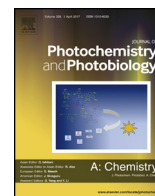




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# Synthesis of quinazolinone derivatives via a visible-light photocatalyzed denitrogenation rearrangement process

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### ABSTRACT

The photoredox chemistry has been proposed to rely on the ability of photoexcited catalysts to engage in single-electron-transfer with organic molecules, and energy transfer, the fundamental decay pathway of photoexcited states, is also a catalytic mode for the photoredox chemistry. Although the triplet–triplet energy transfer process is considered to be a powerful activation mechanism in organic photochemistry, it has not been widely applied in organic transformations. Here, we demonstrate a novel visible light photocatalysis by such an activation method: the energy transfer from photoexcited  $^1\text{Ir}(\text{ppy})_3$  produces excited-state 1,2,3-benzotriazinones for the synthesis of quinazolinone derivatives. This method offers a mild and operationally simple access to diverse quinazolinone derivatives with a broad substrate scope.

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## 1. Introduction

Quinazolinone derivatives are an important class of fused heterocycles which are widely used in the fields of biomedicine, material science and organic synthesis [1–5]. Like other quinazolinone members, 2,3-dihydroquinazolin-4(1H)-one (DHQ) derivatives are also natural products that are widely distributed in nature and display a wide range of biological activities [6–8]. Therefore, many chemists have been focusing on the development of novel and efficient methods for the synthesis of these compounds. DHQ derivatives are usually synthesized by the reaction of anthranilamides with corresponding carbonyl compounds under either acidic or basic conditions [9–11], where anthranilamides generally consist of *o*-aminobenzoic acids, *o*-amino-benzonitriles, and isatoic anhydrides as starting materials [12–15] (Scheme 1a). However, these methods still suffer from some disadvantages which include complex, time-consuming procedures, low product yields, and limited substrate scopes, etc. Thus, the development of simple and efficient methods to construct DHQ heterocyclic motifs is still highly desirable.

1,2,3-benzotriazinones had attracted considerable attention as a kind of very useful compounds in transition-metal-catalyzed denitrogenative cyclization. Murakami's group reported a nickel catalyzed cyclization of 1,2,3-benzotriazinones with various unsaturated compounds, from which nickelacycles were generated

[16–18] (Scheme 1b). Notably, Yu and co-workers reported a visible-light photocatalyzed denitrogenative alkyne insertion reaction of 1,2,3-benzotriazinones, which provided a regioselective synthetic approach to isoquinolones [19]. And various products were obtained by irradiating the 1,2,3-benzotriazinones with high intensity ultraviolet light [20,21]. From the above examples, we envisioned that there was still great potential to develop a novel visible-light induced denitrogenative reaction of 1,2,3-benzotriazinone to construct complex molecular scaffolds.

In recent years, the visible-light photoredox catalysis has become a powerful tool to generate various radical intermediates via single-electron-transfer and energy transfer pathways [22–32]. However, for most organic compounds, it is not easy to form triplet states when the molecules absorb radiation since excitation to a triplet state involves an additional “forbidden” spin transition and requires a lot of energy. In order to solve this problem, photosensitizers are usually used to absorb light before a triplet–triplet energy transfer process occurs with substrates. Although the triplet–triplet energy transfer process has been considered to be a powerful activation pathway in organic photochemistry, it has not been widely applied in organic transformations. Herein we report a method for the synthesis of quinazolinone derivatives by a visible-light photocatalyzed energy transfer process (Scheme 1c).

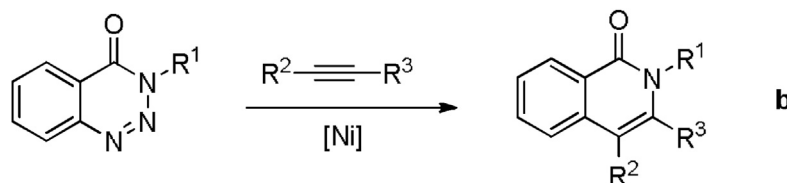
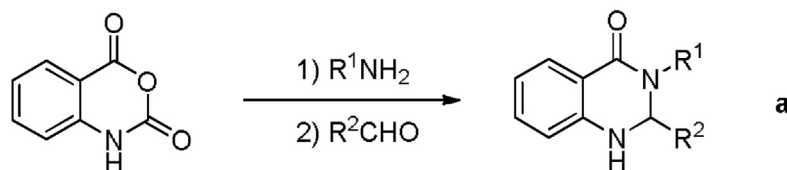
## 2. Results and discussion

To test our hypothesis, 3-phenyl-1,2,3-benzotriazinone **1a** and benzylamine **2a** were chosen as the model substrates for the reaction. Surprisingly, the desired product **3a** was afforded in a

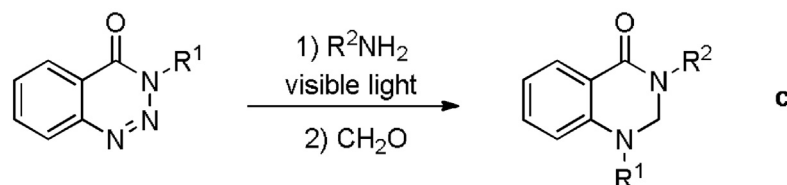
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## Previous work



## This work



Scheme 1. Synthesis of quinazolinones.

yield of 50% when the substrate **1a** (0.1 mmol) and **2a** (2.0 equiv) in degassed toluene were irradiated with a 5 W blue LED in the presence of *fac*-Ir(ppy)<sub>3</sub> (1 mol%) for 12 h at room temperature, and then paraformaldehyde (2.0 equiv) and TFA (5.0 equiv) were added to the mixture which was stirred for another 4 h at room temperature (Table 1, entry 1). However, when either Ru(bpy)<sub>3</sub>Cl<sub>2</sub> or Eosin Y was used as the photocatalyst, the product **3a** was not produced (entries 2 and 3). To improve the reaction efficiency, a series of solvents were tested, and the results showed that except for THF which gave a poor reaction yield, none of them was effective (entries 4–9). The yield of **3a** was only slightly increased when the reaction time was extended to 72 h (entry 10). To our

delight, increasing the reaction temperature significantly improved the reaction efficiency and increasing the amount of the substrate **2a** to 4 equiv led to the highest reaction yield (entries 11–14). It was also found that changing the amount of the catalyst did not improve the yield and no desired product was obtained without adding benzylamine to the reaction (entries 15–17). Further control experiments revealed that both of *fac*-Ir(ppy)<sub>3</sub> and visible light were necessary for the reaction (entries 18,19).

With the reaction conditions optimized, the synthetic potential of this transformation was further evaluated with the results shown in Scheme 2. 1,2,3-Benzotriazinones with various substituted phenyl groups on the nitrogen atom were tolerated very well under the optimized conditions with the electron-donating substituents giving better yields than the electron-withdrawing ones (**3b–3j**, 56%–97% yields). We speculated that the energy of triplet excited-state of *fac*-Ir(ppy)<sub>3</sub> might be similar to that of the electron-rich substrates' triplet, which could be more capable of energy transfer from the excited-state of *fac*-Ir(ppy)<sub>3</sub>. Similarly, 3-alkylbenzo[d][1,2,3]triazinones did not react due to the energy mismatch. The steric hindrance of the monosubstituted substrate did not affect this reaction, as 3-(*p*-, *m*-, and *o*-tolyl)benzo[d][1,2,3]triazinones gave similar yields of quinazolinones (**3b–3d**, 89%–93%). However, 3-mesitylbenzo[d][1,2,3]triazinone only afforded the product **3f** in 56% yield due to the steric hindrance. The substrate scope of the benzylamines was also explored with **1a** as the substrate. It was found that benzylamines with electron-rich substituents such as *p*-, *m*-, *o*-tolylmethanamine and (*p*-methoxyphenyl) methanamine reacted smoothly to give the corresponding products in good yields (**3k–3n**, 76%–83% yield). In addition, benzylamines with halogen atom substituents were also effective in the reaction (**3o–3q**, 66%–86% yield).

Next, the scope of the amines was examined with the results shown in Scheme 3. Only primary amines worked well in the reaction, which could be attributed to the nucleophilic properties of amines which could break the amide bond of four-membered ring intermediates. 2-Phenylethanamine, *tert*-butylamine, and *n*-butylamine were also suitable for this transformation to obtain the desired product (**3r–3t**, 70%–82% yield), and the structure of **3r**

Table 1  
Optimization of the Reaction Conditions<sup>a</sup>.

Entry	Catalyst	2a (equiv)	Solvent	T (°C)	t (h)	Yield (%) <sup>b</sup>
1	<i>fac</i> -Ir(ppy) <sub>3</sub>	2	toluene	25	48	50
2	Ru(bpy) <sub>3</sub> Cl <sub>2</sub>	2	toluene	25	48	0
3	Eosin Y	2	toluene	25	48	0
4	<i>fac</i> -Ir(ppy) <sub>3</sub>	2	THF	25	48	27
5	<i>fac</i> -Ir(ppy) <sub>3</sub>	2	DCM	25	48	0
6	<i>fac</i> -Ir(ppy) <sub>3</sub>	2	DMSO	25	48	0
7	<i>fac</i> -Ir(ppy) <sub>3</sub>	2	DMF	25	48	0
8	<i>fac</i> -Ir(ppy) <sub>3</sub>	2	MeOH	25	48	0
9	<i>fac</i> -Ir(ppy) <sub>3</sub>	2	MeCN	25	48	0
10	<i>fac</i> -Ir(ppy) <sub>3</sub>	2	toluene	25	72	55
11	<i>fac</i> -Ir(ppy) <sub>3</sub>	2	toluene	40	12	66
12	<i>fac</i> -Ir(ppy) <sub>3</sub>	4	toluene	40	12	87
13	<i>fac</i> -Ir(ppy) <sub>3</sub>	6	toluene	40	12	86
14	<i>fac</i> -Ir(ppy) <sub>3</sub>	8	toluene	40	12	83
15	<i>fac</i> -Ir(ppy) <sub>3</sub>	0	toluene	40	12	0
16 <sup>c</sup>	<i>fac</i> -Ir(ppy) <sub>3</sub>	4	toluene	40	12	76
17 <sup>d</sup>	<i>fac</i> -Ir(ppy) <sub>3</sub>	4	toluene	40	12	80
18 <sup>e</sup>	<i>fac</i> -Ir(ppy) <sub>3</sub>	4	toluene	40	12	0
19	/	4	toluene	40	12	0

<sup>a</sup> Reaction conditions: **1a** (0.1 mmol), catalyst (0.001 mmol), solvent (anhydrous, 2 mL), 5 W blue LED light, rt, under N<sub>2</sub> atmosphere.

<sup>b</sup> Isolated yield.

<sup>c</sup> *fac*-Ir(ppy)<sub>3</sub> (0.0005 mmol).

<sup>d</sup> *fac*-Ir(ppy)<sub>3</sub> (0.002 mmol).

<sup>e</sup> In the dark.

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