Metal and Acid-Free Visible Light-Mediated Friedel-Crafts Alkylation Reactions of Indole with Anilines

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Metal and Acid-Free Visible Light-Mediated Friedel-Crafts Alkylation Reactions of Indole with Anilines

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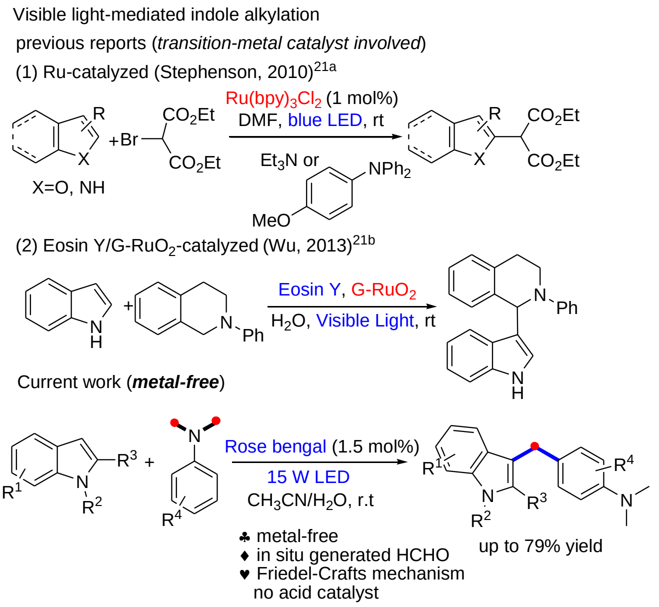
ABSTRACT

Metal and acid-free visible light-induced Friedel-Crafts C3-alkylation reactions of indole derivatives were developed using *N*,*N*-dimethylanilines as the carbon source. A cheap and readily available organic dye, Rose Bengal, was applied as the photocatalyst. This environmentally friendly transformation afforded C3-alkylated indoles in moderate to good yields under mild conditions.

Introduction

In recent years, visible light photoredox catalysis applied in organic transformations has received considerable attention because mild and environmentally friendly conditions are normally achieved by utilizing such catalysts.[1a-d] Ruthenium and iridium polypyridyl complexes are commonly employed as visible light photocatalysts with a relatively long excited state and favorable redox potentials.[2-5] However, such compounds are expensive, rare, and potentially toxic. In contrast, environmentally benign and cheap organic dyes have been used as substitutes of those transition metal complexes in photoredox catalysis.[6,7] In this context, Eosin B,[8a-b] Eosin Y,[9a-h] Rhodamine B,[10a-c] Methylene blue,[11a-c] and Rose Bengal[12a-j] have been reported as photocatalysts to promote photoredox reactions. For examples, Eosin Y was reported to promote direct C-H arylation of heteroarenes with diazonium salts[13] and vinylation of tetrahydrofurans with alkynes;[14] Scaiano group[11a] reported an aryl boronic acid oxidation by Methylene blue catalysis.

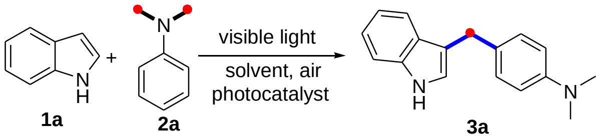
Friedel-Crafts alkylation reaction represents one of the most significant approaches to synthesize alkylated aromatic compounds.[15a-b] As popular aromatic substrates, indoles and their analogues have attracted considerable attention,[16a-d] and many efficient reactions have been developed to synthesize indole derivatives.[17a-c] Friedel-Crafts alkylation of indoles were recently realized through acid mediated,[18a-b,19a-g] transition metal-catalyzed[18a-b,20a-j] and visible light-mediated alkylation reactions.[21a-c] Among them, Stephenson group[21a] reported Ru-catalyzed visible light-mediated C2-alkylation of indoles with malonates (Scheme 1, (1)). In 2013, Wu group[21b] reported a visible light-mediated C3-alkylation of indoles by combining Eosin Y and graphene-supported RuO_2 nanocomposite as the photosensitizer (Scheme 1, (2)). To date, in those documented examples for visible light-mediated alkylation of indoles, either transition metal salt or acid was necessary to promote the reactions. Herein, we report a metal and acid-free visible light-mediated alkylation of indoles with tertiary amines by using Rose Bengal as the photocatalyst, which gave C3-alkylated indoles in moderate to good yields.



Scheme 1. Different protocols for alkylation of indoles

Results and discussion

Table 1. Optimization of Reaction Conditions [a]



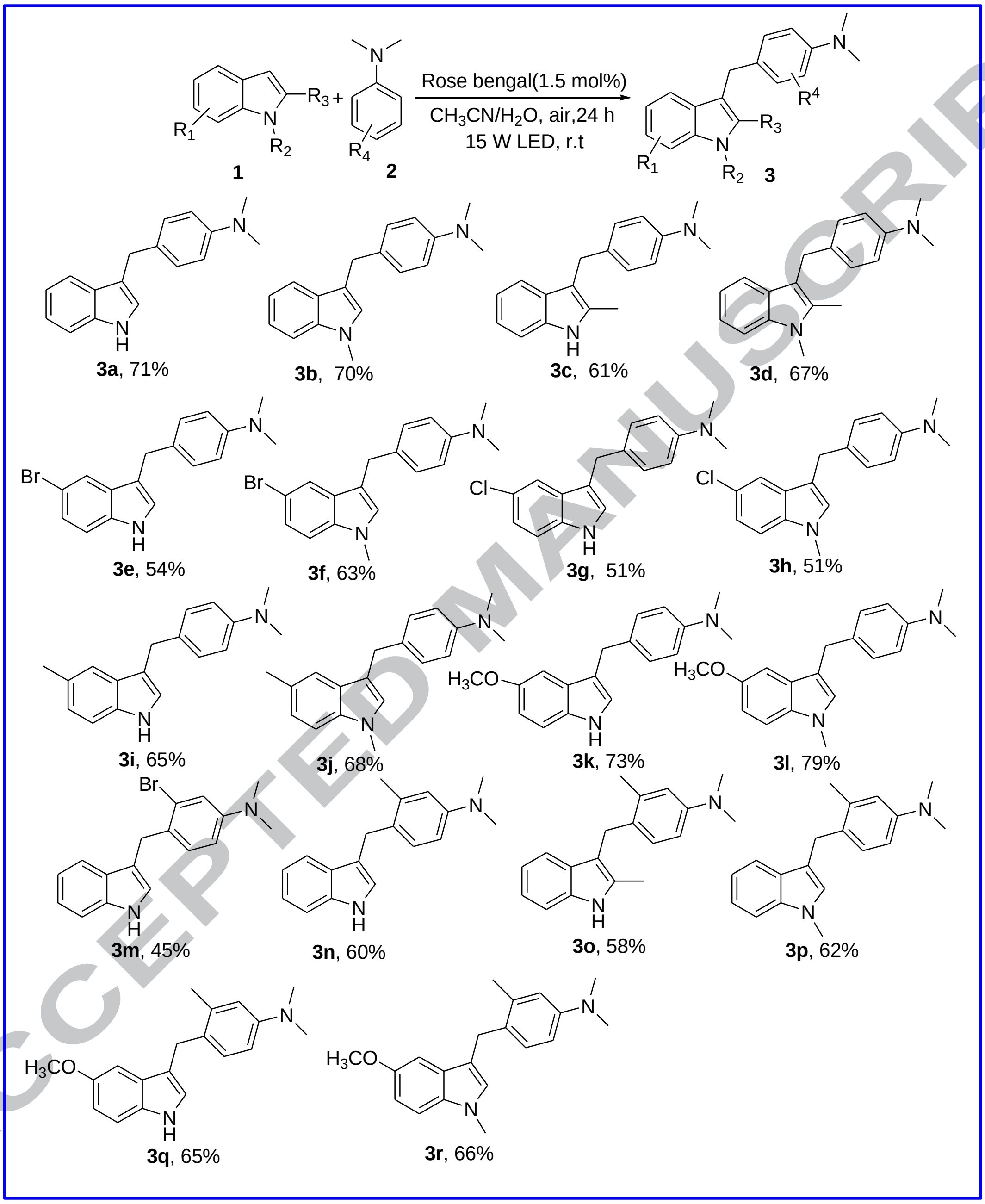
entry	catalyst	solvent	yield(%)[b]
1	Eosin Y	DMF	54
2	Eosin B	DMF	n.r.
3	Rose Bengal	DMF	62
4	Rhodamine B	DMF	n.r.
5	Rose Bengal	H_2O	n.r.
6	Rose Bengal	CH_3CH_2OH	20
7	Rose Bengal	DMSO	trace
8	Rose Bengal	$CHCl_3$	60
9	Rose Bengal	THF	46
10	Rose Bengal	CH_3CN	65
11	Rose Bengal	CH_3CN：H_2O=3：1	66
12	Rose Bengal	CH_3CN：H_2O=5：1	70
13	**Rose Bengal**	**CH_3CN：H_2O=4：1**	**71**
14[c]	Rose Bengal	CH_3CN：H_2O=4：1	69
15[d]	Rose Bengal	CH_3CN：H_2O=4：1	52
16[e]	Rose Bengal	CH_3CN：H_2O=4：1	trace
17[f]	Rose Bengal	CH_3CN：H_2O=4：1	n.r.
18	--	CH_3CN：H_2O=4：1	n.r.

[a]Reaction conditions: 1*H*-indole (1a, 0.5 mmol), *N*,*N*-dimethylaniline (2a, 5 equiv., 2.5 mmol), catalyst (1.5 mol%), solvent (5 mL), open to the air, 15 W LED, 24 h. [b]Isolated yields. [c]For 12 h. [d]5 mol% catalyst. [e]N_2 atmosphere. [f]In the dark.

Initially, we selected 1*H*-indole (**1a**) and *N*,*N*-dimethylaniline (**2a**) as the model substrate under photochemical conditions toward synthesis of C3-alkylated product **3a** (**Table 1**). To our delight, using Eosin Y as the photocatalyst upon irradiation of 15 W light-emitting diode (LED) bulb, **3a** was obtained in 54% yield at room temperature in DMF after 24 h (entry 1). Inspired by this result, we screened other parameters. The Eosin B and Rhodamine B catalysts were no product generated in DMF (entry 2, entry 4), and Rose Bengal gave a moderate yield (62%, **Table 1**, entry 3). The transition-metal-free nature of Rose Bengal motivated us to optimize the reaction conditions using Rose Bengal as the photocatalyst. Thus, a series of different solvents, such as H_2O, C_2H_5OH, DMSO, $CHCl_3$, THF and CH_3CN were screened (entries 5-10). Delightfully, **3a** was obtained in moderate yield (65%) in CH_3CN after 24 h (entry 10). In order to achieve a fast demethylation of tertiary amines, the mixed solvents of CH_3CN/H_2O with different volume ratios were tested and one with a 4:1 ratio gave an improved yield (entry 13, 71%). The appropriate amount of the photocatalyst was 1.5 mol%. Increasing it to 5 mol% did not result in yield enhancement (entry 15). Compared with that of the reaction in the air, the yield of the reaction under N_2 atmosphere was sharply reduced (entry 16). Moreover, no conversion could be observed when the reactions were conducted in the dark and no catalyst (entries 17-18). These results indicate that light, Rose Bengal and air are all essential to achieve the reaction.

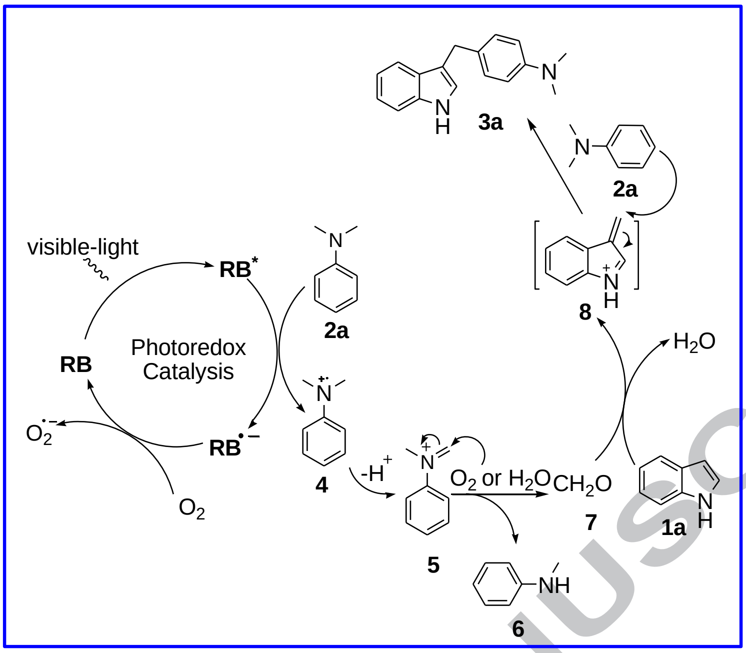
With the optimized reaction conditions in hand, the reactions with a range of indoles and *N*,*N*-dimethylanilines were extended, and totally 18 C3-alkylated indole products were obtained, of which 10 were not previously reported. As shown in **Table 2**, this reaction was compatible with many functional groups. Generally, the indoles bearing an electron-donating group (methoxyl, methyl) had higher yield than those bearing an electron-withdrawing group (halogen). 5-Methoxyl indole and 5-methoxyl-*N*-methyl indole reacted with *N*,*N*-dimethylaniline smoothly affording the corresponding products in 73% and 79% yields, respectively (**Table 2**, **3k** and **3l**). The reactions of methyl-substituted indoles (**Table 2**, **3b-d**, **3i**, **3j**) and halo-substituted indoles (**Table 2**, **3e-h**) with *N*,*N*-dimethylaniline gave moderate yields. It is also shown in **Table 2**, the introduction of substituents to the 3-position of *N*,*N*-dimethylaniline decreased yields (**3m-r**), probably due to the higher steric hindrance caused by 3-position substitutions.

Table 2. Rose Bengal catalyzed synthesis of C3-alkylated indole derivatives[a,b]

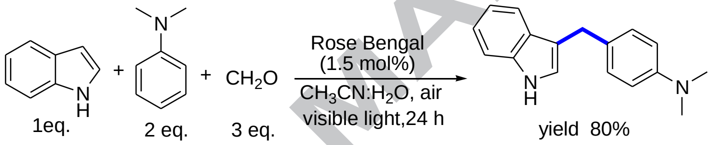


[a]Reaction conditions: indoles (**1**, 0.5 mmol), anilines (**2**, 5 equiv, 2.5 mmol), Rose Bengal (1.5 mol%), CH_3CN/H_2O (4:1 mL), open to the air, irradiation under a 15 W LED at room temperature for 24 h.
[b]Isolated yield.

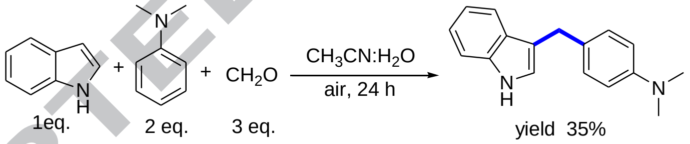
A plausible mechanism was proposed on the basis of the literature reports (**Scheme 2**).[22,24,25] Under visible-light irradiation, Rose Bengal was converted to the excited RB^*, reductive quenching of RB^* by *N*,*N*-dimethylaniline resulted in the formation of Rose Bengal radical anion ($RB^{\bullet-}$) and radical cation **4**. The photoredox cycle is completed by the O_2 oxidation of $RB^{\bullet-}$ to the ground state Rose Bengal.[24] On the other hand, the radical cation **4** losing a proton, presumably to the $O_2^{\bullet-}$ to afford hydrogen peroxide anion and iminium ion **5**. Then, **5** was oxidized or hydrolyzed to give *a*-hydroxylated amine, which subsequently decomposed to afford formaldehyde (**7**) and the *N*-methylaniline (**6**).[25] Finally, the target product **3a** was formed by the three-component reaction of indole with formaldehyde and *N*,*N*-dimethylaniline involving a intermediate 3-methylidene-3*H*-indolium cation **8**, which may be generated by Rose Bengal catalyzed condensation of indole with formaldehyde.[22] To support the postulation, the byproduct *N*-methylaniline (**6**) was isolated from the reaction mixture and confirmed by NMR and mass spectrometry, and the target product **3a** was obtained as expected by a three-component reaction of indole with formaldehyde and *N*,*N*-dimethylaniline using Rose Bengal as the photocatalyst under standard conditions (**Scheme 3**). In addition, another control reaction of indole, formaldehyde and *N,N*-dimethylaniline was performed without visible light and photocatalyst under otherwise same conditions (**Scheme 4**).



Scheme 2. Plausible Mechanism



Scheme 3. Rose Bengal catalyzed three-component coupling reaction of indole, formaldehyde and *N,N*-dimethylaniline



Scheme 4. Three-component coupling reaction of indole, formaldehyde and *N,N*-dimethylaniline without visible light and photocatalyst

Conclusion

In summary, we have successfully developed the metal and acid-free visible light-mediated C3-alkylation reactions of indole derivatives with tertiary amines. Rose Bengal, a cheap and readily available organic dye, was applied as the photocatalyst. The reaction provides a straightforward access to the synthesis of C3-alkylated indoles.

Acknowledgments

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Highlights

- Transition metal-free visible light-induced C3-alkylation of indoles developed.
- Indoles undergo Friedel-Crafts C3-alkylation without acid catalyst.
- The in situ-generated HCHO acts as the carbon source.

Graphical Abstract

Metal and Acid-Free Visible Light-Mediated Friedel-Crafts Alkylation Reactions of Indole with Anilines

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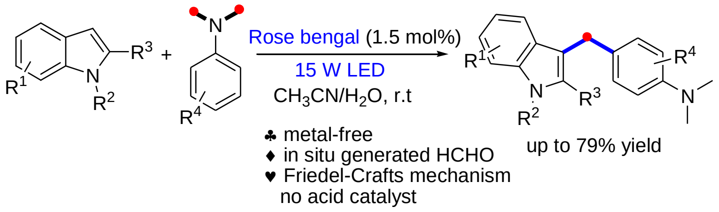

- ♣ metal-free
- ♦ in situ generated HCHO
- ♥ Friedel-Crafts mechanism
  no acid catalyst

up to 79% yield