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Sono-photocatalytic amination of quinoxalin-2(1*H*)-ones with aliphatic amines

Wen-Tao Ouyang[a], Jun Jiang[a], Yan-Fang Jiang[a], Ting Li[a,c], Yuan-Yuan Liu[a], Hong-Tao Ji[a], Li-Juan Ou[b,*], Wei-Min He[a,*]

[a] School of Chemistry and Chemical Engineering, University of South China, Hengyang 421001, China
[b] School of Materials Science and Engineering, Hunan Institute of Technology, Hengyang 421002, China
[c] National Engineering Research Center of Low-Carbon Processing and Utilization of Forest Biomass, Nanjing Forestry University, Nanjing 210037, China

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ABSTRACT

The first example of sono-photocatalytic bond formation was reported. With both visible light and ultrasound wave as the energy, various 3-aminoquinoxalin-2(1*H*)-ones were efficiently obtained with good functional group tolerance in the absence of any additive or external photocatalyst. Compared with the conventional photocatalysis, sono-photocatalysis not only dramatically improved the reaction rates and yields, but also reduced energy consumption.

Visible-light photoredox catalysis has emerged as a highly versatile tool in synthetic synthesis, which employs sustainable light energy to promote organic bond formations [1-5]. Much progress has been achieved in the field of photocatalytic synthesis over the past decades. However, the practical application of photocatalytic synthesis still has limitations due to long reaction times and accompanying undesired side reactions. In recent years, ultrasound (US) has demonstrated its efficacy as an alternative and milder approach to conventional thermal synthesis by accelerating reaction rates, increasing product yields, and reducing the formation of unwanted by-products [6-9]. The cavitation effect produced by ultrasound energy produces extremely high localized pressures and temperature which lead to the enhancement in solubility, diffusivity, and mass transportation. Sono-photocatalysis, which is characterized by merits of the combination of ultrasonic synthesis and visible light photosynthesis, shows interesting advantages at the kinetic level and energy consumption [10-13]. The synergistic effect of ultrasound irradiation and light irradiation can be observed when sono-photocatalytic oxidation rate constant of organic pollutants degradation is higher than that of the photocatalytic counterpart. To the best of our knowledge, the sono-photocatalytic organic bond formation reaction has never been reported.

Quinoxalin-2(1*H*)-one and its derivatives are extensively recognized as valuable *N*-heterocycles due to their abundance in tremendous biologically active molecules [14-15]. Therefore, a series of synthetic protocols for functionalized quinoxalin-2(1*H*)-ones through C–H functionalization have been well developed [16-19], which includes alkylation [20-27], arylation [28-33], acylation [34-37], amidation [38-39], amination [40-45], aminoalkylation [46-51], sulfenylation [52-53] and trifluoromethylation [54-55]. Among these derivatives, 3-aminoquinoxalin-2(1*H*)-ones are particularly attractive due to their unique physiochemical and pharmacological properties. Consequently, various efforts have been made to develop the C–H amination of quinoxalin-2(1*H*)-ones.

The direct application of abundant simple chemical feedstocks for producing value-added chemicals has become a long-standing goal in green and sustainable chemistry. In this regard, amines have been widely used as the amino source in C–N bond formations because of its low cost and commercial availability. In 2016, Cui and colleagues pioneered the copper-catalyzed oxidative amination of quinoxalin-2(1*H*)-ones with aliphatic amines (Scheme 1a) [40]. Later, Nidhi Jain's group reported the molecular iodine-catalyzed aminations with THBP as the oxidant (Scheme 1b) [41]. In 2018, Wei and co-workers developed the first example of visible light induced amination of quinoxalin-2(1*H*)-ones with Eosin Y as the photocatalyst (Scheme 1c) [42]. Although the above-mentioned methods are favorable, there are still some limitations as follows: (1) The requirement of external homogeneous catalysts and/or

* Corresponding authors.
E-mail addresses: oulijuanann@163.com (L.-J. Ou), weiminhe@usc.edu.cn (W.-M. He).

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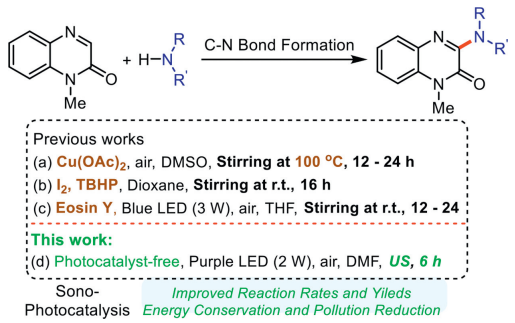
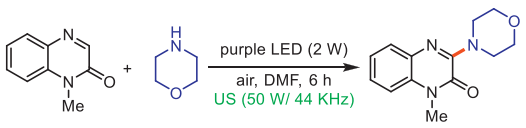


Scheme 1. Amination of quinoxalin-2(1*H*)-ones with aliphatic amines.

stoichiometric harmful chemical oxidants; (2) long reaction time (>12 h). Consequently, developing an environmentally friendly and practical method for the construction of 3-aminoquinoxalin-2(1*H*)-ones under external catalyst-free and mild conditions is highly challenging and desirable. As part of our continuing interest in green synthesis [56-62], we hereby report the sono-photocatalytic amination of quinoxalin-2(1*H*)-ones with aliphatic amines under external photocatalyst-free conditions. To the best of our knowledge, this is the first example of sono-photocatalytic bond formation.

In the initial assessment of sono-photocatalytic amination, the reaction of quinoxalin-2(1*H*)-ones (**1a**) and morpholine (**2a**) was selected as the model reaction. The 3–aminoquinoxalin-2(1*H*)-one (**3aa**) was produced in 83% GC yield by carrying out this reaction with ambient air in DMF upon the irradiation of a purple LED (390 nm, 2 W) under 44 KHz ultrasound irradiation in a cleaning bath (50 W) for 6 h without the addition of any photocatalyst and additive (Table 1, entry 1). Changing the LED light with different wavelengths reduced reaction efficiency (entries 2–4). Increasing the power of LED light from 2 W to 5 W has a negative impact on this amination process, leading to the decomposition of **3aa** (entry 5). Performing the sono-photocatalytic reaction under 30 W/44 KHz or 50 W/22 KHz delivered **3aa** in a lower yield (entries 6 and 7). Only 59% GC yield of **3aa** was observed when the reaction was conducted under conventional stirring at room temperature (entry 8). Replacing DMF with other common solvents resulted in a lower yield (entries 9–12). No improvement in this transformation was observed when pure oxygen was used instead of air (entry 13). The reaction did not occur under a nitrogen atmosphere, demonstrating the critical role of molecular oxygen (entry 14). In addition, no progress was observed in the absence of visible light, which indicated the necessity of visible light to promote the reaction (entry 15).

Table 1
Optimization of reaction conditions.[a]



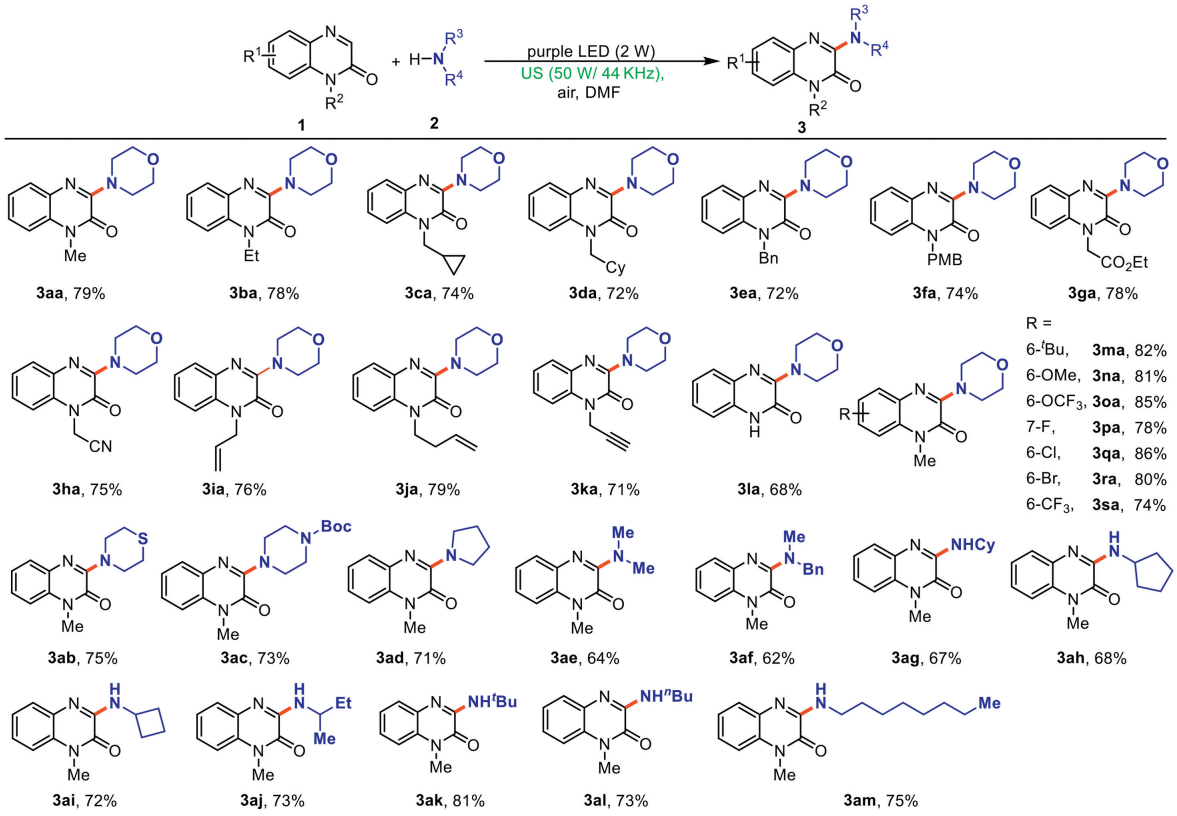
Entry	Varying from the standard conditions	Yield (%)[b]
1	No	83
2	White LED instead of purple LED	29
3	Blue LED instead of purple LED	51
4	Green LED instead of purple LED	trace
5	Purple LED (5 W) instead of purple LED (2 W)	62
6	US (30 W) instead of US (50 W)	68
7	US (22 kHz) instead of US (44 kHz)	73
8	Stirring at r.t. instead of US	59
9	MeCN instead of DMF	48
10	DMSO instead of DMF	53
11	THF instead of DMF	44
12	EtOAc instead of DMF	36
13	O_2 instead of air	81
14	N_2 instead of air	N.R.
15	Without light	N.R.

[a] Conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), DMF (1 mL), purple LED (2 W), US, air, r.t., 6 h.
[b] Estimated by GC using dodecane as an internal reference.

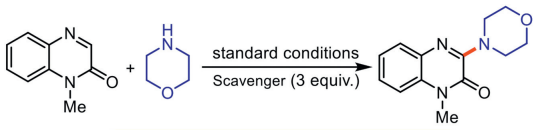
Having established the optimized conditions (Table 1, entry 1), the scope of quinoxalin-2(1*H*)-ones was firstly investigated (Scheme 2). To our delight, a series of *N*-substituted quinoxalin-2(1*H*)-ones **1** reacted well with morpholine **2a** to generate the target products **3** with moderate to good yields. *N*-Substituted quinoxalinones with a variety of aliphatic groups (**3aa**-**3ha**) including methyl, ethyl, cyclopropylmethyl, cyclohexylmethyl, benzyl, *p*-methoxybenzyl (PMB), ethoxycarbonylmethyl and cyanomethyl could well couple with **2a** in the sono-photocatalytic system. The unsaturated alkenyl and alkynyl groups were also compatible under the standard conditions to deliver **3ia**-**3ka** in good yields, respectively. Moreover, the unprotected quinoxalin-2(1*H*)-one was found to be a suitable substrate to give the desired product **3la** with 68% yield. The *N*-methylquinoxalin-2(1*H*)-one **1**, comprising an electron-donating substituents (-^{t}Bu, -OMe and OCF_3) or an electron-withdrawing substituents (-F, -Cl, -Br and -CF_3) at the phenyl part was also compatible with this procedure to afford the corresponding product (**3ma-3sa**) with yields in the range of 74%–86%. Subsequently, the compatibility of aliphatic amines was explored. Both cyclic (thiomorpholine, *N*-Boc-piperazine and pyrrolidine) and acyclic (dimethylamine and *N*-benzylmethylamine) secondary amines showed good reactivities, and the target products **3ab-3af** were generated in moderate to good yields. The present protocol also worked well with primary amines. In addition, primary amines with various isomeric structures and chain lengths had little influence in the reaction outcome as the yields of aminated products (**3ag**-**3am**) were good. However, no reaction was observed between **1a** and aniline.

To gain insights into the mechanism, a series of mechanistic investigations were performed. With a radical scavenger (TEMPO or BHT) as the additive, the amination reaction was fully suppressed (Schemes 3a and b), suggesting that this photocatalytic process was a radical pathway. The addition of a superoxide radical anion ($O_2^{\cdot-}$) scavenger 1,4-benzoquinone (Scheme 3c), a singlet oxygen ($^1O_2$) scavenger 1,4-diazabicyclo[2.2.2]octane (Scheme 3d) or peroxide radical ($HO_2^{\cdot}$) scavenger $FeSO_4$ (Scheme 3e) significantly inhibited this transformation, indicating that $O_2^{\cdot-}$, $^1O_2$ and $HO_2^{\cdot}$ played critical roles in this reaction. By comparison, hydroxyl radical ($HO^{\cdot}$) scavenger isopropanol had no effect upon the reaction efficiency (Scheme 3f). Only a trace amount of **3aa** was observed when a single electron transfer (SET) inhibitor ($CuCl_2$) was added (Scheme 3g), revealing that a SET process might be involved in the coupling process [63]. In addition, the results of ultraviolet visible absorption experiments manifested that the both substrate **1a** and product **3aa** could absorb visible light and act as photocatalysts in the present transformation (Fig. S2 in Supporting information). The light on/off experimental results revealed that continuous light irradiation was indispensable for the transformation, which ruled out any possibility of radical propagation pathway (Fig. S3 in Supporting information).

On the basis of the above experimental results and related literature [64-66], a possible mechanism for this self-photocatalyzed radical amination was proposed in Scheme 4. Upon irradiation by purple LED, the absorption of photons in the substrate **1a** resulted in the formation of excited-species **1a***, which underwent an energy transfer (EnT) process with ground-state triplet oxygen ($^3O_2$) to generate the active excited-state singlet oxygen ($^1O_2$) along with regeneration of ground-state **1a**. The $^1O_2$ reacted with



Scheme 2. Reaction scope. Conditions: **1** (0.2 mmol), **2** (0.4 mmol), DMF (1 mL), purple LED (2 W), US, air, r.t.

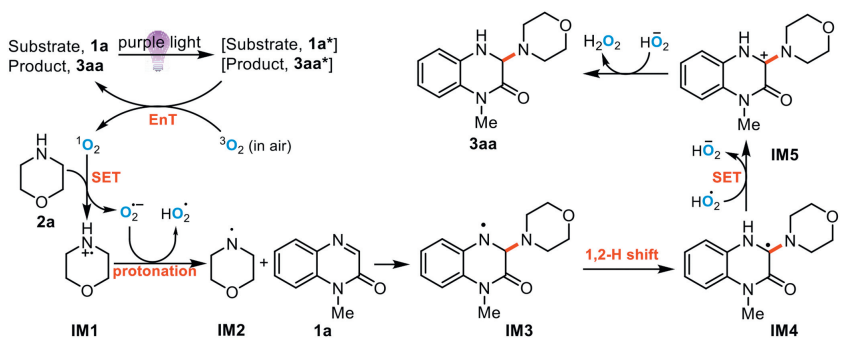


	Scavenger	Active Species	3aa
(a)	TEMPO	radical	trace
(b)	BHT	radical	trace
(c)	1,4-benzoquinone	$O_2^{\cdot-}$	trace
(d)	DABCO	$^1O_2$	trace
(e)	$FeSO_4$	$HOO^{\cdot}$	17%
(f)	*tert*-butanol	$HO^{\cdot}$	78%
(g)	$CuCl_2$	SET	trace

Scheme 3. Control experiments.

morpholine (**2a**) gave a morpholine radical cation (**IM1**) and a $O_2^{\cdot-}$, which abstracted a proton from **IM1** to produce the $HO_2^{\cdot}$ and nitrogen-centered morpholine radical (**IM2**). Next, the radical **IM2** region-selectively attacked quinoxalinone **1a** to yield the nitrogen-centered radical **IM3**, which converted into carbon centered morpholine radical (**IM4**) through the process of a 1,2-H shift. The higher active $HOO^{\cdot}$ oxidized **IM4** into carbocation intermediate **IM5** *via* a SET process. Finally, the dehydrogenation and re-aromatization of **IM5** gave the target aminated product **3aa** along with the generation of H_2O_2 (detected by H_2O_2 test paper). In addition, **3aa** could also serve as the photo-catalyst to achieve the photoredox catalytic cycle.

To sum up, we have developed the first example of sono-photocatalytic C–N bond formation. With both visible light and ultrasound wave as the energy, a series of 3-aminoquinoxalin-2(1*H*)-ones were efficiently obtained with good functional group tolerance in the absence of any additive or external photocatalyst. Compared with the conventional photocatalysis, sono-photocatalysis not only dramatically improved the reaction rates and yields, but also reduced energy consumption. The mechanistic studies manifested that the dual function of quinoxalin-2(1*H*)-ones simpli-



Scheme 4. Proposed reaction mechanism.

fied the reaction system. Moreover, this reaction involved an EnT process, a protonation process, a 1,2-H shift and two SET processes. We believe that the present strategy not only provides an eco-friendly synthetic method for 3-aminoquinoxalin-2(1*H*)-one derivatives but also develops the ultrasound chemistry and visible light photocatalysis.

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.

CRediT authorship contribution statement

Wen-Tao Ouyang: Validation. **Jun Jiang:** Supervision. **Yan-Fang Jiang:** Validation. **Ting Li:** Validation. **Yuan-Yuan Liu:** Validation. **Hong-Tao Ji:** Validation. **Li-Juan Ou:** Supervision. **Wei-Min He:** Writing – original draft.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2024.110038.

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