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I_2-mediated C3-formylation of indoles by tertiary amine and H_2O

Bo Zhang, Bin Liu, Jianbin Chen, Jiehui Wang, Miaochang Liu *

College of Chemistry & Materials Engineering, Wenzhou University, Wenzhou 325035, PR China

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ABSTRACT

An I_2-promoted 3-formylation of free (*N*–*H*) and N-substituted indoles with tetramethylethylenediamine (TMEDA) and H_2O as the carbonyl source is achieved, providing 3-formylindole in moderate to excellent yields with good functional group tolerance. This procedure represents an exceedingly attractive alternative to the traditional formylation methods.

The indole nucleus is an omnipresent component of numerous natural and synthetic molecules with significant biological activity.[1] Therefore, chemo- and regioselective functionalization of indoles has always been of tremendous value in organic synthesis for the diversity of indole derivatives.[2] 3-Formylindoles are not only key intermediates for the preparation of biologically active molecules[3] and indole alkaloids[4] but also important precursors for the synthesis of a variety of indole derivatives because their carbonyl groups can facilely undergo C–C and C–N coupling reactions and reductions.[5] However, a series of well-established classical methods such as Vilsmeier–Haack[4a,5a,6] Reimer–Tiemann,[7] Rieche,[5b,8] and Duff[9] reactions for the construction of 3-formylindoles suffer from several drawbacks such as using environmentally unfriendly $POCl_3$,[4a,6b,10] strong bases[4a,6,7] or acids[9] in workup processes, lack of functionality tolerance,[4a,10c,5a,11] low selectivity,[10a,d] and tedious procedures.[4a,7,10,11a,5b] Accordingly, the development of general and operationally simple approaches using environmentally benign reagents for the formylation of indoles is still highly desirable.

Recently, Cheng and Su reported Cu or Ru catalyzed C3-formylation of indoles using amine as the carbonyl source independently.[12] However, the utility of metal catalysts would result in several problems involved in removing the residual metals from the final products, which was usually a difficult and tedious process, limiting the practical applications of these procedures. Very recently, Cheng reported the NH_4OAc-promoted formylation of indole by DMSO and H_2O at elevated temperatures.[13] The *n*-Bu_4NI-catalyzed 3-formylation of indoles with *tert*-butyl peroxybenzoate (TBPB) as oxidant and *N*-methylaniline as a carbonyl source demonstrated by Wang was an important advancement.[14] However, excess pivalic acid (PivOH) was indispensable in Su or Wang's strategies which was incompatible with the functional groups labile under acidic conditions. We envisioned that the development of a simple metal-free system, using common cheaper and milder molecular iodine as the promotor, might tremendously improve the practicality of formylation reactions. Herein, we report our study on it.

From the outset of this work, 1-methyl-1*H*-indole **1a** with tetramethylethylenediamine (TMEDA) was selected as the test substrates in combination with I_2 as the oxidant (Table 1). To our delight, the reaction proceeded smoothly in the presence of 1.1 equiv of I_2 with Na_2CO_3 (2.0 equiv) as the additive in 1,4-dioxane at 75 °C under 1 atm of O_2 affording the desired product in moderate yield (58%, entry 1). Encouraged by this result, we simply increased the loading of I_2 to 1.5 or 2.0 equiv, and formylated indole **2a** was delivered in good to excellent yields (66% and 83%, entries 2 and 3). Among the bases tested, Na_2CO_3 was the best, providing the formylation product in 91% yield (entry 12), and the yield dramatically decreased to 10% in the absence of base (entry 6). In the presence of 1, 2, and 3 equiv of TMEDA, the formylation product was isolated in 30%, 79%, and 83% yields, respectively. It was worth noting that solvent was critical owing to only traces of **2a** provided in $MeNO_2$ (entry 8), albeit with moderate yield in toluene (52%, entry 7). In contrast, the use of $^nBu_4NI$ or KI[13] previously reported to be an excellent catalyst for formylation of indoles, could not give any products (entries 9 and 10). Attempt to develop a catalytic system failed, as the yield dramatically decreased to 34% and 33% under 100 °C and 75 °C, respectively (entries 13 and 14).

* Corresponding author. Tel./fax: +86 577 88368280.
E-mail address: mcl@wzu.edu.cn (M. Liu).

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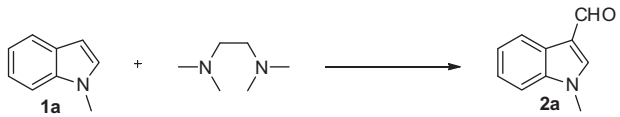
Table 1
Screening the optimized reaction conditions[a]



Entry	Iodide source	Additive	Solvent	T (°C)	Yield (%)
1	I_2 (1.1 equiv)	Na_2CO_3 (2.0 equiv)	1,4-Dioxane	75	58
2	I_2 (1.5 equiv)	Na_2CO_3 (2.0 equiv)	1,4-Dioxane	75	66
3	I_2 (2.0 equiv)	Na_2CO_3 (2.0 equiv)	1,4-Dioxane	75	83
4	I_2 (2.0 equiv)	NaOH (2.0 equiv)	1,4-Dioxane	75	15
5	I_2 (2.0 equiv)	NaO^tBu (2.0 equiv)	1,4-Dioxane	75	70
6	I_2 (2.0 equiv)	—	1,4-Dioxane	75	10
7	I_2 (2.0 equiv)	Na_2CO_3 (2.0 equiv)	Toluene	75	52
8	I_2 (2.0 equiv)	Na_2CO_3 (2.0 equiv)	$MeNO_2$	75	<5
9	$^nBu_4NI$ (2.0 equiv)	Na_2CO_3 (2.0 equiv)	1,4-Dioxane	75	0
10	KI (2.0 equiv)	Na_2CO_3 (2.0 equiv)	1,4-Dioxane	75	0
11	—	Na_2CO_3 (2.0 equiv)	1,4-Dioxane	75	0
12	I_2 (2.0 equiv)	Na_2CO_3 (2.0 equiv)	1,4-Dioxane	100	91(68)[b] (53)[c] (30)[d] (79)[e] (83)[f]
13	I_2 (20 mol %)	Na_2CO_3 (2.0 equiv)	1,4-Dioxane	100	34[g]
14	I_2 (20 mol %)	Na_2CO_3 (2.0 equiv)	1,4-Dioxane	75	33[g]

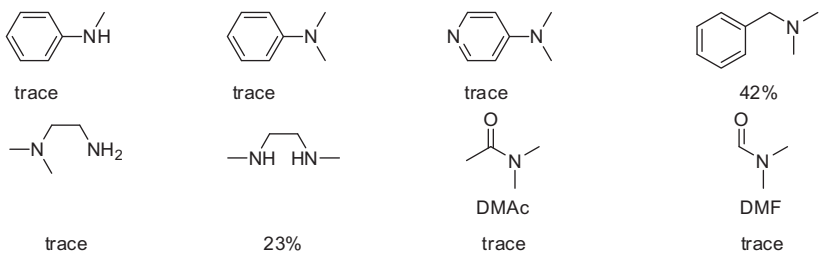
[a] Reaction conditions: 1-methyl-1*H*-indole **1a** (0.2 mmol), TMEDA (0.5 mmol, 2.5 equiv), iodide source with indicated equivalents, H_2O (100 μL), additive (2.0 equiv), solvent (0.5 mL), indicated temperature, O_2 (1 atm), 36 h, isolated yield.
[b] Air.
[c] N_2.
[d] TMEDA (1 equiv).
[e] TMEDA (2 equiv).
[f] TMEDA (3 equiv).
[g] TBHP (4 equiv).

Next, some other amine or amide was tested in this formylation reaction, as shown in Scheme 1.

To learn about the generality of this newly developed protocol, a number of indoles were tested and the results are shown in Table 2. Firstly, substrates bearing different kind of N-protecting groups were surveyed and yields ranged from 50% to 83% (**2a**–**2d**). The substitution on the aromatic ring of indole was then studied, and formylated products were obtained in moderate to excellent yields from the corresponding indoles possessing electron-donating or electron-withdrawing groups on the aromatic ring (**2e**–**2p**). However, electron-donating groups such as methyl and methoxy appeared more effective than electron-withdrawing groups such as nitro and cyano when substitution at C5 (**2e**, **2h** vs **2i**, **2j**). To our delight, a diversity of halogen functional groups were tolerated with good to excellent yields which offer handles for other valuable manipulations (62–76%, **2l**–**2p**). Particularly, the heteroaryl indoles, such as *N*-methyl-1*H*-pyrrolo[2,3-*b*] pyridine **1q**, produced **2q** smoothly in 60% yield. Importantly, groups such as phenyl and acylamino on the pyrrole ring of indole were not detrimental to this process as exemplified by **2r** and **2s** (65% and 50%, respectively). In light of these results, we extend our efforts on the scope of free (*N*–*H*) indoles. As expected, electron-poor or -rich substrates bearing a series of functional groups such as methyl, methoxy, fluoro, chloro, bromo, formyl, cyano, and nitro groups on the aromatic moiety were tolerated well with yields ranging from moderate to excellent (40–76%, **3a**–**3i**). Similarly, substrates bearing a methyl at the C2 position did not diminish the reactivity (63%, **3j**).

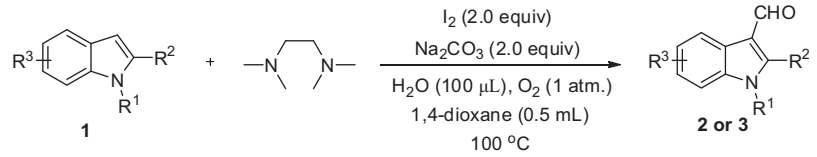
In order to acquire preliminary understanding of this process, several control experiments were conducted (Scheme 2). Initially, the extra added H_2O was replaced by D_2O and **2a** was generated in 90% GC–MS yield which indicated that the hydrogen atom of carbonyl groups did not come from H_2O (Eq. 1). The blank experiment showed that the reaction did not run in the absence of TMEDA. It demonstrated that the carbon atom in the carbonyl group may derive from the added TMEDA (Eq. 2). Subsequently, radical trapping experiments were studied by employing 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) as a radical scavenger and the result confirmed that no change of the reaction outcome happened (Eq. 3), which excluded the radical route. The photo-initiated singlet oxygen was usually involved in the aerobic oxidation reaction system.[15] Hence, 1,4-diazabicyclo-[2.2.2]octane (DABCO) as a singlet oxygen inhibitor was added to the model reaction. However, the approach did not inhibit and run well in 100% conversion, indicating that singlet molecular oxygen might not be involved in our system (Eq. 4).

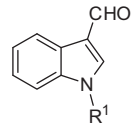
On the basis of the results described above and previous studies[12a,16], a tentative mechanism is illustrated in Scheme 3. Firstly,



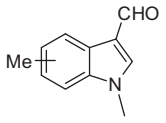
Scheme 1. Screening of amine or amide for the formylation reaction.

Table 2
The scope for 3-formylation of indoles[a]

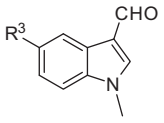




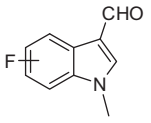
R^1= Me **2a** 83%, 36 h
R^1= Et **2b** 74%, 37 h
R^1= Allyl **2c** 50%, 37 h
R^1= Bn **2d** 70%, 37 h



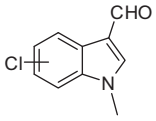
5-Me **2e** 80%, 48 h
6-Me **2f** 56%, 37 h
7-Me **2g** 73%, 38 h



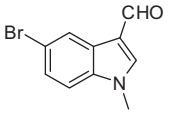
R^3 = MeO **2h** 71%, 60 h
R^3 = NO_2 **2i** 39%, 48 h
R^3 = CN **2j** 54%, 60 h
R^3 = CHO **2k** 60%, 68 h



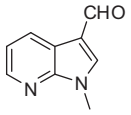
5-F **2l** 64%, 38 h
6-F **2m** 62%, 38 h



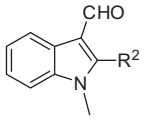
5-Cl **2n** 72%, 65 h
6-Cl **2o** 76%, 36 h



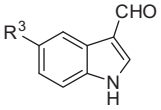
2p 70%, 60 h



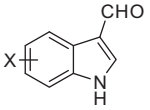
2q 60%, 36 h



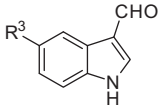
R^2 = Ph **2r** 65%, 64 h
R^2 = CONHMe **2s** 50%, 61 h



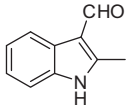
R^3 = H **3a** 75%
R^3 = MeO **3b** 72%
R^3 = Me **3c** 70%



5-F **3d** 76%
6-Cl **3e** 72%
5-Br **3f** 74%

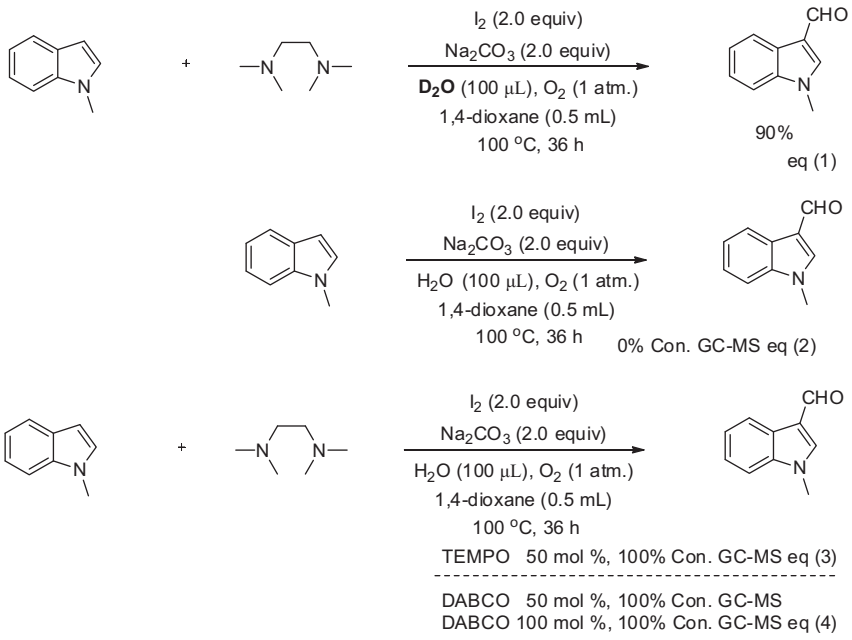


R^3 = NO_2 **3g** 40%
R^3 = CHO **3h** 70%
R^3 = CN **3i** 52%

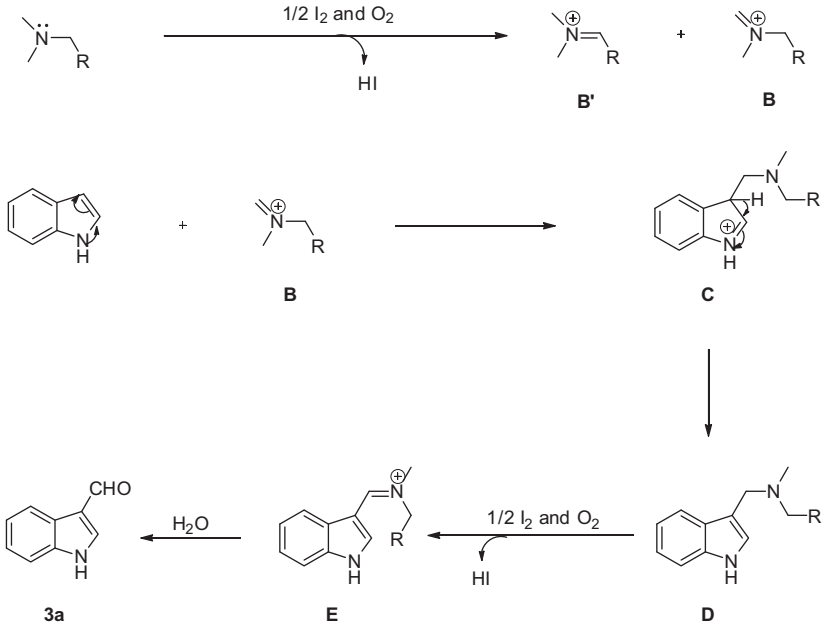


3j 63%

[a] Reaction conditions: indole **1** (0.2 mmol), TMEDA (0.5 mmol, 2.5 equiv), I_2 (0.4 mmol, 2.0 equiv), H_2O (100 μL), Na_2CO_3 (0.4 mmol, 2.0 equiv), 1,4-dioxane (0.5 mL), 100 °C, O_2 (1 atm), indicated time and 36 h for free (*N–H*) indole, isolated yield.



Scheme 2. Isotope labeling experiments and preliminary mechanism study.



Scheme 3. A tentative mechanism.

the oxidation of a tertiary amine by I_2/O_2 took place forming iminium ion intermediate **B** and **B′**. Secondly, because intermediate **B** was more stable, the nucleophilic attack of iminium ion **B** rather than **B′** by indole occurred to deliver species **C**, which generated compound **D** by the loss of H^+. Subsequently, in the presence another molecular iodine and O_2, species **D** was oxidized to a new iminium ion intermediate **E** which was hydrolyzed by H_2O to produce 3-formylindole **3a**.[12a]

In summary, we develop a molecular I_2-promoted 3-formylation of indole approach. This procedure represents an exceedingly attractive alternative to the traditional formylation methods with excellent function group tolerance and good to excellent yields. Investigations aimed at broadening the scope of this transformation and further delineating the mechanism are currently in progress.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.08.024.

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