Solid Phase Synthesis of N-Alkyl-N-(β-Keto)amides and 1,2,4,5-Tetrasubstituted Imidazoles Using a Traceless Cleavage Strategy

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SUPPORTING INFORMATION

Experimental

General. Chemicals and low-loading Merrified resin (1.05 mmol of Cl/g) were purchased from Aldrich Chemical Co. and used without further purification. High-loading Merrifield resin (3.75 mmol of Cl/g) was purchased from Polymer Lab and used without further purification. The loading of the commercial resins was determined by halogen elemental analysis, prior to use. Anhydrous solvents were purchased from Aldrich or Fluka Chemical Corp. General washing procedure for resin samples: for every 100 mg of resin, three aliqouts of 2 mL of DMF, THF, THF/H_2O, THF, MeOH, THF and dichloromethane (DCM) were used in succession. FTIR spectra of resin samples were taken as a gel in CH_2Cl_2. ^{13}C gel phase NMR data were acquired on DRX400 Bruker in $CDCl_3$ and chemical shifts are quoted relative to solvent signals. Standard conditions were used: acquisition time = 0.1 s, 10 ns delay between pulses, no. of scans = 3.5 x 10^5). Elemental analyses were performed by Zeneca Pharmaceuticals, UK.

Synthesis of *N*-benzyl-*N*-methylaminoacetophenones. (1 and 2)[11] A solution of 4-hydroxybenzaldehyde (611 mg, 5 mmol) or vanillin (760 mg, 5 mmol) and methylamine (3.5 mL, 7 mmol, 2M in THF) in THF (2 mL) was stirred for 10 min. at room temperature. Solid $NaBH_4$ (95 mg, 2.5 mmol) was added portionwise, and the mixture stirred for 1 h. α-Bromoacetophenone (1.05 g, 5.25 mmol) was added and stirring was continued at room temperature for 1 h. Water was added

and the mixture was extracted with DCM (3 × 10 mL) and the combined extracts were dried over $MgSO_4$, concentrated and purified by silica gel column chromatography eluting wih 1:1 EtOAc/Hex to yield

N-*(4-hydroxybenzyl)*-N-*methylaminoacetophenone* **1**(6.9 mg, 83%):δ_H (250 MHz) 2.37 (3H, s), 3.63 (2H, s), 3.79 (2H, s), 6.80 (2H, d, *J* = 8.4), 7.17 (2H, d, *J* = 8.4), 7.42 (2H, t, *J* = 7.2), 7.54 (1H, t, *J* = 7.2), 7.92 (2H, d, *J* = 7.2) *in agreement with data published by Venkov* et al.[11]

N-*(4-hydroxy-3-methoxybenzyl)*-N-*methylaminoacetophenone* **2**(6.9 mg, 81%):δ_H (250 MHz) 2.39 (3H, s), 3.61 (2H, s), 3.78 (2H, s), 3.83 (3H, s), 6.77 (1H, d, *J* = 8.0), 6.83 (1H, d, *J* = 8.0), 6.89 (1H, s), 7.42 (2H, t, *J* = 7.2), 7.51 (1H, t, *J* = 7.2), 7.94 (2H, d, *J* = 7.2) *in agreement with data published by Venkov* et al.[11]

Resin-bound Tertiary Amines 3 and 4. Sodium hydride (84 mmol, 2.34 g) was added slowly (in 10 min) to a solution of N-(4-hydroxybenzyl)-N-methylaminoacetophenone (88 mmol, 10.75 g) or N-(4-hydroxy-3-methoxybenzyl)-N-methylaminoacetophenone in anhydrous DMF (150 mL) at 0 °C and stirring was continued for one hour at room temperature. This solution was transferred *via* a syringe to Merrifield resin (3.75 mmol of Cl/g, 37.5 mmol, 10 g, Polymer Lab) pre-swollen in DMF (50 mL) and the suspension stirred at 25 °C for 24 hours. Resin suspension was filtered and washed with dil. HCl/THF and following general procedure and dried for 1 day to yield

Resin-Bound Tertiary Amine 3: υ_{max} 1697; Found: N, 1.28, Cl, 0.37 (90%)

Resin-Bound Tertiary Amine 4: υ_{max} 1697; Found: N, 1.23, Cl, 0.48 (87%)

Resin-Bound Benzaldehyde 5. Sodium hydride (84 mmol, 2.34 g) was added slowly (in 10 min) to a solution of 4-hydroxybenzaldehyde (88 mmol, 10.75 g) and tetrabutylammonium iodide (3.75 mmol, 1.5 g) in anhydrous DMF (150 mL) at 0 °C and stirring was continued for one hour at room temperature. This solution was transferred *via* a syringe to Merrifield resin (3.75 mmol of Cl/g, 37.5 mmol, 10 g, Polymer Lab) pre-swollen in DMF (50 mL) and the suspension stirred at 25 °C for 24 hours. Resin suspension was filtered and washed with dil. HCl/THF and following general procedure and dried for 1 day to yield **5**: υ_{max} 1694, 1685; δ_C (100 MHz) 70.2, 115.0, 130.1, 132.0, 163.8, 190.7.

Resin-Bound Secondary Amine 6a. *n*-Butylamine (redistilled over CaH_2, ~100 mmol, 10 mL) was added to benzaldehyde resin **5** (~20 mmol, 6g) suspension in 2:1 anhydrous THF/TMOF (60 mL). After sonicating for 5 min, the suspension was left stirring overnight at room temperature. Treatment with *n*-butylamine was repeated if reaction appeared incomplete by gel phase FTIR. The resin was drained, washed with THF and resuspended in 2:1 THF/TMOF (60 mL). Portions of lithium borohydride (50 mmol, 1.1 g) were added to the stirred resin suspension and stirring continued for 1 day or until imine band (1641) has disappeared according to gel phase FTIR. Resin suspension was filtered and washed with sat. NH_4Cl/THF and following general procedure and dried for one day to yield **6a**: υ_{max} 3263; Anal. Calcd: N, 3.42. Found: N, 3.24; Loading = 2.30 mmol/g (94%); δ_C (100 MHz) 13.7, 20.0, 28.2, 52.9, 59.0, 70.0, 115.1, 131.0.

Resin-Bound Secondary Amine 6b-d. Same procedure as for **6a** except *iso*-propylamine (**6b**, 10 mmol, 0.85 mL) or benzylamine (**6c**, 10 mmol, 1.1 mL) or aniline (**6d**, 10mmol, 0.9 mL), resin **5** (~2 mmol, 500 mg), 2:1 THF/TMOF (5 mL) and lithium borohydride (5 mmol, 110 mg) were used respectively. FTIR band for the imines is given in *italics*.

Resin 6b: υ_{max} *1641*, 3262; Anal. Calcd: N, 3.54. Found: N, 3.08; Loading = 2.20 mmol/g (87%); δ_C (100 MHz) 21.5, 48.2, 49.6, 70.0, 114.8, 129.3, 130.2.

Resin 6c: υ_{max} *1641*, 3201, 3265; Anal. Calcd: N, 3.16. Found: N, 2.90; Loading = 2.07 mmol/g (92%); δ_C (100 MHz) 53.0, 58.2, 70.0, 114.9, 128.8, 129.7 131.4.

Resin 6d: υ_{max} *1623*, 3417; Anal. Calcd: N, 3.25. Found: N, 3.16; Loading = 2.25 mmol/g (97%); δ_C (100 MHz) 47.6, 70.0, 112.8, 114.8, 117.4, 128.7, 129.2, 131.5, 148.1.

Resin-Bound Tertiary Amine 7a and Cleavage with Acid Chloride (8a). Diisopropylethylamine (0.87 mmol, 153 μL) was added to a suspension of resin-bound secondary amine **6a** (46 mmol, 200 mg) and 4-chlorophenacyl bromide (0.92 mmol, 215 mg) in anhydrous DMF (2.2 mL) and stirring was continued at 45 °C for 16 hours. Resin suspension was filtered and washed with DMF, DMF/H_2O, DMF and following general procedure and dried for one day. A gel phase FTIR spectrum of **7a** was taken. δ_C (100 MHz) 14.0, 20.4, 29.2, 54.2, 58.1, 60.6, 70.0, 114.5, 128.5, 129.9. A portion of this resin **7a** (~1.8 mmol/g, ~0.09 mmol, 50 mg) was suspended

in anhydrous DMF (1 mL) and the mixture stirred at room temperature for 30 min. Acetyl chloride (0.55 mmol, 40 μL) was added dropwise to the resin and the mixture stirred at 45 ℃ for 6 hours. Resin suspension was filtered and washed with THF, MeOH, THF, DCM, MeOH, DCM and the washing was concentrated *in vacuo*. This crude filtrate in DMF was stirred with aminomethylpolystyrene (1.8 mmol/g, 0.9 mmol, 500 mg, Polymer Lab) in DCM for 1 hour at room temperature. The resin-treated solution was either concentrated to yield N-*(*n-*butyl)*-N-*(4'-chlorophenacyl)acetamide* **8a** (19.8 mg, 87%) or cyclised to the imidazole: R_t 11.64; R_f 0.30 (1:1 EtOAc/Hex); υ_{max} 1641, 1704; δ_H (250 MHz) 0.94 (3H, t, *J* = 7.5), 1.34 (2H, sx, *J* = 7.5), 1.56 (2H, qn, *J* = 7.5), 4.72 (2H, s), 7.44 (2H, d, *J* = 8.6), 7.90 (2H, d, *J* = 8.6); δ_C (62 MHz) 13.8, 20.0, 21.0, 30.8, 49.7, 51.8, 129.0, 129.4, 133.69, 139.96, 170.84, 193.42; EIMS *m/z* 268 (M^+), 226 (found: M^+ 267.1026, $C_{14}H_{18}NO_2Cl$ requires M 267.10260).

Resin-Bound Tertiary Amine 5b-d and Cleavage with Acid Chloride (8b-d). Same procedure as for **7a/8a** except resin-bound secondary amine **6b-d** (44 mmol, 200 mg of **6b**; 41 mmol, 200 mg of **6c**; 45 mmol, 200 mg of **6d**)was used respectively.

N-*(*iso*propyl)*-N-*(4'-chlorophenacyl)acetamide* **8b** (6.9 mg, 33%): R_t 10.62; R_f 0.30 (2:1 EtOAc/Hex); υ_{max} 1635, 1702; δ_H (250 MHz) 1.20 (6H, d, *J* = 6.7), 2.23 (3H, s), 2.19 (1H, sp, *J* = 6.7), 4.56 (2H, s), 7.44 (2H, d, *J* = 8.6), 7.93 (2H, d, *J* = 8.6); δ_C (100 MHz) 21.1, 21.3, 46.5, 49.2, 129.0, 129.4, 133.9, 140.0, 170.2, 193.1; EIMS *m/z* 253 (M^+), 210 (found: M^+-43 210.0681, $C_{10}H_9NO_2Cl$ requires M-43 210.06856).

N-*benzyl*-N-*(4'-chlorophenacyl)acetamide* **8c** (13.8 mg, 58%): R_t 12.20; R_f 0.32 (1:1 EtOAc/Hex); υ_{max} 1660, 1700; δ_H (250 MHz) 2.28 (3H, s), 4.66 (2H, s), 4.73 (2H, s), 7.20-7.43 (8H, m), 7.85 (2H, d, *J* = 8.6); δ_C (62 MHz) 21.3, 51.2, 53.0, 126.7, 127.9, 129.0, 129.4, 133.5, 136.1, 140.1, 171.5, 193.2; EIMS *m/z* 301 (M^+), 258 (found: M^+ 301.0858, $C_{17}H_{16}NO_2Cl$ requires M 301.08695).

N-*phenyl*-N-*(4'-chlorophenacyl)acetamide* **8d** (0 mg, 0%)

Resin-Bound Tertiary Amine 57e-m and Cleavage with Acid Chloride (8e-m). Same procedure as for **7a/8a** except 2-bromo-4'-methoxyacetophenone (0.92 mmol, 215 mg for **7e**) or 1-

bromopinacolone (0.92 mmol, 126 μL for **7f**) or 1-bromo-2-butanone (0.92 mmol, 78 μL for **7g**) or α-bromo-4-(1-pyrrolidino)acetophenone (0.92 mmol, 191 mg for **7h**) or α-bromopropiophenone (0.92 mmol, 116 μL for **7i**) or desyl bromide (0.92 mmol, 261 mg for **7j**) or ethyl bromopyruvate (0.92 mmol, 128 μL for **7k**) or 2-chlorocyclopentanone (0.92 mmol, 94 μL for **7l**) or 2-chloro-*N*,*N*-dimethylacetoacetamide (0.92 mmol, 130 μL for **7m**) was used respectively.

N-*(*n-*butyl)*-N-*(4'-methoxyphenacyl)acetamide* **8e** (19.9 mg, 88%): R_t 10.84; R_f 0.33 (2:1 EtOAc/Hex); υ_{max} 1648, 1690; δ_H (250 MHz) 0.94 (3H, t, *J* = 7.2), 1.33 (2H, sx, *J* = 7.2), 1.56 (2H, qn, *J* = 7.2), 2.19 (3H, s), 3.34 (2H, t, *J* = 7.2), 3.86 (3H, s), 4.74 (2H, s), 6.93 (2H, d, *J* = 9.0), 7.95 (2H, d, *J* = 9.0); δ_C (62 MHz) 13.8, 20.1, 21.0, 30.7, 49.6, 51.4, 55.5, 113.9, 128.4, 130.3, 163.8, 170.8, 192.9; EIMS *m/z* 263 (M^+), 220 (found: M^+ 263.1522, $C_{15}H_{21}NO_3$ requires M 263.15213).

N-*(*n-*butyl)*-N-*(1-pinacolone)acetamide* **8f** (16.4 mg, 82%): R_f 0.38 (1:1 EtOAc/Hex); υ_{max} 1639, 1718; δ_H (250 MHz) 0.93 (3H, t, *J* = 7.4), 1.20 (9H, s), 1.32 (2H, sx, *J* = 7.4), 1.50 (2H, qn, *J* = 7.4), 2.13 (2H, s), 3.25 (2H, t, *J* = 7.4), 4.25 (2H, s); δ_C (62 MHz) 13.8, 20.0, 20.9, 26.4, 30.8, 49.8, 50.4, 170.3, 211.3; EIMS *m/z* 214 (M^+), 170 (found: M^+ 214.1804, $C_{12}H_{23}NO_2$ requires M 214.18069).

N-*(*n-*butyl)*-N-*(2-butanone)acetamide* **8g** (14.8 mg, 81%): R_f 0.21 (2:1 EtOAc/Hex); υ_{max} 1639, 1734; δ_H (250 MHz) 0.94 (3H, t, *J* = 7.1), 1.08 (3H, t, *J* = 7.2), 1.32 (2H, sx, *J* = 7.1), 1.52 (2H, qn, *J* = 7.1), 2.14 (3H, s), 2.45 (2H, q, *J* = 7.2), 3.29 (2H, t, *J* = 7.1), 4.08 (2H, s); δ_C (62 MHz) 7.4, 13.8, 20.0, 21.0, 30.9, 33.3, 50.0, 54.8, 170.8, 206.3; EIMS *m/z* 185 (M^+), 143 (found: MH^+ 186.1494, $C_{10}H_{19}NO_2$ requires M 186.14939).

N-*(*n-*butyl)*-N-*(4'-(1"-pyrrolidino)phenacyl)acetamide* **8h** (6.8 mg, 28%): R_t 12.86; R_f 0.34 (2:1 EtOAc/Hex); υ_{max} 1645, 1671; δ_H (400 MHz) 0.93 (3H, t, *J* = 7.3), 1.32 (2H, sx, *J* = 7.3), 1.56 (2H, qn, *J* = 7.3), 2.02-2.07 (4H, m), 2.19 (3H, s), 3.32-3.41 (6H, m), 4.73 (2H, s), 6.50 (2H, d, *J* = 8.9), 7,86 (2H, d, *J* = 8.9); δ_C (100 MHz) 13.8, 20.1, 20.2, 25.4, 30.6, 47.5, 49.4, 50.8, 110.8, 122.8, 130.3, 151.2, 170.7, 192.0; EIMS *m/z* 302 (M^+), 260 (found: M^+ 302.1997, $C_{18}H_{26}N_2O_2$ requires M 302.19942).

N-*(*n-*butyl)*-N-*(α-methylphenacyl)acetamide* **8i** (6.5 mg, 30%): R_t 12.03; R_f 0.39 (2:1 EtOAc/Hex); υ_{max} 1639, 1689; δ_H (400 MHz) 0.94 (3H, t, *J* = 7.3), 1.32 (2H, sx, *J* = 7.3), 1.34 (3H, d, *J* = 7.3), 1.58 (2H, qn, *J* = 7.3), 2.14 (3H, s), 2.45 (2H, q, *J* = 7.3), 3.28 (2H, t, *J* = 7.3), 7.44 (2H, t, *J* = 7.3), 7.55 (1H, t, *J* = 7.3), 7.97 (2H, d *J* = 7.3); δ_C (100 MHz) 13.8, 20.0, 20.3, 21.0, 30.8, 49.9, 54.7, 128.3, 128.7, 133.3, 135.6, 170.5, 199.5; EIMS *m/z* 247 (M^+), 204 (found: M^+ 247.1579, $C_{15}H_{21}NO_2$ requires M 247.15722).

N-*(*n-*butyl)*-N-*desylacetamide* **8j** (~2.4 mg, ~10%): R_t 12.75; R_f 0.45 (1:1 EtOAc/Hex); QTOF *m/z* 310 (M^+), 267 (found: M^+ 310.1815, $C_{20}H_{23}NO_2$ requires M 310.1807); *insufficient material for full characterisation.*

N-*(*n-*butyl)*-N-*(ethylpyruvate)acetamide* **8k**, N-*(*n-*butyl)*-N-*(2*-cyclo-*pentanone)acetamide* **8l** and N-*(*n-*butyl)*-N-*[α-acetyl-α-(*N,N-*dimethylacetamoyl)]acetamide* **8m** (0 mg, 0%)

Resin-Bound Tertiary Amine 57n-p and Cleavage with Acid Chloride (8n-p). Same procedure as for **7a/8a** except acetoxyacetyl chloride (0.55 mmol, 61 μL for **8n**) or ethyl oxalyl chloride (0.55 mmol, 62 μL for **8o**) or cyclohexanecarbonyl chloride (0.55 mmol, 75 μL for **8p**) was used respectively.

N-*(*n-*butyl)*-N-*(4'-chlorophenacyl)acetoxyacetamide* **8n** (14.1 mg, 51%): R_t 11.89; R_f 0.24 (2:1 EtOAc/Hex); υ_{max} 1666, 1701, 1747; δ_H (250 MHz) 0.95 (3H, t, *J* = 7.2), 1.36 (2H, sx, *J* = 7.2), 1.59 (2H, qn, *J* = 7.2), 2.17 (3H, s), 3.30 (2H, t, *J* = 7.2), 4.73 (2H, s), 7.45 (2H, d, *J* = 8.6), 7.89 (2H, d, *J* = 8.6); δ_C (100 MHz) 13.7, 20.0, 20.6, 30.6, 48.0, 51.9, 61.0, 129.1, 129.4, 133.4, 140.2, 167.0, 170.6, 192.7; EIMS *m/z* 326 (M^+), 224 (found: M^+ 326.1174, $C_{16}H_{20}NO_4Cl$ requires M 326.11590)

N-*(*n-*butyl)*-N-*(4'-chlorophenacyl)ethyloxalamide* **8o** (18.0 mg, 65%): R_t 13.03; R_f 0.37 (1:3 EtOAc/Hex); υ_{max} 1676, 1703, 1741; δ_H (250 MHz) 0.92 (3H, t, *J* = 7.4), 1.32 (2H, sx, *J* = 7.4), 1.39 (3H, t, *J* = 7.4), 1.61 (2H, qn, *J* = 7.4), 3.37 (2H, t, *J* = 7.4), 4.38 (2H, q, *J* = 7.4), 4.75 (2H, s), 7.46 (2H, d, *J* = 8.7), 7.91 (2H, d, *J* = 8.7); δ_C (100 MHz) 13.6, 14.0, 19.8, 30.4, 49.1, 50.6, 62.2, 129.2, 129.4, 133.2, 140.4, 162.2, 162.5, 191.5; EIMS *m/z* 325 (M^+), 125 (found: M^+ 325.1091, $C_{16}H_{20}NO_4Cl$ requires M 325.10808).

N-*(*n-*butyl)*-N-*(4'-chlorophenacyl)*cyclo*hexanecarbonamide* **8p** (7.4 mg, 26%): R_t 13.79; R_f 0.33 (1:4 EtOAc/Hex); υ_{max} 1639, 1699; δ_H (400 MHz) 0.96 (3H, t, *J* = 7.3), 1.26-1.83 (14H, m), 2.55 (1H, tt, *J* = 11.4, 3.1), 3.36 (2H, t, *J* = 7.3), 4.67 (2H, s), 7.43 (2H, d, *J* = 8.7), 7.90 (2H, d, *J* = 8.7); δ_C (62 MHz) 13.8, 20.0, 25.9, 29.5, 31.4, 40.6, 48.7, 50.0, 52.0, 129.0, 129.5, 133.8, 139.8, 176.6, 194.0; QTOF *m/z* 336 (MH^+) (found: MH^+ 336.1789, $C_{19}H_{27}NO_2Cl$ requires MH 336.17302).

Resin-Bound Tertiary Amine 7q-s and Cleavage with Acid Chloride (8q-s). Same procedure as for **7a/8a** except benzoyl chloride (0.55 mmol, 63 μL for **8q**) or 4-cyanobenzoyl chloride (0.55 mmol, 92 mg for **8r**) or 4-methoxybenzoyl chloride (0.55 mmol, 94 mg for **8s**) and *N*-methylmorpholine (0.14 mmol, 15 μL) were used respectively.

N-*(*n-*butyl)*-N-*(4'-chlorophenacyl)phenamide* **8q** (23.0 mg, 82%): R_t 13.49; R_f 0.31 (1:3 EtOAc/Hex); υ_{max} 1629, 1698; δ_H (250 MHz) 0.77 (3H, t, *J* = 7.2), 1.12 (2H, sx, *J* = 7.2), 1.50 (2H, qn, *J* = 7.2), 3.30 (2H, t, *J* = 7.2), 4.88 (2H, s), 7.27-7.47 (7H, m), 7.95(2H, d, *J* = 8.2); δ_C (62 MHz) 13.6, 19.7, 30.6, 50.0, 51.0, 126.7, 128.4, 129.1, 129.5, 133.7, 136.1, 140.0, 172.3, 193.0; EIMS *m/z* 329 (M^+) (found: M^+ 329.1164, $C_{19}H_{20}NO_2Cl$ requires M 329.11825).

N-*(*n-*butyl)*-N-*(4'-chlorophenacyl)-(4"-cyano)phenamide* **8r** (25.4 mg, 84%): R_t 13.10; R_f 0.15 (1:3 EtOAc/Hex); υ_{max} 1641, 1699, 2235; δ_H (250 MHz) 0.80 (3H, t, *J* = 7.3), 1.71 (2H, sx, *J* = 7.3), 1.50 (2H, qn, *J* = 7.3), 3.26 (2H, t, *J* 7.3), 4.89 (2H, s), 7.49 (2H, d, *J* = 8.5), 7.60 (2H, d, *J* = 8.1), 7.75 (2H, d, *J* = 8.1), 7.95 (2H, d, *J* = 8.5); δ_C (62 MHz) 13.6 19.7, 30.6, 50.1, 51.0, 113.5, 118.1, 127.5, 129.2, 129.4, 132.4, 140.5, 170.4, 192.2; EIMS *m/z* 355 (MH^+) (found: MH^+ 355.1208, $C_{20}H_{19}N_2O_2Cl$ requires MH 355.12132).

N-*(*n-*butyl)*-N-*(4'-chlorophenacyl)-(4"-methoxy)phenamide* **8s** (~7.6 mg, ~25%): R_t 13.21; R_f 0.18 (1:3 EtOAc/Hex); υ_{max} 1631, 1699; QTOF *m/z* 360 (M^+) (found: M^+ 360.1392, $C_{20}H_{22}NO_3Cl$ requires M 360.1366); *insufficient material for full characterisation*.

Side Product from *N*-Benzoylation of 7a:

N-*(*n-*butyl)*-N-*(4'-chlorophenacyl-α-benzoyl)phenamide*: R_t 15.57; R_f 0.24 (1:7 EtOAc/Hex); δ_H (250 MHz) 0.82 (3H, t, *J* = 7.5), 1.25 (2H, s, *J* = 7.5), 1.66 (2H, qn, *J* = 7.5) 3.78 (2H, t, *J* =

7.5), 6.64 (1H, s), 7.19-7.71 (12H, m), 8.17 (2H, d, J = 8.1); δ_C (62 MHz) 13.7, 20.2, 30.2, 47.0, 119.8, 125.7, 128.2, 128.9, 130.3, 130.8, 132.7, 134.2, 134.3, 135.7, 136.9, 163.6, 170.8; EIMS *m/z* 433 (M^+) (found: M^+ 433.1436, $C_{26}H_{24}NO_3Cl$ requires M 433.14446).

General Procedure for Formation of Imidazole 9. Glacial acetic acid (1 mL), ammonium acetate (9 mmol, 70 mg) was added to the solution of tertiary amide **8** in residual DMF (~1 mL) and the mixture stirred at 90 ℃ for 24 hours. The reaction mixture was concentrated *in vacuo*, resuspended in DCM and filtered through a pack of silica gel to yield **9** after solvent removal.

*1-(*n*-butyl)-2-methyl-4-(4'-chlorophenyl)imidazole* **9a** (17.8 mg, 84%): R_f 0.23 (1:1 EtOAc/Hex); υ_{max} 1606, 1725; δ_H (250 MHz) 0.96 (3H, t, J = 7.2), 1.37, (2H, sx, J = 7.2), 1.74 (2H, qn, J = 7.2), 2.41 (3H, s), 3.83 (2H, t, J = 7.2), 7.07 (1H, s), 7.30 (2H, d, J = 8.5)m 7.65 (2H, d, J = 8.5); δ_C (62 MHz) 13.0, 13.6, 19.8, 32.8, 46.0, 115.1, 125.8, 128.6, 131.8, 133.0, 138.8, 145.0; EIMS *m/z* 248 (M^+) (found: M^+ 248.1082, $C_{14}H_{17}N_2Cl$ requires M 248.10802).

*1-*iso*-propyl-2-methyl-4-(4'-chlorophenyl)imidazole* **9b** (5.0 mg, 26%): R_t 10.55; R_f 0.11 (1:1 EtOAc/Hex); υ_{max} 1598, 1721; δ_H (250 MHz) 1.46 (6H, d, J = 6.7), 2.45 (3H, s), 4.32 (1H, sp, J = 6.7), 7.17 (1H, s), 7.31 (2H, d, J = 8.6), 7.67 (2H, d, J = 8.6); δ_C (62 MHz) 23.4, 32.5, 45.7, 114.9, 126.1, 128.8, 131.6, 132.8, 138.6, 144.9; QTOF *m/z* 235 (MH^+) (found: MH^+ 235.1029, $C_{13}H_{16}N_2Cl$ requires MH 235.10019).

1-benzyl-2-methyl-4-(4'-chlorophenyl)imidazole **9c** (12.1 mg, 54%): R_t 12.00; R_f 0.15 (2:1 EtOAc/Hex); υ_{max} 1602, 1738; δ_H (250 MHz) 2.40 (3H, s), 5.07 (2H, s), 7.10-7.14 (3H, m), 7.29-7.37 (5H m), 7.66 (2H, d, J = 8.6); δ_C (62 MHz) 13.1, 50.0, 115.8, 125.9, 126.8, 128.2, 128.7, 129.1, 132.1, 132.7, 136.0, 139.1, 145.6; EIMS *m/z* 282 (M^+) (found: M^+ 282.0921, $C_{17}H_{15}N_2Cl$ requires M 282.09237).

*1-(*n*-butyl)-2-methyl-4-(4'-methoxyphenyl)imidazole* **9e** (18.0 mg, 79%): R_t 10.87; R_f 0.20 (2:1 EtOAc/Hex); υ_{max} 1604, 1709; δ_H (400 MHz) 0.96 (3H, t, J = 7.3), 1.37, (2H, sx, J = 7.3), 1.73 (2H, qn, J = 7.3), 2.41 (3H, s), 3.81 (3H, s), 3.82 (2H t, J = 7.3), 6.89 (2H, d, J = 8.9), 6.99 (1H, s), 7.64 (H, 2H, d, 8.9); δ_C (62 MHz) 13.0, 13.6, 19.8, 32.8, 45.9, 55.3, 113.8, 113.9,

125.8, 127.3, 139.6, 144.6, 158.4; EIMS *m/z* 244 (M^+) (found: M^+ 244.1584, $C_{15}H_{20}N_2O$ requires M 244.15755).

*1-(*n*-butyl)-2-methyl-4-(*tert*-butyl)imidazole* **9f** (14.6 mg, 80%): R_t 10.07; R_f 0.10 (2:1 EtOAc/Hex); υ_{max} 1600, 1702; δ_H (250 MHz) 0.05 (3H, t, *J* = 7.4), 1.28 (9H, s), 1.34 (2H, sx, *J* = 7.4), 1.70 (2H, qn, *J* = 7.4), 2.46 (3H, s), 3.77 (2H, t, *J* = 7.4); δ_C (100 MHz) 11.6 13.5, 19.8, 29.8, 31.2, 32.4, 40.1. 112.8, 143.7, 147.5; QTOF *m/z* 195 (M^+) (found: M^+ 195.1855, $C_{12}H_{22}N_2$ requires M 195.1861).

*1-(*n*-butyl)-2-methyl-4-ethylimidazole* **9g** (12.8 mg, 78%): R_t 8.75; R_f 0.10 (2:1 EtOAc/Hex); υ_{max} 1606, 1734; δ_H (250 MHz) 0.95 (3H, t, *J* = 7.2), 1.21 (3H, t, *J* = 7.3), 1.35 (2H, sx, *J* = 7.2), 1.69 (2H, qn, *J* = 7.2), 2.41 (3H, s), 2.58 (2H, q, *J* = 7.3), 3.76 (2H, t, *J* = 7.2), 6.51 (1H, s); δ_C (100 MHz) 11.8, 13.5, 19.8, 29.7, 31.1, 32.8, 43.0, 112.6, 144.1, 147.2; QTOF *m/z* 167 (MH^+) (found: MH^+ 167.1567, $C_{10}H_{19}N_2$ requires MH 167.1548).

*1-(*n*-butyl)-2-methyl-4-(4'-(1"-pyrrolidino)phenyl)imidazole* **9h**: R_t 12.01; LCMS *m/z* 284 (MH^+); *cleaved material has low purity and hence not isolated.*

*1-(*n*-butyl)-2-methyl-4-phenyl-5-methylimidazole* **9i** (5.4 mg, 27%): R_t 11.06; R_f 0.39 (1:1 EtOAc/Hex); υ_{max} 1606, 1718; δ_H (250 MHz) 0.99 (3H, t, *J* = 7.3), 1.41 (2H, sx, *J* = 7.3), 1.67 (2H, qn, *J* = 7.3), 2.37 (3H, s), 2.44 (3H, s), 3.80 (2H, t, *J* = 7.3), 7.22 (1H, t, *J* = 7.3), 7.38 (2H, t, *J* = 7.3), 7.61 (2H, d, 7.3); δ_C (62 MHz) 6.3, 13.4, 13.8, 20.1, 32.6, 43.7, 122.7, 125.9, 127.1, 128.3, 135.5, 135.8, 143.3; EIMS *m/z* 228 (M^+) (found: M^+ 228.1629, $C_{15}H_{20}N_2$ requires M 228.16264).

*1-(*n*-butyl)-2-acetoxymethyl-4-(4'-chlorophenyl)imidazole* **9n** (10.4 mg, 40%): R_t 11.67; R_f 0.32 (1:2 EtOAc/Hex); υ_{max} 1604, 1743; δ_H (250 MHz) 0.97 (3H, t, *J* = 7.3), 1.39 (2H, sx, *J* = 7.3), 1.79 (2H, qn, *J* = 7.3), 2.11 (3H, s), 3.97 (2H, t, *J* = 7.3), 5.20 (2H, s), 7.20 (1H, s), 7.32 (2H, d, *J* = 8.6), 7.68 (2H, d, *J* = 8.6); δ_C (62 MHz) 13.8, 19.9, 21.0, 33.3, 46.4, 57.6, 116.8, 126.0, 128.8, 132.2, 132.4, 140.0, 142.4, 170.7; EIMS *m/z* 306(M^+) (found: M^+ 306.1128, $C_{16}H_{19}N_2O_2$ requires M 11350).

1-(n-*butyl)-2-*cyclo*hexyl-4-(4'-chlorophenyl)imidazole* **9p** (6.2 mg, 23%): R_t 13.38; R_f 0.25 (1:7 EtOAc/Hex); υ_{max} 1612, 1706; δ_H (250 MHz) 098 (3H, t, *J* = 7.3), 1.23-1.47 (6H, m), 1.70-1.90 (8H, m), 2.62 (1H, tt, *J* = 11.4, 3.2), 3.86 (2H, t, *J* = 7.3), 7.04 (1H, s), 7.28 (2H, d, *J* = 8.6), 7.67 (2H, d, *J* = 8.6); δ_C (62 MHz) 13.7, 20.0, 25.8, 26.5, 32.1, 33.4, 36.0, 45.4, 114.5, 126,1, 128.5, 131.6, 133.4, 138.9, 152.9; EIMS *m/z* 316 (M^+) (found: M^+ 316.1710, $C_{19}H_{25}N_2Cl$ requires M 316.17062).

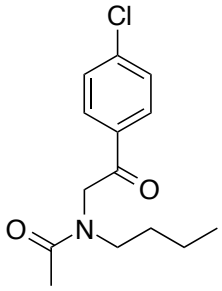
1-(n-*butyl)-2-phenyl-4-(4'-chlorophenyl)imidazole* **9q** (21.4 mg, 81%): R_t 12.42; R_f 0.28 (1:4 EtOAc/Hex); υ_{max} 1600, 1679; δ_H (250 MHz) 0.89 (3H, t, *J* = 7.4), 1.31 (2H, sx, *J* = 7.4), 7.65 (2H, qn, *J* = 7.4), 4.00 (2H, t, *J* = 7.4), 7.61 (2H, d, *J* = 8.6), 7.29-7.48 (6H, m), 7.76 (2H, d, *J* = 8.6); δ_C (100 MHz) 13.5, 19.7, 33.2, 46.7, 116.1, 126.1, 128.6, 129.0, 129.1, 132.2, 140.0, 148.3; EIMS *m/z* 310 (M^+) (found: M^+ 310.1234, $C_{19}H_{19}N_2Cl$ requires M 310.12367).

1-(n-*butyl)-2-(4"-cyanophenyl)-4-(4'-chlorophenyl)imidazole* **9r** (22.9 mg, 80%): R_t 12.20; R_f 0.51 (1:1 EtOAc/Hex); υ_{max} 1607, 1685, 2233; δ_H (250 MHz) 0.91 (3H, t, *J* = 7.4), 1.30 (2H, sx, *J* = 7.4), 1.79 (2H, qn, *J* = 7.4), 4.04 (2H, t, *J* = 7.4), 7.34-7.38 (3H, m), 7.73-7.78 (4H, m); δ_C (62 MHz) 13.5, 19.8, 38.2, 47.1, 126.2, 128.8, 129.4, 132.5, 132.7, 135.1, 141.0, 146.0; QTOF *m/z* 335 (M^+) (found: MH^+ 336.1285, $C_{20}H_{19}N_3Cl$ requires MH 336.1267).

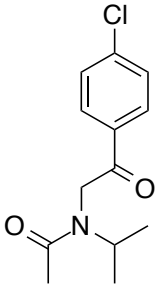
Side Product from Cyclisation of 8o:

2,3-diketo-5-(4'-chlorophenyl)-5,6-dehydropiperidine (12.8 mg, 54%): R_t 10.99;R_f 0.20 (1:4 EtOAc/Hex); υ_{max} 1596, 1695, 1765; δ_H (250 MHz) 0.96 (3H, t, *J* = 7.3), 1.40 (2H, sx, *J* = 7.3), 1.74 (2H, qn, *J* = 7.3), 2.01 (1H, s), 3.84 (2H, t, *J* = 7.3), 6.40 (1H, s), 7.42 (4H, s); δ_C (62 MHz) 13.7, 19.9, 30.5, 49.2, 111.3, 126.4, 129.6; EIMS *m/z* 278 (M^+) (found: M^+ 278.0819, $C_{14}H_{15}N_2O_2Cl$ requires M 278.08220).

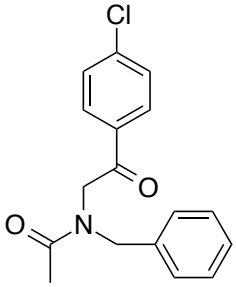
Compound structures



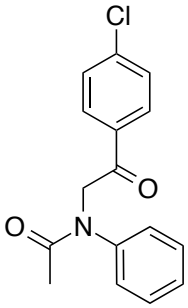
8a, 87 (98)



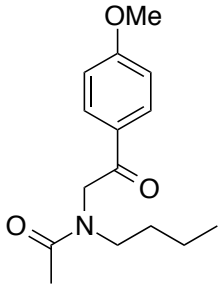
8b, 33 (86)



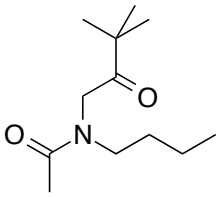
8c, 58 (93)



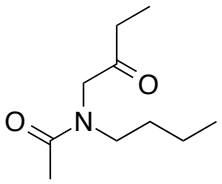
8d, 0



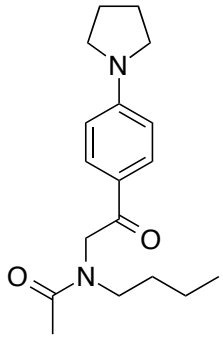
8e, 88 (96)



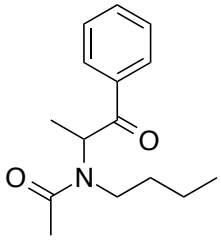
8f, 82 (-)



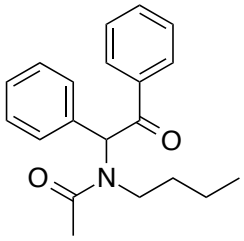
8g, 81 (-)



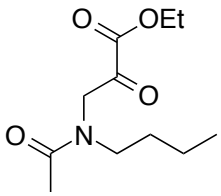
8h, 28 (71)



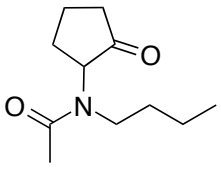
8i, 30 (98)



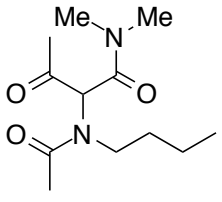
8j, 10 (100)



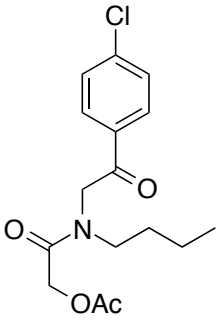
8k, 0



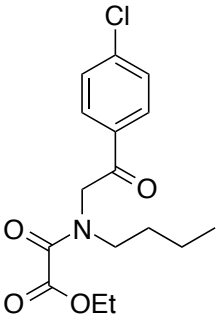
8l, 0



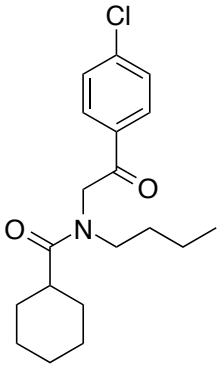
8m, 0



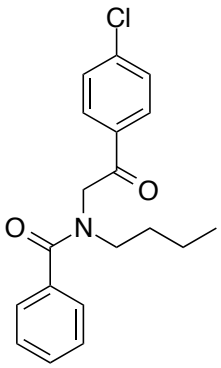
8n, 51 (94)



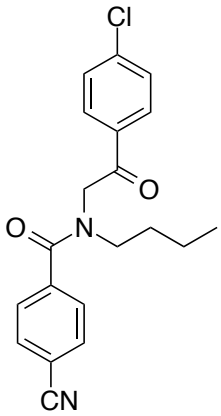
8o, 65 (91)



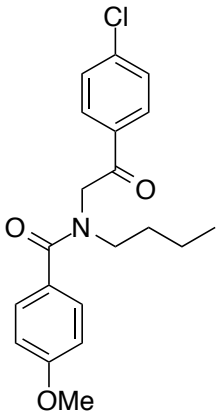
8p, 26 (71)



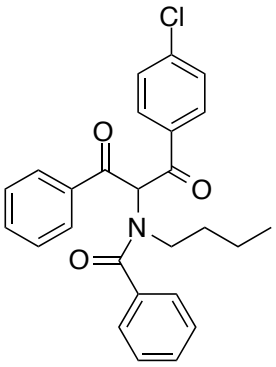
8q, 82 (97)



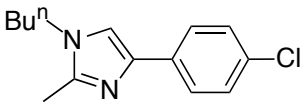
8r, 84 (90)



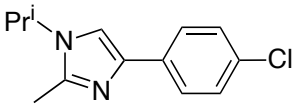
8s, 25 (71)



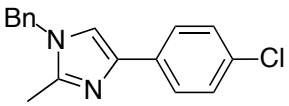
N-(n-butyl)-N-(4'-chloro-α-benzoyl-phenacyl)phen-amide



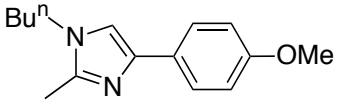
9a, 84 (95)



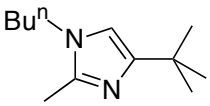
9b, 26 (68)



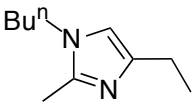
9c, 54 (87)



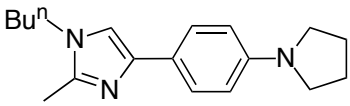
9e, 79 (86)



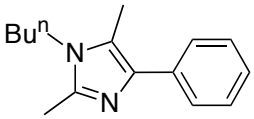
9f, 80 (100)



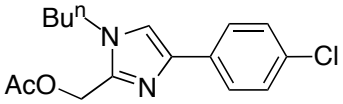
9g, 78 (96)



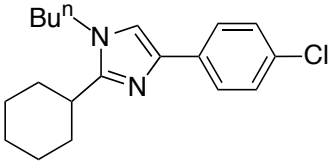
9h, 19 (49)



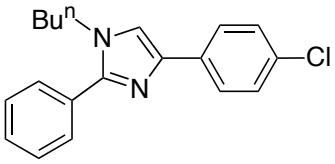
9i, 27 (89)



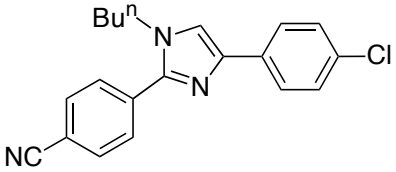
9n, 40 (73)



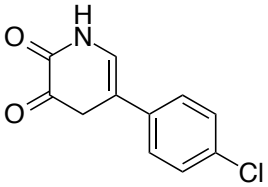
9p, 23 (64)



9q, 81 (96)



9r, 80 (86)



2,3-diketo-5-(4'-chlorophenyl)-5,6-dehydropiperidine 54 (76)

Spectra

Figure 1. Gel phase FTIR spectra of samples **5** (first from top), *n*-butyl imine of **5** (second from top), **6** (second from bottom) and **7a** (bottom).

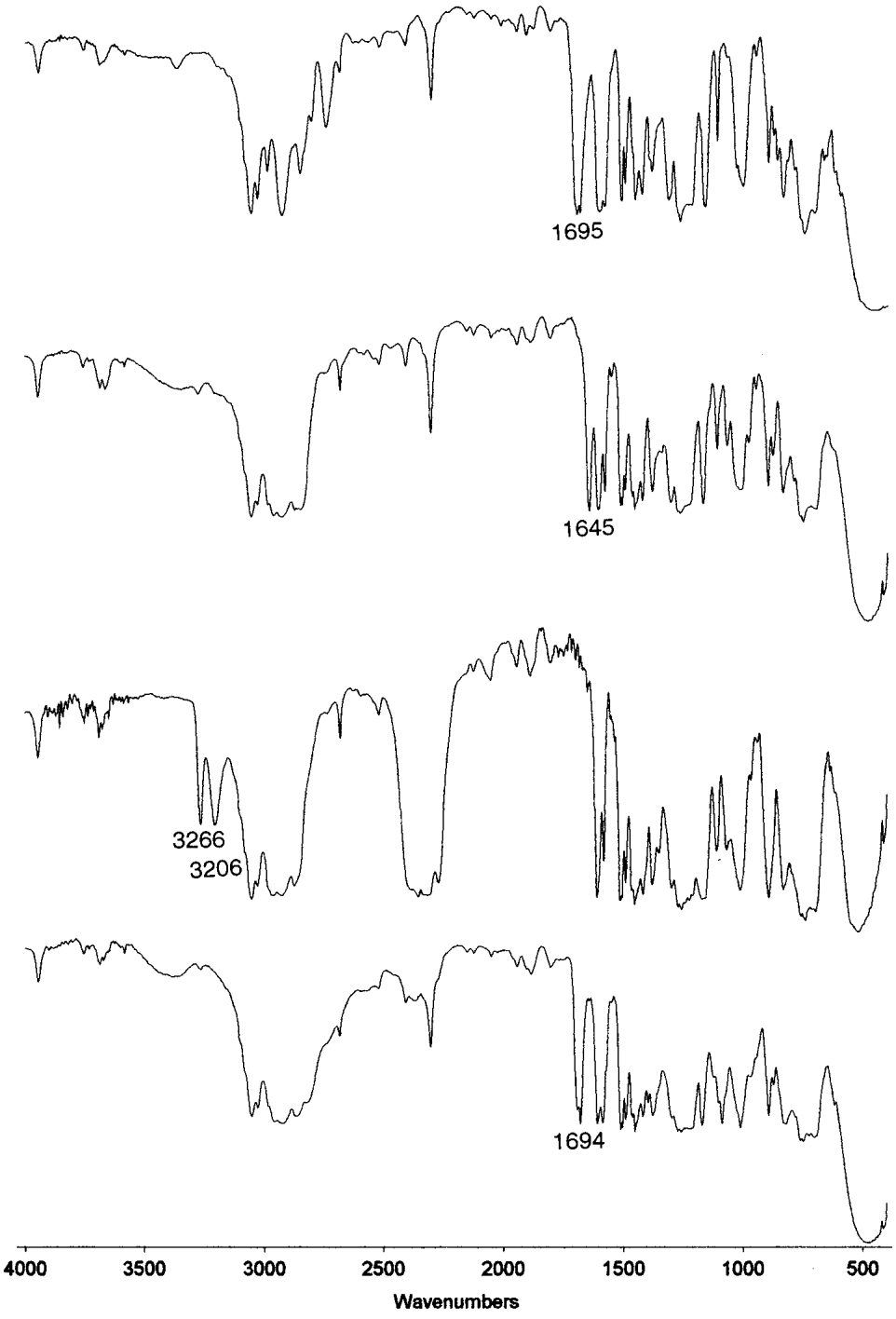


Figure 2. Gel phase 13C NMR spectra of samples **5** (bottom), **6a** (middle) and **7a** (top).

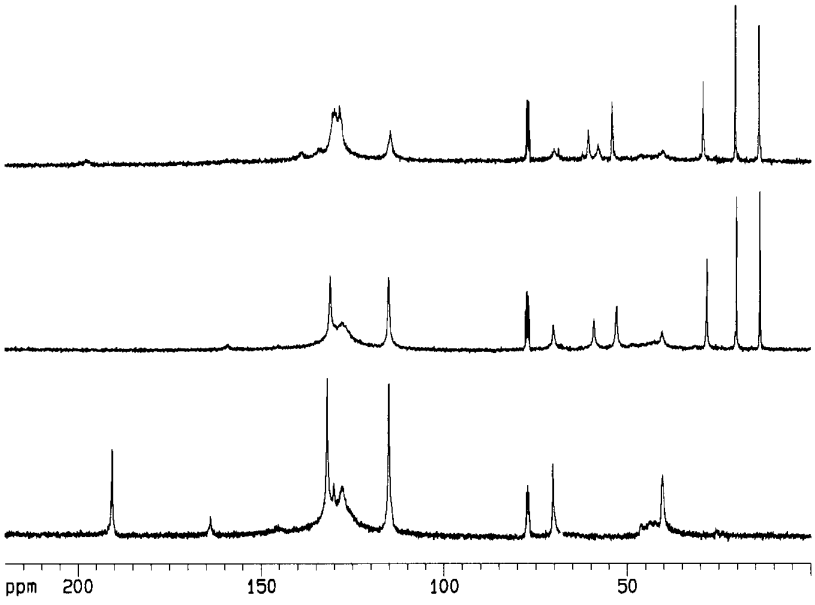


Figure 3. HPLC UV trace of cleavage solution from resin **7a**. Peak 1: benzoic acid; peak 2: dimethoxybenzene internal standard; peak 3: benzoyl chloride; peak 4: tertiary amide **8q**.

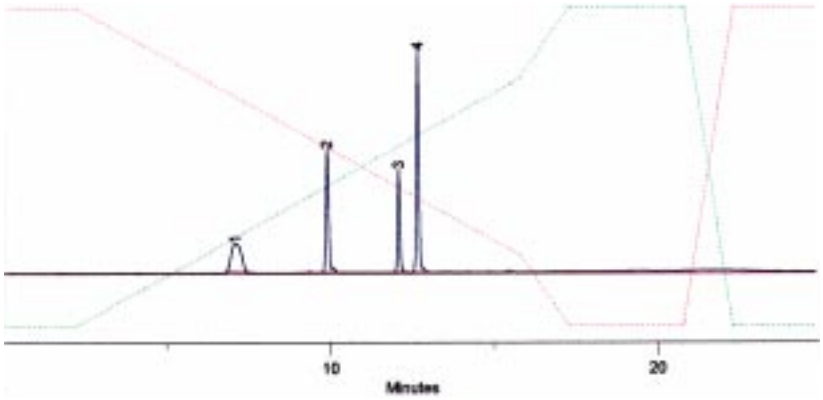


Figure 4. HPLC UV and SEDEX traces of crude reaction mixture of cyclisation of tertiary amide **8q** to imidazole **9q**. Trace **a**: after 8 h of reaction time, some of the tertiary amide, peak 2 has not cyclised to the imidazole, peak 1. Trace **b**: after 24 h of reaction time, all of the tertiary amide has cyclised to the imidazole, peak 3.

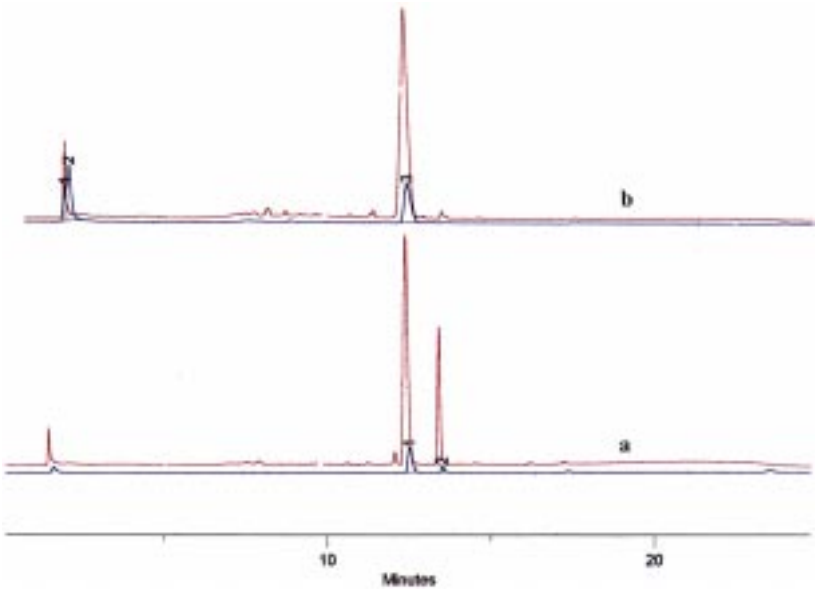


Figure 5. ^{1}H NMR spectrum of crude **8a** in $CDCl_3$ at 400 MHz.

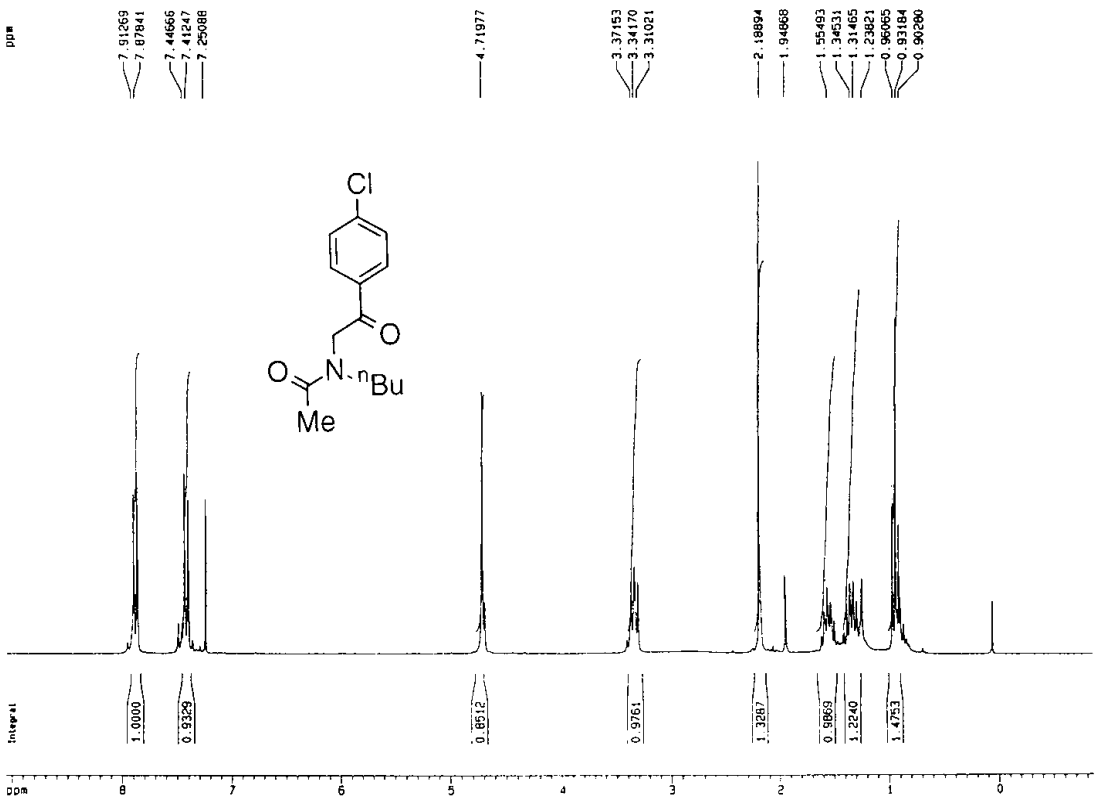


Figure 6. ^{1}H NMR spectrum of crude **9a** in $CDCl_3$ at 250 MHz.