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Photochemical α-Carboxyalkylation of Tryptophols and Tryptamines via C–H Functionalization

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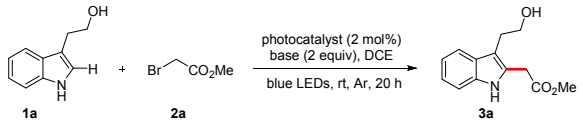
An α-carboxyalkylation of tryptophols and tryptamines by functionalization of C–H bond under visible light irradiation has been developed. The photochemical strategy activated C–Br bonds of α-bromo-alkylcarboxylic esters to provide carbon-centered radicals under the catalysis of Ir(III) photocatalyst and coupled with indole derivatives. This methodology displayed wide functional group tolerance and excellent regioselectivity, and was applied to the late-stage functionalization and the preparation of indole-containing hybrids.

The 2-acetic indole moiety is widely existed in many structurally intricate and biologically important alkaloids, such as akuammicine, vindoline, pandine, and vincadine. The traditional methods for installation of acetic group on C2 of indoles was implemented through multistep sequencesor prepared from C2 substituted indoles. It was discovered that pre-installed directing groups at the N1 position of indoles facilitated the transitional metal catalyzed C–H functionalization to realize the α-carboxyalkylation at C2 position.[1-5] The direct α-carboxyalkylation of indoles was achieved by the activation of C–Br bond with transition-metal catalysis via the redox-type radical addition process.[6-8] Although these reactions were conducted under vigorous conditions (110 ~ 130 °C), and substrate scopes were limited to very few examples of indoles with low yields, the radical addition process exhibited as practical protocol for the direct α-carboxyalkylation at the C2 position of indoles.

The photochemistry provided an alternative strategy to generate radicals for construction of C–C bonds under mild conditions.[9-15] Gryko reported that the α-diazo ester was efficiently converted to α-acetic radical using $Ru(bpy)_3Cl_2$ as photocatalyst for the alkylation of indoles.[16] Glorious developed the alkylation of indoles via the formation of electron donor acceptor (EDA) complexes between Katritzky salts and indoles to generate α-acetic radicals from the fragment of pyridinyl radicals.[17, 18]The bromomalonate was successfully converted to

Table 1. Optimization of Reaction Conditions.



1a 2a 3a

Entry	Catalyst	Base	Yield (%)[b]
1	$Ru(bpy)_3Cl_2$	Et_3N	0
2	*fac*-Ir(ppy)$_3$	Et_3N	<5
3	Ir[(dFCF$_3$ppy)$_2$(dtbpy)]PF$_6$	Et_3N	0
4	Ir[(dFCF$_3$ppy)$_2$(bpy)]PF$_6$	Et_3N	< 5
5	Ir[(dtbbpy)(ppy)$_2$]PF$_6$	Et_3N	< 5
6	Ir[(dmppy)$_2$(dtbbpy)]PF$_6$	Et_3N	18
7	Ir[(dtbbpy)(dtbppy)$_2$]PF$_6$	Et_3N	8
8	Ir[(dmppy)$_2$(dtbbpy)]PF$_6$	4-MeOPhNPh$_2$	10
9	Ir[(dmppy)$_2$(dtbbpy)]PF$_6$	$NaHCO_3$	10
10	Ir[(dmppy)$_2$(dtbbpy)]PF$_6$	$KHCO_3$	56
11	Ir[(dmppy)$_2$(dtbbpy)]PF$_6$	Na_2CO_3	70
12	Ir[(dmppy)$_2$(dtbbpy)]PF$_6$	K_2CO_3	50
13	Ir[(dmppy)$_2$(dtbbpy)]PF$_6$	Na_2HPO_4	84
14	Ir[(dmppy)$_2$(dtbbpy)]PF$_6$	K_2HPO_4	42
15	Ir[(dmppy)$_2$(dtbbpy)]PF$_6$	Na_3PO_4	64
16	Ir[(dmppy)$_2$(dtbbpy)]PF$_6$	K_3PO_4	27
17	Ir[(dmppy)$_2$(dtbbpy)]PF$_6$[c]	Na_2HPO_4	79
18	Ir[(dmppy)$_2$(dtbbpy)]PF$_6$[d]	Na_2HPO_4	56
19	Ir[(dmppy)$_2$(dtbbpy)]PF$_6$[e]	Na_2HPO_4	33
20	Ir[(dmppy)$_2$(dtbbpy)]PF$_6$[f]	Na_2HPO_4	0
21	none	Na_2HPO_4	0

[a] Unless otherwise noted, reactions were performed with **1a** (0.5 mmol), **2a** (1.0 mmol), photocatalyst (0.01 mmol), and base (1.0 mmol) in 1.0 mL DCE, and were placed at approximately 5 cm away from two parallel LED lamps (Ouying-5301, Blue LEDs, 12 W, 44.5 mW/cm^2). [b] Yield of isolated product. [c] Reaction was added 5% H_2O. [d] Reaction was conducted under air. [e] Reaction was placed at approximately 5 cm away from four 23 W CFL. [f] Recation was conducted under dark at 50 °C.

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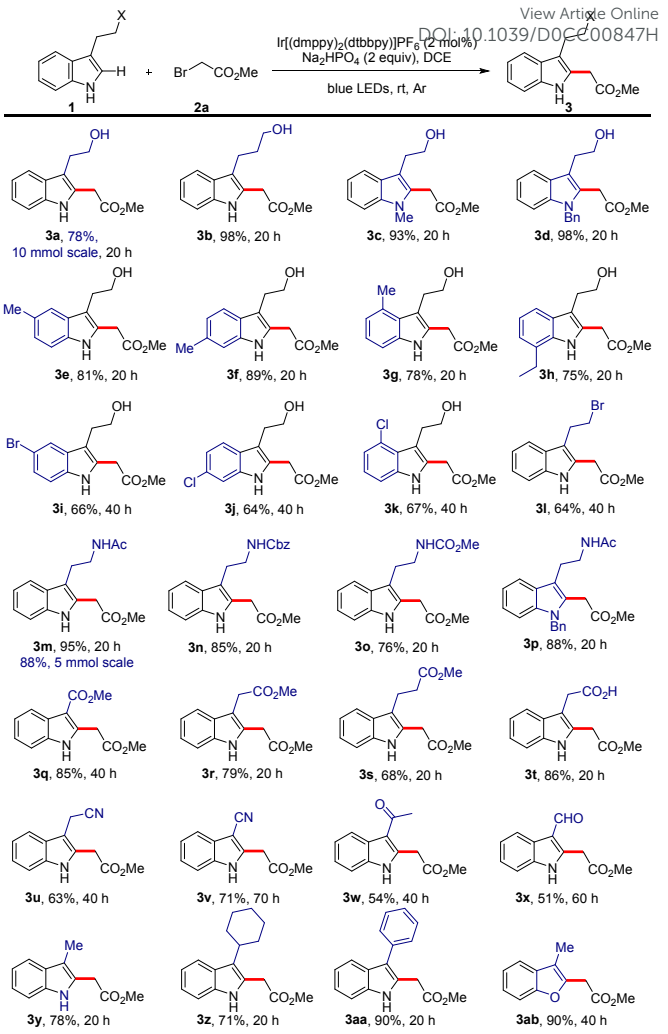
the malonyl radical by photocatalyst (such as $Ru(bpy)_3Cl_2$ or bithiophenes) under visible light irradiation to couple with indoles.[19-22] Meanwhile, a tertiary amine was crucial as sacrificial reductant for these photochemical reactions to cycle the photocatalyst. Both Stephenson and Joo almost simultaneously found that the α-bromo-acetates could be reduced to the corresponding radicals catalyzed by *fac*-$Ir(ppy)_3$ under visible light irradiation.[23, 24] Joo successfully coupled the radicals with electron-rich heteroarenes including indoles, and discovered that the subtle electronic effect of the heteroarene significantly impacts the reactivity.[24] Since most of indole alkaloids contain 2-alkyl moieties instead of 2-malonic moieties, and many complex indole substrates contain additional functional groups, such as tryptophol and tryptamine derivatives, we envisioned that the direct activation of α-halo-alkylcarboxylic esters by photocatalysts would be more practical for syntheses or modification of natural products.

Tryptophol derivatives are common synthetic units in the total synthesis. The traditional reaction normally required the protection of both the nitrogen group and the hydroxyl group of tryptophol. We initiated our research on the photochemical α-carboxyalkylation with the protecting group-free tryptophol **1a** and methyl bromoacetate **2a** as model substrates. We first conducted the reaction by using $Ru(bpy)_3Cl_2$ or *fac*-$Ir(ppy)_3$ as photocatalyst and trimethylamine as sacrificial reductant to activate the C–Br bond.[19, 23, 24] After irradiation under blue LEDs (12 W, λ_{max} = 450 nm) for 20 h, none α-carboxyalkylated product **3a** was detected for $Ru(bpy)_3Cl_2$ and trace amount of **3a** was detected for *fac*-$Ir(ppy)_3$ (Table1, entries 1 and 2). Evaluation of a variety of different photocatalysts (entries 3 - 7) found that $Ir[(dmppy)_2(dtbbpy)]PF_6$ slightly improved the yields (entry 6).[25] Because the trimethylamine might act as a hydrogen atom source to reduce the acetate radical,[19-21] the 4-MeOPhNPh$_2$ was then explored as reductant but resulted in lower yield too (entry 8). The α-carboxyalkylation was distinctly improved to 56% yield when an inorganic base $KHCO_3$ was added to the reaction mixture under the catalysis of $Ir[(dmppy)_2(dtbbpy)]PF_6$ (entry 10). Further screening other inorganic bases, such as Na_2CO_3, K_2CO_3, NaH_2PO_4, KH_2PO_4, Na_3PO_4, etc. (entries 11 – 16), identified that Na_2HPO_4 was the most effective base and the alkylated product was afforded in 84% yield (entry 13). The dry solvent was not necessary for this photochemical reaction, while the presence of oxygen apparently decreased the yields (entries 17 and 18). Moreover, the using of blue LEDs was evidently superior to white CFLs (entry 19). The chloroacetate was also subjected for the α-carboxyalkylation but no products were detected. The photochemical nature of this α-carboxyalkylation was incontestably confirmed as essentially no product was observed when the controlled experiments were performed under dark at 50 °C or without photocatalyst (entries 20 and 21).

With the optimized condition in hand, the substrate scope of indole derivatives was investigated to measure the efficiency and practicability of this photochemical α-carboxyalkylation (Scheme 1). For the synthetic purpose, we first tested the photochemical reaction in gram scale. It was found that this reaction was easily conducted in gram scale after irradiation for

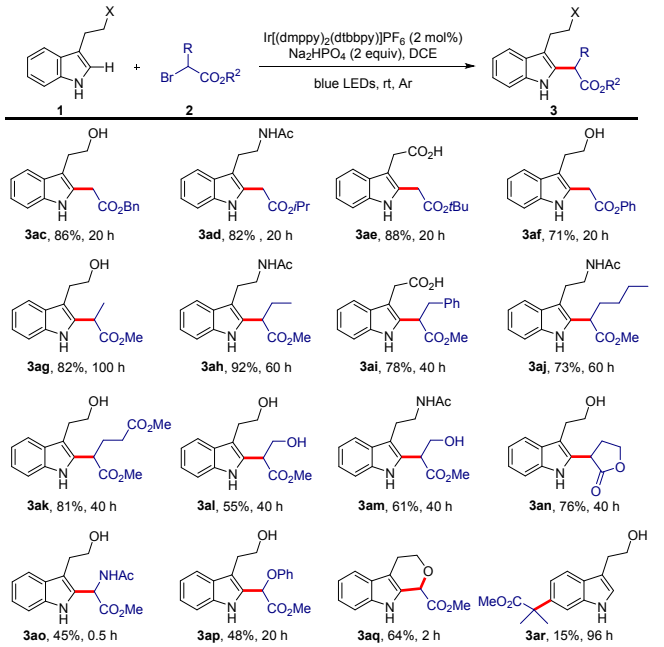


Scheme 1. Investigating the Substrate Scope of Indoles.

20 h at room temperature (**3a**, 78% yield). These results showed that the photochemical reaction was of practical application in preparation of large scale compounds. The homotryptophol was an ideal substrate for the photoreaction and the α-carboxyalkylated product **3b** was afforded in 98% yield. When the tryptophol was *N*-alkylated with methyl or benzyl, they served as perfect examples and resulted in excellent yields too (**3c** and **3d**). Different alkyl substitution patterns at the aromatic moiety of tryptophols were well tolerated, regardless of their position on the phenyl ring (**3e** - **3h**), while the halo-substituted derivatives resulted in relatively lower yields and longer reaction times **(3i** - **3k**). When there had another bromide on the indole, it could not be activated by photocatalyst and thus did not affect the α-carboxyalkylation (**3l**).

Besides the tryptophol derivatives, the tryptamine derivatives were then examined for the photochemical α-carboxyalkylation. The *N*′-acetyl tryptamine was conducted under the standard conditions, and the product **3m** was afforded in 95% yield. Similarly, the gram-scale reaction for *N*′-acetyl tryptamine also proceeded well and 88% yield was achieved in 5 mmol scale. When the tryptamine was protected with other groups, such as Cbz or methyl carbonate, good yields

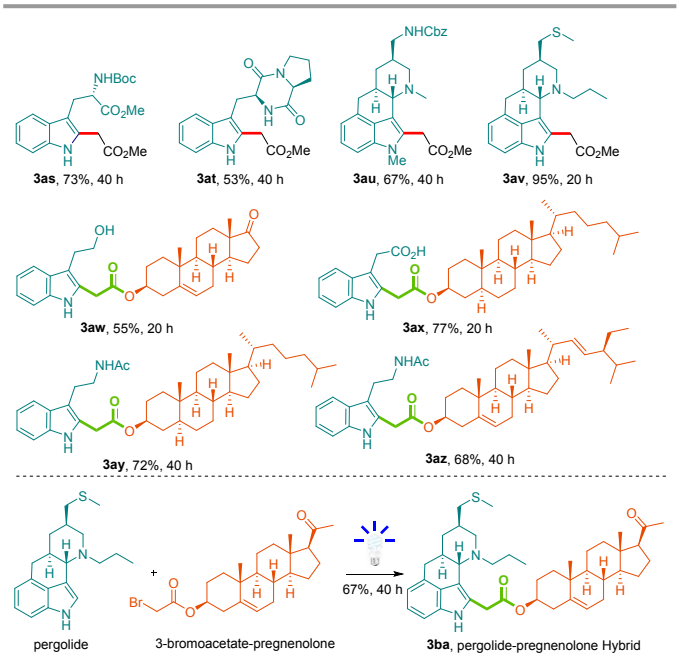
were also harvested (**3n** and **3o**). Additional substation on the N1 position did not affect the α-carboxyalkylation (**3p**, 88% yield). Indole derivatives with various functional groups, such as formate, acetate, propionate, or even acetic acid, also reacted smoothly to afford corresponding α-carboxyalkylated products in moderate to good yields (**3q** - **3t**, 68 - 86% yields). The nitrile, ketone, and aldehyde were also well tolerated, which demonstrated the wide substrate scope of the photochemical α-carboxyalkylation. Moreover, the 3-methyl, cyclohexyl, or phenyl substituted indole was α-carboxyalkylated to give products in good yields (**3y** – **3aa**). This method was also appropriate for functionalization of benzofuran, affording corresponding product **3ab** in excellent yield.



Scheme 2. Investigating the Substrate Scope of α-Bromo-alkylcarboxylic Esters.

To further explore the substrate scope and functional group tolerance, different bromoacetate derivatives were then examined for the photochemical carboxyalkylation (Scheme 2). Changing of the alcohol part of bromoacetate derivatives **2** did not affect the coupling reaction, and corresponding products **3ac** - **3af** were obtained in good yields (71% - 88%). Beside the bromoacetate, more α-bromo-secondary alkyl carboxylic esters were subjected for the photochemical reaction. Although excellent yields for the carboxyalkylation were achieved too, the reaction times were apparently prolonged up to 40 - 100 h, probably due to the steric hindrance and less reactivities of α-aliphatate radicals (**3ag** - **3ak**). The hydroxyl group on α-bromo-aliphatate was also tolerated with applicable yields (**3al** and **3am**). We found that the 2-bromo-γ-butyrolactone was also a suitable substrate for this carboxyalkylation with 76% yield (**3an**). Furthermore, 2-hetero-acetates, such as the α-bromo-*N*-acetylglycine methyl ester and methyl α-bromo-2-phenoxyacetate, were also delivered products in acceptable yields (**3ao** and **3ap**). It was interesting to find that a tricyclic compound **3aq** was afforded in 64% yield with methyl α-bromo-2-methoxyacetate as substrate. Instead, a C6 alkylated product **3ar** was obtained that was presumably due to the steric hindrance and the high stability of tertiary alkyl radicals.

With the wide substrate scope established, we then focused on the coupling of various indole alkaloids with methyl bromoacetate **2a** (Scheme 3). The *N*-Boc-protected L-tryptophan methyl ester was also directly C2 alkylated to form its analogue **3as** in 73% yield without concomitant racemization. Brevianamide F, an indole diketopiperazine alkaloid from holothurian-derived fungus *Aspergillus fumigatus*,[27] was successfully α-carboxyalkylation to afford the product **3at** in moderate yield (53%). Metergoline and pergolide as ergot derivatives, which are psychoactive drugs and long-acting dopamine agonists for the treatment of Parkinson's Disease,[28, 29] reacted with **2a** to give corresponding products **3au** and **3av** (67% and 95% yields).



Scheme 3. Generation of Natural Product Hybrids.

It was discovered that hybrids by combination of parts of different natural products be very promising in the development of leads for both medicinal and agrochemical applications.[30, 31] The preparation of hybrid molecules is normally performed in late-stage step, which requires the coupling reaction should be efficient, mild, regioselective, and wide functional group tolerance. Many natural products contain hydroxyl groups, therefore it could be easily converted to α-bromo-alkylcarboxylic esters for the coupling with indoles at the C2 position under mild visible light irradiation. Biological active sterol derivatives were firstly esterified by bromoacetic anhydride and then be subjected for coupling with different indole derivatives to give corresponding hybrid products in good yields (Scheme 3, **3aw** - **3az**). To demonstrate the efficiency of this photoreaction, two complex natural products, pergolide and pregnenolone, were selected for the preparation of hybrid compounds. The pergolide was subjected for the coupling with 3-bromoacetate-pregnenolone, obtaining the pergolide-pregnenolone hybrid **3ba** in 67% yield. These results

showed that the newly developed photochemical α-carboxyalkylation strategy was practical for the late-stage synthesis C2 α-carboxyalkylated indole derivatives and would be a useful tool for exploring new drug leads.

To gain insight regarding the mechanism of this photochemical α-carboxyalkylation, two controlled experiments were conducted. The reactoin was completely inhibited with TEMPO and the adducted product **4** was isolated, indicating the formation of acetate radical (Scheme S1A in SI). The radical clock experiment with 2-bromo-2-cyclopropylacetate **2b** gave a cyclopentane product **5** (Scheme S1B in SI). We reasoned that the character of radical intermediate was reversed from electrophilic **2c** to nucleophilic **2d** after ring-opening of cyclopropane. The **2d** could not couple with the electron-rich indoles, instead, it coupled with another ring-opened compound **2e**[32] to give the cyclopentane radical **2g**. Finally, the electrophilic radical **2g** reacted with indole to deliver the product **5**.

On basis of above results, a plausible mechanism was proposed (Scheme S2 in SI). The photoexcited state of $Ir[(dmppy)_2(dtbbpy)]PF_6$ (-0.87 V vs SCE)[25] reduced the bromoacetates (≥ -0.88 V vs SCE)[33, 34] to acetate radical **A** through the single-electron transfer process.[35-37] The acetate radical electrophilically coupled with the electron-rich indole to give the benzyl radical **B**.[38] The subsequent oxidation of radical **B** by Ir(IV) gave the benzyl cation **C** and regenerated the Ir(III) photocatalyst. Aromatization of cation **C** by the deprotonation under basic conditions afforded the C2 alkylated product.

In conclusion, we have developed a photochemical α-carboxyalkylation of functional indole derivatives. The reaction directly activated the C–X bond of α-bromo-alkyl carboxylic esters under the visible light irradiation to give the corresponding radical, which coupled to the C2 position of indoles to furnish α-carboxyalkylated products. The developed photoreaction displayed a wide substrate scope and excellent functional groups tolerance and provided an efficient and practical strategy to the late-stage functionalization and the preparation of indole-containing hybrids.

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Conflicts of interest

There are no conflicts to declare.

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