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ARTICLE

Visible-light-induced condensation cyclization to synthesize benzimidazoles using fluorescein as photocatalyst

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A mild strategy for the visible-light-induced for synthesis of benzimidazoles was developed using aromatic aldehydes and *o*-phenylenediamines as the substrates. Using of an organic dye, fluorescein, as an innoxious photocatalyst provided a mild and inexpensive catalytic system to synthesize a series of benzimidazoles in moderate to excellent yields. It was originally applied to this system to obtain benzimidazoles. On top of that, the catalytic system has no need for additional oxidant or metal which was good for the environment.

Introduction

More recently, visible light, as a rich, readily available and renewable clean energy source,[1] has attracted extensive interest in assisting catalytic organic synthesis reaction.[2] Compared with traditional synthetic methods, visible light assisted reactions meet the requirements of mild reaction conditions, simple operation and environmental friendliness.[3] However, most organic molecules cannot absorb visible light, and only the selection of a suitable photocatalyst can promote the reaction. Ruthenium and iridium complexes[4] are the most commonly used photocatalysts in organic reactions such as activation of unactivated C-H bond,[5] direct C-H arylation,[6] aerobic oxidative radical addition[7] or cyclization reaction.[8] Although these complexes have excellent catalytic properties, they are expensive and potentially toxic. Organic dyes, which have shown similar photocatalytic activity in some reactions, have been used as an attractive alternative to transition metal complexes,[9] because they are usually relatively cheap and less toxic. In particular, fluorescein has been very recently employed for radical alkoxycarbonylation of aryldiazonium salts via visible-light catalysis by Wei Guo and co-workers.[10] In addition, Frank Glorius used gold and fluorescein to catalyze intermolecular multicomponent oxyarylation of alkenes.[11] Beyond that, it is rarely used in organic synthesis.

Benzimidazole derivatives exist widely in the molecular skeleton structure of biologically active molecules[12] or as an important structural unit of many medicine of antihypertensive, anticancer, antiviral, psychotropic, antifungal and anti-arrhythmic.[13] Apart from that, they are not only used as important intermediates of organic reactions and ligands of transition metals but also applied in materials science. [14, 15] Hence, it has been particularly attractive to synthesis benzimidazoles and their derivatives, which is precisely based on their great application prospects. Although many strategies have been used to synthesize benzimidazoles till now, the classical method is a condensation reaction between *o*-phenylenediamine and carboxylic acid or its derivatives,[16] nevertheless, the method is obliged to be carried out under spirit of acids conditions or high temperature to ensure the smooth progress of the reaction.[17] In consequence, in order to overcome the above problems, many novel methods of synthesizing them have been reported in recent years. For example, in 2009, Debasree Saha and co-workers used an ionic liquid, [pmim]BF_4, to promote the benzimidazoles synthesis (**Scheme 1a**).[14a] In 2012, Gary A. Molander and his colleagues utilized KHF_2 as an oxidant to form benzimidazoles (**Scheme 1b**).[18] In 2017, J. Chang research group developed the use of molecular iodine to synthesize benzimidazoles under alkaline conditions (**Scheme 1c**).[19] In 2017, David Milstein used cobalt complexes as a catalyst to synthesize benzimidazoles by dehydrogenative coupling of aromatic diamines and alcohols (**Scheme 1d**).[20] In 2018, Palaniswamy Suresh reported Brønsted acidic reduced graphene oxide as a carbocatalyst to synthesize C-2-substituted benzimidazole (**Scheme 1e**).[21] In spite of these methods which are very efficient and satisfying, they also suffer from some restriction in those aspects of temperature, reaction time, catalyst preparation or application and environment. In recent years, some synthetic method of benzimidazole has dominated the development of green catalytic processes to avoid the above problems.[22] For example, in 2015, the Huang group used electrochemical method to synthesize benzimidazole from the alcohol and

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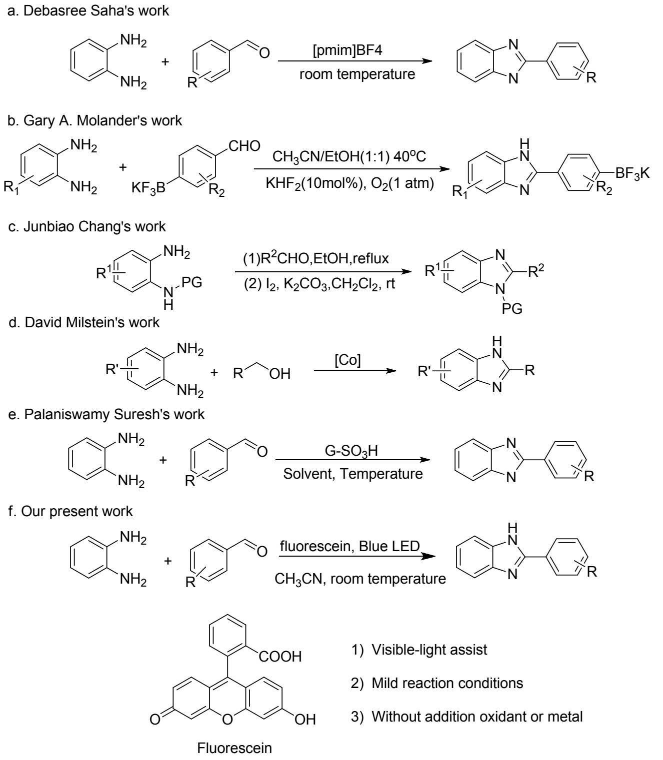
ortho-substituted aniline with a catalytic amount of a Co^{II} salt.[23] In 2017, Sanzhong Luo et al. were able to synthesize benzimidazole from primary amines in high yields under mild conditions with oxygen as the terminal oxidant without any metal promoter.[24]



Scheme 1 Reported works and our work for synthesis of benzimidazoles

Among them, using 1, 2-diaminobenzene and aldehyde as substrates to synthesize benzimidazole is one of the most effective synthesis methods, which received widespread attention. Due to medicinal value of benzimidazoles, it also should be avoided the presence of metals in the catalytic system. Thus it is still very desirable to search for a gentle and applicable green synthesis method.

Therefore, based on the inspiration of literatures and our exploration of visible light assisted catalysis,[25] we envisaged using an organic dye, fluorescein, as photocatalyst to synthesize the benzimidazoles. We are pleased that a novel catalytic system of visible-light assisted is developed, and this method synthesizes benzimidazoles under mild reaction conditions. Herein, we hope to report that this new fluorescein catalyzed using *o*-phenylenediamine and aromatic aldehydes as substrates to obtain benzimidazoles (**Scheme 1f**).

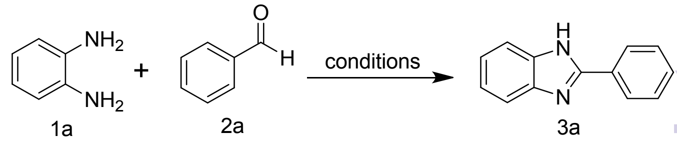
Experimental

In a flat quartz glass jar with magnetic stirrer which contained aromatic aldehyde (0.1 mmol), *o*-phenylenediamine (0.1 mmol), acetonitrile (1.5 mL) and fluorescein (3 mol%). The open-air reaction container was placed under a 10W blue LED lamp and stirred until the end of the reaction which was observed in the Thin-layer chromatography (TLC) analysis. The mixture was extracted three times with ethyl acetate, then the organic layers were combined and dried over anhydrous Na_2SO_4 and the solvent was removed in vacuo. The crude product was purified by silica gel column chromatography to give the target product.

Results and Discussion

In the initial experiment, *o*-phenylenediamine and benzaldehyde were served as the foundational substrates and were irradiated with a blue LED to optimize the reaction conditions (**Table 1**). Primordially, we chose the most common $Ru(bpy)_3$ as a photocatalyst and found that the target product was generated. Taking into account the price issue, we had screened other common organic dyes and found that fluorescein as a photocatalyst exhibited good catalytic effect (**Table 1**, entries 1-4). Subsequently, a bunch of solvents were screened and found to obtain the desired product **3a** in 90% yield in acetonitrile while in other solvents such as methanol, toluene, tetrahydrofuran or DMF with lower yields (**Table 1**, entries 4-8). It is noteworthy that 2 mol% of catalyst loading was found to be the optimum (**Table 1**, entries 4 and 9-10). Then, having tested the different reaction time, 2 hours was the optimum reaction time (**Table 1**, entries 4 and 11-12). Due to most of the cyclization reaction was under alkaline conditions, $Na_2CO_3$was added to the reaction, but had no significant effect on the reaction (**Table 1**, entry 13). Finally, a comparative experiment was conducted, which illustrated both the photocatalyst and the light source were important for the reaction (**Table 1**, entries 14-15).

Table 1 Optimization of the reaction conditions[a]



Entry	Photocatalyst(mol%)	Solvent	Time(h)	Yield(%)[b]
1	$Ru(bpy)_3$ (2mol%)	CH_3CN	2	82
2	Eosin Y (2mol%)	CH_3CN	2	78
3	Rhodmine B (2mol%)	CH_3CN	2	49
4	fluorescein (2mol%)	CH_3CN	2	90
5	fluorescein (2mol%)	MeOH	2	42
6	fluorescein (2mol%)	PhMe	2	56
7	fluorescein (2mol%)	THF	2	45
8	fluorescein (2mol%)	DMF	2	trace
9	fluorescein (1mol%)	CH_3CN	2	73
10	fluorescein (3mol%)	CH_3CN	2	90
11	fluorescein (2mol%)	CH_3CN	1	64
12	fluorescein (2mol%)	CH_3CN	2.5	90
13[c]	fluorescein (2mol%)	CH_3CN	2	91
14[d]	fluorescein (2mol%)	CH_3CN	2	trace
15	-	CH_3CN	2	trace

[a] *o*-Phenylenediamine(0.1mmol), benzaldehyde(0.1mmol), photocatalyst(2mol%), 10 W blue LED, room temperature, air atmosphere. [b] Isolated yields. [c] Under presence of Na_2CO_3 (3 equiv). [d] Without blue LED.

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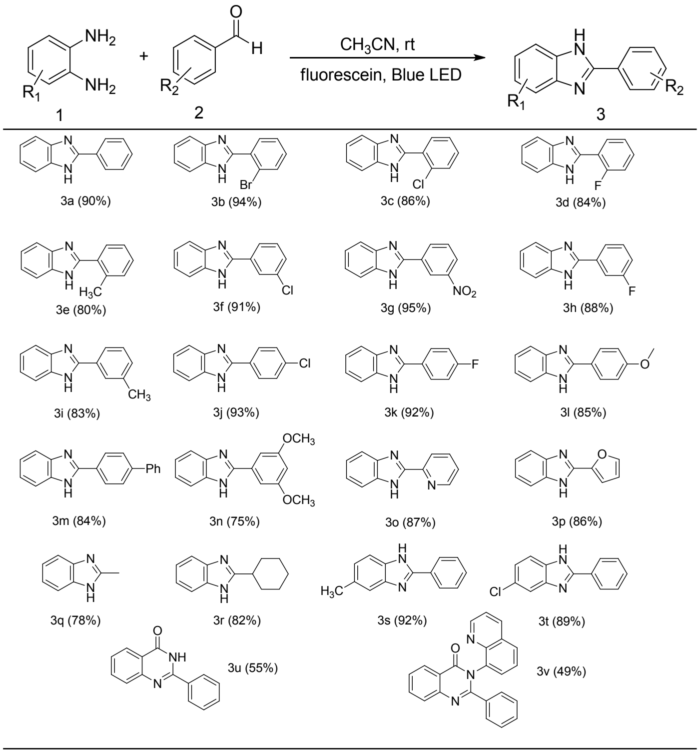
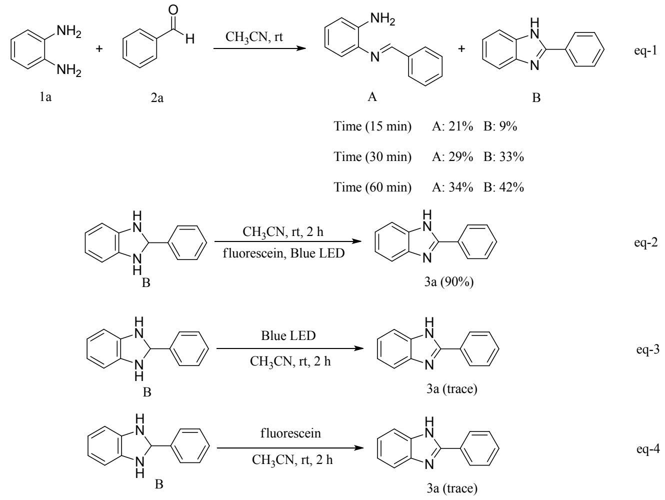
In summary, it was determined that the optimal reaction system was *o*-phenylenediamine and benzaldehyde as the reaction substrates, fluorescein (2 mol%) as photocatalyst, a 10 W blue LED as light source in the air at room temperature for 2 hours.

Table 2. Substrate scope of visible-light-induced condensation cyclization of aromatic aldehydes and *o*-phenylenediamine [a]



[a] *o*-Phenylenediamine(0.1mmol), aromatic aldehydes (0.1 mmol), fluorescein(2mol%), 10 W blue LED, room temperature. [b] Isolated yields.

After determining the optimal reaction system, we further explored the range of photocatalytic condensation reaction of aromatic aldehydes with different substituents, and the results were summarized in **Table 2**. First of all, when there is no substituent on the benzaldehyde **2a**, the yield of the product **3a** could reach 90%. When benzaldehyde has -F, -Cl, -Br and -CH_3 in the *o*-position, it could be found that the yield with electron withdrawing groups were superior to that of the electron donating group (**Table 2**, **3b**-**3e**). When the substituent was in the *m*- and *p*- positions, the target product can be obtained in good yields (**Table 2**, **3f**-**3m**). When the same substituent was at different position, the yield of the *p*-position can be found to be better than the *o*- and *m*- positions because of the steric hindrance effect (**Table 2**, **3d**, **3h** and **3k**). In addition, benzaldehyde with multiple substituents gave a 75% yield (**Table 2**, **3n**). This may be due to the presence of two electron donating groups on the benzaldehyde. It is noteworthy that furaldehyde or picolinaldehyde as the substrates obtained the corresponding products in moderate yields (**Table 2**, **3o**-**3p**), indicating that the catalytic system was also effective for heteroaromatic aldehydes. It is worth mentioning that this system is also suitable for the synthesis of benzimidazoles with an alkyl group and a cycloalkyl group at the 2-position (**Table 2, 3q-3r**). For the *o*-phenylenediamine moiety, the substituents (-Cl, -Me) at the 4-position also gave the desired product in high yield (**Table 2**,**3s**-**3t**). We also tried to use 2-aminobenzamide and 2-amino-*N*-(quinolin-8-yl)benzamide instead of o-phenylenediamine to react with benzaldehyde, the yields of 3u and 3v were moderate at 55% and 49%, respectively; but the reaction time needed to be extended to 16h. In addition, the protocol is not suitable for the preparation of 1,2-disubstituted benzimidazoles.



Scheme 2 Control Experiments

In order to explain the reaction mechanism in more depth, the following control experiments were carried out (**Scheme 2**). As can be seen from **eq-1**, when the reaction time was adjusted to 15, 30 and 60 minutes, the yields of intermediate **A** were 21%, 29% and 34%, respectively, and the yields of were 9%, 33% and 42%. It was indicated that intermediate **A** was first obtained from **1a** and **2a**, and converted to intermediate **B** by intramolecular cyclization. The intermediate **B** was used as the substrate to give the target compound **3a** in good yield under the optimal reaction condition (**eq-2**). According to **eq-1**and **eq-2**, it could be found that **A** and **B** were important intermediates in this reaction. According to **eq-3** and **eq-4** illustrated that both blue light and photocatalyst were essential for this reaction. In addition, fluorescence quenching experiments were also studied to further demonstrate the reaction mechanism, as shown in **Figure S1**. The fluorescence intensity of fluorescein can be significantly quenched by intermediate **B**.

Based on the above experimental results and previous literature reviews,[26] a possible mechanism for obtaining 2-arylbenzimidazoles by visible light assisted catalysis was described in **Scheme 3**. First, *o*-phenylenediamine **1a** and benzaldehyde **2a** are dehydrated and condensed to form imine intermediate **A**. Subsequent intramolecular cyclization gives intermediate **B** (E^{ox} = +0.242 V) as shown in **Figure S2**, the fluorescein (Fl) under visible light generates excited fluorescein* (Fl*) species ($E_{1/2}^{ox}$ = +0.87 V)[27] and oxidation of intermediate **B** to intermediate **C**. Fluorescein radical anion(Fl^{*-}) is oxidized to ground state fluorescein by O_2 (from the air). The desired product **3a** is produced by deprotonation

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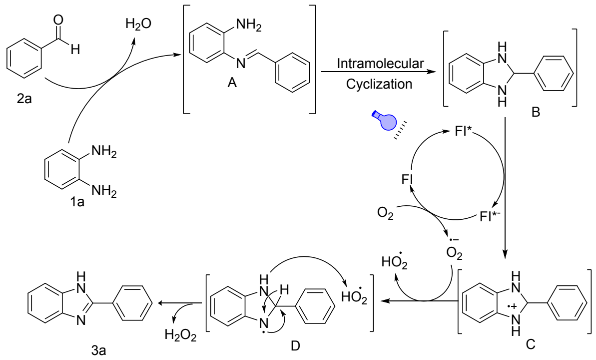
of **C** by superoxide and hydrogen abstraction by hydroperoxyl radicals ($HO_2^{\cdot}$).



Scheme 3 The possible reaction mechanism.

Conclusions

To sum up, we developed a method for the synthesis of by a visible-light-induced condensation cyclization of aromatic aldehydes and *o*-phenylenediamines using fluorescein as photocatalyst. This method could synthesize 2-arylbenzimidazoles in moderate to excellent yields with good functional group tolerance in mild conditions. In addition, the catalytic system avoids the use of oxidants or metals, in line with the concept of green chemistry. The development of other photocatalytic studies is still in progress.

Conflicts of interest

There are no conflicts to declare.

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