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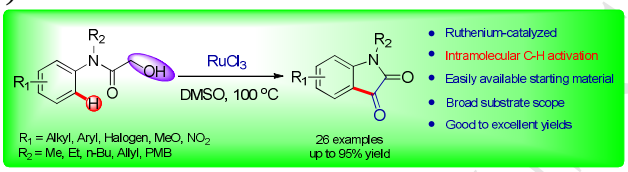

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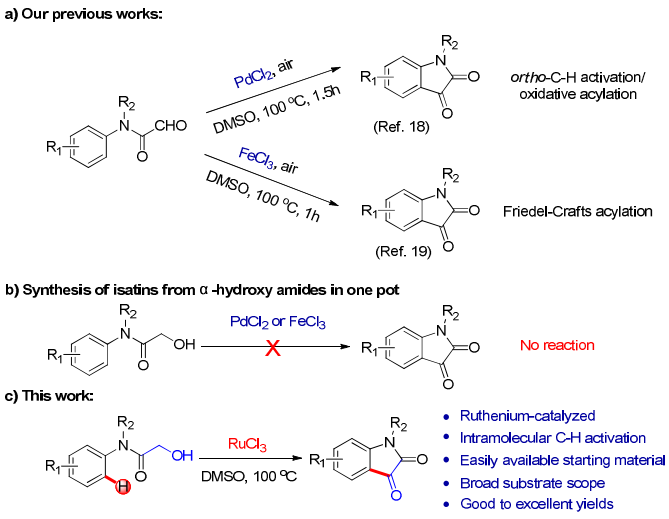
ABSTRACT

A novel and efficient synthesis of isatins from α-hydroxy amides *via* ruthenium-mediated aromatic C-H activation is described. The reactions proceeded smoothly under mild conditions and generated the corresponding products in good to excellent yields. This methodology has a broad substrate scope and opens up an interesting and attractive avenue for the application of intramolecular *ortho*-C-H activation.

1. Introduction

Isatins and their derivatives are a group of important structural units and have been found in many bioactive molecules. For example, they have been used as DNA gyrase inhibitors,[1] caspase 3 inhibitors,[2] antiparkinsonian drugs,[3] alpha-glucosidase inhibitors,[4] apoptosis inducers[5] and diacylglycerol acyltransferase type 2 inhibitors.[6] Besides, isatins are synthetically versatile building blocks for the synthesis of various heterocyclic compounds,[7] such as isatoic anhydrides, indoles, quinolines, and spiro-fused frameworks.[8] Consequently, much attention has been paid to their preparation. Among the traditional ways of synthesizing isatins, three methods stood out from the rest. They are the Sandmeyer procedure,[9] the Stollé procedure[10] and the Martinet procedure.[11] Later, several improved protocols have also been reported, such as the aryne-based methods,[12] Sandmeyer modifications,[13] metal catalyzed oxidations,[14] sulfur ylide mediated carbonyl homologation,[15] and C-H amination.[16] Recently, Ilangovan and co-workers reported a molecular iodine-promoted domino synthesis of isatins from easily accessible 2'-aminophenylacetylenes, 2'-aminostyrenes, and 2'-amino-β-ketoesters.[17] Nevertheless, all these reported methods suffer from some drawbacks, such as the use of expensive or toxic catalyst, long reaction time, tedious synthetic procedures, and low yield of product. Therefore, the development of a more milder, convenient, and environmentally benign process to access isatins is still highly necessary.



Scheme 1. Our previous reports on the synthesis of isatins.

Recently, we have reported the synthesis of isatins from α-formyl amides *via* the palladium-catalyzed intramolecular *ortho*-C-H activation/oxidative acylation[18] or the ferric-catalyzed intramolecular Friedel-Crafts acylation (Scheme 1a).[19] As we all know, α-formyl amide is the oxidation product of α-hydroxy amide. So we are very interested in realizing the transformation from α-hydroxy amides to isatins in one pot. However, no product could be found when the reaction was mediated by $PdCl_2$

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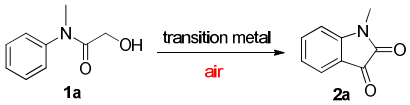
or $FeCl_3$ (Scheme 1b). Therefore, we have made detailed studies on this transformation.

In this paper, we described a novel and efficient one-pot synthesis of isatins from α-hydroxy amides in the presence of ruthenium trichloride (Scheme 1c). To the best of our knowledge, using α-hydroxy amide as the raw material of isatin hasn't been reported before.

2. Results and discussion

Table 1. Optimization of Reaction Conditions.[a]



Entry	Transition-metal	Solvent	Temp (°C)	Yield [b] (%)
1	$PdCl_2$	DMSO	100	0
2	$Pd(TFA)_2$	DMSO	100	11
3	$CoCl_2$	DMSO	100	0
4	$TiCl_4$	DMSO	100	0
5	$FeCl_3$	DMSO	100	0
6	$Fe(TFA)_3$	DMSO	100	40
7	$IrCl_3$	DMSO	100	0
8	$Ni(OAc)_2$	DMSO	100	0
9	$RuCl_3$	DMSO	100	91
10	$[RuCl_2(p\text{-Cymene})]_2$	DMSO	100	37
11 [c]	$RuCl_3$	DMSO	100	65
12 [d]	$RuCl_3$	DMSO	100	88
13 [e]	$RuCl_3$	DMSO	100	83
14	$RuCl_3$	DMF	100	81
15	$RuCl_3$	Dioxane	100	79
16	$RuCl_3$	CH_3CN	100	80
17	$RuCl_3$	PhMe	100	33
18	$RuCl_3$	DMSO	120	59
19	$RuCl_3$	DMSO	50	63
20	$RuCl_3$	DMSO	80	81
21	/	DMSO	100	N.R.[f]

[a] Reaction conditions: **1a** (1 mmol) and transition-metal (1 mmol) in solvent (2 mL) under the corresponding temperature in air for 5h.

[b] Isolated yield.

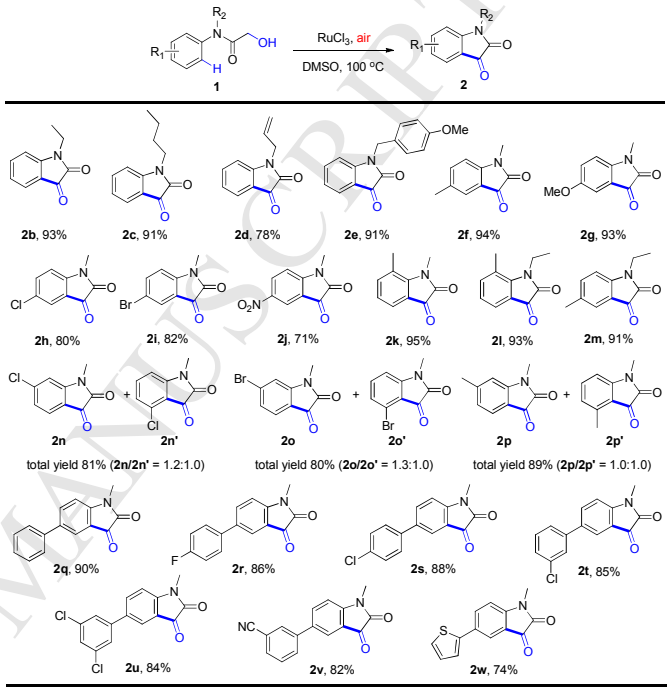
[c] $RuCl_3$ (0.5 mmol).

[d] $RuCl_3$ (2.0 mmol).

[e] In Ar.

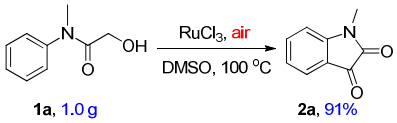
[f] No reaction.

At the beginning of our investigation, experiments were carried out using 2-hydroxy-*N*-methyl-*N*-phenylacetamide (**1a**) as a model substrate. After extensive screenings, $RuCl_3$ turned out to be the best choice for the reaction (Table 1, entries 1-10). For the optimization of the amount of $RuCl_3$ used in the model reaction, one equivalent was found to be adequate, as neither larger nor smaller amount showed better yields (Table 1, entries 11-12). Notably, molecular oxygen and dimethylsulfoxide, as dual oxidants, are very important for the present reaction system and the reaction could not occur without them (Table 1, entries 9 and 13-17). Among various solvents examined, DMSO turned out to be the best choice, while others such as DMF, dioxane, CH_3CN and PhMe were less effective (Table 1, entries 14-17). Further investigation indicated that temperature was important for this transformation. An excellent yield has been obtained when the reaction carried out at 100 °C (Table 1, entry 9). However, when the temperature was increased to 120 °C, the yield of desired product dropped to 59% (Table 1, entry 18). And the decrease of reaction temperature also reduced the yield of isatin (Table 1, entries 19-20). Therefore, as observed in this study, the optimized conditions for the synthesis of isatins tend to be: α-hydroxy amides (1.0 mmol) and $RuCl_3$ (1.0 mmol) in DMSO at 100 °C in air for 5h.



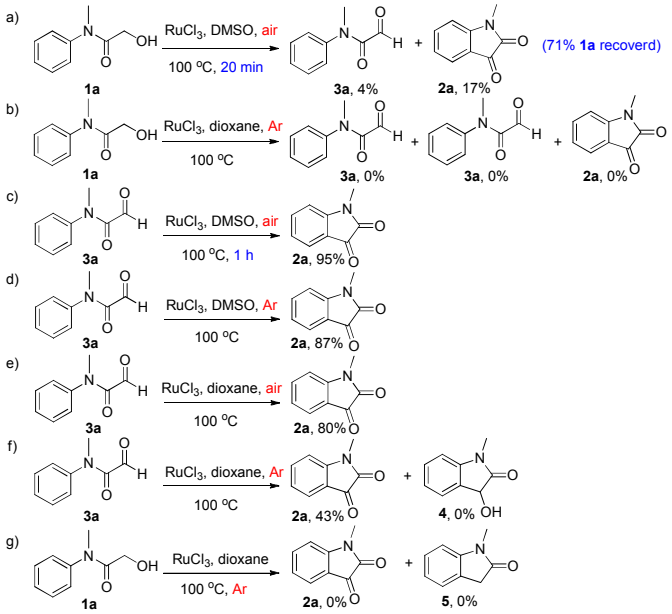
Scheme 2. Transformation of α-hydroxy amides (**1**) to isatins (**2**). Reaction conditions: α-hydroxy amides (**1**, 1.0 mmol) and $RuCl_3$ (1.0 mmol) in DMSO (2 mL) at 100 °C for 5h, air.

To further determine the scope of this new method, a wide range of α-hydroxy amides were reacted under the optimized conditions. And the results were summarized in Scheme 2. A host of α-hydroxy amides bearing either the electron-donating groups such as methyl and methoxy, or electron-withdrawing groups such as nitro and halogen, were well tolerated during the course of the reaction providing the desired compounds **2b-2m** in good to excellent yields. And the results showed that electron-donating groups could improve the reaction yields. Notably, the substrates with *meta*-methyl or halogens on *N*-substituted aromatic ring provided a mixture of 4-substituted and 6-substituted isatins, and **2n-2p** were major products from the transformation, which indicated that steric hindrance had obvious effect on this reaction. Besides, synthetically useful biphenyl, thienyl and allyl were tolerated in this transformation, giving **2d** and **2o-2w** in good yields. Furthermore, a variety of functional groups such as ether, nitryl, halogen, cyano and vinyl were well-suited for this reaction.



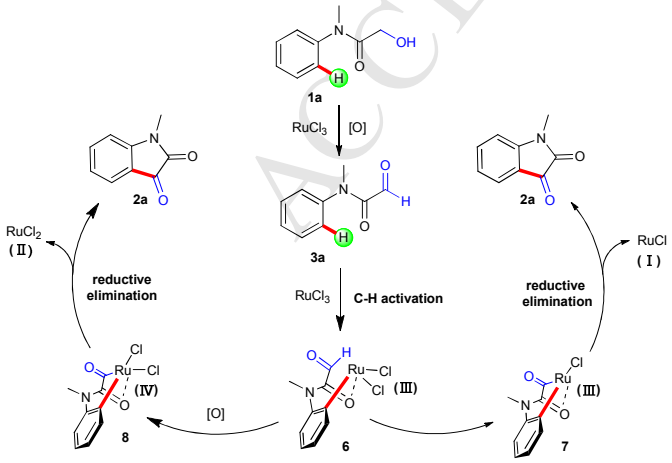
Scheme 3. Large-scale reaction.

Finally, considering the general application of this transformation, we demonstrated the gram-scale progress, and an example of large-scale reaction with excellent yield of the product is shown in Scheme 3.



Scheme 4. Control experiments for the reaction mechanism.

A series of control experiments have also been performed to explore the mechanism of this transformation (Scheme 4). When **1a** was conducted under the optimized conditions for twenty minutes, 4% yield of **3a** was detected (Scheme 4a). And isatin **2a** could be synthesized from **3a** under the optimized conditions in excellent yield (Scheme 4c). These results suggested that α-formyl amide **3** should be an important intermediate in the synthesis of isatin. Besides, $RuCl_3$ plays two roles in this reaction. Firstly, $RuCl_3$ act as an catalyst in the transformation of α-hydroxy amide to α-formyl amide. Secondly, it act as an oxidant in the formation of isatin from α-formyl amide (Scheme 4f). DMSO and air also play the role of oxidant in the whole transformation (Scheme 4a-e). Notably, When **3a** was treated with $RuCl_3$ in 1,4-dioxane under Ar at 100 °C, no product of the Friedel-Crafts reaction (**4**) was obtained (Scheme 4f). Similarly, when **3a** was replaced by **1a**, no compound **5** was formed (Scheme 4g). These suggested that the reaction is not compatible with the Friedel-Crafts mechanism.



Scheme 5. Proposed reaction mechanism.

Based on the preliminary mechanistic investigations and some relevant publications,[20] a plausible mechanism is proposed as shown in Scheme 5. Firstly, α-hydroxy amide **1a** was oxidized into α-formyl amide **3a** in the presence of $RuCl_3$. Secondly, coordination of the carbonyl group of **3a** to ruthenium center followed by ligand exchange with the concomitant generation of HCl gave ruthenium complex **6**, which was then transferred into the Ru□ species **7** and Ru□ species **8**. The subsequent reductive elimination of intermediate **7** and **8** delivered the final cyclization product **2a**.

3. Conclusion

In summary, we demonstrated a novel and efficient synthesis of isatins from α-hydroxy amides. Many functional groups were compatible with this procedure, and a diverse array of isatins were obtained in good to excellent yields. Besides, the present protocol was suitable for gram scale and retained its high yield. Further studies for the utilization of these products are ongoing in our laboratory.

4. Experimental section

4.1. General chemical methods and materials

All the reactions were monitored by thin-layer chromatography (TLC) and were visualized using UV light. The product purification was done using silica gel column chromatography. Thin layer chromatography (TLC) characterization was performed with precoated silica gel GF254 (0.2mm), while column chromatography characterization was performed with silica gel (100-200mesh). ^1H and ^{13}C NMR spectra were recorded with tetramethylsilane as the internal standard. ^1H NMR spectra were recorded at 400 or 600 MHz (Varian) and ^{13}C NMR spectra were recorded 150 MHz (Varian). Chemical shifts are reported in ppm downfield from $CDCl_3$ (δ = 7.26 ppm) for ^1H NMR and relative to the central $CDCl_3$ resonance (δ = 77.0 ppm) for ^{13}C NMR spectroscopy. Coupling constants are given in Hz. Melting points were measured with YRT-3 melting point apparatus (Shantou Keyi Instrument & Equipment Co., Ltd., Shantou, China). High resolution mass spectroscopy data of the products were collected on a Waters Micromass GCT or a Bruker Apex IV FTMS instrument. All the α-hydroxy amides **1** were prepared according to the reported procedures.[21]

4.2. General reaction procedure for the synthesis of isatins

A mixture of α-hydroxy amides **1** (1 mmol) and $RuCl_3$ (1 mmol) were added in 2 mL DMSO and then stirred under air at 100 °C for 5h. After the completion of the reaction (monitored by TLC), the mixture was cooled to room temperature, diluted with water and extracted with ethyl acetate (10 mL x 3). The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate and the solvent was evaporated to dryness. The crude residue was purified by flash chromatography on silica (petroleum ether/ethyl acetate) to afford pure isatins **2** as a red solid.

*4.2.1. 1-methylindoline-2,3-dione (**2a**)*: Yield 91%; red solid; mp. 130-133 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.64-7.58 (m, 2H), 7.15-7.11 (m, 1H), 6.92 (d, *J* = 8.0 Hz, 1H), 3.26 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 183.3, 158.1, 151.4, 138.4, 125.1, 123.8, 117.3, 109.9, 26.2; HRMS (ESI): m/z [M + Na^+] calcd for $C_9H_7NO_2$+Na^+ 184.0374, found 184.0370.

*4.2.2. 1-ethylindoline-2,3-dione (**2b**)*: Yield 93%; red solid; mp. 92-94 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.62-7.58 (m, 2H), 7.14-7.10 (m, 1H), 6.93-6.91 (m, 1H), 3.80 (q, *J* = 7.6 Hz, 2H), 1.32 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 182.3, 158.3, 151.4, 138.2, 125.2, 123.9, 117.0, 109.6, 36.0, 14.4;

HRMS (ESI): m/z [M + Na^+] calcd for $C_{10}H_9NO_2$+Na^+ 198.0531, found 198.0534.

*4.2.3. 1-butylindoline-2,3-dione (**2c**)*: Yield 91%; red solid; mp. 35-36 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61-7.57 (m, 2H), 7.13-7.09 (m, 1H), 6.91-6.88 (m, 1H), 3.76-3.71 (m, 2H), 1.73-1.64 (m, 2H), 1.61-1.55 (m, 1H), 1.44-1.39 (m, 1H), 0.99 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 183.4, 158.5, 151.3, 138.5, 125.1, 123.5, 116.9, 109.8, 43.1, 31.0, 20.7, 13.8; HRMS (ESI): m/z [M + Na^+] calcd for $C_{12}H_{13}NO_2$+Na^+ 226.0844, found 226.0842.

*4.2.4. 1-allylindoline-2,3-dione (**2d**)*: Yield 78%; red solid; mp. 89-90 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.62 (d, *J* = 7.2 Hz, 1H), 7.58-7.56 (m, 1H), 7.14-7.11 (m, 1H), 6.90 (d, *J* = 7.8 Hz, 1H), 5.88-5.82 (m, 1H), 5.31-5.29 (m, 2H), 4.37 (d, *J* = 5.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 183.2, 157.8, 150.8, 138.3, 130.3, 125.4, 123.8, 118.6, 117.5, 110.8, 42.5; HRMS (ESI): m/z [M + Na^+] calcd for $C_{11}H_9NO_2$+Na^+ 210.0531, found 210.0531.

*4.2.5. 1-(4-methoxybenzyl)indoline-2,3-dione (**2e**)*: Yield 91%; red solid; mp. 169-171 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, *J* = 6.8 Hz, 1H), 7.51-7.46 (m, 1H), 7.27 (d, *J* = 8.8 Hz, 2H), 7.10-7.06 (m, 1H), 6.87 (d, *J* = 8.8 Hz, 2H), 6.81 (d, *J* = 8.0 Hz, 1H), 4.86 (s, 2H), 3.78 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 183.3, 159.4, 158.2, 150.7, 138.2, 128.9, 126.4, 125.3, 123.7, 117.6, 114.3, 111.0, 55.2, 43.5; HRMS (ESI): m/z [M + Na^+] calcd for $C_{16}H_{13}NO_3$+Na^+ 290.0793, found 290.0790.

*4.2.6. 1,5-dimethylindoline-2,3-dione (**2f**)*: Yield 94%; red solid; mp. 149-150 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42-7.28 (m, 2H), 6.79 (d, *J* = 8.0 Hz, 1H), 3.23 (s, 3H), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 182.2, 158.7, 151.5, 150.7, 125.3, 124.4, 115.2, 110.8, 26.2, 22.9; HRMS (ESI): m/z [M + Na^+] calcd for $C_{10}H_9NO_2$+Na^+ 198.0531, found 198.0535.

*4.2.7. 5-methoxy-1-methylindoline-2,3-dione (**2g**)*: Yield 93%; red solid; mp. 175-176 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17-7.15 (m, 2H), 6.82 (d, *J* = 8.0 Hz, 1H), 3.81 (s, 3H), 3.23 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 183.8, 158.2, 156.6, 145.7, 124.0, 117.8, 110.9, 109.8, 55.5, 26.1; HRMS (ESI): m/z [M + Na^+] calcd for $C_{10}H_9NO_3$+Na^+ 214.0480, found 214.0482.

*4.2.8. 5-chloro-1-methylindoline-2,3-dione (**2h**)*: Yield 80%; red solid; mp. 171-173 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59-7.56 (m, 2H), 6.86 (d, *J* = 9.2 Hz, 1H), 3.26 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 181.5, 158.2, 152.2, 144.3, 126.4, 124.0, 115.2, 110.5, 26.5; HRMS (ESI): m/z [M + Na^+] calcd for $C_9H_6ClNO_2$+Na^+ 217.9985, found 217.9982.

*4.2.9. 5-bromo-1-methylindoline-2,3-dione (**2i**)*: Yield 82%; red solid; mp. 163-164 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74-7.70 (m, 2H), 6.82 (d, *J* = 8.0 Hz, 1H), 3.26 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 182.1, 157.4, 150.1, 140.6, 128.0, 118.5, 116.6, 111.6, 26.3; HRMS (ESI): m/z [M + Na^+] calcd for $C_9H_6BrNO_2$+Na^+ 261.9480, found 261.9478.

*4.2.10. 1-methyl-5-nitroindoline-2,3-dione (**2j**)*: Yield 71%; red solid; mp. 201-202 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74-7.71 (m, 2H), 6.82 (d, *J* = 8.0 Hz, 1H), 3.26 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 182.1, 157.5, 150.1, 140.6, 128.0, 118.5, 116.6, 111.6, 29.6; HRMS (ESI): m/z [M + Na^+] calcd for $C_9H_6N_2O_4$+Na^+ 229.0225, found 229.0228.

*4.2.11. 1,7-dimethylindoline-2,3-dione (**2k**)*: Yield 95%; red solid; mp. 162-164 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, *J* = 7.2 Hz, 1H), 7.33 (d, *J* = 7.6 Hz, 1H), 7.02-6.98 (m, 1H), 3.53 (s, 3H), 2.57 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 182.7, 158.0, 151.8, 150.5, 125.5, 124.5, 115.5, 110.9, 26.1, 22.9; HRMS (ESI): m/z [M + Na^+] calcd for $C_{10}H_9NO_2$+Na^+ 198.0531, found 198.0527.

*4.2.12. 1-ethyl-7-methylindoline-2,3-dione (**2l**)*: Yield 93%; red solid; mp. 188-190 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (d, *J* = 7.6 Hz, 1H), 7.34 (d, *J* = 7.2 Hz, 1H), 7.02-6.98 (m, 1H), 4.01 (q, *J* = 7.2 Hz, 2H), 2.54 (s, 3H), 1.34 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 184.1, 159.1, 148.4, 142.3, 123.7, 123.5, 121.4, 118.8, 36.9, 18.7, 14.5; HRMS (ESI): m/z [M + Na^+] calcd for $C_{11}H_{11}NO_2$+Na^+ 212.0687, found 212.0683.

*4.2.13. 1-ethyl-5-methylindoline-2,3-dione (**2m**)*: Yield 91%; red solid; mp. 74-76 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42-7.38 (m, 2H), 6.80 (d, *J* = 8.0 Hz, 1H), 3.77 (q, *J* = 7.2 Hz, 2H), 2.39 (s, 3H), 1.30 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 184.0, 159.2, 148.3, 142.5, 123.2, 123.1, 121.7, 118.2, 36.9, 18.7, 14.5; HRMS (ESI): m/z [M + Na^+] calcd for $C_{11}H_{11}NO_2$+Na^+ 212.0687, found 212.0685.

*4.2.14. 6-chloro-1-methylindoline-2,3-dione (**2n**)*: Yield 44.1%; red solid; mp. 177-178 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, *J* = 8.0 Hz, 1H), 7.12 (dd, J_1 = 1.6 Hz, J_2 = 8.0 Hz, 1H), 6.91 (d, *J* = 1.6 Hz, 1H), 3.27 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 181.7, 158.1, 152.4, 144.8, 126.3, 124.0, 115.7, 110.8, 26.4; HRMS (ESI): m/z [M + Na^+] calcd for $C_9H_6ClNO_2$+Na^+ 217.9985, found 217.9983.

*4.2.15. 4-chloro-1-methylindoline-2,3-dione (**2n'**)* Yield 36.8%; Red solid; mp. 192-195 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53-7.49 (m, 1H), 7.08 (d, *J* = 8.0 Hz, 1H), 6.80 (d, *J* = 7.6 Hz, 1H), 3.27 (s, 3H), 3.23 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 181.1, 158.3, 152.3, 144.5, 126.2, 124.0, 115.7, 110.5, 26.4; HRMS (ESI): m/z [M + Na^+] calcd for $C_9H_6ClNO_2$+Na^+ 217.9985, found 217.9981.

*4.2.16. 6-bromo-1-methylindoline-2,3-dione (**2o**)*: Yield 45.2%; red solid; mp. 118-119 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (d, *J* = 7.6 Hz, 1H), 7.30 (dd, J_1 = 1.6 Hz, J_2 = 8.0 Hz, 1H), 7.08 (d, *J* = 1.6 Hz, 1H), 3.25 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 182.3, 157.4, 150.2, 140.6, 128.1, 118.6, 116.5, 111.7, 26.3;HRMS (ESI): m/z [M + Na^+] calcd for $C_9H_6BrNO_2$+Na^+ 261.9480, found 261.9484.

*4.2.17. 4-bromo-1-methylindoline-2,3-dione (**2o'**)*: Yield 34.7%; Red solid; mp. 199-200 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.44-7.41 (m, 1H), 7.26 (d, *J* = 9.0 Hz, 1H), 6.85 (d, *J* = 7.8 Hz, 1H), 3.26 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 182.0, 157.2, 150.3, 140.3, 128.1, 118.5, 116.6, 111.2, 26.3; HRMS (ESI): m/z [M + Na^+] calcd for $C_9H_6BrNO_2$+Na^+ 261.9480, found 261.9483.

*4.2.18. 1,6-dimethylindoline-2,3-dione (**2p**)*: Yield 44.5%; red solid; mp. 150-151 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (d, *J* = 7.6 Hz, 1H), 6.93 (d, *J* = 7.6 Hz, 1H), 6.70 (s, 1H), 3.32 (s, 3H), 2.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 182.6, 158.9, 151.8, 150.7, 125.3, 124.4, 115.3, 110.7, 26.1, 22.9; HRMS (ESI): m/z [M + Na^+] calcd for $C_{10}H_9NO_2$+Na^+ 198.0531, found 198.0533.

*4.2.19. 1,4-dimethylindoline-2,3-dione (**2p'**)*: Yield 44.5%; Red solid; mp. 164-165 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46-7.42 (m, 1H), 6.90 (d, *J* = 7.6 Hz, 1H), 6.69 (d, *J* = 8.0 Hz, 1H), 3.24 (s, 3H), 2.57 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 182.8, 158.8, 151.8, 150.7, 125.4, 124.4, 115.5, 110.8, 26.1, 22.9; HRMS (ESI): m/z [M + Na^+] calcd for $C_{10}H_9NO_2$+Na^+ 198.0531, found 198.0528.

*4.2.20. 1-methyl-5-phenylindoline-2,3-dione (**2q**)*: Yield 90%; red solid; mp. 182-184 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85-7.82 (m, 2H), 7.54-7.51 (m, 2H), 7.47-7.44 (m, 2H), 7.40-7.37 (m, 1H), 6.98 (d, *J* = 8.0 Hz, 1H), 3.29 (s, 3H); ^{13}C NMR ($CDCl_3$,

150 MHz): δ 183.3, 160.1, 150.5, 139.3, 137.2, 136.5, 129.2, 127.9, 126.6, 123.5, 117.8, 110.5, 26.4; HRMS (ESI): m/z [M + Na^+] calcd for $C_{15}H_{11}NO_2$+Na^+ 260.0687, found 260.0689.

*4.2.21. 5-(4-fluorophenyl)-1-methylindoline-2,3-dione (**2r**)*: Yield 86%; red solid; mp. 136-139 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79-7.75 (m, 2H), 7.50-7.46 (m, 2H), 7.16-7.11 (m, 2H), 6.98 (d, *J* = 8.0 Hz, 1H), 3.29 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 183.3, 162.1 (d, J_{C-F} = 246.8 Hz), 158.2, 150.4, 136.6, 136.3, 135.1, 128.2 (d, J_{C-F} = 7.6 Hz), 123.5, 117.8, 115.9 (d, J_{C-F} = 21.4 Hz), 110.3, 26.3; HRMS (ESI): m/z [M + Na^+] calcd for $C_{15}H_{10}FNO_2$+Na^+ 278.0593, found 278.0597.

*4.2.22. 5-(4-chlorophenyl)-1-methylindoline-2,3-dione (**2s**)*: Yield 88%; red solid; mp. 180-182 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (dd, J_1 = 1.6 Hz, J_2 = 8.0 Hz, 1H), 7.60 (d, *J* = 1.6 Hz, 1H), 7.46-7.40 (m, 4H), 6.98 (d, *J* = 8.0 Hz, 1H), 3.29 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 183.2, 158.2, 150.6, 137.4, 136.6, 136.0, 134.0, 129.2, 127.8, 123.5, 117.8, 110.4, 26.4; HRMS (ESI): m/z [M + Na^+] calcd for $C_{15}H_{10}ClNO_2$+Na^+ 294.0298, found 294.0298.

*4.2.23. 5-(3-chlorophenyl)-1-methylindoline-2,3-dione (**2t**)*: Yield 85%; red solid; mp. 188-189 °C;; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81-7.78 (m, 2H), 7.49 (s, 1H), 7.39-7.35 (m, 3H), 6.98 (d, *J* = 8.0 Hz, 1H), 3.29 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 183.2, 158.2, 150.8, 140.7, 136.7, 135.9, 135.0, 130.3, 127.9, 126.7, 124.7, 123.7, 117.9, 110.4, 26.4; HRMS (ESI): m/z [M + Na^+] calcd for $C_{15}H_{10}ClNO_2$+Na^+ 294.0298, found 294.0294.

*4.2.24. 5-(3,5-dichlorophenyl)-1-methylindoline-2,3-dione (**2u**)*: Yield 84%; red solid; mp. 228-230 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (dd, J_1 = 2.0 Hz, J_2 = 8.4 Hz, 1H), 7.94 (d, *J* = 1.6 Hz, 1H), 7.79 (d, *J* = 1.2 Hz, 2H), 7.57 (d, *J* = 2.0 Hz, 1H), 7.24 (d, *J* = 8.4 Hz, 1H), 3.18 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 183.3, 158.6, 151.6, 142.3, 136.8, 134.9, 132.4, 127.0, 125.2, 122.9, 118.2, 111.3, 26.4; HRMS (ESI): m/z [M + Na^+] calcd for $C_{15}H_9C_{l2}NO_2$+Na^+ 327.9908, found 327.9911.

*4.2.25. 3-(1-methyl-2,3-dioxoindolin-5-yl)benzonitrile (**2v**)*: Yield 82%; red solid; mp. 236-237 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (s, 1H), 8.10-8.04 (m, 2H), 7.94 (d, *J* = 1.6 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.67-7.63 (m, 1H), 7.27 (d, *J* = 8.0 Hz, 1H), 3.20 (s, 3H); ^{13}C NMR (DMSO-d_6, 150 MHz): δ 183.4, 158.5, 151.4, 139.8, 136.6, 133.2, 131.2, 130.3, 130.1, 122.7, 118.9, 118.3, 112.3, 111.3, 26.4; HRMS (ESI): m/z [M + Na^+] calcd for $C_{16}H_{10}N_2O_2$+Na^+ 285.0640, found 285.0638.

*4.2.26. 1-methyl-5-(thiophen-2-yl)indoline-2,3-dione (**2w**)*: Yield 74%; red solid; mp. 206-208 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, *J* = 1.6 Hz, 1H), 7.82 (s, 1H), 7.30 (dd, J_1 = 0.8 Hz, J_2 = 4.0 Hz, 1H), 7.27 (d, *J* = 2.4 Hz, 1H), 7.10-7.08 (m, 1H), 6.92 (d, *J* = 8.8 Hz, 1H), 3.28 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 183.1, 158.1, 150.3, 142.3, 135.2, 130.9, 128.2, 125.3, 123.1, 122.4, 117.8, 103.1, 26.4; HRMS (ESI): m/z [M + Na^+] calcd for $C_{13}H_9NO_2S$+Na^+ 266.0252, found 266.0250.

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