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Visible Light-induced Decarboxylative Alkylation of Heterocyclic Aromatics with Carboxylic Acids via Anthocyanin as a Photocatalyst

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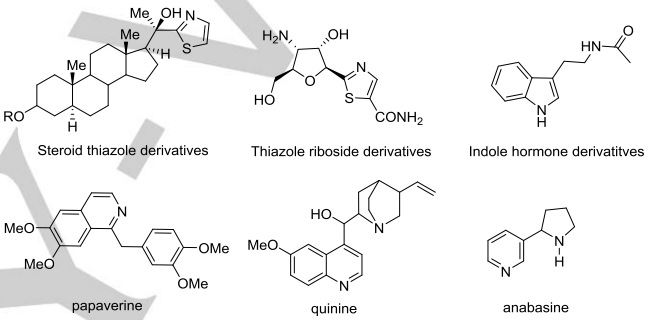
Abstract: A visible light-induced decarboxylative alkylation of heterocyclic aromatics with aliphatic carboxylic acids was developed by using anthocyanins as photocatalyst under mild conditions. A series of alkylated heterocyclic compounds were obtained in moderate to good yields by using the metal-free decarboxylative coupling reaction under blue light. This solving strategy used cheap and readily available carboxylic acids as alkylation reagents with good functional group tolerance and environmental friendliness. It is worth noting that this is the first time that anthocyanin have been used to catalyze the Minisci-type C-H alkylation. The mechanism of decarboxylation alkylation was studied by capturing adduct of alkyl radical and hydroquinone to confirmed the radical mechanism. This protocol also provided an alternative visible light-induced decarboxylative alkylation for the functionalization of heterocyclic aromatics.

Introduction

In recent years, visible light has been widely used in the functionalization of heterocyclic compounds as a renewable energy source[1-3], structural modification of heterocyclic aromatic compounds has become a research focus in organic chemistry, materials chemistry and medicinal chemistry[4-6], because heterocyclic compounds can be used in drugs and functional materials, as well as in the core fragments of this molecules[7-9]. We know that N-heterocyclic compounds are the core structure of alkaloids, and the introduction of alkyl groups into them can directly synthesize many alkaloids[10-12]. Moreover, alkylation of the heterocyclic aromatic compounds can improve the lipophilicity and solubility of the matrix[13], and regulate the π-electron stacking or conjugation[14]. More importantly, a large amount of data indicates that the alkylation of heterocyclic compounds can not only synthesize some alkaloids, but also synthesize other drugs and play an important role in clinical medicine. For example, three known alkaloid structures and some drugs for treating malaria and cancer are shown in **Scheme 1**[15-16]. Therefore, such substances have important research value and application prospects.

Under this premise, various alkylating agents were applied for modifying heterocyclic compounds, such as halogenated hydrocarbons[17], grignard reagent[18], activated esters[19], wittig



Scheme 1. Several drug molecules and alkaloids from alkylated heterocyclic aromatic

Reagents[20], N-*p*-toluenesulfonyl hydrazide[21], N-(acyloxy)phthalimides[22], aliphatic alcohol[23], and unsaturated olefin[24]. For example, in 2017, Wang and his team[25] used palladium to catalyze the alkylation of heterocyclic compounds with halogenated hydrocarbons successfully (**Scheme 2a**). In 2018, Matsui and his colleagues[26] achieved the alkylation of heterocyclic compounds and alkyltrifluoroborate reagents under photocatalytic conditions (**Scheme 2b**). Although these methods are effective and satisfactory, there are some disadvantages that cannot be ignored, such as expensive transition metal catalyst, limited reaction substrate. Compared with other alkylating agents such as halogenated hydrocarbons and organometallic salts, carboxylic acids may become stable and environmentally friendly alkylating agents through decarboxylation.

In 2015, Premi and his team[27] reported a decarboxylation coupling reaction of indoline and carboxylic acids by using palladium and high-valent iodine reagents **(Scheme 2c)**. In 2019, Tian and his colleagues[28] reported a decarboxylative alkylation of heterocyclic compounds and aliphatic carboxylic acids by using iridium and complex cobalt ligands as the catalysts **(Scheme 2d)**.

Although these methods are effective and satisfactory, there are some disadvantages that cannot be ignored, such as expensive transition metal catalyst, limited reaction substrate, high reaction temperature or long reaction time. Carboxylic acid as alkylation reagent is bound to undergo decarboxylation

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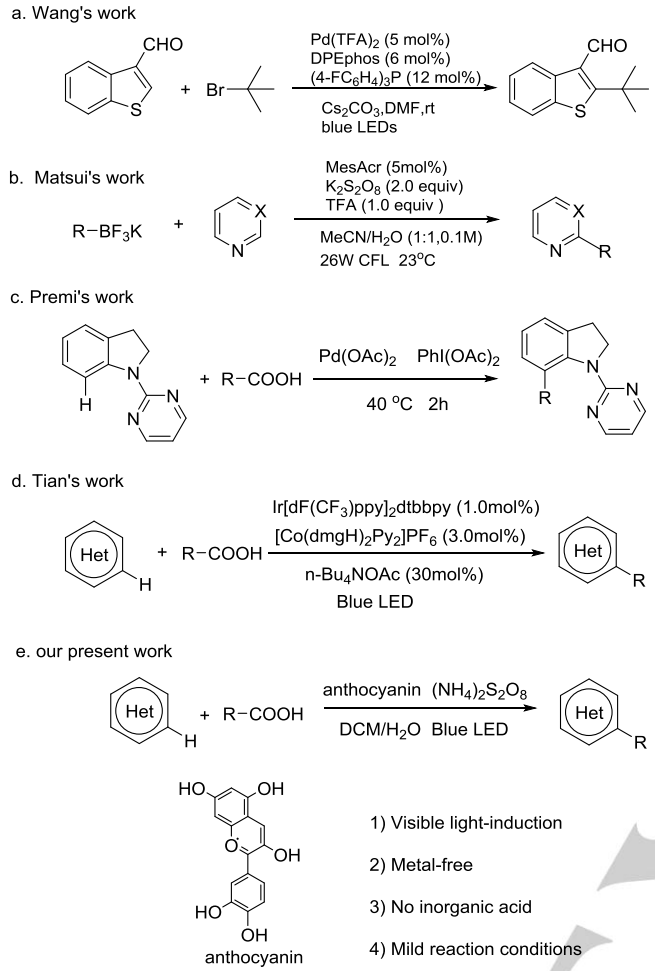


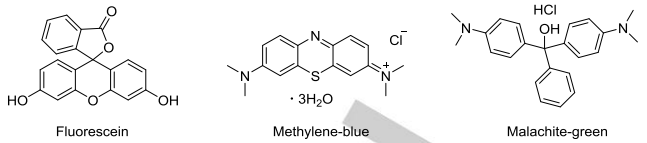
Scheme 2. Reported works and our work for decarboxylation

process, but the conventional decarboxylation coupling reactions require transition metal catalysts or additional bases. Therefore it is important to seek a mild metal-free decarboxylation coupling reaction using a photocatalytic method[29].

Herein, we reported a new visible light-induced catalytic system to realize decarboxylative alkylation of heteroarenes with aliphatic carboxylic acids at room temperature by using organic dye anthocyanin as a photocatalyst (**Scheme 2e**). The synthetic strategy is mild and efficient method to construct C-C bond through radical processes by the generation of carbon centered radicals after visible light-induced decarboxylation. This method avoids the use of metal catalysts, and has the advantages of readily available raw materials, high functional group tolerance and environmental friendliness.

Results and Discussion

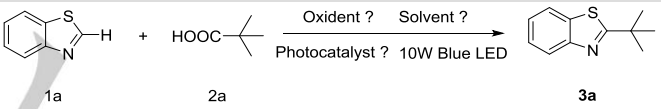
For further study of the reaction, we explored the optimal reaction conditions using benzothiazole (**1a**) and pivalic acid (**2a**) as the model substrates, and results were summarized in **Table 1**. Initially, we chose fac-Ir(ppy)$_3$ as the photocatalyst to provide the target product in a 81% of yield (**Table 1**, entry 1). Due to its expensive factor, we considered using organic dye photocatalysts instead of fac-Ir(ppy)$_3$, including fluorescein, methylene blue, malachite green and anthocyanin, and the molecular structures of them were in **Scheme 3**. Fluorescein,



Scheme 3. Molecular structures of fluorescein, methylene blue and malachite green

methylene blue and malachite green gave the product in 78%, 56% and 61% yields, respectively, while anthocyanin gave a yield of up to 92% (**Table 1**, entries 2-5). Next the equivalent of photocatalyst was investigated. When the equivalent of anthocyanin was reduced to 4 mol%, the yield of **3a** was dropped to 79% (**Table 1**, entry 6). Increasing the equivalent of to 6mol% had no much effect on the yield of **3a** (**Table 1**, entry 7). In the absence of anthocyanin, no product was obtained (**Table 1**, entry 8). Then different oxidants were investigated such as H_2O_2, tert-Butyl hydroperoxide (TBHP), $(NH_4)_2S_2O_8$ and $K_2S_2O_8$. H_2O_2 and TBHP only afforded trace amounts of the product (**Table 1**, entries 9 and 10), $K_2S_2O_8$ gave a yield of 57% (**Table 1**, entry 11), while $(NH_4)_2S_2O_8$ afforded a yield of up to 92% (**Table 1**, entry 5). Next, reaction solvents were screened including dichloromethane (DCM)/H_2O, tetrahydrofuran (THF)/H_2O, MeCN/H_2O, dimethyl sulfoxide (DMSO)/H_2O and $CHCl_3$/H_2O. It was found that the use of solvent THF/H_2O and MeCN/H_2O only afford trace amounts of the product (**Table 1**, entries 12 and 13). The use of solvents DMSO/H_2O and $CHCl_3$/H_2O obtained the product **3a** in yields of 36% and 74%, respectively (**Table 1**, entries 14 and 15). We found that

Table 1. Optimization of the reaction conditions [a]



1a 2a **3a**

Entry	Photocatalyst (mol%)	Oxidant	Solvent	Yield (%)[b]
1	fac-Ir(ppy)$_3$(5 mol%)	$(NH_4)_2S_2O_8$	DCM/H_2O (1:1)	81
2	Fluorescein(5 mol%)	$(NH_4)_2S_2O_8$	DCM/H_2O (1:1)	78
3	methylene-blue(5mol%)	$(NH_4)_2S_2O_8$	DCM/H_2O (1:1)	56
4	malachitegreen(5mol%	$(NH_4)_2S_2O_8$	DCM/H_2O (1:1)	61
5	Anthocyanin(5 mol%)	$(NH_4)_2S_2O_8$	DCM/H_2O (1:1)	**92**; trace[c]
6	Anthocyanin(4 mol%)	$(NH_4)_2S_2O_8$	DCM/H_2O (1:1)	79
7	Anthocyanin(6 mol%)	$(NH_4)_2S_2O_8$	DCM/H_2O (1:1)	90
8	-	$(NH_4)_2S_2O_8$	DCM/H_2O (1:1)	-
9	Anthocyanin(5 mol%)	H_2O_2	DCM/H_2O (1:1)	trace
10	Anthocyanin(5 mol%)	TBHP	DCM/H_2O (1:1)	trace
11	Anthocyanin(5 mol%)	$K_2S_2O_8$	DCM/H_2O (1:1)	57
12	Anthocyanin(5 mol%)	$(NH_4)_2S_2O_8$	THF/H_2O (1:1)	trace
13	Anthocyanin(5 mol%)	$(NH_4)_2S_2O_8$	MeCN/H_2O(1:1)	trace
14	Anthocyanin(5 mol%)	$(NH_4)_2S_2O_8$	DMSO/H_2O(1:1)	36
15	Anthocyanin(5 mol%)	$(NH_4)_2S_2O_8$	$CHCl_3$/H_2O (1:1)	74
16	Anthocyanin(5 mol%)	$(NH_4)_2S_2O_8$	DCM	25
17	Anthocyanin(5 mol%)	$(NH_4)_2S_2O_8$	DCM/H_2O (3:1)	58
18	Anthocyanin(5 mol%)	$(NH_4)_2S_2O_8$	DCM/H_2O (2:1)	76
19	Anthocyanin(5 mol%)	$(NH_4)_2S_2O_8$	DCM/H_2O (1:2)	71

[a] benzothiazole (0.1mmol), pivalic acid (0.15mmol), oxidant (0.2mmol), photocatalyst (5 mol%), 10 W blue LED, DCM/H_2O=1:1(v:v), room temperature for 5h. [b] Isolated yields. [c] Without blue LED.

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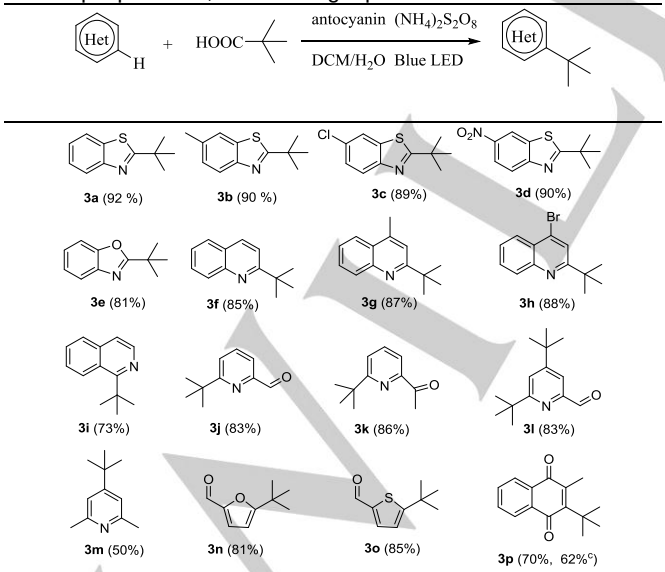
DCM/H_2O was the best solvent to give a yield of up to 92% (**Table 1**, entry 5). Finally, effect of solvent ratio on this reaction was further investigated. It was found that the use of DCM gave a low yield of 25% (**Table 1**, entry 16), while DCM/H_2O (3:1), DCM/H_2O (2:1) and DCM/H_2O (1:2) were used as the solvent to afford the product **3a** in 58%, 76% and 71% of yields, respectively (**Table 1**, entries 17-19). Therefore DCM/H_2O (1:1) was preferable for the reaction of visible light-induced alkylation of heterocyclic compounds. In addition, in the absence of a blue LED source, only trace amounts of the product was obtained (**Table 1**, entry 5[c]).

Based on the above experimental results, the optimal reaction conditions for visible light-induced alkylation of benzothiazole were anthocyanin (5 mol%) as the photocatalyst, $(NH_4)_2S_2O_8$ as the oxidant in DCM/H_2O (1:1) under 10W blue LED lamp at room temperature .

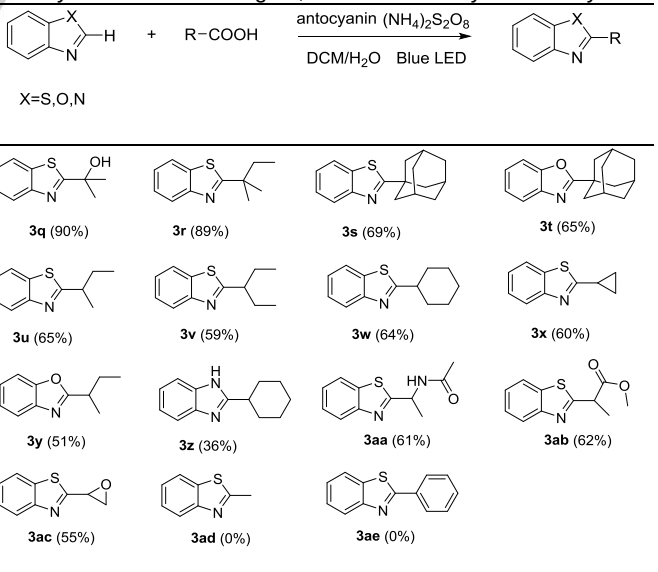
In order to explore the substrate scope of the alkylation, a variety of heterocyclic compounds were firstly investigated by using the above optimal conditions and the results were summarized in **Scheme 4**. Initially, benzothiazoles with different substituents were investigated. The electron-donating group -CH_3 at the C-6-position gave the corresponding product in 90% yield (**3b**), while the electron-withdrawing groups -Cl and -NO_2 at the C-6-position gave the product in 89% and 90% yields, respectively (**3c** and **3d**). At the same time, benzoxazole gave the final product in a yield of 81% (**3e**). Next, we explored quinolines as the substrates. Quinoline afforded the target product in 85% yield (**3f**). 4-Methyl with electron-donating group -CH_3 and 4-bromoquinoline with electron-withdrawing group -Br gave the corresponding product in 87% and 88% yields, respectively (**3g** and **3h**). Furthermore, isoquinoline also afforded the product in a yield of 73% (**3i**). Then, we studied pyridine again as the substrates. The -CHO and -$COCH_3$ at the C-2-position gave thecorresponding product in yields of 83% and 86% (**3j and 3k).** It is worth noting that by increasing the carboxylic acid equivalent, we successfully achieved alkylation at multiple positions, and the target product was obtained in 83% yield (**3l**). Unfortunately, 2,6-dimethylpyridine only afforded the product in a yield of 50% (**3m**). In addition, furan-2-carbaldehyde, thiophene-2-carbaldehyde and menaquinone also gave the corresponding product in 81%, 85% and 70% yields, respectively (**3n**, **3o** and **3p**). It was worth noting that 2-(tert-butyl)-3- methylnaphthalene-1,4-dione (**3p**) is a derivative of vitamin K that has the ability to inhibit malaria parasites and play an antimalarial role[30]. In order to demonstrate the practicability of this protocol, a gram-scale reaction was conducted and afforded an isolated yield in 62% (**3p**[c]). In the previous literature report, **3p** was obtained by using alkyne 4,4-dimethylpent-2-yne and carbene chromium complex as raw materials through complex reaction condition[31]. Compared with the previous method, the protocol can obtain the product **3p** more conveniently and quickly by using direct alkylation of menadione with pivalic acid.

To further explore the substrate scope and limitations of this process, different carboxylic acids were used as alkylation reagents, as shown in **Scheme 5**. Firstly, tertiary alkyl carboxylic acids were investigated including 2-hydroxy-2-methyl- propanoic acid, 2,2-dimethylbutanoic acid and adamantane-1-carboxylic acid to afford corresponding products with yields of 90%, 89%, 69% and 65%, respectively (**3q**-**3t**). However, for the secondary alkyl carboxylic acids, such as 2-methylbutanoic acid, 2-ethylbutanoic acid, cyclohexanecarboxylic acid and cyclopropanecarboxylic acid, the yields of alkylation products were reduced to 36-65% (**3u**-**3z**). In addition, acetylalanine, 3-methoxy-2-methyl-3-oxopropanoic acid and oxirane-2-carboxylic acid could participate in the reaction smoothly and the yields of the alkylation products were 61%, 62% and 55%, respectively (**3aa**-**3ac**). Unfortunately, primary carboxylic acid (acetic acid) and aromatic carboxylic acid (benzoic acid) could not participate in the reaction and the corresponding products (**3ad** and **3ae**) not were obtained. Obviously, carboxylic acids of different properties have different alkylation efficiency in this reaction system. The stability of alkyl radical from the tertiary alkyl carboxylic acid is the strongest, while the stability of the alkyl



[a] N-heteroarene (0.1 mmol), pivalic acid (0.15 mmol), $(NH_4)_2S_2O_8$ (0.2 mmol), anthocyanin (5 mol%), 10 W blue LED, room temperature. [b] Isolated yields. [c] Isolated yields of gram-scale reaction.

Scheme 4. Substrates scope of Heteroarenes [a,b]



[a] N-heteroarene (0.1 mmol), aliphatic carboxylic acid (0.15 mmol), $(NH_4)_2S_2O_8$ (0.2 mmol), anthocyanin (5 mol%), 10 W blue LED, room temperature. [b] Isolated yields.

Scheme 5. Substrates scope of aliphatic carboxylic acid [a, b]

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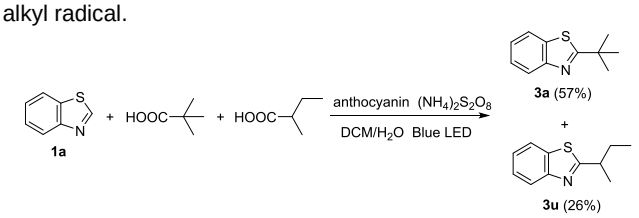
radical from the primary alkyl carboxylic acid is the weakest. The above phenomenon is the result of the difference in the stability of the radical.

Based on our experimental results, we found that the substituents of heterocyclic aromatics had no significant effect on the reaction, but the structure of carboxylic acid had a significant effect on the reaction. Therefore, the reaction mechanism is likely to be through a radical pathway.

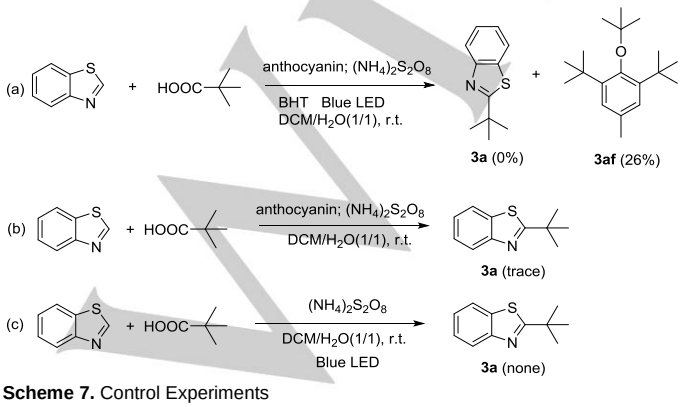
To understand the mechanistic pathway of this reaction, we designed a competitive set of experiments by a reaction of benzothiazole (**1a**) with pivalic acid and 2-methylbutanoic acid (**Scheme 6**). The isolated yield of **3a** (57%) was much higher than that of **3u** (26%). This also proved that the tertiary alkyl radical had higher stability and reactivity than the secondary alkyl radical.



Scheme 6. Competitive Experiment

In order to further explore the reaction mechanism, a radical inhibition experiment was conducted by using BHT as blocker under standard condition, the desired product **3a** was not detected, a adduct **3af** from BHT and *t*-butyl radical was isolated in 26% yield (spectroscopic data are shown in the Supporting Information) (**Scheme 7**(**a**)). It was proved that the reaction mechanism proceeded through the radical pathway. In the absence of blue light or photocatalysts (**Scheme 7**(**b**) and **Scheme 7**(**c**)), almost no products were obtained. Therefore, both blue light and photocatalyst were essential for this reaction.

Then, we conducted the experiments to give insight into the reaction mechanism. First, the UV−vis spectrum of each component and the reaction mixture confirmed that anthocyanin plays as the visible-light photosensitizer (see the **Figure 1**). The UV-visible spectrum showed that the reaction substrates 1a, 2a and $(NH_4)_2S_2O_8$ have the minimal optical absorption in the visible light range, while the absorption of visible light by anthocyanin is significantly enhanced. Based on the above results, we speculate that anthocyanin is easily oxidized after absorbing light. Further exploration of the mechanism is being conducted in



Scheme 7. Control Experiments

our lab. Next, we conducted the luminescence quenching experiments (see the **Figure 2**). Benzothiazole **1a** and pivalic acid **2a** showed quite slight quenching phenomena, but $(NH_4)_2S_2O_8$ displayed an obvious quenching phenomenon (the quenching constant is large and has a high quenching rate). The experiments suggest that single electron transfer (SET) of the exited photocatalyst AN* dominantly occurs with the persulfate ion.

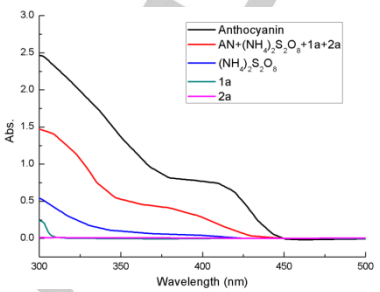


Figure 1 UV-vis absorption spectrum

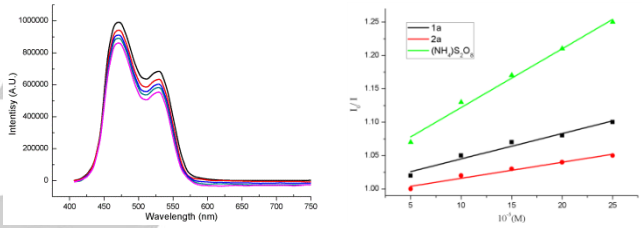


Figure 2 Stern-Volmer fluorescence quenching experiments

On the basis of the above experimental results and previous literature reports[32-33], a plausible mechanism for the alkylation of heterocyclic aromatics was described in **Scheme 8**. First, the photocatalyst anthocyanin (AN) produces an excited state (AN*) under irradiation of a blue LED lamp. AN* participates in single electron reduction with persulfate anion to afford an oxidized AN*$^+$, a sulfate dianion and a sulfate radical anion. After a hydrogen atom transfer (HAT) occurs between pivalic acid (2a) and the sulfate radical anion, 2a produces an alkyl radical A by a decarboxylation. Finally, the radical A interacts with benzothiazole (1a) to produce an intermediate B, in which the intermediate B undergoes a dehydrogenation process and single electron transfer (SET) to provide the desired product (3a) and regenerate AN, completing the entire catalytic cycle. In addition, in order to further confirm the proposed reaction path, we measured the quantum yield of the present reaction system (Φ = 17.42, see the **SI**), and the measurement results of quantum yield showed that the persulfate ion can hardly act as a chain carrier to oxidize B, thereby generating the final product. This also supports the rationality of our proposed reaction path.

Conclusion

In summary, we developed a process for the decarboxylative coupling of heterocyclic aromatics and aliphatic carboxylic acids under mild conditions. A series of alkylated heteroarenes were

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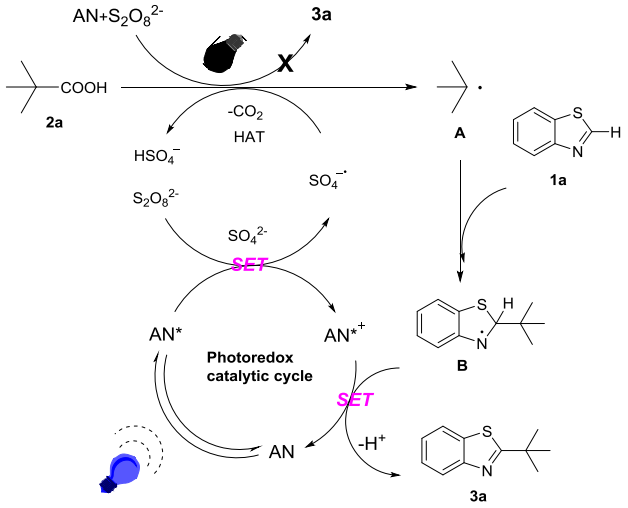

Scheme 8. The possible reaction mechanism.

synthesized with moderate to good yields by using anthocyanin as an inexpensive photocatalyst under blue light. This method of metal-free decarboxylation by using anthocyanin as organic photocatalyst under light conditions not only promoted the application of decarboxylation alkylation but also conformed to green and environmentally friendly concept. Other decarboxylative alkylation reactions continue to be further studied in our laboratory.

Experimental Section

Add N-heteroaromatic hydrocarbons (0.1 mmol), aliphatic carboxylic acid (0.15 mmol), $(NH_4)_2S_2O_8$ (0.2 mmol), DCM/H_2O = 1/1 (V/V) 10mL and anthocyanin (5 mol%) in a 25mL quartz reaction flask for 5h. The reaction vessel was stirred at room temperature under a 10 W blue LED lamp. After the reaction was completed, the reaction mixture was extracted 3 times with dichloromethane (DCM), and then the organic phases were combined and dried over anhydrous sodium sulfate. After removing the solvent by rotary evaporation, the residue was purified by column chromatography (petroleum ether/ethyl acetate = 7:1 as eluent). Characterization of all synthetic products matched to real samples.

Acknowledgements

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Keywords: heterocyclic compounds • decarboxylation • alkylation • anthocyanin • aliphatic carboxylic acid

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FULL PAPER

Visible light-induced Decarboxylative Alkylation of Heterocyclic Aromatics with Carboxylic Acids via Anthocyanin as a Photocatalyst

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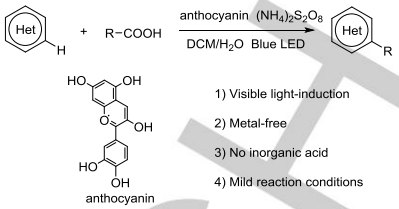

This paper developed a visible light-induceed decarboxylation alkylation of heterocyclic compounds with aliphatic carboxylic acids. Anthocyanin was used as photocatalyst for the first time in a type of decarboxylation reaction. The program overcomes the traditional method that requires the use of metal catalyst or other expensive complex catalysts with complicated synthesis steps. Finally, a series of control experiments verify the reaction path and reaction mechanism.

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