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Ru(III)-mediated intramolecular *ortho*-C(sp^2)–H activation/oxidative acylation: one-pot synthesis of isatins from α-hydroxy amides

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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 three inhibitors,[2] antiparkinsonian drugs,[3] α-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.

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 $PdCl_2$ 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

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, 1 equiv 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 (Table 1, entries 9 and 13–17).

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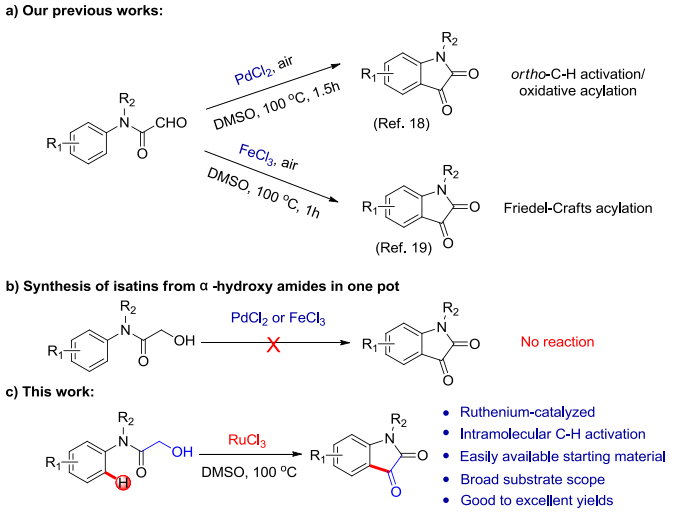
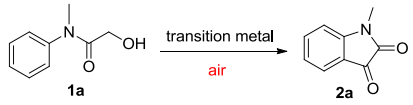


Scheme 1. Our previous reports on the synthesis of isatins.

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 5 h.

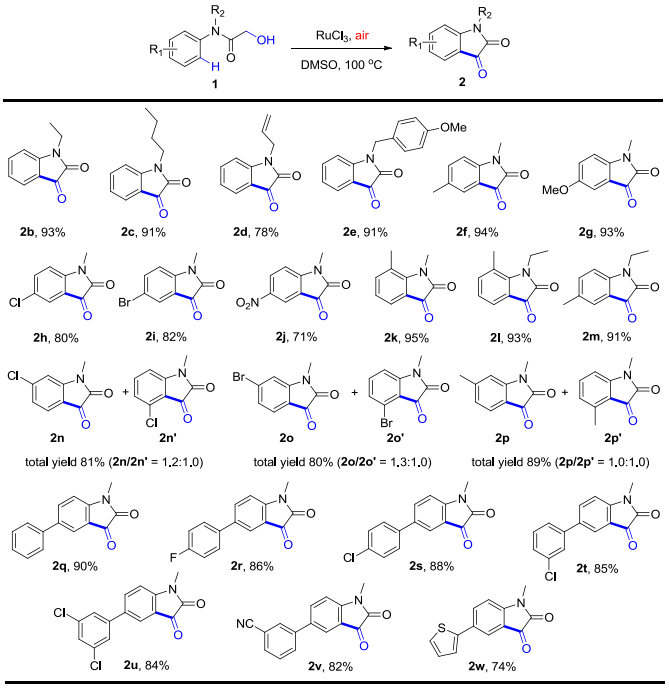
Table 1
Optimization of reaction conditions[a]



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]

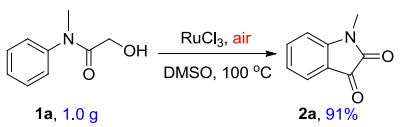
[a] Reaction conditions: **1a** (1 mmol) and transition-metal (1 mmol) in solvent (2 mL) under the corresponding temperature in air for 5 h.
[b] Isolated yield.
[c] $RuCl_3$ (0.5 mmol).
[d] $RuCl_3$ (2.0 mmol).
[e] In Ar.
[f] No reaction.

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 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 5 h, air.

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 3. Large-scale reaction.

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 20 min, 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