11	(piq) ₂ Ir(acac)	DCM	4h/r.t., Air, White LED	83%
12	(piq) ₂ Ir(acac)	THF	4h/r.t., Air, White LED	trace
13	(piq) ₂ Ir(acac)	toluene	4h/r.t., Air, White LED	62%
14	(piq) ₂ Ir(acac)	DCM	4h/r.t., Air, Blue LED	70%
15	(piq) ₂ Ir(acac)	DCM	6h/r.t., Air, White LED	98%
16	(piq) ₂ Ir(acac)	DCM	6h/r.t., Air, in dark	trace
17	-	DCM	6h/r.t., Air, White LED	NR
18 ^[c]	(piq) ₂ Ir(acac)	DCM	6h/r.t., Air, White LED	NR
19 ^[d]	(piq)₂Ir(acac)	DCM	6h/r.t., Air, White LED	NR

[a] Reaction condition: benzyl azide (**1a**) (0.2 mmol), phenylacetylene (**2a**) (0.2 mmol), photocatalyst (5 mol%), solvent (2.0 mL), under an ambient atmosphere and irradiation (26 W white LED or blue LED). [b] Isolated yield. [c] With DMPO (5,5-Dimethyl-1-pyrroline-N-oxide). [d] With BHT (butylated hydroxytoluene).

With the optimized reaction conditions, the substrate scope and generality of the method were investigated and the products were summarized in Fig.2. First, the scope of the reaction was explored with respect to the azide component, and the reactions of various azides produced the corresponding 1,4-disubstituted 1,2,3-triazoles in moderate to excellent isolated yields (53–99%) with excellent regioselectivity. Various functional groups of azide, including halogens (fluorine and bromine) (**3c**, **3l**), trifluoromethyl (**3d**), hydroxyl (**3m**, **3r**), ester (**3f**, **3n**, **3q**), and ketone (**3o**) as well as heterocycle moieties (thiophene and quinoline) (**3g**, **3h**), were compatible with the reaction conditions. Notably, the borate moiety (**3e**) remained intact during the photocatalyzed process, which could be employed for further functionalization.

For the scope of organic alkyne partner, a variety of aromatic and aliphatic alkynes with diverse functional groups, including halogens (4a-4d), borate (4g), ether (4f, 4l), amide (4m, 4n, 4p), BOC (4q), were employed to react with 1a, giving the corresponding products with excellent yields and regioselectivity. Interestingly, the PcAAC reaction was also very efficient for internal alkyne, affording **4r** in 60% yield. In addition, singlecrystal X-ray crystallographic analyses determined the structures of the 1,4-disubstituted 1,2,3-triazoles **3f** and **4l**.

To expand the versatility of the PcAAC, this reaction was also explored to bioactive molecules and pharmaceuticals. 1,4-Triazole hybrids modified with coumarin (5a, 5b),^[17] acridinone (5c),^[18] indole (5),^[19] oxazolinone (5e)^[20] and amino acid (5f)^[21] structures possess promising anti-bacterial, anti-cancer and antiviral activity, were synthesized smoothly with moderate to excellent yields of 65~98% and absolute regioselectivity. Furthermore, glucal-derived triazoles are important in carbohydrate-based biochemistry and organic synthesis.[22] Glucosidase inhibitor derivatives featured of anti-bacterial activity could be obtained with high efficiency using this photocatalyzed click pattern (5g, 5h, 5i). Clodinafop-propargyl with herbicidal activity was employed to react with 1a, generating 5j with 80% vield.^[23] This methodology was also applied in the derivatization of Erlotinib (5k), which is often used for molecular targeted therapy. As observed in almost all cases, the PcAAC reaction showed excellent selectivity, conversions and yields, which represents an important finding to prepare 1,4-substituted 1,2,3triazoles without the use of copper.^[24]

In addition, to illustrate the practicability of reaction protocol, the PcAAC reaction could be scaled up to a 1 g of 0.5 mol with a satisfying yield of 88% (Fig. 3a). The recycling of the photocatalyst was also evaluated and the results demonstrate the photocatalyst is air- and moisture-tolerant and can be readily recovered after use and reused several times. Fig. 3b showed that the photocatalyst retains its own catalytic activity during the continuous recycling experiments (4 cycles) with considerable selectivity and efficiency.



Figure 3. A graphical guide to the PcAAC reaction and recycling experiment. [a] Equipment and TLC analysis of large-scale reaction: azides (0.5 mol), alkyne (0.5 mol), photocatalyst (3 mol%), DCM (25 mL), r.t., air, 6 h and white LED irradiation. [b] The photocatalyst could be reused several times with the corresponding yields of 96% for cycle 1, 90% for cycle 2, 83% for cycle 3, 75% for cycle 4.

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Figure 2. Scope of PcAAC reaction. Standard reaction conditions: azides (0.2 mmol), alkyne (0.2 mmol), photocatalyst (5 mol%), DCM (2.0 mL), r.t., air, 6-12 h and 26W white LED irradiation.

The development of solar synthesis for organic photochemistry is a greatly significant event^[25] because sunlight is effectively an inexhaustible energy source. In light of this, the photocatalyzed click reaction was also performed in the sunlight. Satisfyingly, this solar-click pattern achieved excellent efficiency and regioselectivity in the air even without stirring (Fig. 4a). We also employed our optimized solar-click reaction process for the synthesis at the one gram scale of one triazole-based anti-cancer activity pharmaceutical **5c**, resulted in good yield of 71% (Fig. 4b).

The click chemistry is widely used in bioorthogonal reaction under aqueous conditions for labelling of biomolecules inside living cells and even in animals.^[26] Therefore, we employed water or phosphate buffer saline (PBS) as the solvent for the developed PcAAC reaction, and the results indicate the feasibility of aqueous-based PcAAC reaction with moderate yield of ~40% (Fig. 4c), which would have important and potential applications for chemical biology. Particularly, organic chemists have attempted to remove the toxic copper catalyst from the representative click reaction CuAAC.⁴⁵⁻⁴⁷ Therefore, the preliminary attempt for screening metal-free AAC reaction was also conducted by us, and

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1,4-disubstituted 1,2,3-triazole the corresponding was successfully obtained with excellent regioselectivity by using TPPT-Cl as the photocatalyst with visible light irradiation under an ambient atmosphere for 12 h, despite of the medium yield. Several substrates with different functional groups were employed for this metal-free AAC reaction, generating various 1,4-disubstituted 1,2,3-triazoles with excellent regioselectivity, which well proves the universality and feasibility of it (Fig. 4c). This is the first time for implement of regioselective AAC reaction by metal-free photoredox electron-transfer strategy. Our trials resulted in 'copper-free' click chemistry by developing metal-free PcAAC reaction, which is highly attractive to biological or biomedical researchers.



Figure 4. A graphical guide to solar-click pattern of PcAAC reaction. [a] Five examples for solar-catalyzed AAC reaction (azides (0.2 mmol), alkyne (0.2 mmol), photocatalyst (5 mol%)). [b] Large-scale solar-click reaction for synthesis of anti-cancer activity pharmaceutical. [c] Extension of PcAAC reaction including PcAAC in aueous phase and metal-free PcAAC. The reaction conditions: azides (0.2 mmol), alkyne (0.2 mmol), photocatalyst (5 mol%), H₂O or phosphate buffer solution (PBS) or DCM (2.0 mL), r.t., air, 12 h and white LED irradiation.

Conclusion

In summary, we devised a highly efficient method for regioselective azide-alkyne cycloaddition under photocatalytic conditions by using photoredox electron-transfer strategy. The alkenyl radical cation formed by photocatalyst could rapidly ligate with azide component to generate 1,4-disubstituted 1,2,3-triazole with excellent regioelectivity. The new reaction is air and moisture-tolerant, and the photocatalyst can be readily recovered after use and reused several times, which are applied to a broad range of substrates with high efficiency of yield up to 99%, including the expedient synthesis of various biaocative molecules and pharmaceuticals. Furthermore, the solar-click pattern also achieved excellent efficiency and regioselectivity in the air even without stirring. The metal-free photocatalyzed AAC concept was also put forward first time, and the preliminary attempt indicate the feasibility of it. The novel design strategy for AAC reaction by visible light catalysis via photoredox electron-transfer process would promote the development of click chemistry and enrich the click family, which should find application in organic synthesis, medicinal chemistry, chemical biology and materials science.

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Keywords: click chemistry • photoredox reaction • photocatalysis • cycloaddition • regioselectivity

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Photocatalyzed Azide-Alkyne Cycloaddition (PcAAC)
$R^{1}-N_{3}$ + Photocatalyzed Click Chemistry $R^{1}-N_{N}N_{P^{2}}$
photoredox electron-transfer cyclization
● Excellent regioselectivity ● High yield up to 99% ●100% Atom economy
● Good functional group tolerance ● Solar catalysis ● Practical, Scalable

The novel design strategy for azide-alkyne cycloaddition reaction by visible light catalysis via photoredox electron-transfer process was brought up for first time, representing an important development for click chemistry.