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Cascade Arylalkylation of Activated Alkenes: Synthesis of Chloro- and Cyano-Containing Oxindoles

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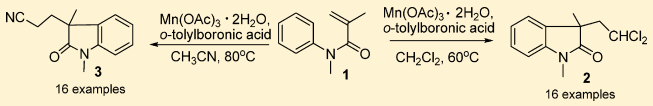
Supporting Information

ABSTRACT: The general method for the oxidative cyclization of arylacrylamides with dichloromethane or acetonitrile has been developed. The reactions described provide novel access to chloro- and cyano-containing oxindoles in good to moderate yields that allow the direct formation of a C−C bond and the construction of an oxindole ring in one reaction. The use of a cheap and easily prepared $Mn(OAc)_3$ represents an added advantage of this method.



INTRODUCTION

As one of the most important heterocyclic compounds, oxindoles have been considered a privileged structure in chemical, pharmaceutical, and materials industries.[1] They are also important intermediates in the synthesis of heterocyclic compounds.[2] Thus, the development of new methods for their synthesis has been a major focus of study.[3] Among the synthetic methods for obtaining oxindoles, the difunctionalization reaction of alkenes through a radical process is well-known. To date, various functional groups such as aryl, CF_3, and NO_2 groups have been successfully introduced into the oxindole skeleton.[4]

On the other hand, halogen-containing organic molecules are prevalent in natural sources. These compounds are of great structural diversity and exhibit a wide variety of biological activities, including antibiotic, antitumor, and analgesic activities.[5] Dichloromethylation is a synthetically useful reaction because the chloro group can easily convert to amino, hydroxyl, and carboxyl groups. The development of efficient methods for the introduction of dichloromethyl functional groups into organic compounds is therefore greatly important and has attracted considerable attention. In 2005, Walsh et al. reported a novel class of halogenating enzymes capable of conducting halogenations at aliphatic carbon centers.[6] In 2010 and 2011, Zakarian et al. reported a stereoselective chloroalkylation reaction of *N*-acyl oxazolidinones by dual Ti−Ru catalysis.[7] Metal-free radical cascade dichloromethylation of activated alkenes was reported by Li and Liu in 2014.[8] Recently, Loh described iron-catalyzed carbodi- and trichloromethylation of activated alkenes with readily available dichloro- and tetrachloromethane.[9] Although these advances have been made in recent years, development of a new method is highly desirable.

Economically and environmentally acceptable manganese salts are attractive because manganese is abundant. In particular, $Mn(OAc)_3$ is one of the most important oxidants used in radical reaction chemistry.[10] We have reported the synthesis of oxindoles via the reaction of arylacrylamides and diaryliodonium salts.[11] In our continuing research, when we replaced diaryliodonium salts with phenylboronic acids (2.0 equiv) mediated by $Mn(OAc)_3$ (2.0 equiv) in dichloromethane, an only 12% yield of phenyl-substituted product was obtained. Surprisingly, a 64% yield of dichloromethyl-substituted oxindole was obtained. Because of the current pharmacologically and synthetically important chloro-containing oxindoles, we investigated the $Mn(OAc)_3$-arylboronic acid-mediated cascade oxidative dichloromethylation and cyclization of arylacrylamides with dichloromethane.

RESULTS AND DISCUSSION

The reaction did not occur at all in the absence of $Mn(OAc)_3 \cdot 2H_2O$ or phenylboronic acid (Table 1, entries 1 and 2). Screening of a few other arylboronic acids, such as 2-methyl- and 2,6-dimethyl-substituted derivatives, revealed that *o*-tolylboronic acid was the best choice and the yield could reach 75% (entries 3−6). However, the yield of product **2a** remained almost the same when the loading of $Mn(OAc)_3 \cdot 2H_2O$ was increased to 3.0 equiv (entries 4 and 7). Further screening indicated that the choice of temperature is also very crucial for the reaction (entries 5, 8, and 9). The reaction performed well at 60 °C and gave **2a** in 75% yield. However, the yield of product **2a** decreased when the temperature was increased to 80 °C or decreased to 50 °C. Furthermore, the yield of product **2a** also decreased greatly when the loading of $Mn(OAc)_3 \cdot 2H_2O$ or *o*-tolylboronic acid was decreased (entries 10 and 11). Other oxidants such as silver salts[12] and TBHP[13] were also investigated, but the reaction did not work well under those conditions (entries 12−14). Moreover, no desired product was obtained when 2.0 equiv of TEMPO was added to the reaction mixture using the optimal conditions (entry 15). Product **2a** was obtained in only 47% yield when the reaction was conducted under aerobic conditions (entry 16). After

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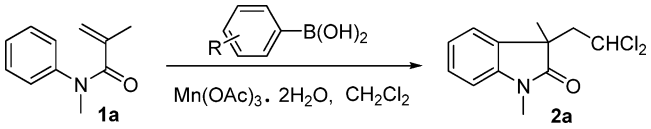
Table 1. Optimization of Reaction Conditions[a]



entry	R	oxidant	T^b (°C)	yield[c] (%)
1	–	$Mn(OAc)_3$ (2 equiv)	60	0
2	H	–	80	0
3	H	$Mn(OAc)_3$ (2 equiv)	room temperature	64
4	H	$Mn(OAc)_3$ (3 equiv)	60	68
5	2-Me	$Mn(OAc)_3$ (2 equiv)	60	75
6	2,6-Dime	$Mn(OAc)_3$ (2 equiv)	60	0
7	2-Me	$Mn(OAc)_3$ (3 equiv)	60	75
8	2-Me	$Mn(OAc)_3$ (2 equiv)	80	72
9	2-Me	$Mn(OAc)_3$ (2 equiv)	50	57
10	2-Me (1.5 equiv)	$Mn(OAc)_3$ (2 equiv)	60	53
11	2-Me	$Mn(OAc)_3$ (1.5 equiv)	60	39
12	2-Me	$AgNO_3$ (0.5 equiv)	60	trace
13	2-Me	AgOAc (3 equiv)	60	trace
14	2-Me	Bu_4NI (0.2 equiv) and TBHP (3 equiv)	60	trace
15	2-Me	$Mn(OAc)_3$ (2 equiv) and TEMPO (2 equiv)	60	trace
16	2-Me	$Mn(OAc)_3$ (2 equiv) and air	60	47

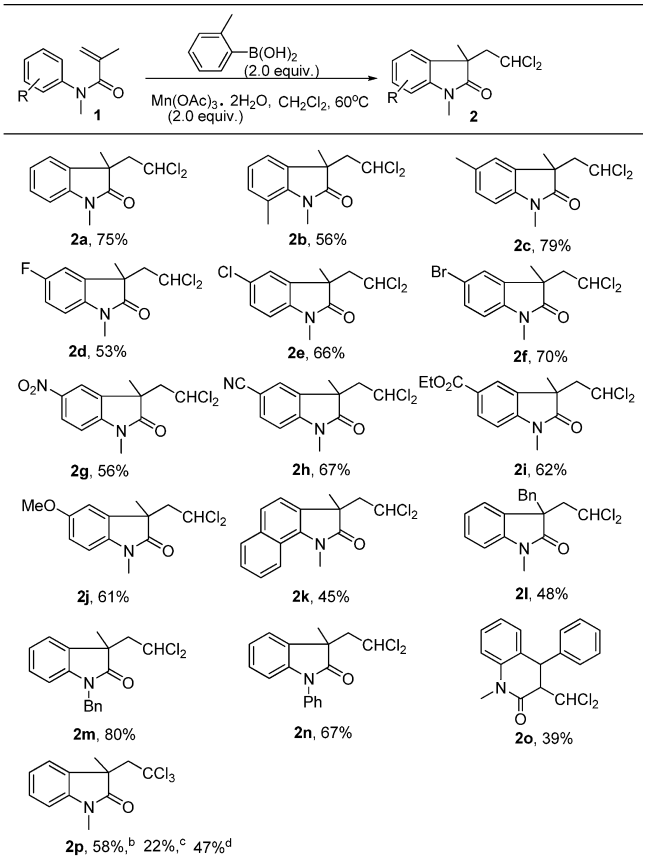
[a]Reaction conditions: **1a** (0.6 mmol), arylboronic acid, oxidant, CH_2Cl_2 (2.0 mL) under N_2 in a sealed Schlenk tube, 12 h. [b]Oil bath temperature. [c]Isolated yield.

optimization of the reaction conditions, we established a highly efficient route to the dichloromethylation and cyclization of arylacrylamides.

Subsequently, we evaluated the scope of substituted arylacrylamides **1** with dichloromethane, and the results are summarized in Table 2. In general, a variety of functional groups on the phenyl ring of arylacrylamides were compatible under this procedure, affording the desired products in moderate to good yields. The ortho-substituted arylacrylamides exhibited a particularly distinct steric hindrance effect (**2b** and **2c**), and the corresponding oxindole **2b** was obtained in low yield. Halo-substituted acrylamides worked well to afford the corresponding products in good yields (**2d**–**2f**), which could allow for further synthetic transformations. The substituted arylacrylamides with electron-withdrawing groups, such as nitro, nitrile, and acyl groups, reacted with dichloromethane efficiently and gave the desired products **2g**–**2i** in 56–67% yields. Treatment of dichloromethane with methoxy-substituted arylacrylamide led to the formation of product **2j** in 61% yield. More bulky substrates such as naphthalene acrylamide also smoothly reacted with dichloromethane and gave product **2k** in 45% yield. 2-Benzyl-*N*-methyl-*N*-phenylacrylamide also exhibited a distinct steric hindrance effect to afford **2l** in 48% yield. Different N-protection groups such as phenyl and benzyl were tolerated, leading to the corresponding products in good yields (**2m** and **2n**). When *N*-methyl-*N*-phenylcinnamamide was used, the desired six-membered ring **2o** was obtained in 39% yield. Trichloromethane and carbon tetrachloride could be also used as the starting materials, generating the trichloromethylation of arylacrylamide **2p** in slightly lower yields.

Encouraged by the findings described above, we continued to explore the synthesis of cyano-containing oxindoles. The

Table 2. Dichloromethylation of Arylacrylamides[a]



[a]Reaction conditions: arylacrylamide (0.6 mmol), $Mn(OAc)_3{\cdot}2H_2O$ (1.2 mmol), and *o*-tolylboronic acid (1.2 mmol) in CH_2Cl_2 (2.0 mL) under N_2 at 60 °C for 12 h. [b]CH_2Cl_2 in footnote [a] was replaced with $CHCl_3$. [c]CH_2Cl_2 in footnote [a] was replaced with CCl_4. [d]CH_2Cl_2 in footnote [a] was replaced with $CDCl_3$.

demand for cyano-containing organic compounds has stimulated extensive studies of the C–H activation of acetonitrile catalyzed by Fe, Rh, Ru, Ir, Ni, Au, Pd, and Cu.[14] To our delight, when acetonitrile was employed as the cyano source, the reaction took place under slightly modified conditions. The optimal reaction conditions are arylacrylamide (0.6 mmol), $Mn(OAc)_3{\cdot}2H_2O$ (1.2 mmol), and *o*-tolylboronic acid (1.2 mmol) in acetonitrile at 80 °C for 12 h under a nitrogen atmosphere.

We next examined the reactions of various substituted arylacrylamides **1** with acetonitrile to probe the scope of the reaction (Table 3). It was found that a wide range of arylacrylamides proceeded efficiently. Various arylacrylamides with electron-donating substitutents were investigated; the corresponding products were obtained in moderate to good yields (**3b**–**3g**). In addition, this reaction was also compatible with halogen substituents on the aromatic ring of arylacrylamides **1**. Thus, *p*-fluoro-, *p*-chloro-, and *p*-bromoacrylamides reacted with acetonitrile to give products **3h**–**3j** in 61, 57, and 68% yields, respectively. Electron-withdrawing substrates led to the formation of products **3k**–**3m** in good yields. 2-Benzyl-*N*-methyl-*N*-phenylacrylamide and *N*-benzyl-*N*-phenylacrylamide also reacted well with acetonitrile to afford **3n** and **3o** in 62 and 58% yields, respectively.

To gain insights into the mechanistic pathway, a series of control experiments were conducted (Scheme 1). A 7% yield of

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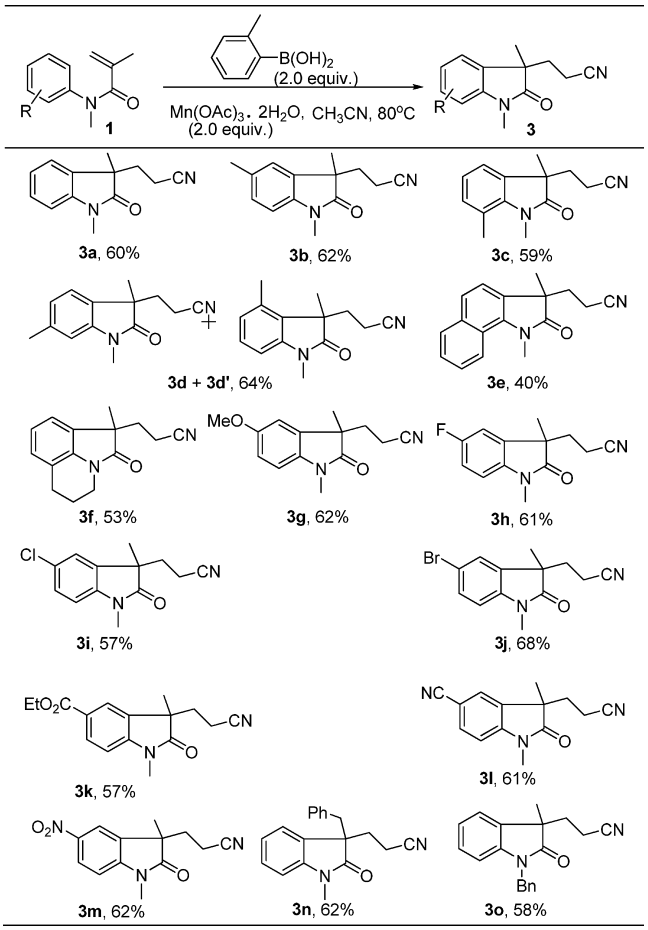
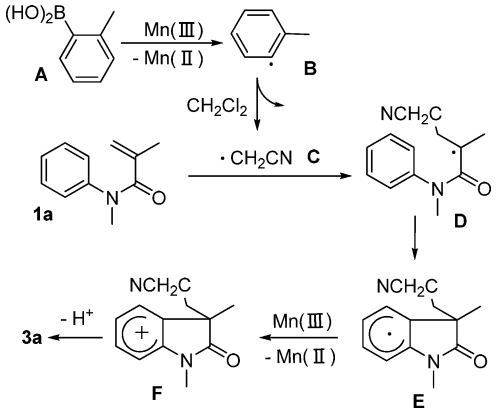
Table 3. Synthesis of Cyano-Containing Oxindoles



the phenyl-substituted product was obtained when the reaction proceeded in acetonitrile. Arylboronic acids serve as aryl radical precursors via oxidative carbon−boron bond cleavage in this reaction.[15] When 2.0 equiv of TEMPO was added to the reaction mixture under the optimal conditions, a 3% yield of 2-(2,2,6,6-tetramethylpiperidin-1-yloxy)acetonitrile was obtained and verified by MS (Scheme 1). This result suggests that the acetonitrile radical was trapted by TEMPO. In an effort to improve our understanding of the reaction profile, deuterium labeling studies were conducted. The use of $CDCl_3$ led to a slightly lower yield [47%, **2p** (Table 2)], and the use of CD_2Cl_2 or CD_3CN resulted in a very low yield. On the basis of this result, a mechanistic pathway for the manganese(III)-*o*-tolylboronic acid-mediated radical oxidative cyanomethylation and cyclization of arylacrylamides with acetonitrile is proposed in Scheme 2.[16] The reaction of *o*-tolylboronic acid **A** with

Scheme 2. Possible Reaction Mechanism



Mn(III) salt generated aryl radical **B**, which then abstracted a hydrogen of acetonitrile to generate cyanomethyl radical **C**. The selective addition of **C** to a C═C double bond of *N*-arylacrylamide **1a** delivered intermediate **D**, which intramolecularly cyclized to form **E**. Subsequently, cationic intermediate **F** was formed through single-electron oxidation by Mn(III), which ultimately aromatized to afford cyano-containing oxindole **3a**.

CONCLUSION

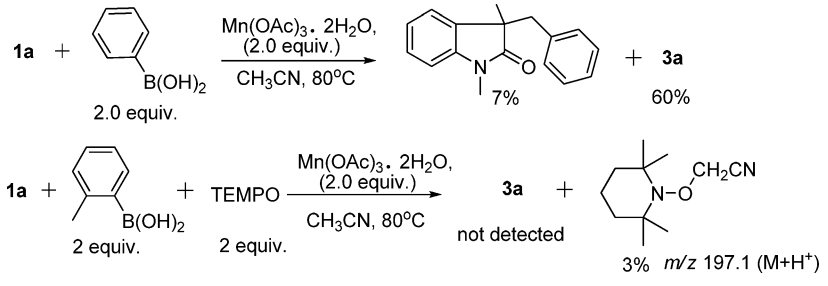
In conclusion, we have successfully developed a simple, highly efficient, and general method for the preparation of chloro- and cyano-containing oxindoles through $Mn(OAc)_3$-mediated radical dichloromethylation and cyanomethylation of arylacrylamides under relatively mild reaction conditions. As one of its notable features, the radical process allows the direct formation of a C−C or C−N bond and the construction of an oxindole ring in one reaction. Moreover, varieties of useful functional groups are also tolerated, which is attributed to the mild conditions. Finally, the use of a commercially available, cheap, and easily prepared $Mn(OAc)_3$ represents an added advantage of this method.

EXPERIMENTAL SECTION

General. All reactions were conducted under a nitrogen atmosphere. All reagents were purchased and used without further purification. All new compounds were further characterized by HRMS (FT-ICR-MS).

Experimental Procedure for the Synthesis of $Mn(OAc)_3 \cdot 2H_2O$.[10e] The $Mn(OAc)_3 \cdot 2H_2O$ was prepared by heating a mixture of 125 mL of acetic acid and 12 g of $Mn(OAc)_2 \cdot 4H_2O$ to reflux for 20 min and then slowly adding 2.0 g of $KMnO_4$. After being refluxed for an additional 30 min, the mixture was cooled to room temperature, and 20 mL of water was added. The manganic acetate was filtered off

Scheme 1. Experiment for the Mechanistic Study



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after 2 h, washed with cold acetic acid and diethyl ether, and then air-dried.

Experimental Procedure for the Synthesis of Dichloro-Containing Oxindoles. An oven-dried Schlenk tube containing $Mn(OAc)_3{\cdot}2H_2O$ (1.2 mmol) and *o*-tolylboronic acid (1.2 mmol) was evacuated and purged with nitrogen three times. Arylacrylamide (0.6 mmol) in CH_2Cl_2 (2 mL) was added to the system at room temperature. The reaction mixture was heated while being stirred at 60 °C for 12 h. The reaction solution was concentrated in vacuo, and then 15 mL of a saturated sodium bicarbonate solution was added and the mixture extracted with EtOAc (3 × 10 mL). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography using a petroleum ether/AcOEt mixture [from 15:1 to 5:1 (v/v)] as the eluent to give the corresponding products.

Experimental Procedure for the Synthesis of Cyano-Containing Oxindoles. An oven-dried Schlenk tube containing $Mn(OAc)_3{\cdot}2H_2O$ (1.2 mmol) and *o*-tolylboronic acid (1.2 mmol) was evacuated and purged with nitrogen three times. Arylacrylamide (0.6 mmol) in CH_3CN (2 mL) was added to the system at room temperature. The reaction mixture was heated while being stirred at 80 °C for 12 h. The reaction solution was concentrated in vacuo, and then 15 mL of a saturated sodium bicarbonate solution was added and the mixture extracted with EtOAc (3 × 10 mL). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography using a petroleum ether/AcOEt mixture [from 15:1 to 5:1 (v/v)] as the eluent to give the corresponding products.

*3-(2,2-Dichloroethyl)-1,3-dimethylindolin-2-one (**2a**) (CAS Registry No. 1627605-52-0).* Colorless oil. Yield: 116 mg, 75%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (t, J = 7.6 Hz, 1 H), 7.20 (d, J = 7.3 Hz, 1 H), 7.10 (t, J = 7.4 Hz, 1 H), 6.88 (d, J = 7.8 Hz, 1 H), 5.41−5.37 (m, 1 H), 3.21 (s, 3 H), 3.07−2.98 (m, 1 H), 2.73−2.69 (m, 1 H), 1.40 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.0, 143.4, 131.1, 129.8, 128.6, 122.7, 108.6, 69.7, 50.2, 47.2, 26.4, 25.4. MS-ESI: m/z 280.0 [M + Na]$^+$.

*3-(2,2-Dichloroethyl)-1,3,7-trimethylindolin-2-one (**2b**) (CAS Registry No. 1627605-56-4).* Colorless oil. Yield: 91 mg, 56%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.02−7.00 (m, 3 H), 5.38 (d, J = 4.6 Hz, 1 H), 3.48 (s, 3 H), 3.05−2.99 (m, 1 H), 2.66 (d, J = 14.6 Hz, 1 H), 2.58 (s, 3 H), 1.37 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.9, 141.3, 132.4, 131.8, 122.7, 120.7, 120.4, 69.8, 50.6, 46.6, 29.9, 25.9, 19.2. MS-ESI: m/z 294.0 [M + Na]$^+$.

*3-(2,2-Dichloroethyl)-1,3,5-trimethylindolin-2-one (**2c**) (CAS Registry No. 1627605-60-0).* Colorless oil. Yield: 128 mg, 79%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.12−7.10 (m, 1 H), 7.00 (s, 1 H), 6.76 (d, J = 7.9 Hz, 1 H), 5.42−5.39 (m, 1 H), 3.18 (s, 3 H), 3.05−2.99 (m, 1 H), 2.70−2.66 (m, 1 H), 2.37 (s, 3 H), 1.38 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.0, 141.2, 132.4, 131.2, 130.0, 123.6, 108.4, 69.9, 50.3, 47.3, 26.6, 25.5, 21.2. MS-ESI: m/z 294.0 [M + Na]$^+$.

*3-(2,2-Dichloroethyl)-5-fluoro-1,3-dimethylindolin-2-one (**2d**) (CAS Registry No. 1627605-61-1).* Colorless oil. Yield: 87 mg, 53%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.05−7.00 (m, 1 H), 6.98−6.96 (m, 1 H), 6.82−6.78 (m, 1 H), 5.45−5.41 (m, 1 H), 3.20 (s, 3 H), 3.06−3.00 (m, 1 H), 2.72−2.67 (m, 1 H), 1.40 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.7, 159.4 (d, J = 242.3 Hz), 139.5, 133.0 (d, J = 7.8 Hz), 115.0 (d, J = 23.4 Hz), 111.1 (d, J = 24.9 Hz), 109.2 (d, J = 8.1 Hz), 69.5, 50.1, 47.8, 26.7, 25.5. MS-ESI: m/z 298.0 [M + Na]$^+$.

*5-Chloro-3-(2,2-dichloroethyl)-1,3-dimethylindolin-2-one (**2e**) (CAS Registry No. 1627605-62-2).* Colorless oil. Yield: 116 mg, 66%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31−7.29 (m, 1 H), 7.19 (d, J = 2.0 Hz, 1 H), 6.80 (d, J = 8.2 Hz, 1 H), 5.44−5.41 (m, 1 H), 3.20 (s, 3 H), 3.06−3.00 (m, 1 H), 2.72−2.67 (m, 1 H), 1.40 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.6, 142.1, 133.1, 128.7, 128.2, 123.4, 109.6, 69.5, 50.1, 47.5, 26.7, 25.5. MS-ESI: m/z 314.0 [M + Na]$^+$.

*5-Bromo-3-(2,2-dichloroethyl)-1,3-dimethylindolin-2-one (**2f**) (CAS Registry No. 1627605-63-3).* Colorless oil. Yield: 141 mg, 70%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (d, J = 8.2 Hz, 1 H), 7.33 (s, 1 H), 6.76 (d, J = 8.2 Hz, 1 H), 5.44−5.42 (m, 1 H), 3.19 (s, 3 H), 3.07−3.00 (m, 1 H), 2.69 (d, J = 13.6 Hz, 1 H), 1.39 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.5, 142.6, 133.4, 131.2, 126.1, 115.4, 110.2, 69.5, 50.0, 47.5, 26.7, 25.6. MS-ESI: m/z 358.0 [M + Na]$^+$.

*3-(2,2-Dichloroethyl)-1,3-dimethyl-5-nitroindolin-2-one (**2g**).* White solid. Mp: 135−136 °C. Yield: 102 mg, 56%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (d, J = 8.2 Hz, 1 H), 8.13 (s, 1 H), 6.98 (d, J = 8.6 Hz, 1 H), 5.45 (d, J = 3.8 Hz, 1 H), 3.30 (s, 3 H), 3.12−3.06 (m, 1 H), 2.82 (d, J = 14.8 Hz, 1 H), 1.47 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.1, 149.1, 143.6, 132.3, 126.1, 118.8, 108.3, 69.2, 49.8, 47.3, 27.0, 25.6. HRMS calcd for $C_{12}H_{13}Cl_2N_2O_3$ (M + H)$^+$, 303.0303; found, 303.0307.

*3-(2,2-Dichloroethyl)-1,3-dimethyl-2-oxoindolin-5-carbonitrile (**2h**) (CAS Registry No. 1627605-67-7).* Colorless oil. Yield: 113 mg, 67%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, J = 7.9 Hz, 1 H), 7.50 (s, 1 H), 6.96 (d, J = 8.2 Hz, 1 H), 5.42−5.40 (m, 1 H), 3.25 (s, 3 H), 3.08−3.02 (m, 1 H), 2.78−2.74 (m, 1 H), 1.43 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.7, 147.3, 134.0, 132.5, 126.3, 119.0, 106.0, 69.2, 49.8, 47.1, 26.8, 25.5. MS-ESI: m/z 305.0 [M + Na]$^+$.

*Ethyl 3-(2,2-Dichloroethyl)-1,3-dimethyl-2-oxoindoline-5-carboxylate (**2i**).* Colorless oil. Yield: 122 mg, 62%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10−8.07 (m, 1 H), 7.88 (d, J = 1.5 Hz, 1 H), 6.93 (d, J = 8.2 Hz, 1 H), 5.41−5.38 (m, 1 H), 4.42−4.37 (m, 2 H), 3.25 (s, 3 H), 3.09−3.03 (m, 1 H), 2.80−2.75 (m, 1 H), 1.44−1.40 (m, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.4, 166.3, 147.6, 131.4, 131.2, 125.2, 124.0, 108.2, 69.6, 61.2, 50.0, 47.1, 26.8, 25.6, 14.5. HRMS calcd for $C_{15}H_{17}Cl_2NNaO_3$ (M + Na)$^+$, 352.0483; found, 352.0484.

*3-(2,2-Dichloroethyl)-5-methoxy-1,3-dimethylindolin-2-one (**2j**) (CAS Registry No. 1627605-66-6).* Colorless oil. Yield: 105 mg, 61%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.85−6.77 (m, 3 H), 5.45−5.41 (m, 1 H), 3.82 (s, 3 H), 3.28 (s, 3 H), 3.05−3.00 (m, 1 H), 2.70−2.65 (m, 1 H), 1.39 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.7, 156.3, 137.0, 132.7, 112.6, 110.7, 109.0, 69.8, 56.0, 50.3, 47.7, 26.6, 25.6. MS-ESI: m/z 310.0 [M + Na]$^+$.

*3-(2,2-Dichloroethyl)-1,3-dimethyl-1H-benzo[g]indol-2(3H)-one (**2k**).* Yellow cream. Yield: 83 mg, 45%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, J = 7.9 Hz, 1 H), 7.58−7.52 (m, 2 H), 7.44 (t, J = 8.2 Hz, 1 H), 7.37 (d, J = 7.1 Hz, 1 H), 6.96 (d, J = 7.2 Hz, 1 H), 5.36 (t, J = 6.9 Hz, 1 H), 3.61−3.55 (m, 1 H), 3.52 (s, 3 H), 2.83 (d, J = 14.7 Hz, 1 H), 1.72 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1, 136.6, 135.6, 133.7, 127.0, 126.9, 123.0, 122.8, 119.5, 108.9, 70.7, 55.0, 46.4, 33.5, 30.0. HRMS calcd for $C_{16}H_{16}Cl_2NO$ (M + H)$^+$, 308.0609; found, 308.0608.

*3-Benzyl-3-(2,2-dichloroethyl)-1-methylindolin-2-one (**2l**) (CAS Registry No. 1627605-73-5).* Colorless oil. Yield: 96 mg, 48%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26−7.21 (m, 1 H), 7.14−7.03 (m, 5 H), 6.77 (d, J = 6.6 Hz, 2 H), 6.61 (d, J = 7.8 Hz, 1 H), 5.45−5.41 (m, 1 H), 3.21−3.15 (m, 1 H), 3.10 (d, J = 12.8 Hz, 1 H), 3.99 (d, J = 12.8 Hz, 1 H), 2.93 (s, 3 H), 2.87−2.82 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.7, 144.2, 134.4, 130.2, 128.8, 128.4, 127.6, 127.0, 123.8, 122.3, 108.4, 69.8, 53.2, 48.8, 45.2, 26.2. MS-ESI: m/z 356.0 [M + Na]$^+$.

*1-Benzyl-3-(2,2-dichloroethyl)-3-methylindolin-2-one (**2m**) (CAS Registry No. 1627605-54-2).* Colorless oil. Yield: 160 mg, 80%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (t, J = 8.9 Hz, 5 H), 7.23 (d, J = 6.5 Hz, 2 H), 7.09 (t, J = 7.4 Hz, 1 H), 6.82 (d, J = 7.8 Hz, 1 H), 5.50−5.48 (m, 1 H), 5.04 (d, J = 15.5 Hz, 1 H), 4.84 (d, J = 15.5 Hz, 1 H), 3.15−3.09 (m, 1 H), 2.79 (d, J = 14.5 Hz, 1 H), 1.48 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.2, 142.7, 135.8, 131.3, 128.8, 128.6, 127.8, 127.6, 122.8, 122.8, 109.8, 69.7, 50.1, 47.3, 44.2, 26.2. MS-ESI: m/z 356.0 [M + Na]$^+$.

*3-(2,2-Dichloroethyl)-3-methyl-1-phenylindolin-2-one (**2n**).* Colorless oil. Yield: 129 mg, 67%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57−7.53 (m, 2 H), 7.45−7.41 (m, 3 H), 7.30−7.25 (m, 2 H), 7.18−7.15 (m, 1 H), 6.89 (d, J = 7.9 Hz, 1 H), 5.54−5.51 (m, 1 H), 3.21−3.15 (m, 1 H), 2.85−2.80 (m, 1 H), 1.55 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.5, 143.6, 134.6, 131.0, 129.8, 128.7, 128.3, 126.5, 123.3, 123.1, 110.1, 70.0, 50.5, 47.4, 26.3. HRMS calcd for $C_{17}H_{15}Cl_2NNaO$ (M + Na)$^+$, 342.0428; found, 342.0429.

*3-(Dichloromethyl)-1-methyl-4-phenyl-1,2,3,4-tetrahydroquinoline (**2o**).* Colorless oil. Yield: 75 mg, 39%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47−7.31 (m, 1 H), 7.32−7.26 (m, 3 H), 7.18−7.12 (m, 3

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H), 7.07 (d, J = 7.2 Hz, 2 H), 5.87 (d, J = 6.6 Hz, 1 H), 4.67 (d, J = 3.4 Hz, 1 H), 3.59−3.57 (m, 1 H), 3.45 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.2, 140.4, 139.3, 131.1, 129.8, 129.2, 128.8, 127.6, 125.6, 124.2, 115.3, 71.5, 59.2, 44.3, 30.3. HRMS calcd for $C_{17}H_{15}Cl_2NNaO$ $(M + Na)^+$, 342.0428; found, 342.0429.

*1,3-Dimethyl-3-(2,2,2-trichloroethyl)indolin-2-one (**2p**) (CAS Registry No. 1627605-74-6).* Colorless oil. Yield: 101 mg, 58%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36−7.29 (m, 2 H), 7.08−7.04 (m, 1 H), 6.88 (d, J = 7.8 Hz, 1 H), 3.70 (d, J = 14.9 Hz, 1 H), 3.34 (d, J = 14.9 Hz, 1 H), 3.23 (s, 3 H), 1.40 (s, 3 H) . ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.7, 143.4, 129.7, 128.6, 125.7, 122.1, 108.5, 96.3, 60.0, 48.1, 26.9, 26.7. MS-ESI: m/z 314.0 $[M + Na]^+$.

*3-(1,3-Dimethyl-2-oxoindolin-3-yl)propanenitrile (**3a**) (CAS Registry No. 4148-26-9).* Colorless oil. Yield: 77 mg, 60%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (t, J = 6.1 Hz, 1 H), 7.20 (d, J = 6.6 Hz, 1 H), 7.13 (d, J = 7.1 Hz, 1 H), 6.88 (d, J = 7.4 Hz, 1 H), 3.23 (s, 3 H), 2.33 (d, J = 13.7 Hz, 1 H), 2.09−2.00 (m, 3 H), 1.40 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.0, 143.3, 131.8, 128.8, 123.2, 122.7, 118.9, 108.6, 47.4, 33.5, 26.4, 23.6, 12.9. MS-ESI: m/z 237.0 $[M + Na]^+$.

*3-(1,3,5-Trimethyl-2-oxoindolin-3-yl)propanenitrile (**3b**) (CAS Registry No. 1632149-26-8).* Colorless oil. Yield: 85 mg, 62%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.11 (d, J = 7.8 Hz, 1 H), 7.00, (s, 1 H), 6.77 (d, J = 8.0 Hz, 1 H), 3.20 (s, 3 H), 2.36 (s, 3 H), 2.33−2.27 (m, 1 H), 2.10−1.96 (m, 3 H), 1.38 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.0, 140.8, 132.8, 131.8, 129.0, 123.5, 119.0, 108.4, 47.5, 33.6, 26.4, 23.6, 21.2, 12.9. MS-ESI: m/z 251.0 $[M + Na]^+$.

*3-(1,3,7-Trimethyl-2-oxoindolin-3-yl)propanenitrile (**3c**) (CAS Registry No. 1356668-26-2).* Colorless oil. Yield: 81 mg, 59%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.05−6.97 (m, 3 H), 3.50 (s, 3 H), 2.59 (s, 3 H), 2.34−2.27 (m, 1 H), 2.10−1.96 (m, 3 H), 1.37 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.7, 141.1, 132.5, 123.1, 120.6, 120.3, 119.0, 46.8, 33.9, 29.7, 24.0, 19.1, 12.9. MS-ESI: m/z 251.0 $[M + Na]^+$.

*3-(1,3,6-Trimethyl-2-oxoindolin-3-yl)propanenitrile (**3d**) (CAS Registry No. 1356668-28-4) and 3-(1,3,4-Trimethyl-2-oxoindolin-3-yl)propanenitrile (**3d′**) (CAS Registry No. 1632149-27-9).* **3d** and **3d′** in 1:1.6 ratio. Colorless oil. Yield: 88 mg, 64%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (t, J = 7.7 Hz, 1.6 H), 7.06 (d, J = 7.2 Hz, 1 H), 6.92 (d, J = 7.5 Hz, 1 H), 6.88 (d, J = 7.8 Hz, 1.6 H), 6.74 (s, 1 H), 6.71 (d, J = 3.8 Hz, 1.6 H), 3.21 (s, 4.8 H), 3.20 (s, 3 H), 2.40 (s, 3 H), 2.38 (s, 4.8 H), 2.31 (d, J = 5.6 Hz, 1 H), 2.28−2.25 (s, 1.6 H), 2.09−2.02 (m, 3 H), 2.00−1.79 (m, 4.8 H), 1.48 (s, 4.8 H), 1.38 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.3, 179.0, 143.6, 143.3, 139.0, 134.5, 128.8, 128.7, 128.3, 125.7, 123.6, 122.4, 119.0, 118.7, 109.6, 106.4, 48.5, 47.3, 33.6, 31.6, 26.5, 26.3, 23.6, 21.9, 21.8, 18.3, 13.1, 12.9. MS-ESI: m/z 251.0 $[M + Na]^+$.

*3-(1,3-Dimethyl-2-oxo-2,3-dihydro-1H-benzo[g]indol-3-yl)-propanenitrile (**3e**) (CAS Registry No. 1356668-43-3).* Colorless oil. Yield: 63 mg, 40%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, J = 8.2 Hz, 1 H), 7.59−7.54 (m, 2 H), 7.48−7.40 (m, 2 H), 7.99 (d, J = 7.5 Hz, 1 H), 3.54 (s, 3 H), 2.86−2.79 (m, 1 H), 2.27−2.00 (m, 3 H), 1.69 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.9, 136.4, 135.9, 133.7, 127.4, 127.1, 126.9, 123.1, 122.7, 119.7, 119.1, 109.1, 47.1, 38.5, 31.4, 30.0, 13.8. MS-ESI: m/z 287.0 $[M + Na]^+$.

*3-(1-Methyl-2-oxo-2,4,5,6-tetrahydro-1H-pyrrolo[3,2,1-ij]-quinolin-1-yl)propanenitrile (**3f**) (CAS Registry No. 1635420-93-7).* Colorless oil. Yield: 76 mg, 53%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.07−6.99 (m, 3 H), 3.71 (d, J = 5.0 Hz, 2 H), 2.80 (t, J = 5.5 Hz, 2 H), 2.34−2.26 (m, 1 H), 2.14−2.00 (m, 5 H), 1.4 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.8, 139.1, 130.4, 127.5, 122.6, 120.7, 120.5, 118.9, 48.7, 39.0, 33.4, 24.6, 23.3, 21.3, 13.0. MS-ESI: m/z 263.0 $[M + Na]^+$.

*3-(5-Methoxy-1,3-dimethyl-2-oxoindolin-3-yl)propanenitrile (**3g**) (CAS Registry No. 855608-58-1).* Colorless oil. Yield: 91 mg, 62%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.85−6.82 (m, 1 H), 6.80−6.77 (m, 2 H), 3.81 (s, 3 H), 3.20 (s, 3 H), 2.35−2.28 (m, 1 H), 2.12−1.98 (m, 3 H), 1.39 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.6, 156.6, 136.7, 133.2, 118.9, 112.7, 110.4, 108.9, 56.0, 47.9, 33.6, 26.5, 23.6, 12.9. MS-ESI: m/z 267.0 $[M + Na]^+$.

*3-(5-Fluoro-1,3-dimethyl-2-oxoindolin-3-yl)propanenitrile (**3h**) (CAS Registry No. 1356668-32-0).* Colorless oil. Yield: 85 mg, 61%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.06−7.01 (m, 1 H), 6.97−6.95 (m, 1 H), 6.83−6.80 (m, 1 H), 3.22 (s, 3 H), 2.36−2.28 (m, 1 H), 2.15−2.02 (m, 3 H), 1.41 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.6, 159.6 (d, J = 242.2 Hz), 139.2, 133.5 (d, J = 7.6 Hz), 118.6, 115.0 (d, J = 23.5 Hz), 111.0 (d, J = 24.8 Hz), 109.2 (d, J = 8.1 Hz), 47.9, 33.4, 26.6, 23.5, 12.9. MS-ESI: m/z 255.0 $[M + Na]^+$.

*3-(5-Chloro-1,3-dimethyl-2-oxoindolin-3-yl)propanenitrile (**3i**) (CAS Registry No. 1356668-33-1).* Colorless oil. Yield: 85 mg, 57%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31−7.29 (m, 1 H), 7.18 (d, J = 2.0 Hz, 1 H), 6.81 (d, J = 8.3 Hz, 1 H), 3,21 (s, 3 H), 2.36−2.27 (m, 1 H), 2.14−2.02 (m, 3 H), 1.40 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.5, 141.9, 133.6, 128.8, 128.6, 123.3, 118.5, 109.6, 47.6, 33.4, 26.5, 23.5, 12.9. MS-ESI: m/z 271.0 $[M + Na]^+$.

*3-(5-Bromo-1,3-dimethyl-2-oxoindolin-3-yl)propanenitrile (**3j**) (CAS Registry No. 1356668-34-2).* Colorless oil. Yield: 119 mg, 68%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (d, J = 8.2 Hz, 1 H), 7.31 (s, 1 H), 6.77 (d, J = 8.2 Hz, 1 H), 3.21 (s, 3 H), 2.35−2.30 (m, 1 H), 2.12−2.05 (m, 3 H), 1.40 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.4, 142.4, 134.0, 131.7, 126.1, 118.5, 115.8, 110.1, 47.6, 33.4, 26.5, 23.5, 12.9. MS-ESI: m/z 315.0 $[M + Na]^+$.

*Ethyl 3-(2-Cyanoethyl)-1,3-dimethyl-2-oxoindoline-5-carboxy-late (**3k**) (CAS Registry No. 1635420-90-4).* Colorless oil. Yield: 98 mg, 57%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09−8.07 (m, 1 H), 7.87 (d, J = 1.3 Hz, 1 H), 6.93 (d, J = 8.3 Hz, 1 H), 4.39 (d, J = 7.0 Hz, 2 H), 3.27 (s, 3 H), 2.39−2.30 (m, 1 H), 2.16−2.06 (m, 3 H), 1.42 (t, J = 7.1 Hz, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.3, 166.2, 147.3, 131.8, 131.4, 125.5, 123.9, 118.5, 108.1, 61.1, 47.2, 33.3, 26.6, 23.5, 14.5, 12.9. MS-ESI: m/z 309.0 $[M + Na]^+$.

*3-(2-Cyanoethyl)-1,3-dimethyl-2-oxoindoline-5-carbonitrile (**3l**) (CAS Registry No. 1635420-91-5).* Colorless oil. Yield: 87 mg, 61%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68−7.66 (m, 1 H), 7.48 (d, J = 1 Hz, 1 H), 6.98 (d, J = 8.1 Hz, 1 H), 3.26 (s, 3 H), 2.37−2.31 (m, 1 H), 2.16−2.06 (m, 3 H), 1.43 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.7, 147.1, 134.1, 133.0, 126.2, 118.9, 118.2, 109.1, 106.2, 47.1, 33.0, 26.6, 23.4, 12.9. MS-ESI: m/z 262.0 $[M + Na]^+$.

*3-(1,3-Dimethyl-5-nitro-2-oxoindolin-3-yl)propanenitrile (**3m**) (CAS Registry No. 1356668-29-5).* Colorless oil. Yield: 96 mg, 62%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33−8.31 (m, 1 H), 8.12 (s, 1 H), 7.00 (d, J = 8.6 Hz, 1 H), 3.31 (s, 3 H), 2.44−2.34 (m, 1 H), 2.19−2.12 (m, 3 H), 1.48 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.1, 148.9, 143.8, 132.8, 126.1, 118.8, 118.2, 108.3, 47.4, 33.0, 26.9, 23.5, 12.9. MS-ESI: m/z 282.0 $[M + Na]^+$.

*3-(3-Benzyl-1-methyl-2-oxoindolin-3-yl)propanenitrile (**3n**) (CAS Registry No. 3389-80-8).* Colorless oil. Yield: 108 mg, 62%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28−7.24 (m, 1 H), 7.17−7.05 (m, 5 H), 6.82 (d, J = 6.9 Hz, 2 H), 6.65 (d, J = 7.8 Hz, 1 H), 3.15 (d, J = 12.9 Hz, 1 H), 3.04 (d, J = 12.8 Hz, 1 H), 2.99 (s, 3 H), 2.57−2.49 (m, 1 H), 2.28−2.20 (m, 1 H), 2.14−2.06 (m, 1 H), 2.00−1.92 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.7, 143.9, 134.9, 129.9, 128.9, 128.8, 127.7, 126.9, 123.7, 122.7, 118.8, 108.4, 53.8, 44.1, 32.1, 26.1, 13.0. MS-ESI: m/z 313.0 $[M + Na]^+$.

*3-(1-Benzyl-3-methyl-2-oxoindolin-3-yl)propanenitrile (**3o**) (CAS Registry No. 1632149-23-5).* Colorless oil. Yield: 101 mg, 58%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (t, J = 6.4 Hz, 2 H), 7.27 (d, J = 6.9 Hz, 3 H), 7.20 (t, J = 7.7 Hz, 2 H), 7.08 (t, J = 7.5 Hz, 1 H), 6.89 (d, J = 7.8 Hz, 1 H), 4.95−4.86 (m, 2 H), 2.44−2.32 (m, 1 H), 2.16−1.97 (m, 3 H), 1.45 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.2, 142.2, 135.9, 131.9, 129.0, 128.7, 127.9, 127.4, 123.2, 122.8, 118.9, 109.7, 47.5, 44.0, 33.7, 23.9, 13.0. MS-ESI: m/z 313.0 $[M + Na]^+$.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H NMR and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

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Notes

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