A Mild Thermal and Acid Catalysed Rearrangement of O-Aryl Ethers into ortho-Hydroxy Arenes

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General Experimental

Melting points (m.p.) were measured using a Thomas-Hoover capillary tube melting point apparatus and are uncorrected.

Infra-red spectra were recorded on a Nicolet Fourier Transform Spectrometer (225 to 4400 cm^{-1}). The samples were prepared as evaporated films on sodium chloride disks. Absorption maxima (ν_{max}) are quoted in wavenumbers (cm^{-1}).

^{1}H and ^{13}C NMR spectra were recorded on a General Electric QE-300 Spectrometer operating at ambient probe temperature using an internal deuterium lock (300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR). Chemical shifts are reported in parts per million (δ) at lower frequencies relative to tetramethylsilane (TMS) and are referenced internally. They are reported as; position, multiplicity and coupling constant (Hz). Standard abbreviations are used throughout (s-singlet, d-doublet, dd-doublet of doublets, t-triplet, q-quartet, m-multiplet, br-broad).

Mass spectra including chemical ionisation (C.I.) and HRMS were recorded on a VG ZAB2E or a Finnigan TSQ70 quadrupole mass spectrometer. Accurate mass measurements are correct to ± 0.001.

The solvents used were either distilled over appropriate drying agents, or of analytical grade. All other commercially available reagents were purified as necessary following standard procedures.^{1}

Flash chromatography^{2} was performed using EMD silica gel (40-63 microns). Analytical thin layer chromatography (TLC) was carried out using Merck® silica gel 60 F_{254} plates with visualisation using either UV light or alkaline potassium permanganate.
General Experimental Methods

Method A - Ether formation using cesium carbonate
The phenol (0.34 mmol, 2.0 equiv.) and Cs$_2$CO$_3$ (0.68 mmol, 4.0 equiv.) in CH$_2$Cl$_2$ (5.0 mL) were stirred at room temperature under an argon atmosphere for 10 min. The chloride (0.17 mmol, 1.0 equiv.) was added portion-wise and the solution stirred at room temperature for 15 h. Water (2.0 mL) was added and the mixture extracted with CH$_2$Cl$_2$ (3 × 2.0 mL). The combined organic layers were washed with water (2 × 2.0 mL), dried (Na$_2$SO$_4$) and concentrated under reduced pressure to yield the crude product.

Method B - Ether formation using potassium carbonate
A mixture of the phenol (0.78 mmol, 2.0 equiv.), the chloride (0.39 mmol, 1.0 equiv.) and K$_2$CO$_3$ (1.6 mmol, 4.0 equiv.) in acetonitrile (5.0 mL) was heated at reflux for 2 h. Water (2.0 mL) was added and the mixture extracted with EtOAc (3 × 2.0 mL). The combined organic layers were washed with water (2 × 2.0 mL), dried (Na$_2$SO$_4$) and concentrated under reduced pressure to yield the crude product.

Method C - Ether formation using triethylamine
Triethylamine (2.2 mmol, 1.2 equiv.) was added dropwise to a solution of the phenol (1.85 mmol, 1.0 equiv.) in CH$_2$Cl$_2$ (10.0 mL) at 0 °C under an argon atmosphere. The chloride (2.05 mmol, 1.1 equiv.) was added portion-wise and the solution stirred at 0 °C for 3 h. Water (5.0 mL) was added and the mixture extracted with CH$_2$Cl$_2$ (3 × 5.0 mL). The combined organic layers were washed with water (2 × 5.0 mL), dried (Na$_2$SO$_4$) and concentrated under reduced pressure to yield the crude product.

Method D - Thermal rearrangement
A mixture of the ether (0.31 mmol, 1.0 equiv.) in benzene (10 mL) was heated at reflux in a sealed tube for 15 h. The solution was concentrated under reduced pressure to yield the crude product.
Method E- Acid catalyzed rearrangement
Catalytic CF₃CO₂H (1 drop) was added to a solution of the aryl ether (0.29 mmol, 1.0 equiv.) in benzene (10 mL) and the solution stirred at room temperature, under an argon atmosphere, for 15 h. Water (5.0 mL) was added and the mixture extracted with EtOAc (3 × 3.0 mL). The combined organic layers were washed with water (2 × 3.0 mL), dried (Na₂SO₄) and concentrated under reduced pressure to yield the crude product.

Experimental Details:

5-{3-[4-((S)-2-Benzyloxycarbonylamino-2-tert-butoxycarbonyl-ethyl)-phenoxy]-7-bromo-1-methoxymethyl-2-oxo-2,3-dihydro-1H-indol-3-yl]-2-((R)-1-tert-butoxycarbonylamino-2-methylpropyl)-oxazole-4-carboxylic acid methyl ester (6)

Cesium carbonate (130 mg, 0.4 mmol) was added to a solution of Cbz-Tyr-O tBu (99 mg, 0.267 mmol) in toluene (1 ml) under argon at room temperature, and the resulting reaction mixture was stirred for 20 minutes. A solution of chloride 5 (78 mg, 0.133 mmol) in toluene (1 ml) was then added, and the resulting reaction mixture was stirred for 7 hours. The reaction mixture was then taken up in NH₄Cl aq. soln and ethyl acetate, and extracted twice with ethyl acetate. The combined organic layers were washed with sat. brine, dried over sodium sulfate, filtered and concentrated in vacuo. The resulting crude was purified by flash column chromatography, eluting with 25:75 ethyl acetate:hexanes to obtain the title compound (91 mg, 74%) as a pale yellow foam: m.p. 64-68°C; ν max/cm⁻¹ 3334, 2975, 2930, 1718, 1516, 1507; δH (300 MHz, CDCl₃) 7.47 (0.5H, d, J 8.0), 7.45 (0.5H, d, J 8.0), 7.38-7.24 (6H, m), 6.93-6.89 (3H, m), 6.76 (2H, d, J 8.3), 5.45 (0.5H, d, J10.9), 5.44 (0.5H, d, J10.9), 5.32-5.28 (2H, m), 5.16 (1H, d, J7.5),
5.08 (2H, s), 4.90-4.82 (1H, m), 3.73 (1.5H, s), 3.71 (1.5H, s), 3.25 (1.5H, s), 3.23 (1.5H, s), 3.02-2.89 (2H, m), 2.25-2.14 (1H, m), 1.44 (4.5H, s), 1.43 (4.5H, s), 1.37 (4.5H, s), 1.35 (4.5H, s), 0.96-0.90 (6H, m); $\delta_C$ (75 MHz, CDCl$_3$) 171.6, 171.6, 170.2, 170.2, 163.9, 163.6, 161.1, 155.4, 155.2, 152.7, 151.3, 151.2, 140.8, 137.1, 136.2, 132.7, 132.6, 130.2, 129.0, 128.8, 128.5, 128.3, 128.2, 128.1, 128.0, 124.9, 124.9, 124.7, 122.1, 121.9, 103.5, 103.4, 82.3, 80.0, 77.2, 71.9, 66.8, 56.5, 55.0, 54.9, 54.2, 54.2, 52.3, 37.4, 32.9, 28.3, 27.9, 18.7, 17.9, 17.7; Found: [M+H]$^+$, 921.2876. C$_{45}$H$_{53}$N$_4$O$_7^{79}$Br+H$^+$ requires: [M+H]$^+$, 921.2922.

5-[[3-[[5-((S)-2-Benzyloxycarbonylamino-2-tert-butoxycarbonyl-ethyl)-2-hydroxy-phenyl]-7-bromo-1-methoxymethyl-2-oxo-2,3-dihydro-1H-indol-3-yl]-2-[[R]-1-tert-butoxycarbonylamino-2-methylpropyl]-oxazole-4-carboxylic acid methyl ester (7)

![Chemical Structure](image)

A solution of 6 (134 mg, 0.145 mmol) in benzene (5 ml) was heated at reflux for 2 hours, then was allowed to cool to room temperature and concentrated in vacuo. The resulting crude was purified by flash column chromatography, eluting with 25:75 ethyl acetate:hexanes, then was further purified by flash column chromatography, eluting with 2:98 methanol:dichloromethane to obtain the title compound (108 mg, 81%) as a yellow foam: m.p. 85-90°C; $v_{max}$/cm$^{-1}$ 3337, 2976, 1716, 1653, 1647, 1601, 1577, 1558, 1539, 1506; $\delta_H$ (300 MHz, CDCl$_3$) 9.05 (0.5H, s), 8.89 (0.5H, s), 7.55 (0.5H, d, J8.7), 7.50 (0.5H, d, J8.3), 7.36-7.33 (5H, m), 7.12-6.81 (4H, m), 6.60 (0.5H, s), 6.48 (0.5H, s), 5.64-5.58 (1H, m), 5.46-5.41 (1H, m), 5.34 (0.5H, d, J9.0), 5.25-5.20 (0.5H, m), 5.13 (2H, s), 5.13-4.98 (1H, m), 4.68-4.59 (1H, m), 4.50-4.46 (0.5H, m), 4.37-4.31 (0.5H, m), 3.75 (1.5H, s), 3.72 (1.5H, s), 3.33 (1.5H, s), 3.33 (1.5H, s), 2.96-2.84 (2H, m), 2.09-1.97 (1H, m), 1.41 (9H, s), 1.33 (9H, s), 0.88-0.83 (6H, m); $\delta_C$ (75 MHz, CDCl$_3$) 178.6, 178.5,
170.2, 169.8, 163.3, 162.3, 161.2, 161.2, 155.6, 155.5, 155.2, 155.0, 154.9, 153.6, 139.5, 136.1, 135.5, 135.4, 131.9, 131.6, 129.8, 128.5, 128.3, 128.0, 127.9, 127.8, 125.4, 125.0, 125.0, 122.7, 122.4, 120.1, 104.2, 103.9, 81.9, 79.7, 77.1, 72.4, 72.3, 66.6, 56.5, 56.1, 55.9, 55.8, 54.8, 54.6, 54.5, 53.9, 53.7, 52.2, 52.1, 37.7, 37.0, 33.0, 32.8, 28.0, 27.7, 27.7, 18.2, 17.9, 17.7, 17.5; Found: [M+H]+, 921.2915. C_{45}H_{53}N_4O_{12} requires: [M+H]+, 921.2922.

5-(7-Bromo-3-chloro-2-oxo-2,3-dihydro-1H-indol-3-yl)-2-((S)-1-tert-butoxycarbonylamino-2-methylpropyl)-oxazole-4-carboxylic acid methyl ester (8)

A solution of the tertiary alcohol (150 mg, 0.29 mmol, 1.0 equiv.) and pyridine (227 mg, 2.87 mmol, 10.0 equiv.) in ether (3.0 mL) was stirred at 0 °C for 15 min. Thionyl chloride (136 mg, 1.15 mmol, 4.0 equiv.) was added and the solution stirred for 30 min. Water (2.0 mL) was added and the solution concentrated under reduced pressure. The residue was washed with sat. aqueous bicarbonate solution (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organics were washed with brine (25 mL), dried (Na₂SO₄), filtered and concentrated under reduced pressure. Purification by column chromatography (SiO₂; 50 % EtOAc:hexanes) gave the title compound (90 mg, 40 %) as a yellow foam: \( \nu_{\text{max}}(\text{CHCl}_3)/\text{cm}^{-1} \) 3282, 2973, 1747, 1715, 1699, 1616, 1506, 1472, 1367, 1218, 1126, 910, 734; \( \delta_H \) (300 MHz, CDCl₃) 8.57 (1H, d, \( J = 18 \text{ Hz} \), NH); 7.43 (1H, d, \( J = 8.0 \text{ Hz} \)), 7.15 (1H, dd, \( J = 7.5 \text{ and } 7.5 \text{ Hz} \), 6.89-6.97 (1H, m), 5.29-5.36 (1H, m), 4.86-4.93 (1H, m), 3.71 (3H, s), 2.21-2.30 (1H, m), 1.44 (9H, s), 0.89-1.00 (6H, m); \( \delta_C \) (75 MHz, CDCl₃) 170.5, 164.1, 163.9, 160.7, 155.1, 155.0, 149.3, 149.2, 139.9, 133.4, 129.4, 129.3, 128.2, 128.1, 124.5, 123.0, 103.3, 80.0, 58.0, 54.1, 52.1, 52.9, 32.7, 28.1, 27.3, 20.8, 18.5, 17.8,
17.7; \( m/z \) (C.I.) 452, 486, 488, 542 (100 \%, M + H\(^+\)); HRMS (Found: MH\(^+\), 542.0667. C\(_{22}H_{26}N_3O_6ClBr\) requires 542.0693.

5-{3-[4-((S)-2-Benzoxycarbonylamino-2-tert-butoxycarbonyl-ethyl)-phenoxy]-7-bromo-2-oxo-2,3-dihydro-1H-indol-3-yl]-2-((R)-1-tert-butoxycarbonylamino-2-methylpropyl)-oxazole-4-carboxylic acid (9)

Tertiary chloride 8 (10 mg, 0.018 mmol, 1.0 equiv.) and the phenol (18 mg, 0.043 mmol, 2.0 equiv.) were treated according to Method A. Purification by column chromatography (SiO\(_2\); 50 \% EtOAc:hexanes) gave the title compound (12 mg, 75 \%) as a colourless oil: \( \nu_{\text{max}}(\text{CHCl}_3)/\text{cm}^{-1} \) 3282, 2976, 1723, 1716, 1506, 1472, 1367, 1214, 1165, 734; \( \delta_{\text{H}}(300 \text{ MHz, CDCl}_3) \) 7.64 (1H, s), 7.25-7.38 (7H, m), 6.81-6.95 (4H, m), 5.30 (2H, s), 5.13 (2H, s), 5.00-5.40 (1H, m), 4.80-4.90 (1H, m), 4.40-4.50 (1H, m), 3.75 (3H, s), 2.96-3.00 (2H, m), 2.05-2.15 (1H, m), 1.44 (9H, s), 1.35 (9H, s), 0.86-0.99 (6H, m); \( \delta_{\text{C}}(75 \text{ MHz, CDCl}_3) \) 1705., 164.1, 163.9, 160.7, 155.1, 155.0, 149.3, 149.2, 139.9, 133.4, 129.4, 129.3, 128.2, 128.1, 124.5, 123.0, 105.3, 80.0, 58.0, 54.1, 52.1, 32.9, 32.7, 28.1, 27.3, 20.8, 18.5, 17.8, 17.7; \( m/z \) (C.I.) 777, 821, 877 (100 \%, M + H\(^+\)); HRMS (Found: MH\(^+\), 876.2593. C\(_{43}H_{49}N_4O_{11}Br\) requires 876.2581).
5-{3-[(S)-2-Benzylxycarbonylamino-2-tert-butoxycarbonyl-ethyl]-2-hydroxyphenyl}-7-bromo-2-oxo-2,3-dihydro-1H-indol-3-yl}-2-((R)-1-tert-butoxycarbonylamino-2-methylpropyl)-oxazole-4-carboxylic acid methyl ester (10)

O-Arylether 9 (12 mg, 0.014 mmol, 1.0 equiv.) in deuterated chloroform (1.0 mL) was heated in a sealed tube at 80°C for 12 h. Purification by column chromatography (SiO₂; 50 % EtOAc:hexanes) gave the title compound (12 mg, 100 %) as a colourless oil: \( \nu_{\text{max}}(\text{CHCl}_3)/\text{cm}^{-1} 3306, 3232, 2974, 1715, 1701, 1157, 733; \delta_H(300 \text{ MHz, CDCl}_3) 8.91 (1H, s, brs), 7.88 (1H, d, \text{J} 9.0 \text{ Hz}), 7.21-7.47 (8H, m), 6.50-7.10 (3H, m), 5.30-5.36 (1H, m), 5.00-5.24 (2H, m), 4.32-4.70 (2H, m), 3.70 (3H, s), 2.81-3.02 (2H, m), 2.01-2.08 (1H, m), 1.32 (9H, s), 1.28 (9H, s), 0.70-0.88 (6H, m); m/z (C.I.) 876 (100 %, M + H⁺); HRMS (Found: MH⁺, 876.2593. C₄₃H₄₉N₄O₁₁Br requires 876.2581).

7-Bromo-3-chloro-3-phenyl-1,3-dihydroindol-2-one (11)

A solution of 7-bromo-3-hydroxy-3-phenyl-1,3-dihydroindol-2-one³ (0.28 g, 0.92 mmol, 1.0 equiv.) and pyridine (0.74 mL, 9.2 mmol, 10 equiv.) in diethyl ether (10 mL) was stirred at 0 °C under an argon atmosphere for 15 min. Thionyl chloride (0.27 mL, 3.6 mmol, 4.0 equiv.) was added dropwise and the solution stirred at 0 °C for 30 min. Water (5.0 mL) was added and the mixture extracted with EtOAc (4 × 5.0 mL). The combined organic layers were washed with water (2 × 5.0 mL), dried (Na₂SO₄) and concentrated
under reduced pressure to yield the crude product. Recrystallisation from hot 
EtOAc:hexane yielded the title compound (0.20 g, 67 %) as yellow needles: m.p. 186-187 
°C; \( R_f \) (1:1 hexane:EtOAc) 0.45; \( \nu_{\text{max}}(\text{CHCl}_3)/\text{cm}^{-1} \) 3300 (NH), 3090 (CH), 1732 (C=O); 
\( \delta_{\text{H}} \) (300 MHz, CDCl\(_3\)) 7.30-7.48 (4H, m), 7.50-7.55 (3H, m), 7.05 (1H, t, \( J \) 7.7 Hz); \( \delta_{\text{C}} \) (75 
MHz, CDCl\(_3\)) 172.4, 132.8, 129.7, 129.4, 129.0, 128.7, 128.5, 128.1, 127.5, 127.1, 124.9, 
124.6; \( m/z \) (C.I.) 324 (100 %, M + H\(^+\)); HRMS (Found: M\(^+\), 321.9634. C\(_{14}\)H\(_{10}\)NOClBr 
requires 321.9624).

**7-Bromo-3-phenyl-3-p-tolyloxy-1,3-dihydroindol-2-one (12)**

![Chemical Structure](image)

7-bromo-3-chloro-3-phenyl-1,3-dihydroindol-2-one 11 (0.20 g, 0.62 mmol, 1.0 equiv.) and 
\( p \)-cresol (0.13 mL, 1.24 mmol, 2.0 equiv.) were treated according to **Method A**. The crude 
product was purified by recrystallisation from hexane:EtOAc to afford the title compound 
(0.16 g, 67 %) as orange needles: m.p. 153-154 °C; \( R_f \) (1:1 hexane:EtOAc) 0.50; 
\( \nu_{\text{max}}(\text{CHCl}_3)/\text{cm}^{-1} \) 3210 (NH), 3088 (CH), 1732 (C=O); \( \delta_{\text{H}} \) (300 MHz, CDCl\(_3\)) 7.80 (1H, 
brs), 7.50-7.55 (2H, m), 7.35-7.45 (4H, m), 7.24 (1H, d, \( J \) 7.6 Hz), 7.02 (1H, t, \( J \) 7.6 Hz), 
6.90 (2H, d, \( J \) 8.4 Hz), 6.78 (2H, d, \( J \) 8.4 Hz), 2.20 (3H, s); \( \delta_{\text{C}} \) (75 MHz, CDCl\(_3\)) 174.7, 
152.8, 140.0, 137.8, 133.1, 132.7, 129.9, 129.5, 128.7, 128.4, 126.2, 125.3, 124.2, 120.4, 
103.4, 20.5; \( m/z \) (C.I.) 395 (100 %, M + H\(^+\)); HRMS (Found: M\(^+\), 394.0429. C\(_{21}\)H\(_{16}\)NO\(_2\)Br 
requires 394.0443).

**7-Bromo-3-(2-hydroxy-5-methylphenyl)-3-phenyl-1,3-dihydroindol-2-one (13)**

![Chemical Structure](image)
7-Bromo-3-phenyl-3-p-tolyloxy-1,3-dihydroindol-2-one 12 (45 mg, 0.1 mmol) was treated according to **Method D**. The crude product was purified by flash column chromatography (SiO₂; 100 % CH₂Cl₂) to afford the **title compound** (37 mg, 82 %) as a white solid: m.p. 202-203 ºC; \( R_f(100 \% \text{ CH}_2\text{Cl}_2) 0.40; \) \( \nu_{\text{max}}(\text{CHCl}_3)/\text{cm}^{-1} 3214 (\text{OH, NH}), 3075 (\text{CH}), 1699 (\text{C}=\text{O}); \) \( \delta_{\text{H}}(300 \text{ MHz, CDCl}_3) 8.50 (1\text{H, brs}), 8.30 (1\text{H, brs}), 7.42 (1\text{H, dd, } J 8.5 \text{ and } 3.0 \text{ Hz}), 7.24-7.38 (3\text{H, m}), 7.00-7.17 (5\text{H, m}), 6.90 (1\text{H, d, } J 8.1 \text{ Hz}), 6.70 (1\text{H, s}), 2.20 (3\text{H, s}); \) \( \delta_{\text{C}}(75 \text{ MHz, CDCl}_3) 181.5, 154.2, 139.5, 138.7, 134.1, 131.2, 130.8, 129.4, 129.3, 128.9, 127.8, 126.5, 126.1, 124.6, 124.4, 120.0, 103.7, 64.0, 30.9, 20.7; \) \( \text{m/z (C.I.) 395 (100 \%, M + H^+); HRMS (Found: M}^+, 394.0444. \text{C}_{21}\text{H}_{16}\text{NO}_2\text{Br requires 394.0443).} \)

**3-Chloro-3-phenyl-1,3-dihydroindol-2-one (14)**

A solution of 3-hydroxy-3-phenyl-1,3-dihydroindol-2-one ⁴ (6.32 g, 28.1 mmol, 1.0 equiv.) and pyridine (22.7 mL, 281 mmol, 10 equiv.) in diethyl ether (200 mL) was stirred at 0 ºC under an argon atmosphere for 15 min. Thionyl chloride (8.20 mL, 112 mmol, 4.0 equiv.) was added dropwise and the solution stirred at 0 ºC for 30 min. Water (50 mL) was added and the mixture extracted with EtOAc (4 × 50 mL). The combined organic layers were washed with water (2 × 50 mL), dried (Na₂SO₄) and concentrated under reduced pressure to yield the crude product. Recrystallisation from hot EtOAc:hexane yielded the **title compound** (3.60 g, 55 %) as needles. Data was consistent with that already reported: m.p. 145-146 ºC (lit.⁴ 145-146 ºC); \( R_f(1:1 \text{ hexane:EtOAc}) 0.60; \) \( \delta_{\text{H}}(300 \text{ MHz, CDCl}_3) 8.40 (1\text{H, brs}), 7.55 (2\text{H, dd, } J 4.3 \text{ and } 2.8 \text{ Hz}), 7.26-7.40 (5\text{H, m}), 7.18 (1\text{H, t } J 7.4 \text{ Hz}), 6.98 (1\text{H, d, } J 7.7 \text{ Hz}); \) \( \text{m/z (C.I.) 244 (100 \%, M + H}^+); \) \( \text{HRMS (Found: MH}^+, 244.0448. \text{C}_{14}\text{H}_{10}\text{NOCl requires 244.0451).} \)
3-Phenoxy-3-phenyl-1,3-dihydroindol-2-one (15a)

3-Chloro-3-phenyl-1,3-dihydroindol-2-one 14 (0.10 g, 0.41 mmol, 1.0 equiv.) and phenol (80 mg, 0.82 mmol, 2.0 equiv.) were treated according to Method A. The crude product was purified by flash column chromatography (SiO₂; 100 % CH₂Cl₂) to afford the title compound (88 mg, 73 %) as a white solid: m.p. 159-160 ºC; Rᵣ(100 % CH₂Cl₂) 0.45; νₘₐₓ(CHCl₃)/cm⁻¹ 3254 (NH), 3064 (CH), 1716 (C=O); δₓ(300 MHz, CDCl₃) 8.80 (1H, brs), 7.55 (2H, dd, J 4.0 and 2.7 Hz), 7.38-7.40 (3H, m), 7.24-7.30 (2H, m), 7.06-7.13 (3H, m), 6.86-7.05 (4H, m); δₓ(C(75 MHz, CDCl₃) 176.5, 155.3, 140.7, 138.3, 138.2, 130.1, 128.9, 128.5, 128.4, 126.3, 126.2, 126.1, 123.1, 123.0, 119.9, 110.6, 84.8; m/z (C.I) 302 (100 %, M + H⁺); HRMS (Found: MH⁺, 302.1182. C₂₀H₁₆NO₂ requires 302.1181).

3-Phenyl-3-p-tolyloxy-1,3-dihydroindol-2-one (15b)

3-chloro-3-phenyl-1,3-dihydroindol-2-one 14 (0.10 g, 0.41 mmol, 1.0 equiv.) and p-cresol (0.10 mL, 0.82 mmol, 2.0 equiv.) were treated according to Method A. The crude product was purified by flash column chromatography (SiO₂; 100 % CH₂Cl₂) to afford the title compound (0.10 g, 76 %) as a white solid: m.p. 140-141 ºC; Rᵣ(100 % CH₂Cl₂) 0.45; νₘₐₓ(CHCl₃)/cm⁻¹ 3243 (NH), 2976 (CH), 1724 (C=O); δₓ(300 MHz, CDCl₃) 8.45 (1H, brs), 7.55 (2H, dd, J 4.3 and 2.5 Hz), 7.25-7.40 (5H, m), 7.52 (1H, t, J 8.5 Hz), 6.85 (3H, m), 6.78 (2H, d, J 7.9 Hz), 2.18 (3H, s); δₓ(C(75 MHz, CDCl₃) 176.5, 153.0, 140.8, 138.4, 132.6, 130.0, 129.4, 128.6, 128.4, 128.3, 126.4, 126.2, 123.0, 120.1, 110.5, 85.0, 20.4; m/z (C.I) 316 (100 %, M + H⁺); HRMS (Found: MH⁺, 316.1332. C₂₁H₁₈NO₂ requires 316.1338).
3-(4-Isopropylphenoxy)-3-phenyl-1,3-dihydroindol-2-one (15c)

3-Chloro-3-phenyl-1,3-dihydroindol-2-one 14 (0.10 g, 0.41 mmol, 1.0 equiv.) and 4-isopropylphenol (0.11 g, 0.82 mmol, 2.0 equiv.) were treated according to Method A. The crude product was purified by flash column chromatography (SiO₂: 1:1 hexane :EtOAc) to afford the title compound (89 mg, 64 %) as a white solid: m.p. 171-172 ºC; \( R_f (1:1 \text{ hexane:EtOAc}) \) 0.65; \( \nu_{\text{max}}(\mathrm{CHCl}_3)/\text{cm}^{-1} \) 3231 (NH), 2963 (CH), 1728 (C=O); \( \delta_H(300 \text{ MHz, CDCl}_3) \) 8.20 (1H, brs), 7.52-7.55 (2H, m), 7.26-7.40 (5H, m), 7.08 (1H, t, \( J \) 7.4 Hz), 6.90 (2H, d, \( J \) 8.6 Hz), 6.86 (1H, d, \( J \) 7.6 Hz), 6.78 (2H, d, \( J \) 8.6 Hz), 2.75 (1H, sept, \( J \) 6.8 Hz), 1.18 (6H, d, \( J \) 6.8 Hz); \( \delta_C(75 \text{ MHz, CDCl}_3) \) 176.4, 153.5, 143.6, 140.8, 138.7, 130.2, 128.9, 128.6, 128.5, 126.9, 126.6, 126.4, 123.3, 119.9, 110.6, 84.9, 33.2, 23.9; \( m/z \) (C.I.) 344 (100 %, M + H⁺); HRMS (Found: MH⁺, 344.1651. C\(_{23}\)H\(_{22}\)NO\(_2\) requires 344.1650).

3-(4-Nitrophenoxy)-3-phenyl-1,3-dihydroindol-2-one (15d)

3-Chloro-3-phenyl-1,3-dihydroindol-2-one 14 (0.10 g, 0.41 mmol, 1.1 equiv.) and 4-nitrophenol (50 mg, 0.37 mmol, 1.0 equiv.) were treated according to Method C. The crude product was purified by recrystallisation from hexane:EtOAc to afford the title compound (0.11 g, 79 %) as yellow needles: m.p. 199-200 ºC; \( R_f (100 \text{ % CH}_2\text{Cl}_2) \) 0.60; \( \nu_{\text{max}}(\mathrm{CHCl}_3)/\text{cm}^{-1} \) 3258 (NH), 3064 (CH), 1732 (C=O); \( \delta_H(300 \text{ MHz, CDCl}_3) \) 8.50 (1H, brs), 8.04 (2H, d, \( J \) 7.0 Hz), 7.20-7.51 (7H, m), 7.14 (1H, t, \( J \) 7.4 Hz), 7.08 (1H, d, \( J \) 7.4 Hz), 6.92 (2H, d, \( J \) 7.0 Hz); \( \delta_C(75 \text{ MHz, CDCl}_3) \) 175.0, 160.6, 142.5, 140.4, 137.2, 130.8, 129.0, 128.6, 127.2, 126.0, 125.9, 125.3, 123.7, 118.4, 110.9, 84.7; \( m/z \) (C.I.) 347 (100 %, M + H⁺); HRMS (Found: MH⁺, 347.1033. C\(_{20}\)H\(_{15}\)N\(_2\)O\(_4\) requires 347.1032).
3-(4-Chlorophenoxy)-3-phenyl-1,3-dihydroindol-2-one (15e)

3-chloro-3-phenyl-1,3-dihydroindol-2-one 14 (0.10 g, 0.41 mmol, 1.0 equiv.) and 4-chlorophenol (0.11 g, 0.82 mmol, 2.0 equiv.) were treated according to Method A. The crude product was purified by flash column chromatography (SiO₂; 5:1 hexane:EtOAc) to afford the title compound (0.11 g, 76 %) as a white solid: m.p. 157-158 ºC; Rₜ(5:1 hexane:EtOAc) 0.45; νₘₚₜ(CHCl₃)/cm⁻¹ 3242 (NH), 3025 (CH), 1724 (C=O); δₜ(300 MHz, CDCl₃) 8.33 (1H, brs), 7.50-7.54 (2H, m), 7.25-7.41 (6H, m), 7.08 (2H, d, J 8.8 Hz), 6.88 (1H, d, J 7.7 Hz), 6.84 (2H, d, J 8.8 Hz); δₜ(75 MHz, CDCl₃) 175.9, 154.0, 140.9, 138.1, 130.6, 129.1, 128.9, 128.7, 128.6, 128.2, 126.6, 126.4, 123.5, 121.9, 110.7, 85.4; m/z (C.I.) 336 (100 %, M + H⁺); HRMS (Found: MH⁺, 336.0792. C₂₀H₁₅N₂O₂Cl requires 336.0791).

3-(4-Acetylphenoxy)-3-phenyl-1,3-dihydroindol-2-one (15f)

3-chloro-3-phenyl-1,3-dihydroindol-2-one 14 (0.10 g, 0.41 mmol, 1.0 equiv.) and 4-hydroxyacetophenone (0.11 g, 0.82 mmol, 2.0 equiv.) were treated according to Method A. The crude product was purified by flash column chromatography (SiO₂; 2:1 hexane:EtOAc) to afford the title compound (0.11 g, 78 %) as a white solid: m.p. 152-153 ºC; Rₜ(2:1 hexane:EtOAc) 0.50; νₘₚₜ(CHCl₃)/cm⁻¹ 3250 (NH), 3060 (CH), 1720 (C=O), 1673 (C=O); δₜ(300 MHz, CDCl₃) 9.15 (1H, brs), 7.72 (2H, d, J 8.6 Hz), 7.49-7.53 (2H,
m), 7.23-7.38 (6H, m), 7.05 (1H, t, J 7.2 Hz), 6.88 (2H, d, J 8.6 Hz), 2.45 (3H, s); δC(75 MHz, CDCl3) 196.8, 176.1, 159.7, 140.8, 137.9, 131.9, 130.6, 130.2, 128.9, 128.7, 128.0, 126.3, 126.1, 123.6, 118.5, 111.1, 84.7, 30.9, 26.3; m/z (C.I.) 344 (100 %, M + H+); HRMS (Found: MH+, 344.1285. C22H18NO3 requires 344.1287).

3-Phenyl-3-o-tolyloxy-1,3-dihydroindol-2-one (15h)

\[
\text{Ph} \quad \text{O} \\
\text{H} \quad \text{O} \\
\text{Ph} \\
\text{N}
\]

3-chloro-3-phenyl-1,3-dihydroindol-2-one 14 (0.10 g, 0.41 mmol, 1.0 equiv.) and o-cresol (0.10 mL, 0.82 mmol, 2.0 equiv.) were treated according to Method A. The crude product was purified by flash column chromatography (SiO2; 100 % CH2Cl2) to afford the title compound (0.10 g, 74 %) as a white solid: m.p. 164-165 ºC; Rf(100 % CH2Cl2) 0.55; νmax(CHCl3)/cm⁻¹ 3242 (NH), 3056 (CH), 1720 (C=O); δH(300 MHz, CDCl3) 8.85 (1H, brs), 7.56 (2H, dd, J 4.3 and 2.3 Hz), 7.38 (3H, m), 7.30 (1H, d, J 8.1 Hz), 7.12 (2H, m), 7.02 (1H, d, J 7.8 Hz), 6.92 (1H, d, J 7.8 Hz), 6.82 (2H, m), 6.50 (1H, m), 2.38 (3H, s); δC(75 MHz, CDCl3) 176.9, 154.1, 140.9, 138.9, 130.9, 130.3, 129.6, 129.0, 128.6, 128.5, 126.5, 126.3, 125.9, 123.4, 122.4, 115.9, 110.8, 84.3, 17.1; m/z (C.I.) 316 (100 %, M + H+); HRMS (Found: MH+, 316.1339. C21H18NO2 requires 316.1338).

3-(4-Hydroxy-3,5-dimethylphenyl)-3-phenyl-1,3-dihydroindol-2-one (16)

\[
\text{Ph} \quad \text{O} \\
\text{H} \\
\text{OH}
\]

2,6-dimethylphenol (50 mg, 0.42 mmol, 2.0 equiv.) and Cs₂CO₃ (0.26 g, 0.82 mmol, 4.0 equiv.) in toluene (5.0 mL) were stirred at room temperature under an argon atmosphere for 20 min. 3-Chloro-3-phenyl-1,3-dihydroindol-2-one 14 (50 mg, 0.21 mmol, 1.0 equiv.) in toluene (2.0 mL) was added dropwise and the solution stirred at reflux for 18 h. Water
(2.0 mL) was added and the mixture extracted with CH$_2$Cl$_2$ (3 × 2.0 mL). The combined organic layers were washed with water (2 × 2.0 mL), dried (Na$_2$SO$_4$) and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO$_2$; 100 % CH$_2$Cl$_2$) to afford the title compound (40 mg, 59 %) as a white solid: m.p. 161-162 ºC; $R_f$(100 % CH$_2$Cl$_2$) 0.70; $\nu_{\max}$(CHCl$_3$)/cm$^{-1}$ 3056 (NH, OH), 2928 (CH), 1716 (C=O); $\delta_H$(300 MHz, CDCl$_3$) 7.24-7.32 (9H, m), 7.10 (1H, t $J$ 7.7 Hz), 6.92 (1H, d, $J$ 7.7 Hz), 6.86 (2H, s), 2.20 (6H, s); $\delta_C$(75 MHz, CDCl$_3$) 177.8, 156.2, 143.0, 142.0, 136.8, 133.2, 130.7, 128.8, 128.4, 128.3, 128.2, 127.2, 126.0, 122.8, 108.4, 62.0, 59.6, 26.7, 16.2; m/z (C.I.) 330 (100 %, M + H$^+$); HRMS (Found: MH$^+$, 330.1864. C$_{22}$H$_{19}$NO$_2$ requires 330.1897).

3-(2-Hydroxyphenyl)-3-phenyl-1,3-dihydroindol-2-one (17a)$^5$

3-Phenoxy-3-phenyl-1,3-dihydroindol-2-one 15a (88 mg, 0.29 mmol) was treated according to Method D. The crude product was purified by flash column chromatography (SiO$_2$; 2:1 hexane:EtOAc) to afford the title compound (65 mg, 75 %) as a white solid: m.p. 181-182 ºC; $R_f$(1:1 hexane:EtOAc) 0.65; $\nu_{\max}$(CHCl$_3$)/cm$^{-1}$ 3258 (NH, OH), 3056 (CH), 1689 (C=O); $\delta_H$(300 MHz, CDCl$_3$) 9.06 (1H, brs), 8.42 (1H, brs), 7.25-7.30 (6H, m), 7.10-7.17 (3H, m), 7.00-7.05 (3H, m), 6.85 (1H, t, $J$ 7.8 Hz); $\delta_C$(75 MHz, CDCl$_3$) 182.7, 156.6, 139.8, 138.8, 132.6, 129.9, 128.9, 128.7, 128.4, 128.3, 127.4, 127.2, 126.2, 124.7, 123.3, 119.8, 110.7, 60.2; m/z (C.I.) 302 (100 %, M + H$^+$); HRMS (Found: MH$^+$, 302.1177. C$_{20}$H$_{16}$NO$_2$ requires 302.1181).
3-(2-Hydroxy-5-methylphenyl)-3-phenyl-1,3-dihydroindol-2-one (17b)

3-Phenyl-3-p-tolyloxy-1,3-dihydroindol-2-one 15b (98 mg, 0.31 mmol) was treated according to Method D. The crude product was purified by flash column chromatography (SiO2: 2:1 hexane:EtOAc) to afford the title compound (64 mg, 68 %) as a white solid: m.p. 205-206 °C; Rf (1:1 hexane:EtOAc) 0.60; v\textsubscript{max}(CHCl\textsubscript{3})/cm\textsuperscript{-1} 3238 (NH, OH), 2950 (CH), 1698 (C=O); δ\textsubscript{H}(300 MHz, CDCl\textsubscript{3}) 8.95 (1H, brs), 8.85 (1H, brs), 7.10-7.29 (9H, m), 7.10 (1H, d, J 8.2 Hz), 6.95 (1H, d, J 8.2 Hz), 6.80 (1H, s), 2.18 (3H, s); δ\textsubscript{C}(75 MHz, CDCl\textsubscript{3}) 183.0, 154.4, 140.1, 139.1, 132.9, 130.6, 129.5, 129.2, 128.9, 128.5, 127.5, 127.4, 124.8, 123.4, 119.9, 110.8, 62.7, 29.2, 20.7; m/z (C.I.) 316 (100 %, M + H\textsuperscript{+}); HRMS (Found: MH\textsuperscript{+}, 316.1346. C\textsubscript{21}H\textsubscript{18}NO\textsubscript{2} requires 316.1338).

3-(2-Hydroxy-5-isopropylphenyl)-3-phenyl-1,3-dihydroindol-2-one (17c)

3-(4-Isopropylphenoxy)-3-phenyl-1,3-dihydroindol-2-one 15c (89 mg, 0.26 mmol) was treated according to Method D. The crude product was purified by flash column chromatography (SiO2: 2:1 hexane:EtOAc) to afford the title compound (56 mg, 63 %) as a white solid: m.p. 177-178 °C; Rf (1:1 hexane:EtOAc) 0.60; v\textsubscript{max}(CHCl\textsubscript{3})/cm\textsuperscript{-1} 3254 (NH, OH), 2959 (CH), 1704 (C=O); δ\textsubscript{H}(300 MHz, CDCl\textsubscript{3}) 8.90 (1H, brs), 8.10 (1H, s), 2.18 (3H, s); δ\textsubscript{C}(75 MHz, CDCl\textsubscript{3}) 182.7, 154.6, 140.4, 140.3, 138.9, 132.9, 128.9, 128.5, 127.7, 127.5, 127.4, 127.2, 126.4, 124.5,
3-(2-Hydroxy-5-nitrophenyl)-3-phenyl-1,3-dihydroindol-2-one (17d)

\[
\begin{align*}
\text{NO}_2 & \\
\text{Ph} & \\
\text{OH} & \\
\end{align*}
\]

3-(4-Nitrophenoxy)-3-phenyl-1,3-dihydroindol-2-one (15d) (0.1 g, 0.29 mmol) was treated according to Method D. The crude product was purified by flash column chromatography (SiO₂; 3:1 hexane:EtOAc) to afford the title compound (58 mg, 73%) as a white solid: m.p. 196-197 °C; Rf(3:1 hexane:EtOAc) 0.45; ν\text{max}(\text{CHCl}_3)/\text{cm}^{-1} 3277 (\text{NH, OH}), 2916 (\text{CH}), 1716 (C=O); δ\text{H}(300 MHz, CDCl₃) 10.30 (1H, brs), 8.20 (1H, dd, J 8.8 and 1.9 Hz), 8.08 (1H, s), 7.22-7.40 (4H, m), 7.06-7.18 (6H, m); δ\text{C}(75 MHz, CDCl₃) 178.8, 140.4, 139.8, 131.9, 129.9, 129.3, 129.2, 128.9, 128.7, 128.6, 128.4, 126.2, 125.4, 125.2, 125.1, 123.6, 110.3, 29.7; m/z (C.I.) 347 (100%, M + H⁺); HRMS (Found: MH⁺, 347.1031. C₂₀H₁₅N₂O₄ requires 347.1032).

3-(5-Chloro-2-hydroxyphenyl)-3-phenyl-1,3-dihydroindol-2-one (17e)

3-(4-Chlorophenoxy)-3-phenyl-1,3-dihydroindol-2-one (15e) (0.1 g, 0.29 mmol) was treated according to Method D. The crude product was purified by flash column chromatography (SiO₂; 3:1 hexane:EtOAc) to afford the title compound (71 mg, 71%) as a white solid: m.p. 170-171 °C; Rf(3:1 hexane:EtOAc) 0.45; ν\text{max}(\text{CHCl}_3)/\text{cm}^{-1} 3394 (NH), 3211 (OH), 2815 (CH), 1693 (C=O); δ\text{H}(300 MHz, CDCl₃) 9.30 (1H, brs), 8.75...
3-(5-Acetyl-2-hydroxyphenyl)-3-phenyl-1,3-dihydroindol-2-one (17f)

\[
\begin{align*}
\text{HN} & \\
\text{O} & \\
\text{Ph} & \\
\text{OH} & \\
\text{O} & \\
\end{align*}
\]

3-(4-Acetylphenoxy)-3-phenyl-1,3-dihydroindol-2-one 15f (0.11 g, 0.32 mmol) was treated according to Method D. The crude product was purified by flash column chromatography (SiO\textsubscript{2}; 2:1 hexane:EtOAc) to afford the title compound (75 mg, 68 %) as a white solid: m.p. 164-165 °C; \(R_f(2:1 \text{hexane:EtOAc}) 0.65; \nu_{\text{max}}(\text{CHCl}_3)/\text{cm}^{-1} 3250 (\text{NH, OH}), 2928 (\text{CH}), 1720 (\text{C=O}), 1681 (\text{C=O}); \delta_{\text{H}}(300 \text{ MHz, CDCl}_3) 9.87 (1H, brs), 8.10 (1H, dd, \text{J} 8.2 \text{ and } 1.9 \text{ Hz}), 7.80 (1H, d, \text{J} 1.9 \text{ Hz}), 7.26-7.34 (4H, m), 7.15 (1H, d, \text{J} 6.7 \text{ Hz}), 7.05-7.12 (5H, m), 2.45 (3H, s); \delta_{\text{C}}(75 \text{ MHz, CDCl}_3) 196.6, 182.4, 161.7, 139.5, 138.8, 132.1, 131.2, 130.1, 126.7, 129.1, 128.9, 127.9, 127.3, 126.2, 124.8, 123.9, 120.0, 111.0, 96.4, 62.7, 26.2; m/z (C.I.) 344 (100 %, M + H\textsuperscript{+}); HRMS (Found: MH\textsuperscript{+}, 344.1286. C\textsubscript{22}H\textsubscript{18}NO\textsubscript{3} requires 344.1287).

3-(2-Hydroxy-5-methoxyphenyl)-3-phenyl-1,3-dihydroindo-2-one (17g)

\[
\begin{align*}
\text{MeO} & \\
\text{HN} & \\
\text{O} & \\
\text{Ph} & \\
\text{OH} & \\
\end{align*}
\]

3-chloro-3-phenyl-1,3-dihydroindol-2-one 14 (0.12 g, 0.49 mmol, 1.0 equiv.) and \(p\)-methoxyphenol (0.12 g, 0.99 mmol, 2.0 equiv.) were treated according to Method A. The crude product was purified by flash column chromatography (SiO\textsubscript{2}; 3:1 hexane:EtOAc) to
afford the title compound (70 mg, 50 %) as a white solid: m.p. 148-149 ºC; $R_t$(1:1 hexane:EtOAc) 0.55; $\nu_{\text{max}}$(CHCl$_3$)/cm$^{-1}$ 3254 (NH, OH), 2928 (CH), 1712 (C=O); δ$_{\text{H}}$(300 MHz, CDCl$_3$) 9.16 (1H, brs), 8.78 (1H, brs), 7.10-7.38 (9H, m), 6.98 (1H, t, $J$ 7.6 Hz), 6.82 (1H, d, $J$ 7.6 Hz), 6.62 (1H, s), 3.70 (3H, s); δ$_{\text{C}}$(75 MHz, CDCl$_3$) 182.9, 171.2, 153.1, 150.4, 139.9, 132.7, 128.9, 128.6, 127.6, 127.1, 126.4, 126.2, 123.5, 120.5, 115.9, 114.1, 111.0, 62.7, 55.6, 14.2; m/z (C.I.) 332 (100 %, M + H$^+$); HRMS (Found: MH$^+$, 332.1293. C$_{21}$H$_{18}$NO$_3$ requires 332.1287).

3-(2-Hydroxy-3-methylphenyl)-3-phenyl-1,3-dihydroindo-2-one (17h)

3-Phenyl-3-o-tolyloxy-1,3-dihydroindol-2-one 15h (96 mg, 0.30 mmol) was treated according to Method D. The crude product was purified by flash column chromatography (SiO$_2$; 100 % CH$_2$Cl$_2$) to afford the title compound (91 mg, 85 %) as a white solid: m.p. 178-179 ºC; $R_t$(100 % CH$_2$Cl$_2$) 0.50; $\nu_{\text{max}}$(CHCl$_3$)/cm$^{-1}$ 3262 (NH, OH), 3056 (CH), 1700 (C=O); δ$_{\text{H}}$(300 MHz, CDCl$_3$) 9.04 (1H, brs), 8.24 (1H, brs), 7.20-7.34 (4H, m), 7.05-7.19 (5H, m), 7.00 (1H, d, $J$ 7.6 Hz), 6.85 (1H, dd, $J$ 7.9 and 1.3 Hz), 6.74 (1H, t, $J$ 7.6 Hz), 2.25 (3H, s); δ$_{\text{C}}$(75 MHz, CDCl$_3$) 182.9, 154.9, 140.2, 138.9, 133.2, 131.5, 128.9, 128.4, 127.6, 127.5, 126.9, 126.3, 124.6, 123.4, 119.4, 110.7, 62.8, 16.5; m/z (C.I.) 316 (100 %, M + H$^+$); HRMS (Found: MH$^+$, 316.1337. C$_{21}$H$_{18}$NO$_2$ requires 316.1338).

3-(2-Hydroxy-3-methoxyphenyl)-3-phenyl-1,3-dihydroindo-2-one (17i)

3-Chloro-1-methyl-3-phenyl-1,3-dihydroindol-2-one 14 (0.10 g, 0.41 mmol, 1.0 equiv.) and guiacol (0.09 mL, 0.82 mmol, 2.0 equiv.) were treated according to Method A. The
crude product was purified by flash column chromatography (SiO\textsubscript{2}; 100 % CH\textsubscript{2}Cl\textsubscript{2}) to afford the title compound (65 mg, 55 %) as a white solid: m.p. 176-177 °C; \(R_t(100 \text{ % CH}_2\text{Cl}_2)\) 0.40; \(\nu_{\text{max}}(\text{CHCl}_3)/\text{cm}^{-1}\) 3262 (OH, NH), 2932 (CH), 1704 (C=O); \(\delta_H(300 \text{ MHz, CDCl}_3)\) 8.95 (1H, brs), 7.60 (2H, dd, \(J \) 7.9 and 1.9 Hz), 7.30-7.39 (3H, m), 7.25 (1H, t, \(J \) 7.8 Hz), 7.14 (1H, d, \(J \) 8.0 Hz), 6.85-6.94 (4H, m), 6.75 (1H, d, \(J \) 8.0 Hz), 6.8 (1H, t, \(J \) 7.8 Hz), 3.70 (3H, s); \(\delta_C(75 \text{ MHz, CDCl}_3)\) 177.3, 152.1, 145.0, 141.3, 138.9, 130.0, 128.4, 126.7, 126.4, 124.3, 122.6, 120.9, 120.4, 112.1, 110.3, 85.6, 60.4, 55.4; \(m/z\) (C.I.) 332 (100 %, M + H\textsuperscript{+}); HRMS (Found: MH\textsuperscript{+}, 332.1285. C\textsubscript{21}H\textsubscript{18}NO\textsubscript{3} requires 332.1287).

3-(4-Hydroxyphenyl)-3-phenyl-1,3-dihydroindol-2-one (18a)

\[
\begin{array}{c}
\text{Ph} \\
\text{OH} \\
\text{N} \\
\text{O} \\
\text{Ph}
\end{array}
\]

3-Phenoxy-3-phenyl-1,3-dihydroindol-2-one 15a (90 mg, 0.29 mmol) was treated according to Method E. The crude product was purified by recrystallisation from hexane:EtOAc to afford the title compound (65 mg, 73 %) as a white solid: m.p. 195-196 °C; \(R_t(1:1 \text{ hexane:EtOAc})\) 0.75; \(\nu_{\text{max}}(\text{CHCl}_3)/\text{cm}^{-1}\) 3363 (OH), 3258 (NH), 3025 (CH), 1697 (C=O); \(\delta_H(300 \text{ MHz, CDCl}_3)\) 9.20 (1H, brs), 8.00 (1H, brs), 7.10-7.33 (8H, m), 7.15 (2H, d, \(J \) 8.6 Hz), 6.94 (1H, d, \(J \) 7.8 Hz), 6.75 (2H, d, \(J \) 8.6 Hz); \(\delta_C(75 \text{ MHz, CDCl}_3)\) 179.8, 154.9, 141.8, 139.8, 138.8, 133.5, 129.8, 128.5, 128.3, 128.2, 127.3, 126.3, 122.9, 115.3, 110.1, 62.2, 60.4; \(m/z\) (C.I.) 302 (100 %, M + H\textsuperscript{+}); HRMS (Found: MH\textsuperscript{+}, 302.1181. C\textsubscript{20}H\textsubscript{16}NO\textsubscript{2} requires 302.1181).

3-(4-Hydroxy-3-methylphenyl)-3-phenyl-1,3-dihydroindol-2-one (18b)
3-Phenyl-3-o-tolyloxy-1,3-dihydroindol-2-one 15h (90 mg, 0.29 mmol) was treated according to Method E. The crude product was purified by recrystallisation from hexane:EtOAc to afford the title compound (65 mg, 73%) as a white solid; m.p. 142-143 °C; \( R_f(100 \% \text{CH}_2\text{Cl}_2) 0.45; \nu_{\text{max}}(\text{CHCl}_3)/\text{cm}^{-1} 3366 (\text{OH}), 3258 (\text{NH}), 3060 (\text{CH}), 1700 (\text{C} = \text{O}) \); \( \delta_{\text{H}}(300 \text{ MHz, CDCl}_3) 8.50 (1\text{H}, \text{brs}), 7.20-7.29 (7\text{H}, \text{m}), 7.05 (1\text{H}, \text{d, } J 8.3 \text{ Hz}), 7.02 (1\text{H}, \text{s}), 6.92 (2\text{H}, \text{t, } J 7.5 \text{ Hz}), 6.65 (1\text{H}, \text{d, } J 8.3 \text{ Hz}), 2.18 (3\text{H}, \text{s}); \delta_{\text{C}}(75 \text{ MHz, CDCl}_3) 178.6, 154.5, 142.5, 141.3, 133.7, 131.8, 130.2, 128.2, 128.0, 127.9, 126.8, 126.4, 125.9, 123.5, 121.8, 114.3, 109.8, 61.4, 30.6, 16.1; m/z (C.I.) 316 (100 %, M + H⁺); HRMS (Found: MH⁺, 316.1335. C₂₁H₁₈N₂O₂ requires 316.1338).

3-(4-Hydroxy-3-methoxyphenyl)-3-phenyl-1,3-dihydroindol-2-one (18c)

![Chemical Structure]

3-(2-Hydroxy-3-methoxyphenyl)-3-phenyl-1,3-dihydroindol-2-one 17h (65 mg, 0.19 mmol, 1.0 equiv.) was treated according to Method E. The crude product was purified by flash column chromatography (SiO₂; 100 % CH₂Cl₂) to afford the title compound (48 mg, 74 %) as a white solid; m.p. 190-191 °C; \( R_f(100 \% \text{CH}_2\text{Cl}_2) 0.45; \nu_{\text{max}}(\text{CHCl}_3)/\text{cm}^{-1} 3258 (\text{OH, NH}), 2928 (\text{CH}), 1700 (\text{C} = \text{O}) \); \( \delta_{\text{H}}(300 \text{ MHz, CDCl}_3) 8.48 (1\text{H}, \text{brs}), 7.40-7.55 (7\text{H}, \text{m}), 7.27 (1\text{H}, \text{d, } J 7.2 \text{ Hz}), 7.16 (1\text{H}, \text{d, } J 7.6 \text{ Hz}), 7.08 (1\text{H}, \text{d, } J 1.9 \text{ Hz}), 7.02 (1\text{H}, \text{d, } J 8.3 \text{ Hz}), 6.95 (1\text{H}, \text{d, } J 8.3 \text{ and 1.9 Hz}), 3.80 (3\text{H}, \text{s}); \delta_{\text{C}}(75 \text{ MHz, CDCl}_3) 178.4, 147.2, 145.9, 142.5, 141.3, 135.5, 132.1, 128.3, 128.1, 127.9, 126.8, 125.9, 121.8, 120.7, 115.1, 112.7, 109.9, 61.6, 55.6, 30.6; m/z (C.I.) 332 (100 %, M + H⁺); HRMS (Found: MH⁺, 332.1288. C₂₁H₁₈N₂O₃ requires 332.1287).
3-Chloro-1-methyl-3-phenyl-1,3-dihydroindol-2-one (19)\textsuperscript{6}

\[
\begin{array}{c}
\text{Ph} \\
\text{Cl} \\
\text{O} \\
\text{N}
\end{array}
\]

A solution of 3-hydroxy-1-methyl-3-phenyl-1,3-dihydroindol-2-one\textsuperscript{7} (2.30 g, 9.6 mmol, 1.0 equiv.) and pyridine (7.76 mL, 96 mmol, 10 equiv.) in diethyl ether (100 mL) was stirred at 0 °C under an argon atmosphere for 15 min. Thionyl chloride (2.80 mL, 38.4 mmol, 4.0 equiv.) was added dropwise and the solution stirred at 0 °C for 30 min. Water (20 mL) was added and the mixture extracted with EtOAc (4 × 20 mL). The combined organic layers were washed with water (2 × 20 mL), dried (Na\textsubscript{2}SO\textsubscript{4}) and concentrated under reduced pressure to yield the crude product. Recrystallisation from hot EtOAc:hexane yielded the title compound (1.82 g, 74 %) as needles: m.p. 105-106 °C (lit.\textsuperscript{6} 108-109 °C); \( R_f \) (1:1 hexane:EtOAc) 0.65; \( \nu_{\text{max}} \) (CHCl\textsubscript{3})/\( \text{cm}^{-1} \) 3055 (CH), 1732 (C=O); \( \delta_{\text{H}} \) (300 MHz, CDCl\textsubscript{3}) 7.54-7.58 (2H, m), 7.35-7.45 (5H, m), 7.20 (1H, d, \( J \) 7.2 Hz), 6.90 (1H, d, \( J \) 7.2 Hz), 3.28 (3H, s); \( \delta_{\text{C}} \) (75 MHz, CDCl\textsubscript{3}) 173.2, 142.6, 136.4, 130.2, 128.7, 128.3, 127.3, 125.8, 123.4, 108.7, 26.7; \( m/z \) (C.I.) 259 (100 %, M + H\textsuperscript{+}); HRMS (Found: MH\textsuperscript{+}, 258.0677. C\textsubscript{15}H\textsubscript{13}NOC\textsubscript{1} requires 258.0686).

1-Methyl-3-(4-nitrophenoxo)-3-phenyl-1,3-dihydroindol-2-one (20c)

\[
\begin{array}{c}
\text{Ph} \\
\text{O} \\
\text{NO}_2
\end{array}
\]

3-Chloro-1-methyl-3-phenyl-1,3-dihydroindol-2-one 19 (0.10 g, 0.39 mmol, 1.0 equiv.) and \( p \)-nitrophenol (0.10 g, 0.78 mmol, 2.0 equiv.) were treated according to Method B. The crude product was purified by recrystallisation from hexane:EtOAc to afford the title compound (82 mg, 60 %) as needles: m.p. 163-164 °C; \( R_f \) (1:1 hexane:EtOAc) 0.45; \( \nu_{\text{max}} \) (CHCl\textsubscript{3})/\( \text{cm}^{-1} \) 3064 (CH), 1728 (C=O); \( \delta_{\text{H}} \) (300 MHz, CDCl\textsubscript{3}) 8.05 (2H, d, \( J \) 7.8 Hz), 7.87 (2H, d, \( J \) 7.8 Hz), 7.56-7.62 (2H, m), 7.36-7.46 (5H, m), 7.12 (1H, d, \( J \) 7.8 Hz), 6.89 (1H, d, \( J \) 7.8 Hz), 3.22 (3H, s); \( \delta_{\text{C}} \) (75 MHz, CDCl\textsubscript{3}) 173.6, 142.6, 136.4, 130.2, 128.7, 128.3, 127.3, 125.8, 123.4, 108.7, 27.0; \( m/z \) (C.I.) 295 (100 %, M + H\textsuperscript{+}); HRMS (Found: MH\textsuperscript{+}, 294.0721. C\textsubscript{16}H\textsubscript{16}NO\textsubscript{3} requires 294.0725).
7.26-7.48 (7H, m), 7.18 (1H, t, J 7.5 Hz), 7.00 (1H, d, J 7.8 Hz), 6.85 (2H, d, J 7.8 Hz), 3.25 (3H, s); δ(75 MHz, CDCl₃) 173.4, 160.9, 143.6, 142.8, 137.5, 131.0, 129.2, 128.7, 127.1, 126.4, 126.1, 125.9, 125.4, 123.8, 118.8, 115.6, 109.2, 84.8, 26.7; m/z (C.I.) 361 (100 %, M + H⁺); HRMS (Found: MH⁺, 361.1188. C₂₁H₁₇N₂O₄ requires 361.1188).

1-Methyl-3-(2-nitrophenoxy)-3-phenyl-1,3-dihydroindol-2-one (20e)

![Chemical structure](image)

3-Chloro-1-methyl-3-phenyl-1,3-dihydroindol-2-one 19 (0.35 g, 1.36 mmol, 1.0 equiv.) and 2-nitrophenol (0.38 g, 2.72 mmol, 2.0 equiv.) were treated according to Method B. The crude product was purified by flash column chromatography (SiO₂; 100 % CH₂Cl₂) to afford the title compound (0.35 g, 72 %) as a pale yellow solid: m.p. 142-143 ºC; Rf (100 % CH₂Cl₂) 0.60; νₘₐₓ(CHCl₃)/cm⁻¹ 2935 (CH), 1728 (C=O); δ(300 MHz, CDCl₃) 7.70 (1H, d, J 7.7 Hz), 7.52 (2H, dd, J 7.4 and 2.3 Hz), 7.20-7.42 (6H, m), 7.00-7.09 (2H, m), 6.95 (1H, d, J 7.8 Hz), 6.75 (1H, d, J 8.4 Hz), 3.30 (3H, s); δ(75 MHz, CDCl₃) 173.4, 143.5, 133.1, 130.7, 128.7, 128.6, 128.5, 127.8, 127.5, 127.1, 126.2, 125.7, 125.5, 125.1, 123.6, 123.1, 122.6, 119.7, 108.8, 85.6, 26.5; m/z (C.I.) 361 (100 %, M + H⁺); HRMS (Found: MH⁺, 361.1185. C₂₁H₁₇N₂O₄ requires 361.1188).

3-(2-Hydroxyphenyl)-1-methyl-3-phenyl-1,3-dihydroindol-2-one (21a)

![Chemical structure](image)

3-Chloro-1-methyl-3-phenyl-1,3-dihydroindol-2-one 19 (0.10 g, 0.39 mmol, 1.0 equiv.) and phenol (0.10 g, 0.78 mmol, 2.0 equiv.) were treated according to Method A. The crude product was purified by recrystallisation from hexane:EtOAc to afford the title compound (75 mg, 63 %) as needles: m.p. 226-227 ºC; Rf (1:1 hexane:EtOAc) 0.60; νₘₐₓ(CHCl₃)/cm⁻¹
3339 (OH), 3064 (CH), 1681 (C=O); δH(300 MHz, CDCl3) 7.23-7.34 (7H, m), 7.08 (3H, m), 6.90 (1H, d, J 7.9 Hz), 6.75 (2H, dd, J 7.9 and 1.7 Hz), 5.15 (1H, brs), 3.30 (3H, s);
δC(75 MHz, CDCl3) 177.9, 154.9, 142.9, 142.1, 133.7, 133.2, 129.8, 128.4, 128.3, 128.2, 127.2, 125.9, 122.8, 115.3, 108.5, 61.9, 26.7; m/z (C.I.) 316 (100 %, M + H+); HRMS (Found: MH+, 316.1339. C21H18NO2 requires 316.1338).

3-(2-Hydroxy-5-methylphenyl)-1-methyl-3-phenyl-1,3-dihydroindol-2-one (21b)

3-Chloro-1-methyl-3-phenyl-1,3-dihydroindol-2-one 19 (0.10 g, 0.39 mmol, 1.0 equiv.) and p-cresol (0.10 mL, 0.78 mmol, 2.0 equiv.) were treated according to Method A. The crude product was purified by recrystallisation from hexane:EtOAc to afford the title compound (70 mg, 68 %) as needles: m.p. 164-165 ºC; Rf(1:1 hexane:EtOAc) 0.50; νmax(CHCl3)/cm⁻¹ 3277 (OH), 3056 (CH), 1681 (C=O); δH(300 MHz, CDCl3) 9.25 (1H, brs), 7.07-7.36 (9H, m), 7.05 (1H, d, J 8.1 Hz), 6.95 (1H, d, J 8.1 Hz), 6.80 (1H, s), 3.40 (3H, s), 2.20 (3H, s); δC(75 MHz, CDCl3) 180.9, 154.7, 142.1, 140.5, 132.4, 130.5, 129.3, 128.9, 128.8, 128.5, 127.4, 127.1, 126.3, 124.8, 123.5, 120.1, 109.3, 62.4, 26.8, 20.7; m/z (C.I.) 330 (100 %, M + H+); HRMS (Found: MH+, 330.1494. C22H20NO2 requires 330.1494).
3-(2-Hydroxy-5-nitrophenyl)-1-methyl-3-phenyl-1,3-dihydroindol-2-one (21c)

1-Methyl-3-(4-nitrophenoxy)-3-phenyl-1,3-dihydroindol-2-one 20c (82 mg, 0.23 mmol) was treated according to Method D. The crude product was purified by flash column chromatography (SiO₂; 100 % CH₂Cl₂) to afford the title compound (54 mg, 67 %) as a white solid: m.p. 225-226 °C; Rf(100 % CH₂Cl₂) 0.45; νmax(CHCl₃)/cm⁻¹ 3168 (OH), 2928 (CH), 1681 (C=O); δH(300 MHz, CDCl₃) 10.75 (1H, brs), 8.18 (1H, dd, J 8.8 and 2.7), 8.08 (1H, s), 7.42-7.45 (2H, m), 7.18-7.30 (5H, m), 7.02-7.08 (3H, m), 3.26 (3H, s); δC(75 MHz, CDCl₃) 180.2, 163.5, 141.8, 140.7, 139.1, 130.9, 129.4, 129.2, 128.0, 126.9, 126.1, 125.4, 124.5, 120.5, 109.9, 62.2, 30.9, 27.1; m/z (C.I.) 361 (100 %, M + H⁺); HRMS (Found: M⁺, 361.1190. C₂₁H₁₇N₂O₄ requires 361.1188).

3-(2-Hydroxy-3-methylphenyl)-1-methyl-3-phenyl-1,3-dihydroindol-2-one (21d)

3-Chloro-1-methyl-3-phenyl-1,3-dihydroindol-2-one 19 (0.10 g, 0.39 mmol, 1.0 equiv.) and o-cresol (0.10 mL, 0.78 mmol, 2.0 equiv.) were treated according to Method A. The crude product was purified by flash column chromatography (SiO₂; 100 % CH₂Cl₂) to afford the title compound (73 mg, 57 %) as needles: m.p. 157-158 °C; Rf(100 % CH₂Cl₂) 0.55; νmax(CHCl₃)/cm⁻¹ 3374 (OH), 3056 (CH), 1712 (C=O); δH(300 MHz, CDCl₃) 9.50 (1H, brs), 7.50 (1H, m), 7.36-7.43 (2H, m), 7.05-7.27 (7H, m), 6.95 (1H, d, J 7.6 Hz), 6.80 (1H, dd, J 7.6 and 3.2 Hz), 3.25 (3H, s), 2.38 (3H, s); δC(75 MHz, CDCl₃) 180.9, 174.5, 155.2, 154.2, 143.9, 142.0, 140.5, 139.1, 127.4, 127.2, 126.7, 126.4, 126.3, 125.7,
123.4, 122.5, 116.1, 108.7, 26.6, 17.2; m/z (C.I.) 330 (100 %, M + H\(^+\)); HRMS (Found: MH\(^+\), 330.1490. C\(_{22}\)H\(_{20}\)NO\(_2\) requires 330.1494).

### 3-(2-Hydroxy-3-nitrophenyl)-1-methyl-3-phenyl-1,3-dihydroindol-2-one (21e)

![](image)

1-Methyl-3-(2-nitrophenoxy)-3-phenyl-1,3-dihydroindol-2-one (20e) (0.15 g, 0.42 mmol, 1.0 equiv.) was treated according to **Method D**. The crude product was purified by flash column chromatography (SiO\(_2\); 100 % CH\(_2\)Cl\(_2\)) to afford the **title compound** (0.12 g, 77 %) as a pale yellow solid: m.p. 191-192 °C; \(R_t(100\ %\ \text{CH}_2\text{Cl}_2)\) 0.65; \(\nu_{\text{max}}(\text{CHCl}_3)/\text{cm}^{-1}\) 3260 (OH), 2929 (CH), 1708 (C=O); \(\delta_{\text{H}}(300\ \text{MHz, CDCl}_3)\) 10.58 (1H, brs), 7.95 (1H, dd, \(J 7.8\) and \(2.3\) Hz), 7.62 (1H, dd, \(J 7.8\) and \(2.3\) Hz), 7.10-7.39 (9H, m), 6.90 (1H, d, \(J 7.8\) Hz), 3.36 (3H, s); \(\delta_{\text{C}}(75\ \text{MHz, CDCl}_3)\) 176.5, 154.3, 142.7, 140.8, 138.2, 133.9, 132.8, 131.4, 128.7, 128.6, 128.5, 127.7, 127.5, 125.6, 124.1, 123.1, 120.1, 108.8, 61.1, 26.6; m/z (C.I.) 361 (100 %, M + H\(^+\)); HRMS (Found: MH\(^+\), 361.1182. C\(_{21}\)H\(_{17}\)N\(_2\)O\(_4\) requires 361.1188).

### 3-(4-Hydroxy-3-nitrophenyl)-1-methyl-3-phenyl-1,3-dihydroindol-2-one (22)

1-Methyl-3-(2-nitrophenoxy)-3-phenyl-1,3-dihydroindol-2-one (20e) (0.15 g, 0.42 mmol, 1.0 equiv.) was treated according to **Method E**. The crude product was purified by flash column chromatography (SiO\(_2\); 100 % CH\(_2\)Cl\(_2\)) to afford the **title compound** (90 mg, 60 %) as a pale yellow solid: m.p. 200-201 °C; \(R_t(100\ %\ \text{CH}_2\text{Cl}_2)\) 0.55; \(\nu_{\text{max}}(\text{CHCl}_3)/\text{cm}^{-1}\)
3384 (OH), 2929 (CH), 1711 (C=O); $\delta$H(300 MHz, CDCl3) 7.05-7.39 (10H, m), 7.10 (1H, t, J 7.8 Hz), 6.90 (1H, t, J 7.8 Hz), 3.80 (1H, brs), 3.28 (3H, s); $\delta$C(75 MHz, CDCl3) 171.5, 143.4, 140.1, 131.6, 129.7, 128.5, 128.4, 128.3, 128.2, 127.9, 126.3, 125.3, 124.9, 123.5, 108.6, 77.9, 53.0, 26.4; m/z (C.I.) 361 (100 %, M + H+); HRMS (Found: MH+, 361.1182. C21H17N2O4 requires 361.1188).

References: