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Visible-Light-Induced Carbonylation of Indoles with Phenols under Metal-Free Conditions: Synthesis of Indole-3-carboxylates

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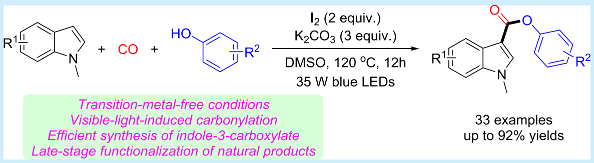
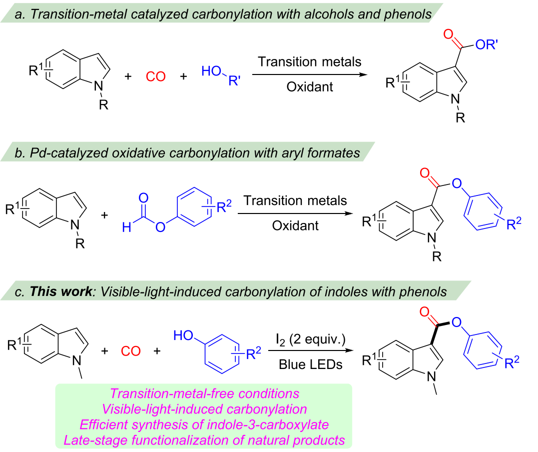
ABSTRACT: A visible-light-induced carbonylation of indoles with phenols for the synthesis of indole-3-carboxylates has been developed. The reaction proceeded via a radical carbonylation process in which elementary I_2 was used as an effective photosensitive initiator and, thus, avoided the use of transition metal catalysts. A series of different aryl indole-3-carboxylates were prepared in moderate to good yields. The broad applicability of this methodology was further highlighted by the late-stage functionalization of several phenol-containing natural products and pharmaceuticals.



Indole derivatives are ubiquitous scaffolds in pharmaceuticals, functional materials, and natural products.[1] Numerous approaches have been established for the construction of diversely functionalized indole derivatives.[2] Among them, the direct C−H functionalization of indole plays an important part. The traditional method for the synthesis of indole-3-carboxylate derivatives involves multistep synthesis via the intermediacy of the corresponding carboxylic acid or acid chloride. An alternative strategy for indole-3-carboxylate synthesis is the transition metal-catalyzed oxidative carbonylation of indoles with alcohol or phenol as the nucleophile (Scheme 1a).[3] For example, the Lei group developed a Pd-catalyzed aerobic oxidative carbonylation of N-substituted and unsubstituted indoles to synthesize indole-3-carboxylates.[4] Xia and Li reported a Rh-catalyzed regioselective procedure for indole-3-carboxylates via carbonylation of indoles.[5] Later, the same group developed a Pd-catalyzed oxidative carbonylation of indole with alcohol and phenol to synthesize indole-3-carboxylates.[6] This reaction proceeds via an oxidative iodination followed by a Pd^0-catalyzed carbonylation process. In addition, aryl formates were also used as efficient CO surrogates. For example, Lan, You, and their colleagues reported a Pd-catalyzed C−H carbonylation of (hetero)arenes with aryl formates to prepare (hetero)aryl carboxylic esters (Scheme 1b).[7]

Scheme 1. Oxidative Carbonylation of Indole Derivatives



In the past few decades, photocatalytic radical carbonylations[8] have attracted an increasing amount of attention from the synthetic community owing to their distinctive features. In this respect, visible-light photoredox catalysis has attracted considerable attention because of its mild reaction conditions as well as the abundance of visible light in nature.[9] Several groups, including Lu and Xiao, Wangelin, Gu, Polyzos, Li, and others, have demonstrated that visible-light photoredox catalysis could generate a variety of previously inaccessible radicals, which could undergo radical carbonylation in the presence of CO or its surrogates to form diversely functionalized carbonyl compounds under mild conditions.[10] Usually, aryl diazonium salts, Katritzky salts, carboxylic acids, and alkyl iodides were used as radical precursors. Ru- and Ir-based complexes or organic dyes such as eosin Y and fluorescein were used as photocatalysts.

On the contrary, elementary I_2-promoted C−H functionalization under visible-light conditions has showed excellent activity.[11] Recent works from the groups of Muñiz,[11a−d] Nagib,[11e] Shibata,[11f] and Jiang[11h] demonstrated that elemen-

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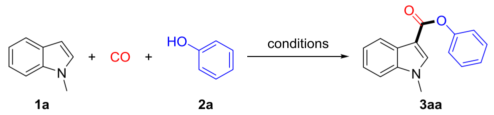
tary I_2 could serve as an efficient initiator for radical catalysis in combination with visible-light irradiation. With a continuous interest in developing efficient carbonylation under mild conditions, we herein report a visible-light-induced carbonylation of indoles with phenols under metal-free conditions, in which elementary I_2 was used as a photosensitive initiator (Scheme 1c).

Initially, we examined this carbonylation reaction using *N*-methyl indole **1a** and phenol **2a** as substrates (Table 1). To our delight, the anticipated reaction proceeded smoothly when the reaction mixture was treated with I_2 in the presence of $Mo(CO)_6$ and K_2CO_3 under irradiation with a 35 W white light-emitting diode (LED). Desired ester product **3aa** was separated in 56% yield when DMF was used as the solvent at 130 °C (entry 1). Inspired by this exciting result, we investigated different reaction parameters for this transformation. First, different solvents were examined. Amide solvents such as *N*-methyl pyrrolidone (NMP) and *N,N*-diethylformamide (DEF) afforded desired product **3aa** in moderate yields (entries 2 and 3, respectively). Other solvents, including THF, MeCN, dioxane, and toluene, were ineffective for this reaction [entry 4 (see details in the Supporting Information)]. DMSO was found to be an optimal solvent and produced **3aa** in 71% yield (entry 5). Different bases were then tested. When Cs_2CO_3 was used as the base, the yield of **3aa** decreased to 66% (entry 6). Other common bases such as *t*-BuOK and NEt_3 failed to produce the expected product [entry 7 (see details in the Supporting Information)]. The reaction temperature and the ratio of **1a** to **2a** affected the yield of this reaction, as well. A lower temperature and a smaller amount of phenol led to decreased reaction efficiencies (entries 8 and 9, respectively). Further sceening of additives did not improve the reaction yield (see details in the Supporting Information). Subsequently, visible-light sources were investigated (entries 10−13). To our delight, product **3aa** was obtained in 92% yield when a 35 W blue LED instead of white light was used (entry 10). Moreover, implementation of a less powerful 18 W blue LED resulted in a slightly decreased yield (entry 13). Only a trace of **3aa** was detected without light irradiation (entry 14). Unfortunately, the carbonylation attempts with a catalytic amount of I_2 in the presence of external oxidants failed (see details in the Supporting Information).

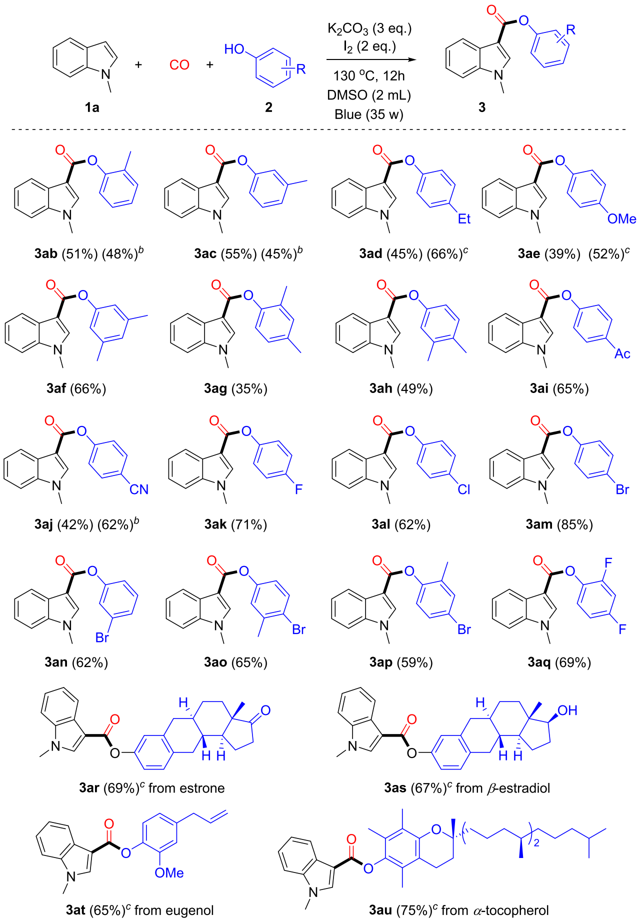
Table 1. Optimization of the Reaction Conditions[a]



entry	light source	solvent	base	temp (°C)	yield (%)[b]
1	white (35 W)	DMF	K_2CO_3	130	56
2	white (35 W)	NMP	K_2CO_3	130	63
3	white (35 W)	DEF	K_2CO_3	130	61
4	white (35 W)	THF	K_2CO_3	130	trace
5	white (35 W)	DMSO	K_2CO_3	130	71
6	white (35 W)	DMSO	Cs_2CO_3	130	66
7	white (35 W)	DMSO	NEt_3	130	NR
8	white (35 W)	DMSO	K_2CO_3	90	63
9[c]	white (35 W)	DMSO	K_2CO_3	130	39
10	blue (35 W)	DMSO	K_2CO_3	130	92
11	green (35 W)	DMSO	K_2CO_3	130	89
12	red (35 W)	DMSO	K_2CO_3	130	81
13	blue (18 W)	DMSO	K_2CO_3	130	88
14	without light	DMSO	K_2CO_3	130	trace

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1.5 mmol), $Mo(CO)_6$ (0.5 mmol), I_2 (1.0 mmol), base (1.5 mmol), solvent (2 mL), LED irradiation, N_2 atmosphere, 12 h. Abbreviations: DMF, *N,N*-dimethylformamide; NMP, *N*-methyl pyrrolidone; DEF, *N,N*-diethylformamide. [b] Isolated yields. [c] **2a** (2.0 equiv) was added.

Scheme 2. Substrate Scope of Phenols[a]

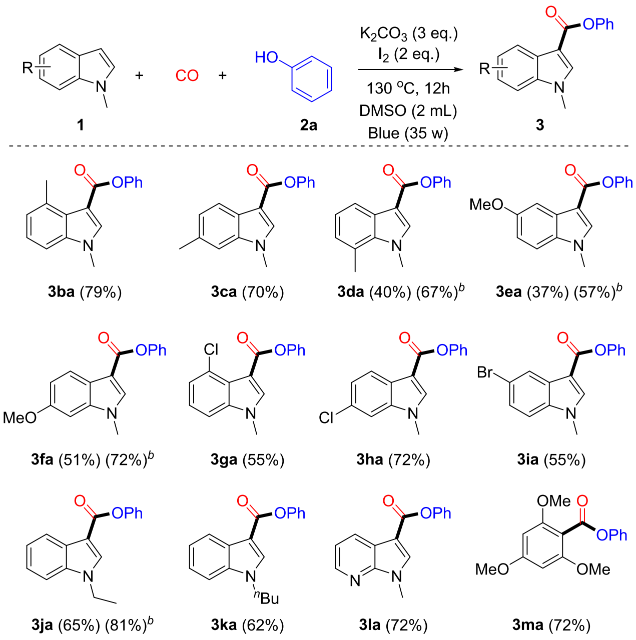


[a] Reaction conditions: **1a** (0.5 mmol), **2** (1.5 mmol), $Mo(CO)_6$ (0.5 mmol), I_2 (1.0 mmol), K_2CO_3 (1.5 mmol), DMSO (2 mL), N_2 atmosphere, 130 °C, 12 h, isolated yields. [b] At 90 °C. [c] *N*-Methylindole **1a** (3.0 equiv) was added.

With the optimal reaction conditions in hand, we then examined the generality of this visible-light-induced carbonylation reaction. As shown in Scheme 2, the scope of phenol **2** was first investigated. A series of phenol derivatives with electron-donating groups (**3ab**−**3ah**) and electron-withdrawing groups (**3ai**−**3aq**) smoothly gave the corrsponding desired indole-3-carboxylates in moderate to good yields. Compared with phenols with electron-donating groups, electron-withdrawing substituents gave slightly higher yields (**3ab**−**3aq**). Notably, the steric hindrance of the substituent had little effect on the efficiency of this reaction (**3ab** and **3ad** vs **3ac**). In addtion, a series of functional groups, including ether (**3ae**), acetyl (**3ai**), cyano (**3aj**), and halide (**3ak**−**3aq**) groups, were compatible with this carbonylation reaction. It should be mentioned that the reaction temperature could be decreased to 90 °C with slight decreases in the reaction yields (**3ab** and **3ac**). However, for a substrate bearing a sensitive functional group such as cyano, an even higher yield could be obtained at a lower temperature (**3aj**). Moreover, the synthetic utility of this process is further highlighted by the late-stage diversification of several phenol-containing pharmaceuticals and natural products. For example, when estrone (an estrogen receptor agonist) and eugenol (a naturally occurring guaiacol) were treated with 3.0 equiv of *N*-methylindole **1a**, products **3ar** and **3at** were separated in 69% and 65% yields, respectively. Of particular note was the fact that β-estradiol was esterified selectively at the phenolic hydroxy group with the other aliphatic one remaining untouched, thus producing **3as** in 67% yield. The essential vitamin α-tocopherol, with a hydroxy group encumbered by the two *ortho* methyl groups, also successfully engaged in this reaction and delivered product **3au** in 75% yield.

Subsequently, a series of indole derivatives as the other reaction partner for this carbonylation were reacted with phenol **2a** to explore the generality of the reaction. As shown in Scheme 3, a variety of *N*-methylindole derivatives could afford the corresponding phenyl esters in moderate to good yields. Both electron-donating (**3ba**−**3fa**) and electron-withdrawing (**3ga**−**3ia**) substituents on the indole skeleton were tolerated. In addition, we also investigated the effect of substituents on the nitrogen of indoles. Generally, *N*-alkyl-substituted indoles reacted smoothly to give expected products **3ja** and **3ka** in moderate yields.[12] However, indoles substituted with *N*-electron-withdrawing groups (including Ac, Boc, Piv, and Ts) failed to give the desired products under the standard conditions. In addition, other (hetero)arenes such as *N*-methyl 7-azaindole and 1,3,5-trimethoxybenzene also engaged in this reaction and afforded the corresponding phenyl esters **3la** and **3ma**, respectively, in good yields.

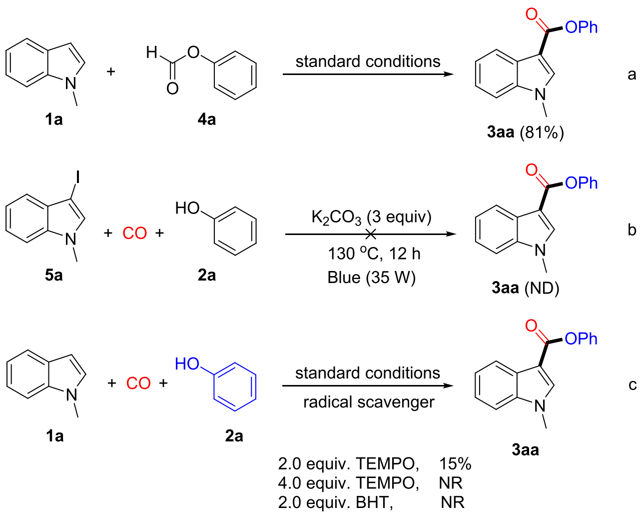
Scheme 3. Substrate Scope of (Hetero)arenes[a]



[a]Reaction conditions: **1** (0.5 mmol), **2a** (1.5 mmol), $Mo(CO)_6$ (0.5 mmol), I_2 (1.0 mmol), K_2CO_3 (1.5 mmol), DMSO (2 mL), N_2 atmosphere, 130 °C, 12 h, isolated yields. [b]Indole (3.0 equiv) was added.

To gather further insight into this visible-light-induced carbonylation reaction, the following control experiments were conducted. First, when *N*-methylindole **1a** was treated with 3.0 equiv of phenyl formate **4a** under the standard conditions, product **3aa** was obtained in 81% yield (Scheme 4a). This observation indicates that phenyl formate could be converted to the possible intermediate under the standard conditions. On the contrary, no desired product **3aa** was detected when 3-iodo-1-methyl-1*H*-indole **5a** was subjected to the standard reaction conditions without the addition of I_2, which excluded the possibility of 3-iodo-indole as an intermediate in this reaction (Scheme 4b). Then, two commen radical scavengers, 2,2,6,6-tetramethylpiperidinooxy (TEMPO) and butylated hydroxytoluene (BHT), were employed in the reaction of *N*-methylindole **1a** and phenol **2a** (Scheme 4c). As a result, the yield decreased severely to 15% when 2.0 equiv of TEMPO was added. The reactions were completely shut down when an excess of TEMPO or BHT was used. These phenomena indicate that this transformation proceeds by a radical mechanism.

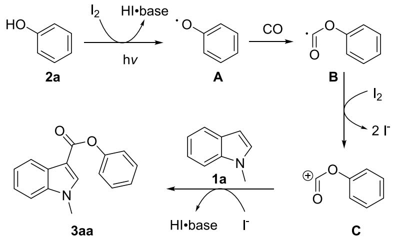
Scheme 4. Control Experiments



Then, we analyzed the UV−vis absorbance spectra of **1a**, **2a**, **4a**, I_2, and different reaction mixtures in DMSO (see details in the Supporting Information). The solutions of **1a**, **2a**, and **4a** have no absorption in the visible region. The solutions of molecular I_2 (λ_{max} = 366 nm), **1a** and I_2 (λ_{max} = 367 nm), and **2a** and I_2 (λ_{max} = 365 nm) have similar visible range absorption. These results indicated that I_2 acted as a photosensitive initiator in this reaction.

A plausible reaction pathway for this carbonylation reaction is proposed on the basis of the control experimental results and previous reports (Scheme 5). First, a single-electron oxidation of phenol **2a** with I_2 under visible-light irradiation generates phenol radical **A**. Then, trapping of a CO molecule yields benzoyl radical **B**, which was further oxidized by I_2 to give acylium ion **C**. Finally, nucleophilic attack of *N*-methylindole **1a** on the carbonyl center of acylium ion **C** gives desired product **3aa**. The use of elementary I_2 as an efficient initiator for radical catalysis under visible-light irradiation has been elegantly demonstrated in previous reports. Importantly, the product yields severely decreased when the reaction was conducted under dark conditions (Table 1, entry 14). Accordingly, it is reasonable that this carbonylation reaction

Scheme 5. A Plausible Reaction Pathway



proceeds via a visible-light-induced radical process. In addition, the fact that indoles substituted with *N*-electron-withdrawing groups failed to give the desired products indicates that indole acts as the nucleophile that attacks intermediate **C** to afford the desired product.

In summary, an efficient protocol for the construction of indole-3-carboxylates via visible-light-induced carbonylation of indoles with phenols under metal-free conditions is described. The reaction proceeds via a radical carbonylation process in which elementary I_2 is used as an effective photosensitive initiator. A range of functionalized indole-3-carboxylates were obatained in moderate to good yields from easily available starting materials. Importantly, the broad applicability of this method is further highlighted by the late-stage functionalization of several phenol-containing natural products and pharmaceuticals.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01494.

Experimental procedures and compound characterization (PDF)

FAIR data, including the primary NMR FID files, for compounds **3aa−3au**, **3ba−3ja**, **3la**, and **3ma** (ZIP)

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Notes

The authors declare no competing financial interest.

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(12) When *N*-benzyl indole was employed under the standard conditions, phenyl 1*H*-indole-3-carboxylate was obtained in 60% yield. The deprotection of the benzyl group might have resulted from the strong reducing property of HI, which can be generated in this reaction as a byproduct.