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Visible-light photocatalytic α-amino C(sp^3)-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.

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 activity (Figure 1).[2] Because of its importance, there is continuing interest in the development of synthetic methods for 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.

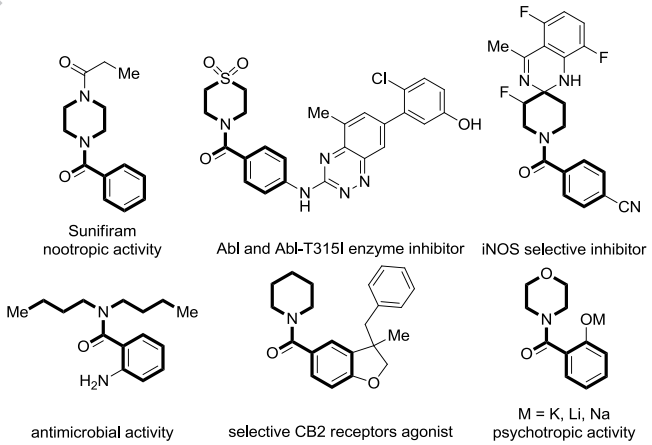
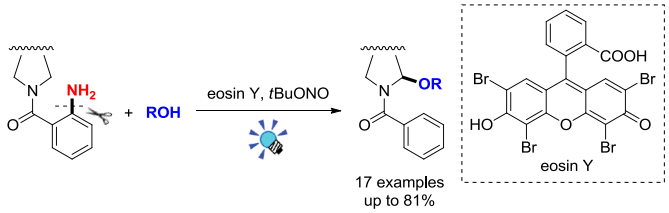


Figure 1. Representative biologically active compounds containing benzamide scaffold.

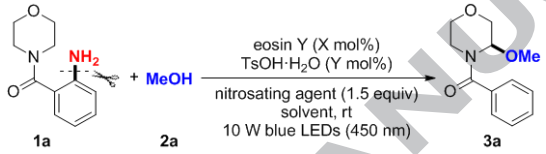


Scheme 1. Visible-light photocatalytic synthesis of α-alkoxybenzamides through radical translocation.

In recent years, a variety of methods have been established for the preparation of α-substituted saturated amines through a C(sp^3)-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(sp^3)-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; (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(sp^3)-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).

Table 1. Optimization of reaction conditions[a]



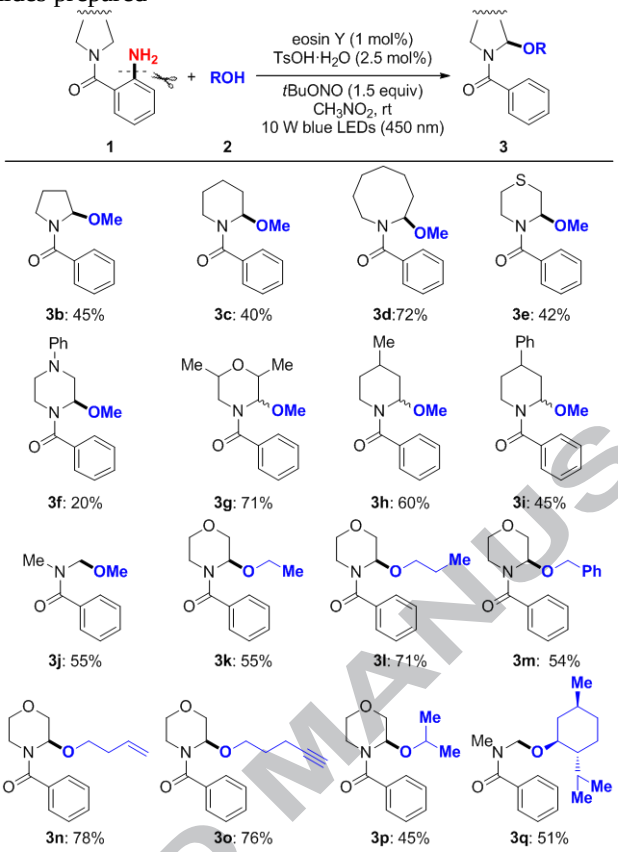
entry	X	Y	nitrosating agent	amount of **2a**	solvent	yield[b] (%)
1	5	0	*t*BuONO	2.0 mL	none	12
2	5	5	*t*BuONO	2.0 mL	none	80
3	0	5	*t*BuONO	2.0 mL	none	20
4[c]	5	5	*t*BuONO	2.0 mL	none	10
5	5	5	*t*BuONO	5.0 equiv	CH_3CN	72
6	5	5	*t*BuONO	3.0 equiv	CH_3CN	62
7	5	5	*t*BuONO	1.5 equiv	CH_3CN	54
8	5	5	*t*BuONO	5.0 equiv	DCM	67
9	5	5	*t*BuONO	5.0 equiv	DMF	55
10	5	5	*t*BuONO	5.0 equiv	DMSO	61
11	5	5	*t*BuONO	5.0 equiv	CH_3NO_2	76
12	5	5	$NaNO_2$	5.0 equiv	CH_3NO_2	0
13	5	5	amylONO	5.0 equiv	CH_3NO_2	18
14	**1**	**2.5**	***t*BuONO**	**5.0 equiv**	**CH_3NO_2**	**81**

[a] Reaction conditions: **1a** (0.4 mmol), **2a**, eosin Y, TsOH·H_2O, 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 N_2 for 24 h. [b] Isolated yields. [c] The reaction was conducted in the absence of light.

We decided to use eosin Y as the organophotoredox catalyst because it has been already demonstrated that the aryl radicals can be generated by 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 (450 nm) at room temperature under N_2 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 is 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, entry 3 and 4). These results imply that both eosin Y and light are essential for this transformation. To make the alcohol as 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 CH_3CN, **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, entry 6 and 7). Solvent effects were then investigated, and the results indicate that CH_3NO_2 is the best solvent for this transformation (Table 1, entry 8-11). However, the reaction did not perform well in the presence of other nitrosating agents, such as $NaNO_2$ and amylONO (Table 1, entry 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. Various α-alkoxybenzamides prepared[a,b]



[a] Reaction condition: **1** (0.4 mmol), **2** (2.0 mmol), eosin Y (0.004 mmol), $TsOH·H_2O$ (0.01 mmol), and *t*BuONO (0.6 mmol) in CH_3NO_2 (2.0 mL) were irradiated with 10 W blue LEDs (450 nm) at room temperature under N_2 for 24 h. [b] Isolated yields.

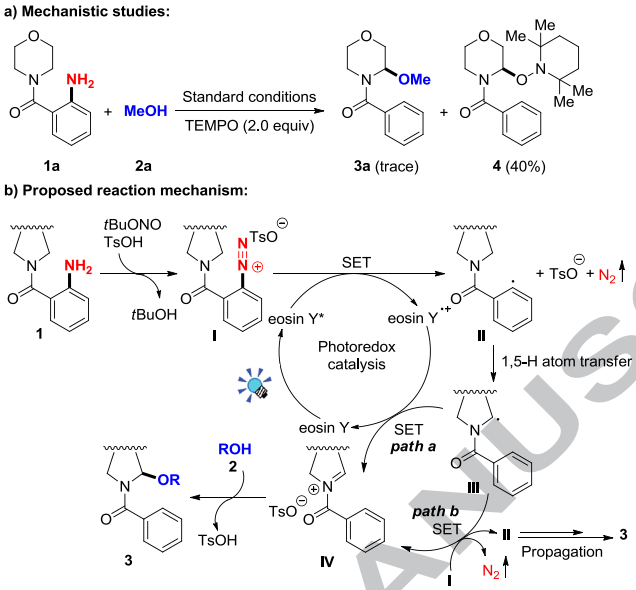
(Table 2). We first investigated the scope with respect to the *o*-aminobenzamides **1**. Five-, six-, and eight-membered cyclic amines **1b-1d** proceeded well with moderate to good yields. When the reaction was conducted on three and four-membered cyclic amines, the desired products were not obtained likely due to the instability of starting materials under current reaction system. The thiomorpholine derivative **1e** is a suitable substrate and afforded the desired product **3e** in 42% yield. The piperazine derivative **1f** provided a low yield due to some side reactions. The substituted cyclic amines **1g-1i** underwent this transformation smoothly to provide the corresponding products **3g-3i** in moderate to good yields, which are formed as a single diastereomer with rotamerism. In addition, the reaction of α-substituted amine was investigated. Unfortunately, the reaction provided a mixture, which could not be identified as the targeted product. When the reaction was conducted on the acyclic aliphatic amine **1j**, the targeted product **3j** was obtained in 55% yield. For diethyl amine as the substrate, the reaction only provided the dealkylated product rather than the desired cross-coupling product. For substrates **1b-1j** providing **3b-3j**, we also tested these substrates by using methanol as the solvent. Compared to these reactions in CH_3NO_2 as the solvent, lower yields were obtained (these results are not shown in Table 2).

We then surveyed the scope of alcohols **2** (Table 2). Different aliphatic alcohols worked well and afforded the corresponding α-alkoxybenzamides **3k-3m** in good yields (54-71%). In addition, alcohols containing alkene and alkyne were tolerated under optimized conditions, leading to the targeted products in good yields (**3n**: 78%, **3o**: 76%). The sterically more hindered alcohol equally served as a good substrate and provided the product **3p** in 45% yield. Notably, this photocatalytic system can be applied to the late-stage functionalization of natural alcohols. For instance, (-)-carveol was proved to be competent and was successfully converted to the desired product **3q** in 51% yield. The feasibility for the introduction of natural alcohols into biologically important benzamides is very important for structure-activity relationship (SAR) studies and discovery of new lead compounds. It is important to note that regiocontrol of the current method was very high. All of the reactions preferably occurred at the α-position of aliphatic amines. We did not observe any β-substituted product in these reactions.

To gain mechanistic insights into the reaction pathway, some preliminary studies were conducted. The reaction of **1a** with **2a** was conducted in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) as the radical scavenger. When TEMPO was added to the reaction mixture, the formation of **3a** was suppressed, and the TEMPO-adduct **4** was isolated in 40% yield (Scheme 2, a). This result supports the hypothesis that sequential generation of aryl radical and 1,5-hydrogen-atom transfer may be involved in this transformation.

On the basis of the above experiments and previous reports,[6,9] a plausible reaction mechanism is proposed. First, the *o*-aminobenzamide **1** reacts with *t*BuONO and sequentially takes place anion exchange with the anion of TsOH to the diazonium salt **I**

and *t*BuOH.[10] Subsequently, the diazonium salt **I** is reduced through single electron transfer (SET) process by the excited state of eosin Y to the aryl radical **II**,[9] which abstracts a hydrogen atom from a remote aliphatic C-H bond to the alkyl radical **III** (racial translocation event). The alkyl radical **III** was further oxidized through SET by eosin Y radical cation to the iminium intermediate **IV**. However, an alternative pathway



Scheme 2. a) Mechanistic studies. b) Proposed reaction mechanism.

involving the transformation of **III** into **IV** by radical chain propagation cannot be excluded at the current stage.[11] Finally, **IV** is trapped by alcohol **2** to form the product **3**. Further studies are ongoing to understand the mechanism in more detail.

In summary, we have presented the first visible-light photocatalytic synthesis of valuable α-alkoxybenzamides starting with readily prepared *o*-aminobenzamides and alcohols through radical translocation. These transformations proceed efficiently under metal-free and mild conditions. Reactions are very easy to conduct, and products were obtained in moderate to good yields.

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Highlights

•Metal-free approach to α-alkoxybenzamides through radical translocation.

•This photocatalytic system can be applied to the late-stage functionalization of nature alcohols.

•The reaction features complete regioselectivity, operational simplicity, and good practicality.