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Copper-Catalyzed Intramolecular C−H Oxidation/Acylation of Formyl-*N*-arylformamides Leading to Indoline-2,3-diones

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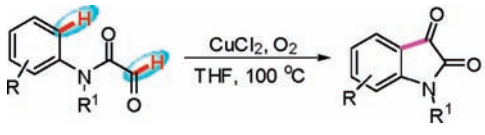
Indoline-2,3-diones (isatins), an important class of heterocycles, are commonly found in natural compounds, pharmaceuticals, and dyes; they are also versatile synthetic blocks in organic synthesis.[1,2] Traditionally, there are two practical approaches to their synthesis:[1,3−6] one involves strong acid- (often H_2SO_4) or base-mediated condensation of aniline with diethyl ketomalonate (Martinet procedure),[3] oxalyl chloride (Stollé procedure),[4] or chloral hydrate (Sandmeyer procedure),[5] and the other involves introduction of substituents onto a preexisting aromatic ring.[6] Although these methods provided useful access to substituted indoline-2,3-diones, there are noticeable drawbacks associated with them, such as relatively harsh reaction conditions, inaccessible substrates, and excess amount of acid or base catalysts. Therefore, the design of general and direct strategies for the preparation of indoline-2,3-diones, particularly involving a transition-metal-catalyzed process, would be highly interesting.

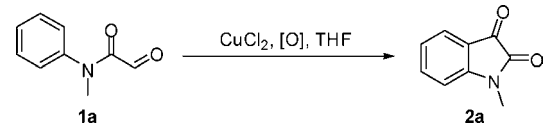
Recently, direct acylation of aldehydes with the arene π-systems *via* transition-metal-catalyzed C−H activation has been emerged as a powerful tool to give aryl ketones.[7−9] However, only a few papers on this method have been published: these have employed noble metal combined with ligand as the catalytic systems and expensive aryl halides[7] or arylboronic acids[8] as the arene π-system sources. Cheng and co-workers have disclosed an alternative method that utilizes an arene sp^2 C−H bond of 2-arylpyridines for Pd-catalyzed intermolecular oxidative acylation with an aldehyde.[9] However, their method requires a chelation assistant for arene sp^2 C−H bond activation and is limited to aryl aldehydes. Here, we describe a new, efficient route to indoline-2,3-diones by Cu-catalyzed intramolecular C−H oxidation/acylation of formyl-*N*-arylformamides using O_2 as the terminal oxidant (eq 1).[10] *To the best of our knowledge, it is the first example of the synthesis of indoline-2,3-diones using a transition-metal-catalyzed process.*



(1)

Our investigation began with the reaction of *N*-methyl-2-oxo-*N*-phenylacetamide (**1a**) under the reported Pd[7,9] or other conditions,[11] but it failed. After a series of trials, we found that substrate **1a** could be successfully cyclized with 20 mol % of $CuCl_2$ and 1 atm of O_2 in THF at 100 °C, affording the desired product **2a** in 90% yield (entry 1, Table 1).[12] Identical yields were obtained using either 10 or 5 mol % of $CuCl_2$, the latter requiring prolonged time (entries 2 and 3). Gratifyingly, a moderate yield was still achieved at 2 mol % of $CuCl_2$ (entry 4). We noted that the reaction cannot take place without Cu catalysis (entry 5). Using air as the terminal oxidant led to an unsatisfactory yield (entry 6), and in argon only <5% yield was observed (entry 7).[13] The activity of substrate **1a** was lowered sharply at 80 °C (entry 8).

Table 1. Cyclization of *N*-Methyl-2-oxo-*N*-phenylacetamide (**1a**)[a]



1a **2a**

entry	$CuCl_2$ (mol %)	additive	*T* (°C)	time (h)	isolated yield (%)
1	20	O_2	100	4	90
2	10	O_2	100	4	89
3	5	O_2	100	12	86
4	2	O_2	100	24	66
5	0	O_2	100	24	0
6	10	air	100	24	58
7	10	argon	100	24	<5
8	10	O_2	80	24	54

[a] Reaction conditions: **1a** (0.2 mmol), $CuCl_2$, additive (1 atm), and THF (3 mL).

A series of substrates with different substituents on both the nitrogen atom and the aromatic ring of **1** were examined (Table 2). While treatment of 2-oxo-*N*-phenylacetamide with $CuCl_2$ and O_2 afforded a trace amount of the desired product **2b**, both *N*-benzyl and *N*-allyl substrates gave the target products **2c** and **2d** in 80% and 74% yields, respectively. To our delight, several functional groups, such as methyl, methoxy, fluoro, chloro, acetyl, phenyl, and thiophen-2-yl groups, on the aromatic moiety were well-tolerated, giving the corresponding products **2e**−**p** in moderate to good yields. For methyl-substituted substrates, the order of activity is *meta* > *para* > *ortho* in terms of yields (**2e**−**h**). We found that substituents at the *para* position affected the reaction: the electron-donating or weak electron-withdrawing groups worked well and furnished the targets products **2i**−**k**,**n** in moderate yields, but the electron-withdrawing groups, acetyl and CF_3 groups, lowered the yields to 50% (**2l**) and 30% (**2m** obtained at 40 mol % of $CuCl_2$). Notably, substrates with a *meta* substituent gave a mixture of 3-acylated and 6-acylated products with the ratio of 1.6:1 (**2f**/**f′** or **2o**/**o′**). The introduction of olefin, heterocycles, or carbocycles into this system makes this meth-

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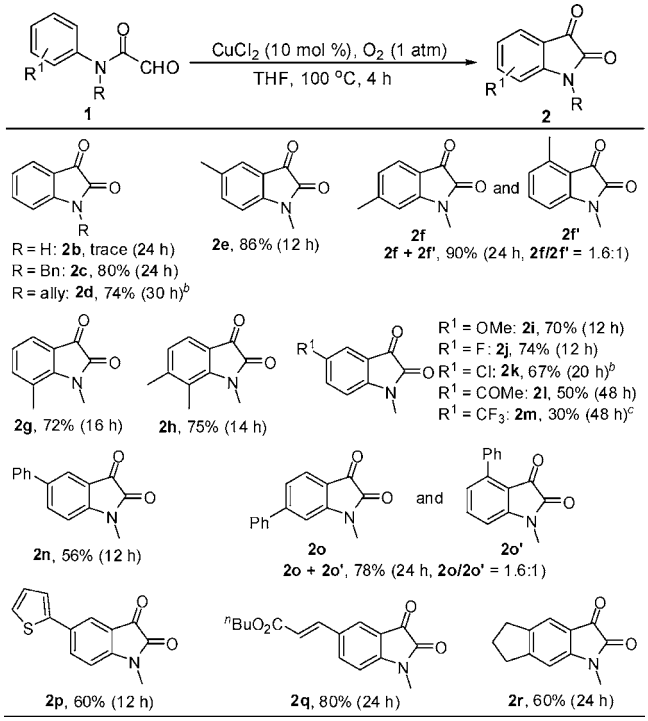
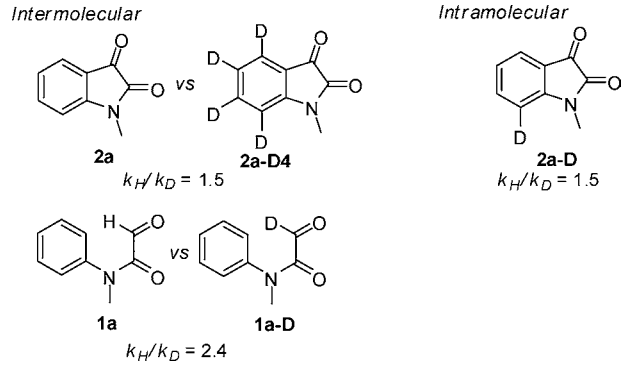
Table 2. $CuCl_2/O_2$-Catalyzed Synthesis of Indoline-2,3-diones (**2**)[a]



[a] Reaction conditions: **1a** (0.2 mmol), $CuCl_2$ (10 mol %), O_2 (1 atm), and THF (3 mL) at 100 °C. [b] $CuCl_2$ (20 mol %). [c] $CuCl_2$ (40 mol %).

Scheme 1. Kinetic Isotope Effect Experiments

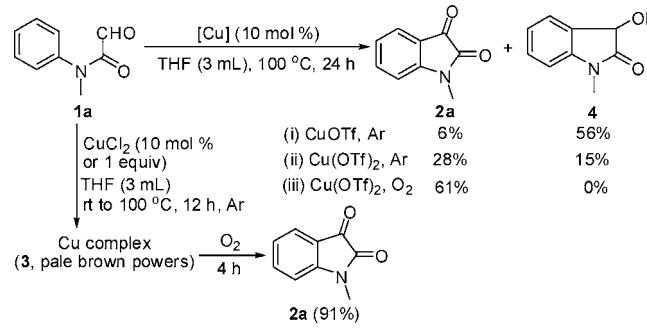


odology more useful for the preparation of pharmaceuticals and nature products (**2p**−**r**).

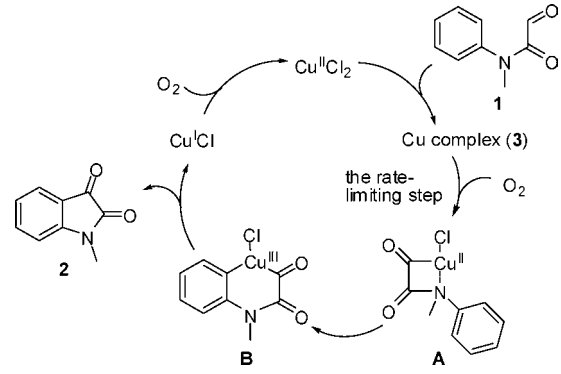
The same values of the inter- and intramolecular kinetic isotope effects ($k_H/k_D = 1.5$) imply that this reaction does not proceed *via* a chelation-assisted C−H bond cleavage (Scheme 1).[10,14] The intramolecular kinetic isotope effect also indicates that the mechanism of the C−H activation is not compatible with the SEAr mechanism[14] or the free radical mechanism.[15] Moreover, the free radical mechanism can be ruled out because this reaction is not affected by two radical inhibitors, 1,1-diphenylethylene or TEMPO.[7e,15] The kinetic isotope effect ($k_H/k_D = 2.4$) was observed by comparison with the rates of **1a** and the monodeuterated aldehyde substrate **1a**-D by FTIR analysis, suggesting that aldehyde C−H bond cleavage is the rate-limiting step.[7e]

Interestingly, a Cu complex (**3**) was obtained when $CuCl_2$ reacted with substrate **1a** under an argon atmosphere (Scheme 2). However, it was sensitive to oxygen and readily decomposed to **2a** in air.[13]

Scheme 2. Some Controlled Experiments



Scheme 3. A Possible Mechanism



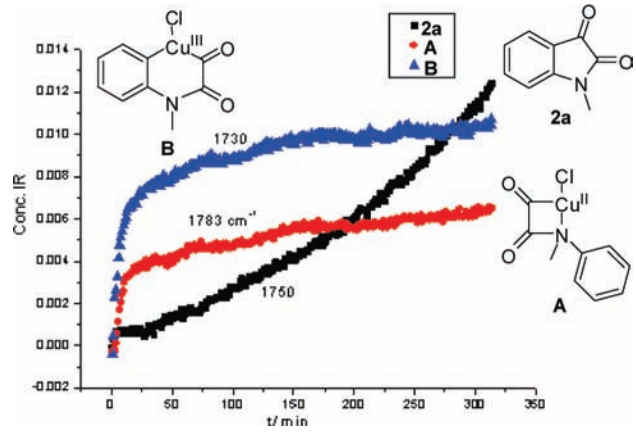


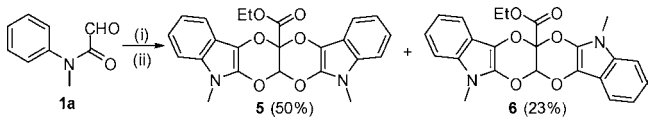
Figure 1. Data of *in situ* FTIR analysis during the reaction of Cu complex under air atmosphere.

As expected, a Friedel−Crafts product **4**, together with **2a**, was isolated when CuOTf or $Cu(OTf)_2$ was used for catalysis in argon.[16] We reason that product **4** can be readily oxidized, resulting in **2a**.[13] These results suggest that the present reaction proceeds not *via* a Friedel−Crafts process.

Consequently, a possible mechanism as outlined in Scheme 3 was proposed on the basis of the present results.[7−10,13−16,18] The C−H bond activation of aldehyde from the Cu complex **3** affords intermediate **A** with the aid of O_2. Intermediate **A** then undergoes the sp^2 arene C−H bond activation to yield Cu^{III} intermediate **B**.[10c,d,18] Reductive elimination of intermediate **B** gives the product **2** and Cu^I species. Intermediates **A** and **B** are supported by the C=O stretch data of *in situ* FTIR analysis (Figure 1

):[7e,19] Generally, 1783 cm^{-1} is a C=O stretch in a four-membered ring, 1750 cm^{-1} is a C=O stretch in a five-membered ring (indoline-2,3-dione), and 1730 cm^{-1} is a C=O stretch in a

Scheme 4. Application to the One-Pot Synthesis of Polyethers



(i) $CuCl_2$ (10 mol %), O_2 (1 atm), THF, 100 °C, 4 h.
(ii) ethyl propiolate, LiOH (2 equiv), DMF, rt, 0.5 h.

six-membered ring. Moreover, the results of the HRMS (ESI) analysis also support the formation of intermediates **A** and **B**.[13]

This novel methodology was also applied to the one-pot synthesis of polyethers **5** and **6**, a motif in enzyme mimics, receptor site models, and selective ionophores,[17] through a C−H oxidation/acylation reaction followed by bis-addition with ethyl propiolate (Scheme 4).

In summary, we have developed a novel copper-catalyzed intramolecular C−H oxidation/acylation protocol using two C−H bonds as the reaction partners and O_2 as the terminal oxidant. Importantly, the reaction could be a valuable method for preparing substituted indoline-2,3-diones with high tolerance of functional groups. The mechanism was also discussed according to the kinetic isotope effect experiments, *in situ* FTIR, and HRMS (ESI) analysis.

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Supporting Information Available: Experimental procedures and spectral data for all products **2**,**4**−**6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) See the controlled experiments in the Supporting Information (Scheme S1). The decomposition of the Cu salt **3** process was monitored *in situ* by FTIR and HRMS (ESI) analysis (Figure S1), and no Friedel−Crafts product **4** was determined by comparison with the standard sample **4**.

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