Room-temperature One-pot Palladium-Catalyzed Synthesis of 3-Hydroxyisoindolin-1-ones with phenylglyoxylic acids

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I. General information
All the solvents and commercially available reagents were purchased from commercial sources and used directly. All the reactions mentioned in this article were monitored by thin layer chromatography (TLC) at 254 nm under a UV lamp with the following eluent system: petroleum ether/ethyl acetate. Column chromatography separations were obtained on silica gel (200–300 mesh, purchased from Qing Dao Hai Yang Chemical Industry) eluting with petroleum ether/ethyl acetate (5/1 to 3/1). %Purity of the products (> 97%) were determined by HPLC analysis (UV detector, wavelength: 289 nm). 1H NMR and 13C NMR spectra on a Bruker AV 300 MHz spectrometer were recorded in CDCl3 and DMSO-d6, respectively. Chemical shifts were recorded in δ (ppm) units relative to TMS. High-resolution mass spectra (HRMS) were recorded on a HewlettePackard 1100 LC/MSD spectrometer.

II. Experimental Section
General Procedure A: Synthesis of N-methoxybenzamides

1g and 1k were prepared following the procedure reported by Guimond et al [1]. Other N-methoxybenzamides were purchased from Sigma-Aldrich, TCL Alfa Aesar or Acros.

General Procedure B: Synthesis of α-Oxocarboxylic Acids
2a was prepared from oxidation of corresponding methyl ketones with SeO2 according to the reported procedure [2]. Other α-oxocarboxylic acids were purchased from Sigma-Aldrich, TCI, Alfa Aesar or Acros.

General Procedure C: Synthesis of 3-Hydroxyisoindolin-1-ones
A solution of benzamides (0.5 mmol), α-oxocarboxylic acids (0.6 mmol), Pd(OAc)$_2$ (10 mol%) and (NH$_4$)$_2$S$_2$O$_8$ (4 mmol) in THF (3 mL) was stirred in a sealed tube at room temperature for 3h. The reaction mixture was diluted with EtOAc and filtered through a pad of Celite. The filtrate was washed with saturated aqueous Na$_2$CO$_3$ to remove the acid. The organic layer was dried over anhydrous Na$_2$SO$_4$, filtered and the solvent was removed under vacuo to provide the crude product. The purification was performed by flash column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 4/1, v/v) to give 3-Hydroxyisoindolin-1-ones.

III. $^1$H and $^{13}$C NMR Data
$^1$H-NMR Date of 1g, 1k and 2a

N-methoxy-3,5-dimethylbenzamide (1g). $^1$H NMR (300 MHz, DMSO): $\delta$ 11.63 (s, 1H), 7.35 (s, 2H), 7.17 (s, 1H), 3.68 (s, 3H), 2.30 (s, 6H).

4-cyano-N-methoxybenzamide (1k). $^1$H NMR (300 MHz, DMSO) $\delta$ 11.99 (s, 1H), 7.97 (d, $J = 8.4$ Hz, 2H), 7.89 (d, $J = 8.4$ Hz, 2H), 3.73 (s, 3H).
2-(4-chlorophenyl)-2-oxoacetic acid (2a). \(^1\)H NMR (300 MHz, DMSO): \(\delta\) 7.96 (d, \(J = 8.8\) Hz, 2H), 7.69 (d, \(J = 8.8\) Hz, 2H).

\(^1\)H and \(^{13}\)C NMR Spectra of Products

5-chloro-3-(4-chlorophenyl)-3-hydroxy-2-methoxyisoindolin-1-one (3a). Following the general procedure C, 3a was isolated as a white solid (140 mg, 80%): Mp 192-194\(\text{°C}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 7.73 (d, \(J = 8.1\) Hz, 1H), 7.46 (dd, \(J = 8.1, 1.9\) Hz, 1H), 7.44–7.39 (m, 2H), 7.38–7.33 (m, 2H), 7.25 (d, \(J = 1.9\) Hz, 1H), 3.89 (s, 3H), 3.87–3.79 (m, 1H); \(^{13}\)C NMR (75 MHz, DMSO-d\(_6\)): \(\delta\) 161.72, 148.05, 138.20, 133.32, 130.18, 128.63, 128.18, 126.58, 124.97, 123.02, 89.66, 65.19; HRMS (ESI) m/z calcd for C\(_{15}\)H\(_{11}\)Cl\(_2\)NO\(_3\)\([M+Na]^+\) 346.0116; found 346.0119.

5-chloro-3-(3-chlorophenyl)-3-hydroxy-2-methoxyisoindolin-1-one (3b). Following the general procedure C, 3a was isolated as a white solid (122 mg, 70%): Mp 196-198\(\text{°C}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 7.68 (d, \(J = 8.1\) Hz, 1H), 7.50 (s, 1H), 7.42 (dd, \(J = 8.1, 1.8\) Hz, 1H), 7.33–7.27 (m, 1H), 7.25–7.18 (m, 3H), 3.85 (s, 3H), 3.82 (s, 1H); \(^{13}\)C NMR (75 MHz, DMSO-d\(_6\)): \(\delta\) 161.69, 147.79, 140.87, 138.20, 133.28, 130.56, 130.21, 128.59, 126.52, 124.95, 124.84, 123.06, 89.48, 65.18; HRMS (ESI) m/z calcd for C\(_{15}\)H\(_{11}\)Cl\(_2\)NO\(_3\)\([M+Na]^+\) 346.0116; found 346.0114.

5-chloro-3-(3-fluorophenyl)-3-hydroxy-2-methoxyisoindolin-1-one (3c). Following the general procedure C, 3a was isolated as a white solid (146 mg, 88%): Mp 158-160\(\text{°C}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 7.74 (d, \(J = 8.1\) Hz, 1H), 7.47 (d, \(J = 8.0\) Hz, 1H), 7.34 (dd, \(J = 13.9, 7.9\) Hz, 1H), 7.28 (d, \(J = 7.9\) Hz, 2H), 7.19 (dd, \(J = 7.9, 7.9\) Hz, 2H), 3.89 (s, 3H), 3.87–3.79 (m, 1H); \(^{13}\)C NMR (75 MHz, DMSO-d\(_6\)): \(\delta\) 161.72, 148.05, 138.20, 133.32, 130.18, 128.63, 128.18, 126.58, 124.97, 123.02, 89.66, 65.19; HRMS (ESI) m/z calcd for C\(_{15}\)H\(_{11}\)Cl\(_2\)NO\(_3\)\([M+Na]^+\) 346.0116; found 346.0119.
5-chloro-3-(4-fluorophenyl)-3-hydroxy-2-methoxyisoindolin-1-one (3d). Following the general procedure C, 3a was isolated as a white solid (132 mg, 80%): Mp 151-154 °C; \(^1^H\) NMR (300 MHz, CDCl\(_3\)): δ 7.71 (d, \(J = 8.0\) Hz, 1H), 7.51 – 7.40 (m, 3H), 7.27 – 7.26 (m, 1H), 7.07 (t, \(J = 8.6\) Hz, 2H), 3.88 (s, 3H), 3.85 (s, 1H); \(^1^3^C\) NMR (75 MHz, DMSO-\(d_6\)): δ 163.71, 161.60, 160.46, 148.24, 138.09, 134.56 (d, \(J = 2.9\) Hz), 130.04, 128.41 (d, \(J = 8.6\) Hz), 126.56, 124.88, 122.96, 115.51, 115.23, 89.65, 65.08; HRMS (ESI) m/z calcd for C\(_{15}\)H\(_{11}\)ClFNO\(_3\) [M+Na]\(^+\) 330.0411; found 330.0410.

5-chloro-3-(2-chlorophenyl)-3-hydroxy-2-methoxyisoindolin-1-one (3f). Following the general procedure C, 3a was isolated as a white solid (71 mg, 41%): Mp 205-207 °C; \(^1^H\) NMR (300 MHz, CDCl\(_3\)): δ 8.24 (d, \(J = 6.7\) Hz, 1H), 7.70 (d, \(J = 8.0\) Hz, 1H), 7.48 – 7.28 (m, 4H), 7.17 (s, 1H), 4.10 (s, 1H), 3.78 (s, 3H); \(^1^3^C\) NMR (75 MHz, DMSO-\(d_6\)): δ 162.04, 146.81, 137.72, 133.97, 130.96, 130.90, 130.84, 130.71, 130.03, 128.72, 127.44, 124.57, 122.47, 87.91, 64.57; HRMS (ESI) m/z calcd for C\(_{15}\)H\(_{11}\)Cl\(_2\)NO\(_3\) [M+Na]\(^+\) 346.0116; found 346.0113.
3-(4-bromophenyl)-5-chloro-3-hydroxy-2-methoxyisoindolin-1-one (3g). Following the general procedure C, 3a was isolated as a white solid (128 mg, 65%): Mp 190-193°C; 1H NMR (300 MHz, CDCl₃): δ 7.74 (d, J = 8.1 Hz, 1H), 7.53 (d, J = 1.9 Hz, 1H), 7.52–7.49 (m, 1H), 7.47 (dd, J = 8.1, 1.8 Hz, 1H), 7.38–7.35 (m, 1H), 7.33 (d, J = 1.8 Hz, 1H), 7.25 (s, 1H), 3.90 (s, 3H), 3.68 (s, 1H); 13C NMR (75 MHz, DMSO-d₆): δ 161.66, 147.96, 138.15, 137.82, 131.50, 130.13, 128.45, 126.55, 124.91, 122.99, 121.90, 89.65, 65.13; HRMS (ESI) m/z calcd for C₁₅H₁₁BrClNO₃ [M+Na]⁺ 389.9611; found 389.9614.

5-chloro-3-hydroxy-2-methoxy-3-(3-(trifluoromethyl)phenyl)isoindolin-1-one (3h). Following the general procedure C, 3a was isolated as a white solid (117 mg, 61%): Mp 171-173°C; 1H NMR (300 MHz, CDCl₃): δ 7.89 (s, 1H), 7.75 (d, J = 8.1 Hz, 1H), 7.68–7.60 (m, 1H), 7.55–7.46 (m, 3H), 7.26 (s, 1H), 3.93 (s, 1H), 3.89 (s, 3H); 13C NMR (75 MHz, DMSO-d₆): δ 161.73, 147.96, 139.87, 138.28, 130.32, 129.91, 129.53, 129.47, 126.56, 125.54, 125.50, 125.01, 123.11, 122.63 (dd, J = 7.6, 3.7 Hz), 89.50, 65.22; HRMS (ESI) m/z calcd for C₁₆H₁₁ClF₃NO₃ [M+Na]⁺ 380.0380; found 380.0384.

5-chloro-3-hydroxy-2-methoxy-3-(o-tolyl)isoindolin-1-one (3i). Following the general procedure C, 3a was isolated as a white solid (86 mg, 53%): Mp 166-169°C; 1H NMR (300 MHz, CDCl₃): δ 7.49 (s, 1H), 7.38–7.32 (m, 3H), 7.23 (d, J = 7.8 Hz, 1H), 7.14 (t, J = 6.6 Hz, 2H), 3.80 (s, 1H), 3.68 (s, 3H), 2.72 (s, 3H); 13C NMR (75 MHz, DMSO): δ 160.48 (s), 147.83 (s), 139.51 (s), 138.11 (s), 135.67 (s), 134.83 (s), 132.76 (s), 132.31 (s), 132.05 (s), 129.06 (s), 128.33 (s), 127.78 (s), 125.65 (s), 123.60 (s), 64.53 (s), 21.34 (s); HRMS (ESI) m/z calcd for C₁₆H₁₄ClNO₃ [M+Na]⁺ 326.0662; found 326.0661.
**5-chloro-3-hydroxy-2-methoxy-3-(m-tolyl)isoindolin-1-one (3j).** Following the general procedure C, 3a was isolated as a white solid (141 mg, 87%): Mp 154-156 °C; $^1$H NMR (300 MHz, CDCl3): δ 7.75 (d, $J = 8.1$ Hz, 1H), 7.45 (dd, $J = 8.1, 1.8$ Hz, 1H), 7.26 (s, 4H), 7.19 (d, $J = 6.1$ Hz, 1H), 3.91 (s, 3H), 3.60 (s, 1H), 2.35 (s, 3H); $^{13}$C NMR (75 MHz, DMSO): δ 161.51 (s), 148.43 (s), 138.15 (s), 137.79 (s), 137.60 (s), 129.72 (s), 128.99 (s), 128.31 (s), 126.46 (s), 126.34 (s), 124.67 (s), 123.09 (s), 122.75 (s), 89.91 (s), 64.84 (s), 20.99 (s); HRMS (ESI) m/z calcd for C$_{16}$H$_{14}$ClNO$_3$ [M+Na]$^+$ 326.0662; found 326.0665.

![Structure of 3j](image)

**3-(4-chlorophenyl)-3-hydroxy-2-methoxyisoindolin-1-one (4b).** Following the general procedure C, 3a was isolated as a white solid (138 mg, 89%): Mp 180-182 °C; $^1$H NMR (300 MHz, CDCl3): δ 7.76 (d, $J = 7.1$ Hz, 1H), 7.50 (dt, $J = 19.9, 7.5$ Hz, 2H), 7.39 (d, $J = 8.5$ Hz, 2H), 7.31 (d, $J = 8.5$ Hz, 2H), 7.24 (s, 1H), 3.87 (s, 3H), 3.73 (s, 1H); $^{13}$C NMR (75 MHz, DMSO-d$_6$): δ 162.65, 146.26, 138.16, 133.45, 132.98, 129.75, 128.48, 128.06, 127.78, 122.81, 89.92, 65.04; HRMS (ESI) m/z calcd for C$_{15}$H$_{12}$ClNO$_3$ [M+Na]$^+$ 312.0506; found 312.0511.

![Structure of 4b](image)

**3-(4-chlorophenyl)-3-hydroxy-2-methoxy-7-methylisoindolin-1-one (4c).** Following the general procedure C, 3a was isolated as a white solid (126 mg, 77%): Mp 174-177 °C; $^1$H NMR (300 MHz, CDCl3): δ 7.42–7.39 (m, 1H), 7.39–7.33 (m, 2H), 7.32–7.26 (m, 2H), 7.20 (d, $J = 7.7$ Hz, 1H), 7.03 (d, $J = 7.5$ Hz, 1H), 3.86 (s, 3H), 3.35 (s, 1H), 2.65 (s, 3H); $^{13}$C NMR (75 MHz, DMSO-d$_6$): δ 163.87, 146.90, 138.47, 136.50, 132.86, 131.38, 128.38, 128.12, 128.04, 124.52, 120.26, 89.14, 64.90, 16.88; HRMS (ESI) m/z calcd for C$_{16}$H$_{14}$ClNO$_3$ [M+Na]$^+$ 326.0662; found 326.0659.

![Structure of 4c](image)
3-(4-chlorophenyl)-3-hydroxy-2,7-dimethoxyisoindolin-1-one (4d). Following the general procedure C, 3a was isolated as a white solid (152 mg, 88%): Mp 158-160°C; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.51–7.45 (m, 1H), 7.43 (d, J = 8.7 Hz, 2H), 7.32 (d, J = 8.7 Hz, 2H), 6.90 (d, J = 8.4 Hz, 1H), 6.82 (d, J = 7.5 Hz, 1H), 3.95 (s, 3H), 3.87 (s, 3H), 3.08 (br s, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 162.21, 156.43, 148.63, 138.51, 135.26, 132.82, 128.38, 114.58, 112.58, 88.91, 64.87, 55.85; HRMS (ESI) m/z calcd for C$_{16}$H$_{14}$ClNO$_4$ [M+Na]$^+$ 342.0611; found 342.0611.

3-(4-chlorophenyl)-3-hydroxy-2-methoxy-6-methylisoindolin-1-one (4e). Following the general procedure C, 3a was isolated as a white solid (124 mg, 76%): Mp 165-169°C; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.59 (s, 1H), 7.44–7.38 (m, 2H), 7.38–7.30 (m, 3H), 7.15 (d, J = 7.8 Hz, 1H), 3.89 (s, 3H), 3.57 (s, 1H), 2.41 (s, 3H); $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 162.83, 143.58, 139.58, 138.40, 134.01, 132.87, 128.39, 128.02, 127.89, 122.91, 122.60, 89.84, 64.98, 20.92; HRMS (ESI) m/z calcd for C$_{16}$H$_{14}$ClNO$_3$ [M+Na]$^+$ 326.0662; found 326.0666.

7-chloro-3-(4-chlorophenyl)-3-hydroxy-2-methoxyisoindolin-1-one (4f). Following the general procedure C, 3a was isolated as a white solid (92 mg, 53%): Mp 200-202°C; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.50 – 7.32 (m, 6H), 7.17 (d, J = 6.3 Hz, 1H), 3.89 (s, 3H), 3.81 (s, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 160.69, 148.80, 137.56, 134.84, 133.21, 131.02, 129.37, 128.55, 128.14, 123.74, 121.89, 88.72, 65.02; HRMS (ESI) m/z calcd for C$_{18}$H$_{14}$Cl$_2$NO$_3$ [M+Na]$^+$ 346.0116; found 346.0114.
3-(4-chlorophenyl)-3-hydroxy-2-methoxy-4,6-dimethylisoindolin-1-one (4g). Following the general procedure C, 3a was isolated as a white solid (146 mg, 85%): Mp 177-179°C; 1H NMR (300 MHz, CDCl3): δ 7.34 (s, 1H), 7.29 (s, 1H), 7.25–7.15 (m, 3H), 7.04 (s, 1H), 3.72 (s, 3H), 3.40 (s, 1H), 2.29 (s, 3H), 1.96 (s, 3H); 13C NMR (75 MHz, DMSO) δ 162.46 (s), 140.30 (s), 139.62 (s), 137.27 (s), 135.63 (s), 133.23 (s), 132.68 (s), 128.56 (s), 128.19 (s), 120.40 (s), 89.61 (s), 64.90 (s), 20.73 (s), 16.59 (s); HRMS (ESI) m/z calcd for C17H16ClNO3 [M+Na]+ 340.0819; found 340.0820.

3-(4-chlorophenyl)-3-hydroxy-2,6-dimethoxyisoindolin-1-one (4h). Following the general procedure C, 3a was isolated as a white solid (100 mg, 58%): Mp 147-149°C; 1H NMR (300 MHz, CDCl3): δ 7.42 (d, J = 8.7 Hz, 2H), 7.34 (d, J = 8.7 Hz, 2H), 7.25 (d, J = 2.4 Hz, 1H), 7.18 (d, J = 8.4 Hz, 1H), 7.07 (dd, J = 8.4, 2.4 Hz, 1H), 3.90 (s, 3H), 3.84 (d, J = 6.6 Hz, 3H); 13C NMR (75 MHz, DMSO-d6): δ 162.62, 160.48, 138.49, 138.35, 132.84, 129.34, 128.39, 128.01, 124.11, 120.10, 106.67, 89.79, 64.97, 55.77; HRMS (ESI) m/z calcd for C16H14ClNO4 [M+Na]+ 342.0611; found 342.0617.

6-chloro-3-(4-chlorophenyl)-3-hydroxy-2-methoxyisoindolin-1-one (4i). Following the general procedure C, 3a was isolated as a white solid (154 mg, 88%): Mp 195-197°C; 1H NMR (300 MHz, CDCl3): δ 7.77 (d, J = 1.9 Hz, 1H), 7.52 (dd, J = 8.1, 1.9 Hz, 1H), 7.41 (d, J = 8.8 Hz, 2H), 7.35 (d, J = 8.7 Hz, 2H), 7.22 (d, J = 8.1 Hz, 1H), 3.90 (s, 3H), 3.54 (s, 1H); 13C NMR (75 MHz, DMSO-d6): δ 161.25, 144.74, 137.54, 134.58, 133.40, 133.25, 129.89, 128.59, 128.13, 124.91, 122.74, 89.76, 65.15; HRMS (ESI) m/z calcd for C15H11Cl2NO3 [M+Na]+ 346.0116; found 346.0115.
3-(4-chlorophenyl)-3-hydroxy-2,5-dimethoxyisoindolin-1-one (4j). Following the general procedure C, 3a was isolated as a white solid (110 mg, 64%): Mp 142-145°C; ¹H NMR (300 MHz, CDCl₃): δ 7.66 (d, J = 8.3 Hz, 1H), 7.38–7.27 (m, 3H), 7.20 (s, 1H), 6.98–6.80 (m, 1H), 6.66 (d, J = 2.2 Hz, 1H), 3.82 (s, 3H), 3.73 (s, 3H), 3.56 (s, 1H); ¹³C NMR (75 MHz, DMSO-d₆): δ 163.63, 163.07, 148.69, 138.32, 132.93, 128.43, 128.09, 124.72, 119.89, 115.98, 107.67, 89.72, 65.06, 55.88; HRMS (ESI) m/z calcd for C₁₆H₁₄ClNO₄ [M+Na]+ 342.0611; found 342.0611.

3-(4-chlorophenyl)-3-hydroxy-2-methoxy-1-oxoisoindoline-5-carbonitrile (4k). Following the general procedure C, 3a was isolated as a white solid (117 mg, 69%): Mp 172-175°C; ¹H NMR (300 MHz, CDCl₃): δ 7.92 (d, J = 7.7 Hz, 1H), 7.79 (d, J = 7.7 Hz, 1H), 7.57 (s, 1H), 7.47–7.33 (m, 4H), 4.10 (s, 1H), 3.90 (s, 3H); ¹³C NMR (75 MHz, DMSO): δ 160.70 (s), 146.63 (s), 136.86 (s), 134.21 (s), 133.43 (s), 131.84 (s), 128.60 (s), 128.22 (s), 126.87 (s), 124.01 (s), 117.85 (s), 115.56 (s), 89.75 (s), 65.16 (s); HRMS (ESI) m/z calcd for C₁₆H₁₁ClN₂O₃ [M+Na]+ 337.0458; found 337.0455.

IV. References

V. ¹H and ¹³C NMR Spectra
2a