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Isoquinolone Synthesis through S_NAr Reaction of 2-Halobenzonitriles with Ketones Followed by Cyclization

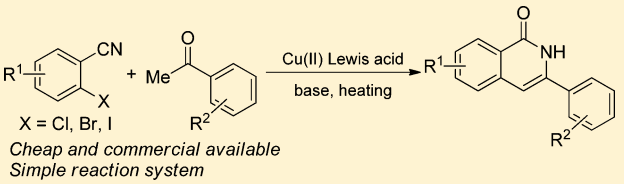
Muhammad Shareef Mayo,[†] Xiaoqiang Yu,*[,†] Xiujuan Feng,[†] Yoshinori Yamamoto,[†,‡] and Ming Bao*[,†]

[†]State Key Laboratory of Fine Chemicals, Dalian University of Technology, Dalian 116023, China

[‡]WPI-AIMR (WPI-Advanced Institute for Materials Research), Tohoku University, Sendai 980-8577, Japan

Supporting Information

ABSTRACT: An efficient method for the synthesis of isoquinolones through base KO^{t}Bu-promoted S_NAr reaction of 2-halobenzonitriles with ketones followed by Lewis acid Cu(OAc)$_2$-catalyzed cyclization is described. Isoquinolone derivatives were obtained in satisfactory to good yields.



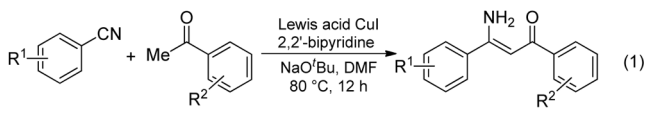
INTRODUCTION

The isoquinolone structural motif has attracted considerable attention in organic synthesis because of its presence in many natural products[1] and its incredible pharmacological and biological activities.[2] Moreover, the compounds of this class are well-known for their antiulcer, antidepressant, analgesic, and antihypertensive activities; several of these compounds are also employed for the treatment of human brain cells and stomach tumors.[3] Therefore, numerous approaches have been developed over the past years for the synthesis of isoquinolone derivatives; these approaches include the classical methods[4−10] and the recently reported transition-metal catalysis.[11−15] However, these methodologies have drawbacks, such as the use of special or noncommercial starting materials, expensive catalysts, multiple-step procedures, photostimulation, and harsh reaction conditions.

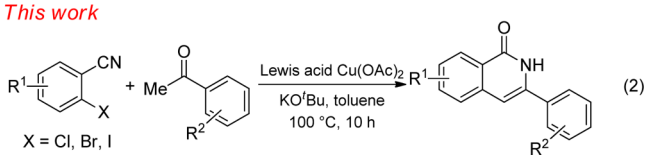
During the course of our recent studies on enaminone synthesis from aromatic nitriles and ketones (Scheme 1, eq 1),[16] when 2-bromobenzonitrile was treated with acetophenone in toluene, a cyclized product, 3-arylisoquinolin-1(2*H*)-one, was observed (Scheme 1, eq 2). Given this finding, systematic studies were conducted to optimize the conditions for this reaction, and the results are summarized in Table 1. In this study, a new method for the synthesis of isoquinolone derivatives is reported.

Scheme 1. Different Reaction Pathways of Benzonitriles with Ketones

Our previous work



This work



RESULTS AND DISCUSSION

Initially, the reaction of 2-bromoobenzonitrile (**1a**) with acetophenone (**2a**) was conducted in the absence of Lewis acid catalyst. Fortunately, the desired product, 3-phenylisoquinolin-1(2*H*)-one (**3a**), was observed though the yield was unsatisfactory (entry 1). The failure in yield improvement either through base loading or heating required us to add Lewis acid catalyst. Therefore, various Lewis acid catalysts, such as TiO_2, Cu_2O, $FeCl_3$, $ZnCl_2$, CuI, CuCl, and Cu(OAc)$_2$, were assessed in the presence of KO^{t}Bu in toluene at 100 °C (entries 2−8). Of these, Cu(OAc)$_2$ (entry 8) exhibited the best catalytic activity. Thus, different bases were then examined using Cu(OAc)$_2$ as a Lewis acid catalyst. Among the inorganic bases, KOH resulted in low yield, and Cs_2CO_3 failed to produce the desired product (entries 9 and 10). Weak organic bases such as Et_3N and pyridine also failed to produce the desired product (entries 11 and 12). On the basis of these results, a strong base is the key for this reaction. Among the screening solvents (entries 13−17), none was comparable to toluene. Finally, the loading of base KO^{t}Bu and Lewis acid catalyst Cu(OAc)$_2$ as well as the reaction temperature were optimized (entries 18−20). A set of optimum conditions [Cu(OAc)$_2$ as Lewis acid catalyst, KO^{t}Bu as base in toluene at 100 °C for 10 h] was selected to explore the scope of the reaction.

2-Bromobenzonitrile was used as a starting material to determine the scope of ketone substrate. The results are shown in Table 2. The desired product **3a** was isolated in 82% yield when **1a** was treated with **2a** (entry 1). Excellent yields were obtained when ketones **2b** and **2c**, having electron-donating groups (Me and MeO, respectively) at *para*-position, were treated with **1a** under optimum conditions (entries 2 and 3;

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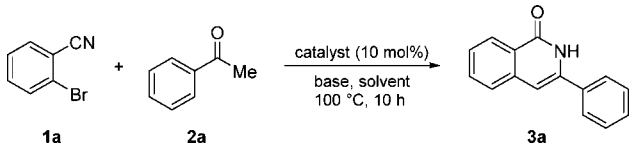
Table 1. Reaction Condition Screening[a]



1a 2a 3a

entry	catalyst	base	solvent	yield (%)[b]
1	none	KO^{t}Bu	toluene	40[c]
2	TiO_2	KO^{t}Bu	toluene	54
3	Cu_2O	KO^{t}Bu	toluene	38
4	$FeCl_3$	KO^{t}Bu	toluene	43
5	$ZnCl_2$	KO^{t}Bu	toluene	34
6	CuI	KO^{t}Bu	toluene	67
7	CuCl	KO^{t}Bu	toluene	72
8	$Cu(OAc)_2$	KO^{t}Bu	toluene	88
9	$Cu(OAc)_2$	KOH	toluene	30
10	$Cu(OAc)_2$	Cs_2CO_3	toluene	NR[d]
11	$Cu(OAc)_2$	pyridine	toluene	NR[d]
12	$Cu(OAc)_2$	Et_3N	toluene	NR[d]
13	$Cu(OAc)_2$	KO^{t}Bu	dioxane	56
14	$Cu(OAc)_2$	KO^{t}Bu	EtOH	48
15	$Cu(OAc)_2$	KO^{t}Bu	CH_3CN	trace
16	$Cu(OAc)_2$	KO^{t}Bu	DMF	35
17	$Cu(OAc)_2$	KO^{t}Bu	DCE	NR[d]
18[e]	$Cu(OAc)_2$	KO^{t}Bu	toluene	49
19[f]	$Cu(OAc)_2$	KO^{t}Bu	toluene	67
20[g]	$Cu(OAc)_2$	KO^{t}Bu	toluene	79

[a]Reaction conditions: 2-bromobenzonitrile (**1a**, 0.5 mmol, 90.48 mg), acetophenone (**2a**, 120 mg, 1.0 mmol), Lewis acid catalyst (10 mol %), and base (1.5 mmol) in 4.0 mL of solvent at 100 °C for 10 h. [b]^{1}H NMR yield; 4-bromophenylacetonitrile was used as an internal standard. [c]The product **3a** was separated in 35% yield. [d]No reaction. [e]1.0 mmol of KO^{t}Bu was used. [f]Reaction was performed at 80 °C. [g]5 mol % of $Cu(OAc)_2$ was used.

85% and 88% yields, respectively). However, a relatively low yield (65%) of product **3d** was observed when 2-methylacetophenone (**2d**) was treated with **1a** (entry 4). This low yield was attributed to the steric hindrance created by the *ortho*-methyl group in **2d**. The reactions of ketone substrates **2e**−**2g** bearing an electron-withdrawing group (F or CF_3) provided the corresponding products **3e**−**3g** in low to moderate yields (entries 5−7, 32%−76%). Owing to the instability of the iodide compound, the isoquinolone product **3h** could be only separated in 50% yield (entry 8) from the reaction of ketone substrate, 1-(4-iodophenyl)ethan-1-one (**2h**). Propiophenone (**2i**) exhibited low reactivity to produce the isoquinolone product **3i** in low yield (entry 9, 34%). The reactions of ketone substrates **2j** and **2k** that have a naphthalene ring proceeded smoothly to provide the corresponding products **3j** and **3k** in moderate yields (entries 10 and 11; 67% and 70%, respectively). Finally, aliphatic ketone substrates **2l** and **2m** were examined. Isoquinolone products **3l** and **3m** were obtained in relatively low yields (entries 12 and 13; 60% and 25%, respectively).

To investigate the effect of different halogen atoms at *ortho*-position and different substituents linked to 2-bromobenzonitrile, we examined the aromatic nitriles **1b**−**1e** with aromatic ketones **2a**, **2c**, and **2g**. The results are shown in Table 3. When 2-chlorobenzonitrile (**1b**) and 2-iodobenzonitrile (**1c**) were treated with **2a**, the desired product **2a** was obtained in moderate yield (entries 1 and 2, 53% or 69%) compared with that of **1a**. The relatively low yield could be attributed to the strength of the C−Cl bond and the instability of C−I bond. The reactions of 4-methyl-2-bromobenzonitrile (**1d**) and 5-chloro-2-bromobenzonitrile (**1e**) with **2a** also proceeded smoothly to produce the desired products 6-methyl-3-phenylisoquinolin-1(2*H*)-one (**3n**) and 7-chloro-3-phenylisoquinolin-1(2*H*)-one (**3o**) in 72% and 66% yields, respectively (entries 3 and 4). Finally, the nitrile substrates **1b** and **1c** were examined with 4-methoxyacetophenone (**2c**) and 4-trifluoromethylacetophenone (**2g**) separately to afford the desired products **3c** and **3g** in low to moderate yields (entries 5−8, 47%−55%). These results indicate that the reaction yield depended on the type of halogen at C2 of the nitrile substrates. Isoquinolone products could be obtained in relatively high yield from the reaction of 2-bromobenzonitriles. All the new products were identified through their NMR and HRMS data as well as IR spectra. All the known products were identified through their NMR data and the literature data. The product **3a** was further identified by determining its X-ray structure.[17]

On the basis of the fact that the isoquinolone **3a** can be obtained in 35% isolated yield even in the absence of Lewis acid (Table 1, entry 1), a possible reaction mechanism is shown in Scheme 2. The nucleophilic substitution reaction of **1a** with acetophenone under basic conditions could occur via an addition−elimination route to produce intermediate **5** (S_NAr).[18] Intermediate **5** could undergo electrocyclization in the presence of Lewis acid catalyst Cu(II) and base KO^{t}Bu via enolate intermediate **6** to produce intermediate **7**. Protonation of intermediate **7** with HO^{t}Bu, generated in the initial step, could produce intermediate **8**, which could convert to the desired product **3a** under basic conditions.[19]

CONCLUSION

In summary, an efficient method for the synthesis of isoquinolones has been developed under basic conditions with affordable and simple starting materials in a single step. The wide availability of the starting materials, affordability of the Lewis acid catalyst, the mild reaction conditions, and experimental simplicity could make the present methodology highly useful in organic chemistry.

EXPERIMENTAL SECTION

General Information. All solvents were purified by standard techniques. NMR spectra were run in $CDCl_3$ or DMSO-d_6 at the following frequencies: proton (^{1}H, 400 MHz), carbon (^{13}C, 100 MHz). The chemical shifts are reported in parts per million (ppm) downfield (δ) from TMS, and the coupling constants J are given in hertz (Hz). The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. The starting materials **1a**−**1e** and **2a**−**2m** are commercially available.

Representative Procedure for the Synthesis of Isoquinolones. An oven-dried reaction tube (25 mL) with a magnetic stir bar was charged with $Cu(OAc)_2$ (9.1 mg, 0.1 mmol), KO^{t}Bu (168.0 mg, 1.5 mmol), 2-bromobenzonitrile (**1a**, 90.5 mg, 0.5 mmol), acetophenone (**2a**, 120.0 mg, 1.0 mmol), and toluene (4.0 mL). The reaction mixture was sealed and stirred at 100 °C for 10 h. The solvent was removed under reduced pressure and the residue obtained was purified via silica gel chromatography (eluent: ethyl acetate/petroleum ether = 1:2) to afford 3-phenylisoquinolin-1(2*H*)-one (**3a**) as a white solid (90.7 mg, 82% yield).

3-Phenylisoquinolin-1(2H)-one (3a).[15a] White solid (90.7 mg, 82% yield), mp 204−205 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79 (s, 1H), 7.45−7.55 (m, 4H), 7.60 (d, J = 7.6 Hz, 1H), 7.65−7.69 (m, 1H), 7.75−7.78 (m, 2H), 8.41 (d, J = 8.0 Hz, 1H), 10.44 (s, 1H); ^{13}C NMR

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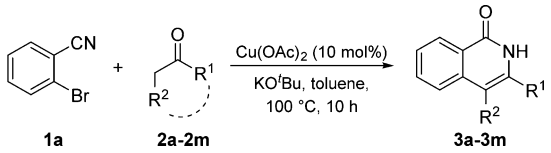
Table 2. Cyclization of 2-Bromobenzonitrile with Various Ketones[a]



1a 2a-2m 3a-3m

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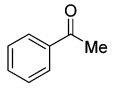
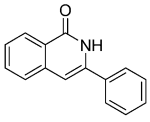
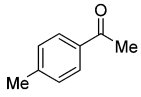
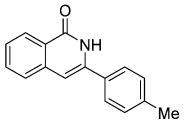
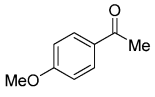
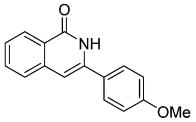
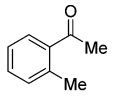
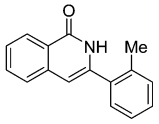
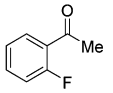
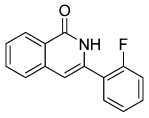
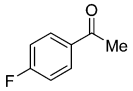
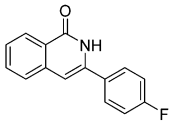
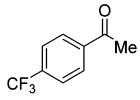
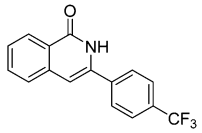
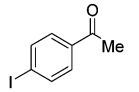
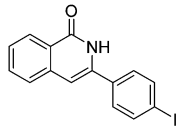
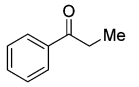
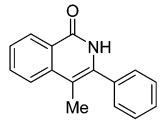
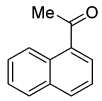
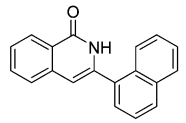
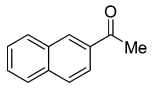
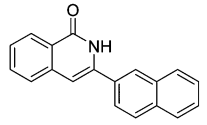
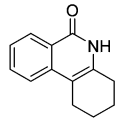
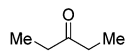
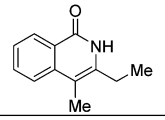
1			82
2			85
3			88
4			65
5			32
6			65
7			76
8			50
9			34
10			67
11			70
12			60
13			25

[a]Reaction conditions: 2-bromobenzonitrile (**1a**, 0.5 mmol, 90.48 mg), ketone (**2**, 1.0 mmol), $Cu(OAc)_2$ (9.1 mg, 10 mol %), and KO^tBu (1.5 mmol, 168.0 mg) in toluene (4.0 mL) at 100 °C for 10 h. [b]Isolated yield.

(100 MHz, $CDCl_3$) δ 104.4, 125.0, 126.2, 126.6, 126.7, 127.5, 129.2, 129.6, 132.9, 134.3, 138.3, 139.6, 164.1.

3-(p-Tolyl)isoquinolin-1(2H)-one ***(3b).***[14a] White solid (99.9 mg, 85% yield), mp 224−226 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43 (s, 3H), 6.76 (s, 1H), 7.32 (d, J = 8.0 Hz, 2H), 7.46−7.50 (m, 1H), 7.59 (d, J = 7.7 Hz, 1H), 7.64−7.67 (m, 3H), 8.41 (d, J = 8.0 Hz, 1H), 10.23 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 103.8, 124.9, 126.0, 126.4, 127.5, 129.9, 131.4, 132.8, 138.4, 139.6, 139.8, 164.0.

3-(4-Methoxyphenyl)isoquinolin-1(2H)-one ***(3c).***[14a] White solid (110.5 mg, 88% yield), mp 237−239 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.07 (s, 3H), 7.10 (s, 1H), 7.30 (d, J = 8.6 Hz, 2H), 7.68−7.72 (m, 1H), 7.92−8.02 (m, 4H), 8.44 (d, J = 8.0 Hz, 1H), 11.71 (s, 1H).

3-(o-Tolyl)isoquinolin-1(2H)-one ***(3d).***[14a] White solid (76.4 mg, 65% yield), mp 182−184 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.31 (s, 3H), 6.48 (s, 1H), 7.26−7.38 (m, 4H), 7.48 (dd, J = 7.8, 6.8 Hz, 1H), 7.65−7.72 (m, 2H), 8.21 (d, J = 8.0 Hz, 1H), 11.44 (s, 1H).

3-(2-Fluorophenyl)isoquinolin-1(2H)-one ***(3e).*** Light yellow solid (38.5 mg, 32% yield), mp 243−245 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.72 (s, 1H), 7.30−7.37 (m, 2H), 7.49−7.54 (m, 2H), 7.60−7.64 (m, 1H), 7.69−7.74 (m, 2H), 8.21 (d, J = 8.9 Hz, 1H), 11.53 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 106.4, 116.4, 116.7, 125.2, 125.5, 127.1, 127.2, 127.3, 131.1, 133.1, 135.7, 138.0, 162.7; IR (KBr) 3426, 2926, 1662, 1488, 1350, 1152, 1112, 941, 873, 834, 747 cm^{-1}; HRMS (ES) Calcd for $C_{15}H_{11}FNO$: 240.0825 $[M + H]^+$; found: 240.0824.

3-(4-Fluorophenyl)isoquinolin-1(2H)-one ***(3f).***[14a] White solid (77.7 mg, 65% yield), mp 222−223 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.89 (s, 1H), 7.33 (dd, J = 8.4, 8.4 Hz, 2H), 7.48−7.50 (m, 1H), 7.68−7.73 (m, 2H), 7.82−7.85 (m, 2H), 8.19 (d, J = 7.9 Hz, 1H), 11.55 (s, 1H).

3-(4-(Trifluoromethyl)phenyl)isoquinolin-1(2H)-one ***(3g).***[14a] Light yellow solid (109.9 mg, 76% yield), mp 270−272 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.05 (s, 1H), 7.52−7.56 (m, 1H), 7.76 (d, J = 3.7 Hz, 2H), 7.86 (d, J = 8.4 Hz, 2H), 8.02 (d, J = 8.2 Hz, 2H), 8.24 (d, J = 8.0 Hz, 1H), 11.70 (s, 1H).

3-(4-Iodophenyl)isoquinolin-1(2H)-one ***(3h).***[14a] Light yellow solid (86.8 mg, 50% yield), mp 261−263 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.94 (s, 1H), 7.48−7. 52 (m, 1H), 7.59 (d, J = 8.6 Hz, 2H), 7.71−7.73 (m, 2H), 7.86 (d, J = 8.6 Hz, 2H), 8.20 (d, J = 7.7 Hz, 1H), 11.56 (s, 1H).

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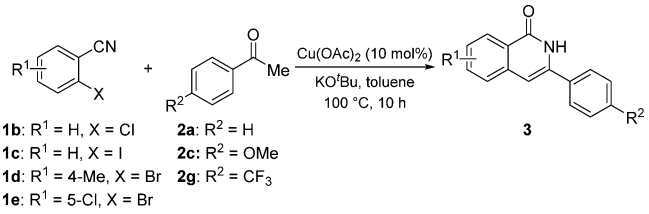
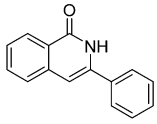
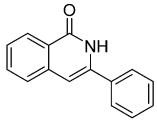
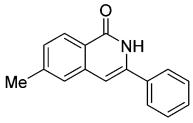
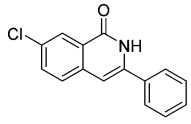
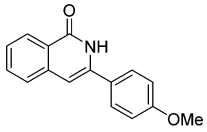
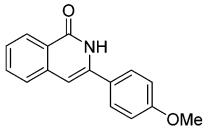
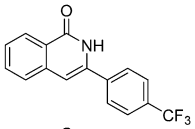
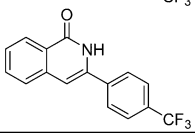
Table 3. Cyclization of Various 2-Halobenzonitriles with Aromatic Ketones 2a, 2c, and 2g[a]



1b: R^1 = H, X = Cl **2a**: R^2 = H
1c: R^1 = H, X = I **2c**: R^2 = OMe
1d: R^1 = 4-Me, X = Br **2g**: R^2 = CF_3
1e: R^1 = 5-Cl, X = Br

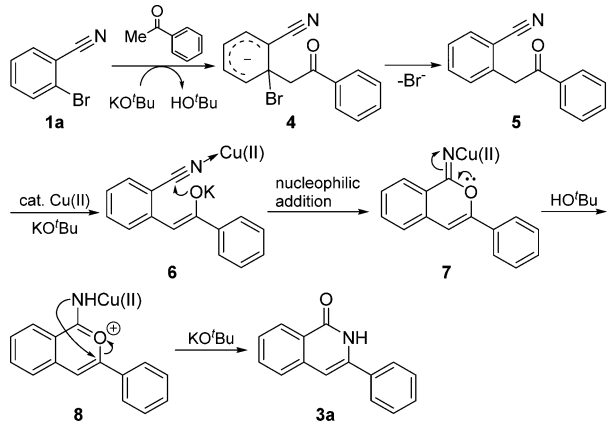
entry	nitrile 1	ketone 2	product 3		yield (%)[b]
1	**1b**	**2a**		**3a**	53
2	**1c**	**2a**		**3a**	69
3	**1d**	**2a**		**3n**	72
4	**1e**	**2a**		**3o**	66
5	**1b**	**2c**		**3c**	47
6	**1c**	**2c**		**3c**	48
7	**1b**	**2g**		**3g**	55
8	**1c**	**2g**		**3g**	55

[a]Reaction conditions: 2-halobenzonitriles (**1b**–**1e**, 0.5 mmol), ketones (**2a**, **2c**, and **2g**, 1.0 mmol), $Cu(OAc)_2$ (10 mol %, 9.1 mg), and KO^{t}Bu (1.5 mmol, 168.0 mg) in toluene (4.0 mL) at 100 °C for 10 h. [b]Isolated yield.

4-Methyl-3-phenylisoquinolin-1(2H)-one ***(3i).***[14a] White solid (40.0 mg, 34% yield), mp 186–188 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.27 (s, 3H), 7.45–7.55 (m, 6H), 7.76 (dd, J = 1.1, 4.2 Hz, 2H), 8.46 (d, J = 8.0 Hz, 1H), 8.83 (s, 1H).

3-(Naphthalen-1-yl)isoquinolin-1(2H)-one ***(3j).***[14a] White solid (90.8 mg, 67% yield), mp 244–246 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.66 (s, 1H), 7.53–7.63 (m, 5H), 7.69–7.75 (m, 2H), 7.92 (dd, J = 1.8, 8.5 Hz, 1H), 8.01–8.06 (m, 2H), 8.29 (d, J = 8.0 Hz, 1H), 11.68 (s, 1H).

Scheme 2. A Proposed Mechanism



3-(Naphthalen-2-yl)isoquinolin-1(2H)-one ***(3k).***[14a] White solid (95.0 mg, 70% yield), mp 236–238 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.10 (s, 1H), 7.49–7.53 (m, 1H), 7.56–7.61 (m, 2H), 7.74 (dd, J = 6.6, 8.0 Hz, 2H), 7.91–8.04 (m, 4H), 8.24 (d, J = 8.0 Hz, 1H), 8.42 (s, 1H), 11.64 (s, 1H).

1,3,4,5-Tetrahydrophenanthridin-6(2H)-one ***(3l).***[14a] White solid (59.5 mg, 60% yield), mp 244–247 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.74–1.79 (m, 4H), 2.49–2.51 (m, 4H), 7.41–7.45 (m, 1H), 7.61 (d, J = 8.0 Hz, 1H), 7.68–7.72 (m, 1H), 8.18 (dd, J = 8.0, 1.0 Hz, 1H), 11.03 (s, 1H).

3-Ethyl-4-methylisoquinolin-1(2H)-one ***(3m).***[20] White solid (23.4 mg, 25% yield), mp 151–152 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (t, J = 7.6 Hz, 3H), 2.28 (s, 3H), 2.74 (q, J = 7.6 Hz, 2H), 7.43–7.47 (m, 1H), 7.66–7.71 (m, 2H), 8.45 (d, J = 7.8 Hz, 1H), 10.66 (s, 1H).

6-Methyl-3-phenylisoquinolin-1(2H)-one ***(3n).***[14a] White solid (84.6 mg, 72% yield), mp 211–213 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.50 (s, 3H), 6.72 (s, 1H), 7.30 (dd, J = 1.1, 8.2 Hz, 1H), 7.38 (s, 1H), 7.44–7.48 (m, 1H), 7.50–7.54 (m, 2H), 7.75 (dd, J = 1.5, 7.0 Hz, 2H), 8.29 (d, J = 8.2 Hz, 1H), 10.28 (s, 1H).

7-Chloro-3-phenylisoquinolin-1(2H)-one ***(3o).*** White solid (84.2 mg, 66% yield), mp 258–260 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.10 (s, 1H), 6.61–6.67 (m, 3H), 6.90–6.94 (m, 4H), 7.28 (dd, J = 0.8, 1.0 Hz, 1H), 10.86 (s, 1H)); ^{13}C NMR (100 MHz, DMSO-d_6) δ 103.2, 126.1, 126.5, 127.2, 129.2, 129.5, 129.9, 131.3, 133.2, 134.1, 137.1, 141.1, 162.2; IR (KBr) 3432, 1656, 1469, 1385, 1348, 1127, 903, 872, 842, 763 cm^{-1}; HRMS (ES) Calcd for $C_{15}H_{11}ClNO$: 256.0529 [M + H]$^+$; found: 256.0519

■ ASSOCIATED CONTENT

Supporting Information

The X-ray crystallographic data of compound **3a** and copies of spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: yuxiaoqiang@dlut.edu.cn.
*E-mail: mingbao@dlut.edu.cn.

Notes

The authors declare no competing financial interest.

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