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Visible-light-induced C—H arylation of quinoxalin-2(1*H*)-ones in H_2O

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ABSTRACT

An efficient visible-light-induced C—H arylation of quinoxalin-2(1*H*)-ones in H_2O is developed, which has the advantages of mild reaction conditions, environmental friendliness and good functional group tolerance. This strategy provides a simple operation method to access various 3-aryl quinoxalin-2(1*H*)-ones in moderate to good yields.

Introduction

Nitrogen-containing heterocycles are significant structures featured in diverse pharmaceutical drug and biological compounds [1]. Especially, C3-substituted quinoxalin-2-ones are important pharmaceutical intermediates because of its biological activity [2]. For instance, STK33 inhibitor [3], polymers [4], CFTR activators and ALE2 inhibitors [1] have a 3-arylquinoxalin-2(1*H*)-one unit in their molecular structures (Figure 1). Therefore, there is a great significance of functionalization of quinoxalin-2(1*H*)-ones at C3 position.

Although in recent years, a number of methods for the formations of C—C [5], C—N [6], C—O [7], C—P [8] bonds from C—H functionalization of quinoxalin-2(1*H*)-ones have been reported, there is still a substantial interest in the formation of C(sp^2)-C(sp^2) bond in order to introduce functional aryl groups into quinoxalin-2(1*H*)-ones. In 2013, Alami and co-workers reported a palladium-catalyzed oxidation with arylboronic acids, which provided a new strategy for arylation of quinoxalin-2(1*H*)-ones (Scheme 1a) [9]. Zhang and coworkers reported a C—H arylation of quinoxalin-2(1*H*)-ones using iodine(III) compounds as arylation reagent (Scheme 1b) [10]. Qu's group and Lee's group reported an efficient method to realize C—H arylation of quinoxalin-2(1*H*)-ones through deamination of arylamine or arylhydrazines respectively

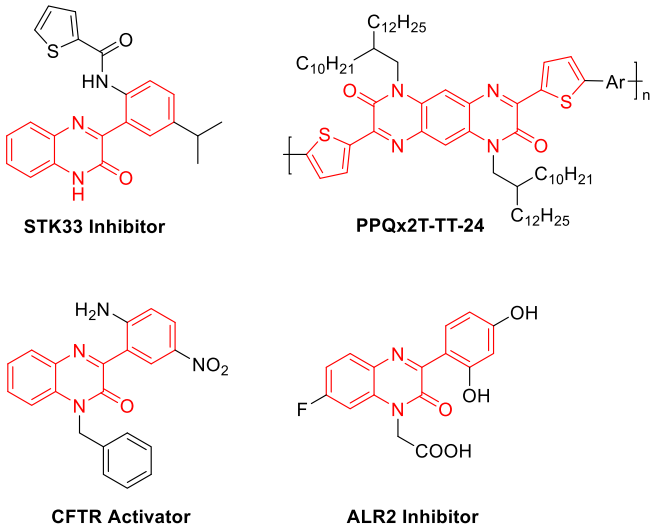

Fig. 1. Selecting structures of bearing 3-aryl-quinoxalin2(1*H*)-one.

(Scheme 1c, d) [11]. Reddy et al. performed the C—H arylation of quinoxalin-2-one with $Mn(OAc)_3$ and arylboronic acid at 120 °C (Scheme 1e) [12]. Despite their utilities, the reported approaches usually require transition metal, toxic organic solvent or high reaction temperatures, failing to meet the demand of green chemistry [13].

Photocatalysis has been considering as an ideal green chemistry because of its advantages of environmental friendliness, mild

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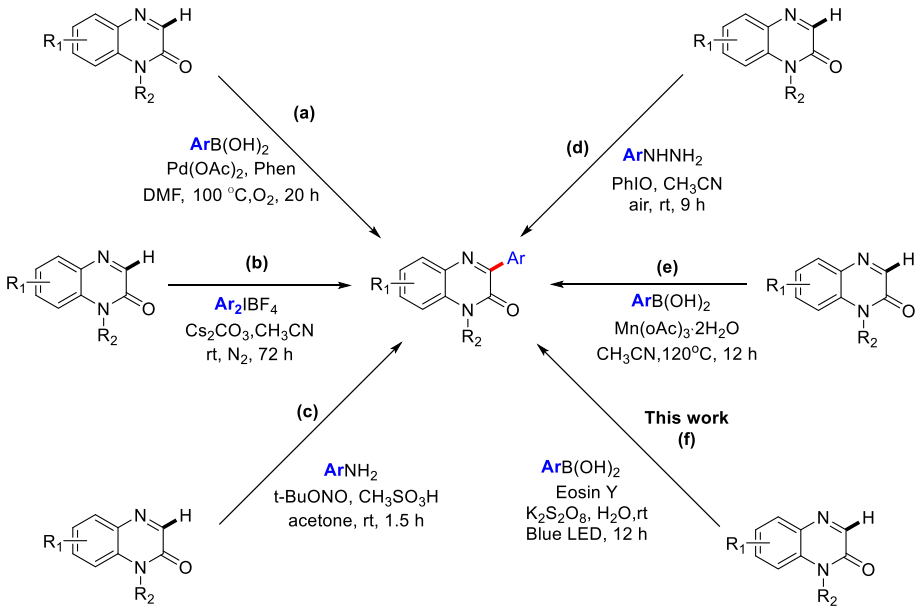
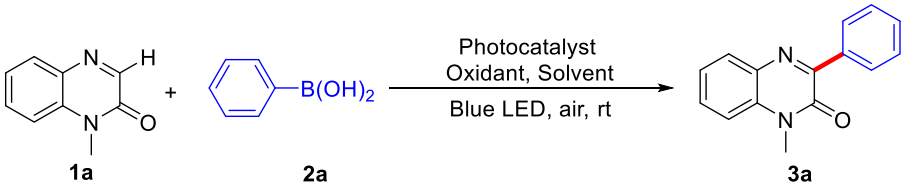


Scheme 1. Synthesis of 3-arylquinoxalin-2(1*H*)-ones.

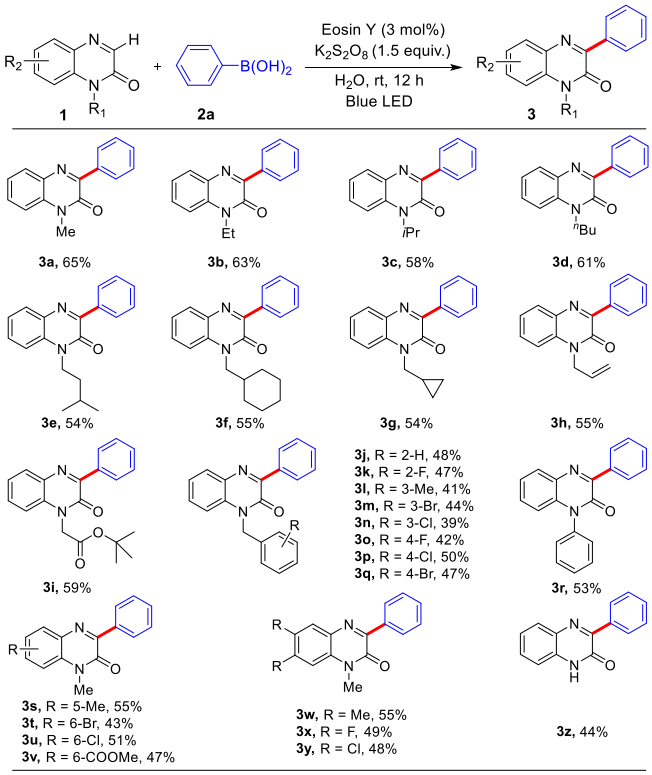
Table 1
Screening of reaction conditions.[a,b]



Entry	Photocatalyst	Oxidant	Solvent	Yield(%)[b]
1	Eosin Y	$K_2S_2O_8$	DCE	27
2	Eosin Y	$K_2S_2O_8$	DMSO	24
3	Eosin Y	$K_2S_2O_8$	DMF	NR
4	Eosin Y	$K_2S_2O_8$	CH_3CN	28
5	Eosin Y	$K_2S_2O_8$	THF	26
6	Eosin Y	$K_2S_2O_8$	DCE/H_2O[c]	51
7	Eosin Y	$K_2S_2O_8$	CH_3CN/H_2O[c]	48
8	Eosin Y	$K_2S_2O_8$	H_2O	65
9	$Ru(bpy)_3Cl_3$	$K_2S_2O_8$	H_2O	55
10	Rhodamine B	$K_2S_2O_8$	H_2O	37
11	Acid Red 94	$K_2S_2O_8$	H_2O	42
12	–	$K_2S_2O_8$	H_2O	0
13	Eosin Y	oxone	H_2O	5
14	Eosin Y	TBHP	H_2O	20
15	Eosin Y	DTBP	H_2O	NR
16	Eosin Y	$PhI(TF(A)_2$	H_2O	45
17	Eosin Y	KHS_2O_8	H_2O	5
18	Eosin Y	$(NH_4)_2S_2O_8$	H_2O	22
19	Eosin Y	$Na_2S_2O_8$	H_2O	43
20	Eosin Y	–	H_2O	14
21	Eosin Y	$K_2S_2O_8$	H_2O	32[d], 53[e]
22	Eosin Y	$K_2S_2O_8$	H_2O	45[f], 62[g]
23	Eosin Y	$K_2S_2O_8$	H_2O	44[h], 63[i]
24	Eosin Y	$K_2S_2O_8$	H_2O	12[j]

NR = No reaction.
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), oxidant (0.3 mmol), photocatalyst (3 mol%), solvent (2.0 mL), at room temperature under blue LED in air for 12 h.
[b] Isolated yields.
[c] Organic solvent/H_2O (v/v = 1:1, 2.0 mL).
[d] Oxidant (0.1 mmol).
[e] Oxidant (0.4 mmol).
[f] **2a** (0.2 mmol).
[g] **2a** (0.6 mmol).
[h] Eosin Y (1 mol%).
[i] Eosin Y (5 mol%).
[j] In the dark.

Table 2
Substrate scope of quinoxalin-2(1*H*)-ones.[a,b]



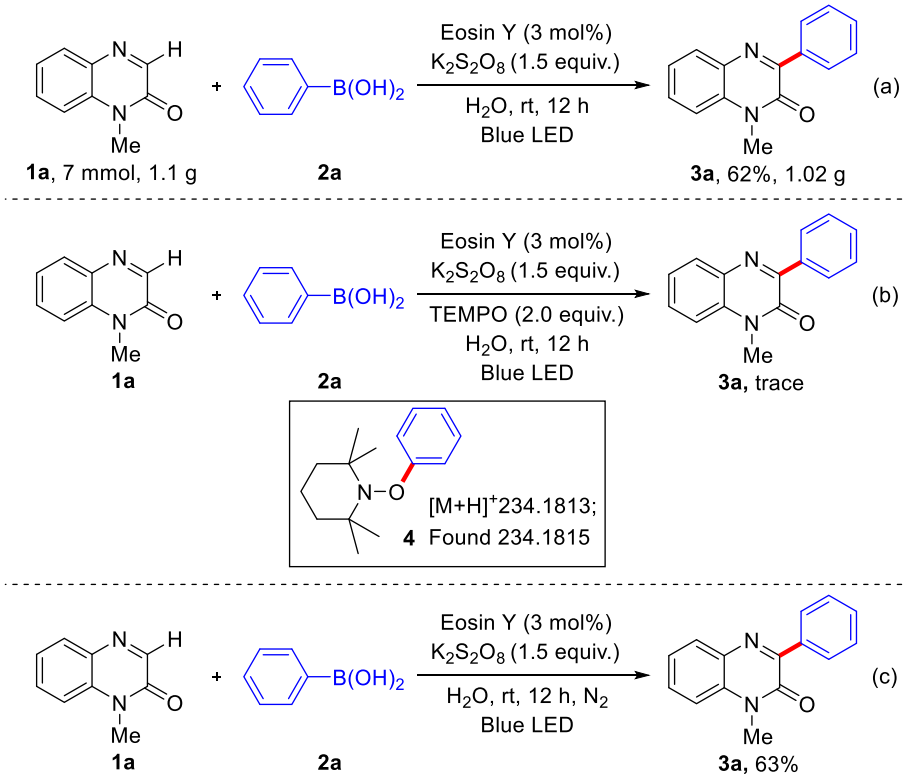
[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.3 mmol), $K_2S_2O_8$ (0.3 mmol), Eosin Y (3 mol%), H_2O (2.0 mL), at room temperature under blue LED in air for 12 h.
[b] Isolated yields.

conditions, functional group tolerance and simple operation [14]. Based on our previous work of the C—H functionalization of *N*-containing heterocycles [1b,15] and the concept of green chemistry, herein, we developed a new strategy for the C—H arylation of quinoxalin-2(1*H*)-ones with aryboronic acid in H_2O through photocatalysis.

Results and discussion

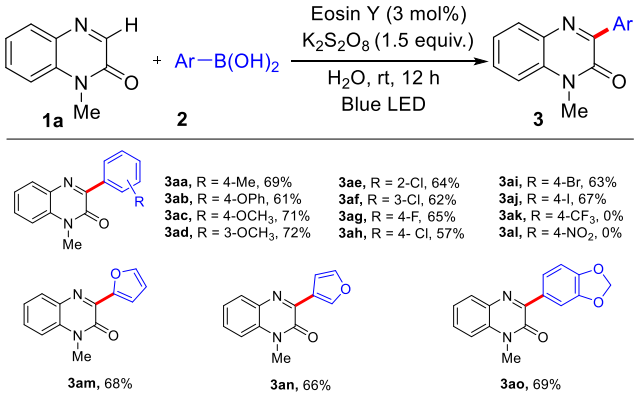
We started our work with the reaction of 1-methylquinoxalin-2(1*H*)-one **1(a)** with phenylboronic acid **2(a)** using Eosin Y as photocatalyst, $K_2S_2O_8$ as oxidant in DCE under blue LEDs for 12 h. As shown in Table 1, the desired product **3(a)** was obtained in 27% yield. Other organic solvents such as DMSO, DMF, CH_3CN and THF could not enhance the yield (Table 1, entry 2–5). To meet the demand of green chemistry, H_2O as co-solvent was added to the reaction mixture (Table 1, entry 6–7). To our delight, the yield was increased. The yield could be further enhanced to 65%, if H_2O was chosen as solvent (Table 1, entry 8). We think that the usage of H_2O enhanced the solubility of phenylboronic acid **2(a)** and $K_2S_2O_8$, which was beneficial to the reaction. Further optimization in the type and amount of photocatalysts and oxidants did not improve the reaction yield (Table 1, entry 9–24).

With the optimized conditions in hand, we then evaluated the scope of substituted quinoxalin-2(1*H*)-ones (**1**) with phenylboronic acid **2(a)** (Table 2). To our delight, quinoxalin-2(1*H*)-ones with a variety of *N*-protecting groups, including methyl, ethyl, isopropyl, *N*-butyl, isopentyl, cyclohexylmethyl, could be transformed into the desired products in good yield (**3a-f**). Notably, some sensitive groups in the reaction, including alkenes, cyclopropyl and ester, were well tolerated (**3 g-i**). However, when various substituted benzyl were employed as *N*-protecting groups (**3j-q**), the



Scheme 2. Gram-scale synthesis and control experiment.

Table 3
Substrate scope of arylboronic acids.[a,b]



[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.3 mmol), $K_2S_2O_8$ (0.3 mmol), Eosin Y (3 mol%), H_2O (2.0 mL), at room temperature under blue LED in air for 12 h.
[b] Isolated yields.

desired products were isolated in lower yields. This result might be caused by the low solubility of *N*-benzyl quinoxalin-2(1*H*)-ones. The *N*-aryl quinoxalin-2(1*H*)-one has been tested under the standard condition, and the corresponding product (**3r**) was obtained in 53% yield. Quinoxalin-2(1*H*)-ones with methyl, fluorine, chlorine, bromine and ester groups on the benzene ring were also compatible, giving the products (**3 s-3y**) in 43–55% yields. Further investigation found that *N*-free protecting quinoxalinone was also suitable for the transformation (**3z**).

Subsequently, a number of boronic acids (**2**) were tested with 1-methylquinoxalin-2(1*H*)-one **1(a)** under the standard condition (Table 3). Phenyl boronic acid with electron-donating groups (–CH_3, –OCH_3, -OPh) and halogen were compatible with the reaction in a good yield (**3aa**-**aj**). Unfortunately, no desired product (**3ak**, **3al**) was observed If the substituents of phenyl boronic acids were displaced with strong electron-withdrawing groups (–CF_3, –NO_2). The heterocycle-containing boronic acids were also compatible, yielding the corresponding products (**3am-ao**) in 66–69% yields. Unfortunately, *N*-heteroarenes including quinoline, isoquinoline, *N*-methylindole and aliphatic boronic acids such as isopropylboric acid are not suitable for this reaction.

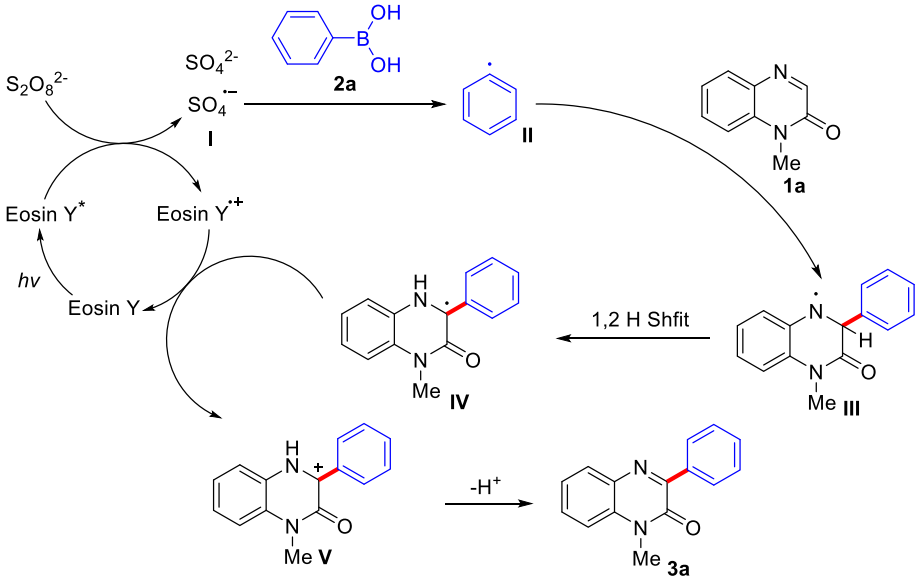
To demonstrate the application value of such method, the gram-scale synthesis of C-3 arylated quinoxalin-2(1*H*)-ones (**1**) was performed, providing the corresponding product in 62% yield (Scheme 2a).

To elucidate the possible reaction pathway, a control reaction was carried out (Scheme 2b). The reaction was inhibited when 2.0 equiv. of 2,2,6,6-tetramethyl-piperdin-1-oxyl (TEMPO) was added. Furthermore, the adduct **4** was detected by HRMS. These results indicated that a radical process was involved in the reaction. The reaction could also be performed under nitrogen atmosphere, to afford the corresponding product in 63% yield, indicating that oxygen do not take part in the transformation (Scheme 2c).

Based on the results and previous reports [14d,16], a possible mechanism was proposed (Scheme 3). Firstly, Eosin Y was activated under irradiation of blue LED, which reduced the $K_2S_2O_8$ to generate radical I. Then the radical **I** reacted with boronic acid **2(a)** to produce aryl radical **II**, which subsequently attacked quinoxalin-2(1*H*)-ones (**1**) to form nitrogen radical intermediate III. The generated intermediate III underwent a 1,2-hydrogen shift process to produce carbon radical IV, which was oxidized by Eosin $Y^{\cdot+}$ to form carbon cation V. The final product 3a was generated through a deprotonation process.

Conclusion

In conclusion, we have developed a mild and green strategy for C—H arylation of quinoxalin-2(1*H*)-ones in H_2O through photocatalysis. Various substrates were well compatible under standard condition, providing an environmentally benign route to construct various 3-arylated quinoxalin-2(1*H*)-ones.



Scheme 3. Plausible mechanism.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.152841.

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