A Highly Regioselective Synthesis of N-Acyl-2-acyl(aroyl)indolium Chloride through Palladium-Copper Catalysis followed by Friedel–Crafts Reaction

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General Experimental
Melting points were determined in open capillary tubes on Gallenkamp (England) melting point apparatus and are uncorrected. IR spectra were recorded on a Shimadzu FTIR spectrophotometer. $^1$H NMR and $^{13}$C NMR spectra were recorded on a Bruker DPX-400 spectrophotometer (400MHz) and Bruker DPX-500 spectrophotometer (500MHz) using tetramethylsilane as internal reference. Analytical thin-layer chromatography (TLC) was performed on precoated silica gel 60F-254 (E. Merck), and the spots were visualized with UV light. Column chromatography was performed on silica gel (60–120 mesh). Bis(triphenylphosphine)palladium(II)chloride and other reagents were purchased from E. merck (Germany) and Fluka (Switzerland).

Synthesis of 2-iodonitrobenzene 20: 2-Nitroaniline 19 5.0 g (36.0 mmol) was stirred with 7.5 g (4.10 mL) of conc. H$_2$SO$_4$ and 40 ml of water for 1 hour. The mixture was cooled in a freezing point (0-5°C) and was stirred mechanically. A solution of 2.5 g (36.0 mmol) of sodium nitrite in 7.5 mL of water was added to the mixture. The filtrate was poured into an ice cooled solution of 10 g (60.0 mmol) potassium iodide in 30 mL water with stirring. The precipitate formed was collected by filtration under reduced pressure and finally dried & recrystallized from ethanol. Yellow solid, mp 48-49°C, IR (KBr): $\nu_{max}$ 1581.7, 1517 (C=C), 1470(Ar-NO$_2$), 1330.2, 1296.0, 779, 723 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.04 (d, 1H, $J$ = 8.3 Hz, H-3), 8.01 (d, 1H, $J$=7.5 Hz, H-6), 7.85 ( t, 1H, $J$=7.5 Hz, H-4) and 7.60 (t, 1H, $J$=7.5 Hz, H-5).

Synthesis of 2-iodoaniline 21: In a 250 mL round bottom flask, equipped with a reflux condenser, a mixture of 5 g (20.0 mmol) of 2 -iodonitrobenzene 20, 3.92 g (70.0 mmol) of granulated iron were stirred and then the mixture of 4.7 g (8 mL) of glacial acetic acid and 80 mL ethanol were poured one by one into this mixture and was shaken the contents of the flask steadily. The reaction mixture was refluxed for 3 hours with constant stirring at 118°C. The reaction mixture was diluted with 100 mL water and neutralized with dil. NaOH (aq) solution. The product was separated by steam distillation and finally extracted with CHCl$_3$. The organic layer was washed with distilled water, dried with anhydrous
sodium sulfate and concentrate under reduced pressure. The crude product was purified with column chromatography on silica gel using n-hexane to afford the compound 21 in good yield.

White solid, mp 55-58°C, IR (KBr): ν_max 3392.6, 3288.4 (NH_2), 1622, 1473.5 (C=C), 570 (C-I), 1438, 1006.3, 779 cm⁻¹; ^1^H NMR (500 MHz, CDCl_3): δ 7.74 (d, 1H, J = 7.3 Hz, H-3), 7.63 (t, 1H, J =7.5 Hz, H-5), 7.13 ( t, 1H, J =7.5 Hz, H-4), 6.47 (d, 1H, , J =7.5 Hz, H-6), 4.10 (br. s, 2H, NH_2).

**Synthesis of substituted 2-idoaniline 24–27**

A solution of substituted aniline 22,23 (10 g; 93.30 mmol), potassium iodide (10.37 g; 62.52 mmol) and potassium iodate (6.59 g; 30.79 mmol) was prepared in methanol (50 mL) and water (200 mL). The aqueous solution of hydrochloric acid (10 mL, 95.71 mmol) was added drop wise to the mixture for 40 to 45 minutes. The reaction mixture was diluted with water (500 mL) after 3 hours and extracted with dichloromethane (3×50 mL). The combined organic extract was washed with dilute sodium thiosulphate (5%), water, brine water, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using n-hexane /ethyl acetate (4:1) as eluant and 2-idoanilines 24,25 and 2,6-diidoanilines 26,27 were isolated in good yield.

**2-Iodo-4-methylaniline 24**: Brown crystalline solid, mp 92-95 °C, R_f Value: 0.62 (n-hexane/ethyl acetate = 4:1); IR (KBr): ν_max 3408.0, 3317.3 (NH_2), 1604.7, 1442.7 (C=C), 580 (C-I) cm⁻¹; ^1^H NMR (500 MHz, CDCl_3): δ 7.58 (d, 1H, J = 2.3 Hz, H-3), 7.08 (dd, 1H, J = 2.3, 8.4 Hz, H-5), 6.64 (d, 1H, J = 8.4 Hz, H-6), 4.07(br. s, 2H, NH_2).

**2,6-Diido-4-methylaniline 26**: Yellow solid. mp 110-111 °C, R_f Value: 0.85 (n-hexane/ethyl acetate = 4:1); IR (KBr): ν_max 3406.1 & 3317.3 (NH_2), 3037.7(C-H aromatic), 2898.8 (C-H aliphatic), 1608.5, 1460.0 (C=C), 650(C-I) cm⁻¹; ^1^H NMR (500 MHz, CDCl_3): δ 7.45 (s, 2H, H-3, H-5), 4.19 (br. s, 2H, NH_2), 2.15 (s, 3H, Ar-CH_3).

**4-Chloro-2-ido aniline 25**: Light brown crystalline solid, mp 40-42°C; R_f Value: 0.70 (n-hexane/ethyl acetate = 4:1); IR (KBr): ν_max 3408.1, 3317.3 (NH_2), 1604.7, 1442.7(C=C), 722(C-Cl), 550 (C-I), 1402.2, 868.0 cm⁻¹; ^1^H NMR (400 MHz, CDCl_3): δ 7.58 (d, 1H, J = 2.3 Hz, H-3), 7.08 (dd, 1H, J = 2.3, 8.4 Hz, H-5), 6.64(d, 1H, J = 8.4 Hz, H-6), 4.07 (br, s, 2H, NH_2).

**1, 2-Diido-4-chloroaniline 27**: Yellowish amorphous solid, mp 127-129 °C, R_f Value: 0.87 (n-hexane/ethyl acetate = 4:1); IR (KBr): ν_max 3408.0, 3317.3 (NH_2), 1604.7 (Ar-C-
H), 1442.7 (C=C), 502 (C-I), 730 (C-Cl) cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.60 (s, 2H, H-3, H-5), 4.59 (br. s, 2H, NH\(_2\)).

**Synthesis of substituted 2-idoacetalanilides 1–3**

2-Iodoanilines 21,24,25 (2. 2 g, 0.01 mole) were added separately to the mixture of acetic acid (5 mL, 0.08 mole) and acetic anhydride (1.02 g, 0.01 mole) in presence of small amount of zinc dust and stirred at room temperature for half an hour. The reaction mixture was refluxed for 3 hours with constant stirring at 80\(^\circ\) C. The hot reaction mixture was poured into a beaker containing 200 mL of cold water with constant stirring and extracted with chloroform (3x50 mL). The combined organic layer was washed with distilled water, dried over anhyd. Na\(_2\)SO\(_4\) and concentrated under reduced pressure. The crude product was purified by chromatography on a column of silica gel and crystallization from ethanol to afford desired products 1–3 in good yield.

**2-Iodoacetalanilide 1**: White crystalline solid, mp 108-109 °C, \(R_f\) value 0.36 (n-Hexane), IR (KBr): \(\nu\)\(_{\text{max}}\) 3273.0 (NH), 1660.6 (C=O), 1573.8, 1529.4, 1463.9, 14433.0, 1411.8, 1292.2, 1253.6, 1014.5, 750.3, 663.5 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 8.15 (s, 1H, Ar-H), 7.75 (d, 1H, \(J = 8.0\) Hz, Ar-H), 7.42 (br. s, 1H, NH), 7.31 ( t, 1H, \(J = 8\) Hz, Ar-H), 6.82 (t, 1H, \(J = 8.0\) Hz, Ar-H), 2.20 (s, 3H, COCH\(_3\)).

**2-Iodo-4-methylacetanilide 2**: Brown crystalline solid, mp 128-130 °C, \(R_f\) Value: 0.6 (n-hexane/ethyl acetate = 4:1), IR (KBr): \(\nu\)\(_{\text{max}}\) 3265.3 (NH), 1654.8 (C=O), 1290.3 (C-N) cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.99 (d, 1H, \(J = 8.0\) Hz, H-6), 7.59 (s, 1H, H-3), 7.32 (br. s, 1H, NH), 7.12 (d, 1H, \(J = 8.0\) Hz, H-5), 2.26 (s, 3H, COCH\(_3\)), 2.10 (s, 3H, Ar-CH\(_3\)).

**4-Chloro-2-idoacetanilide 3**: White crystalline solid, mp 125-127°C, \(R_f\) Value: 0.5 (n-hexane/ethyl acetate = 4:1), IR (KBr): \(\nu\)\(_{\text{max}}\) 3274.9 (NH), 1658.7(C=O), 1577.7, 1463.9 (C=C), 1568.0, 1521.7, 1375.2, 1288.4 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 8.15 (d, 1H, \(J = 8.0\) Hz, H-6), 7.74 (d, 1H, \(J = 2.0\) Hz, H-3), 7.36 (br. s, 1H, NH), 7.30 (dd, 1H, \(J = 8.0, 2.0\) Hz, H-5), 2.22 (s, 3H, COCH\(_3\)).

**Synthesis of 2-Trimethylsilylethynyl acetanilide 5–7**

A mixture of substituted 2-idoacetanilide 1–3 (500 mg, 1.92 mmol), bis(triphenylphosphine)palladium(II)chloride (47.30 mg, 1.92 mmol), copper (II) iodide (29.3 mg,1.92 mmol), and trimethylsilylacetylene (387 mg, 1.92 mmol) was stirred in DMF (5-7 mL) under nitrogen atmosphere. Then triethylamine (780 mg, 1.92 mmol) was added drop wise to this mixture and stirring continued at room temperature for 24-48 h. The mixture was evaporated to dryness under reduced pressure. The residue extracted
with chloroform (3×50 mL), the combined chloroform extracts washed with distilled water (3×50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using pet ether/chloroform (3:1) as eluant to afford the desired compounds 5–7 in good yield.

**2-Trimethylsilylethynyl acetanilide 5:** Crystalline solid, yield 65%, mp. 94-95 °C; IR (KBr) vₓmax 3327 (NH), 2158 (C≡C), 1695(C=O), 1672, 1516, 1444 cm⁻¹; ¹H NMR (400 MHz CDCl₃): δ 8.39 (d, 1H, J = 8.3 Hz, Ar-H), 7.99 (br. s, 1H, NH), 7.41 (d, 1H, J = 8.0 Hz, Ar-H), 7.32 (dd, 1H, J = 8.0 Hz, 8.3 Hz, Ar-H), 7.01 (t, 1H, J = 8.0 Hz, Ar-H), 2.21 (s, 3H, COCH₃), 0.30 (s, 9H, SiMe₃). ¹³C NMR (100 MHz, CDCl₃): δ 168.0 (CO), 139.5, 131.4, 129.9, 123.10, 111.5, 102.2, 100.2, 24.7 (COCH₃), 0.10 (SiMe₃). UV (EtOH): λₓmax 296.2, 250.8 nm. Anal. Calcd. for C₁₃H₁₇SiNO: C, 67.48; H, 7.40; N, 6.05. Found: C, 67.09; H, 7.43; N, 6.03.

**4-Methyl-2-trimethylsilylethynylacetanilide 6:** White crystalline solid, mp. 42-45°C; Rₓ Value: 0.75 (n-hexane/ethyl acetate = 5:1); IR (KBr): vₓmax 3435.0 (NH), 1662.5(C=O), 2170 (C≡C), 2923.9 (ArC-H), 2850(C-H) cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 8.28 (br. s, 1H, NH), 8.21 (d, 1H, J = 8.5 Hz, H-6), 7.85 ( d, 1H, J = 2.0 Hz, H-3), 7.42 (t, 1H, J= 2.5 Hz, H-5), 6.99 (t, 1H, J= 6.0 Hz, H-4).

**4-Chloro-2-trimethylsilylethynylacetanilide 7:** White crystalline solid. mp 48-50°C; Rₓ Value: 0.70 (n-hexane/ethyl acetate = 5:1); IR (KBr): vₓmax 3290.0 (NH), 1690.9 (C=O), 1516.9, 1541.0 (C≡C), 1388, 1276, 1168.8, 756.0 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 8.00 (br. s, 1H, NH), 7.82 (d, 1H, J = 8.2 Hz, H-6), 7.45 (s, 1H, H-3), 7.18 (d, 1H, J = 6.8Hz, H-7) 7.15(s, 1H, H-4), 2.95 (s, 3H, COOCH₃), 2.73 (s, 3H, COCH₃); ¹³C NMR (100 MHz, CDCl₃): δ 180.02, 170.01(C=O), 144.13, 134.90, 131.20, 128.63, 123.47, 115.94, 107.52, 22.65 (COCH₃), 0.13 (SiCH₃).

**Synthesis of N-acetyl-2-acetyl(aroyl) -1H-indolium chloride 13–18**

To ice cold solution of 5–7 (200 mg, 0.865 mmol) in tetrachloroethane (5 mL), acetyl(aroyl)chloride (121.15 mg, 0.865 mmol) and anhydrous aluminium chloride (4 equiv, 460.18 mg, 3.45 mmol) were added separately. The mixture was warmed up to room temperature and stirred further two hours. Then the mixture was poured into ice cold solution of 1.0 M HCl and the organic layer was extracted with CHCl₃ (3×50 mL). The combined organic layer was washed with distilled H₂O (2×30 mL), saturated NaHCO₃ solution (2×30mL) and distilled water (2×30 mL) respectively. After drying over anhydrous Na₂SO₄ and removal of solvent the residues were obtained. The crude
mass was purified by column chromatography (Silica gel). Elution with n-hexane-ethylacetate (2:1) furnished the products 13–18 in good yield.

**N-Acetyl-2-acetyl indolium chloride 13:** Crystalline solid, mp 84–86 °C;
IR (KBr): \( \nu_{\text{max}} \) 3221(NH), 1684 (C=O), 1652, 1608, 1576, 1560, 1502, 1130 cm\(^{-1}\); \(^1\)H NMR (400 MHz CDCl\(_3\)): \( \delta \) 11.05 (bs, 1H, NH), 8.59 (d, 1H, \( J = 8.0 \text{ Hz} \), Ar–H), 7.65 (t, 1H, \( J = 8.0 \text{ Hz} \), Ar–H), 7.46 (d, 1H, \( J = 8.0 \text{ Hz} \), Ar–H), 7.05 (t, 1H, \( J = 8.0 \text{ Hz} \), Ar–H), 6.10 (s, 1H, H-3), 2.18 (s, 3H, COCH\(_3\)), 2.12 (s, 3H, COCH\(_3\)). \(^{13}\)C NMR (400 MHz, CDCl\(_3\)): \( \delta \) 194.31 (C=O), 185.31 (C=O), 168.89, 140.152, 135.85, 133.83, 129.06, 122.41, 121.02, 98.02, 25.40 (COCH\(_3\)), 23.15 (COCH\(_3\)). UV (EtOH): \( \lambda_{\text{max}} \) 334, 305.4, 259.8, 238.4 nm.

**N-Acetyl-2-benzoyl-1H-indolium chloride 14:** White crystalline solid, mp 63-64°C; \( R_f \) Value: 0.75(n-hexane/ethyl acetate = 5:1); IR (KBr): \( \nu_{\text{max}} \) 3274.9 (NH), 3076.2 (C-H), 1703.0 (C=O), 1575.7, 1529.7 (C=C) and 1463.9, 1380.9, 1276.8cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 11.08 (br. s, 1H, NH), 8.64 (d, 1H, \( J = 8.4 \text{ Hz} \), Ar-H), 7.94 (d, 2H, \( J = 7.2 \text{ Hz} \), Ar-H)), 7.82 (d,1H, \( J = 8.0 \text{ Hz} \), Ar-H) 7.52 (m, 4H, Ar-H), 7.13(t, 1H, Ar-H) 6.79 (s, 1H, H-3), 2.23 (s, 3H, COCH\(_3\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 194.70 (C=O), 179.53 (C=O), 168.98, 140.11, 133.99, 133.84, 132.58, 129.15, 128.82, 126.91, 123.12, 122.79, 121.51, 94.99, 25.49 (COCH\(_3\)).

**N-Acetyl-2-anisoyl indolium chloride 15:** Light yellow crystal, mp. 112–113 °C; IR (KBr): \( \nu_{\text{max}} \) 3327.9 (NH), 1683.7 (C=O), 1610, 1576.7, 1500, 1413, 1360, 1175 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 11.04 (br. s, 1H, NH), 8.62 (d, 1H, \( J = 8.0 \text{ Hz} \), Ar-H), 7.91 (d, 2H, \( J = 8.0 \text{ Hz} \), Ar-H), 7.77 (d, 1H, \( J = 8.0 \text{ Hz} \), Ar-H), 7.51 (t, 1H, \( J = 7.2 \text{ Hz} \), Ar–H), 7.12 (d, 1H, \( J = 7.2 \text{ Hz} \), Ar–H), 6.97 (d, 2H, \( J = 8 \text{ Hz} \), Ar–H), 6.70 (s, 1H, H-3), 3.88 (s, 3H, Ar-OCH\(_3\)), 2.22 (s, 3H, COCH\(_3\)). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 193.46 (C=O), 180 (C=O), 168.93, 163.41, 139.83, 133.60, 131.17, 128.99, 126.14, 123.38, 122.75, 121.46, 114.09, 94.00, 55.53 (OCH\(_3\)) 25.48 (COCH\(_3\)). UV (EtOH): \( \lambda_{\text{max}} \) 380.80, 360.6, 238.0 nm. Anal. Calcd for C\(_{18}\)H\(_{16}\)ClNO\(_3\): C, 65.56; H, 4.89; N, 4.25. Found: C, 65.87; H, 4.75; N, 4.52.

**N-Acetyl-2-toluoyl indolium chloride 16:** Amorphous solid, mp. 64–65 °C.
IR (KBr): \( \nu_{\text{max}} \) 3325 (NH), 1687(C=O), 1569, 1508, 1446, 1423, 1365, 1190, 756 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 11.07 (br. s, 1H, NH), 8.63 (d, 1H, \( J = 8.0 \text{ Hz} \), Ar–H), 7.83 (d, 2H, \( J = 8.0 \text{ Hz} \), Ar–H), 7.78 (d, 1H, \( J = 8.0 \text{ Hz} \), Ar–H), 7.49 (t, 1H, \( J = 7.2 \text{ Hz} \), Ar–H).
Ar--H), 7.27 (d, 2H, J = 7.2, Ar--H), 7.11 (t, 1H, J = 8.0 Hz, Ar--H), 6.74 (s, 1H, H-3),
2.41 (s, 3H, COCH$_3$), 2.21 (s, 3H, Ar-CH$_3$). $^{13}$C NMR (100 MHz, CDCl$_3$) : δ 198.92
(C=O), 179.85 (C=O), 168.88, 143.45, 139.97, 133.74, 131.71, 128.83, 126.16, 123.16,
122.68, 121.12, 120.81, 94.48, 25.48 (COCH$_3$), 21.62(Ar-CH$_3$). UV (EtOH): $λ_{max}$ 361.4,
256.6 nm. Anal. Calcd for C$_{18}$H$_{16}$ClNO$_2$: C, 68.90; H, 5.14; N, 4.46. Found: C, 69.20; H,
5.40; N, 4.77.

$N$-Acetyl-2-acetyl-5-methyl-1H-indolium chloride 17: White crystalline solid, mp 69-
71°C; R$_f$ Value: 0.65 (n-hexane/ethyl acetate = 4:1); IR (KBr): v$_{max}$ 3473.6 (NH), 2925.8
1784.0 (C=O), 1685.7 (C=O) 1591.2 (C=C), 1425.4, 1321.1 cm$^{-1}$; $^1$H NMR (500 MHz,
CDCl$_3$): δ 8.68 (br. s, 1H, NH), 8.41 (d, 1 H, J = 8.0 Hz, H-7), 7.78 ( d, 1H, J = 8.0 Hz,
H-6), 7.40 (s, 1H, H-4), 6.99 (s, 1H, H-3), 2.89 (s, 3H, COCH$_3$), 2.48 (s, 3H, COCH$_3$),
2.33 (s, 3H, Ar-CH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 179.85 (C=O), 169.32 (C=O),
138.07, 133.00, 131.45, 130.98, 129.85, 127.41, 121.37, 111.18, 27.10 (COCH$_3$),
24.67(COCH$_3$), 21.14 (Ar-CH$_3$)

$N$-acetyl-2-acetyl-5-chloro-1H-indolium chloride 18: White crystalline solid. mp 51-
52°C; R$_f$ Value: 0.75(n-hexane/ethyl acetate = 5:1); IR (KBr): v$_{max}$ 3298.0 (NH), 1706.9
(C=O), 1581.5, 1541.0 (C=C), 1438, 1276, 1168.8, 756.0 cm$^{-1}$; $^1$H NMR (400 MHz,
CDCl$_3$): δ 8.00 (br. s, 1H, NH), 7.80 (d, 1H, J = 9.2 Hz, H-7), 7.41(d, 1H, J = 2.0 Hz, H-
4), 7.18 (dd, 1H, J = 9.2, 2.0 Hz, H-6), 6.34 (s, 1H, H-3), 2.97(s, 3H, COCH$_3$), 2.72(s, 3H,
COCH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 180.05 (C=O), 170.05(C=O), 144.13, 134.90,