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A CONVENIENT SYNTHESIS OF 4-ALKOXY(OR ARYLOXY)-3-ARYLISOQUINOLIN-1(2*H*)-ONES FROM 2-[ALKOXY(OR ARYLOXY)METHYL]BENZONITRILES

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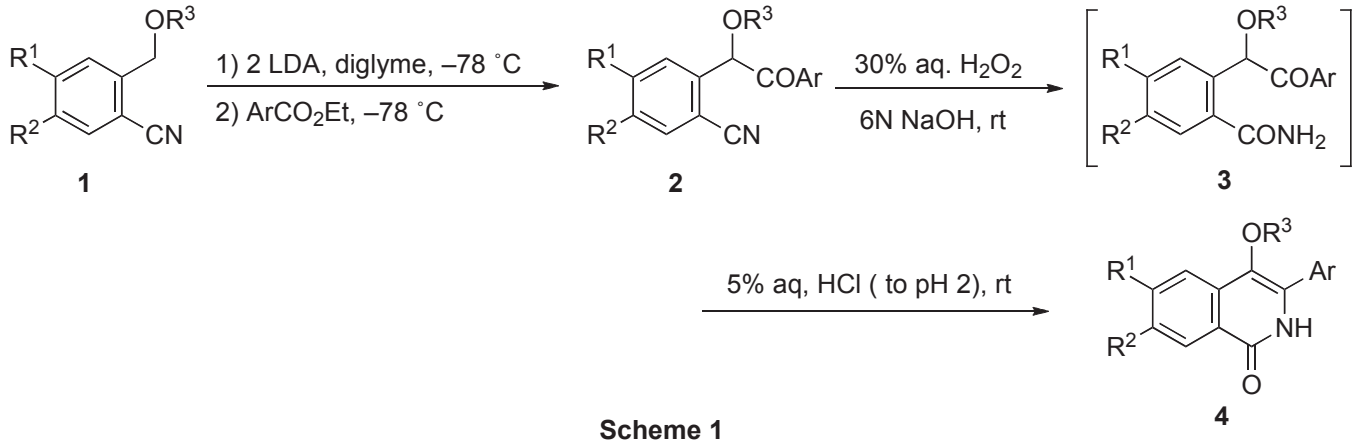
Abstract – A facile two-step preparation of 4-alkoxy(or aryloxy)-3-arylisoquinolin-1(2*H*)-ones from 2-[alkoxy(or aryloxy)methyl]benzonitriles has been achieved. The benzylic carbanions, generated by deprotonation of the starting nitriles with lithium diisopropylamide (LDA) in diglyme at –78 ˚C, react with ethyl benzoates to give 2-[alkoxy(or aryloxy)(aroyl)methyl]benzonitriles. These aroylated benzonitriles can be converted into the corresponding desired isoquinolinones by hydrolysis under alkaline conditions followed by acidification of the resulting benzamide intermediates at room temperature.

Compounds having the isoquinolin-1(2*H*)-one skeleton are of interest in medicinal chemistry.[1] Therefore, a number of efficient methods for the preparation of isoquinolin-1(2*H*)-one derivatives have been developed.[2] However, there have been few reports on the general synthesis of the derivatives bearing an alkoxy (or aryloxy) group at the 4-position, in spite of their biological utilities.[3] Herein we wish to report a convenient two-step procedure for the preparation of 4-alkoxy(or aryloxy)-3-arylisoquinolin-1(2*H*)-ones (**4**). We have found that 2-[alkoxy(or aryloxy)methyl]benzonitriles (**1**) can be deprotonated efficiently on treatment of with LDA in diglyme at –78 ˚C to generate 2-[alkoxy(or aryloxy)-(lithio)methyl]benzonitriles, which can be aroylated with ethyl benzoates to give 2-[alkoxy(or aryloxy)(aroyl)methyl]benzonitriles (**2**), and that these aroylated benzonitriles can be converted into the desired isoquinolinones under mild conditions.

The synthesis of 4-alkoxy(or aryloxy)-3-arylisoquinolin-1(2*H*)-ones (**4**) from 2-[alkoxy(or aryloxy)-methyl]benzonitriles (**1**), easily obtainable by the reaction of the respective 2-(bromomethyl)benzonitriles with sodium alk(or aryl)oxides, was carried out according to the sequence outlined in Scheme 1. We have found that the use of two molar amounts of LDA as base in diglyme at –78 ˚C was effective for the

deprotonation of the benzylic position of **1** to generate 2-[alkoxy(or aryloxy)(lithio)methyl]benzonitriles intermediates, which were allowed to reacted with ethyl benzoates. Quenching with saturated aqueous ammonium chloride and subsequent extractive workup afforded the corresponding aroylated products, 2-[alkoxy(or aryloxy)(aroyl)methyl]benzonitriles (**2**), in moderate yields as summarized in Table 1. In the case of using 4,5-dimethoxy-2-(methoxyethoxymethyl)benzonitrile (**1e**), the yield of the corresponding product (**2j**) was somewhat lower than those of the others. This may be ascribed to low acidity of the corresponding benzylic hydrogens of **1e** owing to the electron donating methoxy groups at the benzene ring. The use of 1,2-dimethoxyethane (DME) as a solvent gave a rather decreased yields of the aroylated products, and in the case of using THF considerably intractable mixtures of products containing only trace amounts of the desired aroylated products. Unfortunately, it was found that when aliphatic esters, such as ethyl propanoate and ethyl 2-methylpropanoate, were employed for the acylating reaction under the above-mentioned successful conditions, only trace amounts of the desired acylated products were obtained. This result may be attributable to rapid proton abstraction from these esters by 2-[alkoxy(or aryloxy)(lithio)methyl]benzonitriles or excess LDA.



Scheme 1

Table 1. Preparation of 4-Alkoxy(or aryloxy)-4-arylisoquinolin-1(2*H*)-ones (**4**) *via* **2**

Entry	**1**	Ar	**2** (Yield/%)[a]	**4** (Yield/%)[a]
1	**1a** ($R^1 = R^2 = H$, $R^3 = Me$)	Ph	**2a** (51)[b]	**4a** (68)
2	**1a**	*p*-Tol	**2b** (46)	**4b** (68)
3	**1a**	3-BrC_6H_4	**2c** (54)	**4c** (70)
4	**1b** [$R^1 = R^2 = H$, $R^3 = (CH_2)_2OMe$]	Ph	**2d** (52)	**4d** (54)
5	**1c** ($R^1 = R^2 = H$, R^3 = *p*-Tol)	Ph	**2e** (55)	**4e** (73)
6	**1c**	*p*-Tol	**2f** (46)	**4f** (70)
7	**1c**	3-BrC_6H_4	**2g** (55)	**4g** (72)
8	**1c**	3-$MeOC_6H_4$	**2h** (47)	**4h** (73)
9	**1d** (R^1 = Br, $R^2 = H$, R^3 = Bn)	Ph	**2i** (46)	**4i** (72)
10	**1e** [$R^1 = R^2$ = OMe, $R^3 = (CH_2)_2OMe$]	Ph	**2j** (34)	**4j** (49)

[a] Isolated yields. [b] The use of an equimolar amount of LDA caused decrease in the yield (15%).

Hydrolysis of aroylated products (**2**), thus obtained, under alkaline conditions followed by acidification of the resulting mixtures gave the corresponding 4-alkoxy(or aryloxy)-3-arylisoquinolin-1(2*H*)-ones (**4**) in generally fair-to-good yields as summarized in Table 1 as well. Thus, compounds (**2**) were treated with 6N sodium hydroxide in the presence of 30% aqueous hydrogen peroxide[4] at room temperature to give 2-[alkoxy(or aroyloxy)(aroyl)methyl]benzamides (**3**), which underwent efficient cyclization by adjusting pH of the mixture to 2 with 5% hydrochloric acid at the same temperature to give the desired products (**4**). The yields of the 4-methoxyethoxy derivatives (**4d**) and (**4j**) were somewhat lower compared to those of the others; the reactions gave somewhat intractable mixtures of products probably due to liability of the methoxyethoxy moiety under these hydrolysis and/or cyclization conditions.

The above-mentioned results demonstrate that two-step sequence starting from aroylation of 2-[alkoxy(or aryloxy)(lithio)methyl]benzonitriles followed by hydrolytic cyclization provides a convenient method for the preparation of 4-alkoxy(or aroyloxy)-3-arylisoquinolin-1(2*H*)-ones. Major advantages of the present method are that the starting materials are readily available and that the operations are very simple. Further work to explore the utilization of 2-[alkoxy(or aryloxy)(lithio)methyl]benzonitriles to the synthesis of related heterocycles is in progress.

EXPERIMENTAL

The melting points were obtained on a Laboratory Devices MEL-TEMP II melting apparatus and are uncorrected. IR spectra were recorded with a Shimadzu FTIR-8300 spectrophotometer. The ^{1}H NMR spectra were recorded using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 500 MHz or JEOL LA400FT NMR spectrometer operating at 400 MHz. The ^{13}C NMR spectra were recorded using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 125 MHz. Low-resolution MS spectra (EI, 70 eV) were measured by a JEOL JMS AX505 HA spectrometer. TLC was carried out on a Merck Kieselgel 60 PF_{254}. Column chromatography was performed using WAKO GEL C-200E. All of the organic solvents used in this study were dried over appropriate drying agents and distilled prior to use.

Starting Materials. 2-(Bromomethyl)-4,5-dimetyhoxybenzonitrile,[5] 4-bromo-2-(bromomethyl)-benzonitrile,[6] and 2-(methoxymethyl)benzonitrile (**1a**)[7] were prepared by the appropriate reported procedure. *n*-BuLi was supplied by Asia Lithium Corporation. All of the other chemicals used in this study were commercially available.

2-[Alkoxy(or aryloxy)methyl]benzonitriles (1b-e). These compounds were prepared by treating 2-(bromomethyl)benzonitriles with sodium alk(or aryl)oxides, generated from the respective alcohols and sodium hydride, in DMF at 0 °C.[7]

2-(Methoxyethoxymethyl)benzonitrile (1b): 61% yield; a colorless oil; R_f 0.24 (3:7 Et_2O–hexane); IR (neat) 2226, 1600 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.41 (s, 3H), 3.62–3.64 (m, 2H), 3.73–3.76 (m,

2H), 4.77 (s, 2H), 7.39 (ddd, J = 7.8, 7.3, 1.4 Hz, 1H), 7.57–7.66 (m, 3H). Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.08; H, 6.99; N, 7.19.

2-(4-Methylphenoxymethyl)benzonitrile (1c): 75% yield; colorless needles; mp 54–55 °C (hexane); IR (KBr) 2228, 1613 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.30 (s, 3H), 5.24 (s, 2H), 6.90 (d, J = 8.7 Hz, 2H), 7.10 (d, J = 8.7 Hz, 2H), 7.42 (t, J = 7.8 Hz, 1H), 7.62 (t, J = 7.8 Hz, 1H), 7.69 (d, J = 7.8 Hz, 2H). Anal. Calcd for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.50; H, 5.97; N, 6.35.

4-Bromo-2-(benzyloxymethyl)benzonitrile (1d): 65% yield; a colorless oil; R_f 0.35 (1:10 Et_2O–hexane); IR (neat) 2226 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.67 (s, 2H), 4.71 (s, 2H), 7.32–7.41 (m, 5H), 7.49 (d, J = 8.2 Hz, 1H), 7.53 (dd, J = 8.2, 1.8 Hz, 1H), 7.80 (d, J = 1.8 Hz, 1H). Anal. Calcd for $C_{15}H_{12}BrNO$: C, 59.62; H, 4.00; N, 4.64. Found: C, 59.49; H, 4.00; N, 4.59.

4,5-Dimethoxy-2-(2-methoxyethoxymethyl)benzonitrile (1e): 64% yield; colorless needles; mp 40–41 °C (hexane–Et_2O); IR (KBr) 2218, 1604 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.40 (s, 3H), 3.60–3.62 (m, 2H), 3.70–3.72 (m, 2H), 3.89 (s, 3H), 3.95 (s, 3H), 4.71 (s, 2H), 7.04 (s, 1H), 7.11 (s, 1H). Anal. Calcd for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 62.12; H, 6.96; N, 5.37.

Typical Procedure for the Preparation of 2-[Alkoxy(or aryloxy)(aroyl)methyl]benzonitriles (2). 2-[(Benzoyl)(methoxy)methyl]benzonitrile (2a). To a stirred solution of LDA (3.9 mmol), generated from i-Pr_2NH and n-BuLi by the standard method, in diglyme (6 mL) at –78 °C was added **1a** (0.29 g, 2.0 mmol). After 15 min, $PhCO_2Et$ (0.29 g, 2.0 mmol) was added to the resulting dark-purple solution of the carbanion. The dark-purple color turned into light-red gradually (*ca*. 15 min). The reaction was quenched by adding saturated aqueous NH_4Cl and water (10 mL each) and the mixture was warmed to room temperature. The organic materials were extracted with AcOEt three times (10 mL each), and the combined extracts were washed with water five times and dried over anhydrous Na_2SO_4. After evaporation of the solvent the residue was purified by column chromatography on silica gel (1:5 THF–hexane) to give **2a** (0.25 g, 51%); a pale-yellow oil; R_f 0.25; IR (neat) 2226, 1695 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.52 (s, 3H), 6.01 (s, 1H), 7.42–7.47 (m, 3H), 7.55–7.61 (m, 3H), 7.70 (d, J = 7.8 Hz, 1H), 8.00 (d, J = 7.3 Hz, 2H). Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.45; H, 5.30; N, 5.51.

2-[(Methoxy)(4-methylbenzoyl)methyl]benzonitrile (2b): a pale-yellow oil; R_f 0.23 (1:7 AcOEt–hexane); IR (neat) 2226, 1694, 1607 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.39 (s, 3H), 3.51 (s, 3H), 5.99 (s, 1H), 7.25 (d, J = 8.2 Hz, 2H), 7.42 (dd, J = 7.8, 7.3 Hz, 1H), 7.55 (d, J = 7.3 Hz, 1H), 7.58 (t, J = 7.3 Hz, 1H), 7.69 (d, J = 7.3 Hz, 1H), 7.91 (d, J = 8.2 Hz, 2H). Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.87; H, 5.71; N, 5.51.

2-[(3-Bromobenzoyl)(methoxy)methyl]benzonitrile (2c): a yellow solid; mp 94–95 °C (hexane); IR (KBr) 2226, 1699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.51 (s, 3H), 5.92 (s, 1H), 7.34 (t, J = 7.8 Hz, 1H), 7.46 (ddd, J = 7.8, 7.3, 0.9 Hz, 1H), 7.53 (d, J = 7.8 Hz, 1H), 7.62 (dd, J = 7.8, 7.3 Hz, 1H), 7.69 (dt, J =

7.8, 0.9 Hz, 1H), 7.72 (d, *J* = 7.8 Hz, 1H), 7.92 (dd, *J* = 7.8, 0.9 Hz, 1H), 8.14 (t, *J* = 0.9 Hz, 1H). Anal. Calcd for $C_{16}H_{12}BrNO_2$: C, 58.20; H, 3.66; N, 4.24. Found: C, 58.23; H, 3.75; N, 4.06.

2-[Benzoyl(methoxyethoxy)methyl]benzonitrile (2d): a pale yellow oil; R_f 0.27 (1:3 AcOEt–hexane); IR (neat) 2224, 1693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.30 (s, 3H), 3.62 (dd, *J* = 4.9, 3.9 Hz, 2H), 3.78 (dt, *J* = 11.7, 3.9 Hz, 1H), 3.87 (dt, *J* = 11.7, 4.9 Hz, 1H), 6.25 (s, 1H), 7.40–7.47 (m, 3H), 7.54–7.58 (m, 3H), 7.69 (d, *J* = 7.8 Hz, 1H), 8.03 (dd, *J* = 7.3, 1.4 Hz, 2H). Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.03; H, 5.95; N, 4.54.

2-[Benzoyl(4-methylphenoxy)methyl]benzonitrile (2e): a pale-yellow oil; R_f 0.30 (1:10 AcOEt–hexane); IR (neat) 2226, 1699, 1610 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.27 (s, 3H), 6.80 (s, 1H), 6.87 (d, *J* = 8.7 Hz, 2H), 7.07 (s, *J* = 8.7 Hz, 2H), 7.45 (t, *J* = 7.3 Hz, 1H), 7.47 (dd, *J* = 7.8, 7.3 Hz, 2H), 7.59 (ddd, *J* = 7.8, 7.3, 0.9 Hz, 1H), 7.61 (dd, *J* = 7.8, 7.3 Hz, 1H), 7.69 (d, *J* = 7.8 Hz, 1H), 7.71 (d, *J* = 7.8 Hz, 1H), 8.04 (dd, *J* = 7.8, 0.9 Hz, 2H). Anal. Calcd for $C_{22}H_{17}NO_2$: C, 80.71; H, 5.23; N 4.28. Found: C, 80.50; H, 5.24; N 4.21.

2-[4-Methylbenzoyl(4-methylphenoxy)methyl]benzonitrile (2f): a pale-yellow oil; R_f 0.23 (1:10 AcOEt–hexane); IR (neat) 2226, 1694, 1607 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.26 (s, 3H), 2.40 (s, 3H), 6.78 (s, 1H), 6.86 (d, *J* = 8.7 Hz, 2H), 7.06 (d, *J* = 8.7 Hz, 2H), 7.27 (d, *J* = 8.2 Hz, 2H), 7.44 (td, *J* = 7.8, 1.4 Hz, 1H), 7.60 (td, *J* = 7.8, 1.4 Hz, 1H), 7.69 (d, *J* = 7.8 Hz, 1H), 7.71 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.95 (d, *J* = 8.2 Hz, 2H). Anal. Calcd for $C_{23}H_{19}NO_2$: C, 80.92; H, 5.61; N 4.10. Found: C, 80.82; H, 5.74; N 4.05.

2-[3-Bromobenzoyl(4-methylphenoxy)methyl]benzonitrile (2g): a white solid; mp 123–124 °C (hexane–AcOEt); IR (KBr) 2226, 1703, 1607 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.27 (s, 3H), 6.70 (s, 1H), 6.85 (d, *J* = 8.7 Hz, 2H), 7.07 (d, *J* = 8.7 Hz, 2H), 7.35 (dd, *J* = 8.2, 7.8 Hz, 1H), 7.47 (ddd, *J* = 7.8, 7.3, 1.4 Hz, 1H), 7.62 (ddd, *J* = 7.8, 7.3, 1.4 Hz, 1H), 7.67 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.70–7.73 (m, 2H), 7.95 (dt, *J* = 7.8, 1.4 Hz, 1H), 8.16 (t, *J* = 1.4 Hz, 1H). Anal. Calcd for $C_{22}H_{16}BrNO_2$: C, 65.04; H, 3.97; N 3.45. Found: C, 64.81; H, 4.00; N 3.42.

2-[3-Methoxybenzoyl(4-methylphenoxy)methyl]benzonitrile (2h): a white solid; mp 109–110 °C (hexane–CH_2Cl_2); IR (KBr) 2230, 1695 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.26 (s, 3H), 3.82 (s, 2H), 6.79 (s, 1H), 6.87 (d, *J* = 8.7 Hz, 2H), 7.06 (d, *J* = 8.7 Hz, 2H), 7.13 (ddd, *J* = 8.2, 2.3, 1.4 Hz, 1H), 7.37 (dd, *J* = 8.2, 7.8 Hz, 1H), 7.45 (ddd, *J* = 7.8, 7.3, 1.4 Hz, 1H), 7.54 (dd, *J* = 2.3, 1.4 Hz, 1H), 7.61 (ddd, *J* = 7.8, 7.3, 1.4 Hz, 1H), 7.65 (ddd, *J* = 7.8, 1.4, 1.4 Hz, 1H), 7.70 (dd, *J* = 7.8, 1.4 Hz, 2H), 7.71 (dd, *J* = 7.8, 1.4 Hz, 1H). Anal. Calcd for $C_{23}H_{19}NO_3$: C, 77.29; H, 5.36; N, 3.92. Found: C, 77.22; H, 5.27; N, 3.80.

2-[Benzoyl(benzyloxy)methyl]-4-bromobenzonitrile (2i): a colorless viscous oil; R_f 0.24 (1:9 AcOEt–hexane); IR (neat) 2226, 1694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.68 (s, 2H), 6.12 (s, 1H), 7.33–7.39 (m, 5H), 7.45 (t, *J* = 7.3 Hz, 2H), 7.52 (d, 8.3 Hz, 1H), 7.57–7.60 (m, 2H), 7.82 (d, *J* = 2.0 Hz,

1H), 7.94 (d, *J* = 7.3 Hz, 2H). Anal. Calcd for $C_{22}H_{16}BrNO_2$: C, 65.04; H, 3.97; N, 3.45. Found: C, 64.93; H, 4.01; N, 3.40.

2-[Benzoyl(2-methoxyethoxy)methyl]-4,5-dimethoxybenzonitrile (2j): a pale-yellow oil; R_f 0.36 (2:3 AcOEt–hexane); IR (neat) 2220, 1694 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.31 (s, 3H), 3.61–3.63 (m, 2H), 3.72–3.76 (m, 1H), 3.83–3.86 (m, 1H), 3.87 (s, 3H), 3.89 (s, 3H), 6.25 (s, 1H), 7.02 (s, 1H), 7.04 (s, 1H), 7.46 (dd, *J* = 7.8, 7.3 Hz, 2H), 7.56 (tt, *J* = 7.3, 1.4 Hz, 1H), 8.02 (dd, *J* = 7.8, 1.4 Hz, 2H). Anal. Calcd for $C_{20}H_{21}NO_5$: C, 67.59; H, 5.96; N, 3.94. Found: C, 67.53; H, 6.06; N, 3.79.

Typical Procedure for the Preparation of Isoquinolin-1(2*H*)-ones (4). 4-Methoxy-3-phenylisoquinolin-1(2*H*)-one (4a). A solution of **2a** (0.25 mg, 1.0 mmol) in EtOH (8 mL) containing 30% H_2O_2 (10 mL) and 6N NaOH (1.0 mL) was stirred for 1.5 h at rt. The mixture was then made acidic (pH 2) by adding 5 % aqueous HCl and stirring was continued overnight at the same temperature. Ethanol was removed by evaporation and the precipitate was collected by filtration and recrystallized to give **4a** (0.17 g, 68%); colorless needles; mp 244–246 ˚C (hexane–$CHCl_3$); IR (KBr) 3291, 1645, 1622, 1605 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.54 (s, 3H), 7.47 (tt, *J* = 7.3, 1.4 Hz, 1H), 7.51–7.57 (m, 3H), 7.75–7.79 (m, 3H), 7.91 (d, *J* = 8.2 Hz, 1H), 8.42 (dd, *J* = 7.3, 0.9 Hz, 1H), 8.86 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 60.90, 121.40, 125.65, 126.92, 127.35, 128.34, 128.93, 129.07, 131.27, 131.59, 132.76, 134.33, 134.87, 160.86; MS *m/z* 251 (M^+, 100). Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.48; H, 5.40; N, 5.56.

3-(4-Methylphenyl)-4-methoxyisoquinolin-1(2*H*)-one (4b): colorless needles; mp 240–242 ˚C (hexane–$CHCl_3$); IR (KBr) 3295, 1649, 1620, 1605 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.44 (s, 3H), 3.54 (s, 3H), 7.32 (d, *J* = 7.8 Hz, 2H), 7.53 (ddd, *J* = 7.8, 7.3, 0.9 Hz, 1H), 7.66 (d, *J* = 7.8 Hz, 2H), 7.76 (ddd, *J* = 7.8, 7.3, 0.9 Hz, 1H), 7.89 (dd, *J* = 7.8, 0.9 Hz, 1H), 8.41 (dd, *J* = 7.8, 0.9 Hz, 1H), 8.88 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 20.90, 60.72, 121.28, 125.51, 126.70, 127.28, 128.66, 128.86, 128.88, 131.21, 132.66, 134.36, 134.65, 138.39, 160.84; MS *m/z* 265 (M^+, 100). Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.91; H, 5.64; N, 5.20.

3-(3-Bromophenyl)-4-methoxyisoquinolin-1(2*H*)-one (4c): a pale-yellow solid; mp 240–241 ˚C (hexane–$CHCl_3$); IR (KBr) 3295, 1645, 1618, 1605 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 3.45 (s, 3H), 7.46 (t, *J* = 7.8 Hz, 1H), 7.56–7.59 (m, 1H), 7.65 (d, *J* = 7.8 Hz, 1H), 7.69 (d, *J* = 7.8 Hz, 1H), 7.80–7.84 (m, 3H), 8.23 (d, *J* = 8.2 Hz, 1H), 11.30 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 61.11, 121.41, 121.52, 125.89, 127.21, 127.37, 128.25, 129.76, 130.42, 131.69 (2C), 132.81, 133.71, 134.04, 135.26, 160.73; MS *m/z* 329 (M^+, 100). Anal. Calcd for $C_{16}H_{12}BrNO_2$: C, 58.20; H, 3.66; N, 4.24. Found: C, 58.03; H, 3.69; N, 4.18.

4-(Methoxyethoxy)-3-phenylisoquinolin-1(2*H*)-one (4d): colorless needles; mp 149–151 ˚C (hexane–CH_2Cl_2); IR (KBr) 3256, 1649, 1632, 1607 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.33 (s, 3H), 3.49–3.51 (m, 2H), 3.73–3.75 (m, 2H), 7.46 (tt, *J* = 7.3, 1.4 Hz, 1H), 7.50–7.56 (m, 3H), 7.75–7.80 (m,

3H), 8.03 (d, *J* = 8.2 Hz, 1H), 8.41 (d, *J* = 7.3 Hz, 1H), 9.01 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 58.88, 71.49, 72.60, 121.94, 125.03, 127.25, 127.71, 128.51, 128.69, 129.25, 130.16, 131.09, 133.06, 135.39, 135.92, 162.59; MS *m/z* 295 (M^+, 100). Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.13; H, 5.87; N, 4.68.

4-(4-Methylphenoxy)-3-phenylisoquinolin-1(2*H*)-one (4e): a beige solid; mp 253–255 °C (hexane–$CHCl_3$); IR (KBr) 3293, 1651, 1634, 1607 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.15 (s, 3H), 6.73 (d, *J* = 8.7 Hz, 2H), 6.98 (d, *J* = 8.7 Hz, 2H), 7.35–7.42 (m, 3H), 7.42 (d, *J* = 8.2 Hz, 1H), 7.53 (dd, *J* = 8.2, 7.3 Hz, 1H), 7.57 (dd, *J* = 7.8, 1.4 Hz, 2H), 7.67 (ddd, *J* = 7.8, 7.3, 1.4 Hz, 1H), 8.26 (d, *J* = 7.8 Hz, 1H), 11.48 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 20.01, 114.57, 121.67, 125.88, 127.06, 127.45, 128.21, 128.43, 128.87, 129.12, 130.19, 130.72, 131.11, 132.76, 133.08, 133.82, 156.13, 161.20; MS *m/z* 327 (M^+, 100). Anal. Calcd for $C_{22}H_{17}NO_2$: C, 80.71; H, 5.23; N, 4.28. Found: C, 80.69; H, 5.25; N, 4.10.

4-(4-Methylphenoxy)-3-(4-methylphenyl)isoquinolin-1(2*H*)-one (4f): a pale-yellow solid; mp 234–236 °C (hexane–CH_2Cl_2); IR (KBr) 3295, 1651, 1603 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.15 (s, 3H), 2.28 (s, 3H), 6.72 (d, *J* = 8.8 Hz, 2H), 6.98 (d, *J* = 8.8 Hz, 2H), 7.18 (d, *J* = 8.3 Hz, 2H), 7.40 (d, *J* = 7.8 Hz, 1H), 7.48 (d, *J* = 8.3 Hz, 2H), 7.52 (ddd, *J* = 7.8, 7.3, 0.9 Hz, 1H), 7.66 (td, *J* = 7.3, 0.9 Hz, 1H), 8.25 (d, *J* = 7.3 Hz, 1H), 11.45 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 19.99, 20.83, 114.51, 121.58, 125.74, 126.89, 127.41, 128.21, 128.71, 128.78, 129.11, 129.33, 130.17, 130.65, 132.70, 133.10, 133.87, 138.67, 156.09; MS *m/z* 341 (M^+, 100). Anal. Calcd for $C_{23}H_{19}NO_2$: C, 80.92; H, 5.61; N, 4.10. Found: C, 80.91; H, 5.91; N, 4.05.

3-(3-Bromophenyl)-4-(4-methylphenoxy)isoquinolin-1(2*H*)-one (4g): a white solid; mp 206–208 °C (hexane–CH_2Cl_2); IR (KBr) 3293, 1663, 1609 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.24 (s, 3H), 6.73 (d, *J* = 8.7 Hz, 2H), 6.99 (d, *J* = 8.7 Hz, 2H), 7.27 (t, *J* = 7.8 Hz, 1H), 7.50 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.55 (ddd, *J* = 7.8, 7.3, 1.4 Hz, 1H), 7.61–7.65 (m, 3H), 7.89 (br s, 1H), 8.46 (d, *J* = 7.8 Hz, 1H), 9.79 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 20.46, 114.75, 122.52, 122.75, 125.79, 127.04, 127.63, 128.08, 130.17, 130.19, 130.23, 131.12, 131.48, 131.51, 132.37, 133.06, 133.29, 134.55, 156.17, 162.56; MS *m/z* 405 (M^+, 100). Anal. Calcd for $C_{22}H_{16}BrNO_2$: C, 65.04; H, 3.97; N, 3.45. Found: C, 64.92; H, 4.04; N, 3.44.

3-(3-Methoxyphenyl)-4-(4-methylphenoxy)isoquinolin-1(2*H*)-one (4h): colorless needles; mp 161–163 °C (hexane–CH_2Cl_2); IR (KBr) 3287, 1649, 1632, 1601 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.24 (s, 3H), 3.72 (s, 3H), 6.76 (d, *J* = 8.2 Hz, 2H), 6.92 (dd, *J* = 7.8, 2.0 Hz, 1H), 6.99 (d, *J* = 8.2 Hz, 2H), 7.22–7.25 (m, 2H), 7.32 (t, *J* = 7.8 Hz, 1H), 7.49–7.62 (m, 3H), 8.43 (d, *J* = 7.8 Hz, 1H), 9.52 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 20.44, 55.19, 113.19, 114.75, 115.40, 120.39, 122.43, 125.72, 127.24, 127.94, 129.80, 130.15, 130.33, 131.27, 131.61, 132.71, 132.88, 134.69, 156.48, 159.62, 162.27; MS *m/z* 357 (M^+, 100). Anal. Calcd for $C_{23}H_{19}NO_3$: C, 77.29; H, 5.36; N, 3.92. Found: C, 77.21; H, 5.49; N, 3.65.

4-Benzyloxy-6-bromo-3-phenylisoquinolin-1(2*H*)-one (4i): colorless needles; mp 190–192 °C (hexane–CH_2Cl_2); IR (KBr) 3293, 1653, 1622 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.56 (s, 2H),

7.17–7.19 (m, 2H), 7.29–7.30 (m, 3H), 7.46–7.53 (m, 3H), 7.61 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.77 (dd, *J* = 8.2, 1.4 Hz, 2H), 8.03 (d, *J* = 1.8 Hz, 1H), 8.22 (d, *J* = 8.2 Hz, 1H), 9.75 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 75.71, 124.12, 124.58, 128.38, 128.41, 128.44, 128.46, 128.64, 128.90, 129.62, 129.72, 130.37, 131.79, 132.15, 133.92, 136.02, 136.79, 161.59; MS *m*/*z* 405 (M^+, 100). Anal. Calcd for $C_{22}H_{16}BrNO_2$: C, 65.04; H, 3.97; N, 3.45. Found: C, 64.98; H, 4.08; N, 3.41.

6,7-Dimethoxy-4-(2-methoxyethoxy)-3-phenylisoquinolin-1(2*H*)-one (4j): pale-yellow needles; mp 175–177 °C (hexane–EtOH); IR (KBr) 3122, 1634, 1612 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.21 (s, 3H), 3.40–3.41 (m, 2H), 3.55–3.57 (m, 2H), 3.88 (s, 3H), 3.91 (s, 3H), 7.41 (tt, *J* = 7.3, 1.4 Hz, 1H), 7.45–7.48 (m, 3H), 7.58 (s, 1H), 7.67 (dd, *J* = 7.8, 1.4 Hz, 2H), 11.09 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 55.62, 55.65, 58.23, 70.98, 72.18, 102.47, 107.34, 119.32, 128.31, 128.66, 128.99, 129.69, 129.92, 131.82, 133.57, 149.01, 153.40, 160.28; MS *m*/*z* 355 (M^+, 100). Anal. Calcd for $C_{20}H_{21}NO_5$: C, 67.59; H, 5.96; N, 3.94. Found: C, 67.42; H, 6.01; N, 3.69.

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