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Letter

Visible-Light-Induced Regioselective Dicarbonylation of Indolizines with Oxoaldehydes via Direct C−H Functionalization

Lili Teng, Xiang Liu, Pengfeng Guo, Yue Yu,* and Hua Cao*

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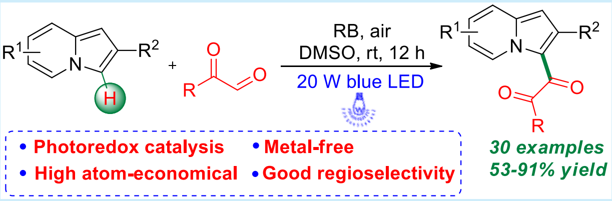
ABSTRACT: A metal-free system for regioselective dehydrogenative cross-couplings between indolizines and oxoaldehydes catalyzed by visible light under mild conditions has been described. As an atom economical and eco-friendly protocol, the reaction proceeds in good yields using inexpensive, readily available visible-light sources and the environmentally friendly oxidant oxygen. Various valuable 1,2-dicarbonyl derivatives attached to an indolizine core were easily accessed by the direct dicarbonylation of the sp^2 C−H bond.

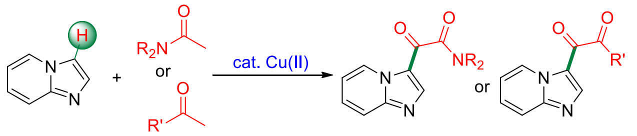


Indolizine derivatives, important and unique single-nitrogen heterocycles that frequently exist in nature, have been extensively applied in biological chemistry, pharmaceuticals, agrochemicals, and functional organic materials.[1,2] Chemists have spent a great deal of time synthesizing a range of indolizine derivatives in the past two decades.[3] Among these synthetic routes, the transition metal-mediated dehydrogenative cross-coupling reaction has exhibited tremendous advantages in building the C−C bond directly from relatively simple starting materials, such as a low catalyst load, ready availability, atom economy, and the lack of a requirement that it be prefunctionalized.[4] In particular, a stupendous and exquisite achievement has been realized in the metal-catalyzed C−H bond dicarbonylation of a nitrogen-containing heterocycle to synthesize 1,2-dicarbonyl compounds.[5] 1,2-Dicarbonyl derivatives are applied as fluorescent materials in the chemical industry and used in bioactive molecules and drug discovery.[6] This key structural unit was generally synthesized by the oxidation of 1,2-diols,[7] alkyne,[8] and alkene.[9] In 2015, our group[10] disclosed a Cu(II)-catalyzed oxidative coupling of imidazo[1,2-*a*]pyridines with N,N-disubstituted acetamide or ketone in the presence of an acidic mixture and an oxygen atmosphere that produced imidazo[1,2-*a*]pyridine-derived 1,2-dicarbonyl compounds (Scheme 1a). Despite some elegant surveys of catalysis by transition metals, the development of a new, cleaner, more environmentally friendly, and greener approach is still highly desirable.

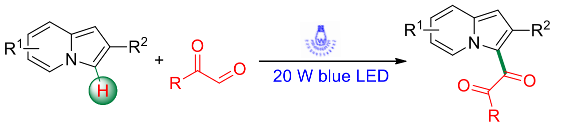
The past decade has witnessed a dramatic increase in the amount of research in the area of organic photocatalysis. Also, photocatalytic transformations are considered to be appealing synthetic protocols for the activation of C−H bonds due to their sustainable and green nature.[11] Recently, organic dyes, as efficient photocatalysts that are inexpensive and readily available, have been widely used in diverse photocatalytic C−H functionalizations.[12] For example, Wu et al. reported the first case of a cross-coupling hydrogen evolution reaction between indole and tertiary amine by a combination of visible-light catalysis utilizing eosin Y as the photosensitizer and G-RuO_2 catalysis.[13] However, to the best of our knowledge, visible-light-driven direct dehydrogenative cross-couplings between indolizines and oxoaldehydes have not been studied. As a continuation of our research on C−H bond functionalization of nitrogen-containing heterocycles,[14] herein we report a straightforward protocol for visible-light-induced regioselective C−H bond dicarbonylation of indolizines using Rose Bengal (RB) as the photosensitizer under an air atmosphere (Scheme 1b).

Scheme 1. Our Study of the Synthesis of 1,2-Diketones via C−H Functionalization

a. Copper-catalyzed dicarbonylation of imidazo[1,2-*a*]pyridines: Our previous work



b. Visible-light-induced regioselective dicarbonylation of indolizines: This work



We choose easily prepared compound 2-phenylindolizine (**1a**) and 2-oxo-2-phenylacetaldehyde (**2a**) as our starting materials to investigate the visible-light-driven dicarbonylation

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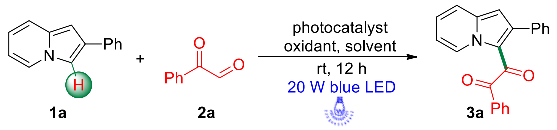
reaction; the screening conditions are summarized in Table 1. When RB was used as the photosensitizer, under 20 W blue light-emitting diode (LED) irradiation, raw materials **1a** and **2a** could react in an air atmosphere at room temperature and be converted to dicarbonylated indolizine in 75% yield (entry 1). To further improve the efficiency of the transformation, we tried to screen different photosensitizers, such as eosin Y, eosin B, rhodamine 6G, and fluorescein. The experimental results showed that although these photosensitizers could also promote the reaction, the yield has not been further improved (Table 1, entries 2−5). As we know, organic solvents have an effect on photochemical reaction, so we studied visible-light-induced dicarbonylation under various solvents, such as CH_2Cl_2, DMSO, DMF, toluene, and acetone (entries 6−10, respectively). Inspiringly, the product yield in DMSO was as high as 88%. When the reaction atmosphere was changed from oxygen to open air, the yield of the target product was increased to 91% (entry 11). In addition, some traditional oxidants such as TBHP and $K_2S_2O_4$ have been added to the reaction mixture, which has led to a dramatic decrease in the yield of dicarbonyl compounds (entry 12).

Table 1. Optimization of Reaction Conditions[a]

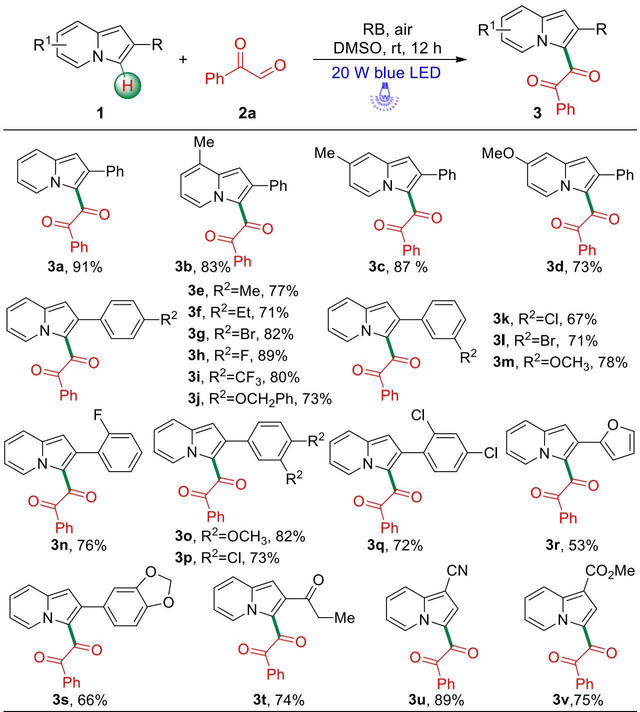


entry	photocatalyst	oxidant	solvent	yield (%)[b]
1	RB	O_2	MeCN	75
2	eosin Y	O_2	MeCN	63
3	eosin B	O_2	MeCN	65
4	rhodamine 6G	O_2	MeCN	73
5	fluorescein	O_2	MeCN	70
6	RB	O_2	CH_2Cl_2	73
7	RB	O_2	DMSO	88
8	RB	O_2	DMF	78
9	RB	O_2	toluene	69
10	RB	O_2	acetone	56
11	RB	air	DMSO	91
12	RB	TBHP	DMSO	25

[a]Conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), photocatalyst (3 mol %), solvent (2 mL), 20 W blue LED, room temperature, air atmosphere, 12 h. [b]Determined by GC analysis.

Under the optimal photocatalytic conditions, we explored the functional group tolerance and substrate applicability of coupling reactions using numbers of substituted indolizines and 2-oxo-2-phenylacetaldehyde (**2a**). As shown in Scheme 2, various valuable 1,2-dicarbonyl derivatives attached to the indolizine core were easily produced (**3a**−**3v**). A substituent, such as -Me and -OMe, on the indolizine ring has little effect on the efficiency of the reaction and afforded the coupling products (**3b**−**3d**) in 73−87% yields. We further explored the effects of aryl substituents at position 2 of the indolizine (**1a**) on the reaction. These different aryl-substituted indolizines efficiently reacted with 2-oxo-2-phenylacetaldehyde to generate the respective C-3 dicarbonylated indolizine derivatives (**3e**−**3n**). In particular, the bromo-substituted 1,2-dicarbonyl indolizine derivative is a promising candidate for further transformations by a visible-light-induced intermolecular coupling reaction. To our delight, the reaction of 2-(furan-2-yl)indolizine with 2-oxo-2-phenylacetaldehyde (**2a**) was performed smoothly to produce product **3r** in 53% yield. Alkyl ketone at position 2 of the indolizine could efficiently undergo photocatalytic transformation to give the dicarbonylated indolizine product (e.g., **3t**, 74%). Additionally, cyano and esteryl indolizine produced molecules **3u** and **3v** in good yields (89% and 75%, respectively). On the basis of the results presented above, this work provided an atom economical and eco-friendly method for the preparation of functionalized indolizines under metal-free conditions.

Scheme 2. Substrate Scope of Indolizines[a]

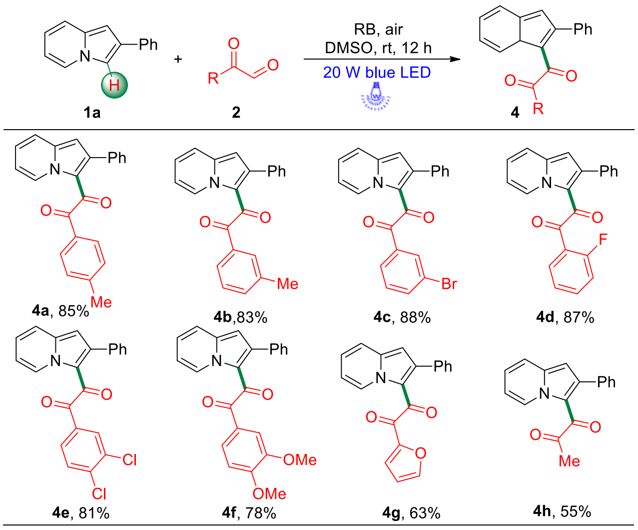


[a]Conditions: **1a** (0.5 mmol), **2a** (2.0 equiv), RB (3 mol %), DMSO (3 mL), 20 W blue LED, room temperature, air atmosphere, 12 h. Isolated yields.

To extend the substrate scope and limitations, we explored the use of 2-oxo-2-phenylacetaldehyde to synthesize C-3 dicarbonylated indolizine derivatives under optimized reaction conditions. As shown in Scheme 3, oxoaldehydes with substituents such as methyl, bromo, and fluoro groups at different positions of the aromatic ring also performed well with 2-phenylindolizine to give the coupling products (**4a**−**4d**) in 83−88% yields. Products **4e** and **4f**, in which the parent oxoaldehydes contained two chlorine and alkoxy groups, could be further derivatized in 81% and 78% yields, respectively. Notably, the use of 2-(furan-2-yl)-2-oxoacetaldehyde resulted in a moderate yield (**4g**, 63%). An alkylglyoxal such as methylglyoxal under the photocatalytic conditions gave product **4h** in a relatively low yield (55%).

As mentioned above, many indolizine derivatives exhibit good fluorescence properties and could be used as valuable fluorescent sensors in the field of luminescent materials. Therefore, we further investigated the photophysical property of dicarbonylated indolizine derivatives prepared by the method presented here. The relevant data are listed in Table 2 and shown in Figures 1 and 2. For example, compound **3a** displayed strong absorption (λ_{abs}) at a wavelength of ~380 nm in DMSO, MeCN, MeOH, DCM, DMF, and DCE and

Scheme 3. Substrate Scope of Oxoaldehydes[a]



[a]Conditions: **1a** (0.5 mmol), **2a** (2.0 equiv), RB (3 mol %), DMSO (3 mL), 20 W blue LED, room temperature, air atmosphere, 12 h. Isolated yields.

Table 2. Spectroscopic Data of Compound 3a in Different Solvents[a]

	DMSO	MeCN	MeOH	DCM	DMF	DCE
λ_{abs}[b] (nm)	385	382	383	384	384	384
λ_{em}[c] (nm)	435	430	434	434	430	478

[a]The extinction coefficient $\varepsilon = 4.23 \times 10^3$ L mol^{-1} cm^{-1}. [b]Longest wavelength absorption maximum. [c]Excited at the longest wavelength absorption maximum.

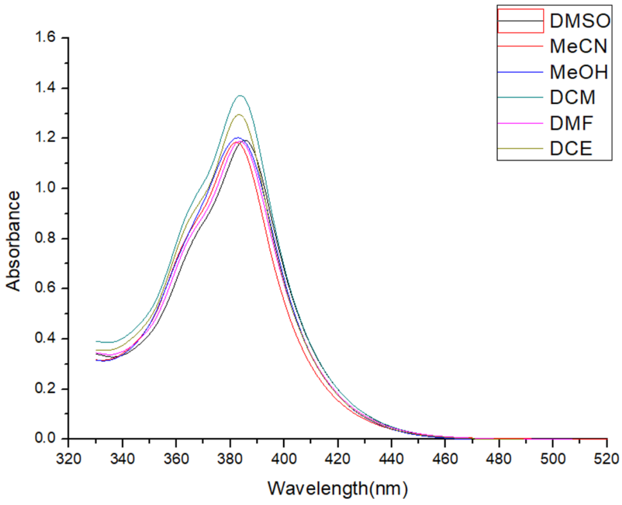


Figure 1. Absorption spectra of compound **3a**.

emission (λ_{em}) in the purple region (430−435 nm) in DMSO, MeCN, and DMF. It is worth noting that **3a** had the highest absorption intensity in DCM and the highest fluorescence emission intensity when using DMSO as the solvent.

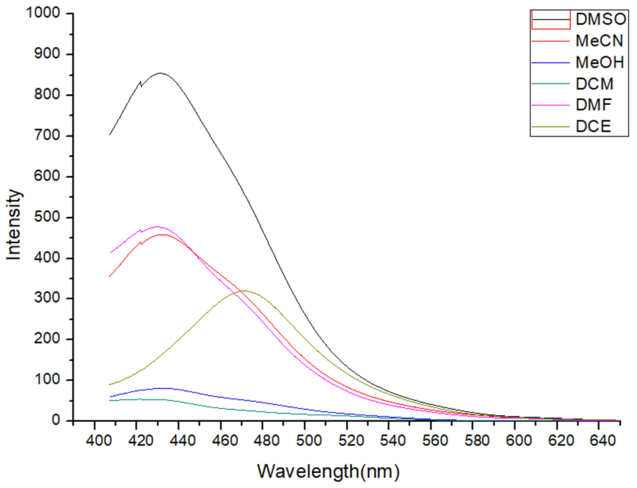
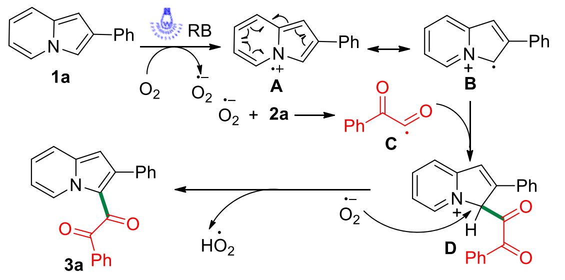


Figure 2. Emission spectra of compound **3a**.

Scheme 4. Possible Mechanism of the Photocatalytic Reaction



A possible mechanism based on our previous work[14d] and the literature reports[15] is depicted in Scheme 4. First, the photosensitizer RB was excited to its excited state Rose Bengal* under visible-light irradiation. Then, 2-phenylindolizine **1a** interacted with active Rose Bengal* in an oxygen atmosphere to generate radical intermediate **A** and superoxide radical anion ($O_2^{\bullet-}$) in the photoredox cycle. Intermediate **A** was quickly transformed to its radical resonance **B**. Also, **2a** was oxidized by the anion radical of O_2 to produce radical intermediate **C**. Subsequently, indolizine radical intermediate **B** could couple with carbonyl radical **C** to afford dicarbonylated indolizine cation **D**. Finally, cation **D** underwent electron transfer to give product **3a** along with H_2O_2.

In conclusion, we have developed an efficient and straightforward visible-light-induced approach to synthesize a number of dicarbonylated indolizine derivatives from indolizines and oxoaldehydes via dehydrogenative cross-couplings under metal-free conditions. This catalytic reaction proceeded with some unique advantages, such as good functional group tolerance, atom economy, good regioselectivity, and clean operation. In addition, the photophysical property of dicarbonylated indolizine derivatives has been documented. This transformation represents the first photocatalyzed dicarbonylation of indolizines.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01094.

Experimental details, characterization data, and NMR spectra of new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Yue Yu − *School of Chemistry and Chemical Engineering and Guangdong Cosmetics Engineering & Technology Research*

Center, Guangdong Pharmaceutical University, Zhongshan 528458, P. R. China; Email: yuyue@gdpu.edu.cn

Hua Cao − *School of Chemistry and Chemical Engineering and Guangdong Cosmetics Engineering & Technology Research Center, Guangdong Pharmaceutical University, Zhongshan 528458, P. R. China*; orcid.org/0000-0001-8825-0175; Email: caohua@gdpu.edu.cn

Authors

Lili Teng − *School of Chemistry and Chemical Engineering and Guangdong Cosmetics Engineering & Technology Research Center, Guangdong Pharmaceutical University, Zhongshan 528458, P. R. China*

Xiang Liu − *School of Chemistry and Chemical Engineering and Guangdong Cosmetics Engineering & Technology Research Center, Guangdong Pharmaceutical University, Zhongshan 528458, P. R. China*; orcid.org/0000-0001-6973-3809

Pengfeng Guo − *School of Chemistry and Chemical Engineering and Guangdong Cosmetics Engineering & Technology Research Center, Guangdong Pharmaceutical University, Zhongshan 528458, P. R. China*

Complete contact information is available at:
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Notes

The authors declare no competing financial interest.

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