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Copper-catalyzed aerobic oxidative intramolecular amidation of 2-aminophenylacetylenes: A domino process for the synthesis of isatin†

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A novel CuI-catalyzed oxidative amidation of 2-aminophenylacetylenes leading to the formation of isatins by using open air as an oxygen source has been developed. The reaction proceeded smoothly and provided a variety of isatin derivatives in good yields. The advantages of this one-pot reaction protocol include the green oxidant, low-price catalyst, facile conditions and easy handling.

Introduction

Heterocyclic compounds are of great importance as pharmaceuticals,natural products, agrochemicals,materials and as building blocks in organic synthesis.[1]In fact, these compounds have occupied central stage of organic chemistry.Among the myriad of metal-catalyzed synthetic transformations, domino reaction is defined as a powerful synthetic tool for the preparation of heterocyclic systems, since they can directly construct complex molecules in a one-pot operation from readily available precursors.[2] Particularly, the domino reactions catalyzed by transition-metal have become a hotspot of the research during the last few decades, for their ability to milder the reaction conditions, shorten reaction procedures, and reduce wastes.[3]Among transition metals, copper-catalyzed reactions have indisputable advantages as they are of great catalytic potential in numerous synthetic transformations and are inexpensive, low toxic, easy to handle and environmentally benign.[4] On the other hand, several reagents such as peroxides (TBHP, DTBP, H_2O_2, mCPBA), $PhI(OAc)_2$, O_2, etc. are used as common oxidizing agents among which molecular oxygen is most preferable due to its inexhaustible and environmentally benign features as well as it is inexpensive.[5] From the viewpoint of sustainable and green chemistry, copper/O_2 catalytic system is considered as an ideal choice for many synthetic transformations since molecular oxygen act as a source of oxygen atoms for the construction of oxygen containing bioactive molecules.[6] Therefore, the synthesis of bioactive heterocyclic systems under aerobic conditions using copper salts as catalysts is an emerging field of synthetic organic chemistry in respect of ecological as well as economical points of view.

Isatin (Indoline-2,3-dione) is a privileged core structural motif found in numerous bioactive natural products, synthetic molecules and pharmaceutical drugs (**Figure 1**)[7] that display a wide range of pharmaceutical properties such as anti-HIV,[8] antimalarial,[9] antibacterial,[10] anticancer,[11] antifungal,[12] anti-inflammatory[13] and anticonvulsant.[14] Isatins have been widely used as powerful building blocks for the construction of biologically active heterocyclic systems and spirocyclic compounds.[15]

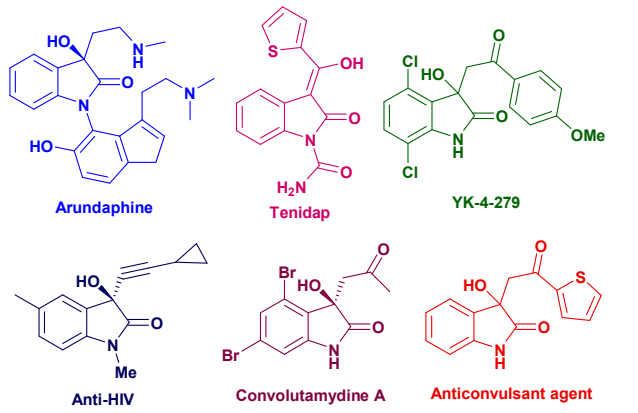

Fig. 1 Representative biologically active isatin molecules.

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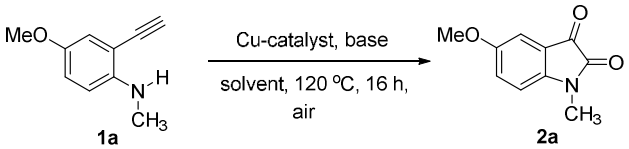
Previously, several reports have been documented for the synthesis of isatins,[16] however, most of these existing methods are still inadequate due to some flaws, such as use of peroxides as oxidants, harsh reaction conditions, poor atom-efficiency, longer reaction time, use of hazardous reagents, and generation of a waste that not only reduce process efficiency but also raises problems to the environment. Because of the ubiquitous presence of the isatins in biologically active synthetic and natural compounds and of their extensive applications as important synthetic intermediates, development of a simple, efficient, environment friendly and promising method to access isatins is highly desirable and in great demand. In this context,herein, we report a domino process for the preparation of isatins from 2-aminophenylacetylenes using a CuI as the catalyst under aerobic conditions via oxidative amidation.

Results and discussion

At the outset, 2-ethynyl-4-methoxy-*N*-methylaniline (**1a**) was selected as the model substrate to optimize the reaction conditions using differentcatalysts, reaction solvents, additives, and the loadings of the catalyst. The results are summarized in Table 1. Initially, we started our investigations by testing various solvents with 20 mol% CuI as a catalyst and 1.5 equiv. $CsCO_3$ as a base at 120 °C under an air atmosphere for 16 h. We have obtained the desired product **2a** in 35% yield using dimethyl sulfoxide (DMSO) as the most suitable solvent (Table 1, entry 2). A series of additives (bases) were then investigated, which revealed that pyridine was the best for the yield of **2a** (82% yield) as compared to LiO^tBu, KO^tBu, DIPEA, TEA and 2,6 Lutidine (Table1, entries 4-9). When the copper catalyst loading was reduced to 10 mol% or 5 mol%, the yield of the product **2a** decreased (Table1, entries 10, 11). In addition, when the reaction was carried out in the presence $Cu(CH_3CN)_4.BF_4$catalyst the desired product **2a** was obtained in 50% yield (Table 1, entry 12). Other copper salts, including CuCl, CuO, Cu_2O and $Cu(OTf)_2$ (Table 1, entries 13-16) were probed as catalysts, and showed no catalytic activity in this reaction. Similarly, in the absence of Cu-catalyst, no product was observed and the starting material was recovered. Notably, by fixing CuI (20 mol%) as catalyst and pyridine (1.5 equiv.) as an additive, different solvents like DMF, xylene and toluene were also screened, and no product was observed (Table 1, entries 17-19). When the reaction was carried out using O_2 as oxidative agent instead of open air condition, the isolated yield of the product **2a** decreased to 36% (Table 1, entry 20). Moreover, switching to nitrogen atmosphere led to the no formation of product (Table 1, entry 21). Finally, the reaction period and the temperature effect on the reaction were also examined. The experimental results indicated that longer reaction time and raising of the temperature (150 °C) or lowering of the temperature (40 °C) were not beneficial to improve the yield of the desired product **2a** (Table 1, entries 22-23). Therefore, the combination of substrate **1a** (0.5 mmol), CuI (20 mol %) and pyridine (1.5 equiv.) in DMSO under an air atmosphere at 120 °C was chosen as the optimal reaction conditions, providing the desired product 5-methoxy-1-methylindoline-2,3-dione (**2a**) in 82% yield (Table 1, entry 9).

Table 1. Optimization of Reaction Conditions[a]



1a 2a

Entry	Catalyst	Base	Solvent	Yield (%)[b]
1	CuI (20 mol%)	CS_2CO_3	DMF	NR
2	CuI (20 mol%)	CS_2CO_3	DMSO	35
3	CuI (20 mol%)	CS_2CO_3	Xylene	NR
4	CuI (20 mol%)	LiO^tBu	DMSO	25
5	CuI (20 mol%)	KO^tBu	DMSO	20
6	CuI (20 mol%)	DIPEA	DMSO	55
7	CuI (20 mol%)	TEA	DMSO	50
8	CuI (20 mol%)	2,6 Lutidine	DMSO	65
9	CuI (20 mol%)	Pyridine	DMSO	82
10	CuI (10 mol%)	Pyridine	DMSO	60
11	CuI (5 mol%)	Pyridine	DMSO	50
12	$Cu(CH_3CN)_4.BF_4$ (20 mol%)	Pyridine	DMSO	57
13	CuCl (20 mol%)	Pyridine	DMSO	NR
14	CuO (20 mol%)	Pyridine	DMSO	NR
15	Cu_2O (20 mol%)	Pyridine	DMSO	NR
16	$Cu(OTf)_2$ (20 mol%)	Pyridine	DMSO	Trace
17	CuI (20 mol%)	Pyridine	DMF	NR
18	CuI (20 mol%)	Pyridine	Xylene	Trace
19	CuI (20 mol%)	Pyridine	Toluene	NR
20[c]	CuI (20 mol%)	Pyridine	Toluene	36
21[d]	CuI (20 mol%)	Pyridine	Toluene	NR
22[e]	CuI (20 mol%)	Pyridine	Toluene	42
23[f]	CuI (20 mol%)	Pyridine	Toluene	82

[a]Reaction conditions: Unless otherwise mentioned, all reactions were carried out using 2-ethynyl-4-methoxy-*N*-methylaniline **1a**(0.5 mmol), base (1.5 equiv) and copper catalyst (20 mol %) in 3 mL solvent at 120 °C for 16 h under open atmosphere.
[b]Isolated yields.
[c]O_2 balloon.
[d]Under N_2 atmosphere.
[e]Reaction at 40 °C.
[f]Reaction at 150 °C.
NR: No Reaction

After having established the optimum reaction conditions, we next explored the substrate scope of the CuI-catalyzed aerobic oxidative amidation reaction of 2-aminophenylacetylenes (**Scheme 1**). In general, different substituent groups such as OMe, F, Cl, and Br, on the aromatic ring, and various alkyl substituent groups on amine group of 2-

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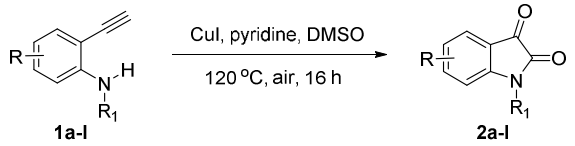
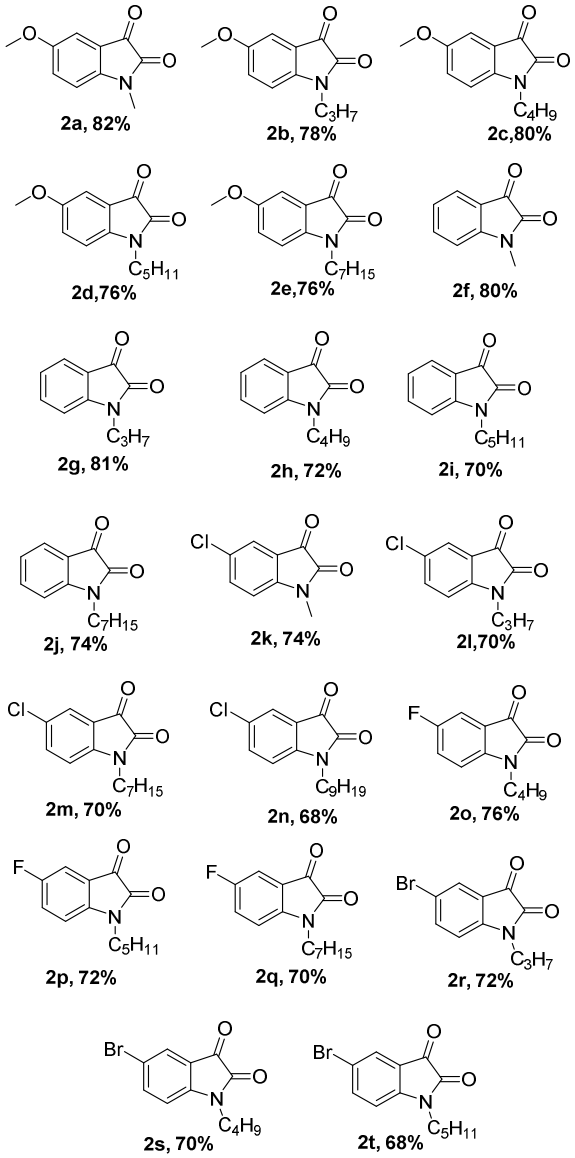
aminophenylacetylenewere well tolerated in the reactions and provided corresponding isatin derivatives in good to excellent yields.

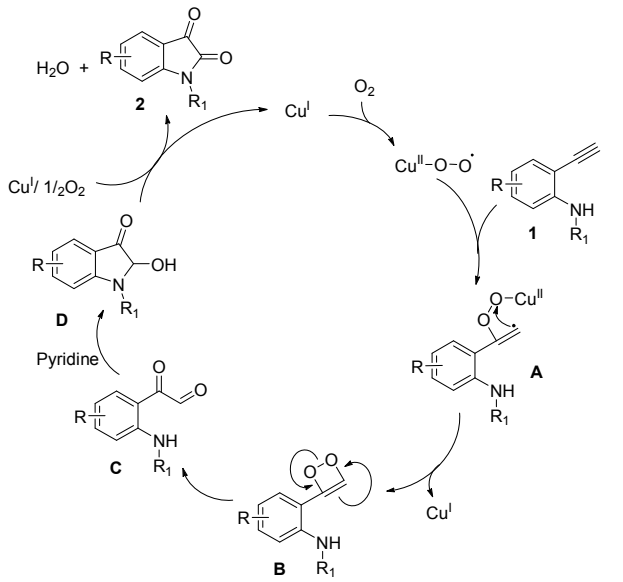
Scheme 1. Copper-Catalyzed Aerobic Oxidative Amidation of 2-Aminophenylacetylenes[a,b]





[a]Reaction conditions: **1** (0.5 mmol), pyridine (1.5 equiv), CuI (20 mol %), DMSO (3 mL), open air, 120 °C, 16 h.
[b]Isolated yield.

Based on the previous Cu-catalyzed reports[17] and the formation of isatin as the product, a plausible reaction pathway for this domino reaction is proposed, as shown in **Scehem 2**. Initially, Cu^{II} complex A was formed from the substrate (**1**) through a radical addition of superoxide radical–Cu^{II} intermediate,[18] which intern could be generated *via* oxidation of CuI by molecular oxygen. Further rearrangement leads to the formation of intermediate **B**. The O–O bond cleavage of dioxetane intermediate **B** could provide aryl glyoxal **C**, which further oxidized to final product **2** through the formation of possible intermediate **D**.



Scheme 2. A Plausible Mechanism for the Copper-Catalyzed Aerobic Oxidative Synthesis of Isatin.

Conclusions

In conclusion, we have successfully developed a facial one pot, open air promoted oxidative amidation domino process for the preparation of biologically important isatin derivatives in good yields. The proposed method preceded using catalytic amounts of an inexpensive CuI and atmospheric air as the oxidizing agent, making this transformation practical and sustainable.

Experimental Section:

General experimental procedure for the synthesis of isatins from 2-aminophenylacetylenes: In a 10 mL round bottom flask2-aminophenylacetylene**1** (0.5 mmol), pyridine (1.5 equiv), CuI (20 mol %), DMSO (3 mL)were taken. The reaction mixture was stirred under refluxing conditions in open air for 16 h. The progress of the reaction was monitored by TLC. After the consumption of the starting materials, the reaction mixture was allowed to cool, and subsequently extracted with EtOAc (2x10 mL). The combined organic extracts were dried

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over anhydrous Na_2SO_4. Concentration of the material in vacuo followed by flash chromatography on silica gel column afforded isatin derivatives **2** in good yield.

Spectral Data:

5-Methoxy-1-methylindoline-2,3-dione (2a):[16k]Red Solid, Yield: 82%, 78 mg; mp: 172-174 °C;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 – 7.09 (m, 2H), 6.83 (d, *J* = 8.5 Hz, 1H), 3.81 (s, 3H), 3.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.77, 158.34, 156.60, 145.33, 124.58, 117.83, 110.97, 109.68, 56.02, 26.28; ESIMS: *m/z* 214 $[M+Na]^+$; Anal. Calcd for $C_{10}H_9NO_3$: C, 62.82; H, 4.75; N, 7.33. Found: C, 62.56; H, 4.69; N, 7.21.

5-Methoxy-1-propylindoline-2,3-dione (2b): Red Solid,Yield: 78%, 85 mg; mp: 178-181 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 – 7.08 (m, 2H), 6.89 – 6.73 (m, 1H), 3.81 (s, 3H), 3.65 (dd, *J* = 15.3, 7.9 Hz, 2H), 1.79 – 1.65 (m, 2H), 0.99 (dd, *J* = 9.5, 5.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.00, 158.23, 156.33, 144.87, 124.50, 117.90, 111.26, 109.66, 55.94, 41.74, 20.62, 11.32; ESIMS: *m/z* 220 $[M+H]^+$; Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.88; H, 6.01; N, 6.44.

1-Butyl-5-methoxyindoline-2,3-dione (2c): Red Solid, Yield: 80%, 93 mg; mp: 180-182 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 – 7.08 (m, 2H), 6.84 (dd, *J* = 8.1, 0.7 Hz, 1H), 3.80 (d, *J* = 5.3 Hz, 3H), 3.69 (t, *J* = 7.3 Hz, 2H), 1.72 – 1.62 (m, 2H), 1.40 (dt, *J* = 14.7, 7.4 Hz, 2H), 0.97 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.14, 158.24, 156.35, 144.75, 124.49, 117.87, 111.48, 109.87, 56.04, 40.00, 29.25, 20.09, 13.68; ESIMS: *m/z* 234 $[M+H]^+$; Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.83; H, 6.45; N, 6.03.

5-Methoxy-1-(penta-1,3-diyn-1-yl)indoline-2,3-dione (2d): Red Solid,Yield: 76%, 93 mg; mp: 188-190 °C;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (dt, *J* = 5.7, 2.8 Hz, 2H), 6.85 – 6.80 (m, 1H), 3.81 (s, 3H), 3.72 – 3.66 (m, 2H), 1.70 (dd, *J* = 14.1, 7.0 Hz, 2H), 1.42 – 1.32 (m, 4H), 0.94 – 0.87 (t, 3H);^{13}C NMR (100 MHz, $CDCl_3$) δ 184.04, 158.18, 156.36, 144.89, 124.56, 117.97, 111.21, 109.67, 55.96, 40.21, 28.96, 26.93, 22.29, 13.91; ESIMS: *m/z* 270 $[M+Na]^+$; Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 68.21; H, 6.89; N, 5.70.

1-Heptyl-5-methoxyindoline-2,3-dione (2e): Red Solid, Yield: 76%, 104 mg; mp: 194-196 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 – 7.08 (m, 2H), 6.88 – 6.74 (m, 1H), 3.81 (s, 3H), 3.68 (t, *J* = 7.3 Hz, 2H), 1.68 (dt, *J* = 14.6, 7.4 Hz, 2H), 1.41 – 1.20 (m, 8H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.04, 158.18, 156.37, 144.90, 124.56, 117.98, 111.21, 109.67, 55.97, 40.25, 31.65, 28.88, 27.26, 26.84, 22.53, 14.02; ESIMS: *m/z* 276 $[M+H]^+$; Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.92; H, 7.65; N, 5.11.

1-Methylindoline-2,3-dione (2f):[16k]Red Solid, Yield: 80%, 64 mg; mp: 119-121 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.50 (m, 2H), 7.19 – 7.09 (m, 1H), 6.98 – 6.85 (m, 1H), 3.30 – 3.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.53, 158.30, 151.36, 138.79, 125.11, 123.94, 117.17, 110.31, 26.32; ESIMS: *m/z* 184 $[M+Na]^+$; Anal. Calcd for $C_9H_7NO_2$: C, 67.08; H, 4.38; N, 8.69. Found: C, 67.22; H, 4.40; N, 8.64.

1-Propylindoline-2,3-dione (2g):[16g]Red Solid, Yield: 81%, 77 mg; mp: 125-127 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.48 (m, 2H), 7.18 – 7.05 (m, 1H), 6.91 (d, *J* = 7.9 Hz, 1H), 3.71 – 3.68 (m, 2H), 1.79 – 1.71 (m, 2H), 1.00 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.68, 158.21, 151.10, 138.40, 125.38, 123.62, 117.53, 110.26, 41.80, 20.64, 11.36; ESIMS: *m/z* 212 $[M+Na]^+$; Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.68; H, 5.81; N, 7.37.

1-Butylindoline-2,3-dione (2h): [16g]Red Solid, Yield: 72%, 77 mg; mp: 133-135 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.53 (m, 2H), 7.11 (t, *J* = 7.4 Hz, 1H), 6.91 (d, *J* = 8.1 Hz, 1H), 3.73 (t, *J* = 7.4 Hz, 2H), 1.69 (ddd, *J* = 15.1, 11.2, 7.6 Hz, 2H), 1.42 (dq, *J* = 14.8, 7.4 Hz, 2H), 0.97 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.79, 158.25, 151.05, 138.63, 125.36, 123.71, 117.46, 110.44, 40.04, 29.26, 20.12, 13.68; ESIMS: *m/z* 204 $[M+H]^+$; Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.80; H, 6.48; N, 6.86.

1-Pentylindoline-2,3-dione (2i): Red Solid, Yield: 70%, 76 mg;mp: 141-143 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (ddd, *J* = 9.1, 5.8, 2.0 Hz, 2H), 7.18 – 7.05 (m, 1H), 6.90 (d, *J* = 7.9 Hz, 1H), 3.78 – 3.62 (m, 2H), 1.76 – 1.65 (m, 2H), 1.41 – 1.33 (m, 4H), 0.94 – 0.86 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.68, 158.12, 151.04, 138.43, 125.31, 123.60, 117.51, 110.26, 40.21, 28.95, 26.92, 22.27, 13.90; ESIMS: *m/z* 218 $[M+H]^+$; Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.95; H, 6.92; N, 6.47.

1-Heptylindoline-2,3-dione (2j): Red Solid, Yield: 74%, 91 mg; mp: 150-151 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 – 7.56 (m, 2H), 7.11 (tt, *J* = 4.8, 2.4 Hz, 1H), 6.89 (t, *J* = 9.5 Hz, 1H), 3.72 (dd, *J* = 13.6, 6.3 Hz, 2H), 1.70 (dt, *J* = 14.8, 7.4 Hz, 2H), 1.40 – 1.32 (m, 4H), 1.28 (td, *J* = 7.0, 3.7 Hz, 4H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.67, 158.11, 151.04, 138.44, 125.29, 123.59, 117.50, 110.28, 40.24, 31.64, 28.86, 27.24, 26.83, 22.52, 14.02; ESIMS: *m/z* 246 $[M+H]^+$; Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.58; H, 7.87; N, 5.75.

5-Chloro-1-methylindoline-2,3-dione (2k):[16k]Red Solid, Yield: 74%, 71 mg; mp: 157-159 °C;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.50 (m, 2H), 6.89 (d, *J* = 8.3 Hz, 1H), 3.26 (s, 3H);^{13}C NMR (100 MHz, $CDCl_3$) δ 182.56, 157.87, 149.75, 137.98, 129.72, 125.20, 118.19, 111.58, 26.60; ESIMS: *m/z* 218 $[M+Na]^+$; Anal. Calcd for $C_9H_6ClNO_2$: C, 55.26; H, 3.09; N, 7.16. Found: C, 55.36; H, 3.11; N, 7.11.

5-Chloro-1-propylindoline-2,3-dione (2l): Red Solid, Yield: 70%, 78 mg; mp: 163-165 °C;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (dd, *J* = 7.2, 2.0 Hz, 2H), 6.93 – 6.83 (m, 1H), 3.77 – 3.60 (m, 2H), 1.82 – 1.63 (m, 2H), 1.08 – 0.93 (m, 3H);^{13}C NMR (100 MHz, $CDCl_3$) δ 182.66, 157.65, 149.37, 137.74, 129.32, 125.15, 118.31, 111.66, 41.94, 20.56, 11.31; ESIMS: *m/z* 224 $[M+H]^+$; Anal. Calcd for $C_{11}H_{10}ClNO_2$: C, 59.07; H, 4.51; N, 6.26. Found: C, 59.22; H, 4.48; N, 6.21.

5-Chloro-1-heptylindoline-2,3-dione (2m): Red Solid, Yield: 70%, 98 mg; mp: 174-176 °C;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.51 (m, 2H), 6.86 (d, *J* = 8.2 Hz, 1H), 3.79 – 3.63 (m, 2H), 1.77 – 1.63 (m, 2H), 1.41 – 1.32 (m, 4H), 1.31 – 1.22 (m, 4H), 0.94 – 0.81 (m, 3H);^{13}C NMR (100 MHz, $CDCl_3$) δ 182.67, 157.60, 149.35, 137.68, 129.41, 125.32, 118.41, 111.49, 40.46, 31.65, 28.87, 27.20, 26.84, 22.55, 14.04; ESIMS: *m/z* 280 $[M+H]^+$; Anal. Calcd for $C_{15}H_{18}ClNO_2$: C, 64.40; H, 6.49; N, 5.01. Found: C, 64.32; H, 6.52; N, 4.97.

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5-Chloro-1-nonylindoline-2,3-dione (2n): Red Solid, Yield: 68%, 104 mg; mp: 175-177 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 – 7.48 (m, 2H), 6.87 (dd, *J* = 7.9, 1.0 Hz, 1H), 3.71 (t, *J* = 7.4 Hz, 2H), 3.45 – 3.36 (m, 2H), 1.90 – 1.80 (m, 2H), 1.75 – 1.65 (m, 2H), 1.48 – 1.40 (m, 2H), 1.33 (d, *J* = 8.6 Hz, 2H), 0.92 – 0.81 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.1, 157.30, 148.90, 137.92, 129.0, 124.6, 118.06, 111.8, 40.80, 33.59, 32.47, 29.08, 28.83, 26.82, 26.82, 22.3, 13.7;ESIMS: *m/z* 308 $[M+H]^+$; Anal. Calcd for $C_{17}H_{22}ClNO_2$: C, 66.33; H, 7.20; N, 4.55. Found: C, 66.52; H, 7.25; N, 4.52.

1-Butyl-5-fluoroindoline-2,3-dione (2o): Red Solid, Yield: 76%, 83 mg; mp: 155-157 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.25 (m, 2H), 6.93 (dd, *J* = 8.6, 3.6 Hz, 1H), 3.74 (t, *J* = 7.3 Hz, 2H), 1.75 – 1.62 (m, 2H), 1.48 – 1.34 (m, 2H), 0.98 (t, *J* = 7.3, 3.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.24, 160.39, 158.01, 147.12, 125.04, 124.80, 118.04, 111.82, 40.16, 29.13, 20.07, 13.62; ESIMS: *m/z* 222 $[M+H]^+$; Anal. Calcd for $C_{12}H_{12}FNO_2$: C, 65.15; H, 5.47; N, 6.33. Found: C, 65.01; H, 5.50; N, 6.37.

5-Fluoro-1-pentylindoline-2,3-dione (2p): Red Solid, Yield: 72%, 85 mg; mp: 160-162 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.28 (m, 2H), 6.91 (dd, *J* = 8.6, 3.6 Hz, 1H), 3.77 – 3.68 (m, 2H), 1.77 – 1.63 (m, 2H), 1.46 – 1.33 (m, 4H), 0.96 – 0.85 (t, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.09, 160.34, 157.85, 147.09, 124.83, 124.59, 118.00, 111.55, 40.28, 28.87, 26.77, 22.20, 13.83; ESIMS: *m/z* 236 $[M+H]^+$; Anal. Calcd for $C_{13}H_{14}FNO_2$: C, 66.37; H, 6.00; N, 5.95. Found: C, 66.50; H, 6.04; N, 5.98.

5-Fluoro-1-heptylindoline-2,3-dione (2q): Red Solid, Yield: 70%, 95 mg; mp: 165-168 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.24 (m, 2H), 6.93 – 6.85 (m, 1H), 3.72 (t, *J* = 7.4 Hz, 2H), 1.75 – 1.65 (m, 2H), 1.40 – 1.19 (m, 8H), 0.92 – 0.83 (t, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.10, 160.18, 157.89, 147.11, 124.77, 118.12, 112.31, 111.44, 31.63, 27.14, 22.51, 14.00; ESIMS: *m/z* 264 $[M+H]^+$; Anal. Calcd for $C_{15}H_{18}FNO_2$: C, 68.42; H, 6.89; N, 5.32. Found: C, 68.21; H, 6.85; N, 5.34.

5-Bromo-1-propylindoline-2,3-dione (2r): Red Solid, Yield: 72%, 95 mg;mp: 161-163 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (td, *J* = 4.4, 2.1 Hz, 2H), 6.89 – 6.78 (m, 1H), 3.77 – 3.63 (t, 2H), 1.79 – 1.66 (m, 2H), 1.06 – 0.91 (t, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.49, 157.48, 149.81, 140.58, 128.06, 118.68, 116.37, 112.05, 41.95, 20.57, 11.33; ESIMS: *m/z* 268, 266 $[M+H]^+$; Anal. Calcd for $C_{11}H_{10}BrNO_2$: C, 49.28; H, 3.76; N, 5.22. Found: C, 49.44; H, 3.80 N, 5.25.

5-Bromo-1-butylindoline-2,3-dione (2s): Red Solid, Yield: 70%, 98 mg; mp: 172-174^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.68 (m, 2H), 6.83 (t, *J* = 5.8 Hz, 1H), 3.72 (t, *J* = 7.3 Hz, 2H), 1.71 – 1.62 (m, 2H), 1.39 (dt, *J* = 14.6, 7.4 Hz, 2H), 1.00 – 0.93 (t, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.81, 157.65, 149.79, 140.90, 128.12, 118.59, 116.51, 112.42, 40.29, 29.15, 20.12, 13.71; ESIMS: *m/z* 284, 282 $[M+H]^+$; Anal. Calcd for $C_{12}H_{12}BrNO_2$: C, 51.09; H, 4.29; N, 4.96. Found: C, 49.91; H, 4.27; N, 4.94.

5-Bromo-1-pentylindoline-2,3-dione (2t): Red Solid, Yield: 68%, 100 mg; mp: 180-182 ^{o}C;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 – 7.67 (m, 2H), 6.83 (d, *J* = 9.0 Hz, 1H), 3.71 (t, *J* = 7.1 Hz, 2H), 1.74 – 1.61 (m, 2H), 1.36 (m, 4H), 0.90 (t, 3H);^{13}C NMR (100 MHz, $CDCl_3$) δ 182.50, 157.40, 149.78, 140.58, 128.03, 118.70, 116.35, 112.05, 40.39, 28.93, 26.84, 22.27, 13.91; ESIMS: *m/z* 297, 295 $[M+H]^+$; Anal. Calcd for $C_{13}H_{14}BrNO_2$: C, 52.72; H, 4.76; N, 4.73. Found: C, 52.56; H, 4.80 N, 4.75.

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Notes and references

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GRAPHICAL ABSTRACT

Copper-catalyzed aerobic oxidative intramolecular amidation of 2-aminophenylacetylenes: A domino process for the synthesis of isatin

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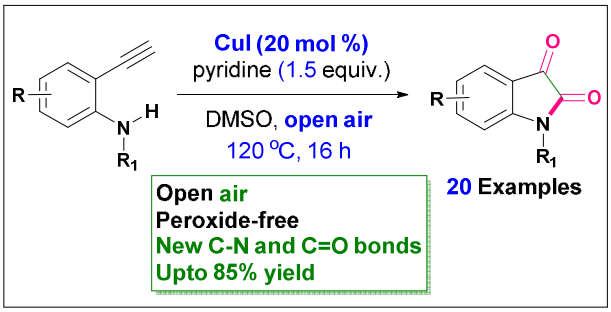

A novel CuI-catalyzed oxidative amidation of 2-aminophenylacetylenes leading to the formation of isatins by using open air as an oxygen source has been developed. The reaction proceeded smoothly and provided a variety of isatin derivatives in good yields. The advantages of this one-pot reaction protocol include green oxidant, low-price catalyst, facile conditions and easy handling.