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Visible-light-mediated C2-amination of thiophenes by using DDQ as organophotocatalyst

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In this work, a direct C-H activation of thiophenes was presented via oxidation pathway under visible-light irradiation, in which the thiophene radical cation serves as the key intermediate. Various thiophenes and azoles could be transformed into the corresponding amination products well, and H_2O was the only byproduct which is environmentally benign. Our results showed tert-butyl nitrite (TBN) served the electron transfer mediator and O_2 as the terminal oxidant to regenerate photocatalyst DDQ and revive the photocatalytic cycle.

The functionalized thiophenes, vital heterocyclic compounds, have long been privileged structures in the natural products, pharmaceuticals and conjugated polymers.¹ Moreover, 2aminothiophene and its derivatives are always employed as the building blocks in bioactive compounds.² Therefore, the sustainable preparation of these valuable 2-aminothiophenes is important for organic synthesis. As we know, the transition-metal catalyzed cross coupling of aryl halides has served as a powerful tool for constructing C-N bonds.3 The transition-metal catalyzed (Pd, Cu etc) amination of halothiophenes have been developed to construct 2aminothiophenes (Scheme 1A).⁴ Nevertheless, directly using simple arene (Ar-H) to replace aryl halide (Ar-X) is undoubtedly the most step- and atom-economical method, representing an ideal route for C-N bond formation.⁵ Along with this direct strategy, the synthesis of 2-aminothiophene partners have been achieved via direct C-H amination of thiophenes (Scheme 1B).⁶ However, these strategies required high temperatures and stoichiometric quantities of oxidant, which caused the high consumption of materiel and energy. Therefore, developing an environmentally friendly and metal-free catalytic system was highly desired, especially when removal of metal traces is of real concern to the pharmaceutical industry.

Over these years, the photocatalysis mediated by visible light has been widely developed, serving as a mild and powerful tool for bond formations.⁷ The ruthenium and iridium polypyridyl complexes have demonstrated great versatility in photocatalysis and often used in organic synthesis. Different from transition-metal promoted photocatalysis, the organic photoredox catalysis, in which several organic molecules could be used as the photocatalysts, has presented a new way for photocatalysis and received wide attention.⁸ Recent advances defined that photocatalysis could provide a mild and general route for C-N bond formation,⁹ especially the development of oxidative C-H/N-H cross coupling reactions.¹⁰ The 2,3-dichloro-5,6-dicyano-p-benzoquinone (DDQ) is commercially available and cheap, and be known as a powerful organic oxidizing reagent for a number of organic transformations¹¹ relying on its one-electron reduction potential of DDQ ($E_{red} = 0.51$ V vs SCE). What's more, DDQ can also be excited by visible light to triplet state with a high oxidation potential ($E_{red} = 3.18$ V vs SCE), which shows the great

A. Transition-metal (Pd or Cu) catalyzed Amination of Halothiophene

B. Copper-Catalyzed Amination of Thiophene

X= CI, Br, I

C. This work: Visible-Light-Mediated C2-Amination of Thiophene



Scheme 1. Strategies for C2-Amination of Thiophene. (A) Transition-metal (Pd or Cu) catalyzed amination of halothiophene. (B) Copper-catalyzed amination of thiophene. (C) This work: visible-light-mediated C2-amination of thiophene.

capacity of DDQ to participate in organic transformation as a photocatalyst.¹² In recent years, Fukuzumi and co-workers have pioneered the development of oxidative C-O bond formation to

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phenol derivatives from benzene derivatives by using DDQ as a photocatalyst.^{12c} The development of C-H amination of thiophenes mediated by triplet DDQ catalyst is important and highly desirable (Scheme 1C).

The C-H activation of thiophene was usually with the assistance of transition-metal.¹³ In this work, we presented a new route for C-H activation of thiophene via oxidation pathway. Our idea on C-H amination of thiophene was described in Scheme 2. The thiophene derivatives 1 can be initially oxidized by the excited-state of photocatalyst ³DDQ^{*} to generate the radical cation intermediate I. Subsequently, the addition of N-containing nucleophile would furnish a carbon radical intermediate II, which is further oxidized by DDQ⁻ to form the C2-functionalization product 3 and DDQH₂. And the regioselective was controlled by radical cation intermediate I, which the radical located on C2 position DDQH₂ is known to be oxidized by reaction with TBN via NO₂ to generate DDQ.¹⁴ Hu and co-workers demonstrated a series work that the TBN can be regenrated by O2.15 This method we herein reported would provide a new strategy for direct oxidative C-H/C-N coupling of thiophene with DDQ as a photocatalyst.



Scheme 2. Our Strategy for Visible-Light-Mediated C2-Amination of Thiophenes using DDQ as Organophotocatalyst.

With above hypothesis, we initially chose thiophene and pyrazole derivatives as the substrates to synthesize valuable compounds, by using DDQ as a photocatalyst, tert-butyl nitrite (TBN) as electron mediator and oxygen as terminal oxidant under visible-light irradiation. In a typical reaction mixture for the photocatalytic reaction, 1 mmol of the thiophene (1a), 0.5 mmol of the 4-chloro-1H-pyrazole (2a), 15 mol % of DDQ and 15 mol % of TBN, in 3 mL 1,2-dichloroethane (DCE) with an air-balloon were used to give the desired product 3a in 82% yield, which was under the irradiation of blue LEDs light for 4 h (Table 1, Entry 1). When choosing other quinones as the photocatalyst, such as benzoquinone and tetrachloro-p-benzoquinone, the yields of 3a were much lower than model reaction (Table 1, Entry 2-3). Neither increasing nor decreasing the amount of catalyst could improve the yield (Table 1, Entry 4-5). Moreover, when oxygen instead of air as a reaction gas atmosphere was used, the transformation gave a slight decrease in the yield (Table 1, Entry 6). Control experiments indicated no desired reaction would be observed without the photocatalyst DDQ or light (Table 1, Entry 7-8). Only a spot of the product could be detected in the absence of catalyst TBN, because the photocatalyst couldn't be recycled (Table 1, Entry 9).

	CI 15 m	ol % DDQ, ol %TBN, air	CI
SH	H ^N N blue I	mL DCE _EDs, r.t., 4 h	S' N_/
1a	2a		3a
Entry	Variation from Standard Conditions ^a		GC-Yield $(\%)^{[b]}$
1	standard conditions		82
2	benzoquinone instead of DDQ		trace
3	p-chloranil instead of DDQ		11
4	10 mol% DDQ, 10 mol%TBN were used		68
5	20 mol% DDQ, 20 mol%TBN were used		80
6	O2 instead of air		77
7	no light		N.D. ^[c]
8	no photosensitizer DDQ		N.D.
9	no catalyst TBN		13

[a] Standard conditions: reactions were performed with 1a (1.0 mmol), 2a (0.5 mmol), DDQ (15 mol %, 0.075 mmol), and TBN (15 mol %, 0.075mmol) in 3 mL 1,2-dichloroethane irradiated by blue LEDs for 4 h. [b] GC yields are determined by using biphenyl as an internal standard. [c] N.D. implies no product was detected by GC-MS and GC

To probe the versatility of this catalytic system, the scope and limitation of thiophenes were evaluated. As shown in Table 2, thiophenes containing an electron-donating group such as methyl, dioxolan or trimethylsiyl reacted smoothly under the optimized conditions and gave the corresponding products (3b, 3c, 3e and 3f) with good efficiency.

Table 2. Substrate Scope of Thiophenes^a



^a Standard conditions: reactions were performed with 1 (1.0 mmol), 2a (0.5 mmol), DDQ (15 mol %, 0.075mmol), and TBN (15 mol %, 0.075mmol) in 3 mL 1,2-dichloroethane was irradiated by blue LED for 4 h. Unless otherwise

Table 1. Optimization of Reaction Conditions^a

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noted, isolated yields are shown. Regioselectivity was determined by NMR. ^bThe yields were determined by GC with the biphenyl of an internal standard.

However, the oxidation side reaction of ethyl group resulted in a slight decrease in yield of **3d**. Furthermore, with no effect on halogen group, the C2 or C3 position amination of halide substituted thiophenes (**3g-3i**) could be reacted well and provided a handle for further synthetic manipulations. The bromo substituent at the C2 position of the thiophenes gave the lower yields compared with the chloro substituent on thiophene ring (**3h**). Mono- and di- halide substituted thiophenes were both suitable in this reaction system (**3j-3l**). Moreover, it should be mentioned that two different functional groups on thiophenes were also performed well, with moderate to good levels of yields (**3m-3n**).

Subsequently, various nitrogen sources were also explored for this amination reaction (Table 3). Multifarious benzotriazole could be tolerated in this transformation with moderate yields, including different electron-withdrawing or electron-donating substituted benzotriazoles (4a-4i). When substituted benzotriazoles were used as substrates, the product obtained was a mixture of two isomers. Benzotriazole and 5-methyl-benzotriazole could give the desired product in 58% and 45% yields (4a and 4b). Halide substituents on the aromatic ring were well tolerated in this transformation and afforded the moderate yields (4c-4e). Notably, benzotriazoles bearing the strong electron-deficient substituents such as trifluoromethyl or ester were also suitable in the reaction system (4f-4g)

Table 3. Scope of Nitrogen Source Coupling Partner^a



^{*a*} Standard conditions: reactions were performed with **1** (1.0 mmol), **2** (0.5 mmol), DDQ (15 mol %, 0.075mmol), and TBN (15 mol %, 0.075mmol) in 3

mL 1,2-dichloroethane was irradiated by blue LED for 4 h. Unless otherwise noted, isolated yields are shown. Regioselectivity was determined by NMR.

The presence of α -substitution on the aromatic ring was welltolerated (**4h**). As expected, di-methyl substituted benzotriazole is furnishing the expected adducts with medium yield (**4i**). We were also pleased to observe that triazole were willing to react, albeit in slightly diminished yield (**4j-4k**). The slight lower yield of some substractes ratio due to the poor reactivity with low conversion. What's more, pyrazols substituted with bromine or nitryl had good reactivities and obtained the desired products in moderated yields (**4l-4m**).

To further explore the utility of this method for constructing C2amination of thiophenes, we tried to expand the reaction to gram scale. A good reaction selectivity and yield could still be obtained (Scheme 3). Obviously, this photocatalysis system had a great advantage over the palladium or copper mediated processes according to the demand for metal-free, atom-economical and sustainable chemistry.



Scheme 3. Gram Scale Reaction

To understand the reaction process of this system, the intermolecular isotope effect experiments were also carried out (Scheme S1). When the following two reactions containing 1m and 1m-D proceeded under the standard conditions for 10 minutes respectively, the products 3ml and 3ml' could be obtained at the ratio of $k_{\rm H}/k_{\rm D} = 1.4$. This result indicated that the C-H bond cleavage of thiophene might not be involved in the rate-determined step of the reaction. The radical-inhibiting experiments indicated that the reaction might be involved a radical process (Scheme S2). Furthermore, on the basis of the control experiments (Scheme S3), we could reach the following conclusion that ground state DDQ couldn't oxidize a substrate, even under high temperatures. And an equivalent DDQ could also achieve this transformation in 60% yield under visible light irradiation. Based on above mechanistic studies, we could conclude that the DDQ served as not only the photocatalyst but also the oxidant in this C-H amination reaction.

In conclusion, we have developed the direct C2-amination of thiophene under visible-light irradiation for the first time. By using a catalytic amount of cheap photocatalyst DDQ, electron mediator TBN and terminal oxidant oxygen, various thiophenes could be selectively transformed into their corresponding amination products in high yields and H_2O is the only byproduct. This strategy could tolerate multiple halogens, facilitating a handle for the further synthetic manipulations. Compared with previous methods, this transformation undergoes smoothly with no use of metal, thus avoids the post treatment process, which is economical and has high efficiency.

4m. 43%

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Notes and references

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