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Acyl Radicals from α-Keto Acids: Metal-Free Visible-Light-Promoted Acylation of Heterocycles

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Cite This: *Org. Lett.* 2021, 23, 2976−2980 Read Online

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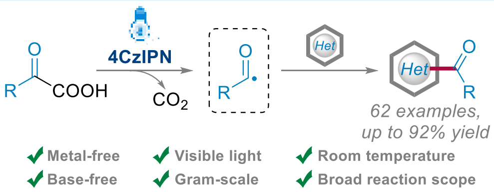
ABSTRACT: A general and metal-free visible-light-induced decarboxylative arylation procedure at room temperature was described for the construction of acylated heterocyclic derivatives, such as benzimidazo/indolo[2,1-*a*]isoquinolin-6(5*H*)-ones, aroylazaspiro[4.5]trienones, thioflavones, and so on. This practical arylation procedure was conducted by using 2,4,5,6-tetra(9*H*-carbazol-9-yl)isophthalonitrile (4CzIPN) as a photocatalyst under mild conditions, which avoided the use of an additional base, traditional heating, and metal reagents.

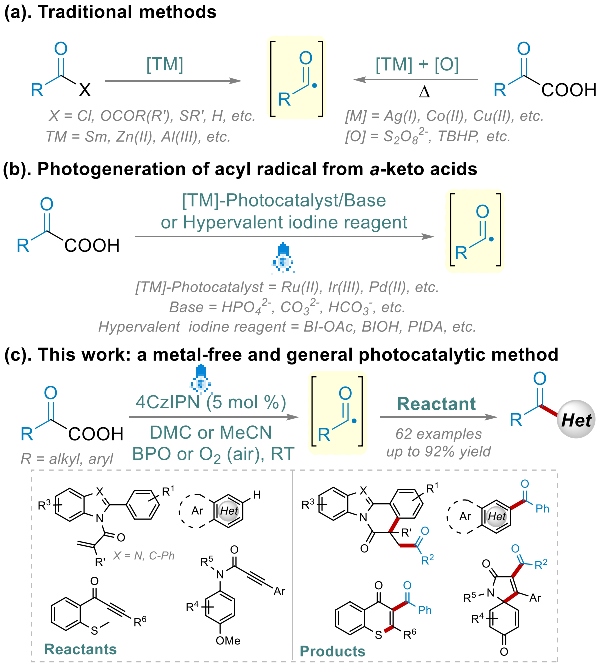


Ketone derivatives are an extremely essential class of carbonyl compounds that are usually employed as crucial structural scaffolds for organic synthesis and are one of the most common structural units in various organic molecules such as pesticides, natural bioactive products, and various drugs.[1] Thus the preparation of ketone derivatives has received extensive attention, and the radical acylation reaction is undoubtedly a quite efficient synthetic route. In general, acyl radicals could be produced from the C−X bond cleavage of RC(O)X[2] or the decarboxylation of α-keto acids[3] in the presence of transition metals/oxidants (Scheme 1a). However, these methods generally require elevated temperatures. From a green chemistry point of view, the development of an acylation reaction under mild conditions is highly attractive.

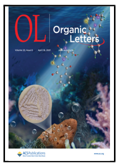
Visible-light-promoted organic reactions have arisen as sustainable strategies over the past decades.[4] Because of the mild conditions, the photogeneration of acyl radicals has been an alternative to the previously mentioned traditional methods.[5] With the irradiation of visible light, α-keto acids could be converted into acyl radicals for further transformations under mild conditions.[6] However, in most cases, high-cost noble-metal-based photocatalysts or stoichiometric amounts of hypervalent iodine reagents were necessary (Scheme 1b). Consequently, the exploration of metal-free and inexpensive photocatalytic procedures for the decarboxylative arylation reaction from α-keto acids has been enthusiastically pursued. Recently, metal-free organocatalysts including rose bengal,[7] eosin B,[8] and 2-chloro-thioxanthen-9-one[9] were demonstrated to be useful photocatalysts in the decarboxylation of α-keto acids. With our continuing interests in heterocycle synthesis and visible-light-induced reactions,[10] we herein disclose a metal-free and general photocatalytic procedure for the construction of various arylated heterocycles under mild conditions (Scheme 1c).

We initially started our study by using *N*-methacryloyl-2-phenylbenzoimidazole (**1a**) and phenylglyoxylic acid (**2a**) as model substrates under various conditions, as summarized in Table S1. After experimentation, the target product **3aa** was obtained in 86% yield under the optimal conditions: **1a** (0.2

Scheme 1. Synthesis of Acylated Heterocyclic Derivatives



Received: February 23, 2021
Published: March 29, 2021

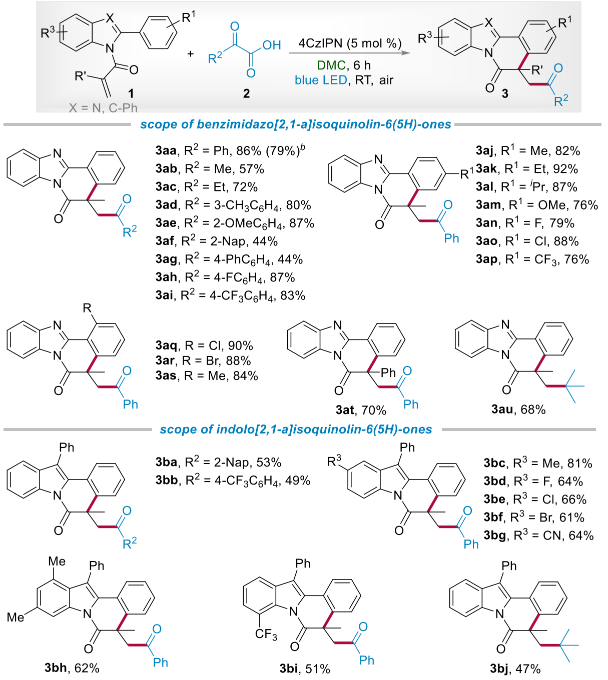


https://doi.org/10.1021/acs.orglett.1c00655
Org. Lett. 2021, 23, 2976−2980

mmol), **2a** (0.4 mmol), and 2,4,5,6-tetra(9*H*-carbazol-9-yl)isophthalonitrile (4CzIPN) (5 mol %) in dimethyl carbonate (DMC, 2 mL) as a green solvent at room temperature under the irradiation of a blue LED (5 W) and an air atmosphere for 6 h.

With the optimal conditions in hand, we further explored the scope of this reaction (Scheme 2). Initially, the suitability of a series of α-oxocarboxylic acids was investigated. As anticipated, the aliphatic and aromatic α-keto acids with both electron-donating and electron-withdrawing substituents such as −Me, −Ph, −OMe, −F, and $-CF_3$ could be converted into the desired annulation products (**3aa**−**3ai**) in good yields (44−87%). In general, aliphatic α-keto acids (**3ab**, **3ac**) provided slightly lower yields compared with aromatic α-keto acids (**3aa** and **3ad**−**3ai**). To our delight, *N*-methacryloyl-2-arylbenzoimidazoles bearing various electron-donating groups or electron-withdrawing groups could react with **2a** to give the corresponding target products (**3aj**−**3as**) in 76−92% yields. Specifically, when *N*-phenylacryloyl-2-phenylbenzoimidazole **1t** was employed as a substrate to react with **2a** under the standard conditions, the corresponding product **3at** was given in 70% yield. Next, the scope of the 2-aryl indoles was investigated. Halosubstituted indole derivatives, including F-, Cl-, and Br-bearing indoles, could afford the desired indolo[2,1-*a*]isoquinoline derivatives **3bd**−**3bf** in moderate yields (61−66%). Moreover, −Me, $-CF_3$, and −CN on the indole ring could also be compatible to provide the corresponding products (**3bc**, **3bg**−**3bl**) in 51−81% yields. Additionally, when we used 3,3-dimethyl-2-oxobutyric acid as the acyl radical precursor, the unexpected products (**3au** and **3bj**) were obtained in 68 and 47% yields, respectively. In this process, the *in situ* generated acyl radical was converted into the more stable *tert*-butyl radical via decarbonylation. Moreover, to evaluate the practicability of this acylation reaction, the gram-scale synthesis of **3aa** was carried out, and a 79% yield was obtained, suggesting that the current protocol is practical and promising for preparative synthesis. (For details, see the Supporting Information.)

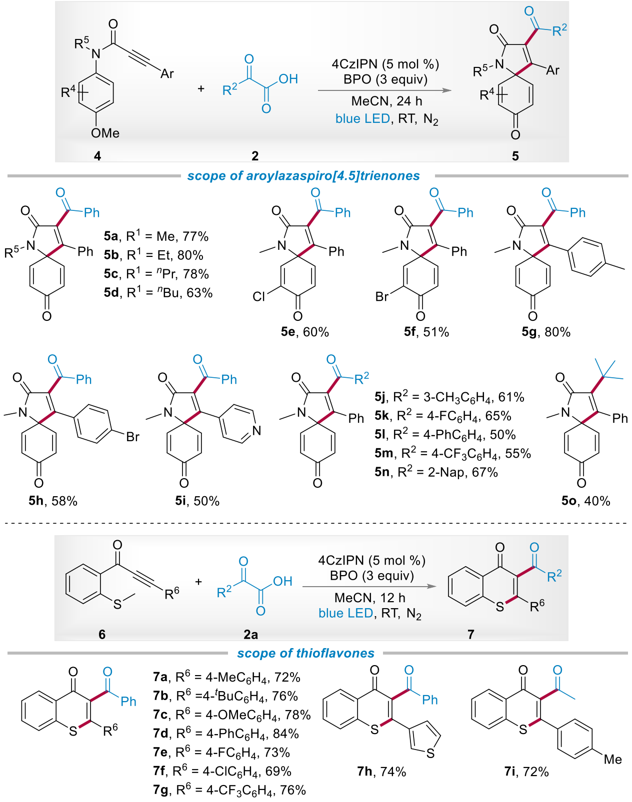
Scheme 2. Synthesis of Benzimidazo/Indolo[2,1-*a*]isoquinolin-6(5*H*)-ones[a]



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), and 4CzIPN (5 mol %) in DMC (2 mL) at room temperature for 6 h in an air atmosphere under a blue LED. Isolated yields are given. [b]On the gram scale.

To explore the applicability of this photocatalytic system, we next investigated substrates other than **1**. (For details, see the Supporting Information.) For instance, the reaction of *N*-arylpropiolamides **4a** and **2a** using benzoyl peroxide (BPO) as an oxidant in CH_3CN under a N_2 atmosphere gave the acylated azaspiro[4.5]trienone (**5a**) in 77% yield (Scheme 3).

Scheme 3. Synthesis of Aroylazaspiro[4.5]trienones and Acylated Thioflavones[a]

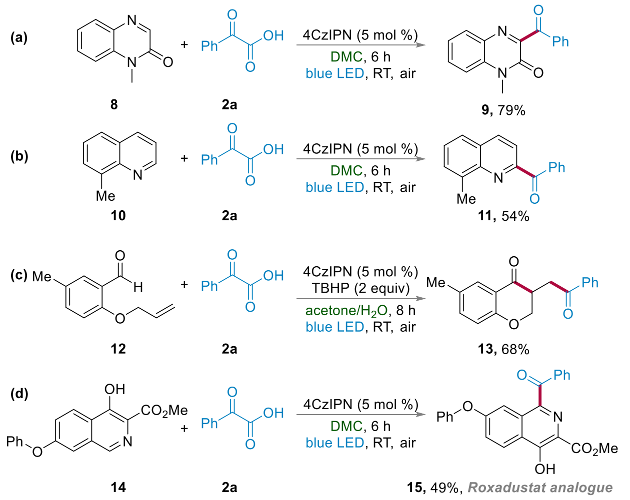


[a]Reaction conditions: **4** or **6** (0.2 mmol), **2** (0.4 mmol), 4CzIPN (5 mol %), and BPO (3 equiv) in CH_3CN (2.5 mL) with the irradiation of a blue LED at room temperature under N_2. Isolated yields are given.

Subsequently, the scope of various substituted *N*-arylpropiolamides **4** and α-keto acids **2** was further surveyed. The desired products (**5a**−**5o**) were afforded in 50−80% yields. Furthermore, when methylthiolated alkynones **6** were employed to react with both aliphatic and aromatic α-keto acids, the corresponding products, thioflavones **7a**−**7i**, were synthesized in good yields (69−84%).

To our satisfaction, the approach was also suitable for the construction of acylated heterocycles, including quinoxalin-2(1*H*)-one (**9**), acylated quinolone (**11**), chroman-4-one (**13**), and isoquinoline (**15**) (Scheme 4). Importantly, the strategy was well tolerated by the phenol group to give the desired product **15**,[11] an analog of Roxadustat, which is an oral drug to regulate erythropoiesis and iron metabolism.

Scheme 4. Preparation of Acylated Heterocycles



Subsequently, we conducted some experiments to explore the reaction mechanism. First, the results of Stern−Volmer experiments in Figure 1i clearly showed that the excited 4CzIPN was dramatically quenched by **2a**. Subsequently, the linear relationship between I_0/I and the concentration of **2a** indicated that **2a** was an efficient quencher of excited 4CzIPN (Figure S3). In addition, experimental redox potentials of **1a** and **2a** were further analyzed by cyclic voltammetry (CV) (Figure 1ii). An obvious oxidation peak of **1a** was observed ($E_{1/2}^{\text{ox}}$ = +1.73 V vs saturated calomel electrode (SCE)), and the oxidation potential of **2a** was measured ($E_{1/2}^{\text{ox}}$ = +1.07 V vs SCE). By comparing the redox potentials of the substrates and 4CzIPN ($E_{1/2}(\text{p}^*/\text{p}^-)$ = +1.35 V vs SCE),[12] it could be reasoned that the excited 4CzIPN can oxidize **2a** rather than **1a**. On the basis of these results, we speculated that a single-electron transfer (SET) process should be involved between α-keto acids and 4CzIPN in this reaction.

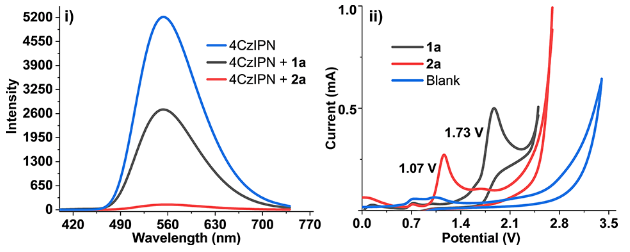


Figure 1. (i) Luminescence quenching study. (ii) Cyclic voltammetry of **1a** and **2a** in CH_3CN.

Furthermore, the reproducibility of this acylation reaction was evaluated based on the method reported by Glorius.[13] The variations in concentration, temperature, light intensity, oxygen level, scale, and water level were surveyed and compared with the standard conditions. (For details, see the Supporting Information.) Among them, light intensity and oxygen level were found to be essential parameters in this reaction. Other parameters like the concentration and temperature cause only negligible effects, indicating that this strategy has good reproducibility (Figure 2).

To further study the mechanism of this strategy, some control experiments were further explored. When radical scavengers 2,2,6,6-tetramethylpiperidin-1-yl-oxidanyl (TEMPO) and 2,6-di-*tert*-butyl-4-methylphenol (BHT) were added, respectively, the model reaction was completely inhibited, suggesting that a radical pathway might be engaged. As illustrated in Scheme 5, when the reaction solution with TEMPO was analyzed by high-resolution mass spectrometry (HRMS), a signal at m/z 262.1801 was detected, suggesting that the adduct **3a′** was formed by TEMPO and the benzoyl radical (Figure S2).

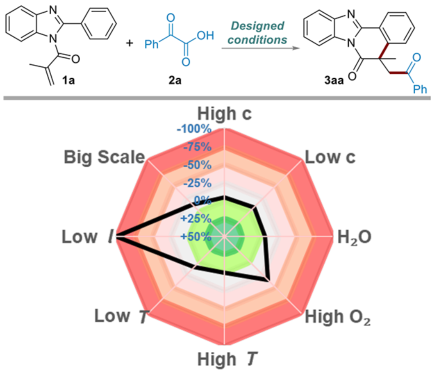
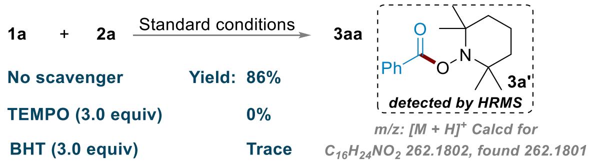


Figure 2. Sensitivity assessment.

Scheme 5. Control Experiments

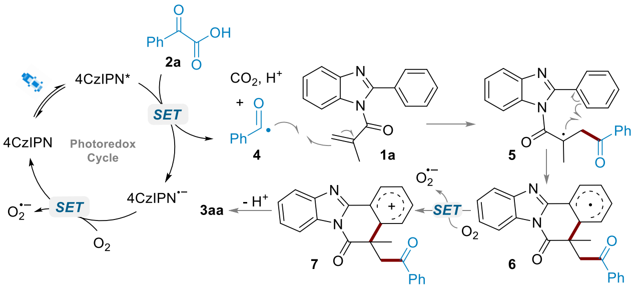


1a + 2a	Standard conditions	3aa
No scavenger	Yield: 86%	
TEMPO (3.0 equiv)	0%	
BHT (3.0 equiv)	Trace	

m/z: [M + H]$^+$ Calcd for $C_{16}H_{24}NO_2$ 262.1802, found 262.1801

On the basis of the experimental outcomes and previous literature reports, a plausible reaction pathway is proposed in Scheme 6. Initially, visible-light excitation of 4CzIPN gave 4CzIPN*, which reacted with **2a** via SET to form benzoyl radical **4** and 4CzIPN$^{\bullet-}$ with the release of CO_2 and H^+. 4CzIPN$^{\bullet-}$ was further oxidized by O_2 to produce the superoxide radical $O_2^{\bullet-}$ and regenerate 4CzIPN for the next photocatalytic cycle. The benzoyl radical **4** was then added to **1a** to deliver a more stable tertiary radical **5**, which then suffered an intramolecular radical cyclization to produce the aryl radical intermediate **6**. Subsequently, **6** was further oxidized by O_2 to produce the cation **7** via a SET process. Finally, rapid deprotonation of cation **7** occurred, and the product **3aa** was formed.

Scheme 6. Plausible Reaction Mechanism



In conclusion, we have disclosed a metal-free visible-light-promoted decarboxylative acylation approach for the construction of acylated heterocycles by using 4CzIPN as a photocatalyst in one pot with the irradiation of blue light. The remarkable merits of this method include the transition-metal-free, base-free, and mild conditions, the wide reactant scope, and the easy scalability. Further synthetic application of this strategy and other photocatalytic reactions by 4CzIPN is ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00655.

General experimental procedures and spectroscopic data for the corresponding products including characterization data and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Dedicated to the 100th anniversary of Chemistry at Nankai University. We acknowledge the financial support from the National Natural Science Foundation of China (21971224, 22071222), 111 Project (D20003), the Key Research Projects of Universities in Henan Province (20A150006, 21A150053), and the Natural Science Foundation of Henan Province (202300410375).

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