JOC The Journal of Organic Chemistry

pubs.acs.org/joc Article

Synthesis of 3-Hydroxyisoindolin-1-ones through 1,4-Dioxane-Mediated Hydroxylhydrative aza-Cyclization of 2-Alkynylbenzamide in Water

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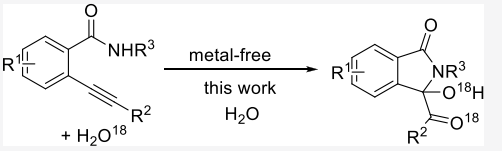
Cite This: https://dx.doi.org/10.1021/acs.joc.9b03466 Read Online

ABSTRACT: In this work, 1,4-dioxane-mediated hydroxylhydrative aza-cyclization of 2-alkynylbenzamide is developed for the synthesis of 3-hydroxylisoindolin-1-ones. The transformation proceeds smoothly in water with good yields and a broad reaction scope. Mechanistic studies show that regioselective brimonative 5-exo-dig aza-cyclization, bromohydration of the resulting alkene groups, and hydrolysis of dibromo compounds are involved. Compared to the traditional methodologies, the synthetic procedure reported herein represents a cleaner route toward 3-hydroxylisoindolin-1-ones.



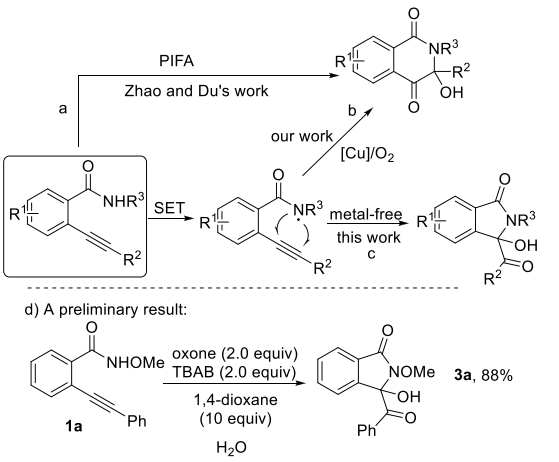
INTRODUCTION

As a powerful building block, alkynes have attracted the attention of scientific community, and alkyne-based chemistry has proved to be highly efficient for synthesizing diverse synthons and biologically interesting architectures.[1] One of the demanding challenges associated with alkynes is the regioselectivity control. Electronic, steric, and directing-group cumulatively determine the regioselectivity in alkyne-based chemistry. Keeping the directing-group-assisted transformation strategy in mind, a series of dual-functionalized substrates with alkynyl and reactive groups at the ortho position have been developed in the past few years.[2]

2-Alkynylbenzamide, one of the versatile dual-functionalized substrates, dominantly underwent O-attacked 5-exo-dig/6-endo-dig cyclizations to produce diverse heterocyclic compounds.[3−5] To the best of our knowledge, the reactions under the Lewis acid-promoted conditions[4] and electrophilic conditions[5] were prior to offer O-attacked cyclization products, and yet N-attacked cyclization remains rare.[6] Recently, several research groups found that the use of indium salt,[7a,b] platinum salt,[7c] copper salt,[7d] and silver salt[7e] could enable the N-attacked 6-endo-cyclization to produce isoquinolin-1-ones.[7] Subsequently, a metal-free synthesis was realized by Zhao and Du toward 3-hydroxylisoquinolin-1,4-diones through a hypervalent iodine reagent-mediated oxidative 6-endo aza-cyclization of 2-alkynylbenzamide (Scheme 1, eq a).[8] Inspired by what has been mentioned above, it is of high desire to further develop N-attacked cyclization of 2-alkynylbenzammide under mild conditions.

Over the past few years, our group has been focusing on developing a cleaner, safer, and more economic system to realize regioselective transformations of alkynes.[9] The initial emphasis in our group was put on copper-catalyzed oxidative 6-endo-dig aza-cyclization of 2-alkynylbenzamide (Scheme 1, eq b).[10] As expected, 2 mol % $CuCl_2$ under an O_2 atmosphere enabled the above N-attacked 6-endo cyclization toward 3-hydroxylisoquinolin-1,4-diones. Different from Zhao and Du's work,[8] our work was ascribed to the N-center radical pathway. In light of the above findings, it is of high significance to realize regioselective N-attacked 5-exo-dig aza-cyclization of 2-alkynylbenzamide. We envisioned that an amide N-center

Scheme 1. Proposed Route for the Synthesis of 3-Hydroxyisoindolin-1-one from 2-Alkynylbenzamide



Received: December 23, 2019
Published: March 31, 2020

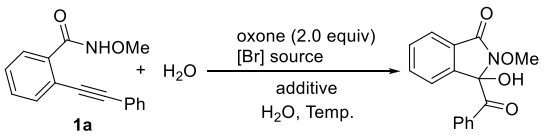
https://dx.doi.org/10.1021/acs.joc.9b03466
J. Org. Chem. XXXX, XXX, XXX−XXX

radical[11] cyclization pathway under metal-free condition could enable the synthesis of 3-hydroxylisoindolin-1-ones (Scheme 1, eq c), a ubiquitous structural core in many natural products.[12]

Very recently, we disclosed a *n*-tetrabutyl ammonium bromide (TBAB)/oxone system-promoted 2,4-dibromohydration of 2-enynylbenzoate. In the process, assistance of the ortho-ester group contributed to the regioselectivity control of this reaction.[13a] Considering our continuous interest in oxone chemistry,[13] the reaction of 2-alkynylbenzamide was then explored using the TBAB/oxone system. However, under this reaction condition, an *O*-attacked regioselective 5-exo-dig cyclization took place to solely produce isofunran-1-imines with high efficiency.[13b] Interestingly, by adding 10 equiv of 1,4-dioxane, it is surprising to find that the use of TBAB/oxone made the N-attacked 5-exo-dig cyclization of *N*-methoxyl-2-alkynylbenzamide **1a** to proceed in tap water, with the formation of 3-hydroxylisoindolin-1-one **3a** in a 88% yield (Scheme 1, eq d).

Imaginably, this paper provides another protocol to realize N-attacked cyclization of 2-alkynylbenzamide, thus serving as an important supplementary in the field of 2-alkynylbenzamide-based chemistry. Together with high importance of 3-hydroxylisoquinolin-1-one core and a few synthetic methodologies,[12] we started to optimize the reaction. The results are illustrated in Table 1.

Table 1. Optimization of the Reaction Conditions[a]



entry	[Br] (equiv)	additives (equiv)	temp. (°C)	yield of **3a**[a,b]
1	TBAB (2)	1,4-dioxane (10)	80	88
2	TBAB (2)		80	nd
3	TBAB (2)	THF (10)	80	43
4	TBAB(2)	^{t}BuOMe (10)	80	67
5	TBAB(2)	1,4-dioxane (20)	80	87
6	TBAB(2)	1,4-dioxane (5)	80	40
7	KBr(2)	1,4-dioxane (10)	80	45
8	ZnBr2 (1)	1,4-dioxane (10)	80	51
9	NBS (2)	1,4-dioxane (10)	80	57
10	TBAC (2)	1,4-dioxane (10)	80	83
11	TBAI (2)	1,4-dioxane (10)	80	complex
12	TBAB (1)	1,4-dioxane (10)	80	41
13	TBAB(0.5)	1,4-dioxane (10)	80	20
14	TBAB (2)	1,4-dioxane (10)	50	53

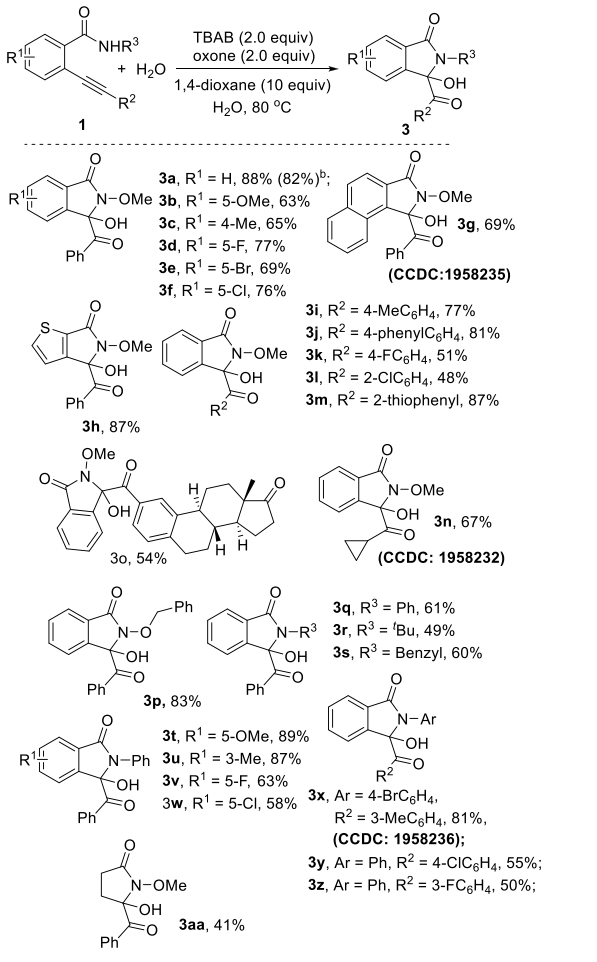
[a]Isolated yield based on 2-alkynylbenzamide **1a**. [b]Standard conditions: 2-alknylbenzamide **1a** (0.2 mmol), TBAB (2.0 equiv), oxone (2.0 equiv), 1,4-dioxane (10.0 equiv), H_2O (2.0 mL), 80 °C, overnight. TBAB = *n*-tetrabutyl ammonium bromide; TBAC = *n*-tetrabutyl ammonium chloride; TBAI = *n*-tetrabutyl ammonium iodide; NBS = *N*-Bromosuccinimide; oxone = $2KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$; nd = no desired product.

RESULTS AND DISCUSSION

Based on the preliminary result, the desired product **3a** afforded when 2.0 equiv of TBAB, 2.0 equiv of oxone, and 10.0 equiv of 1,4-dioxane in tap water were used (entry 1, Table 1). No better yields were observed when 1, 4-dioxane was replaced with tetrahydrofuran (THF) and ^{t}BuOMe (entries 3−4, Table 1). A blank reaction without 1,4-dioxane did not produce the desired **3a**, but a O-attacked benzoisofuran-1-imine (entry 2, Table 1). A similar result was obtained when the loading of 1,4-dioxane was increased from 10.0 to 20.0 equiv (entry 5, Table 1). However, the use of 5.0 equiv of 1,4-dioxane was unfavorable for the reaction, leading to the desired product **3a** in a 40% yield (entry 6, Table 1). Other bromide sources including KBr, $ZnBr_2$, and NBS were also explored, and inferior yields were detected (entries 7−9, Table 1). The use of *n*-tetrabutyl ammonium chloride (TBAC) and *n*-tetrabutyl ammonium iodide (TBAI) as replacements of TBAB did not give rise to better yields (entries 10−11, Table 1). Decrease of TBAB loading was not favorable for the outcomes (entries 12−13, Table 1). For instance, the reaction was greatly retarded when 0.5 equiv of TBAB was used (entry 13, Table 1). Lowering of temperature was not helpful for the reaction (entry 14, Table 1). Therefore, the optimized conditions are 2.0 equiv of TBAB, 2.0 equiv of oxone, 10 equiv of 1,4-dioxane, and water, 80 °C

After optimizing the conditions, we then explored the reaction generality. The results are outlined in Scheme 2. As shown in Scheme 2, a series of substituted 3-hydroxylisoindolin-1-ones were achieved in good yields.

Scheme 2. Generation of 3-Hydroxyisoindolin-1-one 3 through Regioselective 5-exo-trig Hydroxylcarbonylative Cyclization of 2-Alkynylbenzamide[a,b]



[a]Isolated yield based on **1**; [b]1 mmol scaled-reaction was conducted.

https://dx.doi.org/10.1021/acs.joc.9b03466
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The substituent effects of R^1 were investigated. The results revealed that electron-donating groups and electron-rich groups were compatible for the reactions. For example, the reaction with the substrate containing a 4-methyl group on R^1 afforded the desired 3-hydroxylisoindolin-1-one **3c** in a 65% yield, whereas the substrate having 5-fluoro substitution gave the corresponding product **3d** in a 77% yield. Other substituents including methoxyl, chloro, and bromo groups were suitable for the reaction, leading to the corresponding products **3b**−**3f** in 63−76% yields. The reactions of the napthalenyl-connected substrate and the thiophenyl-linked substrate also worked well, producing the desired compounds **3g** and **3h** in good yields. In particular, the reaction of *N*-methoxy-5-phenylpent-4-ynamide under standard conditions provided the desired product **3aa** in 41% yield as expected. A 1 mmol scaled-reaction of **1a** was conducted accordingly, and a similar yield (82%) was observed with the formation of the desired **3a**.

Subsequently, we explored the tolerance of R^2 substituents. From the results, it seemed that R^2 substituents could be equal to aryl, vinyl, and alkyl. The corresponding products **3i**−**3n** were achieved in 48−87% yields. For example, the reaction using the substrate with 2-chlorophenyl as the substituent produced the desired 3-hydroxylisoindolin-1-one **3l** in a 48% yield, whereas employing the substrate with 2-thiophenyl as the substituent gave rise to **3m** in a 87% yield. In particular, an estrone-connected 3-hydroxylisoinodin-1-one **3o** could be facilely obtained. It is noteworthy that the reaction of the cyclopropylalkynyl-linked substrate also proceeded smoothly with the formation of the desired product **3n** in a 67% yield. This cyclopropyl-linked substrate was not an efficient reaction partner in the previous works from Zhao and Du's group.[8]

Substrates with other N-protecting groups including benzoxyl, aryl, and alkyl also proved to be efficient reaction partners, leading to the corresponding products **3p**-**3z** in 49−89% yields (Scheme 2). It is worthy to note that by using Zhao's conditions or our previous conditions, the reactions of *N*-aryl/alkyl-2-alkynylbenzamides did not give the corresponding products. The exact structures for compounds **3g**, **3n**, and **3x** were identified by X-ray diffraction.

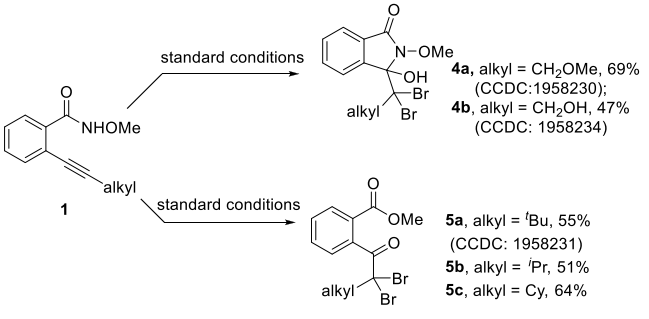
Other alkylalkynyl-connected substrates were also explored. The results are presented in Scheme 3. From the results, it can be seen that the expected 3-hydroxylisoindolin-1-ones were not produced. Under standard conditions, the reactions of *N*-methoxy-2-(3-methoxyprop-1-yn-1-yl)benzamide and 2-(3-hydroxyprop-1-yn-1-yl)-*N*-methoxybenzamide gave rise to dibromo-3-hydroxylisoindolin-1-ones **4a** and **4b** in 69 and 47% yields, respectively. The formation of the products **4a** and **4b** indicated a plausible truth that product **3** was derived from the hydrolysis of product **4**. The exact structures for compounds **4a** and **4b** were all identified by X-ray diffraction.

Interestingly, under standard conditions, we also tried the reactions when the substrates with *tert*-butylethynyl, *iso*-propylethynyl, and cyclohexyl were used. To our surprise, the desired products were not observed. Distinctive dibromo benzoates **5a**−**5c** were afforded in moderate yields. According to previous findings,[14] conversion of *N*-methoxyl benzamide radical into benzoates seemed reliable through the oxidative ring-opening and removal of N_2.[14] The exact structure for **5a** was identified by X-ray diffraction.

To gain insights into the reaction mechanism, some control experiments were carried out. The results are presented in Scheme 4. As shown in Scheme 4, a plausible intermediate **5** was isolated when the reaction was quenched after 4 h, and the reaction of intermediate **5** under standard conditions offered the desired product **3a** in a quantitative yield as expected. Moreover, the oxygen atoms in hydroxyl and carbonyl in products probably came from water on the basis of the O^{18}-labeling experiment.

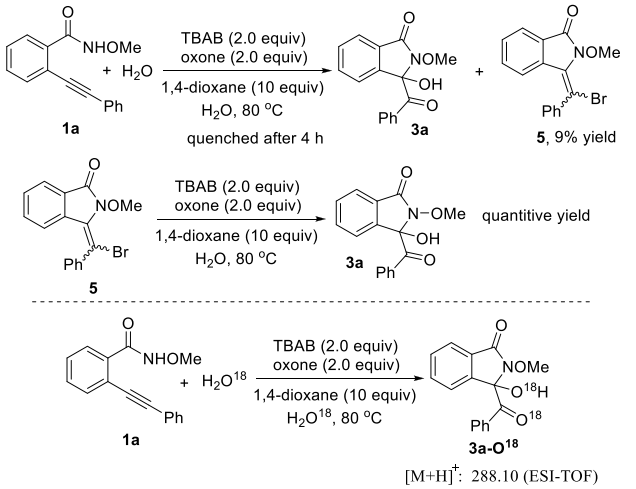
In light of the aforementioned results, a plausible mechanism is proposed in Scheme 5. In the process, oxone oxidized 1,4-dioxane and bromide into 1,4-dioxane radical and bromo radical, respectively. The sequential H-abstraction of 1,4-dioxane radical with 2-alkynylbenzamide provided the key intermediate 2-alkynylbenzamide N-center radical **A**. We thought the in situ generated bromo radical could stablize 2-alkynylbenzamide N-center radical **A** to form another intermediate **B**. The N-center 5-exo-cyclization of intermediate **A** gave bromo-containing isoindolin-1-one species **C**. Subsequently, addition of another bromo-radical to intermediate **C** took place to yield **D**. Followed by oxidation, intermediate **D** converted into intermediate **E**. Finally, the reaction of intermediate **E** and water offered intermediate **4**. Compound **4** was described as an important synthon to deliver 3-hydroxylisoindolin-1-ones **3** through hydrolysis. Interestingly, in the presence of an oxidant, intermediate **4** probably underwent an oxidative ring-opening and removal of N_2 to offer another product **5**.

Scheme 3. Reaction Scope: the Reaction of 2-alkylalkynylbenzamide[a]



[a]Isolated yield based on **1**.

Scheme 4. Control Experiments



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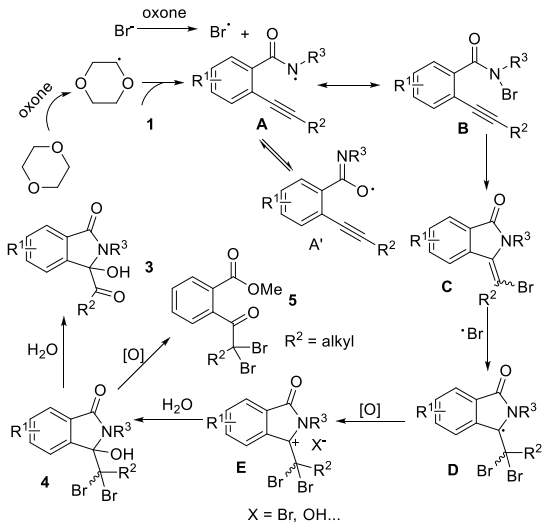
Scheme 5. Plausible Mechanism



In the whole process, the bromo atom was not found to be incorporated into the final product **3**, although stoichiometric TBAB was employed, which probably resulted because the hydrolysis reaction of the dibromo group in **4** proceeded slowly than that of brominative cyclization. In our previous work, the N-center radical **A** was transformed into oxygen-center radical **A′** by resonance.[13b] In this paper, we reasoned the use of 1,4-dioxane to facilitate the formation of 2-alkynylbenzamide N-center radical **B**. However, the substantial evidence for the exact roles of 1,4-dioxane and TBAB is still under exploration. According to the previous findings,[15] we reasoned that 1,4-dioxane served as a radical trigger to facilitate the formation of 2-alkynylbenzamide N-center radical **A**.

CONCLUSIONS

We have developed a 1,4-dioxane-mediated reaction of 2-alkynylbenzamides for the synthesis of 3-hydroxylisoindolin-1-ones. The transformation proceeds smoothly in water. Based on mechanistic studies, it is believed that regioselective brimonative 5-exo azacyclization, bromohydration of the resulting alkene group, and hydrolysis of dibromo compound were involved. Compared to the traditional methodologies, the synthetic procedure reported herein represents a cleaner route toward 3-hydroxylisoindolin-1-ones with a high reaction efficiency and a broad reaction scope.

EXPERIMENTAL SECTION

General Experimental Methods. Unless otherwise stated, all commercial reagents and solvents were used without additional purification. All solvents were dried and distilled according to standard procedures. Flash column chromatography was performed using silica gel (60 Å pore size, 32−63 μm, standard grade). Analytical thin-layer chromatography (TLC) was performed using glass plates precoated with 0.25 mm 230−400 mesh silica gel impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light. Organic solutions were concentrated on rotary evaporators at ∼20 Torr (house vacuum) at 25−35 °C. Commercial reagents and solvents were used as received. Nuclear magnetic resonance (NMR) spectra were recorded in parts per million from internal tetramethylsilane on the δ scale.

General Procedure for the Synthesis of Compound 1a. To a solution of 2-iodobenzoyl chloride (4 g, 15.0 mmol) in AcOEt/H_2O (v/v = 2:1, 180 mL) were added potassium carbonate (4.14 g, 30 mmol) and methoxyamine hydrochloride (1.5 g, 18.0 mmol). The mixture was stirred at room temperature overnight and then extracted with AcOEt (3 × 40 mL), washed with water (50 mL) and brine (50 mL), and dried over $MgSO_4$. Evaporation gave a crude solid that was recrystallized from AcOEt and collected by filtration. Then, 2-iodo-*N*-methoxybenzamide was obtained (white solid, 4.46 g, 84% yield).

Sodium hydride (640 mg, 16 mmol) was added into a solution of 2-iodo-*N*-methoxybenzamide (4.05 g, 14.6 mmol) in dry THF (100 mL) at 0 °C. After that, Boc_2O (3.83 g, 17.5 mmol) was added slowly at 0 °C. The mixture was stirred at room temperature overnight and then quenched with saturated aqueous NH_4Cl solution (30 mL). The mixture was extracted with AcOEt (3 × 30 mL), washed with saturated aqueous bicarbonate solution (30 mL) and brine (30 mL), and dried over $MgSO_4$. Using flash column chromatography, a white solid *tert*-butyl methoxy(2-(phenylethynyl)benzoyl)carbamate was obtained (4.80 g, 87% yield).

To a solution of the above solid, *tert*-butyl methoxy(2-(phenylethynyl)benzoyl)carbamate (1.56 g, 4.4 mmol), in toluene (20 mL) were successively added $PdCl_2(PPh_3)_2$ (308.8 mg, 0.44 mmol), CuI (41.9 mg, 0.22 mmol), phenylacetylene (1.4 mL, 13.2 mmol), and *tert*-butylamine (0.93 mL, 8.8 mmol). The mixture was stirred at 50 °C in an oil bath for 3 h. After completion of the reaction, the crude was filtrated by chromatography on silica gel (pentane/Et_2O 9:1 to 8:2) to afford the crude product. Then, the solvent was removed, and trifluoroacetic acid (3 mL) in CH_2Cl_2 (5 mL) was added at 0 °C. The crude mixture was purified by flash chromatography on silica gel to afford the pure product **1a** (0.905 g, 82%) as a white solid. Other substrates **1** were prepared according to the above procedure.

General Procedure for the Synthesis of Compounds 3 and 4. 2-Alkynylbenzamide **1** (0.2 mmol), TBAB (2.0 equiv), and oxone (2.0 equiv) were added to a test tube, and then solvent H_2O (2.0 mL) and 1,4-dioxane (10.0 equiv) were added. The mixture was stirred at 80 °C in a heating mantle overnight. After the disappearance of the substrate as indicated by TLC, the last mixture was filtrated, and the resulting filtrate was extracted by ethyl acetate (EA) (3 × 2 mL). The organic layers were combined and dried by Na_2SO_4. After another filtration, evaporation of the solvent, and purification by flash column chromatography, the desired products **3** and **4** were obtained.

*N-Methoxy-2-(phenylethynyl)benzamide (**1a**).*[10] Following the general procedure, **1a** was purified by silica gel chromatography (EA/PE = 1/5). Yield: 82%, 906 mg, white solid, mp 107−109 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.88 (s, 1H), 7.83 (d, *J* = 5.8 Hz, 1H), 7.56−7.47 (m, 3H), 7.42−7.29 (m, 5H), 3.86 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 165.1, 133.6, 133.0, 131.5, 130.8, 129.5, 129.1, 128.8, 128.5, 122.0, 119.9, 95.1, 87.1, 64.6.

*N,5-Dimethoxy-2-(phenylethynyl)benzamide (**1b**).*[10] Following the general procedure, **1b** was purified by silica gel chromatography (EA/PE = 1/5). Yield: 80%, 990 mg, white solid, mp 155−158 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.98 (s, 1H), 7.52−7.45 (m, 4H), 7.40−7.33 (m, 3H), 6.99−6.96 (m, 1H), 3.89 (s, 3H), 3.84 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 164.7, 159.9, 134.9, 134.6, 131.3, 128.9, 128.6, 122.2, 118.1, 114.0, 111.7, 94.0, 87.3, 64.6, 55.6.

*5-Fluoro-N-methoxy-2-(phenylethynyl)benzamide (**1d**).*[10] Following the general procedure, **1d** was purified by silica gel chromatography (EA/PE = 1/5). Yield: 81%, 923 mg, white solid, mp 133−135 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.99 (s, 1H), 7.64 (d, *J* = 8.6 Hz, 1H), 7.57−7.50 (m, 3H), 7.37−7.34 (m, 3H), 7.17−7.11 (m, 1H), 3.88 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 162.3 (d, *J* = 252.2 Hz), 135.7, 135.2 (d, *J* = 8.0 Hz), 131.4, 129.3, 128.6, 121.7, 118.5 (d, *J* = 22.3 Hz), 117.0 (d, *J* = 24.4 Hz), 116.0, 113.5, 95.1, 86.2, 64.6.

*5-Bromo-N-methoxy-2-(phenylethynyl)benzamide (**1e**).*[10] Following the general procedure, **1e** was purified by silica gel chromatography (EA/PE = 1/5). Yield: 80%, 1158 mg, white solid, mp 112−114 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.87 (s, 1H), 8.05 (s, 1H), 7.58−7.49 (m, 3H), 7.42−7.37 (m, 4H), 3.88 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 163.6, 134.9, 134.3, 134.0, 132.7, 131.5, 129.4, 128.6, 123.2, 121.6, 118.7, 96.4, 86.3, 64.7.

*5-Chloro-N-methoxy-2-(phenylethynyl)benzamide (**1f**).*[10] Following the general procedure, **1f** was purified by silica gel

https://dx.doi.org/10.1021/acs.joc.9b03466
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chromatography (EA/PE = 1/5). Yield: 78%, 978 mg, white solid, mp 110−112 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.89 (s, 1H), 7.90 (s, 1H), 7.54−7.47 (m, 3H), 7.43−7.35 (m, 4H), 3.89 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 163.7, 135.1, 134.8, 134.2, 131.5, 131.1, 129.9, 129.4, 128.6, 121.5, 118.3, 96.3, 86.2, 64.7.

*N-Methoxy-3-(phenylethynyl)-2-naphthamide (**1p**).*[10] Following the general procedure, **1p** was purified by silica gel chromatography (EA/PE = 1/5). Yield: 62%, 821 mg, white solid, mp 130−132 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.84 (s, 1H), 8.46 (d, *J* = 8.1 Hz, 1H), 7.89−7.83 (m, 3H), 7.66−7.57 (m, 4H), 7.47−7.39 (m, 3H), 3.94 (s, 3H)·$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 165.9, 134.0, 132.7, 132.3, 131.6, 129.4, 129.2, 128.7, 128.3, 127.9, 127.7, 127.0, 125.3, 122.0, 118.1, 100.9, 85.1, 64.7.

*N-Methoxy-2-(p-tolylethynyl)benzamide (**1i**).*[10] Following the general procedure, **1i** was purified by silica gel chromatography (EA/PE = 1/5). Yield: 72%, 840 mg, white solid, mp 109−112 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.87 (s, 1H), 7.92 (d, *J* = 6.2 Hz, 1H), 7.58−7.52 (m, 1H), 7.45−7.38 (m, 4H), 7.17 (d, *J* = 7.9 Hz, 2H), 3.88 (s, 3H), 2.37 (s, 3H).

*2-((4-Fluorophenyl)ethynyl)-N-methoxybenzamide (**1k**).*[10] Following the general procedure, **1k** was purified by silica gel chromatography (EA/PE = 1/5). Yield: 75%, 888 mg, white solid, mp 148−150 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.62 (s, 1H), 7.89 (d, *J* = 6.3 Hz, 1H), 7.57−7.49 (m, 3H), 7.48−7.40 (m, 2H), 7.07 (t, *J* = 8.5 Hz, 2H), 3.89 (s, 3H).

*2-((2-Chlorophenyl)ethynyl)-N-methoxybenzamide (**1l**).*[10] Following the general procedure, **1l** was purified by silica gel chromatography (EA/PE = 1/5). Yield: 76%, 953 mg, white solid, mp 107−109 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.19 (s, 1H), 8.11−8.05 (m, 1H), 7.61 (m, 2H), 7.50−7.42 (m, 3H), 7.35−7.27 (m, 2H), 3.90 (s, 3H).

*2-(Cyclopropylethynyl)-N-methoxybenzamide (**1n**).*[10] Following the general procedure, **1n** was purified by silica gel chromatography (EA/PE = 1/5). Yield: 67%, 634 mg, white solid, mp 80−82 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.94 (s, 1H), 7.91 (d, *J* = 6.1 Hz, 1H), 7.43−7.31 (m, 3H), 3.89 (s, 3H), 1.53−1.46 (m, 1H), 0.97−0.91 (m, 2H), 0.88−0.82 (m, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 165.1, 133.2, 133.1, 130.9, 129.7, 128.1, 120.2, 100.4, 74.1, 64.5, 8.8, 0.2.

*N-(Benzyloxy)-2-(phenylethynyl)benzamide (**1p**).*[10] Following the general procedure, **1p** was purified by silica gel chromatography (EA/PE = 1/5). Yield: 80%, 1151 mg, white solid, mp 129−131 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.86 (s, 1H), 7.97 (s, 1H), 7.58−7.52 (m, 1H), 7.46−7.32 (m, 9H), 7.28−7.25 (m, 3H), 5.06 (s, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 164.9, 135.3, 133.2, 131.6, 131.0, 129.8, 129.1, 128.8, 128.6, 128.5, 128.5, 121.7, 119.9, 95.5, 87.2, 78.4.

*2-(3-Hydroxyprop-1-yn-1-yl)-N-methoxybenzamide (**1q**).*[10] Following the general procedure, **1q** was purified by silica gel chromatography (EA/PE = 1/5). Yield: 44%, 397 mg, white solid, mp 110−112 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.13 (s, 1H), 7.68 (d, *J* = 6.0 Hz, 1H), 7.42−7.29 (m, 3H), 4.47 (s, 2H), 3.95 (s, 1H), 3.81 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 165.3, 133.7, 133.0, 130.8, 129.1, 128.7, 119.8, 93.7, 82.9, 64.4, 51.1.

*3-Benzoyl-3-hydroxy-2-methoxyisoindolin-1-one (**3a**).* **3a** was purified by silica gel chromatography (EA/PE = 1/5). Yield: 88%, 50 mg, white solid, mp 135−137 °C ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (d, *J* = 7.7 Hz, 1H), 7.90 (d, *J* = 7.6 Hz, 1H), 7.77 (t, *J* = 7.5 Hz, 1H), 7.63 (t, *J* = 7.5 Hz, 1H), 7.43−7.39 (m, 2H), 7.30−7.24 (m, 3H), 5.16 (s, 1H), 4.02 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 190.7, 161.4, 136.5, 135.7, 133.4, 130.7, 129.4, 129.2, 128.9, 128.7, 127.4, 126.4, 93.9, 65.3; IR (KBr): 3265, 1702, 1645, 1579, 1384, 1283, 1132, 1024, 991, 869, 757; HRMS (ESI-TOF) *m*/*z*: (M + H)$^+$ calcd for $C_{16}H_{14}NO_4^+$, 284.0917; found, 284.0915.

*3-Benzoyl-3-hydroxy-2,6-dimethoxyisoindolin-1-one (**3b**).* **3b** was purified by silica gel chromatography (EA/PE = 1/5). Yield: 63%, 40 mg, white solid, mp 162−164 °C ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93−7.84 (m, 1H), 7.80−7.79 (m, 1H), 7.40−7.38 (m, 2H), 7.31−7.24 (m, 3H), 7.12−7.09 (m, 1H), 4.98 (s, 1H), 4.02 (s, 3H), 3.95 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 189.5, 165.7, 161.1, 137.0, 133.4, 129.9, 129.2, 128.8, 126.2, 122.0, 120.5, 111.8, 93.5, 65.2, 56.1; IR (KBr): 3259, 1686, 1640, 1594, 1448, 1371, 1131, 1281, 1131, 998, 873, 757; HRMS (ESI-TOF) *m*/*z*: (M + H)$^+$ calcd for $C_{17}H_{16}NO_5^+$, 314.1023; found, 314.1027.

*3-Benzoyl-3-hydroxy-2-methoxy-5-methylisoindolin-1-one (**3c**).* **3c** was purified by silica gel chromatography (EA/PE = 1/5). Yield: 65%, 39 mg, white solid, mp 148−150 °C ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (d, *J* = 8.0 Hz, 1H), 7.70 (s, 1H), 7.59−7.57 (m, 1H), 7.41−7.37 (m, 2H), 7.31−7.23 (m, 3H), 5.02 (s, 1H), 4.02 (s, 3H), 2.40 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 191.0, 161.7, 144.4, 136.6, 136.5, 129.3, 129.1, 128.9, 128.7, 128.2, 127.6, 126.4, 93.9, 65.3, 21.4; IR (KBr): 3266, 1706, 1658, 1644, 1373, 1287, 1125, 1008, 870, 752; HRMS (ESI-TOF) *m*/*z*: (M + H)$^+$ calcd for $C_{17}H_{16}NO_4^+$, 298.1074; found, 298.1074.

*3-Benzoyl-6-fluoro-3-hydroxy-2-methoxyisoindolin-1-one (**3d**).* **3d** was purified by silica gel chromatography (EA/PE = 1/5). Yield: 77%, 47 mg, white solid, mp 149−151 °C ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03−7.88 (m, 2H), 7.42−7.36 (m, 2H), 7.34−7.27 (m, 4H), 5.09 (s, 1H), 4.02 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 189.2, 167.2 (d, *J* = 260.4 Hz), 160.2, 136.3, 133.9 (d, *J* = 9.3 Hz), 130.8 (d, *J* = 9.5 Hz), 129.5, 129.0, 126.3, 125.6 (d, *J* = 3.1 Hz), 121.0 (d, *J* = 22.7 Hz), 115.7 (d, *J* = 24.6 Hz), 93.9, 65.3. IR (KBr): 3296, 1699, 1646, 1602, 1441, 1362, 1277, 1156, 1008, 816, 763; HRMS (ESI-TOF) *m*/*z*: (M + H)$^+$ calcd for $C_{16}H_{13}FNO_4^+$, 302.0823; found, 302.0813.

*3-Benzoyl-6-bromo-3-hydroxy-2-methoxyisoindolin-1-one (**3e**).* **3e** was purified by silica gel chromatography (EA/PE = 1/5). Yield: 69%, 50 mg, white solid, mp 188−189 °C ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56−8.42 (m, 1H), 7.82−7.76 (m, 2H), 7.41−7.36 (m, 2H), 7.33−7.28 (m, 3H), 4.81 (s, 1H), 4.04 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 189.8, 160.2, 136.6, 136.2, 132.0, 131.8, 131.5, 129.6, 129.0, 128.9, 127.7, 126.3, 93.9, 65.4; IR (KBr): 3291, 1700, 1642, 1581, 1424, 1352, 1276, 1136, 875, 717; HRMS (ESI-TOF) *m*/*z*: (M + H)$^+$ calcd for $C_{16}H_{13}BrNO_4^+$, 362.0022; found, 362.0040.

*3-Benzoyl-6-chloro-3-hydroxy-2-methoxyisoindolin-1-one (**3f**).* **3f** was purified by silica gel chromatography (EA/PE = 1/5). Yield: 76%, 48 mg, white solid, mp 169−171 °C ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (s, 1H), 7.88−7.86 (m, 1H), 7.62−7.59 (m, 1H), 7.40−7.38 (m, 2H), 7.32−7.28 (m, 3H), 4.95 (s, 1H), 4.03 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 189.6, 160.3, 142.8, 136.2, 133.6, 132.2, 129.6, 129.0, 128.7, 128.4, 127.4, 126.3, 93.9, 65.4; IR (KBr): 3288, 1701, 1646, 1586, 1449, 1354, 1276, 1136, 1021, 875; HRMS (ESI-TOF) *m*/*z*: (M + H)$^+$calcd for $C_{16}H_{13}ClNO_4^+$, 318.0528; found, 318.0528.

*3-Benzoyl-3-hydroxy-2-methoxy-2,3-dihydro-1H-benzo[f]-isoindol-1-one (**3g**).* **3g** was purified by silica gel chromatography (EA/PE = 1/8). Yield: 69%, 46 mg, white solid, mp 144−146 °C ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06−8.03 (m, 1H), 7.98−7.88 (m, 2H), 7.79−7.76 (m, 1H), 7.60−7.51 (m, 2H), 7.46−7.35 (m, 3H), 7.19−7.15 (m, 2H), 6.22 (s, 1H), 4.03 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 196.4, 165.2, 138.2, 136.2, 134.0, 132.6, 131.9, 129.3, 128.7, 128.6, 128.4, 128.3, 127.8, 127.1, 123.1, 119.5, 90.5, 66.3; IR (KBr): 3349, 1718, 1693, 1444, 1290, 1256, 1170, 1123, 1036, 984, 760; HRMS (ESI-TOF) *m*/*z*: (M + H)$^+$ calcd for $C_{20}H_{16}NO_4^+$, 334.1074; found, 334.1070.

*4-Benzoyl-4-hydroxy-5-methoxy-4H-cyclopenta[b]thiophen-6(5H)-one (**3h**).* **3h** was purified by silica gel chromatography (EA/PE = 1/5). Yield: 87%, 50 mg, white solid, mp 180−182 °C ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, *J* = 5.1 Hz, 1H), 7.47−7.39 (m, 3H), 7.36−7.31 (m, 3H), 4.64 (s, 1H), 4.01 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 185.4, 157.6, 144.8, 137.0, 136.4, 133.3, 129.5, 128.9, 126.3, 125.7, 95.2, 65.5; IR (KBr): 3407, 1702, 1648, 1529, 1354, 1255, 1186, 1011, 956, 849, 756; HRMS (ESI-TOF) *m*/*z*: (M + H)$^+$ calcd for $C_{14}H_{12}NO_4S^+$, 290.0482; found, 290.0488.

*3-Hydroxy-2-methoxy-3-(4-methylbenzoyl)isoindolin-1-one (**3i**).* **3i** was purified by silica gel chromatography (EA/PE = 1/5). Yield: 77%, 46 mg, white solid, mp 127−129 °C ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.39−8.32 (m, 1H), 7.94−7.92 (m, 1H), 7.83−7.77 (m, 1H), 7.68−7.62 (m, 1H), 7.29−7.27 (m, 2H), 7.09 (d, *J* = 8.1 Hz, 2H), 4.79 (s, 1H), 4.05 (s, 3H), 2.26 (s, 3H). $^{13}C\{^1H\}$ NMR (100

https://dx.doi.org/10.1021/acs.joc.9b03466
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MHz, $CDCl_3$): δ 190.7, 161.5 139.5, 135.6, 133.5, 133.3, 130.8, 129.6, 129.2, 128.7, 127.4, 126.3, 93.9, 65.3, 21.0; IR (KBr): 3296, 1706, 1667, 1596, 1581, 1380, 1285, 1117, 1038, 995, 819; HRMS (ESI-TOF) *m/z*: $(M + H)^+$ calcd for $C_{17}H_{16}NO_4^+$, 298.1074; found, 298.1070.

*3-([1,1′-Biphenyl]-4-carbonyl)-3-hydroxy-2-methoxyisoindolin-1-one (**3j**).* **3j** was purified by silica gel chromatography (EA/PE = 1/5). Yield: 81%, 58 mg, white solid, mp 174−176 °C ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38−8.36 (d, *J* = 7.7 Hz, 1H), 7.96 (d, *J* = 7.7 Hz, 1H), 7.85−7.78 (m, 1H), 7.70−7.63 (m, 1H), 7.53−7.47 (m, 6H), 7.43−7.27 (m, 3H), 5.06 (s, 1H), 4.08 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 190.7, 161.5, 142.3, 139.9, 135.7, 135.4, 133.4, 131.9, 130.8, 129.2, 128.8, 128.7, 127.7, 127.6, 127.0, 126.9, 93.9, 65.4. IR (KBr): 3304, 1706, 1659, 1638, 1582, 1387, 1282, 994, 763, 694; HRMS (ESI-TOF) *m/z*: $(M + H)^+$ calcd for $C_{22}H_{18}NO_4^+$, 360.1230; found, 360.1233 360.1230.

*3-(4-Fluorobenzoyl)-3-hydroxy-2-methoxyisoindolin-1-one (**3k**).* **3k** was purified by silica gel chromatography (EA/PE = 1/5). Yield: 51%, 31 mg, white solid, mp 147−149 °C ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (d, *J* = 7.3 Hz, 1H), 7.94−7.92 (m, 1H), 7.83−7.79 (m, 1H), 7.69−7.65 (m, 1H), 7.40−7.37 (m, 2H), 6.99−6.95 (m, 2H), 5.02 (s, 1H), 4.02 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 190.6, 163.2 (d, *J* = 249.8 Hz), 161.4, 135.8, 133.5, 132.4 (d, *J* = 3.1 Hz), 130.6, 129.0, 128.7, 128.5 (d, *J* = 8.7 Hz), 127.5, 115.9 (d, *J* = 22.0 Hz), 93.4, 65.3. IR (KBr): 3270, 1701, 1648, 1597, 1508, 1382, 1284, 1135, 1028, 995, 873, 733; HRMS (ESI-TOF) *m/z*: $(M + H)^+$ calcd for $C_{16}H_{13}FNO_4^+$, 302.0823; found, 302.0805.

*3-(2-Chlorobenzoyl)-3-hydroxy-2-methoxyisoindolin-1-one (**3l**).* **3l** was purified by silica gel chromatography (EA/PE = 1/5). Yield: 48%, 31 mg, white solid, mp 182−184 °C ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24−8.20 (m, 1H), 8.15−8.13 (m, 1H), 8.10−8.06 (m, 1H), 7.81−7.71 (m, 2H), 7.48−7.44 (m, 1H), 7.41−7.33 (m, 2H), 5.27 (s, 1H), 3.46 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 188.5, 161.2, 148.1, 135.1, 133.3, 131.8, 130.6, 130.2, 130.0, 129.9, 129.9, 128.6, 127.2, 127.0, 90.4, 63.6; IR (KBr): 3222, 1720, 1667, 1596, 1348, 1272, 1131, 1023, 859, 754; HRMS (ESI-TOF) *m/z*: $(M + H)^+$ calcd for $C_{16}H_{13}ClNO_4^+$, 318.0528; found, 318.0541.

*3-Hydroxy-2-methoxy-3-(thiophene-2-carbonyl)isoindolin-1-one (**3m**).* **3m** was purified by silica gel chromatography (EA/PE = 1/5). Yield: 87%, 50 mg, yellow solid, mp 112−114 °C ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92−7.90 (m, 1H), 7.61−7.58 (m, 2H), 7.34−7.32 (m, 1H), 7.11 (d, *J* = 4.1 Hz, 1H), 6.93 (d, *J* = 4.2 Hz, 1H), 5.83 (s, 1H), 4.01 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 185.4, 164.1, 140.8, 137.3, 135.9, 133.8, 131.8, 131.2, 129.4, 125.9, 124.3, 122.8, 89.9, 66.2; IR (KBr): 3351, 1709, 1655, 1399, 1304, 1075, 1003, 756, 679; HRMS (ESI-TOF) *m/z*: $(M + H)^+$ calcd for $C_{14}H_{12}NO_4S^+$, 290.0482; found, 290.0486.

*3-(Cyclopropanecarbonyl)-3-hydroxy-2-methoxyisoindolin-1-one (**3n**).* **3n** was purified by silica gel chromatography (EA/PE = 1/5). Yield: 67%, 33 mg, white solid, mp 114−116 °C ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89−7.87 (m, 1H), 7.65−7.55 (m, 2H), 7.33−7.31 (m, 1H), 5.55 (s, 1H), 4.02 (s, 3H), 1.54−1.47 (m, 1H), 1.21−1.13 (m, 1H), 1.05−0.99 (m, 2H), 0.82−0.74 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 204.4, 165.0, 140.0, 133.6, 130.7, 129.9, 124.0, 122.5, 91.3, 66.3, 15.1, 13.5, 13.3; IR (KBr): 3249, 2937, 1720, 1693, 1372, 1225, 1108, 1082, 892, 764; HRMS (ESI-TOF) *m/z*: $(M + H)^+$ calcd for $C_{13}H_{14}NO_4^+$, 248.0917; found, 248.0917.

*3-Hydroxy-2-methoxy-3-((8R,9S,13S,14S)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]-phenanthrene-2-carbonyl)isoindolin-1-one (**3o**).* **3o** was purified by silica gel chromatography (EA/PE = 1/4). Yield: 54%, 50 mg, white solid, mp 99−101 °C ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 (d, *J* = 7.8 Hz, 1H), 7.95 (d, *J* = 7.7 Hz, 1H), 7.84−7.80 (m, 1H), 7.67 (t, *J* = 7.6 Hz, 1H), 7.21−7.10 (m, 3H), 4.71 (s, 1H), 4.06 (s, 3H), 2.93−2.78 (m, 2H), 2.50−2.43 (m, 1H), 2.35−2.27 (m, 1H), 2.15−2.02 (m, 2H), 2.00−1.89 (m, 2H), 1.67−1.53 (m, 2H), 1.52−1.34 (m, 5H), 0.84 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 220.6, 190.7, 161.3, 141.3, 137.5, 135.6, 133.9, 133.3, 130.9, 129.2, 128.7, 127.5, 126.9, 126.0, 123.6, 93.8, 65.3, 50.4, 47.8, 44.2, 37.7, 35.7, 31.4, 29.4, 26.2, 25.4, 21.5, 13.7. IR (KBr): 3387, 2955, 2925, 2853, 1735, 1709, 1661, 1463, 1375, 1280, 992; HRMS (ESI-TOF) *m/z*: $(M + H)^+$ calcd for $C_{28}H_{30}NO_5^+$, 460.2118; found, 460.2110.

*3-Benzoyl-2-(benzyloxy)-3-hydroxyisoindolin-1-one (**3p**).* **3p** was purified by silica gel chromatography (EA/PE = 1/5). Yield: 83%, 60 mg, white solid, mp 159−161 °C ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 (d, *J* = 7.3 Hz, 1H), 7.95 (d, *J* = 7.2 Hz, 1H), 7.83−7.79 (m, 1H), 7.68−7.64 (m, 1H), 7.49−7.40 (m, 4H), 7.29−7.23 (m, 6H), 5.25−5.18 (m, 2H), 4.77 (s, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 190.8, 161.7, 136.7, 135.7, 134.9, 133.3, 130.8, 129.6, 129.3, 129.3, 128.9, 128.6, 128.3, 127.4, 126.4, 123.5, 93.8, 79.6; IR (KBr): 3303, 2893, 1698, 1645, 1580, 1361, 1284, 1179, 1133, 977, 757; HRMS (ESI-TOF) *m/z*: $(M + H)^+$ calcd for $C_{22}H_{18}NO_4^+$, 360.1230; found, 360.1224.

*3-Benzoyl-3-hydroxy-2-phenylisoindolin-1-one (**3q**).* **3q** was purified by silica gel chromatography (EA/PE = 1/10). Yield: 61%, 40 mg, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05−8.01 (m, 1H), 7.65−7.62 (m, 2H), 7.50−7.47 (m, 1H), 7.43−7.36 (m, 5H), 7.33−7.19 (m, 3H), 7.10−7.06 (m, 2H), 6.01 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 195.5, 167.7, 144.0, 134.4, 133.9, 133.8, 132.2, 131.0, 130.9, 129.3, 128.9, 128.1, 124.9, 122.7, 121.3, 91.8; IR (KBr): 3372, 1716, 1682, 1490, 1343, 1180, 1070, 818, 758; HRMS (ESI-TOF) *m/z*: $(M + H)^+$ calcd for $C_{21}H_{16}NO_3^+$, 330.1125; found, 330.1121.

*3-Benzoyl-2-(tert-butyl)-3-hydroxyisoindolin-1-one (**3r**).* **3r** was purified by silica gel chromatography (EA/PE = 1/10). Yield: 49%, 30 mg, yellow solid, mp 115−117 °C ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90−7.84 (m, 1H), 7.66−7.61 (m, 2H), 7.54−7.44 (m, 3H), 7.31−7.25 (m, 2H), 7.16−7.13 (m, 1H), 5.72 (s, 1H), 1.40 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 197.9, 169.7, 144.8, 134.2, 132.9, 132.3, 131.8, 130.3, 129.8, 128.7, 123.9, 121.2, 92.8, 56.9, 28.1; IR (KBr): 3367, 2967, 2928, 1688, 1674, 1599, 1528, 1488, 1394, 1221, 813; HRMS (ESI-TOF) *m/z*: $(M + H)^+$ calcd for $C_{19}H_{20}NO_3^+$, 310.1438; found, 310.1430.

*3-Benzoyl-2-benzyl-3-hydroxyisoindolin-1-one (**3s**).* **3s** was purified by silica gel chromatography (EA/PE = 1/10). Yield: 60%, 41 mg, white solid, mp 120−122 °C ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, *J* = 7.3 Hz, 1H), 7.62−7.52 (m, 2H), 7.33−7.26 (m, 2H), 7.09−6.92 (m, 9H), 6.00 (s, 1H), 4.90 (d, *J* = 15.0 Hz, 1H), 4.31 (d, *J* = 15.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 196.1, 168.5, 144.7, 135.4, 133.7, 133.2, 131.8, 131.5, 130.6, 129.2, 129.2, 128.2, 128.0, 127.3, 124.4, 122.5, 89.9, 42.7; IR (KBr): 3223, 2925, 1692, 1648, 1450, 1288, 1173, 1122, 1069, 710, 698; HRMS (ESI-TOF) *m/z*: $(M + H)^+$ calcd for $C_{22}H_{18}NO_3^+$, 344.1281; found, 344.1289.

*3-Benzoyl-3-hydroxy-6-methoxy-2-phenylisoindolin-1-one (**3t**).* **3t** was purified by silica gel chromatography (EA/PE = 1/10). Yield: 89%, 64 mg, white solid, mp 80−82 °C ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53−7.47 (m, 2H), 7.44−7.37 (m, 4H), 7.29−7.25 (m, 4H), 7.19−7.14 (m, 1H), 7.08−7.04 (m, 2H), 3.93 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 195.9, 167.6, 162.0, 135.9, 134.3, 133.9, 132.8, 132.4, 132.2, 129.3, 128.8, 128.0, 123.7, 121.4, 121.3, 108.1, 91.6, 55.9; IR (KBr): 3381, 2925, 1713, 1693, 1596, 1490, 1351, 1285, 1134, 1011, 826; HRMS (ESI-TOF) *m/z*: $(M + H)^+$ calcd for $C_{22}H_{18}NO_4^+$, 360.1230; found, 360.1212.

*3-Benzoyl-3-hydroxy-4-methyl-2-phenylisoindolin-1-one (**3u**).* **3u** was purified by silica gel chromatography (EA/PE = 1/10). Yield: 87%, 60 mg, white solid, mp 131−133 °C ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, *J* = 7.5 Hz, 1H), 7.56−7.38 (m, 8H), 7.29−7.25 (m, 2H), 7.03−7.00 (m, 2H), 5.92 (s, 1H), 2.19 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 195.8, 167.9, 141.6, 135.5, 134.6, 134.3, 133.4, 132.3, 132.2, 131.3, 130.9, 129.2, 129.0, 128.9, 122.4, 121.8, 91.5, 17.1; IR (KBr): 3387, 1725, 1709, 1668, 1488, 1332, 1113, 1003, 681; HRMS (ESI-TOF) *m/z*: $(M + H)^+$ calcd for $C_{22}H_{18}NO_3^+$, 344.1281; found, 344.1281.

*3-Benzoyl-6-fluoro-3-hydroxy-2-phenylisoindolin-1-one (**3v**).* **3v** was purified by silica gel chromatography (EA/PE = 1/10). Yield: 63%, 43 mg, white oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74−7.68 (m, 1H), 7.55−7.50 (m, 1H), 7.46−7.26 (m, 9H), 7.08−7.02 (m, 2H), 5.96 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 195.1, 166.4, 164.3 (d, *J* = 252.3 Hz), 139.5 (d, *J* = 2.7 Hz), 134.6, 133.5, 132.3, 132.0, 129.3, 129.0, 128.1, 124.6 (d, *J* = 8.7 Hz), 121.5 (d, *J* = 37.2

https://dx.doi.org/10.1021/acs.joc.9b03466
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Hz), 121.1, 112.1, 111.9, 91.3. IR (KBr): 3401, 1719, 1700, 1490, 1441, 1352, 1271, 1123, 825, 804; HRMS (ESI-TOF) m/z: $(M + H)^+$ calcd for $C_{21}H_{15}FNO_3^+$, 348.1030; found, 348.1071.

*3-Benzoyl-6-chloro-3-hydroxy-2-phenylisoindolin-1-one (**3w**).* **3w** was purified by silica gel chromatography (EA/PE = 1/10). Yield: 58%, 42 mg, yellow solid, mp 157−159 °C ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, J = 1.9 Hz, 1H), 7.61−7.59 (m, 1H), 7.53 (t, J = 7.4 Hz, 1H), 7.45−7.43 (m, 2H), 7.40−7.37 (m, 2H), 7.35−7.26 (m, 4H), 7.06−7.02 (m, 2H), 5.98 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 194.9, 166.3, 142.2, 137.3, 134.7, 133.9, 133.4, 132.8, 132.3, 131.9, 129.3, 129.0, 128.1, 125.1, 124.0, 121.7, 91.4; IR (KBr): 3440, 1679, 1631, 1384, 1177, 1102, 748, 618; HRMS (ESI-TOF) m/z: $(M + H)^+$ calcd for $C_{21}H_{15}ClNO_3^+$, 364.0735; found, 364.0735.

*2-(4-Bromophenyl)-3-hydroxy-3-(3-methylbenzoyl)isoindolin-1-one (**3x**).* **3x** was purified by silica gel chromatography (EA/PE = 1/10). Yield: 81%, 68 mg, white solid, mp 140−142 °C ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09−7.99 (m, 1H), 7.67−7.60 (m, 2H), 7.45−7.34 (m, 3H), 7.33−7.26 (m, 2H), 7.15−7.04 (m, 4H), 5.99 (s, 1H), 2.22 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 195.6, 167.6, 144.1, 138.8, 135.3, 133.9, 133.8, 132.2, 132.1, 131.1, 130.8, 130.0, 128.7, 128.2, 126.3, 124.8, 122.7, 121.3, 91.7, 21.2; IR (KBr): 3253, 1698, 1678, 1491, 1371, 1115, 1063, 799, 776; HRMS (ESI-TOF) m/z: $(M + H)^+$ calcd for $C_{22}H_{17}BrNO_3^+$, 422.0386; found, 422.0381.

*3-(4-Chlorobenzoyl)-3-hydroxy-2-phenylisoindolin-1-one (**3y**).* **3y** was purified by silica gel chromatography (EA/PE = 1/10). Yield: 55%, 40 mg, white solid, mp 145−147 °C ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06−8.01 (m, 1H), 7.67−7.63 (m, 2H), 7.43−7.37 (m, 5H), 7.30−7.23 (m, 3H), 7.14−7.00 (m, 2H), 5.93 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 194.4, 167.5, 143.8, 141.2, 133.9, 133.7, 132.3, 131.1, 130.7, 130.4, 129.3, 129.1, 127.9, 126.7, 125.0, 122.7, 91.7; IR (KBr): 3381, 1717, 1694, 1586, 1490,1347, 1092, 1011, 815, 765; HRMS (ESI-TOF) m/z: $(M + H)^+$ calcd for $C_{21}H_{15}ClNO_3^+$, 364.0735; found, 364.0731.

*3-(3-Fluorobenzoyl)-3-hydroxy-2-phenylisoindolin-1-one (**3z**).* **3z** was purified by silica gel chromatography (EA/PE = 1/10). Yield: 50%, 35 mg, white solid, mp 136−138 °C ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08−8.03 (m, 1H), 7.69−7.66 (m, 2H), 7.43−7.38 (m, 3H), 7.23−7.07 (m, 7H), 5.84 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 194.7, 167.5, 162.3 (d, J = 249.6 Hz), 143.6, 133.9, 133.7, 132.3, 131.2, 130.9, 130.7 (d, J = 7.7 Hz), 128.0, 125.0, 124.9 (d, J = 3.3 Hz), 122.7, 121.7, 121.5 (d, J = 6.6 Hz), 116.3 (d, J = 23.5 Hz), 104.9, 91.7. IR (KBr): 3416, 1717, 1685, 1585, 1490, 1177, 1117, 618; HRMS (ESI-TOF) m/z: $(M + H)^+$ calcd for $C_{21}H_{15}FNO_3^+$, 348.1030; found, 348.1053.

*3-(Dibromo(methoxy)methyl)-3-hydroxy-2-methoxyisoindolin-1-one (**4a**).* **4a** was purified by silica gel chromatography (EA/PE = 1/5). Yield: 69%, 54 mg, white solid, mp 177−179 °C ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (d, J = 7.6 Hz, 1H), 7.79 (d, J = 7.4 Hz, 1H), 7.64−7.60 (m, 1H), 7.56−7.53 (m, 1H), 6.07 (s, 1H), 4.83 (d, J = 10.8 Hz, 1H), 4.15 (d, J = 10.8 Hz, 1H), 4.09 (s, 3H), 3.63 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 162.9, 141.3, 132.2, 130.6, 129.9, 124.5, 122.9, 94.5, 83.4, 68.8, 65.7, 59.7. IR (KBr): 3369, 2941, 1716, 1466, 1390, 1203, 1115, 1092, 976, 758; HRMS (ESI-TOF) m/z: $(M + H)^+$ calcd for $C_{12}H_{14}Br_2NO_4^+$, 393.9284; found, 393.9282.

*5-Benzoyl-5-hydroxy-1-methoxypyrrolidin-2-one (**3aa**).* **3aa** was purified by silica gel chromatography (EA/PE = 1/3). Yield: 41%, 19 mg, white oil ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, J = 7.4 Hz, 2H), 7.62 (t, J = 7.4 Hz, 1H), 7.48 (t, J = 7.8 Hz, 2H), 5.44 (s, 1H), 3.90 (s, 3H), 2.76−2.70 (m, 1H), 2.51−2.40 (m, 2H), 2.22−2.14 (m, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 196.7, 170.2, 134.1, 132.2, 129.4, 129.0, 91.0, 65.0, 29.6, 25.6; HRMS (ESI-TOF) m/z: $(M + H)^+$ calcd for $C_{12}H_{14}NO_4^+$, 236.0917; found, 236.0917.

*3-(1,1-Dibromo-2-hydroxyethyl)-3-hydroxy-2-methoxyisoindolin-1-one (**4b**).* **4b** was purified by silica gel chromatography (EA/PE = 1/4). Yield: 47%, 36 mg, white solid, mp 174−176 °C ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (d, J = 7.6 Hz, 1H), 7.81 (d, J = 7.4 Hz, 1H), 7.68−7.62 (m, 1H), 7.61−7.54 (m, 1H), 6.02 (s, 1H), 4.96 (d, J = 12.7 Hz, 1H), 4.38 (d, J = 12.7 Hz, 1H), 4.13 (s, 3H). 3.94 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 163.4, 141.1, 132.4, 130.7, 129.8, 124.5, 123.1, 94.6, 74.0, 73.7, 65.9; IR (KBr): 3250, 1706, 1467, 1359, 1068, 1012, 744, 690; HRMS (ESI-TOF) m/z: $(M + H)^+$ calcd for $C_{11}H_{12}Br_2NO_4^+$, 379.9128; found, 379.9132.

*3-(Bromo(phenyl)methylene)-2-methoxyisoindolin-1-one (**5**).* **5** was purified by silica gel chromatography (EA/PE = 1/50). Yield: 9%, 6 mg, white solid ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, J = 7.9 Hz, 1H), 7.83−7.75 (m, 2H), 7.71 (d, J = 8.0 Hz, 1H), 7.52 (t, J = 7.7 Hz, 1H), 7.49−7.39 (m, 3H), 7.36 (t, J = 7.6 Hz, 1H), 3.96 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 149.2, 147.4, 133.1, 131.3, 130.7, 129.9, 129.6, 128.9, 128.1, 126.2, 123.7, 121.4, 100.6, 62.9; HRMS (ESI-TOF) m/z: $(M + H)^+$ calcd for $C_{16}H_{13}BrNO_2^+$, 330.0124; found, 330.0124.

*2-(2,2-Dibromo-3,3-dimethylbutanoyl)-N-methoxybenzoate (**5a**).* **5a** was purified by silica gel chromatography (EA/PE = 1/100). Yield: 55%, white oil ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98−7.95 (m, 2H), 7.58−7.47 (m, 2H), 3.85 (s, 3H), 1.52 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.1, 166.6, 139.7, 131.3, 130.2, 130.1, 129.6, 129.3, 83.4, 52.5, 44.8, 28.3; IR (KBr): 3401, 2977, 2952, 2931, 1729, 1706, 1434, 1281, 1139, 1091, 710; HRMS (ESI) calcd for $C_{14}H_{17}Br_2O_3^+$, 390.9539 (M^+ + H): found, 390.9539.

*2-(2,2-Dibromo-3-methylbutanoyl)-N-methoxybenzoate (**5b**).* **5b** was purified by silica gel chromatography (EA/PE = 1/100). Yield: 51%, white oil ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99−7.92 (m, 2H), 7.60−7.50 (m, 2H), 3.86 (s, 3H), 2.93−2.83 (m, 1H), 1.31 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.2, 166.5, 138.6, 131.5, 130.2, 129.9, 129.8, 129.6, 78.9, 52.6, 40.0, 20.2; IR (KBr): 3413, 2973, 2943, 1728, 1432, 1284, 1215, 1093, 932, 709; HRMS (ESI) calcd for $C_{13}H_{15}Br_2O_3^+$, 376.9382 (M^+ + H): found, 376.9384.

*2-(2,2-Dibromo-2-cyclohexylacetyl)-N-methoxybenzoate (**5c**).* **5c** was purified by silica gel chromatography (EA/PE = 1/100). Yield: 64%, white oil ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98−7.96 (m, 1H),7.91−7.90 (m, 1H), 7.62−7.54 (m, 1H), 7.54−7.48 (m, 1H), 3.86 (s, 3H), 2.50−2.40 (m, 1H), 2.34−2.28 (m, 2H), 1.89−1.83 (m, 2H), 1.72−1.69 (m, 1H), 1.46−1.31 (m, 4H), 1.28−1.18 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.0, 166.4, 138.6, 131.6, 130.2, 130.0, 129.7, 129.6, 78.3, 52.6, 49.1, 30.0, 26.0, 25.9; IR (KBr): 3428, 2931, 2854, 1727, 1283, 1217, 1138, 1097, 709, 618; HRMS (ESI) calcd for $C_{16}H_{19}Br_2O_3^+$, 416.9695 (M^+ + H): found, 416.9691.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.9b03466.

X-ray crystal structure for compounds (CCDC-1958230, 1958232, 1958234, 1958235, 1958236, and 1958231) (PDF)

Crystallographic data for compounds combined (CIF)

Crystallographic data for compound 5a (CIF)

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https://dx.doi.org/10.1021/acs.joc.9b03466
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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial supports from the Natural Science Foundation of China (nos: 21502069, 21571058, and 21772067) and the Zhejiang Provincial Natural Science Foundation (grant no. LY19B020004) are gratefully acknowledged.

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https://dx.doi.org/10.1021/acs.joc.9b03466
J. Org. Chem. XXXX, XXX, XXX−XXX