First Report on the Synthesis of Isatins via Pyridinium Chlorochromate Catalyzed Intramolecular Cyclization Reactions

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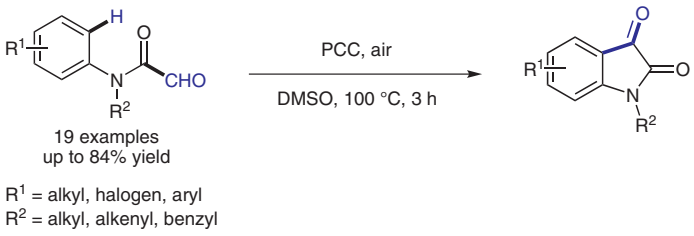


Received: 25.11.2015
Accepted after revision: 15.01.2016
Published online: 09.02.2016
DOI: 10.1055/s-0035-1561372; Art ID: st-2015-w0914-l

Abstract A new and useful strategy to synthesize isatins from α-formyl amides has been developed via one-pot intramolecular cyclization–oxidation reaction with the present of pyridinium chlorochromate (PCC). The reaction proceeded smoothly under air and has good yields of the corresponding products. Also, this methodology has a broad substrate scope, and is operationally simple and atom economic.

Key words isatins, PCC-catalyzed, one-pot, intramolecular cyclization

The isatin (1*H*-indol-2,3-dione) skeleton is one of the most important structural units present in a wide variety of natural products and drug intermediates. Some of isatins and their derivatives show high biological and pharmacological activities, and have been used as antiasthmatic,[1] antimitotic,[2] antiarthritic,[3] and human MCF-7 cell-growth inhibitor,[4] as well as antipsychotc[5] agents (Figure 1). On the other hand, isatin motifs are also considered as versatile synthetic blocks for application in organic reactions, such as nucleophilic addition to high reactivity of C-3 ketone carbonyl[6] and electrophilic substitution at position C-5 and C-7 of the aromatic ring.[7] Due to its importance, many researchers are devoted to the design and development of new synthesis protocols of isatins.

Traditionally, the Sandmeyer procedure is the most practical strategy to synthesize this class of compounds, and involves treating substituted aniline with chloral hydrate and hydroxylamine hydrochloride in sulfuric acid.[8] The Stollé [9] and Martinet procedure[10] are two other traditional methods. However, these methods suffer from harsh conditions, poor yields, and limited substrate scope. Within the past few years, several new effective and powerful routes have been established involving sulfur ylide mediated carbonyl homologation sequence,[11] selenium-mediated oxidations,[12] iodine-promoted C–H functionalization,[13] and CuI-catalyzed intramolecualr oxidative C–H amination.[14] Although these methods have made significant progress compared to the classical routes, there are some drawbacks too, such as the employment of noble metals and/or expensive or toxic catalysts, the multistep synthesis of starting materials, not readily available intermediates or *ortho*-functionalized aromatic rings, and long reaction times. So, further investigation to identify milder, convenient benign processes to access isatins is still warranted.

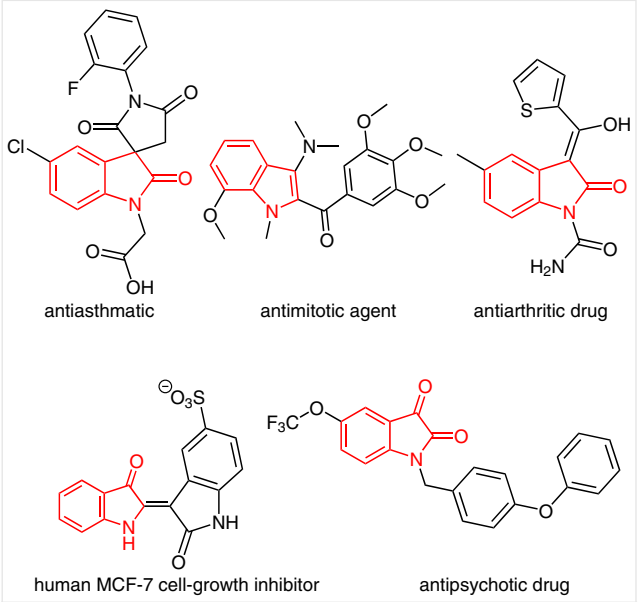
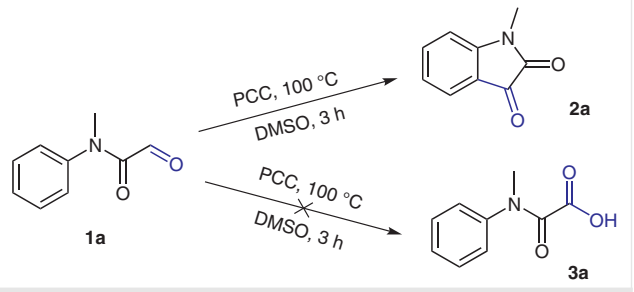


Figure 1 Biological and pharmacological activities containing isatin motifs

Recently, Li and co-workers have reported copper-catalyzed intramolecular C–H oxidation–acylation to synthesize isatin derivatives from α-formyl amides.[15] That is a quite attractive work to obtain isatins in the presence of $CuCl_2$ and O_2 in THF at 100 °C for 12 hours. However, problems of the complicated operation (reacting in a Schlenk tube and charging with O_2), long reaction time, and no large-scale application make the work undesirable. This motivates the development of an operationally simple and cost-effective method in our group.

During recent investigations, we tried to oxidize *N*-methyl-2-oxo-*N*-phenylacetamide **1a** to 2-[methyl(phenyl)-amino]-2-oxoacetic acid **3a** by some oxidants. Interestingly, when PCC was used, the desired acid **3a** was not detected and an unexpected product 1-methylindoline-2,3-dione **2a** was obtained in high yield (Scheme 1). To the best of our knowledge, only very limited ways about PCC-catalyzed intramolecular cyclization reaction have been found, and the usage of PCC in the synthesis of isatins from aldehydes has not been reported before. So, we are very interested in studying the transformation from α-formyl amides to isatins by PCC.

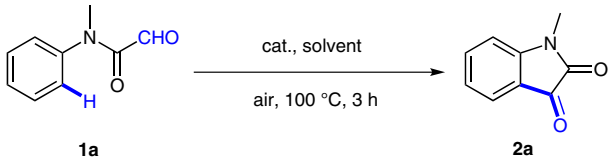


Scheme 1 Reaction of formyl-*N*-arylformamides with PCC

In this paper, we describe the PCC-catalyzed one-pot intramolecular cyclization–oxidation reaction to synthesize isatins from α-formyl amides. Compared with the traditional applications, we developed a new application scope of PCC which is a useful synthesis protocol for the preparation of isatins.

At the beginning of our investigation to synthesize isatins, experiments were carried out using *N*-methyl-2-oxo-*N*-phenylacetamide **1a** as prototypical substrate. Firstly, a series of oxidants, such as CrO_3, SeO_2, MnO_2, TBHP, NaClO, PCC, and I_2 (Table 1, entries 1–7) were screened for this reaction under air. Much to our satisfaction, the reaction was efficiently catalyzed by PCC. For the optimization of the amount of PCC used in the model reaction, one equivalent was found to be adequate, as neither a larger nor a smaller amount showed better yields (Table 1, entries 8 and 9) and no products were obtained in the absence of PCC (Table 1, entry 10). Furthermore, the reaction took place under argon, and the yield was still satisfactory, suggesting O_2 is not necessary (Table 1, entry 11). Moreover, when the reaction was carried out under O_2, the yields did not increase significantly (Table 1, entry 12). Thus, in further optimization, the reaction was carried out under air. Next we looked for a better solvent and found that dimethyl sulfoxide (DMSO) gave the best result among all the solvents such as dimethyl formamide (DMF), acetonitrile (MeCN), toluene (Tol), tetrahydrofuran (THF), and 1,4-dioxane (Table 1, entries 13–17). Out of the experimental results, 100 °C was the best choice for temperature. The transformation under these conditons took only three hours (Table 1, entries 18 and 19). Therefore, as observed in this study, the optimized conditions for the synthesis of isatins was determined to be: *N*-methyl-2-oxo-*N*-phenylacetamide (**1a**) (0.5 mmol) and PCC (0.5 mmol) in DMSO at 100 °C for three hours.

Table 1 Optimization of the Reaction Conditions[a]



Entry	Catalyst (equiv)	Temp (°C)	Solvent	Yield (%)[b]
1	CrO_3 (1)	100	DMSO	10
2	SeO_2 (1)	100	DMSO	40
3	MnO_2 (1)	100	DMSO	0
4	TBHP (1)	100	DMSO	15
5	NaClO (1)	100	DMSO	0
6	PCC (1)	100	DMSO	82
7	I_2 (1)	100	DMSO	20
8	PCC (2)	100	DMSO	81
9	PCC (0.5)	100	DMSO	70
10	–	100	DMSO	0
11[c]	PCC(1)	100	DMSO	81
12[d]	PCC (1)	100	DMSO	83
13	PCC (1)	100	DMF	23
14	PCC (1)	100	MeCN	40
15	PCC (1)	100	Tol	10
16	PCC (1)	100	THF	15
17	PCC (1)	100	1,4-dioxane	18
18	PCC (1)	80	DMSO	70
19	PCC (1)	120	DMSO	77

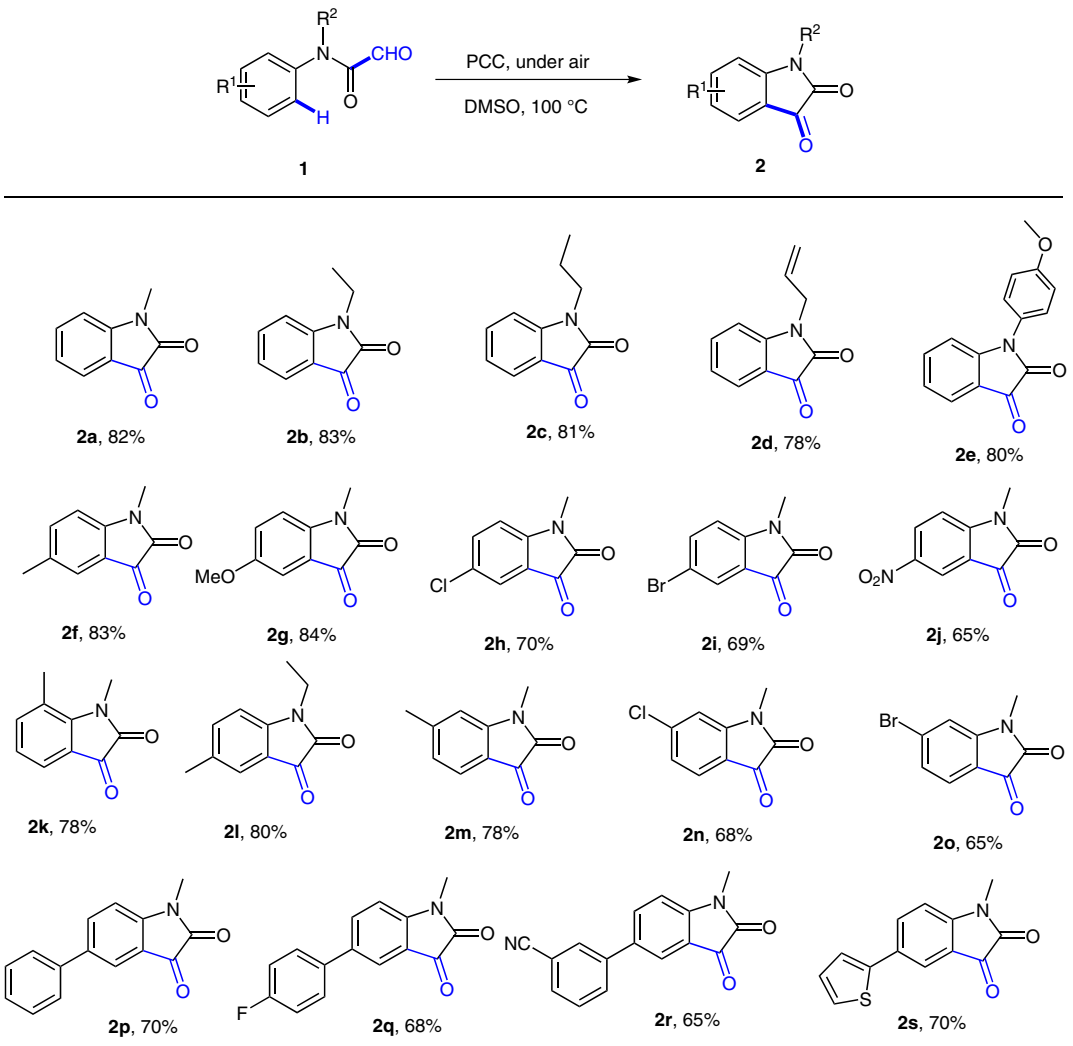
[a] Reaction conditions: **1a** (0.5 mmol), catalyst (as indicated), solvent (2 mL), heating for 3 h under air.
[b] Isolated yield.
[c] Reaction under argon.
[d] Reaction under O_2.

With the optimal parameters established, we turned our attention to the scope of various substituted α-formyl amides, and the results are shown in Scheme 2. Functional

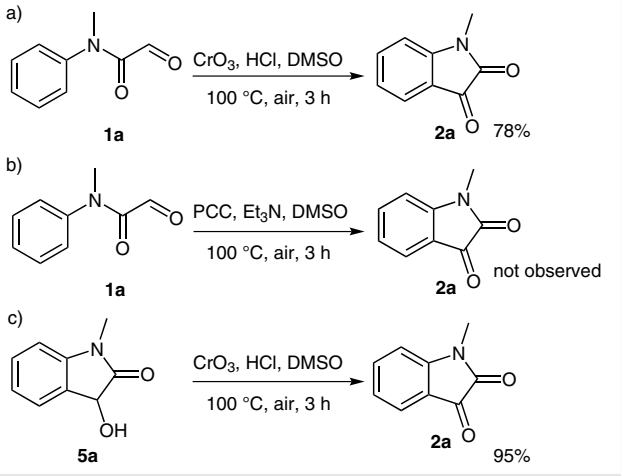
groups attached to a nitrogen atom, such as ethyl, *n*-butyl, and allyl, were well tolerated, giving the corresponding products in good yields (Scheme 2, 2a–e). Additionally, electron-donating and electron-withdrawing groups at the 4-position of the aromatic ring were well tolerated during the reaction (Scheme 2, 2f–j), and the results showed that substrates with electron-donating groups were more reactive. Notably, the substrates with 2-methyl or 2-halogens provided a single regioisomer of 6-substituted indoline-2,3-dione (Scheme 2, 2m–o). This reflects that the steric hindrance has a great influence in our reaction. Other functional groups, such as cyano, substituted phenyls, and heterocycles, were compatible with the optimized conditions (Scheme 2, 2p–s). It was noteworthy that the was easily scaled up; for example, when 3.0 mmol of **1a** (490 mg) were used, this reaction was shown to have similar efficiency.

Further, some control experiments were performed to explore the mechanism of this reaction (Scheme 3). When *N*-methyl-2-oxo-*N*-phenylacetamide (**1a**) was treated with one equivalent of CrO_3 and HCl in DMSO with a condenser heating for three hours under air, the amount of 1-methylindoline-2,3-dione (**2a**) was obtained in 78% yield (Scheme 3, a). We also checked the p*H* value in this reaction, and it turned out that the reaction should be performed under acidic conditions (Scheme 3, b). Additionally, **5a** can be oxidized to **2a** in the presence of PCC in 95% yield after three hours of heating (Scheme 3, c).

According to the control experiments and previous studies,[16] a plausible mechanism as shown in Scheme 4 was proposed. *N*-Methyl-2-oxo-*N*-phenylacetamide (**1a**) undergoes a Friedel–Crafts route leading to 3-hydroxy-1-me-

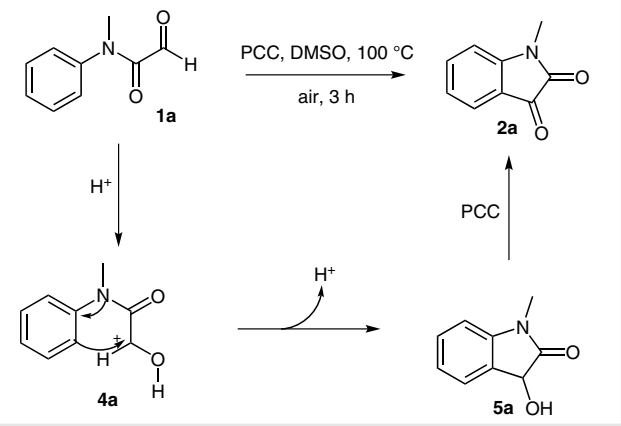


Scheme 2 Transformation of α-formyl amides **1** to isatins **2**. *Reagents and conditions*: α-hydroxy amides **1** (0.5 mmol), PCC (0.5 mmol), DMSO (2 mL), 100 °C, 3h Isolated yields are given.



Scheme 3 Control experiments

thylindolin-2-one (**5a**) via HCl catalysis. Subsequently, intermediate **5a** was further converted into *N*-methylindoline-2,3-dione (**2a**) with the assistance of PCC.



Scheme 4 Plausible mechanism for this reaction

In summary, a novel and highly efficient protocol to synthesize isatins has been established via PCC-catalyzed intramolecular acylation of formyl-*N*-arylformamides.[17,18] The starting materials are cheap and very easy to prepare. In addition, compared to Li's work (reacting in a Schlenk tube, charging with O_2, and long reaction time) the reaction is very simple to run. This atom-economical intramolecular transformation offers the corresponding products in high yields and excellent functional-group tolerance. Further applications of this method to other substrates are in progress.

Acknowledgment

We are grateful financial support from the National Natural Science Foundation of China (NSFC) (grant number 81573286, 21472130).

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561372.

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(17) α-Formyl amides **1** were prepared according to the reported procedures, see: Marc, M.; Johannes, C.; Vogel, W. T. *Org. Biomol. Chem.* **2009**, *7*, 589.
(18) **General Procedure for the Synthesis of 2 (2a as an Example)**
A mixture of *N*-methyl-2-oxo-*N*-phenylacetamide (**1a**, 0.5 mmol) and PCC (0.5 mmol) were added in DMSO (2 mL) with a condenser and then heating for 3 h under air at 100 °C. After the completion of the reaction (monitored by TLC), the reaction mixture was cooled to r.t., diluted with H_2O and extracted with EtOAc. The organic layer was washed with sat. brine, dried over anhydrous Na_2SO_4 and the solvent was evaporated to dryness. The crude residue was purified by flash chromatography on silica (PE–EtOAc, 10:1) to afford pure 1-methylindoline-2,3-dione (**2a**) as a red solid (66 mg, 82% yield).
1-Methylindoline-2,3-dione (2a)
Yield 82%; red solid; mp 130–133 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64–7.58 (m, 2 H), 7.14 (t, *J* = 7.6 Hz, 1 H), 6.92 (d, *J* = 8.0 Hz, 1 H), 3.26 (s, 3 H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 183.3, 158.1, 151.4, 138.4, 125.1, 123.8, 117.3, 109.9, 26.2. ESI-HRMS: *m/z* [M + Na^+] calcd for $C_9H_7NO_2$ + Na^+: 184.0369; found: 184.0370.