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Communication

Facile photochemical synthesis of α -ketoamides and quinoxalines from amines and benzoylacetone nitrile under mild conditions

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ABSTRACT

A selective protocol for the synthesis of either α -ketoamides or quinoxaline derivatives under the same reaction conditions has been achieved simply by varying substitution number of amino-groups. The method features metal-free, room temperature and broad substrate scopes as well as no extra oxidant. This process applies to various substituent groups and gives products in moderate to good yield. Finally, a rational mechanism was proposed.

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The control of reaction conditions for selective synthesis of diverse target products from the same reactants has attracted continuous interest in synthetic chemistry [1]. Various exciting studies using this strategy have recently been reported and researchers have shown great enthusiasm for the synthesis of many different compounds [2]. Biju and coworkers [3] demonstrated the temperature-dependent highly selective synthesis of *N*-unsubstituted and *N*-aryllindoles using the same starting materials. In addition, Sun and Ji [4] developed the tunable synthesis of alkenes or ketones from cinnamic acids and alkanes in the presence of di-*tert*-butyl peroxide (DTBP) or *tert*-Butyl hydroperoxide (TBHP). The different resultant products were obtained simply by varying the peroxide. Furthermore, Yuan and his colleagues [5] also reported a new method for the reaction of β -arylsulfonyl enamines and sulfonamides that depends on the reaction solvent. The reactions proceeded smoothly via I_2 /TBHP-mediated C–H and C–N bond cleavage of tertiary amines. It is noteworthy that the selective synthesis of different target products can be achieved under the same conditions or with the same substrates through a subtle change [6] in time, temperature, solvent, or oxidant. The exploration of new highly selective metal-free methods to access various products under the same conditions is still highly valuable but full of challenges.

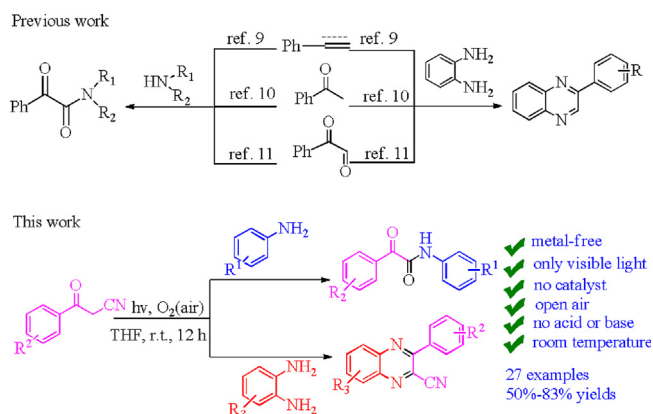
α -Ketoamides and quinoxalines exist in a broad range of bioactive natural compounds [7] and play an important role in the intermediates of organic synthesis. α -Ketoamide compounds are known to possess widespread and powerful pharmacologic properties. Quinoxaline derivatives have antimicrobial, anticancer, antibacterial, and anti-inflammatory properties [8] due to their chemical and biological activities. Many methods have been described for the synthesis of α -ketoamides and quinoxalines. In addition, many α -ketoamide production routes have been found and are based on a broad range of starting materials, such as styrene or phenylacetylene [9], hyponone [10] and phenyl oxalaldehyde [11], and the construction of the quinoxalines are based on the above starting materials too (Scheme 1). In this report, we disclose a mild and highly efficient method, to the best of our knowledge, which serves as the first reliable, base-free method to selectively prepare either α -ketoamides or quinoxalines by simple variation of the substitution number of amino groups at room temperature under visible light irradiation. This protocol has the advantages of readily available starting materials, no additives and high yield.

We first commenced our study with benzoylacetone nitrile and aniline, exposing to a halogen tungsten lamp (500 W) at room temperature. The desired product α -ketoamides was formed in 52% yield after 8 h in THF (Table 1, entry 1). Then control experiment was performed in the absence of visible light (Table 1, entry 2). The results showed that the visible light is essential for the formation of the desired product. Next we study the effect of other parameters on the reaction, including reaction time, molar ratio and solvent. By decreasing the reaction time to 4 h, the product yield was

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**Scheme 1.** Synthesis of α -ketoamides and quinoxalines.**Table 1**
Optimization of reaction conditions.^a

Entry	Solvent	Amine	Time (h)	Yield (%) ^b
1	THF	0.5	8	52
2 ^c	THF	0.5	8	0
3	THF	0.5	4	21
4	THF	0.5	12	59
5	THF	0.5	20	59
6	THF	0.75	8	61
7	THF	0.75	12	72
8	THF	0.75	20	72
9	THF	1.0	12	72
10	THF	1.5	12	72
11	DMSO	0.75	12	55
12	DMF	0.75	12	4
13	NMP	0.75	12	21
14	DCM	0.75	12	34
15	PhCH ₃	0.75	12	16
16	CH ₃ CN	0.75	12	51

^a Reaction conditions: **1a** (0.5 mmol), **2a** (0.5–1.5 mmol), solvent (2 mL), room temperature.^b Isolated yield.^c No visible light.

decreased to 21% while increasing the reaction time to 12 h, which was increased to 59% (Table 1, entries 3 and 4). However, an additional increase in the reaction time did not produce the higher yield (Table 1, entry 5). Then the diverse molar ratio of benzoyl acetonitrile and aniline was studied under the same conditions except reaction time. First, we studied the reaction at different reaction time under the molar ratio is 1:1.5, interestingly, the product yield increased from 61% to 72% and did not change with the time extending to 20 h, which indicate that 12 h may be enough for the substrate to react with each other (Table 1, entries 6–8). No significant improvement of yield was observed when increase the molar ratio above 1:1.5 (Table 1, entries 9 and 10). To further enhance the α -ketoamide yield, an extensive screening of solvents was tested. Among various tested solvents, including DMSO, DMF, DCM, NMP, MeCN, toluene, the yield of **3a** was lower than in THF (Table 1, entry 7 and entries 11–16), which indicates that the reaction is sensitive to reaction media. THF was the best solvent in terms of the reaction yield, hence it was used throughout the present work.

To confirm whether diverse α -ketoamides could be synthesized through the optimized method, the scope of the substrates was investigated. As summarized in Fig. 1, the reaction showed good compatibility and proved to be a general method to construct diverse α -ketoamides. Aniline containing both electron-donating and electron-withdrawing groups reacted with benzoylacetone nitrile to afford the desired products in moderate to good yields (**3a–3n**). The substituents at different positions did not greatly affect the yield (**3b–3e**, 68%–78%). Aniline bearing electron-neutral (H, 4-Me, Et) and electron-donating (OMe and *t*-Bu) groups resulted in successful conversion to the corresponding products in moderate to good yields (**3a** and **3f–3h**, 64%–79%). The scope of the substrates was further extended to various electron-withdrawing halogenated substrate (F, CF₃, Cl), giving the corresponding products with 54%–60% yields (**3i–3k**) successfully. A satisfactory yield was also achieved using secondary amines as the products (**3l**, 83%). Additionally, 1-naphthylamine also proceeded smoothly to generate the corresponding product **3n** with a 60% yield under the standard reaction conditions. Moreover, benzoylacetone nitrile bearing electron-neutral and electron-withdrawing groups or aliphatic acyl acetonitrile reacted well with aniline (**3o–3q**, 68%–78%).

When using 1, 2-diaminobenzene to replace aniline, the experimental products were quite different from our expected results (Scheme S1 in Supporting information). We synthesized quinoxalines from 1, 2-diaminobenzene and benzoylacetone nitrile under our optimized reaction conditions with 76% yield and without by-product. We then expanded the scope of benzoylacetone nitrile. As shown in Fig. 2, the reactions were also highly efficient and smooth with yields of 63% to 72% (**5b–5d**), both electron-withdrawing and electron-donating groups have a relatively low impact on the reaction rate and yield. 2-Thenoylacetone nitrile can also give the corresponding product with 50% yield (**5f**). We also scope the 1,2-diaminobenzene with electron-withdrawing and electron-donating groups, to our satisfactory, the substituted 1,2-diaminobenzene also proceed smoothly with benzoylacetone nitrile. It is noteworthy that under the circumstances of single substituted 1,2-diaminobenzene, two regioisomers were obtained due to the unsymmetric nature of single substituted 1,2-diaminobenzene (**5g–5i**), which react equally well to the C–O double bond. While the symmetric substituted 1,2-diaminobenzene only give one product (**5j**). Importantly, the present method for generating quinoxalines proceeds without the use of a metal or an extra oxidant.

In order to further explore the active site of the reaction, we conducted the following control experiments (Scheme 2). When we converted the carbonyl to sulfone, no reaction was detected, so carbonyl is important in the reaction. At the same time, neither benzoyl cyanide nor benzonitrile was found to react with aniline under this condition, indicating that the cyanogroup and methylene were equally important.

Although we knew that visible light and O₂ were necessary for the success of the reaction, we wondered what is the key factor enabled this catalyst-free process. One possibility is that singlet oxygen is produced and responsible for the oxidative coupling process under our standard conditions. Experiments to determine the presence of photoexcited singlet oxygen in the reaction system were performed (Scheme S2 in Supporting information). Trapping experiments were carried under irradiation using 1,3-diphenylisobenzofuran [12] produced the desired product 1,2-phenylenebis (phenylmethanone), however, the corresponding product was not acquired in the dark, which suggested that under our reaction conditions, visible-light promoted the generation of singlet oxygen. Quenching experiments were conducted, using 1,4-diazabicyclo[2.2.2]octane (DABCO) [13], a common quencher of ¹O₂, only a trace amount of **3a** was produced in the reaction. These quenching and trapping experiments clearly indicated that ¹O₂

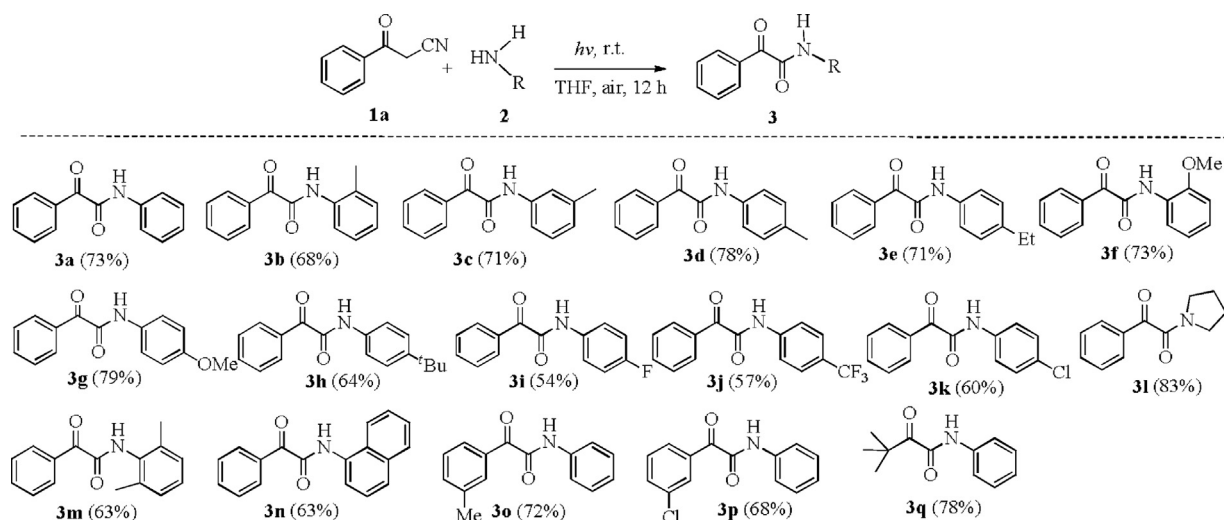


Fig. 1. Substrate scope for α -ketoamides synthesis. Reaction conditions: **1a** (0.5 mmol), **2** (0.75 mmol), solvent (2 mL), room temperature. Isolated yield.

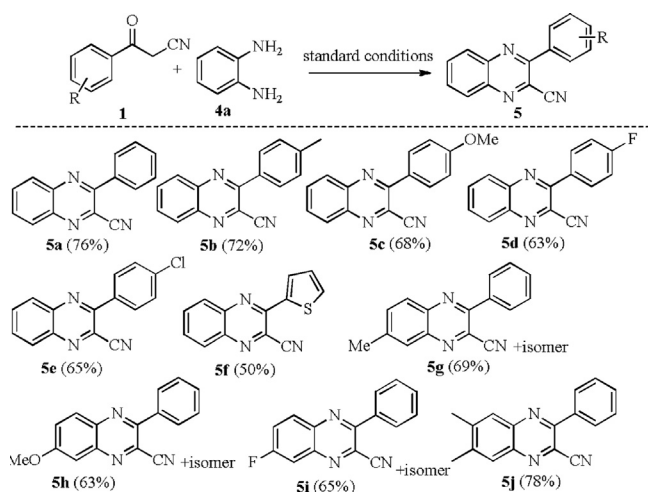
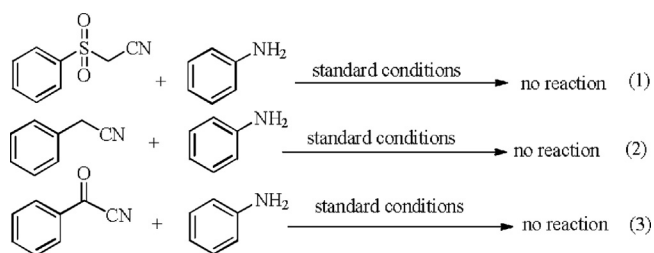


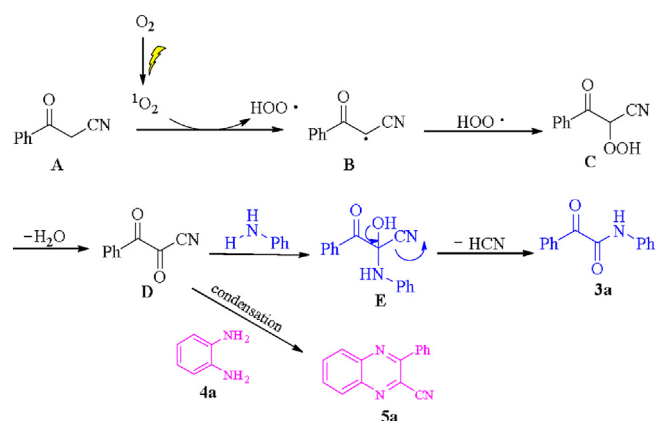
Fig. 2. Substrate scope for α -ketoamides synthesis. Reaction conditions: **1** (0.5 mmol), **4a** (0.75 mmol), solvent (2 mL), room temperature. Isolated yield.



Scheme 2. Control experiments.

was generated from O_2 and acted as an indispensable reactant in our system.

Based on the above results and the recent research by Xu [14], a possible reaction mechanism for α -ketoamide and quinoxalines was obtained and illustrated below (Scheme 3). We reasoned that benzoyl cyanide and oxygen react *via* visible light. Singlet oxygen that is generated from oxygen by visible-light stimulation then extracts an electron from benzoyl cyanide to generate **B**, which reacted with HOO^\bullet radical to give intermediate **C**, then



Scheme 3. A plausible mechanism.

intermediate **C** underwent dehydration to form the intermediate **D**, which then reacts with amines to produce either α -ketoamides or quinoxalines through two pathways: react with aniline to give intermediate **E** and cyanohydrin of **E** to lead to the final product **3a** [15]. While react with 1,2-diaminobenzene underwent condensation to produce the product **5a**.

In conclusion, we have described a novel and efficient visible-light-promoted protocol for selectively preparing α -ketoamides and quinoxalines under mild conditions. This work is the first to demonstrate that the selectivity of target products between primary amines and benzoyl cyanide can be controlled by changing the position of the amino group. The reaction takes place smoothly to generate the corresponding products in moderate to good yields. It is a novel protocol that accommodates different anilines and benzoyl cyanide through visible-light induced electron transfer and oxidative coupling. The reactivity, in the absence of photosensitizer, further improves its practicality. Studies of the detailed mechanism of this process and its application are underway.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.ccl.2018.06.019>.

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