Electronic Supplementary Material (ESI) for RSC Advances

Towards a sustainable synthesis of aniline-derived amides using an indirect chemoenzymatic process: challenges and successes

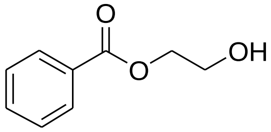
Samridhi Lal and Timothy J. Snape*

School of Pharmacy and Biomedical Sciences, University of Central Lancashire, Preston, PR1 2HE, UK; Tel: (0)1772 895805; Fax: (0)1772 892929; E-mail: tjsnape@uclan.ac.uk

General Experimental

Commercially available reagents were used as received without purification. Analytical thin layer chromatography (TLC) was performed with plastic-backed TLC plates coated with silica G/UV$_{254}$, in a variety of solvents. The plates were visualised by UV light (254 nm). Flash column chromatography was conducted with Davisil silica 60Å (40-63 μm) under bellows pressure. Low resolution mass spectra were recorded on a Thermo Finnigan LCQ Advantage MAX using electron spray ionisation (ESI). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker300 (300 MHz) spectrometer. All chemical shifts (δ) are quoted in parts per million (ppm) relative to a calibration reference of the residual protic solvent; C*H*Cl$_3$ (δ_H 7.26, s) or DMSO (δ_H 2.54, s) was used as the internal standard in ^{1}H NMR spectra, and ^{13}C NMR shifts were referenced using *C*DCl$_3$ (δ_C 77.16, t) with broad band decoupling and the *J* values are measured in Hertz.

Procedure for the synthesis of glycol ester 22 from methyl benzoate and ethylene glycol [1]

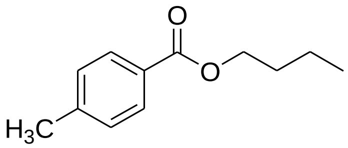


To a solution of methyl benzoate (0.25ml, 1.98 mmoles) in MTBE (10ml) was added ethylene glycol (0.22ml, 3.96 mmoles) and CAL-B (1.5g). The resulting suspension was stirred at 55^{0}C for 8 hours. After which, the solvent was evaporated and the crude mixture was purified by flash chromatography to yield the pure glycol ester as colourless oil (0.25g, 80%, eluted at 70% EtOAc/Petrol), R_f (35% EtOAc/Petrol): 0.20. ^{1}H NMR (CDCl$_3$, 300MHz): δ_H 2.05 (s, 1H), 3.96 (t, 2H, *J*=6.0Hz), 4.46 (t, 2H, *J*=6.0Hz), 7.44 (t, 2H, *J*=6.0Hz), 7.57 (t, 1H, *J*=6.0Hz), 8.05 (d, 2H, *J*=9.0Hz); ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 61.20, 66.65, 128.45, 129.72, 129.85, 133.24, 167.07; MS (ESI$^+$, *m*/*z*): 123 [$(M-C_2H_5O+2H)^+$, 55%), 105 [$(M-C_2H_5O_2)^+$, 100%); IR (neat, cm^{-1}): ν_{max} 1715 (C=O stretching), 3424 (OH stretching).

General procedure for the synthesis of butanoate esters 17 (R = Bu)

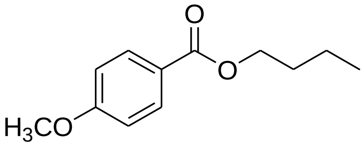
To a solution of the corresponding acid (5g) in 1-butanol (2M) was added concentrated sulfuric acid (6 drops). The resulting suspension was stirred at room temperature for 12 hours. After which, sat. aq. $NaHCO_3$ (50 ml) was added and the product was extracted with ethyl acetate (30 ml) and washed with brine (30 ml). The organic layer was dried ($MgSO_4$) and the solvent evaporated *in vacuo*. The crude product was purified by flash chromatography.

Butyl 4-methylbenzoate[2]



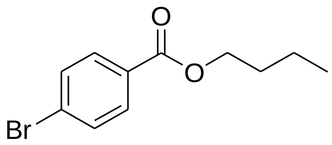
Colourless oil (2.4g, 34%, eluted at 50% EtOAc/Petrol), R_f (35% EtOAc/Petrol): 0.92. ^{1}H NMR ($CDCl_3$, 300MHz): δ_H 0.97 (t, 3H, *J*=7.9Hz), 1.47 (tq, 2H, *J*=7.4Hz), 1.74 (quin, 2H, *J*=6.0Hz), 2.39 (s, 3H), 4.30 (t, 2H, *J*=6.5Hz), 7.22 (d, 2H, *J*=8.0Hz), 7.93 (d, 2H, *J*=8.0Hz); ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 13.85, 19.36, 21.70, 30.86, 64.69, 127.82, 129.07, 129.61, 143.45, 166.81; MS (ESI$^+$, *m*/*z*): 192 ($[M]^+$, 100%); IR (neat, cm^{-1}): ν_{max} 690 (Ar ring), 1432 (chain CH_2 bending), 1714 (C=O stretching), 2959 (Ar ring).

Butyl 4-methoxybenzoate[3]



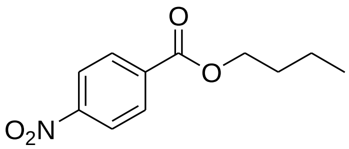
Colourless oil (2.4g, 35%, eluted at 50% EtOAc/Petrol), R_f (10% EtOAc/Petrol): 0.81. ^{1}H NMR ($CDCl_3$, 300MHz): δ_H 0.95 (t, 3H, *J*=7.3Hz), 1.38-1.50 (m, 2H), 1.66-1.76 (m, 2H), 3.81 (s, 3H), 4.26 (t, 2H, *J*=6.57Hz), 6.8 (d, 2H, *J*=8.8Hz), 7.97 (d, 2H, *J*=8.8Hz); ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 13.82, 19.33, 30.86, 55.39, 64.58, 113.55, 122.95, 131.53, 163.25, 166.43; MS (ESI$^+$, *m*/*z*): 208 ([M] $^+$, 7%), 152 [M+H$^+$- C_4H_9, 100%); IR (neat, cm^{-1}): ν_{max} 696 (Ar ring), 1103 (C-O stretching), 1461 (chain CH_2 bending), 1708 (C=O stretching), 2958 (Ar ring).

Butyl 4-bromobenzoate[4]



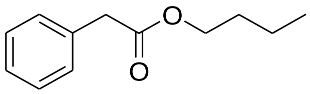
Colourless oil (5.3g, 84%, eluted at 50% EtOAc/Petrol), R_f (10% EtOAc/Petrol): 0.84. ^{1}H NMR ($CDCl_3$, 300MHz): δ_H 0.97 (t, 3H, *J*=7.3Hz), 1.46 (tq, 2H, *J*=6.2Hz), 1.74 (quin, 2H, *J*=7.5Hz), 7.56 (d, 2H, *J*=8.5Hz), 7.89 (d, 2H, *J*=8.5Hz). ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 13.89, 19.38, 30.82, 65.24, 128.01, 129.49, 131.19, 131.77, 166.06. MS (ESI$^+$, *m*/*z*): 202 [(M^{81}Br)+H$^+$- C_4H_9, 73%], 200 [(M^{79}Br)+H$^+$- C_4H_9, 69%], 185 [(M^{81}Br)+H$^+$- C_4H_9, 90%], 183 [(M^{79}Br)+H$^+$- C_4H_9, 100%]; IR (neat, cm^{-1}): ν_{max} 707 (C-Br),1717 (C=O stretching).

Butyl 4-nitrobenzoate[4]



Yellow solid (4.9g, 76%, eluted at 50% EtOAc/Petrol), R_f (35% EtOAc/Petrol): 0.83. ^{1}H NMR ($CDCl_3$, 300MHz): δ_H 0.97 (t, 3H, *J*=7.4Hz), 1.46 (tq, 2H, *J*=6.2Hz), 1.76 (quin, 2H, *J*=5.6Hz), 4.36 (t, 2H, *J*=6.6Hz), 8.22 (d, 2H, *J*=9.0Hz), 8.22 (d, 2H, *J*=9.0Hz); ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 14.50, 19.31, 30.70, 65.89, 123.59, 130.73, 135.93, 150.51, 164.82; MS (ESI$^+$, *m*/*z*): 150 [$(M-C_4H_9O)^+$, 100%], 168 (43); IR (neat, cm^{-1}): ν_{max} 712 (Ar ring), 1273 (N=O sym stretch), 1467 (chain CH_2 bending), 1711 (C=O stretching); M.p. 36-38°C (EtOAc/Petrol).

Butyl 2-phenylacetate[5]

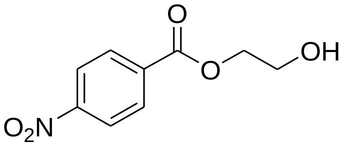


Colourless oil (6.1g, 87%, eluted at 50% EtOAc/Petrol), R_f (35% EtOAc/Petrol): 0.65. ^{1}H NMR ($CDCl_3$, 300MHz): δ_H 0.90 (t, 3H, *J*=8.1Hz), 1.34 (tq, 2H, *J*=6.2Hz), 1.59 (quin, 2H, *J*=5.6Hz), 3.61 (s, 2H), 4.09 (t, 2H, *J*=6.1Hz), 7.29-7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 13.77, 19.15, 30.67, 41.53, 64.82, 127.08, 128.59, 129.31, 134.26, 171.76; MS (ESI$^+$, *m/z*): 192 ([M]$^+$, 100%); IR (neat, cm^{-1}): ν_{max} 696 (Ar ring), 1455 (chain CH_2 bending), 1732 (C=O stretching), 2959 (Ar ring).

General procedure for the synthesis of glycol esters 22-26 from butanoate esters 17 and ethylene glycol

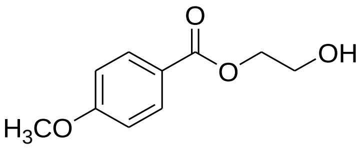
To a solution of the butanoate ester (1.98 mmoles) in MTBE (0.1M) was added ethylene glycol (1.98 or 3.96 mmoles) and CAL-B (0.5g, 0.0039g/mol of ester). The resulting suspension was stirred at 55^{0}C for 8 hours. After which, the enzyme was filtered off and the solvent was evaporated. The crude mixture was purified by flash chromatography to yield the pure glycol ester.

2-Hydroxyethyl 4-nitrobenzoate[6]



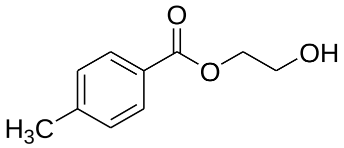
White crystals (0.13g, 32%, eluted at 25% EtOAc/Petrol), R_f (35% EtOAc/Petrol): 0.12. ^{1}H NMR ($CDCl_3$, 300MHz): δ_H 2.27 (br s, 1H), 3.98 (s, 2H), 4.49 (s, 2H), 8.19-8.28 (m, 4H); ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 61.04, 67.42, 123.64, 130.90, 135.33, 150.62, 165.07; MS (ESI$^+$, *m/z*): 211 ([M]$^+$, 11%); 168 [(M-C_2H_5O+ 2H)$^+$, 100%], 150 [(M-$C_2H_5O_2$)$^+$, 74%]; IR (neat, cm^{-1}): ν_{max} 713 (Ar ring),1270 (N=O sym stretch), 1715 (C=O stretching), 2952 (O-H stretching); M.p.79-81°C (EtOAc/Petrol).

2-Hydroxyethyl 4-methoxybenzoate[1]



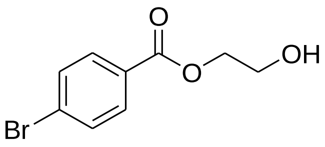
Colourless oil (0.11g, 29%, eluted at 90% EtOAc/Petrol), R_f (35% EtOAc/Petrol): 0.16. ^{1}H NMR ($CDCl_3$, 300MHz): δ_H 3.83 (s, 3H), 3.91 (t, 2H, J=6.0Hz), 4.40 (t, 2H, J=6.0Hz), 6.88 (d, 2H, J=9.0Hz), 7.98 (d, 2H, J=9.0Hz); ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 54.3, 60.2, 65.5, 114.1, 123.2, 128.8, 165.1, 169.2; MS (ESI$^+$, m/z): 196 ($[M]^+$, 10%), 135 [$(M-C_2H_5O+2H)^+$, 100%]; IR (neat, cm^{-1}): ν_{max} 1421 (chain CH_2 bending), 1709 (C=O stretching), 3409 (O-H stretching).

2-Hydroxyethyl 4-methylbenzoate[1]



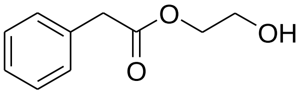
Colourless oil (0.12g, 33%, eluted at 45% EtOAc/Petrol), R_f (35% EtOAc/Petrol): 0.3. ^{1}H NMR ($CDCl_3$, 300MHz): δ_H 2.41 (s, 3H), 3.94 (t, 2H, J=6.0Hz), 4.44 (t, 2H, J=6.0Hz), 7.23 (d, 2H, J=9.0Hz), 7.94 (d, 2H, J=9.0Hz); ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 21.87, 61.58, 66.66, 127.15, 129.24, 129.82, 144.05, 167.18; MS (ESI$^+$, m/z): 181 [$(M+H)^+$, 100%]; IR (neat, cm^{-1}): ν_{max} 1710 (C=O stretching), 3054 (O-H stretching).

2-Hydroxyethyl 4-bromobenzoate[1]



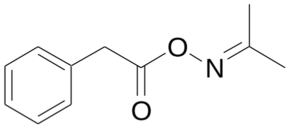
Yellow oil (0.09g, 19%, eluted at 45% EtOAc/Petrol), R_f (35% EtOAc/Petrol): 0.3. ^{1}H NMR ($CDCl_3$, 300MHz): δ_H 2.76 (br s, 1H), 3.93 (t, 2H, J=4.4Hz), 4.42 (t, 2H, J=4.4Hz), 7.54 (d, 2H, J=8.7Hz), 7.87 (d, 2H, J=8.7Hz); ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 61.19, 66.87, 128.42, 128.74, 131.26, 131.82, 166.31; MS (ESI⁺, *m/z*): 203 [$(M^{81}Br-C_2H_5O+2H)^+$, 40%], 201 [$(M^{79}Br-C_2H_5O+2H)^+$, 40%]; IR (neat, cm^{-1}): ν_{max}1715 (C=O stretching), 2951(O-H stretching).

2-Hydroxyethyl 2-phenylacetate[7]



Colourless oil (0.05g, 14%, eluted at 40% EtOAc/Petrol), R_f (35% EtOAc/Petrol): 0.18. ^{1}H NMR ($CDCl_3$, 300MHz): δ_H 2.04 (s, 1H), 3.66 (s, 2H), 3.77 (t, 2H, *J*=6.0Hz), 4.20 (t, 2H, *J*=6.0Hz), 7.24-7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 41.26, 61.09, 66.51, 127.29, 128.71, 129.30, 133.84, 172.09; MS (ESI⁺, *m/z*): 180 ($[M]^+$, 100%); IR (neat, cm^{-1}): ν_{max} 730 (Ar ring), 1453 (CH_2 bending), 1725 (C=O stretching), 2953 (O-H stretching).

Procedure for the synthesis of activated ester 3 (R = Bn, OACT = 7) using acid chloride[8]

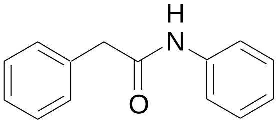


To a solution of phenyl acetic acid (2g, 14.68 mmoles) in dichloromethane (60 ml) was added dimethylformamide (6 drops) and oxalyl chloride (1.24ml, 14.68 mmoles). The resulting solution was stirred at room temperature for 12 hours. After which, 4-dimethylaminopyridine (0.17g, 1.46 mmoles), acetone oxime (1.06g, 14.68 mmoles) and triethylamine (3.06ml, 22 mmoles) were added. The resulting mixture was stirred at room temperature for 8 hours. The solvent was evaporated and the crude mixture purified by flash chromatography to yield the pure activated ester as colourless oil (2.6g, 94%); R_f (50% EtOAc/Petrol): 0.52. ^{1}H NMR ($CDCl_3$, 300MHz): δ_H 1.78 (s, 3H, CH_3), 1.89 (s, 3H, CH_3), 3.61 (s, 2H, CH_2), 7.21-7.27 (m, 5H, Ar-H); ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 16.76, 21.75, 40.14, 127.03, 128.45, 129.11, 133.37, 164.24, 168.65; MS (ESI⁺, *m/z*): 191 ($[M]^+$, 60%); IR (neat, cm^{-1}): ν_{max} 1753 (C=O stretching), 1431 (CH_2 bending), 3031 (Ar ring).

General procedure for the synthesis of amides 28-37

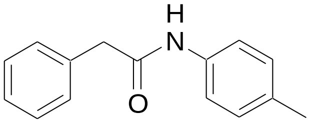
To a solution of the oxime ester (1 eq.) in methyl-*tert*-butyl ether (1M) was added the amine (1 eq.). The resulting solution was stirred at 55 ^{o}C for 8 hours. After which, the suspension was evaporated and the crude *N*-acylated product was purified by flash chromatography (silica gel) to yield the pure amide.

2,*N*-diphenyl-acetamide, 28 [9]



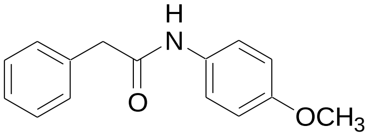
White crystals (0.17g, 81%, eluted at 35% EtOAc/Petrol), R_f (40% EtOAc/Petrol): 0.52. ^{1}H NMR (CDCl$_3$, 300MHz): δ_H 3.75 (s, 2H), 7.02 (br s, 1H), 7.08 (t, 2H, *J*=6.9 Hz), 7.28-7.41 (m, 8H); ^{13}C NMR (CDCl$_3$, 75MHz): δ_C 45.05, 119.89, 124.61, 127.88, 129.09, 129.43, 129.71, 134.52, 137.68, 169.14; MS (ESI$^+$, *m*/*z*): 212 ([M+H]$^+$, 22%); IR (neat, cm^{-1}): ν_{max} 1439 (CH$_2$ bending), 1655 (C=O stretching), 3254 (NH stretching), 3635 (Ar ring); M.p. 120-122°C (EtOAc/Petrol).

2-Phenyl-*N*-p-tolyl-acetamide, 29 [10]



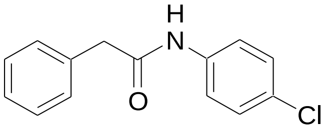
White crystals (0.22g, 100%, eluted at 50% EtOAc/Petrol), R_f (40% EtOAc/Petrol): 0.51. ^{1}H NMR (CDCl$_3$, 300MHz): δ_H 2.28 (s, 3H), 3.73 (s, 2H), 6.99 (br s, 1H), 7.07 (d, 2H, *J*=8.2Hz), 7.25-7.42 (m, 7H); ^{13}C NMR (CDCl$_3$, 75MHz): δ_C 20.95, 44.72, 120.10, 127.60, 129.19, 129.46, 129.57, 134.12, 134.69, 135.20, 169.28; MS (ESI$^+$, *m*/*z*): 225 ([M]$^+$, 100%); IR (neat, cm^{-1}): ν_{max} 1651 (C=O stretching), 3288 (NH stretching); M.p. 134-136°C (EtOAc/Petrol).

N-(4-Methoxy-phenyl)-2-phenyl-acetamide, 32 [11]



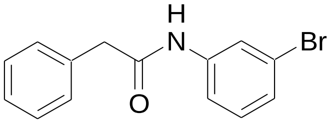
White solid (0.25g, 100%, eluted at 50% EtOAc/Petrol), R_f (35% EtOAc/Petrol): 0.37. ^{1}H NMR (CDCl$_3$, 300MHz): δ_H 3.73 (s, 2H), 3.76 (s, 3H), 6.81 (d, 2H, *J*=8.9 Hz), 6.95 (br s, 1H), 7.29-7.43 (m, 7H); ^{13}C NMR (CDCl$_3$, 75MHz): δ_C 44.61, 55.50, 114.08, 121.96, 127.60, 129.19, 129.58, 130.85, 134.75, 156.54, 169.27; MS (ESI$^+$, *m/z*): 241 ([M]$^+$, 60%); IR (neat, cm^{-1}): ν_{max} 1508 (C=O stretching), 3287 (NH stretching); M.p. 125-127°C (eluted at 50% EtOAc/Petrol).

N-(4-Chloro-phenyl)-2-phenyl-acetamide, 33 [11]



White solid (0.23g, 92%, eluted at 25% EtOAc/Petrol), R_f (35% EtOAc/Petrol): 0.67. ^{1}H NMR (CDCl$_3$, 300MHz): δ_H 3.74 (s, 2H), 7.02 (br s, 1H), 7.23 (d, 1H, *J*=8.9Hz), 7.31-7.44 (m, 8H); ^{13}C NMR (CDCl$_3$, 75MHz): δ_C 44.96, 121.08, 127.99, 129.08, 129.50, 129.69, 134.26, 136.24, 169.16; MS (ESI$^+$, *m/z*): ^{35}Cl ([M]$^+$, 20%), ^{37}Cl ([M]$^+$, 7%); IR (neat, cm^{-1}): ν_{max} 1522 (C=O stretching), 3274 (NH stretching), 3027 (Ar ring); M.p. 162-164°C (EtOAc/Petrol).

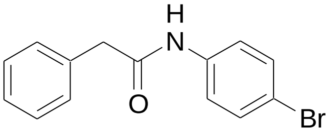
N-(3-Bromo-phenyl)-2-phenyl-acetamide, 34 [12]



White solid (0.12g, 40%, eluted at 28% EtOAc/Petrol), R_f (40% EtOAc/Petrol): 0.46. ^{1}H NMR (CDCl$_3$, 300MHz): δ_H 3.74 (s, 2H), 6.99 (br s, 1H), 7.10-7.44 (m, 9H); ^{13}C NMR (CDCl$_3$, 75MHz): δ_C 44.53, 118.58, 122.52, 123.00, 127.42, 127.66, 129.16, 129.45, 130.23, 134.26, 139.05, 169.84; MS (ESI$^+$, *m/z*): ^{79}Br ([M]$^+$, 54%), ^{81}Br ([M]$^+$, 43%); IR (neat, cm^{-1}): ν_{max} 1472

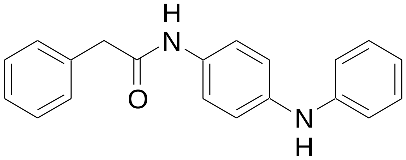
(CH_2 bending), 1653 (C=O stretching), 3256 (NH stretching), 3029 (Ar ring); M.p.108-110°C (EtOAc/Petrol).

N-(4-Bromo-phenyl)-2-phenyl-acetamide, 35 [13]



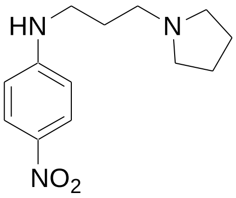
White crystals (0.25g, 83%, eluted at 45% EtOAc/Petrol), R_f (40% EtOAc/Petrol): 0.52. ^{1}H NMR ($CDCl_3$, 300MHz): δ_H 3.73 (s, 2H), 7.02 (br s, 1H), 7.29-7.43 (m, 9H); ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 44.87, 117.13, 121.48, 127.90, 129.40, 129.62, 131.98, 134.23, 136.79, 169.28; MS (ESI$^+$, *m*/*z*): ^{79}Br ([M]$^+$, 18%), ^{81}Br ([M]$^+$, 16%); IR (neat, cm^{-1}): ν_{max} 1487 (CH_2 bending), 1658 (C=O stretching), 3274 (NH stretching), 3026 (Ar ring); M.p. 184-186°C (EtOAc/Petrol).

Preparation of 2-phenyl-*N*-(4-phenylamino-phenyl)-acetamide, 36



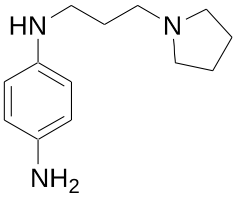
To a solution of the oxime ester (**2**) (0.2g, 1.04 mmoles) in methyl-*tert*-butyl ether (1 ml) was added *N*-phenyl-*p*-phenylenediamine (0.19g, 1.04 mmoles). The resulting solution was stirred at 50 ^{0}C for 8 hours. After which the solvent was evaporated and the crude product was purified by flash chromatography (eluted at 58% EtOAc/Petrol) to yield the pure amide as white crystals (0.29g, 92% isolated yield, R_f (60% EtOAc/Petrol): 0.62. ^{1}H NMR ($CDCl_3$, 300MHz): δ_H 3.64 (s, 2H), 5.54 (br s, 1H), 6.79 (t, 1H, *J*=8.0 Hz), 6.89 (d, 4H, *J*=6.7 Hz), 7.11-7.33 (m, 9H); ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 44.66, 117.20, 118.85, 120.75, 121.75, 127.70, 129.28, 129.44, 129.64, 131.28, 134.68, 139.80, 143.50, 169.24; MS (ESI$^+$, *m*/*z*): 301 ([M]$^+$, 34%), 191 (100); IR (neat, cm^{-1}): ν_{max} 1517 (C=O stretching), 3245 (NH stretching), 3096 (Ar ring); M.p. 137-139°C (EtOAc/Petrol).

Preparation of (4-nitro-phenyl)-(3-pyrrolidin-1-yl-propyl)-amine[14]



To a solution of 1-fluoro-4-nitrobenzene (0.57g, 5.45 mmoles) in dimethylsulfoxide (20 ml) was added 1-(3-aminopropyl) pyrrolidine (0.7g, 5.45 mmoles) and potassium carbonate (1.8g, 13.62 mmoles). The resulting mixture was stirred at 60^0C for 10 hours. After which, 1M HCl (50 ml) was added and the product was extracted with ethyl acetate (30 ml) and washed with brine (30 ml). The organic layer was dried ($MgSO_4$) and the solvent was evaporated *in vacuo*. The crude product was purified by flash chromatography (eluted at 90% MeOH/DCM) to yield the pure product as a yellow solid (0.54g, 40%). R_f (35% EtOAc/Petrol): 0.10. ^{1}H NMR ($CDCl_3$, 300MHz): δ_H 1.8 (m, 6H), 2.53 (m, 4H), 2.65 (t, 2H, J=6.0Hz), 3.29 (d, 2H, J=4.7Hz), 6.44 (d, 2H, J=8.37Hz), 6.50 (br s, 1H), 8.06 (d, 2H, J=8.37Hz); ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 23.69, 26.79, 43.73, 54.24, 55.19, 110.75, 110.85, 126.65, 154.07; MS (ESI$^+$, m/z): 250 ($[M+H]^+$, 90%), 169 (70); IR (neat, cm^{-1}): ν_{max} 1281, 1593 (NO_2 stretching), 3235 (NH stretching), 2811 (Ar ring); M.p.61-63°C.

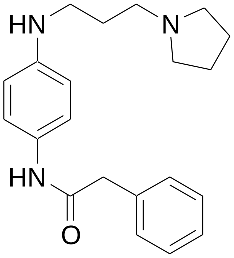
Preparation of *N*-(3-pyrrolidin-1-yl-propyl)-benzene-1,4-diamine[14]



To a solution of (4-nitro-phenyl)-(3-pyrrolidin-1-yl-propyl)-amine (0.54g, 2.17 mmoles) in methanol (22 ml) was added 10% Pd-C (0.054g). The resulting suspension was stirred under a balloon of hydrogen for 5 hours. After which, the reaction mixture was filtered and the solvent was evaporated. The crude product was purified by flash chromatography (eluted in acetone) to yield the pure product as sticky brown oil (0.16g, 34%). R_f (35% EtOAc/Petrol): 0.10. ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 23.23, 28.31, 43.98, 53.99, 54.54, 114.27, 116.69, 137.38, 141.57; MS

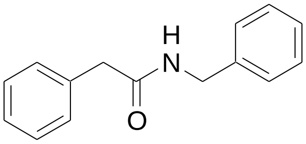
(ESI$^+$, *m*/*z*): 220 ([M+H] $^+$, 100%); IR (neat, cm^{-1}): ν_{max} 3320 (NH stretching), 1045 (alkyl chain).

Preparation of 2-phenyl-*N*-[4-(3-pyrrolidin-1-yl-propylamino)-phenyl]-acetamide, 37



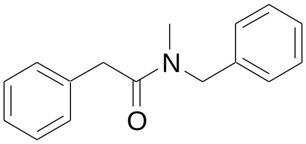
To a solution of the oxime ester (0.03g, 0.20 mmoles) in methyl-*tert*-butyl ether (1 ml) was added *N*-(3-pyrrolidin-1-yl-propyl)-benzene-1,4-diamine (0.22g, 0.10 mmoles). The resulting solution was stirred at 50°C for 8 hours. After which, the solvent was evaporated and a violet sticky oil was obtained. Yield calculated from the NMR of the crude reaction mixture: 71%. MS (ESI$^+$, m/z): 338 ([M+H] $^+$, 100%).

N-Benzyl-2-phenyl-acetamide[9]



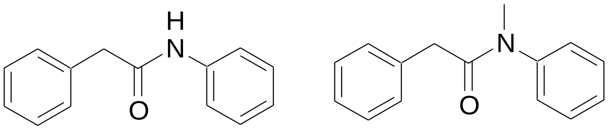
White crystals (0.23g, 100%, eluted at 40% EtOAc/Petrol), R_f (50% EtOAc/Petrol): 0.41. ^{1}H NMR (CDCl$_3$, 300MHz): δ_H 3.63 (s, 2H), 4.41 (d, 2H, *J*=5.7Hz), 5.67 (br s, 1H) 7.16-7.37 (m, 10H); ^{13}C NMR (CDCl$_3$, 75MHz): δ_C 43.47, 43.99, 127.40, 127.57, 127.60, 128.80, 129.22, 129.61, 134.84, 138.22, 170.97; MS (ESI$^+$, *m*/*z*): 225 ([M] $^+$, 34%); IR (neat, cm^{-1}): ν_{max} 1636 (C=O stretching), 3030 (Ar ring), 3284 NH stretching); M.p. 118-120°C (EtOAc/Petrol).

N-Benzyl-*N*-methyl-2-phenyl-acetamide[11]



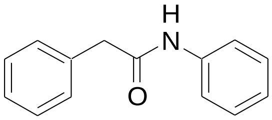
White crystals (0.03g, 13%, eluted at 38% EtOAc/Petrol), R_f (38% EtOAc/Petrol): 0.70. ^{1}H NMR ($CDCl_3$, 300MHz): major rotamer: δ_H 2.92 (s, 3H), 3.80 (s, 2H), 4.63 (s, 2H) 7.27-7.32 (m, 10H); minor rotamer: δ 2.97 (s, 3H), 3.77 (s, 2H), 4.54 (s, 2H), 7.11 (d, 2H, *J*=6.9 Hz), 7.27-7.32 (m, 8H); ^{13}C NMR ($CDCl_3$, 75MHz): δ_C 34.06, 35.26, 40.94, 41.28, 51.01, 53.70, 126.43, 126.86, 126.90, 127.42, 127.71, 128.12, 128.63, 128.76, 128.84, 128.89, 128.98, 135.01, 135.15, 136.53, 137.34, 171.20, 171.54; MS (ESI$^+$, *m*/*z*): 239 ($[M]^+$, 100%); IR (neat, cm^{-1}): ν_{max} 1639 (C=O stretching), 3027 (Ar ring), 2922 (NH stretching); M.p. 66-68°C (EtOAc/Petrol).

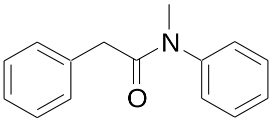
Competition reaction between aniline and *N*-methyl aniline with activated ester, 3 (R = Bn, OACT = 7)



To a solution of the oxime ester (0.2g, 1.04 mmoles) in methyl-*tert*-butyl ether (1 ml) was added *N*-methyl aniline (0.11ml, 1.04 mmoles) and aniline (0.09ml, 1.04 mmoles) pre-dissolved in methyl-*tert*-butyl ether. The resulting solution was stirred at 50°C for 8 hours, after which the suspension was evaporated and the crude *N*-acylated product was purified by flash chromatography to yield the pure amide in 76% yield. (Characterization of the isolated product was identical to 2,*N*-diphenyl-acetamide, prepared above). None of the *N*-methylated amide was obtained in the crude NMR or isolated by column chromatography.

Competition reaction between aniline and *N*-methyl aniline with the corresponding acid chloride





To a solution of phenyl acetic acid (2g, 14.68 mmoles) in dichloromethane (60 ml) was added dimethylformamide (6 drops) and oxalyl chloride (1.24ml, 14.68 mmoles). The resulting solution was stirred at room temperature for 12 hours and 4-dimethylaminopyridine (0.17g, 1.46 mmoles), aniline (0.67ml, 7.34 mmoles) and *N*-Methyl aniline (0.80ml, 7.34 mmoles) (both amines were pre-dissolved separately in dichloromethane) and triethylamine (3.06ml, 22 mmoles) were added. The resulting mixture was stirred at room temperature for 8 hours. The solvent was evaporated and the crude mixture was purified by flash chromatography (eluted at 45% EtOAc/Petrol) to yield the mixture of pure amides as a dark green solid (2.18g, 58% NH and 42% NMe; calculated from the pure NMR of the mixture. R$_f$ (35% EtOAc/Petrol): 0.65. ^{1}H NMR (CDCl$_3$, 300MHz): δ_H 3.32 (s, 3H), 3.52 (s, 2H), 3.66 (s, 2H), 7.12-7.55 (m, 20H), 8.43 (br s, NH); ^{13}C NMR (CDCl$_3$, 75MHz): δ_C 37.54, 40.78, 44.10, 119.97, 123.93, 126.54, 126.96, 127.38, 127.95, 128.23, 128.62, 129.21, 129.66, 134.99, 135.05, 135.19, 138.19, 138.25; MS (ESI$^+$, m/z): 211 ([M]$^+$, 100%); IR (neat, cm^{-1}): ν_{max} 1651, 1596 (C=O stretching), 3253 (NH stretching), 3059, 3024 (Ar ring); M.p. 140-142°C (EtOAc/Petrol).

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