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*n*Bu$_4$NI-catalyzed C3-formylation of indoles with *N*-methylaniline†

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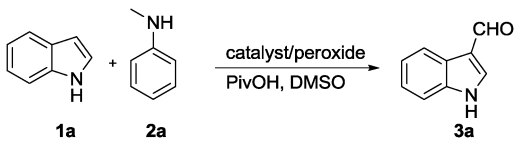
***n*Bu$_4$NI-catalyzed C3-selective formylation of N–H and N-substituted indoles by using *N*-methylaniline as a formylating reagent was first successfully demonstrated.**

The catalytic utilization of hypervalent iodine compounds has received considerable attention due to their mild, safe and environmentally friendly characteristics.[1] The power of recently developed catalytic reactions stems from the reactive iodine(III) or iodine(V) species, which are generated *in situ* from an iodoarene pre-catalyst and a co-oxidant,[1c,d,f,g,i] such as *m*CPBA, peracetic acid, and Oxone®. In 2007, Kirihara *et al.* described the first iodide (I^-) ion-catalyzed oxidative homocoupling reaction of thiols in the presence of a stoichiometric amount of hydrogen peroxide (H_2O_2).[2] Another pioneering study was recently reported by Ishihara *et al.* involving the enantioselective oxidative cycloetherification of ketophenols catalyzed by chiral quaternary ammonium iodide.[3] Using tetra *n*-butylammonium iodide (*n*Bu$_4$NI) with H_2O_2 or *tert*-butyl hydroperoxide (TBHP), they also demonstrated the direct α-oxyacylation of carbonyl compounds with carboxylic acids.[4] Similarly, other groups have reported the metal-free *n*Bu$_4$NI-catalyzed C–H functionalization reactions using either H_2O_2 or TBHP as a cheap, easy to handle and environmentally benign co-oxidant.[5] It is proposed that while the use of an iodide (I^-) ion in combination with a co-oxidant results in the generation of catalytically active species hypoiodite ($[IO]^-$) and iodite ($[IO_2]^-$),[2,3,5d,e,6] which display higher reactivity than the corresponding aryl-λ^3-iodanes and the byproduct iodoarene is completely avoided in these transformations. Additionally, these iodide (I^-) ion pre-catalysts (NaI, KI and *n*Bu$_4$NI) are more economical and readily available than iodoarenes, aryl substituted-λ^3 and λ^5-iodanes.

The prevalence of indoles in many bioactive molecules has prompted the development of synthetically useful methods for their C3-functionalization.[7] C3-formylation of indoles is a key step in the preparation of biologically active natural products, including Homofascaplysin C,[8] FR-900482[9] and indole alkaloids.[10] The traditional methods for the 3-formylindoles synthesis suffer from several drawbacks, such as use of environmentally unfriendly $POCl_3$,[10,11] harsh conditions,[10,11c–f,12] low selectivity,[11b,f] tedious procedures[10,11,12a,13] and lack of functionality tolerance.[10,11c,f,12b,13] Hence, the development of novel access to 3-formylindoles using environmentally benign reagents under mild conditions is still of much significance. More recently, Su and coworkers reported an interesting Ru-catalyzed C3-formylation of indoles using *N*-methylaniline as the carbonyl source.[14] However, the scope of suitable substrates was limited to free (NH)-indoles. From the green and sustainable chemistry point of view, nontoxic and metal-free reagents are preferred. Herein, we report *n*Bu$_4$NI-catalyzed C3-selective formylation of N–H and N-substituted indoles by using *N*-methylaniline as the carbonyl source under metal-free conditions. To our knowledge this is the first example of using the iodide (I^-) ion-mediated oxidative catalysis in formylation reactions.

Our study began by screening a variety of peroxide oxidants for the *n*Bu$_4$NI-catalyzed formylation of indole **1a** with 2 equiv. of *N*-methylaniline **2a** in DMSO at room temperature for 24 h. (Table 1, entries 1–5). Pivalic acid was used as an additive,

Table 1 Optimization of the reaction conditions[a]



1a **2a** **3a**

Entry	**1a** (mmol)	**2a** (mmol)	Catalyst (mmol)	Oxidant (mmol)	Yield (%)
1	0.5	1	*n*Bu$_4$NI (0.05)	TBHP (2)	0[b]
2	0.5	1	*n*Bu$_4$NI (0.05)	H_2O_2 (2)	0[b]
3	0.5	1	*n*Bu$_4$NI (0.05)	CHP (2)	0[b]
4	0.5	1	*n*Bu$_4$NI (0.05)	DTBP (2)	0[b]
5	0.5	1	*n*Bu$_4$NI (0.05)	TBPB (2)	10[b]
6	0.5	1	*n*Bu$_4$NI (0.05)	TBPB (2)	82
7	0.5	1	Me$_4$NI (0.05)	TBPB (2)	44
8	0.5	1	BnMe$_3$NI (0.05)	TBPB (2)	35
9	0.5	1	KI (0.05)	TBPB (2)	52
10	0.5	1	NaI (0.05)	TBPB (2)	57
11	0.5	1	I_2 (0.05)	TBPB (2)	49
12	0.5	1	$RuCl_3$ (0.05)	TBPB (2)	71
13	0.5	1	$FeCl_2$ (0.05)	TBPB (2)	53
14	0.5	1	None	TBPB (2)	15
15	0.5	0.5	*n*Bu$_4$NI (0.05)	TBPB (2)	54
16	0.5	0.7	*n*Bu$_4$NI (0.05)	TBPB (2)	70
17	0.5	1	*n*Bu$_4$NI (0.02)	TBPB (1)	57

[a] Reaction conditions: PivOH (2.5 mmol), DMSO (1 mL), 80 °C, 8 h under nitrogen, GC yield. [b] Room temperature, 24 h.

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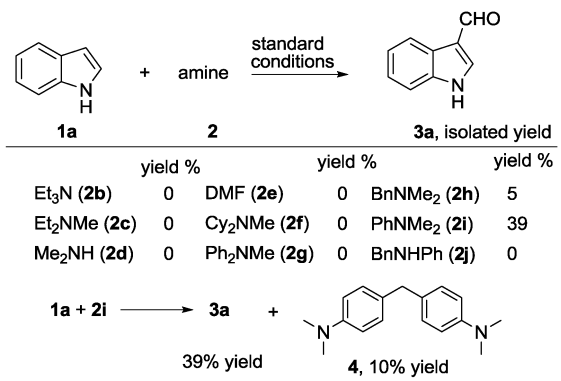
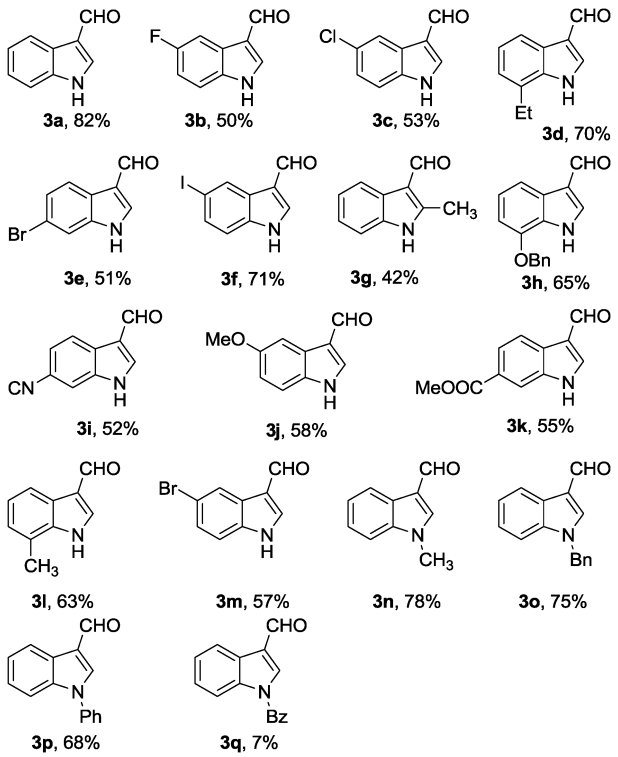
since it has been shown to suppress decomposition of indoles under oxidative conditions.[11f,14,15] We found that most oxidants, including 70% aqueous TBHP, 30% aqueous H_2O_2, cumene hydroperoxide (CHP), and di-*tert*-butyl peroxide (DTBP), were ineffective (Table 1, entries 1–4). In contrast, the reaction proceeded to afford the desired 3-formylindole **3a** in 10% yield when using *tert*-butyl peroxybenzoate (TBPB) (Table 1, entry 5). Gratifyingly, by increasing the temperature to 80 °C, the complete conversion of **1a** was achieved in 8 h, and 3-formylindole **3a** was obtained in 82% yield (Table 1, entry 6). Even after optimizing the reaction temperature, TBHP was completely ineffective at 80 °C, and only a trace product was obtained at 100 °C. The use of H_2O_2 led to no product formation either at 80 °C or 100 °C.[16] We next investigated other iodine-based catalysts including Me_4NI, $BnMe_3NI$, KI, NaI and I_2. With the addition of 10 mol% of catalyst it was found that this reaction provided the desired product **3a** in moderate yields (Table 1, entries 7–11).[17] The metal catalysts were also examined in this transformation, which revealed that $RuCl_3$ and $FeCl_2$ provided lower yields (71% and 53%) than that observed with nBu$_4$NI (Table 1, entries 12 and 13). The yield dropped from 82% to 15% in the absence of nBu$_4$NI, which indicated that the use of nBu$_4$NI was critical for the success of the reaction (Table 1, entry 14). Incomplete conversion of indole **1a** and lower yields were observed when decreasing the amounts of *N*-methylaniline from 2 equivalents to 1.4 equivalents or 1 equivalent (Table 1, entries 15 and 16). Additionally, use of 5 mol% of nBu$_4$NI and 2 equiv. of TBPB resulted in a decrease in yield (Table 1, entry 17). Based on the optimized conditions described above (Table 1, entry 6), we further examined various amines **2b–j** as carbonyl sources for formylation (Scheme 1). Most amines did not produce any formylation product, and starting material indole **1a** was recovered. 3-Formylindole was obtained in 5% yield by use of *N*,*N*-dimethylbenzylamine **2h**. *N*,*N*-Dimethylaniline **2i** gave 39% yield of 3-formylindole, together with 10% yield of product **4**. Oxidative dimerization of *N*,*N*-dimethylaniline **2i** toward 4,4′-methylenebis (*N*,*N*-dimethylaniline) **4** using iron species has been reported.[18] Notably, when *N*-phenylbenzylamine **2j** was subjected to the optimized conditions, neither formylation nor acylation product was obtained.

After achieving the optimized reaction conditions, we next investigated this reaction between various indoles **1** and *N*-methylaniline **2a** (Table 2). The reaction of free (NH)-indoles



Scheme 1 Formylation of indole with various amines.

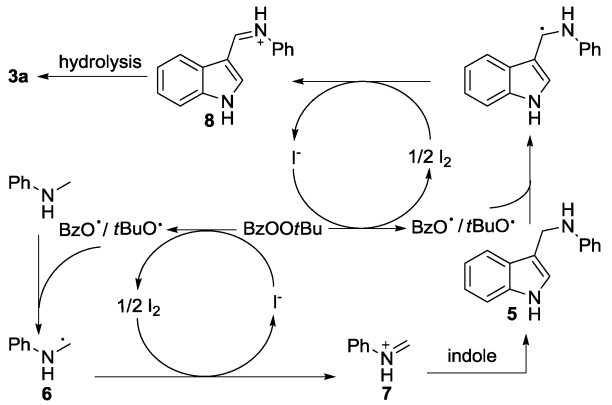
Table 2 Formylation of indoles with *N*-methylaniline



Reaction conditions: indole (0.5 mmol), **2a** (1 mmol), nBu$_4$NI (0.05 mmol), TBPB (2 mmol), PivOH (2.5 mmol), DMSO (1 mL), 80 °C, 8 h under nitrogen, isolated yield.

was compatible with a variety of functional groups, including halides, ether, ester, and cyano groups, and gave the corresponding products **3a–m** in 42–82% yield. Notably, the halo groups (chloro, bromo, iodo) remained unaffected under these reaction conditions. Moreover, the scope was also extended to some N-substituted indoles, including *N*-methylindole, *N*-phenylindole and *N*-benzylindole, which afforded the desired products **3n–p** in good yields (68–78%). Unfortunately, some indoles bearing an electron-withdrawing group on a nitrogen atom, such as acetyl, *tert*-butoxycarbonyl, and *p*-toluenesulfonyl, failed to provide desired products. The reaction of *N*-benzoylindole gave only 7% yield of product **3q**. We reasoned that an N-substituted electron-withdrawing group would weaken nucleophilicity at the C3 position of indole.

To investigate the reaction mechanism, further experiments were carried out. The formylation of **1a** did not occur in the presence of stoichiometric amounts of Bu_4NOH and iodine under present conditions. We speculate that *in situ* generated ammonium hypoiodite ($[Bu_4N]^+[IO]^-$) is not the catalytic species in the formylation reaction. The I(III) and I(V) catalysts, such as $PhI(OAc)_2$ and IBX, have also been examined under the optimized conditions. In sharp contrast, these catalysts halted the present formylation reaction (see ESI†). When a radical inhibitor, TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxyl), was added into the reaction systems of indole **1a** with *N*-methylaniline **2a** the yield of the desired product **3a** decreased dramatically to 30% under optimized conditions, suggesting that the present reaction probably proceeds *via* a



Scheme 2 The proposed mechanism for C3-formylation of indole.

free radical process. When *N*-((1*H*-indol-3-yl)methyl)aniline **5** (Scheme 2) was subjected to the optimized conditions, the formylation product **3a** was obtained in 70% yield (see ESI†). The cross dehydrogenative coupling product **5** may be involved as an intermediate in the present reaction. Based on our observations and studies from other groups,[14,19] a plausible catalytic cycle has been proposed as shown in Scheme 2. Initially, a reaction between an iodide (I^-) ion and TBPB provides a benzoyloxy radical (or *tert*-butyloxy radical) and iodine (I_2). The thus-generated radical abstracts a hydrogen atom from the C–H bond adjacent to a nitrogen atom to afford radical **6**, followed by oxidation to afford the iminium ion **7**. Subsequently, nucleophilic attack of indole **1a** to **7** affords intermediate **5**. Intermediate **5** undergoes a similar process to give the second iminium ion **8**, followed by hydrolysis to give the corresponding 3-formylindole **3a**. We think that the I_2/I^- redox process accelerates the formation of iminium ions **7** and **8**. Investigations that provide a more detailed mechanism are underway in our laboratory.

In summary, the first nBu$_4$NI-catalyzed C3-formylation of indoles with *N*-methylaniline is presented. The method can be applied to N–H and N-substituted indoles without using toxic phosphorus oxychloride and transition metal.

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