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Communication

C(sp²)-H/O-H cross-dehydrogenative coupling of quinoxalin-2(1*H*)-ones with alcohols under visible-light photoredox catalysis

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ARTICLE INFO

Article history:

Received 30 November 2019

Accepted 28 December 2019

Published 5 August 2020

Keywords:

Quinoxalin-2(1*H*)-ones

Alcohols

Visible-light photoredox catalysis

Cross-dehydrogenative coupling

Metal free reaction

ABSTRACT

An efficient and practical route to various 3-alkoxylquinoxalin-2(1*H*)-ones through visible-light photocatalytic C(sp²)-H/O-H cross-dehydrogenation coupling of quinoxalin-2(1*H*)-ones and alcohols, employing ambient air as an oxidant at room temperature under metal-free conditions, was developed.

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Ethers are indispensable structural motifs present in numerous natural products, synthetic pharmaceuticals, and functional materials [1]. Over the past decade, intensive efforts have been devoted to developing several methods for the construction of such compounds. Among these developed methods, the C-H/O-H cross-dehydrogenation coupling (CDC) of heterocycles with alcohols is an ideal choice for the preparation of various heterocyclic ethers given its inherent step-economy and atom-economy [2]. Moreover, alcohols are perfect coupling reagents because they are naturally abundant, have low cost and high stability, and are easy to handle. However, most of these CDC reactions depend on transition-metal catalysts and/or strong oxidants, which often lead to unwanted metal

residues and chemical wastes. In addition, the C-C bond formation competitive reaction adjacent to the oxygen atom of alcohols could compromise the yield and/or selectivity.

Quinoxalin-2(1*H*)-ones are prevalent nitrogen-heterocyclic units [3–18] in a broad range of pharmaceutically and biologically active compounds [19,20]. As a consequence, the development of novel synthetic protocols for the facile diversification of quinoxalin-2(1*H*)-one has been actively explored over the past few years [21]. In particular, a variety of efficient methods for synthesizing various 3-functionalized quinoxalin-2(1*H*)-ones through the direct C-H functionalization of quinoxalin-2(1*H*)-ones has been well-established, which include region-selective alkylation [22–30], arylation [31–35],

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This work was supported by the Hunan Provincial Natural Science Foundation of China (2019JJ20008).

DOI: S1872-2067(19)63526-6 | <http://www.sciencedirect.com/science/journal/18722067> | Chin. J. Catal., Vol. 41, No. 8, August 2020

acylation [36,37], amination [38–44], and phosphonation [45–47] reactions. We were aware that the first example of a copper-catalyzed C(sp²)-H/C(sp³)-H CDC reaction of quinoxalin-2(1*H*)-ones and alcohols, with 3 equiv. of *tert*-butyl peroxybenzoate (TBPB) as the oxidant, was reported by Yuan and Mao (Scheme 1a) [24]. However, in this CDC reaction, the alcohols acted as radical partners to afford corresponding alcoholic 3-hydroxyalkylated quinoxalin-2(1*H*)-ones, which are structurally restricted. Recently, Zhang and Li pioneered a metal-free construction of 3-fluoroalkoxyquinoxalin-2(1*H*)-ones from quinoxalin-2(1*H*)-ones and fluoroalkyl alcohols with 2 equiv. of [bis(trifluoroacetoxy)iodo]benzene as an oxidant (Scheme 1b) [48]. In spite of the above achievements, an efficient catalytic protocol for the synthesis of various 3-alkoxyquinoxalin-2(1*H*)-ones under metal- and strong oxidant-free conditions is in great demand.

Ambient air is a low-cost, abundant, and safe oxidant that ideally fulfils the requirements of green and sustainable chemistry [49–56]. However, the efficient utilization of dioxygen (or ambient air) is challenging, because the existence of a triplet-ground-state of molecular oxygen largely blocks oxygen reduction and selective transformation with a large kinetic barrier, and the four-electron reduction of molecular oxygen involves more electrons than the two-electron substrate oxidation. In the past decade, the photocatalytic reaction using dioxygen (or ambient air) as a terminal oxidant has become a research hotspot of green chemistry [57–69], because it is very consistent with the 12 principles of green chemistry. However, to the best of our knowledge, no example of the synthesis of 3-alkoxyquinoxalin-2(1*H*)-ones through the visible-light photocatalytic CDC reaction with ambient air as the sole oxidant exists. As part of our ongoing interest in green chemistry [70–78], herein, we report an efficient and practical approach to the preparation of various 3-alkoxyquinoxalin-2(1*H*)-ones through a photoredox-catalyzed C(sp²)-H/O-H cross-dehydrogenative coupling of quinoxalin-2(1*H*)-ones and alcohols in the presence of ambient air as an oxidant, under metal- and strong oxidant-free conditions (Scheme 1c).

Our preliminary exploration started from the photocatalytic CDC reaction of *N*-methylquinoxalin-2(1*H*)-one (**1a**) as the template substrate, ethanol (3 equiv., **2a**) as the coupling reagent, and 3 mol% of Rhodamine B as the photocatalyst. When the reaction mixture was irradiated by a 3 W blue LED lamp (465 nm) in acetonitrile under air exposure for 12 h, the ex-

pected 3-ethoxy-*N*-methylquinoxalin-2(1*H*)-one (**3aa**) was generated in 21% NMR yield (Table 1, entry 1). Inspired by this experimental result, various photocatalysts were screened (entries 2–6). Among these examined photocatalysts, 9-mesityl-10-methylacridinium (Acr⁺-MesClO₄[−]) was the optimal catalyst, furnishing product **3aa** in 95% yield (entry 5). Varying the loading of the catalyst (entries 7–9) revealed that the Acr⁺-MesClO₄[−] loading could be reduced to 2 mol% without any impact on the yield of **3aa** (entry 8). Next, the screening of the amount of EtOH did not afford better results (entries 10–11). A series of solvents was investigated (entries 12–16), and the results showed that the solvents played a pivotal role in

Table 1

Optimization of the reaction conditions ^{a,b}.

Entry	Photocatalyst (mol%)	Solvent	Yield (%)
1	Rhodamine B (3)	MeCN	21
2	Rose Bengal (3)	MeCN	N.R.
3	Eosin Y (3)	MeCN	N.R.
4	Eosin B (3)	MeCN	N.R.
5	Acr ⁺ -Mes ClO ₄ [−] (3)	MeCN	95
6	Ru(bpy) ₃ Cl ₂ ·6H ₂ O (3)	MeCN	N.R.
7	Acr ⁺ -Mes ClO ₄ [−] (4)	MeCN	95
8	Acr ⁺ -Mes ClO ₄ [−] (2)	MeCN	95
9	Acr ⁺ -Mes ClO ₄ [−] (1)	MeCN	82
10 ^c	Acr ⁺ -Mes ClO ₄ [−] (2)	MeCN	95
11 ^d	Acr ⁺ -Mes ClO ₄ [−] (2)	MeCN	72
12	Acr ⁺ -Mes ClO ₄ [−] (2)	EtOAc	80
13	Acr ⁺ -Mes ClO ₄ [−] (2)	THF	N.R.
14	Acr ⁺ -Mes ClO ₄ [−] (2)	DMF	N.R.
15	Acr ⁺ -Mes ClO ₄ [−] (2)	DMSO	N.R.
16	Acr ⁺ -Mes ClO ₄ [−] (2)	DCE	N.R.
17 ^e	Acr ⁺ -Mes ClO ₄ [−] (2)	EtOH	75
18 ^f	Acr ⁺ -Mes ClO ₄ [−] (2)	MeCN	N.R.
19 ^g	Acr ⁺ -Mes ClO ₄ [−] (2)	MeCN	trace
20 ^h	Acr ⁺ -Mes ClO ₄ [−] (2)	MeCN	95
21	—	MeCN	N.R.

^a Reaction conditions: **1a** (0.1 mmol), **2a** (0.3 mmol), photocatalyst, solvent (0.5 mL), 3 W blue LED lamp (460–465 nm), r.t., ambient air, 12 h. ^b Estimated by ¹H NMR using diethyl phthalate as internal reference. ^c 4 equiv. of EtOH was used. ^d 2 equiv. of EtOH was used. ^e 0.5 mL of EtOH was used. ^f Under the irradiation of 3 W green LED lamp (525–530 nm). ^g Under the irradiation of sunlight. ^h Pure oxygen gas was used.

Scheme 1. Cross-dehydrogenation coupling reaction of quinoxalin-2(1*H*)-ones and alcohols.

this transformation. Only in acetonitrile and ethyl acetate did the reaction occur smoothly (entries 8 and 12). Other reaction media, such as THF, DMF, DMSO, and DCE, did not support the visible-light photocatalytic CDC reaction (entries 13–16). Changing MeCN to EtOH resulted in the production of the expected product (**3aa**) in a 75% yield (entry 17). When the model reaction was performed under irradiation by the 3W green LED lamp or sunlight, only trace or 16% yield of the desired product (**3aa**) was observed, respectively (entries 18 and 19). The reaction with dioxygen as an oxidant did not provide a better result (entry 20). No CDC reaction was observed in the absence of $\text{Acr}^+-\text{MesClO}_4^-$ (entry 21).

With the optimized conditions (Table 1, entry 8), the reaction scope of quinoxalin-2(1*H*)-ones and the alcohols was explored. The representative results are illustrated in Tables 2 and 3, it is evident that our photocatalytic CDC reaction turned out to be rather general. Firstly, a wide range of functionalized quinoxalin-2(1*H*)-ones was well achieved, and the isolated yields were mostly $\geq 80\%$. The nitrogen atom of quinoxalin-2(1*H*)-one with various chain-length substituents (alkyl and functionalized phenyl substituents) on nitrogen atom underwent the transformation efficiently (**3aa–3ka**). Importantly, a series of valuable functional groups, such as alkenyl (**3da**), alkynyl (**3ea**), and ester (**3ha–3ia**) groups were well compatible in the standard conditions, which made this eco-friendly reaction more useful for further transformations. Quinoxalin-2(1*H*)-ones containing electron-withdrawing, -neutral, and -donating substituents at the phenyl ring could stereo-selectively and highly efficiently generate the desired products (**3la–3ta**). A series of functional groups including nitro (**3la**), fluoro (**3ma**), chloro (**3na**), bromo (**3oa**), and tri-

Table 2

Scope of quinoxalin-2(1*H*)-ones ^a.

^a Reaction conditions: **1** (0.3 mmol), EtOH (0.9 mmol), MeCN (1.5 mL), $\text{Acr}^+-\text{MesClO}_4^-$ (2 mol%), 3 W blue LED lamp, r.t., ambient air, 12 h.

Table 3

Scope of alcohols ^a.

^a Reaction conditions: **1a** (0.3 mmol), ROH (0.9 mmol), MeCN (1.5 mL), $\text{Acr}^+-\text{MesClO}_4^-$ (2 mol%), 3 W blue LED lamp, r.t., ambient air, 12 h.

fluoromethyl (**3pa** and **3qa**) at the different positions of the substrates were well tolerated. Di-substituted quinoxalin-2(1*H*)-ones also delivered the expected products (**3ra–3ta**) in good to excellent yields. However, no alkoxylation product was formed when *N*-free quinoxalin-2(1*H*)-one was used as the substrate.

Subsequently, a wide range of alcohols was investigated under the standard conditions to react with quinoxalin-2(1*H*)-ones (Table 3). Much to our satisfaction, the alcohols with various carbon-chain lengths, isomeric structures, and functional groups underwent the present CDC reaction efficiently generating the desired 3-alkoxyquinoxalin-2(1*H*)-ones in high yields (**3ab–3aq**). The straight-chain alkyl alcohols (**1a–1d** and **1k–1o**) as well as the bulky cycloalkyl alcohols (**1i–1j**) afforded the target products in good to excellent yields. Moreover, the alcohol substrates with important functional groups such as alkoxy (**3ak**), cyano (**3al**), trifluoromethyl (**3am**), and alkynyl (**3an**) groups all afforded the desired products in good yields, which provided an opportunity for subsequent manipulation. The eco-friendly and mild approach was also applied to complex natural alcohols, such as *L*-menthol and borneol, producing the expected products (**3ap** and **3aq**) in 72% and 77% isolated yields, respectively. When phenol was employed as a substrate, no reaction occurred.

To demonstrate the utility of the present photocatalytic CDC reaction, both a large-scale synthetic reaction and a one-pot transformation were carried out. As shown in Scheme 2a, the photocatalytic alkoxylation reaction of *N*-methylquinoxalin-2(1*H*)-one was conducted at 8 mmol scale under the standard conditions, resulting in an 88% yield of **3aa**. However, decreasing the amount of EtOH to 2.5 equiv. led to a decrease in the **3aa** yield (76% yield). In combination with the clean reaction conditions and the outstanding leaving performance of methoxyl group, a one-pot sequential photocatalytic methoxylation/ $\text{S}_{\text{N}}\text{Ar}$ nucleophilic substitution reaction can be successfully achieved (Scheme 2b).

Scheme 2. Large-scale synthetic reaction and one-pot transformation.

Scheme 3. Mechanistic studies.

To gain insight into the reaction mechanism, some control experiments were conducted, as shown in Scheme 3. The addition of a radical scavenger (TEMPO or BHT) into the reaction mixture completely inhibited the photocatalytic reaction, indicating that the present transformation might proceed through a free-radical process (Scheme 3a). When the model reaction was conducted under a nitrogen atmosphere, no product **3aa** was generated and the starting material (**1a**) was quantitatively recovered (Scheme 3b). As shown in Fig. 1, this time-profile of photocatalytic CDC reaction indicated that the developed reaction was entirely suppressed in the absence of visible light irradiation. These experimental results suggested that continuous visible-light irradiation is necessary for the photocatalytic CDC reaction.

A plausible mechanistic cycle for the photocatalytic CDC reaction of quinoxalin-2(1*H*)-ones and alcohols based on the control experiments and literature reports [22,48,57] is shown in Scheme 4. The reaction initiated with the activation of acridinium catalyst **A** by the irradiation of visible light, generating the excited-state species (**B**), which subsequently undergoes a single-electron transfer (SET) process along with quinox-

Fig. 1. On/off experiments.

Scheme 4. Proposed reaction mechanism.

lin-2(1*H*)-one **1** to afford the corresponding radical cation intermediate (**C**) and the acridine radical (**D**). Subsequently, alcohol **2** attacks the C3 position of intermediate **C** as a nucleophile to form radical **E**, which can be oxidized by dioxygen to generate the expected product (**3**) with the release of a hydroperoxy radical. Finally, the hydroperoxy radical oxidizes the acridine radical (**D**) to produce the ground-state catalyst (**A**) and the hydroperoxy anion through a SET process. The hydroperoxy anion coupled with hydrogen ion to form the side-product, hydrogen peroxide.

In conclusion, we have reported for the first time, a visible-light photocatalytic C(sp²)-H/O-H cross-dehydrogenation coupling of quinoxalin-2(1*H*)-ones and alcohols employing ambient air as an oxidant at room temperature, providing an eco-friendly and efficient route to access a wide range of 3-alkoxylquinoxalin-2(1*H*)-ones. The easily available raw materials, low catalyst loading (2 mol%), excellent functional group tolerance, sustainable dioxygen oxidant, metal-free reaction conditions, good to excellent yields, excellent atom-economy, and scalability of the present photocatalytic reaction make it very attractive in the pharmaceutical industry and for organic synthesis.

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Graphical Abstract

Chin. J. Catal., 2020, 41: 1168–1173 doi: S1872-2067(19)63526-6

C(sp²)-H/O-H cross-dehydrogenative coupling of quinoxalin-2(1H)-ones with alcohols under visible-light photoredox catalysis

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An efficient and practical procedure for the synthesis of 3-alkoxyquinoxalin-2(1H)-ones through the visible-light photocatalytic cross-dehydrogenation coupling of quinoxalin-2(1H)-ones and alcohols, with ambient air as the sole oxidant at room temperature, was developed.

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可见光催化喹喔啉-2(1*H*)-酮与醇C(sp²)-H/O-H交叉脱氢偶联反应

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摘要: 杂环化合物和醇的C(sp²)-H/O-H交叉脱氢偶联反应为制备杂环醚类化合物提供了一种原子和步骤经济性的方法。然而, 已经报道的交叉脱氢偶联反应大部分需要使用过渡金属催化剂和/或者强氧化剂, 不仅产生环境问题还增加分离成本。同时, 这些合成方法还存在杂环化合物和醇的C(sp²)-H/C(sp³)-H交叉脱氢偶联反应的竞争反应, 降低了反应的选择性和收率。

喹喔啉-2(1*H*)-酮是生物活性物质和人工药物的核心骨架结构之一, 合成多样性官能化的喹喔啉-2(1*H*)-酮备受关注。近期多种C-3官能化喹喔啉-2(1*H*)-酮的合成方法被报道, 但是目前没有一例通过无金属无强氧化剂条件下的喹喔啉-2(1*H*)-酮与醇C(sp²)-H/O-H交叉脱氢偶联反应合成3-烷氧基喹喔啉-2(1*H*)-酮的相关工作报道。值得一提的是, 利用氧气作为氧化剂的可见光催化反应符合绿色化学的要求, 在最近几年中发展迅速。

本文报道了一种通过可见光催化的喹喔啉-2(1*H*)-酮与醇的C(sp²)-H/O-H交叉脱氢偶联反应合成3-烷氧基喹喔啉-2(1*H*)-酮化合物的绿色制备方法。首先通过对光催化剂、溶剂等参数的筛选, 确定了最佳反应条件为喹喔啉-2(1*H*)-酮化合物0.3 mmol, 醇0.9 mmol, 乙腈1.5 mL, Acr⁺-MesClO₄⁻ 2 mol%, 空气作为氧化剂, 3 W蓝光作为光源。在最佳条件下, 含有供电子、吸电子取代基的喹喔啉-2(1*H*)-酮化合物和含有各种取代基的烷基醇都能很好地进行反应, 得到36种目标化合物, 产率70%~94%。另外, 成功完成了克级放大实验和一锅法串联反应。机理研究证明, 该反应是喹喔啉-2(1*H*)-酮化合物在光催化氧化作用下生成自由基正离子, 醇作为亲核试剂选择性进攻自由基正离子的C3位, 最后得到目标产物。

关键词: 喹喔啉-2(1*H*)-酮; 醇; 可见光催化; 交叉脱氢偶联反应; 无金属反应

收稿日期: 2019-11-30. 接受日期: 2019-12-28. 出版日期: 2020-08-05.

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基金来源: 湖南省自然科学基金(2019JJ20008).

本文的电子版全文由Elsevier出版社在ScienceDirect上出版(<http://www.sciencedirect.com/science/journal/18722067>).