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Selective Nickel-Catalyzed Dehydrogenative-Decarboxylative Formylation of Indoles with Glyoxylic Acid

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Herein we present a new strategy for the dehdrogenativedecarboxylative coupling of indoles with glyoxylic acid. A broad range of indoles were transformed into the corresponding 3formylindoles in moderate to good yields and excellent functional group tolerance. Notably, no *N*-formylation product was detected under our conditions.

Carboxylic acids are valuable and important motifs that widely existed in natural products and pharmaceuticals. Recently, the development of catalytic methods for decarboxylative cross-coupling of carboxylic acids has attracted much attention due to their low cost, great structural diversity and easy to handle and store.¹ As compared to traditional coupling reactions, decarboxylative coupling has many advantages, such as, most decarboxylative coupling reaction worked under neutral conditions, and the only by-product is CO₂ which is non-flammable, nontoxic, and easy to be removed from reaction mixture. Glyoxylic acid as a special type of carboxylic acid can afford a promising protocol for the formylation reaction through decarboxylative crosscoupling reactions. Nevertheless, there are relatively few studies devoted to this area until very recently. In 2017, Wang group have developed a series of formylation methods by employing diethoxyacetic acid or glyoxylic acid as a formyl equivalent.² Xu's group reported an iridium catalyzed Michael addition formylation.³ Tao's group also disclosed a palladium catalysed hydroformylation of terminal arylacetylenes with glyoxylic acid.⁴ More recently, Huang and co-workers described an electrochemical N-formylation of amines with glyoxylic acid.⁵ Yet the reaction of hetero-aromatic compounds with glyoxylic acids is not studied.

On the other hand, the transition-metal catalysed

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dehydrogenative coupling reaction is also an atom-economic transformation. And over the past two decades there has been an explosive growth in the development of methods for dehydrogenative couplings⁶ and the application of these protocols for organic synthesis.⁷ The combination of these two research fields of decarboxylative cross-coupling and dehydrogenative coupling would offer a new transformation and expand the application of carboxylic acid. The main challenges to achieve this reaction derive from the difference reaction rate between two independent processes.⁸

Under these backgrounds and also based on our continuing interests in functionalization of indoles,⁹ we initiated our study by using 1a 1H-indole and glyoxylic acid as the model substrates. To begin, the following conditions were selected: 1a (0.2 mmol, 1.0 equiv.) was stirred with glyoxylic acid monohydrate 2a (6 mmol, 30 equiv.) dissolved in DMSO in the presence of Cu(OAc)₂ (1.0 equiv.) at 130 °C for 15 hours. However, we did not detect any desired product in GC-MS (Table 1, entry 1). We supposed that the decarboxylative process was inhibited in this condition. According to the literatures, silver salts might facilitate the decarboxylative process.¹⁰ Then different silver salts were screened. To our delight, after adding co-oxidant Ag₂CO₃ (0.4 mmol, 2.0 equiv.), we got the desired product 3a 1H-indole-3-carbaldehyde in 37% GC yield (Table 1, entry 4). Other silver salts, such as, AgOTf, AgOAc, AgTFA and oxidant K₂S₂O₈ only afford trace product (Table 1, entries 1-3, 5). Additional bases were observed to have positive effects on this reaction, after screening different bases, NaOAc (0.4 mmol, 2.0 equiv.) were proved to be the best base with the yield increased to 52% (Table 1, entry 7). Other inorganic bases like, KOAc, NaHCO₃, Li₂CO₃, or organic bases DBU and Et₃N were all inferior to NaOAc (Table 1, entries 6, 8-11). Next, diverse additives were applied in this reaction, and we found that the reaction efficiency were slightly improved with Ni(OAc)₂·4H₂O (10 mol%) or FeCl₃ (40 mol%) as the additive (Table 1, entries 17, 20). Finally, we combine these two catalysts together, and the yield was improved to 75% isolated yield (Table 1, entry 23). Notably, with 1.0 equivalent of co-oxidant, the conversion of

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staring material was much lower. However, decreased yield was obtained with 3.0 equivalent of co-oxidant which might due to the further transformation the formylated indole product. The final optimised conditions were found to be: 1.0 equivalent Cu(OAc)₂, 2.0 equivalents Ag₂CO₃, , 2.0 equivalents NaOAc, FeCl₃ (40 mol%) and Ni(OAc)₂·4H₂O (10 mol%) in DMSO at 130°C for 15 hours, which gave **3a** in 75 % isolated yield.

Table 1. Optimization of reaction conditions.^a

	О N + н 1а) ^{ОН} . _{Н2} О — О □ 2а	[Catal] MSO, 130 °C, 15 h	O H H 3a
Entry	Co- oxidant	Base	Catal.	Yield(%) ^b
1	AgOAc	-	-	5 0 ^c
2	AgOTf	-	-	trace
3	AgTFA	-	-	trace
4	Ag_2CO_3	-	-	37
5	$K_2S_2O_8$	-	-	trace
6	Ag ₂ CO ₃	KOAc	-	45
7	Ag ₂ CO ₃	NaOAc	-	52
8	Ag ₂ CO ₃	NaHCO ₃	-	35
9	Ag_2CO_3	Li ₂ CO ₃	-	43
10	Ag_2CO_3	DBU	-	19
11	Ag_2CO_3	Et₃N	-	44
12	Ag_2CO_3	KI	-	46
13	Ag ₂ CO ₃	NaOAc	Mn(acac)₂ (10 mol%)	43
14	Ag ₂ CO ₃	NaOAc	Mn(OAc)₃·2H₂O (10 mol%)	28
15	Ag ₂ CO ₃	NaOAc	NiCl ₂ ·6H ₂ O (10 mol%)	57
16	Ag ₂ CO ₃	NaOAc	Ni(acac)₂ (10 mol%)	58
17	Ag ₂ CO ₃	NaOAc	Ni(OAc) ₂ ·4H ₂ O (10 mol%)	60
18	Ag ₂ CO ₃	NaOAc	Ni(OAc) ₂ ·4H ₂ O (20 mol%)	56
18	Ag ₂ CO ₃	NaOAc	FeCl₃ (10 mol%)	59
19	Ag_2CO_3	NaOAc	FeCl₃ (30 mol%)	63
20	Ag ₂ CO ₃	NaOAc	FeCl₃ (40 mol%)	66
21	Ag ₂ CO ₃	NaOAc	FeCl₃ (50 mol%)	49
22	Ag ₂ CO ₃	NaOAc	FeCl₃ (60 mol%)	46
23	Ag ₂ CO ₃	NaOAc	Ni(OAc)2·4H2O (10 mol%) FeCl3 (40 mol%)	78 (75)

^{*a*} Reaction conditions: Indoles **1a** (0.2 mmol, 1 equiv.), glyoxylic acid monohydrate **2a** (6 mmol, 30 equiv.), Cu(OAc)₂ (0.2 mmol, 1 equiv.), co-oxidant (0.4 mmol, 2 equiv.), base (0.4 mmol, 2

equiv.), and catalyst in DMSO (1 mL) for 15 hours at 130 Scile sealed tubes under air. ^b Yields were determined by GCOSING n-hexadecane as the internal standard. Isolated yield is in parenthesis. ^c without Cu(OAc)₂.

Having determined the best condition, we next evaluated the substrate scope of this reaction with a range of indoles. As show in Table 2, considering the electronic effect of substitutes on indoles might have influence on the reactivity. We first examined indoles with electron-donating group, as shown in table 2 the reaction efficiency did not change much when the 2-position or 5-position of indoles bearing a variety of electron-donating groups (Table 2, entries 2-5). Interestingly, the hydroxyl group in substrate 1e also oxidized into aldehyde with 72% total yield (Table 2, entry 4). Then, we tested various electron-withdrawing groups at different positions of indoles. Delightfully, the corresponding 3- fomylindole products were obtained in moderate to good yield (Table 2, entries 6-11). Various indoles bearing halogen substitutes on the aromatic rings engaged in this reaction efficiently, potentially providing a further synthetic transformation (Table 2, entries 6-8). Furthermore, nitrogenprotected indoles such as 11 1-ethyl-2-methyl-1H-indole and 1m 1-ethyl-2-phenyl-1H-indole were also participated successfully, leading to the corresponding 3-fomylindole products in moderate yield (Table 2, entries 12, 13). Excluding indoles, other aromatic compounds were also investigated in this condition. Nevertheless, none of these substrates can afford the desired product.11

Table 2. Dehydrogenative-Decarboxylative Coupling of Indoles with Glyoxylic Acid.^a <td





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 o Reaction conditions: Indoles 1a (0.2 mmol, 1 equiv.), glyoxylic acid monohydrate 2a (6 mmol, 30 equiv.), Cu(OAc)_2 (0.2 mmol, 1 equiv.), Ag_2CO_3 (0.4 mmol, 2 equiv.), NaOAc (0.4 mmol, 2 equiv.), FeCl_3 (0.08 mmol, 40 mol%), and Ni(OAc)_2·4H_2O (0.02

sealed tubes under air, isolated yields. DOI: 10.1039/C8OB00810H

Next, we turned our attention to investigate the possible reaction pathway. Control experiments were conducted and shown in Scheme 1. When 2-(1*H*-indol-3-yl)-2-oxoacetic acid **1n** was used to replace **1a** under the same condition, only 10% GC yield product was formed and detected by GC. Then **2b** ethyl 2-oxoacetate was selected to react with indole **1a**, and the product **3a** was generated in 22% GC yield. At the same time, **2c** methyl formate and **2d** oxalaldehyde were also tested in this reaction, but no products were detected in GC-MS. Finally, control experiments c) and d) were conducted under the same condition by using **2e** formaldehyde solution (36% in water) and **2f** paraformaldehyde instead of **2a** glyoxylic acid, only 3% and 6% yields of the product were obtained, respectively.

mmol, 10 mol%) in DMSO (1 mL) for 15 hours at 130 % in

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Scheme 1. Control experiments.

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Scheme 2. Proposed reaction pathway.

Based on the results of our control experiments, we excluded the possibilities that involving 2-(1*H*-indol-3-yl)-2-oxoacetic acid (Scheme 2, eq. 1; dehydrogenation prior to decarboxylation) or formaldehyde (Scheme 2, eq. 2; decarboxylation prior to dehydrogenation) as the reaction intermediates. The dehdrogenative coupling step and decarboxylative step may occur in a concurrent manner (Scheme 2, eq. 3). In this system, copper might act as oxidant to regenerate catalyst and silver re-oxidize copper. Iron helps the activation of indole.

In summary, we have studied the dehdrogenativedecarboxylative coupling of indoles with glyoxylic acid. This transformation enables for the facile generation of various 3formylindoles in moderate to good yields with good functional group tolerance. Notably, no *N*-formylation product was detected under our conditions.

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