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Copper-Mediated Oxidative Functionalization of C(sp^3)–H Bonds with Isoquinolines: Two-Step Synthesis of 5-Oxaprotoberberinones

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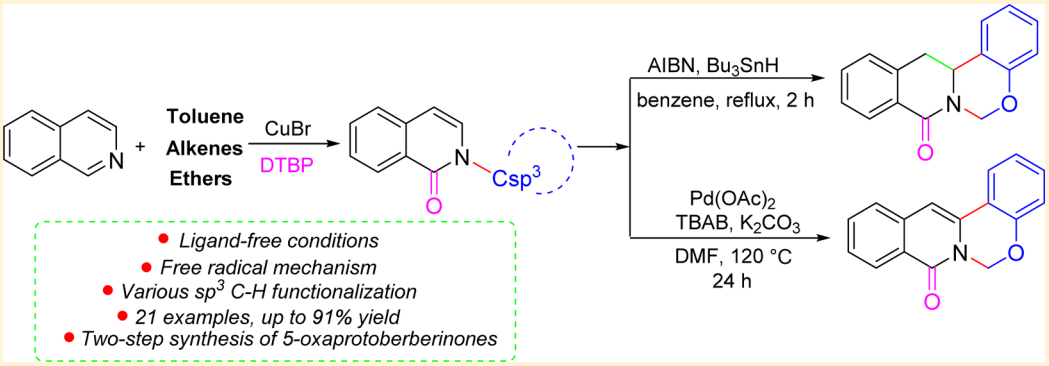
Supporting Information



ABSTRACT: A copper-mediated oxidative functionalization of C(sp^3)–H bonds with isoquinolines via a radical process without ligands was achieved. The present system exhibits a novel pathway for the preparation of *N*-alkyl (benzyl) isoquinolin-1(2*H*)-ones in moderate to high yields. In addition, this procedure provides a simple method to afford 5-oxaprotoberberinones and their derivatives in two steps.

INTRODUCTION

Isoquinolin-1(2*H*)-ones are important structural motifs found in natural products.[1] Therefore, isoquinolin-1(2*H*)-ones have been employed in the synthesis of pharmaceutical compounds, such as dehydrogusanlung D, 6*H*,8*H*-isoquino[2,3-*c*][1,3]-benzoxazin-8-one (**1ab**), and isoindolo [2,1-*b*]isoquinolin-5(7*H*)-one (Figure 1).[2] Thus, the study of synthetic methods

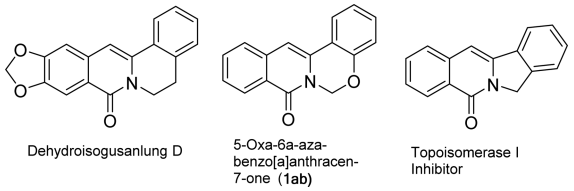


Figure 1. Examples of isoquinolin-1(2*H*)-one-fused natural products and pharmaceutics.

for isoquinolin-1(2*H*)-ones becomes significant. However, after a brief survey of the literature, we have found a lack of general methods for the preparation of these kinds of compounds. Meanwhile, most of the syntheses of these compounds involved various expensive metals as catalysts.[3]

Over the past few decades, there were some methods for the synthesis of *N*-alkylisoquinolin-1(2*H*)-ones.[4] For example, Carlos[4a] disclosed that $CpRuCl(PPh_3)_2$ could catalyze cyclo-isomerizations of aromatic homo- and bis-homopropargy licamines/amides to afford several nitrogen heterocyclic rings in high yields. Anderson[4f] disclosed that the conversion of *O*-alkylated 2-hydroxy pyridines, quinolines, and pyrimidines promoted by LiI gave the corresponding *N*-alkylated heterocycles via *O*- to *N*-alkyl migration. However, these methods are often limited due to involving expensive noble metal catalysts, complicated ligands, and infrequent substrates. For the preparation of *N*-benzylisoquinolin-1(2*H*)-ones, only a few methods were reported using isoquinolines as a substrate. Examples include work by Arakawa[5] and co-workers who reported that *N*-benzylisoquinolin-1(2*H*)-ones were generated in low yields by treating isoquinolines with benzyl bromides in the presence of a large amount of $K_3Fe(CN)_6$ and KOH. Recently, Yang[6] disclosed a novel method to produce *N*-benzylisoquinolin-1(2*H*)-ones in moderate to high yields utilizing isoquinolines and toluene (**2a**) as reactants in the presence of a catalytic amount of iodine as the initiator. This method is simple and highly effective. However, a limitation of this procedure is that only toluenes and their derivatives acted as the effective substrates because the reaction occurred in the presence of a benzyl iodide intermediate. C–N bond formation via C(sp^3)–H activation of alkyl/benzyl has gained much interest in recent years.[7] A wide variety of Cu salts have been employed in these reactions.[8] Therefore, we tried to find a reaction system which has a wider scope of substrates to achieve the construction of *N*-alkyl(benzyl)isoquinolin-1(2*H*)-

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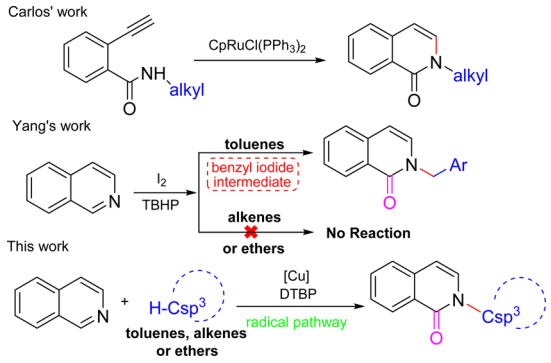
ones via C(sp^3)−H activation. Herein, we would like to report an effective method of oxidative functionalization of various C(sp^3)−H bonds with isoquinolines via a radical process (Scheme 1).

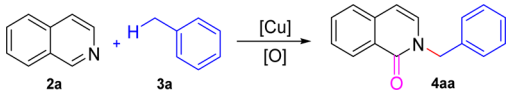
Scheme 1. Various Pathways for the Construction of *N*-Substituted Isoquinolin-1(2*H*)-ones



RESULTS AND DISCUSSION

The initial explorations were completed by using isoquinoline (**2a**) and toluene (**3a**) as substrates under different reaction conditions, including optimization of catalysts, oxidants, and temperature to yield desired *N*-benzylisoquinolinone **4aa**. The results are summarized in Table 1. The reaction was initially

Table 1. Optimization of Reaction Conditions[a]



2a 3a 4aa

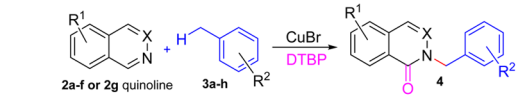
entry	[Cu] (equiv)	oxidant (equiv)	temp (°C)	yield[b] (%)
1	CuOAc (0.2)	DTBP (2.0)	120	12
2	CuSCN (0.2)	DTBP (2.0)	120	trace
3	CuI (0.2)	DTBP (2.0)	120	trace
4	Cu_2O (0.2)	DTBP (2.0)	120	trace
5	CuCl (0.2)	DTBP (2.0)	120	trace
6	CuBr (0.2)	DTBP (2.0)	120	27
7	$CuBr_2$ (0.2)	DTBP (2.0)	120	trace
8	Cu (0.2)	DTBP (2.0)	120	17
9	CuBr (0.2)	TBHP (2.0)	120	trace
10	CuBr (0.2)	TBPB (2.0)	120	trace
11	CuBr (0.2)	$K_2S_2O_8$ (2.0)	120	trace
12	CuBr (0.2)	DCP (2.0)	120	trace
13	CuBr (0.5)	DTBP (2.0)	120	42
14	CuBr (1.0)	DTBP (2.0)	120	57
15	CuBr (1.0)	DTBP (3.0)	120	67
16	CuBr (1.0)	DTBP (4.0)	120	77
17	CuBr (1.0)	DTBP (5.0)	120	75
18	**CuBr (1.0)**	**DTBP (4.0)**	**100**	**78**

[a]Reaction conditions: **2a** (0.30 mmol), **3a** (1.5 mL), 8 h, under a N_2 atmosphere. [b]Yield of isolated product.

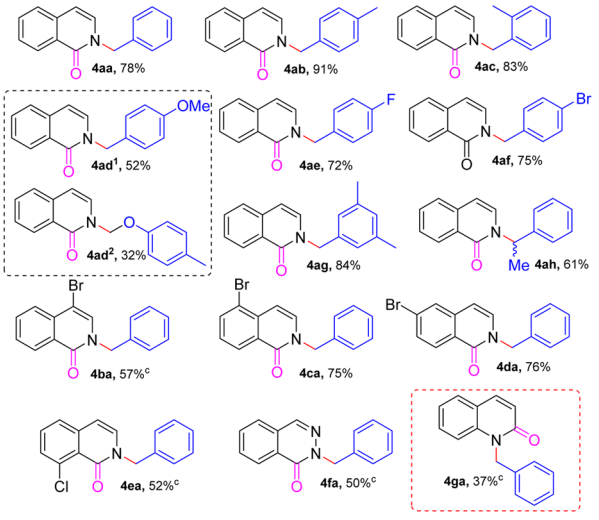
carried out by using CuOAc and di-*tert*-butyl peroxide (DTBP) as a catalyst and an oxidant, respectively (Table 1, entry 1). A small amount of the corresponding product **4aa** was obtained after heating at 120 °C for 8 h under a nitrogen atmosphere in a sealed tube. Inspired by this discovery, different kinds of Cu catalysts such as $CuBr_2$, CuCl, CuSCN, Cu_2O, CuBr, CuOAc, and Cu powder were employed in the reaction (Table 1, entries 1−8). We found that CuBr showed the best results for this reaction. Meanwhile, several oxidants [such as *tert*-butyl hydroperoxide (TBHP), *tert*-butyl perbenzoate (TBPB), $K_2S_2O_8$, etc.] were tested for this transformation. It turned out that only DTBP exhibited reaction activity for the transformation, but TBHP, TBPB, $K_2S_2O_8$, and dicumyl peroxide (DCP) did not induce the reaction (Table 1, entries 9−12). Then, the reaction was carried out by using different amounts of CuBr and DTBP. We found that the best result was obtained with 1.0 equiv of CuBr and 4.0 equiv of DTBP (Table 1, entries 13−17). When the reaction was completed at 100 °C, the yields of the target product **4aa** slightly increased (Table 1, entry 18). On the basis of the results shown in Table 1, the reaction was carried out with 0.3 mmol of isoquinoline (**2a**), 1.5 mL of toluene substrates, 0.3 mmol of CuBr, and 1.2 mmol of DTBP at 100 °C for 8 h.

With optimized conditions in hand, we further carried out the reaction by using various isoquinolines and methylbenzene derivatives to investigate the scope and generality of this protocol (Table 2). A range of methylbenzene derivatives

Table 2. Scope of the Reaction Affording Products 4[a,b]



2a-f or 2g quinoline 3a-h 4



[a]Reaction conditions: **2** (0.30 mmol), **3** (1.5 mL), CuBr (1.0 equiv), and DTBP (4.0 equiv), 4−10 h, under a N_2 atmosphere. [b]Yield of isolated product. [c]120 °C for 12 h.

bearing electron-donating and electron-withdrawing groups reacted with isoquinoline (**2a**) to give the target *N*-benzylisoquinolinones **4**. The reaction occurred in high yields by using methylbenzene derivatives bearing electron-donating substituents as substrates, such as *p*-dimethylbenzene (**3b**), *o*-dimethylbenzene (**3c**), and 1,3,5-trimethylbenzene (**3g**). It is worth noting that we obtained two different products **4ad**[1] and **4ad**[2] when 4-methylanisole (**3d**) was used as a substrate. Meanwhile, different substituted isoquinolines were examined under the standard reaction conditions. The lower yields of the corresponding products **4ba** and **4ea** were observed in the presence of substituents at the 4 or 8 position of isoquinolines. To our delight, apart from isoquinolines, phthalazine (**2f**) and

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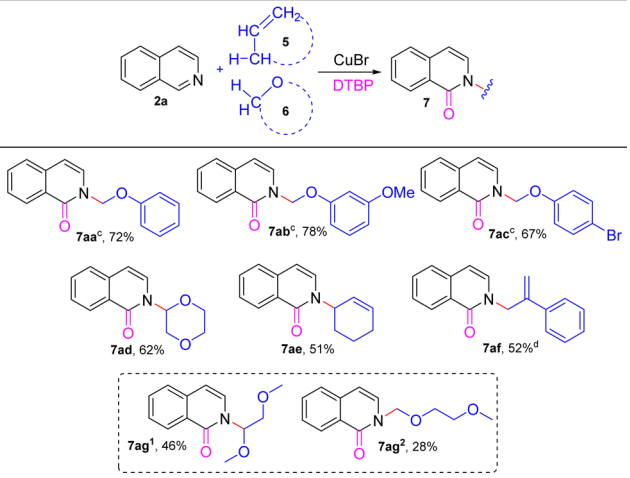
quinoline (**2g**) could also be used as substrates with methylbenzene (**3a**) to afford the desired compounds **4fa** and **4ga** respectively in moderate yields under the reaction conditions.

Encouraged by the exciting results, we tried to apply a few other types of compounds containing C(sp^3)−H bonds such as 1,4-dioxane (**6d**), cyclohexene (**5e**), 1,2-dimethoxyethane (**6g**), methoxybenzene (**6a**), and their derivatives into this transformation under the typical reaction conditions. These compounds satisfactorily could act as effective substrates in the coupling reactions with isoquinoline (**2a**) in moderate yields, and the results were summarized in Table 3. The ratio of

Table 3. Scope of the Reaction Affording Products 7[a,b]

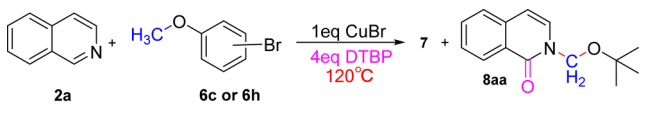


[a]Reaction conditions: **2a** (0.30 mmol), **5** or **6** (1.5 mL), CuBr (1.0 equiv) and DTBP (4.0 equiv), 100 °C, 6−10 h, under a N_2 atmosphere. [b]Yield of isolated product. [c]6.0 equiv of DTBP. [d]2-Phenylpropene as a substrate.

the regioisomeric products **7ag**[1] and **7ag**[2] in the reaction of isoquinoline (**2a**) with 1,2-dimethoxyethane (**6g**) is 46%:28%. Meanwhile, we could not find the target compounds when isoquinoline (**2a**) reacts with ethers or alkenes by using Yang's method[6] (Scheme 1). Besides, we found an interesting phenomenon in the course of the experiments. A mixture of two products (**7ac** and **8aa** or **7ah** and **8aa**) in varying proportions were observed when the reaction was completed at 120 °C by using 2-bromoanisole or 4-bromoanisole (**6c** or **6h**) as a substrate (Scheme 2). The result showed that this competing exchange reaction existed at higher temperatures utilizing anisoles with a bromine group as a substrate.

Furthermore, the versatile synthetic utilization of compound **7** was studied, and the results are summarized in Scheme 3. For the synthesis of 5-oxaprotoberberinones, to our knowledge, only one method has been reported. Protoberberines are important natural isoquinoline alkaloids. In 2014, Cho[9] first employed *o*-toluamide **9** and MOM (methoxymethyl)

Scheme 2. Intermolecular Exchange Reaction



protected *o*-cyanophenol **10** as substrates to yield the target cross-coupling product **1ab**. The reaction was carried out in dry tetrahydrofuran (THF) utilizing *n*-butyllithium as an additive at −78 °C. Then, the MOM group was removed to afford phenol **12** in the presence of 10% HCl or trifluoroacetic acid. Finally, unsubstituted 5-oxaprotoberberinone **1ab** was obtained in moderate yield by an S_N2 reaction, in which compound **12** reacts with diiodomethane by using K_2CO_3 as the base. Cho's method has some drawbacks, such as an intricate preprocess, harsh conditions, and long steps. Therefore, a more convenient method for the generation of this class of compounds is still required. Herein we present a new method for the preparation of 5-oxaprotoberberinones in two steps using the method reported above in this article. The corresponding compound **1ab** was provided in 76% yield utilizing readily available starting materials. Besides, its derivative **1aa** could also be easily assembled in moderate yield by this novel two-step procedure based on Argade's method.[10] Furthermore, isoindolo[2,1-*b*]isoquinolin-5(7*H*)-one (topoisomerase I inhibitor) could also be produced by using the above-mentioned method and Daich's method[11] in combination (Figure 1).

To investigate the mechanism, several control experiments were completed (Scheme 4). First, when the reaction was carried out under the standard conditions by using benzyl bromide intead of toluene, we could not find the target compound **4a** (Scheme 4a). This shows that the corresponding product could not be obtained by a benzyl bromide intermediate. When 4 equiv of 2,6-di-*tert*-butyl-4-methylphenol (BHT) were introduced to this transformation under the optimized conditions, no desired product was detected (Scheme 4b). It was determined that the free radical inhibitor completely suppressed the reaction. Finally, we tried to take advantage of ESI-MS analysis on the model reaction of **2a** and **3a** to further probe the reaction pathway. When the reaction was completed under the standard condition, a few samples from the reaction mixture were directly analyzed by ESI-MS in positive ion mode. Several peaks with *m*/*z* signals characterized for cationic intermediates were trapped. Upon analysis of the present *m*/*z* signals, structures of the cationic intermediates were proposed; the results were summarized in Scheme 4c. The results indicated that a benzylic radical first attack the nitrogen of C═N in the pathway to generate the carbon radical intermediate.

On the basis of these preliminary results, together with previous studies,[7,8] we proposed a plausible mechanism in Scheme 5. Initially, the reaction between $[Cu]^I$ and DTBP would give copper(II) alkoxide **A** and *tert*-butoxy radical **B**. Meanwhile, homolysis of other DTBP gives **B** under heating. Benzyl radical **C** would be generated by abstracting hydrogen from toluene by **B**. Subsequently, isoquinoline **2a** reacts with **A** to afford intermediate **D**, which combined with the benzyl radical **C** produces the intermediate **E**. Then **E** works with **B** to afford the corresponding compound **F**. The reaction of compound **F** with *tert*-butoxy radical **B** would generate free radical intermediate **G** which would reduce the $[Cu]^{II}$ to $[Cu]^I$ and simultaneously generate carbonium ion intermediate **H**. Finally, the desired product **4aa** was formed with the release of a tertiary butyl cation which would generate isobutene involving a *tert*-butoxy ion. Our hypothesis accounts for 1.0 equiv of CuBr employed in this transformation. Quantitative intermediate **D** was yielded to afford compound **F**. Uncoordinated isoquinolines would lose their stability to result in a side

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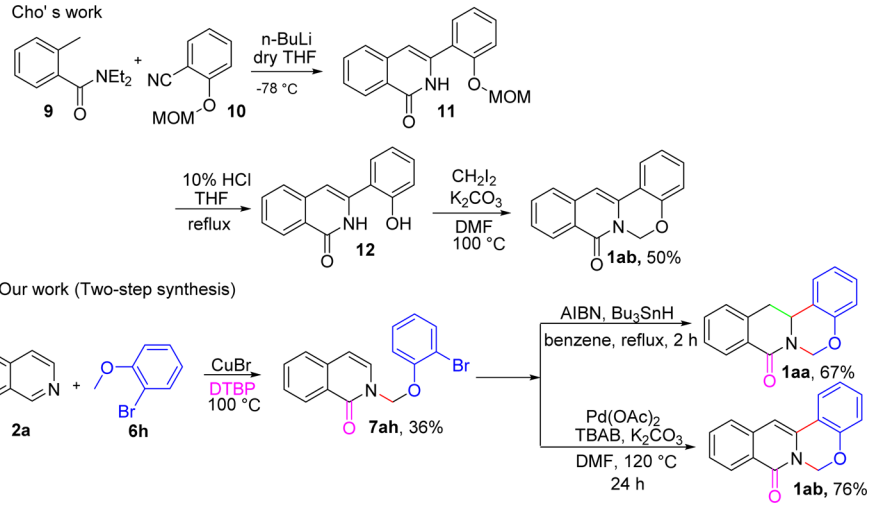
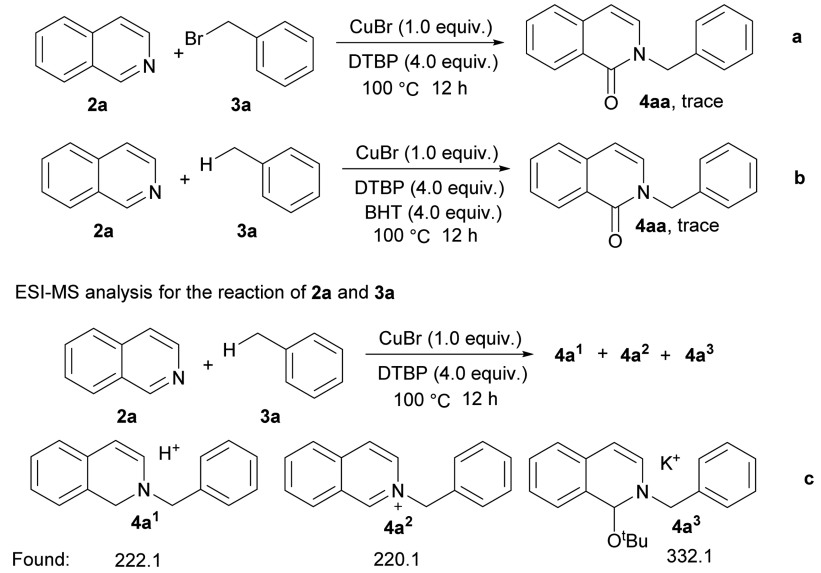
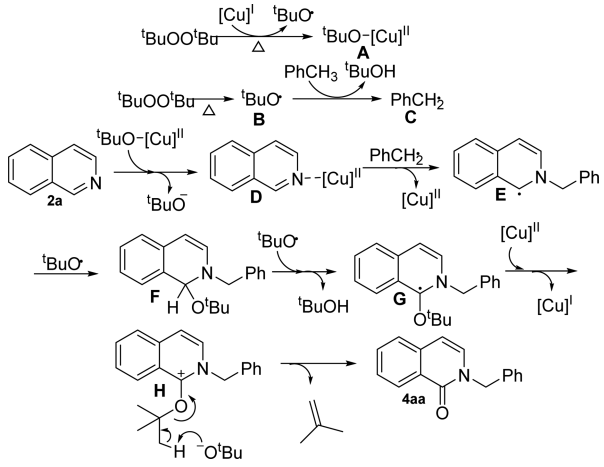
Scheme 3. Transformations of 2-[(2-Bromophenoxy)methyl]isoquinolin-1(2*H*)-one (6ah)



Scheme 4. Control Experiment



Scheme 5. Plausible Mechanism for the Synthesis of 4aa



reaction in the presence of DTBP when the amount of Cu salts was reduced.

CONCLUSION

In conclusion, we have developed an efficient and practical copper-mediated oxidative functionalization of azaarenes with various C(sp^3)–H bonds via a radical process in moderate to high yields without any ligands. This novel transformation provided a useful strategy for the synthesis of *N*-benzyl/alkyl isoquinolinone utilizing readily available starting substrates. Importantly, 5-oxaprotoberberinones and their derivatives could be concisely prepared by using this method. Further investigation of this procedure to focus on the detailed reaction mechanism and synthetic applications is underway in our laboratory.

EXPERIMENTAL SECTION

General Procedure for the Synthesis of the Target Compounds 4. DTBP (1.2 mmol) was added to a solution of **2** (0.3 mmol), **3** (1.5 mL), and CuBr (0.3 mmol), and the reaction mixture was stirred under a nitrogen atmosphere at 100 °C for 4–10 h. Afterward the resulting mixture was cooled to room temperature, transferred to a silica gel column directly, and purified by column

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chromatography with petroleum ether/ethyl acetate (20:1) as eluent to give **4**.

General Procedure for the Synthesis of the Target Compounds 7. DTBP (1.2 mmol or 1.8 mmol) was added to a solution of **2a** (0.3 mmol), **5** or **6** (1.5 mL), and CuBr (0.3 mmol), and the reaction mixture was stirred under a nitrogen atmosphere at 100 °C for 4−10 h. Afterward the resulting mixture was cooled to room temperature, transferred to a silica gel column directly, and purified by column chromatography with petroleum ether/ethyl acetate (20:1) as eluent to give **7**.

*2-Benzylisoquinolin-1(2H)-one (**4aa**).*[6] Yellow solid. Yield: 54.9 mg (78%); mp 65−66 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, J = 8.0 Hz, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.50 (d, J = 8.0 Hz, 2H), 7.33−7.28 (m, 5H), 7.08 (d, J = 8.0 Hz, 1H), 6.48 (d, J = 8.0 Hz, 1H), 5.22 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 137.0, 136.9, 132.2, 131.2, 128.8, 128.1, 127.9, 127.8, 126.8, 126.4, 125.9, 106.3, 51.7.

*2-(4-Methylbenzyl)isoquinolin-1(2H)-one (**4ab**).*[6] Yellow solid. Yield: 67.9 mg (91%); mp 103−105 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, J = 8.0 Hz, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.23 (d, J = 4.0 Hz, 2H), 7.13 (d, J = 8.0 Hz, 2H), 7.08−7.06 (m, 3H), 7.47 (d, J = 8.0 Hz, 1H), 5.18 (s, 2H), 2.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 137.5, 137.0, 133.9, 132.1, 131.2, 129.4, 128.0, 128.0, 126.8, 126.4, 125.8, 106.2, 51.4, 21.0.

*2-(2-methylbenzyl)isoquinolin-1(2H)-one (**4ac**).*[6] Yellow solid. Yield: 62.0 mg (83%); mp 109−110 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, J = 8.0 Hz, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.50 (d, J = 4.0 Hz, 2H), 7.21−7.15 (m, 3H), 7.05 (d, J = 8.0 Hz, 1H), 6.93 (d, J = 8.0 Hz, 1H), 6.46 (d, J = 8.0 Hz, 1H), 5.22 (s, 2H), 2.31 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 136.9, 136.5, 134.4, 132.2, 130.8, 130.7, 128.4, 128.1, 128.0, 126.8, 126.3, 126.2, 125.9, 106.3, 49.3, 19.1.

*2-(4-Methoxybenzyl)isoquinolin-1(2H)-one (**4ad^1**).*[6] Yellow solid. Yield: 41.3 mg (52%); mp 107−108 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, J = 8.0 Hz, 1H), 7.62(d, J = 8.0 Hz, 1H), 7.48 (d, J = 8.0 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 7.08 (d, J = 8.0 Hz, 1H), 6.85 (d, J = 8.0 Hz, 2H), 6.46 (d, J = 8.0 Hz, 1H), 5.15 (s, 2H), 3.77 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 159.3, 137.0, 132.1, 131.1, 129.5, 129.1, 128.0, 126.8, 126.4, 125.8, 114.2, 106.2, 55.2, 51.2.

*2-(4-Methoxybenzyl)isoquinolin-1(2H)-one (**4ad^2**).* White solid. Yield: 25.4 mg (32%); mp 117−118 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, J = 8.0 Hz, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.48 (d, J = 8.0 Hz, 2H), 7.22 (d, J = 8.0 Hz, 1H), 7.06 (d, J = 8.0 Hz, 2H), 6.95 (d, J = 8.0 Hz, 2H), 6.49 (d, J = 8.0 Hz, 1H), 5.94 (s, 2H), 2.25 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 154.1, 137.0, 132.6, 131.8, 130.1, 129.4, 128.2, 127.0, 126.1, 126.0, 115.9, 106.8, 74.2, 20.4. HRMS (ESI) m/z: calcd for $C_{17}H_{19}N_2O_2$: 283.1441 [M + NH_4]$^+$; found: 283.1426.

*2-(4-Fluorobenzyl)isoquinolin-1(2H)-one (**4ae**).*[6] White solid. Yield: 54.6 mg (72%); mp 107−108 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, J = 8.0 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.33 (d, J = 8.0 Hz, 2H), 7.07 (d, J = 8.0 Hz, 2H), 7.08−6.98 (m, 3H), 6.49 (d, J = 8.0 Hz, 1H), 5.17 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4 (d, $^1J_{C-F}$ = 250.0 Hz), 162.2, 137.0, 132.7, 132.7, 132.3, 131.1, 129.8, 129.7, 128.0, 127.0, 126.3, 125.9, 115.8, 115.6, 106.6, 51.2.

*2-(4-Bromobenzyl)isoquinolin-1(2H)-one (**4af**).*[6] Yellow solid. Yield: 70.4 mg (75%); mp 157−158 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.52−7.44 (m, 4H), 7.21 (d, J = 4.0 Hz, 2H), 7.06 (d, J = 8.0 Hz, 1H), 6.50 (d, J = 8.0 Hz, 1H), 5.16 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 136.9, 135.9, 132.3, 131.9, 131.0, 129.6, 128.0, 127.0, 126.3, 125.9, 121.8, 106.6, 51.2.

*2-(3,5-dimethylbenzyl)isoquinolin-1(2H)-one (**4ag**).*[6] White solid. Yield: 66.3 mg (84%); mp 100−103 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, J = 8.0 Hz, 1H), 7.62 (m, 1H), 7.49(d, J = 8.0 Hz, 2H), 7.07 (d, J = 4.0 Hz, 1H), 6.92−6.90 (m, 3H), 6.46 (d, J = 8.0 Hz, 1H), 5.14 (s, 2H), 2.27 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 138.4, 137.0, 136.8, 132.1, 131.3, 129.5, 128.1, 126.8, 125.8, 125.8, 125.7, 106.2, 51.5, 21.2.

*2-(1-Phenylethyl)isoquinolin-1(2H)-one (**4ah**).*[6] Yellow oil. Yield: 45.6 mg (61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, J = 8.0 Hz, 1H), 7.64−7.60 (m, 1H), 7.51−7.46 (m, 2H), 7.35−7.26 (m, 5H), 6.91 (d, J = 8.0 Hz, 1H), 6.59−6.54 (m, 1H), 6.44 (d, J = 8.0 Hz, 1H), 1.76 (d, J = 4.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 140.6, 136.6, 132.1, 128.7, 128.2, 127.9, 127.7, 127.3, 126.7, 126.1, 125.7, 106.4, 52.1, 18.7.

*2-Benzyl-4-bromoisoquinolin-1(2H)-one (**4ba**).*[6] Yellow solid. Yield: 53.5 mg (57%); mp 112−113 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, J = 8.0 Hz, 1H), 7.82−7.73 (m, 2H), 7.58−7.55 (m, 1H), 7.35−7.26 (m, 6H), 5.20 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 136.2, 135.5, 133.0, 132.9, 131.7, 131.6, 128.9, 128.5, 128.1, 128.0, 127.9, 125.8, 51.7.

*2-Benzyl-5-bromoisoquinolin-1(2H)-one (**4ca**).*[6] Yellow solid. Yield: 70.4 mg (75%); mp 110−113 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, J = 8.0 Hz, 1H), 7.87−7.85 (m, 1H), 7.32−7.16 (m, 7H), 6.82 (d, J = 8.0 Hz, 1H), 5.21 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 136.5, 136.3, 136.0, 132. 5, 128.9, 128.0, 127.9, 127.8, 127.7, 127.4, 120.6, 105.0, 51.9.

*2-Benzyl-6-bromoisoquinolin-1(2H)-one (**4da**).*[6] Yellow solid. Yield: 71.6 mg (76%); mp 112−113 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, J = 8.0 Hz, 1H), 7.66−7.56 (m, 2H), 7.32−7.26 (m, 5H), 7.10 (d, J = 8.0 Hz, 1H), 6.38 (d, J = 8.0 Hz, 1H), 5.19 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 138.4, 136.5, 132.6, 130.1, 129.9, 128.9, 128.3, 128.0, 127.9, 127.4, 125.0, 105.2, 51.8.

*2-Benzyl-8-chloroisoquinolin-1(2H)-one (**4ea**).* Yellow oil. Yield: 41.9 mg (52%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J = 8.0 Hz, 2H), 7.36−7.25 (m, 6H), 7.09 (d, J = 8.0 Hz, 1H), 6.39 (d, J = 8.0 Hz, 1H), 5.17 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8, 140.1, 136.7, 135.7, 132.1, 131.9, 130.1, 128.9, 128.8, 128.1, 127.8, 125.1, 105.8, 51.8. HRMS (ESI) m/z: calcd for $C_{17}H_{13}ClNO_3$: 314.0589 [M + COOH]$^-$; found: 314.0586.

*2-Benzylphthalazin-1(2H)-one (**4fa**).*[6] White solid. Yield: 35.4 mg (50%); mp 84−87 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, J = 8.0 Hz, 1H), 8.13 (s, 1H), 7.70−7.24 (m, 8H), 5.40 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 138.0, 137.0, 133.1, 131.6, 130.0, 129.7, 128.6, 128.5, 127.7, 126.8, 126.0, 54.6.

*1-Benzylquinolin-2(1H)-one (**4ga**).*[6] Brown solid. Yield: 26.1 mg (37%); mp 64−67 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 8.0 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.44−7.40 (m, 1H), 7.31−7.16 (m, 7H), 6.82 (d, J = 8.0 Hz, 1H), 5.56 (s, 2H).

*2-(Phenoxymethyl)isoquinolin-1(2H)-one (**7aa**).* White solid. Yield: 54.2 mg (72%); mp 99−100 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, J = 8.0 Hz, 1H), 7.66−7.63 (m, 1H), 7.51−7.48 (m, 2H), 7.28−7.24 (m, 3H), 7.08 (d, J = 8.0 Hz, 2H), 6.99 (d, J = 8.0 Hz, 1H), 6.52 (d, J = 8.0 Hz, 1H), 5.99 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 156.2, 137.0, 132.7, 129.7, 129.3, 128.2, 127.1, 126.10, 126.0, 122.4, 115.9, 106.9, 73.9. HRMS (ESI) m/z: calcd for $C_{16}H_{13}NO_2Na$: 274.0838 [M + Na]$^+$; found: 274.0844.

*2-((3-Methoxyphenoxy)methyl)isoquinolin-1(2H)-one (**7ab**).* Yellow oil. Yield: 65.8 mg (78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, J = 8.0 Hz, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.48 (d, J = 8.0 Hz, 2H), 7.25−7.14 (m, 2H), 6.67 (s, 2H), 6.56−6.50 (m, 2H), 5.96 (s, 2H), 3.75 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 160.9, 157.3, 137.0, 132.7, 130.1, 129.4, 128.2, 127.1, 126.1, 126.0, 108.4, 107.8, 106.9, 102.0, 73.8, 55.3. HRMS (ESI) m/z: calcd for $C_{18}H_{16}NO_5$: 326.1034 [M + COOH]$^-$; found: 326.1043.

*2-((4-Bromophenoxy)methyl)isoquinolin-1(2H)-one (**7ac**).* White solid. Yield: 66.1 mg (67%); mp 151−152 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, J = 8.0 Hz, 1H), 7.67−7.63 (m, 1H), 7.51−7.47 (m, 2H), 7.37−7.35 (m, 2H), 7.21 (d, J = 8.0 Hz, 1H), 6.97 (d, J = 8.0 Hz, 2H), 6.52 (d, J = 8.0 Hz, 1H), 5.95 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 155.1, 137.0, 132.9, 132.6, 129.2, 128.2, 127.3, 126.7, 126.1, 117.7, 114.9, 107.3, 73.8. HRMS (ESI) m/z: calcd for $C_{16}H_{12}BrNO_2Na$: 351.9944 [M + Na]$^+$; found: 351.9926.

*2-(1,4-Dioxan-2-yl)isoquinolin-1(2H)-one (**7ad**).* White solid. Yield: 43.0 mg (62%); mp 118−120 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, J = 8.0 Hz, 1H), 7.67−7.63 (m, 1H), 7.51−7.40 (m, 2H), 7.39 (d, J = 8.0 Hz, 1H), 6.54 (d, J = 8.0 Hz, 1H), 6.27−6.24 (m, 1H), 4.05−4.03 (m, 3H), 3.83 (d, J = 12.0 Hz, 1H), 3.74−3.70 (m, 1H), 3.48−3.43 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 136.6, 132.6, 128.0, 126.9, 126.5, 125.9, 125.7, 106.3, 78.7, 68.8, 67.2, 65.8. HRMS (ESI) m/z: calcd for $C_{13}H_{13}NO_3Na$: 254.0788 [M + Na]$^+$; found: 254.0793.

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*2-(Cyclohex-2-en-1-yl)isoquinolin-1(2H)-one (**7ae**).* Colorless oil. Yield: 34.4 mg (51%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, J = 8.0 Hz, 1H), 7.62−7.48 (m, 3H), 7.20 (d, J = 8.0 Hz, 1H), 6.50 (d, J = 8.0 Hz, 1H), 6.13 (d, J = 8.0 Hz, 1H), 5.71−5.60 (m, 2H), 2.15 (s, 3H), 1.78−1.63 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 136.8, 133.3, 132.0, 128.6, 128.0, 126.9, 126.6, 126.1, 125.7, 105.7, 51.1, 29.6, 24.7, 20.2. HRMS (ESI) m/z: calcd for $C_{15}H_{15}NONa$: 248.1046 $[M + Na]^+$; found: 248.1050.

*2-(2-Phenylallyl)isoquinolin-1(2H)-one (**7af**).* Yellow oil. Yield: 40.7 mg (52%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, J = 8.0 Hz, 1H), 7.63−7.59 (m, 4H), 7.34−7.25 (m, 3H), 7.07 (d, J = 8.0 Hz, 1H), 6.45 (d, J = 8.0 Hz, 1H), 5.56 (s, 1H), 5.10 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 143.6, 138.1, 137.0, 132.1, 130.6, 128.5, 128.2, 128.1, 127.9, 126.8, 126.2, 125.8, 115.1, 106.2, 50.8. HRMS (ESI) m/z: calcd for $C_{18}H_{14}NO$: 260.1081 $[M - H]^-$; found: 260.1110.

*2-(1,2-Dimethoxyethyl)isoquinolin-1(2H)-one (**7ag^1**).* Colorless oil. Yield: 32.2 mg (46%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, J = 8.0 Hz, 1H), 7.67−7.63 (m, 1H), 7.53−7.47 (m, 2H), 7.27 (d, J = 8.0 Hz, 1H), 6.57 (d, J = 4.0 Hz, 1H), 6.28−6.25 (m, 1H), 3.65 (d, J = 4.0 Hz, 2H), 3.41 (s, 3H), 3.36 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 136.8, 132.5, 128.0, 126.8, 126.1, 126.0, 125.9, 106.3, 83.9, 73.2, 59.4, 56.8. HRMS (ESI) m/z: calcd for $C_{13}H_{15}NO_3K$: 272.0684 $[M + K]^+$; found: 272.0654.

*2-((2-Methoxyethoxy)methyl)isoquinolin-1(2H)-one (**7ag^2**).* Colorless oil. Yield: 19.6 mg (32%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, J = 8.0 Hz, 1H), 7.66−7.63 (m, 1H), 7.51−7.47 (m, 2H), 7.21 (d, J = 8.0 Hz, 1H), 6.52 (d, J = 8.0 Hz, 1H), 5.50 (s, 2H), 3.75−3.74 (m, 2H), 3.53−3.52 (m, 2H), 3.36 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8, 137.1, 132.6, 130.2, 128.1, 126.9, 126.1, 125.9, 106.5, 76.9, 71.5, 68.5, 58.9. HRMS (ESI) m/z: calcd for $C_{13}H_{15}NO_3K$: 272.0684 $[M + K]^+$; found: 272.0657.

*2-((2-Bromophenoxy)methyl)isoquinolin-1(2H)-one (**7ah**).* White solid. Yield: 35.5 mg (36%); mp 148−149 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, J = 8.0 Hz, 1H), 7.66−7.62 (m, 1H), 7.53−7.47 (m, 3H), 7.30−7.24 (m, 3H), 6.90−6.86 (m, 1H), 6.53 (d, J = 8.0 Hz, 1H), 6.05 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 152.6, 137.0, 133.5, 132.8, 129.4, 128.7, 128.2, 127.1, 126.1, 126.0, 124.0, 116.6, 113.3, 107.1, 74.6. HRMS (ESI) m/z: calcd for $C_{16}H_{13}BrNO_2$: 330.0124 $[M + H]^+$; found: 330.0145.

*13,13a-Dihydro-6H,8H-isoquino[2,3-c][1,3]benzoxazin-8-one (**1aa**).*[10] White solid. Yield: 18.2 mg (67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, J = 4.0 Hz, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.41−7.37 (m, 1H), 7.27−7.21 (m, 3H), 7.08−7.00 (m, 2H), 6.47 (d, J = 16.0 Hz, 1H), 5.08−5.03 (m, 1H), 4.60 (d, J = 8.0 Hz, 1H), 3.28−3.24 (m, 1H), 3.04−2.96 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3, 153.8, 137.0, 132.5, 128.7, 128.4, 128.1, 127.5, 127.2, 126.0, 123.6, 122.3, 118.0, 70.9, 52.9, 37.0. HRMS (ESI) m/z: calcd for $C_{16}H_{14}NO_2$: 252.1019 $[M + H]^+$; found: 252.1017.

*6H,8H-Isoquino[2,3-c][1,3]benzoxazin-8-one (**1ab**).*[9] White solid. Yield: 20.4 mg (76%); mp 174−175 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, J = 8.0 Hz, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.66−7.63 (m, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.48−7.44 (m, 1H), 7.38−7.34 (m, 1H), 7.18−7.14 (m, 1H), 7.09 (d, J = 8.0 Hz, 1H), 6.89 (s, 1H), 5.91 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5, 154.1, 136.7, 133.2, 132.7, 131.0, 128.0, 126.7, 126.4, 125.2, 124.1, 123.5, 119.1, 117.7, 100.9, 71.6.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02145.

^{1}H and ^{13}C NMR spectral data of all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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