



# Synthesis of 2,5-disubstituted 1,3,4-oxadiazoles by visible-light-mediated decarboxylation–cyclization of hydrazides and diketones

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## ABSTRACT

A visible-light-induced synthesis of 2,5-disubstituted 1,3,4-oxadiazoles from simple diketones and hydrazides with the assistant of the photocatalyst eosin Y catalyzed decarboxylation and cyclization under mild conditions has been discovered. The reaction tolerates a wide range of functional groups and gives a variety of valuable 1,3,4-oxadiazoles in moderate to good yields. Finally, a plausible reaction mechanism was proposed.

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## Introduction

In recent years, visible-light-induced photoredox catalysis was proved to be a powerful method to initiate kinds of organic reaction<sup>1</sup> including cyclizations<sup>2</sup>, C–H functionalizations<sup>3</sup>, and decarboxylative coupling reactions<sup>4</sup> under mild reaction conditions. Organic dye eosin Y, with strong absorption in the visible part of the spectrum, which was less toxic and cheaper compared to transition metal based catalysts, has been widely used in photochemical organic transformations. König's group has demonstrated the use of eosin Y for (a) the formation of C–C and C–P bonds<sup>5</sup>, (b) enantioselective transformations<sup>6</sup>, and (c) the synthesis of substituted aromatic heterocycles.<sup>7</sup> We herewith report the use of eosin Y as a photoredox catalyst, in the reactions of hydrazides and diketones to give 2,5-disubstituted 1,3,4-oxadiazoles.

Functionalized 2,5-disubstituted 1,3,4-oxadiazoles have been extensively utilized for its significant biological activities including antimicrobial, antifungal, and anti-inflammatory. Classic methods<sup>8</sup> for the synthesis of 2,5-disubstituted 1,3,4-oxadiazoles can be divided into two classes: (a) dehydrative cyclization of 1,2-diacylhydrazines<sup>9</sup>; (b) oxidative cyclization of acylhydrazones.<sup>10</sup> Wu and coworkers have reported the copper-catalyzed intramolecular decarboxylative coupling between isatins and hydrazides, giving 1,3,4-oxadiazoles at elevated temperature (Scheme 1, a).<sup>11</sup>

Recently, Fan and coworkers reported a KI/TBHP-mediated oxidative cyclization of  $\alpha$ -keto acids with acylhydrazines for the synthesis of 2,5-disubstituted 1,3,4-oxadiazoles (Scheme 1, b).<sup>12</sup> Due to the high temperature of the reaction and the use of Cu(I) salt or I<sub>2</sub> catalyst, we combined the two reactions and proposed our methods, the results for the synthesis of 2,5-disubstituted 1,3,4-oxadiazoles from hydrazides and diketones using eosin Y in the presence of visible light are reported herein.

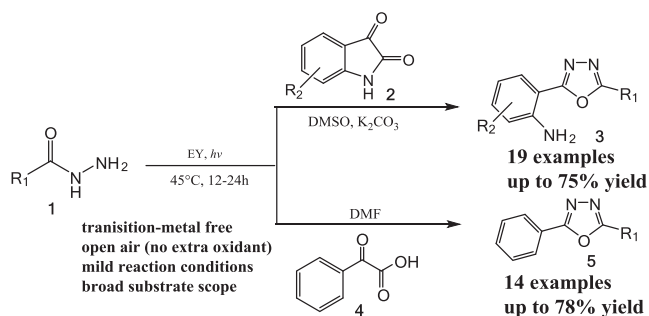
## Results and discussion

At first, we started the investigation by using benzoylhydrazine **1a** and isatin **2a** as model substrates in the presence of 5 mol% of Eosin Y photocatalyst, 2 equiv of K<sub>2</sub>CO<sub>3</sub> in 2 mL DMSO at 45 °C. To our delight, the desired 2,5-disubstituted 1,3,4-oxadiazoles **3aa** was formed in 75% yield under visible-light irradiation (Table 1, entry 1). In addition, a series of control experiments were performed in the absence of any one of visible light, Eosin Y, or K<sub>2</sub>CO<sub>3</sub>, which showed that the visible light, photocatalyst and base are essential for the formation of the desired product in a good yield (Table 1, entries 2–4). Next, we studied the effect of other parameters on the reaction, including base, photocatalysts, and solvents. Several inorganic and organic bases were also tested, but K<sub>2</sub>CO<sub>3</sub> was found to be optimal (Table 1, entries 1 and 5–8). Among various photocatalysts, Eosin Y showed the highest activity (Table 1, entries 1 and 9–11). When use DMF, EtOH, MeCN, THF, and 1,4-Dioxane as solvent, the yield of **3aa** was low (Table 1, entries 1 and 12–16), which indicates that the reaction is sensitive

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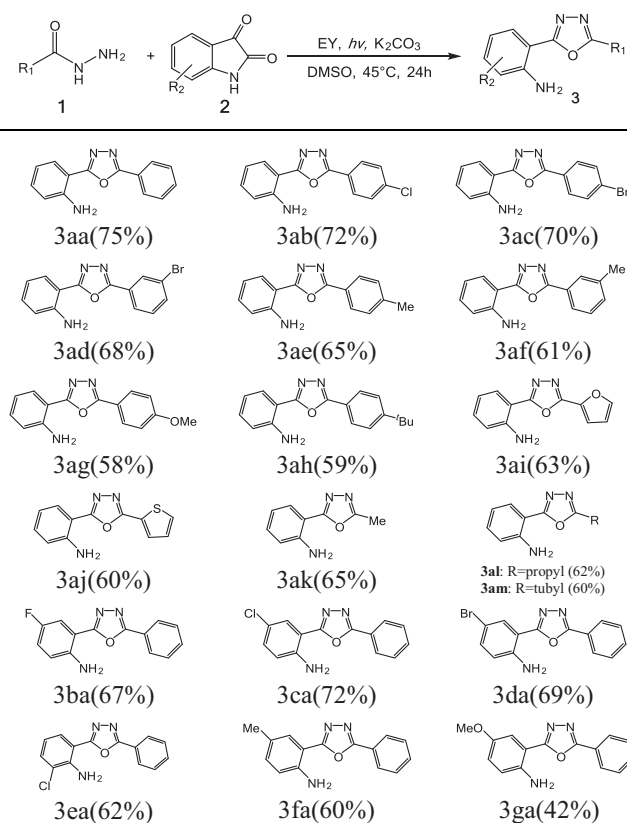


**Scheme 1.** Synthesis of 2,5-disubstituted-1,3,4-oxadiazoles.

to reaction media. DMSO was the best solvent in terms of the reaction yield, hence it was used throughout the present work. Finally, the effect of O<sub>2</sub> was also investigated, which demonstrated that O<sub>2</sub> may be important in the reaction (Table 1, entries 1, 17, and 18).

Under the optimized conditions, decarboxylation-cyclization of various hydrazides with isatin has been examined. As summarized in Table 2, this protocol allows the reaction of a broad range of aromatic, heteroaromatic, and aliphatic hydrazides and proved to be a general method to construct diverse 1,3,4-oxadiazoles. We explored the substrate scope using various benzoylhydrazine derivatives with isatin **2a** (Table 2, 3ab–am). The scope of the substrates was further successfully extended to various electron-withdrawing halogenated substrates (Table 2, 3ab–3ad, 68–72%), which proceeded smoothly to afford the corresponding 1,3,4-oxadiazoles in good yields. Reactions with benzoylhydrazines bearing electron-neutral (H, 4-Me, 3-Me) and electron-donating (4-OMe, 4-<sup>t</sup>Bu) substituents resulted in successful conversion to the corresponding products in moderate to good yields (Table 2, 3aa, 3ae–3ah, 58–75%). Notably, representative heteroaryl hydrazides compounds

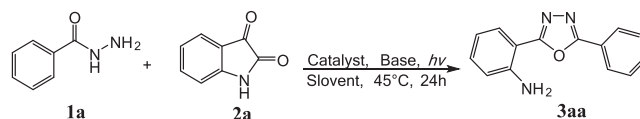
**Table 2**  
Substrate scope for oxadiazole synthesis.<sup>a,b</sup>



<sup>a</sup> Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), photocatalyst (0.025 mmol), K<sub>2</sub>CO<sub>3</sub> (1 mmol), DMSO (3 mL), 45 °C, 24 h, air atmosphere.

<sup>b</sup> Isolated yield.

**Table 1**  
Optimization of reaction conditions.<sup>a</sup>



Entry	PC	Base	Solvent	Yield <sup>b</sup> (%)
1	EY	K <sub>2</sub> CO <sub>3</sub>	DMSO	75
2 <sup>c</sup>	EY	K <sub>2</sub> CO <sub>3</sub>	DMSO	n.r.
3	–	K <sub>2</sub> CO <sub>3</sub>	DMSO	trace
4	EY	–	DMSO	n.r.
5	EY	KHCO <sub>3</sub>	DMSO	65
6	EY	NaHCO <sub>3</sub>	DMSO	36
7	EY	Cs <sub>2</sub> CO <sub>3</sub>	DMSO	<5
8	EY	Et <sub>3</sub> N	DMSO	n.r.
9	Na <sub>2</sub> -EY	K <sub>2</sub> CO <sub>3</sub>	DMSO	55
10	MB	K <sub>2</sub> CO <sub>3</sub>	DMSO	<5
11	RB	K <sub>2</sub> CO <sub>3</sub>	DMSO	16
12	EY	K <sub>2</sub> CO <sub>3</sub>	DMF	<5
13	EY	K <sub>2</sub> CO <sub>3</sub>	EtOH	n.r.
14	EY	K <sub>2</sub> CO <sub>3</sub>	MeCN	n.r.
15	EY	K <sub>2</sub> CO <sub>3</sub>	THF	n.r.
16	EY	K <sub>2</sub> CO <sub>3</sub>	1,4-Dioxane	n.r.
17 <sup>d</sup>	EY	K <sub>2</sub> CO <sub>3</sub>	DMSO	n.r.
18 <sup>e</sup>	EY	K <sub>2</sub> CO <sub>3</sub>	DMSO	72

<sup>a</sup> Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), Base (1 mmol), Photocatalyst (0.025 mmol), Solvent (3 mL), 45 °C, 24 h, air atmosphere, PC = photocatalyst. MB = methylene blue, RB = rhodamine B, n.r. = no reaction.

<sup>b</sup> Isolated yield.

<sup>c</sup> No visible light.

<sup>d</sup> N<sub>2</sub> atmosphere.

<sup>e</sup> O<sub>2</sub> atmosphere.

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