



Visible-light photocatalytic α -amino C(sp³)-H activation through radical translocation: a novel and metal-free approach to α -alkoxybenzamides



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ABSTRACT

Visible-light photocatalytic, metal-free synthesis of valuable α -alkoxybenzamides starting with readily prepared *o*-aminobenzamides and alcohols through radical translocation under mild conditions is reported. This protocol employs eosin Y as an organophotoredox catalyst and readily available *tert*-butyl nitrite as the nitrosating reagent. These transformations occur in the absence of any transition metal and the title compounds are obtained in moderate to good yields.

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Saturated nitrogen heterocycles are ubiquitous in natural products, bioactive molecules, and drugs.¹ Among them, benzamides as a highly important class of saturated nitrogen heterocycles have attracted significant interest from the medicinal chemistry community because of their diverse and prominent biological activities such as enzyme inhibition or nootropic and antimicrobial activities (Fig. 1).² Because of its importance, there is continuing interest in the development of synthetic methods for the diversification of benzamides.³ The development of novel methodology for the introduction of a substituent into α -position of benzamides is beneficial for the adjustment of bioactivities of parent molecules. Importantly, the construction of the related compound library might offer a lot of opportunities of application to discover new lead compounds. Therefore, uncovering novel and efficient approaches to construct α -substituted benzamides is important.

In recent years, a variety of methods have been established for the preparation of α -substituted saturated amines through a C(sp³)-H functionalization strategy.^{4,5} However, to date, none of these methods has been successfully applied to the preparation of α -substituted benzamides. As a complementary way, C(sp³)-H functionalization of saturated amines through radical translocation provides an efficient strategy for the preparation of α -substituted benzamides.^{6,7} For example, the Curran group^{6a} and the Undheim group^{6b} independently reported tin-mediated synthesis of

α -alkylated benzamides through radical translocation. Moreover, Weinreb and co-workers described a metal-catalyzed approach to prepare α -methoxybenzamides through radical translocation under strongly acidic conditions.^{6c,d} Despite these significant advances, the reported approaches also revealed some drawbacks: (a) the use of environmentally harmful metal reagents or catalysts; (b) the need for harsh reaction conditions; and (c) limited substrate scope. Therefore, developing novel ways to prepare α -substituted benzamides under mild and environmentally benign conditions is still of great interest.

Visible-light photoredox catalysis using photosensitizers to activate organic compounds has in recent years emerged as a powerful tool for mild and environmentally benign organic transformations.⁸ However, only a few studies on C(sp³)-H functionalization through radical translocation under visible-light photoredox catalysis have been reported.⁷ⁱ In this context, we became interested in constructing α -alkoxybenzamides through radical translocation using visible-light photoredox catalysis. Herein, we disclose the first results on the visible-light photocatalytic synthesis of α -alkoxybenzamides through radical translocation catalyzed by eosin Y under mild and metal-free conditions (Scheme 1).

We decided to use eosin Y as the organophotoredox catalyst because it has been already demonstrated that the aryl radicals can be generated by the reaction of aryl diazonium salts with eosin Y.⁹ *t*BuONO was chosen as the commercially available nitrosating agent. Radical translocation of readily prepared *o*-aminobenzamide **1a** with methanol **2a** in the presence of blue LED lights

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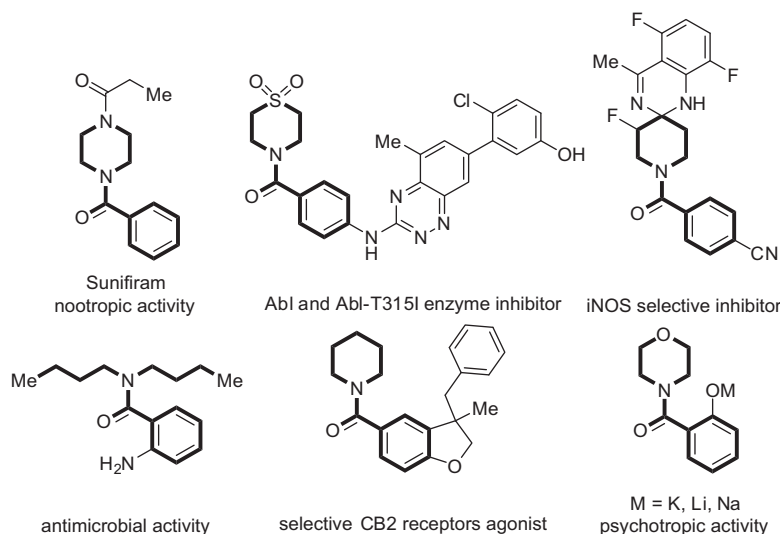
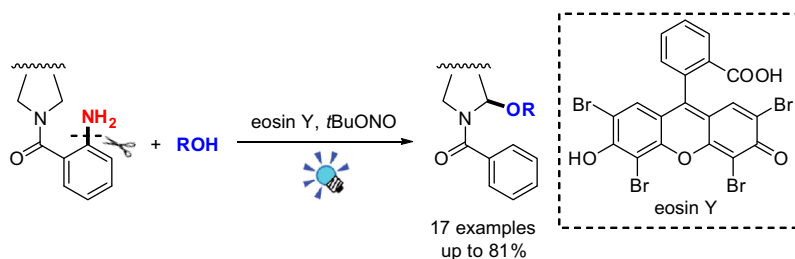


Figure 1. Representative biologically active compounds containing benzamide scaffold.



Scheme 1. Visible-light photocatalytic synthesis of α -alkoxybenzamides through radical translocation.

Table 1
Optimization of reaction conditions^a

Entry	X	Y	Nitrosating agent	Amount of 2a	Solvent	Yield ^b (%)
1	5	0	<i>t</i> BuONO	2.0 mL	None	12
2	5	5	<i>t</i> BuONO	2.0 mL	None	80
3	0	5	<i>t</i> BuONO	2.0 mL	None	20
4 ^c	5	5	<i>t</i> BuONO	2.0 mL	None	10
5	5	5	<i>t</i> BuONO	5.0 equiv	CH ₃ CN	72
6	5	5	<i>t</i> BuONO	3.0 equiv	CH ₃ CN	62
7	5	5	<i>t</i> BuONO	1.5 equiv	CH ₃ CN	54
8	5	5	<i>t</i> BuONO	5.0 equiv	DCM	67
9	5	5	<i>t</i> BuONO	5.0 equiv	DMF	55
10	5	5	<i>t</i> BuONO	5.0 equiv	DMSO	61
11	5	5	<i>t</i> BuONO	5.0 equiv	CH ₃ NO ₂	76
12	5	5	NaNO ₂	5.0 equiv	CH ₃ NO ₂	0
13	5	5	AmylONO	5.0 equiv	CH ₃ NO ₂	18
14	1	2.5	<i>t</i> BuONO	5.0 equiv	CH ₃ NO ₂	81

^a Reaction conditions: **1a** (0.4 mmol), **2a**, eosin Y, TsOH·H₂O, and nitrosating agent (0.6 mmol) in the given solvent (2.0 mL) were irradiated with 10 W blue LEDs (450 nm) at room temperature under N₂ for 24 h.

^b Isolated yields.

^c The reaction was conducted in the absence of light.

(450 nm) at room temperature under N₂ was investigated first. Gratifyingly, the desired product **3a** was obtained in 12% yield (Table 1, entry 1). Based on this promising result, we next screened a large number of reaction conditions and found that catalytic amounts of TsOH are very important for improving the transformation (Table 1, entry 2). When the reaction was run in the absence of eosin Y or light, the yield of **3a** was dramatically decreased to 20% or 10% (Table 1, entries 3 and 4). These results imply that both eosin Y and light are essential for this transformation. To make the alcohol a reagent rather than a solvent, further optimization of reaction conditions was conducted. When the reaction was carried out with 5.0 equiv of methanol **2a** in CH₃CN, **3a** was isolated in 72% yield (Table 1, entry 5). Lowering the amounts of **2a** to 3.0 equiv or 1.5 equiv resulted in poorer results (Table 1, entries 6 and 7). Solvent effects were then investigated, and the results indicate that CH₃NO₂ is the best solvent for this transformation (Table 1, entries 8–11). However, the reaction did not perform well in the presence of other nitrosating agents, such as NaNO₂ and amyONO (Table 1, entries 12 and 13). Organophotoredox catalyst and acid loading could be further lowered to 1 mol % and 2.5 mol % without affecting the yield (Table 1, entry 14).

With optimized reaction conditions in hand, the scope and limitations of the α -alkoxybenzamide synthesis were investigated (Table 2). We first investigated the scope with respect to the *o*-aminobenzamides **1**. Five-, six-, and eight-membered cyclic amines **1b–1d** proceeded well with moderate to good yields. When the reaction was conducted on three and four-membered cyclic amines, the desired products were not obtained likely due to the instability of starting materials under current reaction system. The

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