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Ferric(III) chloride catalyzed intramolecular cyclization of *N*-alkyl-2-oxo-acetanilides: a facile access to isatins

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ABSTRACT

A facile strategy for the synthesis of isatins in high yield from *N*-alkyl-2-oxo-acetanilides has been developed via Friedel–Crafts alkylation using $FeCl_3$ as catalyst under air. This reaction proceeds through direct intramolecular addition and oxidation in one pot. Also this methodology is operationally simple, atom economical, and environment friendly.

Indoline-2,3-dione, commonly known as isatin, is a ubiquitous unit in a wide range of natural products and synthetic organic compounds. Isatin and its derivatives exhibit a board array of biological and pharmacological activities, and have been used as antiviral,[1] antimalarial,[2] antiplatelet,[3] antiasthmatic,[4] and analgesic[5] agents (Fig. 1). The isatin motifs are also considered as the privileged synthetic intermediates that can be found in applications of organic reactions, such as the nucleophilic addition to the C-3 ketone carbonyl[6] and the electrophilic substitution at C-5 and C-7 of the aromatic ring.[7] Giving such importance of isatins, much effort have been put into the preparation of this compound.

Classically, the Sandmeyer procedure is used in the synthesis of isatins. This procedure involves a treatment of aniline with chloral hydrate, hydroxylamine hydrochloride in an aqueous sodium sulfate medium.[8] The Stollé procedure[9] and Martinet procedure,[10] which involve the condensation of aniline with oxalyl chloride or diethyl ketomalonate, are another two common strategies to synthesize isatins. However, these methods suffer from harsh conditions, poor yields, and limited diversification. This prompts the development of better methods on the construction of isatins to overcome these limitations. Gratifyingly, a number of new methods have been proved efficient in building this useful framework, such as the I_2-mediated[11] or Cu-catalyzed[12] intramolecular cyclic amidation from substituted anilines, the ylide-mediated carbonyl homologation of anthranilic acids,[13] the metal complexes mediated oxidation of indoles,[14] and the base-promoted oxidation of indolin-2-one.[15] However, there are some drawbacks in these methods too, such as the employment of noble metals and/or expensive ligands, the hazardous reagent, the not readily available intermediates or pre-functionalized aromatic substrates, high temperature, and low yield. Moreover, some methods are also not atom economical. Therefore, considering the importance of isatins in medicinal chemistry and organic synthesis, improved methods are still highly desirable.

Recently, Li and co-workers have reported copper-catalyzed intramolecular C–H oxidation/acylation to isatin derivatives (Scheme 1a).[16] That is a quite attractive work. Firstly, the starting material formyl-*N*-arylformamides can be easily prepared, and secondly isatins can be smoothly obtained in the presence of $CuCl_2$ and O_2 in THF at 100 °C for 12 h. However, problems of the complicated operation (reacting in Schlenk tube and charging with O_2), long reaction time, and no large-scaled application make the work undesirable. This motivates the development of an operationally simple and cost-effective method in our study. Herein we present a $FeCl_3$-catalyzed intramolecular Friedel–Crafts alkylation to synthesize isatin derivatives under air within a short time (Scheme 1b). This protocol is simple, environment friendly and atom economical. Also, it obtains isatin units in high-yield without the preparation of *ortho*-substituted anilides or other complicated intermediates.

Due to our interest in isatins and their inherent importance, we envisioned that finding an efficient protocol for the synthesis of isatins would be interesting. During our previous research, we

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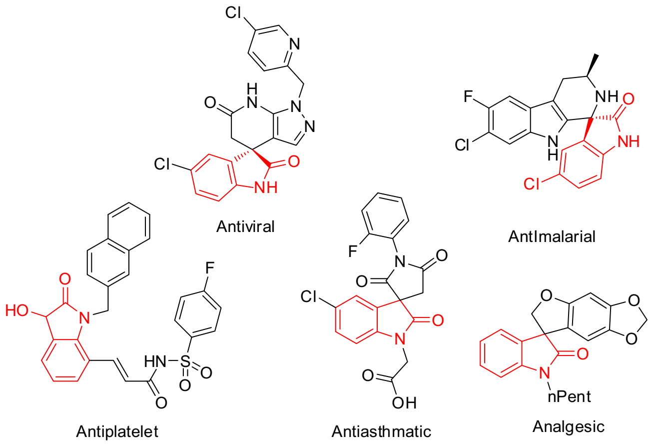
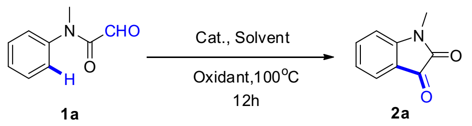


Figure 1. Selected biological and pharmacological activities containing isatin motifs.

Table 1
Optimization of the reaction conditions[a]

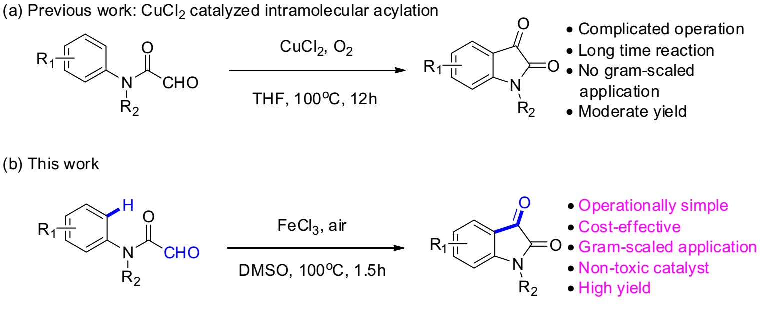


Entry	Catalyst	Oxidant	Temp (°C)	Solvent	Yield[b] (%)
1	$AlCl_3$	O_2	100	Toluene	84
2	$SnCl_2$	O_2	100	Toluene	41
3	$TiCl_4$	O_2	100	Toluene	72
4	$MnCl_2$	O_2	100	Toluene	Trace
5	$CoCl_2$	O_2	100	Toluene	66
6	$NiCl_2$	O_2	100	Toluene	21
7	Hg_2SO_4	O_2	100	Toluene	Trace
8	$CuSO_4$	O_2	100	Toluene	Trace
9	$AgNO_3$	O_2	100	Toluene	Trace
10	$IrCl_3$	O_2	100	Toluene	60
11	$CeCl_3$	O_2	100	Toluene	86
12	$RhCl_3$	O_2	100	Toluene	68
13	$FeCl_3$	O_2	100	Toluene	90
14	–	O_2	100	Toluene	0
15	$FeCl_3$	$K_2S_2O_8$	100	Toluene	63
16	$FeCl_3$	TBHP	100	Toluene	86
17	$FeCl_3$	$Cu(OAc)_2$	100	Toluene	74
18	$FeCl_3$	$PhI(OAc)_2$	100	Toluene	83
19	$FeCl_3$	–	100	Toluene	Trace
20	$FeCl_3$	Air	100	Toluene	90
21	$KFe(CN)_3$	Air	100	Toluene	83
22	$FeBr_3$	Air	100	Toluene	88
23	$Fe(TFA)_3$	Air	100	Toluene	90
24	$FeCl_3$	Air	100	DMF	75
25	$FeCl_3$	Air	100	Dioxane	83
26	$FeCl_3$	Air	100	MeCN	37
27	$FeCl_3$	Air	100	EtOH	31
28	$FeCl_3$	Air	100	THF	65
29[c]	$FeCl_3$	Air	100	DMSO	93
30[c]	$FeCl_3$[d]	Air	100	DMSO	76
31[c]	$FeCl_3$[e]	Air	100	DMSO	92
32	$FeCl_3$	Air	80	DMSO	56
33[c]	$FeCl_3$	Air	120	DMSO	87

[a] Reaction conditions: **1a** (0.4 mmol), catalyst (10 mol %), solvent (2.0 mL), oxidant (0.6 mmol or 1 atm) were heated at 100 °C for 12 h. TFA = trifluoroacetate; TBHP = *tert*-butyl hydroperoxide.
[b] Isolated yield.
[c] Reaction for 1.5 h.
[d] 5 mol % $FeCl_3$.
[e] 20 mol % $FeCl_3$.

had synthesized *N*-methyl-2-oxo-acetanilide **1a.**[17] Thus, our investigation started with **1a** as prototypical substrate in toluene. Firstly a series of metal salts were screened for this reaction under O_2 (Table 1, entries 1–13). To our delight, $FeCl_3$ had excellent reaction efficiency (Table 1, entry 13). It was found that this transformation would not be a success without the presence of any metal salts (Table 1, entry 14). Further optimization of the reaction conditions was needed in order to improve the yield. When O_2 was replaced by other oxidants, including $K_2S_2O_8$, *tert*-butyl hydroperoxide (TBHP), $Cu(OAc)_2$ and $PhI(OAc)_2$, the yield of *N*-methyl-indoline-2,3-dione **2a** was not increased (Table 1, entries 15–18). Notably no corresponding product was detected when replacing O_2 with argon, which revealed that an oxidant was necessary (Table 1, entry 19). Surprisingly, we observed that the reaction still proceeded smoothly under air. This observation was quite interesting as employing air as an oxidant is quite easy, and a reaction which could run under air system is obviously simple to operate (Table 1, entry 20). Thus, air was chosen as oxidant for further optimization. Additionally, the examination of other iron complexes was set. Out of cost concerns, $FeCl_3$ was chosen as the most suitable iron catalyst (Table 1, entries 21–23). Furthermore, the choice of various solvents was evaluated. Dimethyl sulfoxide (DMSO) was more effective among all the solvents such as dimethylformamide (DMF), acetonitrile (MeCN), ethanol (EtOH), tetrahydrofuran (THF) and 1,4-dioxane (Table 1, entries 24–29). It was notable that in DMSO, conversion of **1a** could be completed in 1.5 h (Table 1, entry 29). The use of 10 mol % of $FeCl_3$ was necessary to achieve a satisfactory yield. When 5 mol % of $FeCl_3$ was used, the reaction yield decreased to 76%, whereas the yield was not enhanced when $FeCl_3$ loading was up to 20 mol % (Table 1, entries 30–31). Moreover, further investigation on evaluating reaction temperature suggested that 100 °C was the best choice as increasing or decreasing the temperature from 100 °C only led to a decrease in yield (Table 1, entries 32–33). Accordingly, the reaction conditions are optimized as follows: 10 mol % $FeCl_3$ under air atmosphere in DMSO at 100 °C for 1.5 h.

With the optimum reaction conditions in hand, we investigated the substrate scope as following trials. Results are shown in Figure 2. Methyl, ethyl, *n*-butyl, allyl, and 4-methoxyl phenyl groups that attached to amine gave a high yield of corresponding



Scheme 1. Typical pathway for the synthesis of isatins.

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