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Base-Promoted Cascade C−C Coupling/*N*-α-sp^{3}C−H Hydroxylation for the Regiospecific Synthesis of 3-Hydroxyisoindolinones

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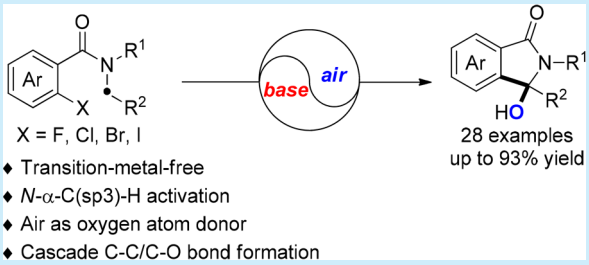
Supporting Information

ABSTRACT: A base-promoted cascade reaction for the regiospecific synthesis of substituted 3-hydroxyisoindolinones under transition-metal-free conditions is developed. The base-mediated C−C bond coupling and *N*-α-sp^{3}C−H bond hydroxylation are involved in this procedure, which features high regioselectivity, efficiency, and environmental friendliness. Various substituted 3-hydroxyisoindolinones, including some bioactive molecules, were provided in up to 93% yield for 28 examples.



The 3-hydroxyisoindolinone motif is common to an important class of N-heterocyles with potent biological activities. As illustrated in Figure 1, Chilenine,[1] Chlortalidone,[2]

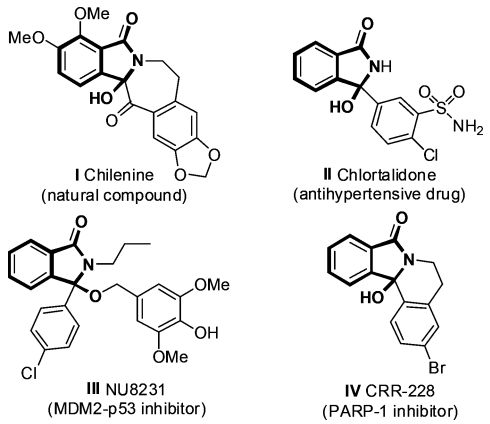


Figure 1. Biologically active compounds with a 3-hydroxyisoindolinone skeleton.

NU8231,[3] and CRR-228[4] are all biologically active ingredients that contain 3-hydroxyisoindolinone. Moreover, 3-hydroxyisoindolinones are also versatile building blocks for α-chiral amines[5] and other heterocycles.[6] Accordingly, the development of efficient approaches to 3-hydroxyisoindolinones has received considerable attention.

The addition of phthalimides with the corresponding organometallic reagents represents a conventional approach to 3-hydroxyisoindolinones,[7] but it suffers from harsh reaction conditions and poor regioselectivity. While the *o*-carboxybenzophenone-based synthesis developed by Hardcastle et al.[3a,b] allows the preparation of 3-hydroxyisoindolinone with diverse substitution, its versatility would be limited to those precursors which are conveniently prepared. In recent years, the transition-metal-catalyzed acylation/annulations of functional benzoic acid derivatives offer complementary strategies to 3-hydroxyisoindolinones with excellent regioselectivity and efficiency.[8] However, the expensive and complex trasition metal catalysts have to be completely removed from the product, especially in the pharmaceutical industry. Therefore, a practical and efficient method for the synthesis of 3-hydroxyisoindolinones under mild conditions is still required.

The earth-abundant alkali metal salts have been widely applied in organic synthesis since they are inexpensive, of low toxicity, and easily removable. Recently, the alkali metal salts mediated coupling reactions have been rapidly developed (Scheme 1a).[9] For C−C bond coupling, the base-promoted cyclization of benzoic amide derivatives to isoindolinones has been realized by Clayden,[10] Kalyani,[11] and Kumar.[12] On the other hand, alkali metal salts catalyzed/promoted α-hydroxylation of carbonyl compounds with molecular oxygen (O_2) as the oxygen source has also been achieved by Jiao[13] and Kim,[14] providing tertiary α-hydroxycarbonyl compounds in an environmentally friendly manner (Scheme 1b). However, with more classical organic substrates, the alkali metal salts mediated *N*-α-sp^{3}C−H hydroxylation with O_2 as the oxygen source remains unprecedented. Here, we present a transition-metal-free KOtBu-promoted cascade C−C bond coupling/*N*-α-sp^{3}C−H bond hydroxylation for the regiospecific synthesis of substituted 3-hydroxyisoindolinones (Scheme 1c). This protocol uses readily available *o*-halobenzamides (including F, Cl, Br, I) as substrates and O_2 (in air) as an oxygen source; it features high regioselectivity, efficiency, and environmental friendliness. Moreover, the isoindolinone/3-hydroxyisoindolinone products are tunable by choosing appropriate reaction conditions (under N_2 or air).

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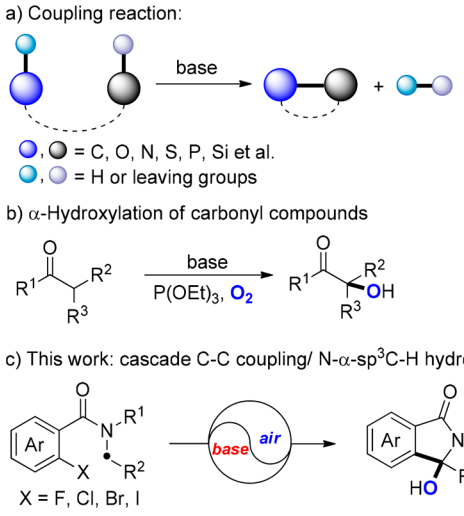
Scheme 1. Alkali-Metal-Mediated Reactions

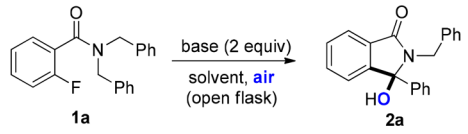


Initially, *N*,*N*-dibenzyl-2-fluorobenzamide **1a** was chosen as a model substrate to begin our exploration of the reaction conditions. To our delight, the desired product **2a** was successfully obtained in a 75% yield in the DMSO/NaOH system after 6 h (entry 1). Good to excellent yields were achieved in the presence of other strong bases, such as KOH, NaOtBu, and KOtBu (entries 2−4). The combination of KOtBu/DMSO was found to be the most effective (yield of **2a** being 61%, entry 4). In contrast, **1a** remained unreactive when relatively weak bases, such as Cs_2CO_3 and K_3PO_4, and an organic base (DBU) were used (entries 5−7). The solvent screening experiments were subsequently carried out, and DMSO was determined to be optimal (entries 4, 8−12). Increasing or decreasing the reaction temperature led to a lower yield (entries 13, 14). A 2 equiv loading of KOtBu was crucial for a complete conversion. When the loading of KOtBu was decreased to 1 equiv, the yield of the product was decreased to 73% (entry 15). An O_2 atmosphere did increase the reaction rate but provided the desired product in a decreased yield (entry 16). Finally, the standard reaction conditions were identified as follows: 2 equiv of KOtBu as the additive and DMSO as the solvent at 100 °C for 2 h.

With the optimized reaction conditions (entry 4, Table 1) in hand, the generality and substrate scope of this transformation were then investigated. The effect of the X substituent on the formation of 3-hydroxyisoindolinones **2** was first investigated. As illustrated in Scheme 2, the yield of the final product was affected when the fluoro group was changed to a chloro, bromo, or iodo group. The fluoro-, chloro-, bromo-, and iodo-substituted substrates gave 3-hydroxyisoindolinone **2a** in 93%, 83%, 76%, and 71% yield, respectively. These observations show this transformation may involve a nucleophilic substitution reaction where the leaving group ability of the halide shows a clear trend (F > Cl > Br > I).[15] The steric hindrance on the aryl ring did not influence this reaction; 3-, 4-, and 5-mehtyl substituted substrates all gave the desired products in excellent yields (89−92%, **2b**−**2d**). Halogens, such as Cl and Br, were also tolerated, and the corresponding products were given in acceptable yields (65% and 51%, **2e**−**2f**). Picolinamides were also suitable substrates and gave the hydroxyl *N*-heterocycles in good yields (69−72%, **2g**−**2h**).

The substituents on N atom were also explored. When R^2 was an aryl group, R^1 could be various alkyl groups, such as methyl, ethyl, *n*-propyl, *i*-propyl, and *n*-butyl, and the 2-alkyl-3-hydroxyisoindolinones were provided in 55−93% yields (**2i**−

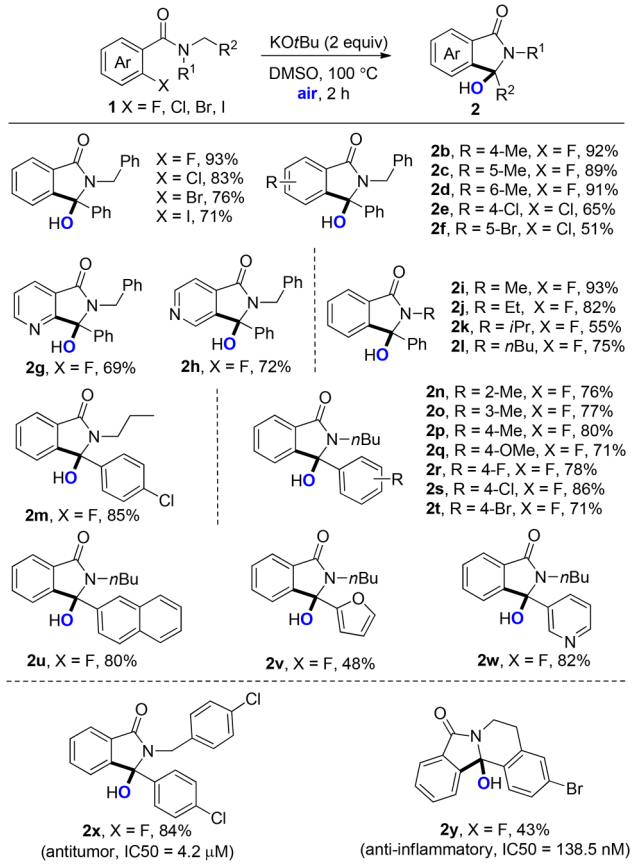
Table 1. Optimization of Reaction Conditions[a]



entry	base	solvent	temp (°C)	*t* (h)	yield (%)[b]
1	NaOH	DMSO	100	6	75
2	KOH	DMSO	100	4	88
3	NaOtBu	DMSO	100	3	91
4	**KOtBu**	**DMSO**	**100**	**2**	**93**
5	K_3PO_4	DMSO	100	12	N.R.
6	Cs_2CO_3	DMSO	100	12	N.R.
7	DBU	DMSO	100	12	N.R.
8	KOtBu	DMF	100	12	23
9	KOtBu	NMP	100	2	88
10	KOtBu	EtOH	100	12	N.R.
11	KOtBu	THF	100	12	N.R.
12	KOtBu	toluene	100	12	N.R.
13	KOtBu	DMSO	110	2	92
14	KOtBu	DMSO	90	2	88
15[c]	KOtBu	DMSO	100	12	73
16[d]	KOtBu	DMSO	100	1	48

[a]Reaction conditions: **1a** (0.2 mmol), base (0.4 mmol), in 2 mL of solvent under an air atmosphere. [b]Isolated yields. N.R. = No Reaction. [c]0.2 mmol of base was used. [d]Under an O_2 atmosphere. DMF = *N*,*N*-dimethylformamide. DMSO = dimethyl sulfoxide. NMP = *N*-methyl-2-pyrrolidone. THF = tetrahydrofuran.

Scheme 2. Substrate Scope



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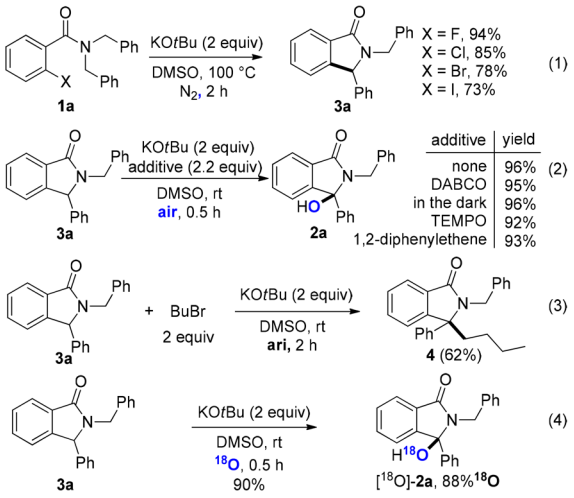
2m). In particular, 3-hydroxyisoindolinone **2m**, the precursor of NU8321[3a] (a MDM2-p53 inhibitor, **III**, Scheme 1), could be efficiently prepared from a readily available amide substrate. When R^1 was an aryl group (phenyl for example), only the corresponding amine from deacylation was obtained. On the other hand, when R^1 was an alkyl group, R^2 could be various aryl groups. Substrates with an electron-donating or -withdrawing group all proceeded efficiently (**2n**−**2t**, 71−86%). Moreover, the steric hindrance did not influence this reaction, as *ortho*-, *meta*-, and *para*- methyl substituted substrates gave similar yields (76%, 77%, and 80%). The fused aryl and heteroaryl groups, including naphthyl, furanyl, and pyridyl, were also suitable, and the desired 3-hydroxyisoindolinones were offered in 48−82% yields. However, when R^1 and R^2 were H or alkyl groups, this reaction could not occur.

3-Hydroxyisoindolinones with potent biological activities could also be prepared in this reaction. 2-(4-Chlorobenzyl)-3-(4-chlorophenyl)-3-hydroxyisoindolin-1-one **2x**, a MDM2-p53 inhibitor with antitumor activity (IC50 = 4.2 μM),[3b] was prepared in an 84% yield in one step. CRR-228 **2y** (**IV**, Scheme 1), a PARP-1 inhibitor with anti-inflammatory activity (IC50 = 138.5 nM),[4] could also be provided in a 43% yield in one step.

To gain an understanding of the mechanism, some control experiments were carried out. Under a N_2 atmosphere, the crucial intermediate, isoindolinone **3a**, was exclusively obtained without any hydroxylation product. The fluoro-, chloro-, bromo-, and iodo-substituted substrates gave isoindolinone **3a** in decreasing yields (Scheme 3, eq 1), which was inconsistent

Scheme 3. Mechanism Exploration

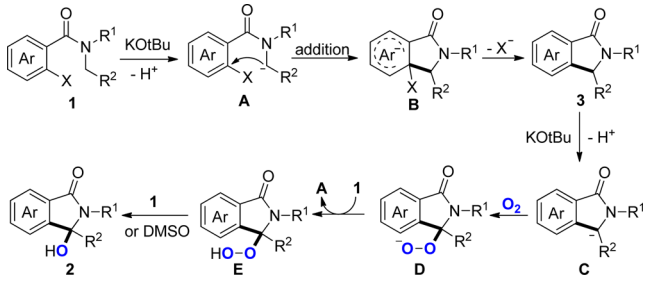


with a typical nucleophilic substitution reaction (F > Cl > Br > I).[15] Hence, it may be an S_NAr reaction for the C−C bond coupling to the isoindolinone intermediates. Under aerobic conditions, the base-promoted hydroxylation of **3a** could rapidly proceed and form 3-hydroxyisoindolinone **2a** in an almost quantitative yield (96%). When DABCO (1,4-diazabicyclo[2,2,2]octane, a singlet oxygen inhibitor[16]) was added to the reaction, the reaction was not inhibited, allowing **2a** to be isolated in 95% yield. Furthermore, the reaction also proceeded well in the dark (eq 2). As a result, the participation of singlet molecular oxygen could be excluded. The radical inhibitor, 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) or 1,1-diphenylethylene, also did not inhibit the reaction (eq 2), indicating that a radical mechanism may not be involved in this reaction.

On the other hand, in the presence of an electrophile (BuBr), the hydroxylation was suppressed, and the substitution product **4** was isolated in 62% yield (eq 3). These observations suggested that this KOtBu mediated hydroxylation might be an anion-initiated reaction. Finally, the ^{18}O labeling experiment proved that the oxygen atom in the hydroxy group originated from molecular oxygen (eq 4).[17]

On the basis of the aforementioned observations, a tentative reaction mechanism was proposed, as depicted in Scheme 4.

Scheme 4. Proposed Reaction Mechanism



Initially, substrate **1** undergoes a KOtBu-initiated deprotonation to produce carbanion **A**. Subsequently, a nucleophilic aromatic substitution (S_NAr) reaction gives the isoindolinone intermediate **3**. Deprotonation of isoindolinone **3** produces the corresponding carbanion **C**. Carbanion **C** reacts with O_2 and then extracts a proton from substrate **1** to generate the superoxide **E**. Finally, the 3-hydroxyisoindolinone product **2** is formed by the reduction of **E** by substrate **1** or DMSO.[14,18]

In conclusion, an efficient base-promoted cascade approach to substituted 3-hydroxyisoindolinones from readily available *o*-halo arylamide has been developed. A novel cascade C−C coupling/*N*-α-sp^3C−H hydroxylation was applied in this reaction. This protocol only required 2 equiv of KOtBu as an additive and used environmentally benign O_2 (in air) as an oxygen source, which allows this process to be environmentally friendly. 3-Hydroxyisoindolinone derivatives with various biological activities may be prepared by this approach without the concern of potential transition metal contamination.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02442.

Experimental procedures, compound characterization (PDF)

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Notes

The authors declare no competing financial interest.

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(17) When **1a** was used as reaction substrate, operating in 100 °C under $^{18}O_2$, the yield of [^{18}O]-**2a** was 47%.

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