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Iodine-catalyzed C3-formylation of indoles via C—N bond cleavage of tertiary amines under aerobic conditions

Lin Lu, Qiheng Xiong, Shengmei Guo *, Tianqiang He, Feng Xu, Jiuhan Gong, Zheng Zhu, Hu Cai *

College of Chemistry, Nanchang University, Nanchang, Jiangxi 330031, China

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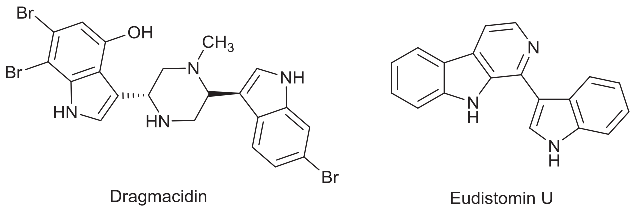
ABSTRACT

A novel route was developed for the C3-formation of indoles using iodine as the catalyst. This transformation involves the cleavage of the C—N bond of tertiary amines by the Cross-Dehydrogenative Coupling reaction (CDC), and is well tolerated by a range of 1*H*-indoles under aerobic conditions. Moreover, this method can be applied to gram-scale synthesis.

1. Introduction

3-Formylindoles and their derivatives are very important and widely used building blocking for the preparation of biologically active natural products and drugs.[1] For example, 3-formylindoles have been used as starting materials for the synthesis of dragmacidin[2] and edudistomin U,[3] which exhibit anti-inflammatory and antitumor activities. Therefore, developing efficient strategies for synthesizing these synthons has been a longstanding goal in organic synthesis.[4] Traditionally, methods to synthesize these compounds via direct indole functionalization involve the Vilsmeier—Haack reaction,[5] Reimer—Tiemann reaction,[6] Rieche reaction,[7] Gattermann—Koch reaction,[8] and the Duff reaction.[9] However, the above reactions are disadvantageous owing to the stoichiometry of $POCl_3$, and acid used, which are either toxic or environmentally harmful, moreover, reaction conditions are harsh and difficult to control. In recent years, elegant strategies have been developed to overcome these shortcomings. For example, Jiao and Wang reported the transition-metal-catalytic C—N cleavage of DMF to independently form indole aldehydes.[10] More recently, Chiba and Cheng reported the formation of such compounds with DMSO as the C-1 carbon source.[11] Despite significant advances in the preparation of 3-formylindoles, a general, mild, and operational method is highly desirable (Scheme 1).



Scheme 1. Dragmacidin and Eudistomin U.

Dehydrogenative coupling is of significant interest to synthetic chemists since it avoids the use of functionalized substrates and is a more atom-economic and environmentally friendly method.[12] Recently, several groups have reported excellent results for the synthesis of 3-formylindoles via dehydrogenative coupling using amines as the formyl source. Su and et al. pioneered the Ru-catalyzed C—N bond cleavage of *N*-methylaniline to synthesize these compounds.[13] The groups of Li and Cheng independently reported the Cu-catalyzed C3-formylation of indoles using *N*,*N*,*N*,*N*-tetramethylethane-1,2-diamine (TMEDA) as the carbonyl source.[14] However, there have been few reports of metal-free catalytic reactions of amines to afford 3-formylindoles.[15] Herein, we report the C3-formylation of indoles by dehydrogenative coupling between

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* Corresponding authors. Tel.: +86 791 83969514; fax: +86 791 88109568; e-mail addresses: smguo@ncu.edu.cn (S. Guo), caihu@ncu.edu.cn (H. Cai).

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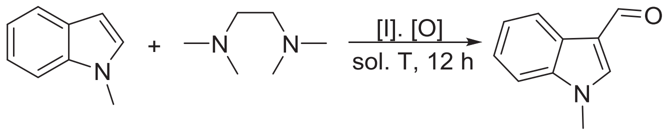
indoles and TMEDA using O_2 as the oxidant and molecular iodine as the catalyst.

2. Result and discussion

Initially, we screened and optimized the reaction conditions using 1-methyl-1*H*-indole (**1a**, 0.5 mmol) and TMEDA (**2a**, 0.6 mmol) as substrates in the presence of 0.2 equiv of catalyst using di-*tert*-butyl peroxide (DTBP) as oxidant (Table 1). First, various catalysts were screened, when KI and NaI were used as catalysts, the reaction afforded the desired product in 16% and 21% isolated yields (Table 1, entries 1 and 2). Molecular iodine was found to be a more effective catalyst, and the desired product was obtained in 34% yield (Table 1, entry 3). No product was obtained in the absence of iodine (Table 1, entry 4). Next, we studied the influence of the oxidants on the reaction behavior, *m*-CPBA, $K_2S_2O_8$, H_2O_2, and TBHP (70%) afforded the desired product in only trace amounts (Table 1, entries 5–8). While air afforded the product in 22% yield (Table 1, entry 9). To our delight, the yield improved to 70% when dioxygen was used as an oxidant (Table 1, entry 10), whereas, no reaction occurred in the presence of nitrogen (Table 1, entry 11). Subsequently, we studied the influence of solvents on the reaction. Unfortunately, we found that xylene, toluene, THF, and EA afforded the product in trace amounts (Table 1, entries 12–15). On the other hand, DMSO, ethylene glycol dimethyl ether (DME), dioxane, and CH_3CN afforded the product with lower yields (Table 1, entries 16–19, respectively). DMA and DMF were the best solvents, affording the corresponding product in 70% and 66% yields (Table 1, entries 10 and 20). Decreasing the catalyst loading afforded a lower yield of the product, and increasing the catalyst amount did not improve the reaction yield (Table 1, entries 21 and 22, respectively). Finally, we examined the ratio of substrates, reaction time, and reaction temperature, results showed that the optimized reaction conditions were 1-methyl-1*H*-indole (**1a**, 0.5 mmol) and TMEDA (0.6 mmol) using 20 mol % I_2 as the catalyst with DMF as the solvent at 100 °C under dioxygen for 12 h.

With the optimized reaction conditions in hand, we evaluated the scope of the reaction, Table 2 summarized the results. To our disappointment, *N*-substituted indoles such as 1-ethyl-1*H*-indole and 1-benzyl-1*H*-indole gave the corresponding products in moderate yields (Table 2, entries 2 and 3, respectively). Moreover, 1-tosyl-1*H*-indole did not give any reaction under the same conditions (Table 2, entry 4). Hence, we wondered whether 1*H*-indole would be reactive. To our delight, indole successfully underwent the reaction, affording the desired product in 66% yield (Table 2, entry 5). The effect of aromatic ring substituents on the indoles was investigated, we found that indole with both electron-donating and electron-withdrawing groups on the aromatic ring underwent the reaction to afford products in moderate yields. However, indoles with electron-withdrawing groups on the aromatic ring were less reactive than those with electron-donating groups. For instance, 5-methyl indole and 5-methoxyl indole afforded the corresponding products in 59% and 57% yields, respectively (Table 2, entries 6 and 7), however, 5-nitroindole and 5-cyanoindole afforded the desired products in 47% and 35% yields (Table 2, entries 8 and 9). Of note indoles with halogens on the aromatic ring efficiently converted to the corresponding formylindoles in good to excellent yields. For example, 5-bromo-, 5-chloro-, and 5-fluoro-indole afforded the desired products with 82%, 73%, and 60% yields (Table 2, entries 10–12, respectively), however, 6-bromoindole and 7-bromoindole were less reactive (Table 2, entries 13 and 14). We also studied the influence of steric effect of the substrates on the reaction, and we found that the substituents exerted a marginal effect. For instance, ethyl 1*H*-indole-2-carboxylate, 2-methylindole, and 6-fluoro-2-methyl indole afforded the desired products in moderate

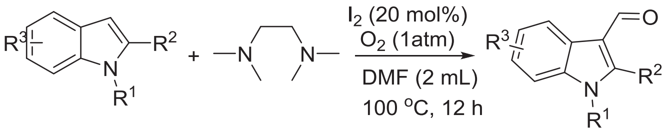
Table 1
Screening for optimal conditions[a]



Entry	Cat.	Oxidant	Solvent	Yield[b] (%)
1	NaI	DTBP	DMF	16
2	KI	DTBP	DMF	21
3	I_2	DTBP	DMF	34
4	—	DTBP	DMF	—
5	I_2	m-CPBA	DMF	Trace
6	I_2	$K_2S_2O_8$	DMF	Trace
7	I_2	H_2O_2	DMF	Trace
8	I_2	TBHP	DMF	Trace
9	I_2	Air	DMF	22
10	I_2	O_2	DMF	70
11	I_2	N_2	DMF	—
12	I_2	O_2	Xylene	Trace
13	I_2	O_2	Toluene	Trace
14	I_2	O_2	THF	Trace
15	I_2	O_2	EA	Trace
16	I_2	O_2	DMSO	21
17	I_2	O_2	DME	18
18	I_2	O_2	Dioxane	14
19	I_2	O_2	CH_3CN	28
20	I_2	O_2	DMA	66
21[c]	I_2	O_2	DMF	43
22[d]	I_2	O_2	DMF	68
23[e]	I_2	O_2	DMF	65
24[f]	I_2	O_2	DMF	72
25[g]	I_2	O_2	DMF	70

[a] Reaction conditions: indole (0.5 mmol), TMEDA (0.6 mmol), cat. (20 mol %), solvents (2 mL), oxidant (1.0 mmol), O_2 (1 atm) 100 °C for 12 h.
[b] Isolated yield.
[c] I_2 (10 mol %).
[d] I_2 (30 mol %).
[e] TMEDA (1.5 equiv).
[f] 24 h.
[g] 120 °C.

Table 2
Scope of the substrates[a]



1 2

Entry	R¹	R²	R³	Yield[b] (%)
1	Me	H	H	70 (**2a**)
2	Et	H	H	44 (**2b**)
3	Bn	H	H	42 (**2c**)
4	Ts	H	H	0 (**2d**)
5	H	H	H	66 (**2e**)
6	H	H	5-Me	59 (**2f**)
7	H	H	5-OMe	57 (**2g**)
8	H	H	5-NO_2	47 (**2h**)
9	H	H	5-CN	35 (**2i**)
10	H	H	5-Br	82 (**2j**)
11	H	H	5-Cl	73 (**2k**)
12	H	H	5-F	60 (**2l**)
13	H	H	6-Br	48 (**2m**)
14	H	H	7-Br	60 (**2n**)
15	H	2-Ethyl formate	H	50 (**2o**)
16	H	2-Me	H	44 (**2p**)
17	H	2-Me	5-F	49 (**2q**)
18	H	H	Py	48 (**2r**)
19[c]	H	H	H	54 (**2a**)

[a] Reaction conditions: **1** (0.5 mmol), TMEDA (1.2 equiv), I_2 (20 mol %), DMF (2 mL), O_2 (1 atm), 100 °C for 12 h.
[b] Isolated yield.
[c] **1** 10 mmol.

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