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Late-Stage Photoredox C−H Amidation of N-Unprotected Indole Derivatives: Access to *N*-(Indol-2-yl)amides

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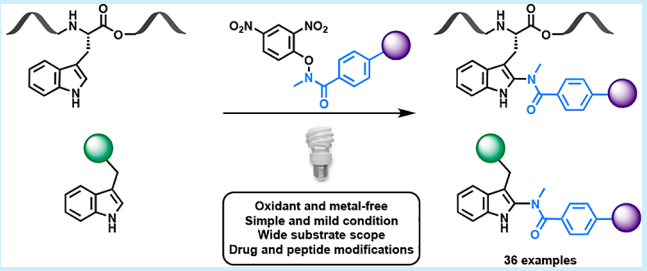
ABSTRACT: The late-stage functionalization of N-unprotected indoles can be useful for modifying low-molecular-weight drugs and bioactive peptides. Whereas indole carboxamides are valuable in pharmaceutical applications, the preparation *N*-(indol-2-yl)-amides with similar structures continues to be challenging. Herein we report on visible-light-induced late-stage photoredox C−H amidation with N-unprotected indoles and tryptophan-containing peptides, leading to the formation of *N*-(indol-2-yl)amide derivatives. N-Unprotected indoles and aryloxyamides that contain an electron-withdrawing group could be coupled directly to eosin Y as the photocatalyst by irradiation with a green light-emitting diode at room temperature. Mechanistic studies and density functional theory calculations indicate that the transformation might proceed through the oxidative C−H functionalization of indole with a PS* to $PS^{\bullet-}$ cycle. This protocol provides a new toolkit for the late-stage modification labeling and peptide−drug conjugation of N-unprotected indole derivatives.

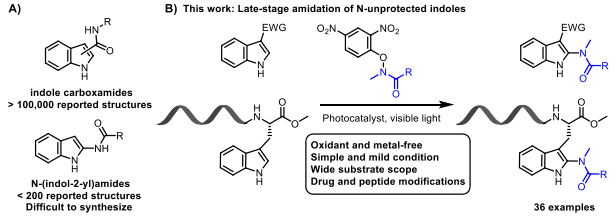


Many indole derivatives function as intercellular signal molecules in living systems, where they play a role in affecting various bacterial physiology characteristics.[1] Functionalized indoles are common motifs in bioactive peptides, natural products, and pharmaceuticals.[2] Previous studies have shown that transition-metal-catalyzed protocols are attractive routes to the production of C2- or C3-substituted indoles.[3,4] The direct catalytic C−H functionalization of N-unprotected indoles has been limited due to the inherently higher reactivity of the N−H group.[5] Because of this, the N−H bond of indoles is usually preprotected prior to the modification of indole derivatives. These methods are suitable for constructing small building blocks but could not be extended to large and complex molecules. Thus developing a simple, high-chemoselectivity, and mild strategy for the direct C−H functionalization of unprotected indoles would be highly desirable.

Because of the hydrogen-bonding characteristics of amides, they can be used as inhibitors of a variety of enzymes and proteins.[6] Of the more than 100 000 structures of indole carboxamides, fewer than 200 structures bearing the *N*-(indol-2-yl)amide pattern have been reported.[7] Because of the rarity of the *N*-(indol-2-yl)amide structure, there is no straightforward methodology for preparing these structures. However, the indole scaffold is important in drug discovery, and expanding the availability of *N*-(indol-2-yl)amide structures would be highly desirable in terms of constructing drug design libraries (Scheme 1A).

Over the last several decades, C−H functionalization has experienced growth, and several reports of late-stage functionalization (LSF) that could be useful for the modification of small-molecule drugs and bioactive peptides have appeared.[8,9] Photoredox catalysis strategies for developing novel, complex molecules have recently become more popular, and breakthroughs compared with a traditional synthesis methodology appear to be likely.[10] For example, Taylor[11] and Melchiorre[12] recently reported on a photochemical process for the selective modification of tryptophan residues in peptides and small proteins by utilizing *N*-carbamoylpyridinium salts and light irradiation. Herein we report on the photoredox late-stage C−H amidation of N-unprotected indole derivatives and

Scheme 1. (A) General Structures of Indole Carboxamides and *N*-Indolylamides and (B) Late-Stage C−H Amidation of Indoles through Photoredox Catalysis



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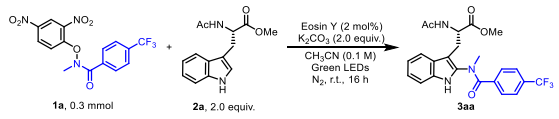
tryptophan-containing peptides coupled to aryloxyamides to generate a series of *N*-(indol-2-yl)amide compounds (Scheme 1B). Under photoredox conditions, aryloxyamides benefit from easy production and possess a weak N−O bond that could generate the amidyl radical.[13]

To establish appropriate reaction parameters for photocatalytic amidation with indoles and aryloxyamides, we began our investigation by examining the reaction of *N*-(2,4-dinitrophenoxy)-*N*-methyl-4-(trifluoromethyl)benzamide (**1a**) and the N-unprotected mono amino acid tryptophan, methyl *N*-acetyl-L-tryptophanate (**2a**), as model coupling partners (Table 1). After a series of screenings of reaction conditions,

Table 1. Optimization of Reaction Conditions[a]



entry	variation of standard conditions	yield (%)
1	none	71
2	acetone instead of CH_3CN	66
3	MeOH instead of CH_3CN	n.d.
4	CH_3CN/H_2O 1:1 instead of CH_3CN	28
5	$CsCO_3$ instead of K_2CO_3	31
6	K_3PO_4 instead of K_2CO_3	39
7	Et_3N instead of K_2CO_3	11
8	air instead of N_2	38
9	blue LEDs instead of green LEDs	70
10	no K_2CO_3	6
11	no light	trace
12	no eosin Y	14
13	no eosin Y, blue LEDs	63

[a]Standard conditions: **1a** (1.0 equiv, 0.3 mmol), **2a** (2.0 equiv, 0.6 mmol), eosin Y (2 mol %), CH3CN (0.1 M, 3 mL), N, 3 W green LEDs, room temperature, 16 h, isolated yield. n.d. = not detected.

the target product (**3aa**) could be obtained in 71% isolated yield when **1a** and **2a** were treated with eosin Y (EY) as the photosensitizer and K_2CO_3 as the additive in CH_3CN under irradiation with a green light-emitting diode (LED) (Table 1, entry 1). The organic solvent used in the reaction played a role in this transformation. For example, in comparison with CH_3CN, acetone gave a comparable yield. However, when MeOH was used as the solvent, the reaction was inhibited (Table 1, entries 2 and 3). Interestingly, using a mixed-aqueous system, **3aa** was produced in an acceptable yield (Table 1, entry 4), suggesting that this system could be used in a biological system. The effect of alkali on the reaction was also examined. In comparison with the results for other inorganic bases ($CsCO_3$ and K_3PO_4) and an organic base (Et_3N), we found that the use of K_2CO_3 promoted the transformation the most efficiently (Table 1, entries 5−7). Subsequently, control experiments, such as replacing N_2 with air and the absence of a base, light, or photosensitizer, resulted in substantially lower yields of **3aa** (Table 1, entries 8, 10, 11, and 12). When a blue LED light was used in place of a green LED, a comparable product yield of 70% was observed, indicating that blue LEDs can be used in this reaction (Table 1, entry 9). Additionally, in the absence of a photosensitizer, the desired product was produced in 63% yield under irradiation with a blue LED (Table 1, entry 13). This observation suggests that the blue LED might induce N−O bond cleavage with the production of an amidyl radical.

With the optimized conditions in hand, we screened a series of different aryloxyamides to evaluate the applicability (Figure 1). The effect of substituents on the benzene ring of the

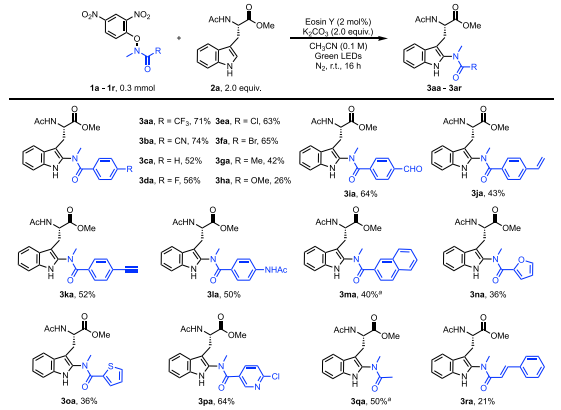


Figure 1. Substrate scope of aryloxy amides. Reaction conditions: **1** (1.0 equiv, 0.3 mmol), **2a** (2.0 equiv, 0.6 mmol), eosin Y (2 mol %), CH_3CN (0.1 M, 3 mL), N_2, 3 W green LEDs, room temperature, 16 h, isolated yield. [a]Acetone as solvent.

aryloxyamides was first examined. Electron-withdrawing groups and halogens at different positions reacted smoothly to yield the corresponding products with good efficiencies (**3aa**−**3fa**). In contrast, electron-donating groups such as methyl and methoxyl groups resulted in relatively lower yields of products (**3ga** and **3ha**). Additionally, potentially applicable substituents for a bio-orthogonal handle, such as carbonyl, alkenyl, alkynyl, and amide groups, resulted in moderate yields (**3ia**−**3la**). This transformation was also found to be compatible with the naphthalenyl group (**3ma**), and heteroarenes, such as furanyl and pyridinyl groups (**3na**−**3pa**), were also tolerated. Moreover, methoxyamide participated in the reaction when acetone was used as the solvent (**3qa**). A cinnamamidyl group (**3ra**) also participated in this transformation. On the contrary, the selectivity of other aromatic amino acids was examined by using the dipeptides of Tyr−Trp and His−Trp in the optimized reaction conditions with **1a**. According to the results of ^{19}F-NMR, both dipeptides would react slightly with the aryloxyamides to generate the Trp−amide products (~10% NMR yield), demonstrating the good Trp selectivity, but the formation of amide-bound dipeptides would be influenced by the nearby aromatic amino acids (Figures S2 and S3).

To explore the applications, various oligopeptides containing tryptophan were introduced into this system (Figure 2). Using the standard conditions, **1a** was introduced as a coupling partner, and dipeptides that contained relatively inert residues such as glycine (**3ab**), valine (**3ac**), and leucine (**3ad**) were also tolerated along with the thioether of methionine (**3ae**), the phenyl group of phenylalanine (**3af**), and the hydroxyl group of serine (**3ag**). In addition, to evaluate the applicability of this procedure, a variety of oligopeptides were successfully transformed by employing this protocol (**3aq**−**3as**).

This protocol can also be used in late-stage reactions of a diverse array of N-unprotected indole derivatives (Table 2). First, skatole **4a** and further modifiable hydroxyl-, bromo-, amidyl-, and esteryl-substituted indoles (**4b**−**4f**) participated

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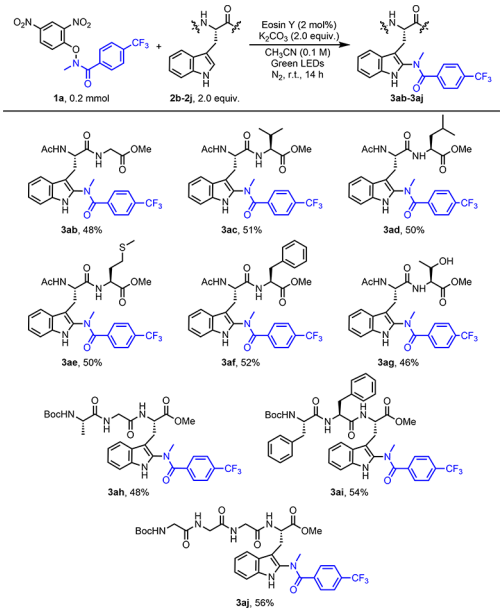
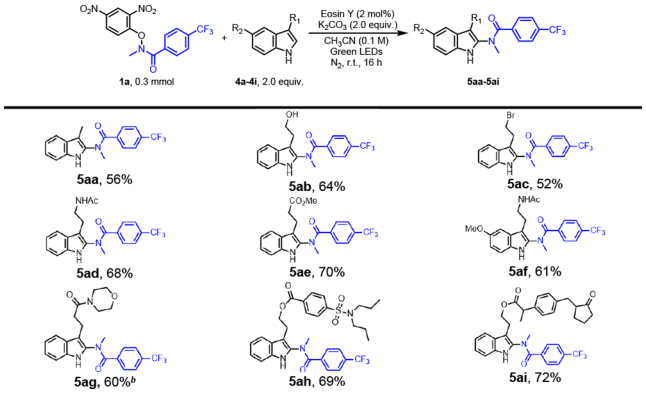


Figure 2. Scope of the late-stage functionalization of Trp-containing oligopeptides. Reaction conditions: **1a** (1.0 equiv, 0.2 mmol), **2** (2.0 equiv, 0.6 mmol), eosin Y (2 mol %), CH_3CN (0.1 M, 3 mL), N_2, 3 W green LEDs, room temperature, 14 h, ^{19}F NMR yield.

Table 2. Scope of Late-Stage Functionalization of Three-Substituted Indoles[a]



[a]Reaction conditions: **1a** (1.0 equiv, 0.3 mmol), **2** (2.0 equiv, 0.6 mmol), eosin Y (2 mol %), CH_3CN (0.1 M, 3 mL), N_2, 3 W green LEDs, room temperature, 16 h, isolated yield. [b]Acetone as solvent.

in this transformation, with the corresponding products (**5aa**–**5af**) being produced. Furthermore, an amidyl-containing 5-methoxyindole (**4af**), which possesses the electron-donating group, could be used to generate the product, indicating that the electron-rich indole can be used in the reaction. When the morpholinyl-attached indole was used as a substrate, the desired product was obtained in moderate yield (**5ag**). Notably, pharmaceuticals such as probenecid- and loxoprofen-substituted indoles could be successfully modified by this conversion with moderate product yields (**5ah**, **5ai**).

On the basis of the results of the substrate screening, we concluded that this protocol proceeds more favorably when electron-withdrawing substrates are used. In the case of electron-withdrawing indoles or aryloxyamides, the efficiency of the transformation was increased, and the N–H functionalization side reactions could be avoided. For example, the yield of the oligopeptide **3aj** was better than that of the dipeptide **3ab**, the formation of the 5-methoxy-substituted **5af** was lower than that for **5ad**, and the electron-withdrawing aryloxyamides of CF_3-substituted **1a** and CN-substituted **1b** were preferable to the methoxy-substituted **1h** in the reaction with tryptophan.

Therefore, we proposed two possible mechanisms for this photocatalytic unprotected indole amidation based on the previously reported findings (Scheme 2). In the oxidative coupling pathway **A**, the excited state of EY forms upon irradiation with a green LED. Subsequently, in an individual single-electron transfer (SET) oxidation with the indole derivative, an indole radical cation species and $EY^{\bullet-}$ are produced. N–O bond cleavage then results in the formation of an amidyl radical with the oxidation of $EY^{\bullet-}$ to complete the photoredox catalytic cycle. Meanwhile, the amidyl radical reacts directly with the indole radical cation to generate a cationic intermediate.

The desired product is then produced after a facile protonation. On the contrary, in the reductive coupling pathway **B**, the SET reduction of aryloxyamides occurs upon EY excitation, generating the amidyl radical and $EY^{\bullet+}$. Consequently, an intermolecular radical addition reaction takes place to establish the C–N bond, which then closes the photoredox cycle and provides the product.

However, in comparison with the protected indole showing a higher redox potential (~1.5 V vs SCE), the redox potential of electron-withdrawing N-unprotected indoles is at approximately 0.8 V, and it makes both pathways **A** (PS* to $PS^{\bullet-}$) and **B** (PS* to $PS^{\bullet+}$) possible. Therefore, to gain more insights into the reaction mechanism, we examined some different photosensitizers that prefer to proceed via the oxidative coupling pathway, such as eosin B, $Ir(ppy)_3$, $Ru(bpy)_3(PF_6)_2$, and $TPT^+BF_4^-$ under irradiation. As a result, the reactions successfully proceeded with the previously described PS* to $PS^{\bullet-}$ photoredox system (Figure 3). In addition, according to the charge localization of the indole radical cation obtained by density functional theory (DFT) calculations, which supports the notion that the indole radical cation will react more favorably at the C2 position of indole under the oxidation environment being used, this would react more readily with the amidyl radical (Figure S1). Because the oxidation potential of the electron-withdrawing indoles would significantly decrease, the oxidative ability of indoles might fit the requirement for the PS*. Hence, to explain the amidation, we prefer to hypothesize that the PS* to $PS^{\bullet-}$ cycle is initially involved in the oxidization of the N-unprotected indole, generating an indole radical cation (pathway **A**), but we could not exclude the possibility of pathway **B**.

Moreover, to further explore the utilities of this protocol, the reaction was performed under conditions of sunlight irradiation without stirring, and the desired product was formed in 75% yield. Meanwhile, 1.47 g of **3aa** was efficiently produced in a gram-scale synthesis. This result indicates that this type of photochemical synthesis has the potential for practical industrial production (Figure 4).

In conclusion, we report on the development of the general and efficient visible-light-induced C–H amidation reaction of N-unprotected indoles. The key to functionalizing the N-unprotected indoles is the employment of an electron-withdrawing indole system, such as a tryptophan-containing peptide, and under these conditions, three-substituted-indoles react with aryloxyamides under the photoredox conditions.

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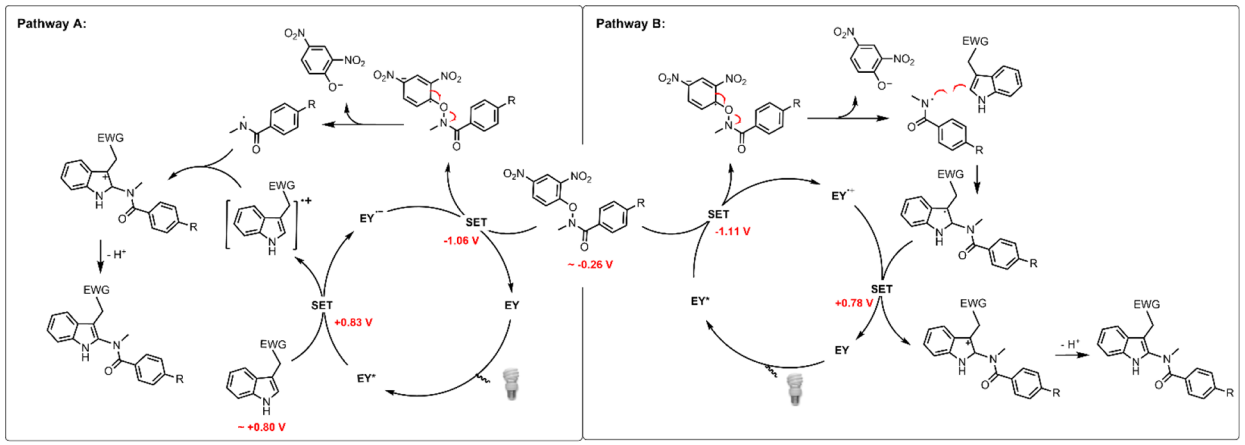
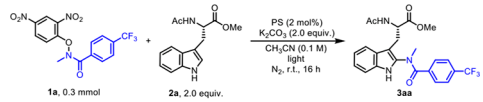
Scheme 2. Proposed Mechanisms





Entry	Variation of standard conditions	Yield (%)
1	Eosin Y, green LEDs	71
2	Eosin B, green LEDs	66
3	$Ir(ppy)_3$, blue LEDs	66
4	$Ru(bpy)_3(PF_6)_2$, blue LEDs	73
5	TPT^+BF^{4-}, blue LEDs	72

Figure 3. Mechanistic studies by altering photocatalysts and light sources.

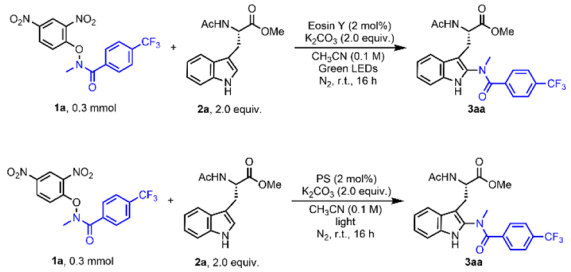


Figure 4. Investigations and applications of this protocol. (A) Photoredox amidation experiment performed under sunlight. (B) Gram-scale synthesis.

This process tolerates an extensive variety of functional groups and oligopeptides, providing various late-stage-modified amidyl-indole derivatives. Moreover, mechanistic studies provide support that the reaction proceeds through a PS* to $PS^{\bullet-}$ photoredox cycle. The value of this transformation was highlighted via the visible-light-catalyzed amidation of some oligopeptides and drug derivatives with aryloxyamides at room temperature.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00609.

Experimental details and characterization data for all new compounds (PDF)

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‖Y.W. and B.D. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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