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Aerobic Transition-Metal-Free Visible-Light Photoredox Indole C-3 Formylation Reaction

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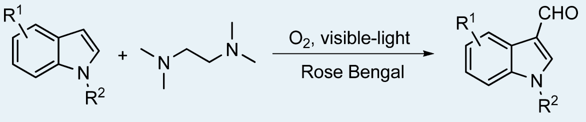
Supporting Information

ABSTRACT: An aerobic visible-light-promoted indole C-3 formylation reaction catalyzed by Rose Bengal has been developed. This transition-metal-free process employs molecular oxygen as the terminal oxidant and uses TMEDA as the one-carbon source through C−N bond cleavage. The reaction is compatible with a variety of functional groups.



KEYWORDS: *aerobic oxidation, visible light photoredox, indole formylation, Rose Bengal, transition-metal-free*

The chemistry of indole derivatives has attracted and continues to attract interest from synthetic organic chemists because the indole moiety exists in countless biologically active molecules. Indole C-3 formylation is one of the important methods for direct C-3 functionalization of indole. The traditional methods for the synthesis of 3-formylindoles were Vilsmeier−Haack[1] and Reimer−Tiemann[2] reactions. These protocols suffered from harsh conditions, low selectivity, and lack of functionality tolerance. In 2011, Su and co-workers reported a Ru-catalyzed indole C-3 formylation using *N*-methylaniline as the carbonyl source.[3] Cu-catalyzed C-3 indole formylation reactions using TMEDA[4] or DMSO[5] as the one-carbon units were developed soon after. Recently, metal-free indole C-3 formylation reactions were reported using similar carbonyl sources.[6] In the above-mentioned reports, the key strategy was the C−N or C−S bond cleavage of the nontraditional formyl sources through the formation of iminium ion or sulfur ylide intermediates.

Organic dyes,[7] such as Rose Bengal and eosin Y, and Ru/Ir polybipyridyl complexes are known to oxidize amine to the corresponding radical cation under visible light irradiation.[8] Upon losing a hydrogen atom, the amine radical cation forms an iminium ion. Many new visible-light-promoted reactions have been developed utilizing the iminium ion intermediate.[9] Iminium ion generated by visible-light photoredox catalysis could undergo electrophilic substitution with indole,[10] resulting in new indole C-3 functionalization reactions.[11] In continuation of our interest in visible-light-promoted aerobic oxidation reactions,[12] we started our investigation of the visible-light-promoted indole C-3 functionalization reaction utilizing molecular oxygen as the terminal oxidants.

To our delight, upon irradiation of visible light, the reaction of *N*-methylindole (**1a**) with TMEDA[13] in the presence of 2 mol % Rose Bengal under air afforded 3-formyl-*N*-methylindole (**3a**) in 12% yield in acetonitrile (Table 1, entry 1). Water was added into the reaction because it was required to hydrolyze the iminium ion intermediate to afford the final product. The yield of **3a** was indeed increased to 35% (Table 1, entry 2). We then screened a variety of photosensitizers, including Ru/Ir polybipyridyl complexes and several organic dyes. It turned out that Rose Bengal was the best catalyst among all the sensitizers tested (entries 3−8). A survey of solvents, such as DMF, DMSO, DMA, and CH_2Cl_2, mixed with water did not provide a better yield than MeCN (entries 9−12). It was found that MeCN/H_2O (5:1) was the optimal mixed solvent system. The desired product was obtained in 48% (entry 13). To obtain a synthetically useful protocol, we further optimized the reaction conditions using an O_2 balloon (53%, entry 14), raising the reaction temperature to 60 °C (60%, entry 15), and adding 4 equiv of KI as the additive (75%, entry 16). At this stage, a set of control reactions were carried out. No product **3a** was observed in the absence of catalyst, without visible-light irradiation, or under N_2 atmosphere (entries 14−16). The results indicated that the reaction was a visible-light photoredox reaction and molecular oxygen was required. Although our reaction conditions are analogous to the reported Cu-catalyzed diindolemethane from indoles and TMEDA,[4b,c] no diindolemethane side-product was observed in our reaction mixture. A reaction performed in a more diluted solution did not improve the yield, either.

With the optimized conditions in hand, we then turned our focus to the scope and functional group compatibility of the reaction. First, the substitution groups on the indole nitrogen were studied. Primary and secondary alkyl groups, methyl, ethyl, and isopropyl groups afforded 70%, 60%, and 71% yields, respectively (Table 2, **3a−c**). Allyl, cyclopropylmethyl, and benzyl groups were tolerated (55%, 74%, and 47% respectively for **3d−f**). 2-(1*H*-indol-1-yl)Ethanol with a free hydroxyl group afforded 45% yield of the corresponding C-3 formylated product (**3g**), and its Boc-protected derivative gave the desired

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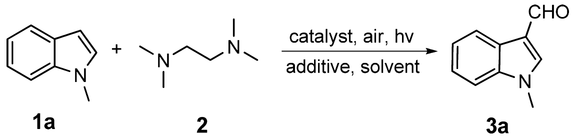
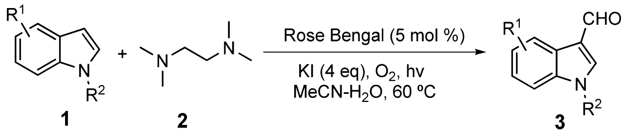
Table 1. Optimization of Reaction Conditions[a]

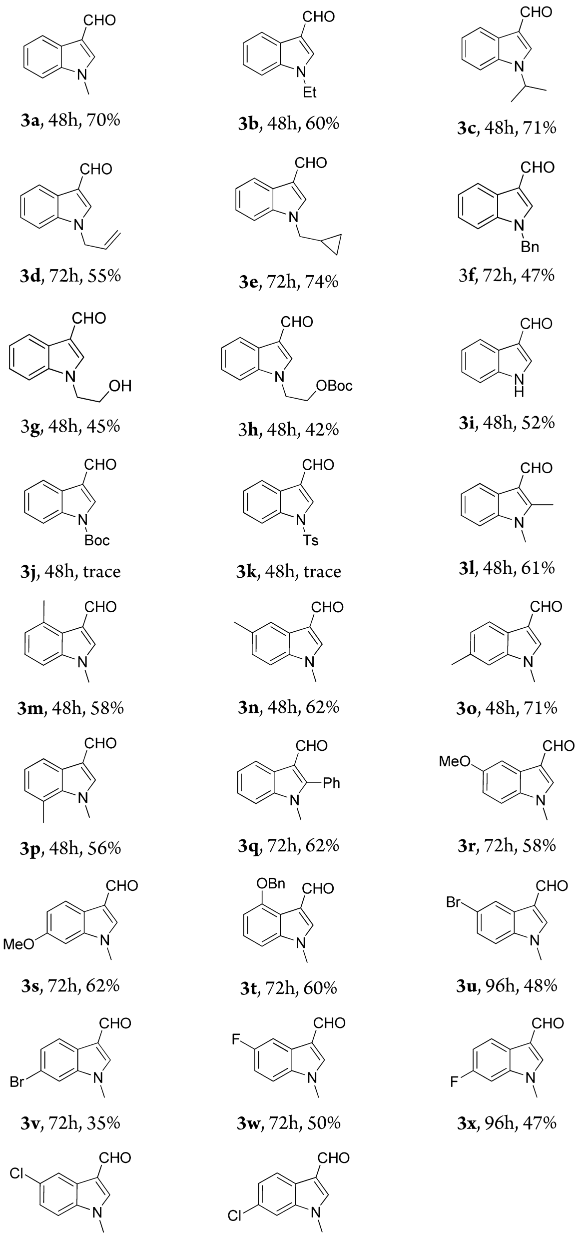


entry	catalyst	solvent	yield[b]
1	Rose Bengal[c]	MeCN	12%
2	Rose Bengal	MeCN–H_2O (100:1)	35%
3	$Ru(bpy)_3(PF_6)_2$[c]	MeCN–H_2O (100:1)	25%
4	$Ru(bpy)_3Cl_2$[c]	MeCN–H_2O (100:1)	28%
5	$Ir(ppy)_3$[c]	MeCN–H_2O (100:1)	trace
6	Rhodamine B	MeCN–H_2O (100:1)	trace
7	Alzarin Red S	MeCN–H_2O (100:1)	trace
8	Eosin Yellowish	MeCN–H_2O (100:1)	<5%
9	Rose Bengal	DMSO–H_2O (100:1)	trace
10	Rose Bengal	DMF–H_2O (100:1)	5%
11	Rose Bengal	CH_2Cl_2–H_2O (100:1)	22%
12	Rose Bengal	DMA–H_2O (100:1)	trace
13	Rose Bengal	MeCN–H_2O (5:1)	48%
14	Rose Bengal	MeCN–H_2O (5:1), O_2 ballon	53%
15	Rose Bengal	MeCN–H_2O (5:1), O_2 balloon, 60 °C	60%
16	Rose Bengal	MeCN–H_2O (5:1), 4 equiv KI, O_2 balloon, 60 °C	75%[d]
17		MeCN–H_2O (5:1), 4 equiv KI, O_2 balloon, 60 °C	N.R.[d]
18	Rose Bengal	MeCN–H_2O (5:1), 4 equiv KI, O_2 balloon, 60 °C, no light	N.R.[d]
19	Rose Bengal	MeCN–H_2O (5:1), 4 equiv KI, N_2 balloon, 60 °C	N.R.[d]

[a] Reaction conditions: *N*-methylindole (0.5 mmol), TMEDA (2 equiv), photocatalyst (5 mol %), solvent (3 mL), room temp, air balloon, using a 14 W fluorescent lamp as the visible light source, 72 h. [b] GC yield. [c] 2 mol % catalyst was used. [d] 48 h.

Table 2. Visible-Light-Promoted Aerobic C-3 Formylation of Indoles[a,b]





3a, 48h, 70%
3b, 48h, 60%
3c, 48h, 71%
3d, 72h, 55%
3e, 72h, 74%
3f, 72h, 47%
3g, 48h, 45%
3h, 48h, 42%
3i, 48h, 52%
3j, 48h, trace
3k, 48h, trace
3l, 48h, 61%
3m, 48h, 58%
3n, 48h, 62%
3o, 48h, 71%
3p, 48h, 56%
3q, 72h, 62%
3r, 72h, 58%
3s, 72h, 62%
3t, 72h, 60%
3u, 96h, 48%
3v, 72h, 35%
3w, 72h, 50%
3x, 96h, 47%
3y, 96h, 46%
3z, 96h, 37%

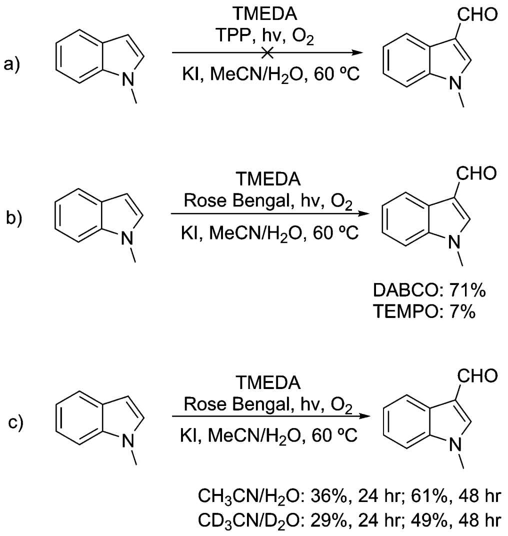
[a] Reaction conditions: indoles (1 mmol), TMEDA (2 equiv), Rose Bengal (5 mol %), KI (4 equiv), MeCN–H_2O (5:1, 6 mL), under O_2 balloon at 60 °C, using a 14 W fluorescent lamp as the visible light source. [b] Isolated yield.

product, too (42%, **3h**). It was notable that free indole worked under the standard conditions and gave 3-formylindole in 52% isolated yield (**3i**). Not surprisingly, when indole nitrogen was protected with strong electron-withdrawing groups, such as *N*-Boc and *N*-Ts, very little products were observed (**3j** and **3k**). Presumably, the electron-withdrawing groups lowered the electron density of the indole ring and retarded the electrophilic attack of iminium ion.

The substitution groups on the carbon skeleton of *N*-methylindole ring were investigated, as well. For methyl substitution at different positions, little impact on the reaction outcome was observed. Substitution at the C-6 position afforded a little better yield (71%, **3o**) than the others (61%, 58%, 62%, and 56% for 2-, 4-, 5-, and 7-substitution, respectively, **3l**–**n**, **3p**). Larger substitution at the C-2 position did not affect the reaction (2-Ph for 62%, **3q**). Electron-donating groups did not facilitate the reaction (58% for 5-OMe, 62% for 6-OMe, and 60% for 4-OBn, **3r**–**t**). Halogen functionalities gave slightly lower yields. Substituents on the C-6 position generally afforded lower yields than that on the C-5 position (**3u** vs **3v**, **3w** vs **3x**, and **3y** vs **3z**). Again, strong electron-withdrawing groups, 7-aza- or 4-CN, shut down the reaction. Other electron-rich aromatic compounds, such as furan and pyrrole, were subjected to the standard conditions; however, no desired formylated products were observed.

It is known that molecular oxygen could form two reactive species—singlet oxygen (O_2^1) through energy transfer or superoxide radical anion ($O_2^{\bullet-}$) via single electron transfer—under visible light irradiation sensitized by Rose Bengal. Several reactions were carried out to investigate the reaction pathway (Scheme 1). Tetraphenylporphine (TPP), a porphyrin dye sensitizer known to generate singlet oxygen,[14] was used as the catalyst instead of Rose Bengal. No C-3 formylated product was observed in either MeCN–H_2O or CH_2Cl_2 (eq a). Although the addition of DABCO, a singlet oxygen quencher, did not

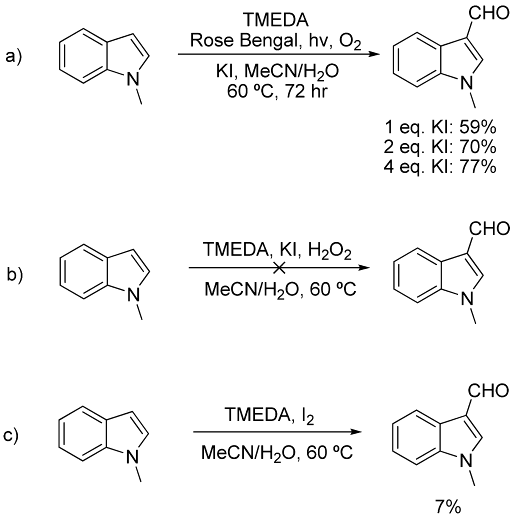
Scheme 1. Investigations of Reaction Pathway



change the reaction outcome, the addition of TEMPO, a radical scavenger, significantly reduced the yield of the reaction to only 8% (eq b). Deuterated solvent increases the lifetime of singlet oxygen, so a reaction was performed in CD_3CN and D_2O (eq c). The reaction progress was monitored by GC. No rate acceleration or yield increase was observed compared with the reaction in nondeuterated solvent. The results from the above reactions strongly suggested that the reaction underwent the superoxide radical anion pathway, not the singlet oxygen pathway.

The role of KI in the reaction was studied, too (Scheme 2). Different equivalents of KI were tested in the reaction. It turned out that the yields increased with an increase in the KI loading (eq a). I_2 generated in situ through the oxidation of KI by trace amount of H_2O_2 might act as the catalyst. To rule out this possibility, stoichiometric H_2O_2 was added to the mixture of *N*-methylindole, TMEDA, and KI. No 3-formyl-*N*-methylindole was formed (eq b). When a stoichiometric amount of I_2 was added to the mixture of *N*-methylindole and TMEDA, a fast formation of 3-iodo-*N*-methylindole was observed, and it was converted to unknown messy products as the reaction time progressed. Only 7% of C-3 formylated product was detected (eq c). Therefore, it was believed that the combination of KI/H_2O_2 or I_2 did not promote the reaction. The real function of KI in this reaction needs further investigation.

Scheme 2. Investigations of the Role of KI



On the basis of the above mechanistic studies and literature reports, a possible mechanism is proposed (Figure 1).

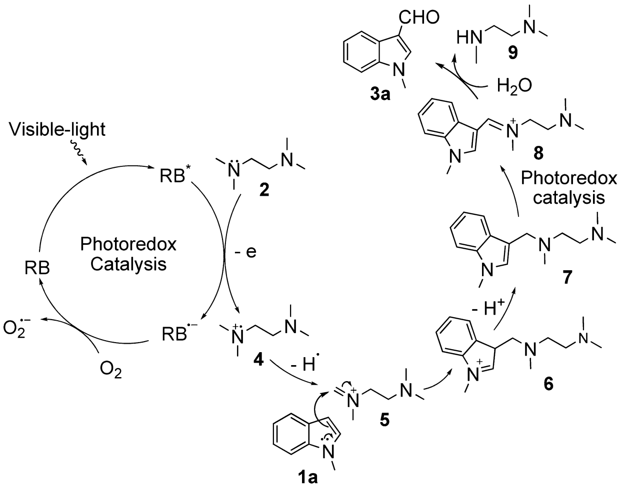


Figure 1. Proposed mechanism.

Oxidative quenching of the visible-light-excited Rose Bengal (RB*) by TMEDA resulted in the formation of Rose Bengal radical anion ($RB^{\bullet-}$) and radical cation **4**. Upon transfer of an electron to O_2 to form the superoxide radical anion, Rose Bengal was regenerated and completed the photoredox cycle. On the other hand, the radical cation **4** gave up a hydrogen atom, presumably to the superoxide radical anion to afford hydrogen peroxide anion and iminium ion **5**. Alternatively, the radical cation **4** could give up a proton and form an α-amino carbon radical, which could go through a second oxidation to afford iminium ion **5**. Electrophilic addition of iminium ion **5** to *N*-methylindole (**1a**) gave indole iminium ion **6**. Upon rearomatization by giving up a proton, C-3-substituted *N*-methylindole intermediate **7** was formed. Because it was more facile for intermediate **7** to form iminium ion than TMEDA, a second visible-light photoredox cycle occurred and generated iminium ion **8**. Hydrolysis of **8** cleaved the C−N bond and afforded 3-formyl-*N*-methylindole (**3a**). To support the postulation, the reaction of *N*-methylindole with TMEDA under standard conditions was analyzed by LC−MS. In the reaction mixture, the mass of intermediate **7** and *N*,*N*,*N*′-trimethylethylenediamine (**9**) were observed. In addition, *N*-[2-(dimethylamino)ethyl]-*N*-methylformamide, a byproduct presumably from the hydrolysis of iminium ion intermediate **5**, was detected by mass spectrometry (see Supporting Information). These observations were good evidence for the proposed reaction pathway.

In summary, a mild transition-metal-free visible-light photoredox indole C-3 formylation reaction using TMEDA as the one-carbon source was developed. The reaction uses molecular oxygen as the terminal oxidant. Inexpensive and readily available organic dye, Rose Bengal, acts as the photosensitizer in the reaction.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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