Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Synthesis of heteroarenes using cascade radical cyclisation *via* iminyl radicals

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2,6-Dibromopyridine-4-carboxylic acid

Citrazinic acid **11** (18.26 g, 0.118 mol) and phosphorus oxybromide (100 g, 0.349 mol) were heated at 180 ˚C under nitrogen for 1 h. The reaction mixture was cooled to room temperature and ice water added cautiously and left for 12 h. The dark precipitate was filtered and purified using column chromatography with MeOH/EtOAc as eluant to give 2,6-dibromopyridine-4-carboxylic acid (26.26 g, 80%), mp 182-184 ˚C (methanol) (lit.,[1] 184-185˚C). (Found: M^+, 278.8530. $C_6H_3Br_2NO_2$ requires 278.8531); ν_{max}(Nujol)/cm^{-1} 1702 (C=O), 1579, 1528, 1377, 1348 and 761; δ_H (DMSO-d_6) 7.99 (2 H, s, 3-H, 5-H); δ_C127.71 (3-C), 140.98, 149.63 (2-C, 4-C) and 164.63 (C=O); *m/z* 281 (100%), 279 (M^+, 53), 264 (5), 202 (31), 200 (32), 174 (8), 172 (8), 156 (5), 154 (5), 146 (6), 144 (6), 131 (7), 129 (7), 119 (5), 117 (5), 108 (2), 106 (4), 92 (16), 81 (4), 77 (5), 76 (33), 64 (10), 53 (3), 50 (28) and 45 (16).

2-Bromo-6-methoxypyridine-4-carboxylic acid 12

A solution of 2,6-dibromopyridine-4-carboxylic acid (8.57 g, 0.0307 mol) and sodium methoxide (8.30 g, 0.1536 mol) in anhydrous methanol (48 cm^3) was heated under reflux at 60 °C for 48 h under an atmosphere of nitrogen. The resultant mixture was cooled to room temperature, water was added and extracted with ethyl acetate. The organic layers were dried and evaporated under reduced pressure to give a light brown solid (8.153 g). The residue was purified by column chromatography with MeOH/EtOAc as eluent to yield 2-bromo-6-methoxypyridine-4-carboxylic acid **12** as a light brown solid (6.83 g, 96%), mp 237-238 ˚C (Found: M^+, 230.9531. $C_7H_6BrNO_3$ requires 230.9531); ν_{max}(Nujol)/cm^{-1} 1643 (C=O), 1586, 1537, 1240, 1041, 983, 909, 890, 849 and 793; δ_H (DMSO-d_6) 3.85 (3 H, s, OMe), 7.20 (1 H, s, 3-H) and 7.56 (1 H, s, 5-H); δ_C 54.34 (OMe), 109.56 (3-C), 120.98 (5-C), 137.57, 153.33 (2-C, 4-C), 163.93 and 167.02 (6-C, 7-C); *m/z* 230 (M^+, 13%), 216 (25), 202 (12), 192 (8), 188 (10), 186 (11), 166 (24), 138 (42), 133 (7), 125 (6), 122 (6), 108 (21), 96 (43), 94 (46), 81 (21), 79 (17), 76 (14), 66 (21), 64 (41), 59 (15), 50 (9), 44 (CO_2, 100), 39 (13) and 38 (13).

Methyl 2-bromo-6-methoxypyridine-4-carboxylate

A mixture of 2-bromo-6-methoxypyridine-4-carboxylic acid **12** (20.185 g, 87.40 mmol) and concentrated sulfuric acid (7.9 cm^3) in methanol (188 cm^3) was heated at 60 ˚C for 5 h. Water was added and the mixture extracted with DCM. The organic extracts were dried and evaporated to dryness. The residue was purified using column chromatography with DCM/light petroleum as eluant to yield methyl 2-bromo-6-methoxypyridine-4-carboxylate as a white solid (18.63 g, 87%), mp 94-95 ˚C (Found: M^+, 244.9688. $C_8H_8BrNO_3$ requires 244.9688); (Found: C, 39.09 ; H, 3.29 ; N, 5.68. $C_8H_8BrNO_3$ requires C, 39.05; H, 3.28; N, 5.69%); ν_{max}(Nujol)/cm^{-1} 3106, 3086, 1739 (C=O), 1602, 1548, 1537, 1435, 1315, 1260, 1098, 895, 882, 845, 766 and 732; δ_H 3.94, 3.97 (3 H each, s, OMe, CO_2Me), 7.23 (1 H, s, 3-H) and 7.58 (1 H, s, 5-H); δ_C 52.89 (ester OMe), 54.62 (OMe), 109.94 (3-C), 119.60 (5-C), 139.24, 142.01 (2-C, 4-C) and 164.27 (6-C, *C*O_2Me, overlap); *m/z* 246 ([M+H]$^+$, 100%), 216 (40), 230 (5) 202 (10), 173 (5), 160 (30), 138 (20), 108 (30), 92 (50), 77 (35), 64 (100) and 49 (75).

Methyl 2-cyano-6-methoxypyridine-4-carboxylate 13

A solution of methyl 2-bromo-6-methoxypyridine-4-carboxylate (5.90 g, 24.08 mmol) and copper(I) cyanide (9.51 g, 0.106 mol) in anhydrous dimethylformamide (109 cm^3) under an atmosphere of nitrogen was heated under reflux at 150 °C for 48 h. The resultant solution was cooled to room temperature and poured into a solution of iron(III) chloride ($FeCl_3.6H_2O$) (13.16 g, 48.697 mmol) and conc. hydrochloric acid (32%, 0.99 cm^3) in methanol (355 cm^3). The reaction mixture was heated at 70 °C for 20 min, cooled to room temperature extracted with DCM. The combined organic layers were evaporated under reduced pressureto give a green oil which was purified by column chromatography with DCM/light petroleum as eluent to yield the product methyl 2-cyano-6-methoxypyridine-4-carboxylate **13** as a white solid (1.84 g, 40%) mp 132.5-133.2 °C (DCM/light petroleum) (Found: C, 56.29; H, 4.03; N, 14.36. $C_9H_8N_2O_3$ requires C, 56.25; H, 4.20; N, 14.58%); ν_{max}(DCM)/cm^{-1} 2242 (CN), 1729 (C=O), 1606, 1562, 1460, 1393, 1370, 1244, 1195, 1183, 1103, 1045, 976, 876, 770 and 756; δ_H 3.98 and 4.01 (3 H each, s, OMe, ester OMe), 7.52 (1 H, s, 5-H) and 7.81 (1 H, s, 3-H); δ_C 53.19, 54.76 (OMe, ester OMe), 116.45 (5-C), 116.75 (CN), 121.17 (3-C), 131.23 (2-C), 141.11 (4-C), 163.68 and 165.14 (C=O, 6-C); *m/z* 192 (M^+, 98%, Found: 192.0536. $C_9H_8N_2O_3$ requires 192.0535), 193 (10), 191 [(M-H)$^+$, 100], 177 (8), 162 (56), 147 (37), 133 (21), 119 (11), 103 (8), 92 (8), 81 (24), 76 (8) and 66 (13).

Ethyl 2-[(4-chloro-5*H*-1,2,3-dithiazol-5-yliden)amino]-benzene-1-carboxylate 24

4,5-Dichloro-1,2,3-dithiazolium chloride[28] **23** (6.2, 29.973 mmol) was added to a solution of ethyl 2-aminobenzoate **22** (3.30 g, 20.0 mmol) in DCM (25 cm^3) under nitrogen.[26] Pyridine (3.6 cm^3) was added slowly and the solution stirred at ambient temperature for 24 h under nitrogen. The reaction mixture was evaporated under reduced pressure and the residue was purified by column chromatography using DCM/light petroleum/EtOAc as eluent to give ethyl 2-[(4-chloro-5*H*-1,2,3-dithiazol-5-yliden)amino]-benzene-1-carboxylate **24** (5.50 g, 92%) as a dark red viscous oil. (Found: M^+, 299.9794. $C_{11}H_9ClN_2O_2S_2$ requires 299.9794); ν_{max}(DCM)/cm^{-1} 1713 (ester), 1594, 1568, 1475, 1445, 1366, 1293, 1249, 1218, 1131, 1080, 1041, 857 and 761; δ_H 1.27 (3 H, t, *J* 7.1, Me), 4.27 (2 H, q, *J* 7.1, CH_2), 6.98-6.96 (1 H, m), 7.26-7.23 (1 H, m), 7.59-7.55 (1 H, m) and 8.04-8.02 (1 H, m); δ_C 14.49 (Me), 61.50 (CH_2), 118.86 (CH), 120.87 (C), 126.16 (CH), 132.36 (CH), 134.63 (CH), 147.24 (C), 152.89 (C), 160.92 (C), and 165.89 (C=O); *m/z* 300 (M^+, 20%), 272 (2), 255 (9), 239 (15), 201 (62), 173 (93), 162 (15), 146 (100), 134 (13), 108 (5), 102 (15), 90 (14), 76 (8) and 64 (11).

3-[(*Z*)-2-Iodo-3-phenylprop-2-enyl]-4-oxo-3,4-dihydroquinazoline-2-carbonitrile 27

The quinazoline **25** was alkylated with 1-[(*Z*)-3-bromo-2-iodoprop-1-enyl]benzene[14] **15** using the procedure for the alkylation of 4-oxo-3,4-dihydro-quinazoline-2-carbonitrile **25**. After considerable chromatography a 'pure' but inseparable mixture of 3-[(*Z*)-2-iodo-3-phenylprop-2-enyl]-4-oxo-3,4-dihydroquinazoline-2-carbonitrile **27** (16%) and 1-[(*Z*)-2-iodo-3-phenylpropen-2-yl]-4-oxo-1,4-dihydro-quinazoline-2-carbonitrile **30** (6%) was obtained. The 3-*N* isomer **27** was fully characterised when synthesised by the alternative procedure and the1-*N* isomer was partially characterised in the mixture. GCMS showed almost identical mass spectra.

(*Z*)-2-Iodo-3-phenylprop-2-ene-1-amine 32

2-[(*Z*)-2-Iodo-3-phenylprop-2-enyl]-2,3-dihydro-1H-isoindole-1,3-dione: Mitsunobu reaction.– Triphenylphosphine (3.025 g, 11.53 mmol) and phthalimide (1.697 g, 11.53) were added to anhydrous tetrahydrofuran (45 cm^3) at –5 ˚C under nitrogen. Diisopropyl azodicarboxylate (2.33 g, 11.53 mmol) was added followed by the dropwise addition of (*Z*)-2-iodo-3-phenylprop-2-en-1-ol[14] dissolved in anhydrous tetrahydrofuran (5 cm^3). The resultant mixture was stirred at –5 ˚C for 1 h and at 0 ˚C for 30 min. The mixture was allowed to warm to room temperature and stirred for 22 h. The reaction mixture was evaporated under reduced pressure and the residue purified by column chromatography using DCM/light petroleum as eluent to yield 2-[(*Z*)-2-iodo-3-phenylprop-2-enyl]-2,3-dihydro-1*H*-isoindole-1,3-dione as colourless crystals (2.99 g, 100%), mp 117-117.5 ˚C (DCM/light petroleum), (Found: C, 52.4; H, 3.0; N, 3.6. $C_{17}H_{12}INO_2$ requires C, 52.46; H, 3.11; N, 3.60%); ν_{max}(Nujol)/cm^{-1} 1768 (C=O, *E* isomer), 1708 (C=O, *Z* isomer) 1611, 1414, 1386, 1337, 1321, 1265, 1112, 942, 751, 711, 695 and 668; δ_H 4.78 (2 H, s, CH_2), 7.08 (1 H, s, alkene-H), 7.33-7.30 (3 H, m, phenyl 3,4,5-H), 7.50-7.48 (2 H, m, phenyl 2,6-H), 7.74-7.72 (2 H, m, 5,6-H), 7.89-7.87 (2 H, m, 4,7-H); δ_C 50.49 (CH_2), 98.31 (*C*-I), 134.20 (CH), 128.11 (CH), 128.21 (CH), 123.55 (CH), 128.60 (CH), 131.85 (C) 137.07 (C) and 167.44 (C=O); *m/z* (FAB) 389 [$(M+H)^+$, 100%, Found: 389.9988. $C_{17}H_{12}INO_2$ requires 389.9992], 262 (95), 165 (35), 160 (95), 121 (38), 115 (48), and 105 (51); *m/z* (EI) 262 (M^+, 100%), 232 (25), 204 (20), 178 (6), 160 (60), 147 (43), 133 (15), 115 (72), 104 (46), 76 (65), 63 (20) and 50 (29).

2-[(Z)-2-iodo-3-phenylprop-2-enyl]-2,3-dihydro-1H-isoindole-1,3-dione: Gabriel synthesis.–1-[(*Z*)-3-Bromo-2-iodoprop-1-enyl]benzene (3.0 g, 9.32 mol, contains some of *E*-isomer) was added to a solution of potassium phthalimide (1.845, 9.959 mmol) in anhydrous dimethylformamide (20 cm^3) and the solution refluxed for 4.5 h. The reaction mixture was cooled to room temperature, water added, and the solution extracted with DCM. The DCM fractions were evaporated under reduced pressure and the residue purified by column chromatography using DCM/light petroleum as eluent to yield 2-[(Z)-2-iodo-3-phenylprop-2-enyl]-2,3-dihydro-1*H*-isoindole-1,3-dione as a colourless crystals (2.52 g, 70%). The mp, TLC and spectroscopic data were identical to authentic material.

(Z)-2-Iodo-3-phenylprop-2-ene-1-amine 32.–Aqueous hydrazine hydrate (55%, 5.0 cm^3) was added to a solution of 2-[(*Z*)-2-iodo-3-phenylprop-2-enyl]-2,3-dihydro-1*H*-isoindole-1,3-dione (1.7 g, 4.37 mmol) in ethanol (17 cm^3). The resulting solution was heated at 75 ˚C for 6.5 h. Water was added and the mixture extracted with ethyl acetate. The organic layers evaporated under reduced pressure and the resulting oil purified by column chromatography using DCM/EtOAc as eluent to yield (*Z*)-2-iodo-3-phenylprop-2-ene-1-amine **32** (0.860 g, 76%) as a yellow oil. (Found: M^+, 258.9862. $C_9H_{10}IN$ requires 258.9858); ν_{max}(DCM)/cm^{-1} 3372, 3302, 1598, 1490, 1386 and 1336; δ_H 1.72 (2 H, s, NH_2), 3.64 (2 H, s, 1-H), 6.91 (1 H, s, 3-H), 7.34-7.27 (3 H, m, phenyl 3,4,5-H), 7.49-7.47 (2 H, m, phenyl 2,6-H); δ_C 56.43 (1-C), 137.42 (phenyl 1-C), 132.91 (3-C), 128.54, 128.22 (phenyl 2,5-C), 128.04 (phenyl 4-C) and 112.22 (2,6-C); *m/z* 259 (M^+, 3%), 245 (9), 220 (14), 160 (30), 132 (98), 115 (100), 103 (22), 89 (12), 77 (26), 63 (13), 51 (18) and 44 (31).

(*E*)-3-Phenylprop-2-ene-1-amine 33

2-[(*E*)-3-Phenylprop-2-enyl]-2,3-dihydro-1H-isoindole-1,3-dione.–Cinnamyl bromide (25.0 g, 0.127 mol) was added to a solution of potassium phthalimide (23.497 g, 0.127 mol) in anhydrous dimethylformamide (250 cm^3) and the solution refluxed for 4.5 h. The reaction mixture was cooled to room temperature, water added, and the solution extracted with DCM. The organic fractions were evaporated under reduced pressure and the residue purified by column chromatography using DCM/light petroleum as eluent to yield 2-[(*E*)-3-phenylprop-2-enyl]-2,3-dihydro-1*H*-isoindole-1,3-dione (23.1 g, 70%) as a white solid, mp 153-154.5 ˚C (DCM/ light petroleum) (lit.,[2] 155-156 ˚C), (Found: C, 77.2; H, 4.9; N, 5.3. $C_{17}H_{13}NO_2$ requires C, 77.55; H, 4.98; N, 5.32%); ν_{max}(Nujol)/cm^{-1} 1770 (C=O, *E* isomer), 1707 (C=O, *Z* isomer) 1613, 1497, 1427, 1322, 1193, 1108, 954 and 858; δ_H 4.43 (2 H, d, *J* 6.2, CH_2), 6.23-6.28 (1 H, m, alkene 2-H), 6.64 (1 H, d, *J* 16.0, alkene 3-H), 7.19-7.28 (3 H, m, phenyl 3,4,5-H), 7.32-7.34 (2 H, m, phenyl 2,6-H), 6.67-6.69 (2 H, m, 5,6-H) and 7.82-7.84 (2 H, m, aryl 4,7-H); δ_C 39.64 (CH_2), 122.76 (CH), 123.25 (CH), 126.50 (CH), 127.85 (CH), 128.50 (CH), 132.15 (C), 133.73 (CH), 133.92 (CH), 136.23 (C) and 167.87 (C=O); *m/z* 263 (M^+, 32%, Found: M^+, 263.0942. $C_{17}H_{13}NO_2$ requires 263.0946), 245 (16), 234 (8), 218 (5), 206 (5), 189 (5), 172 (5), 160 (5), 148 (45), 130 (15), 116 (100), 104 (14), 91 (8), and 77 (15).

(*E*)-3-Phenylprop-2-ene-1-amine 33.–The same procedure as used for *(Z)*-2-iodo-3-phenylprop-2-ene-1-amine gave (*E*)-3-phenylprop-2-ene-1-amine **33** (3.11g, 75%) as a yellow oil. (Found: M^+, 133.0892. $C_9H_{11}N$ requires 133.0891); ν_{max}(DCM)/cm^{-1} 3374, 3263 (NH_2), 3028, 1629, 1596, 1571, 1493, 1448, 1404, 1341 and 966; δ_H 1.63 (2 H, br, NH_2), 3.46 (2 H, dd, *J* 8.0, 1-H), 6.27-6.34 (1 H, m, 2-H), 6.49 (1 H, d, *J* 16.0, 3-H), 7.21-7.23 (1 H, m), 7.27-7.31 (2 H, m) and 7.35-7.37 (2 H, m); δ_C 44.26 (1-C), 126.23 (CH), 127.30 (CH),128.55 (CH), 129.51 (CH), 131.17 (CH) and 137.19 (phenyl 1-C); *m/z* 133 (M^+, 100%), 115 (63), 104 (14), 91 (29), 89 (9), 77 (30), 74 (5), 63 (13), 56 (37), 54 (10) and 51 (20).

4-oxo-3-[(*E*)-3-phenylprop-2-enyl]-3,4-dihyroquinazoline-2-carbonitrile 28 using amine 33

The same procedure was used as for the synthesis of **27** using amine **32**. (*E*)-3-Phenylprop-2-ene-1-amine **33** (2.07 g, 15.5 mmol) and **24** (0.932 g, 3.1 mmol) gave 4-oxo-3-[(*E*)-3-phenylprop-2-enyl]-3,4-dihyroquinazoline-2-carbonitrile **28** (0.357 g, 40%). The product had identical spectroscopic data to the product isolated from the reaction between 4-oxo-3,4-dihydro-quinazoline-2-carbonitrile **28** and cinnamyl bromide. GCMS showed the same retention time and the same EI mass spectrum.

2-[(*E*)-3-phenylprop-2-enyl]-3*H*-quinazolin-4-one 41

4-Phenylbut-3-enoic acid (1.00 g, 6.17 mmol) was dissolved in anhydrous DCM (30 cm^3). DMF (3 drops) and oxalyl chloride (1.61 cm^3, 18.49 mmol) were added and the reaction mixture stirred for 2 h at room temperature. The solution was evaporated under reduced pressureto yield 4-phenylbut-3-enoyl chloride which was used without further purification.

The crude 4-phenylbut-3-enoyl chloride (1.11 g, 6.17 mmol) was dissolved in anhydrous toluene (40 cm^3). Anthranilamide **39** (0.79 g, 5.86 mmol) was added and the reaction stirred at

room temperature for 2 h. After this time a catalytic quantity of *p*-toluenesulfonic acid was added and the mixture heated under Dean-Stark conditions for 48 h. The solution was evaporated under reduced pressure and the residue purified by column chromatography using neutral alumina as absorbent and light petroleum/EtOAc as eluent to yield 2-[(*E*)-3-phenylprop-2-enyl]-3*H*-quinazolin-4-one **41** as a pale yellow solid (0.13 g, 9%). (Found M^+, 262.1106. $C_{17}H_{14}N_2O$, requires: 262.1106); ν_{ma}(thin film)/cm^{-1} 3257, 3026, 1669, 1580, 1526, 1446, 1290, 1166 and 968; δ_H 3.40 (2 H, dd, *J* 7.3, 1.3, CH_2), 6.37 (1 H, d, *J* 15.8, 7.3, propenyl 2-H), 6.69 (1 H, dd, *J* 15.8, 1.3, propenyl 3-H), 7.16 (1 H, ddd, *J* 7.6, 7.6, 1.0, phenyl *p*-H), 7.26 -7.31 (1 H, m, phenyl *o*-H), 7.33-7.35 (2 H, m, phenyl *m*-H), 7.42-7.44 (2 H, m, 6-H, phenyl *o*-H), 7.54-7.58 (2 H, m, 7,8-H), 7.97 (1 H, brs, NH) and 8.38 (1H, d, *J* 8.4, 5-H); δ_C (100 MHz) 42.1 (CH_2), 102.6 (phenyl 1-C), 116.6 (4a-C), 121.2 (CH), 121.7 (CH), 124.7 (CH), 126.9 (CH), 128.4 (CH), 129.0 (CH), 132.6 (8-C), 134.5 (7-C), 136.66 (8a-C), 136.69 (5-C), 140.6 (2-C) and 169.6 (4-C); *m/z* 262 (M^+, 35%), 144 (35), 117 (100), 91 (19), 77 (2) and 65 (3). The synthesis was not optimised.

3-[(*E*)-3-Phenylpropen-2-yl]-3*H*-quinazolin-4-one 43

Sodium hydride (0.39 g, 10 mmol) was added at 0 °C to 3*H*-quinazolin-4-one **42** (0.73 g, 5 mmol) in dry DMF (5 ml) and dry glyme (10 ml) and stirred for 1 h under an atmosphere of nitrogen. Lithium bromide (0.86 g, 10 mmol) was added and the reaction stirred for15 min. Cinnamyl bromide (3.9 g, 20 mmol) was added and the reaction stirred for 2 h. Excess sodium hydride was quenched by dropwise water (5 cm^3). The reaction mixture was extracted into DCM (50 cm^3) and washed with water. The organic layer was dried and evaporated to dryness. The crude product was purified using column chromatography with silica gel as absorbent and light petroleum:ethyl acetate (4:1) as eluent to yield 3-[(*E*)-3-phenylpropen-2-yl)]-3*H*-quinazolin-4-one **43** as a pale yellow solid (0.51 g, 1.96 mmol, 40%); (Found: M^+, 263.1182. $C_{17}H_{14}N_2O$ requires 263.1179); ν_{max}(thin film)/cm^{-1} 3423, 1670, 1652, 1608, 1558, 1473 and 773; δ_H (400 MHz) 4.79 (2 H, dd, *J* 6.4, 1.4, CH_2), 6.34 (1 H, dt, *J* 15.8, 6.4, propenyl-2-H), 6.66 (1 H, dd, *J* 15.8, 1.4, propenyl-3-H), 7.23-7.38 (5 H, m, phenyl-H), 7.53, (1 H, ddd, *J* 8.0, 8.0, 1.0, 6-H), 7.73 (1 H, ddd, *J* 8.0, 8.0, 1.0, 7-H), 7.76 (1 H, dd, *J* 8.0, 1.0), 8.11 (1 H, s, 2-H) and 8.34 (1 H, dd, *J* 8.0, 1.0, 5-H); δ_C (100 MHz) 48.15 (CH_2), 122.16 (4a-C), 122.77 (propenyl-2-C), 126.50 (phenyl-2,6 or 3,5-C), 126.82 (5-C), 127.41 (6-C), 127.41 (6-C), 127.54 (7-C), 128.30 (phenyl-4-C), 128.68 (phenyl-2,6 or 3,5-C), 134.35 and 134.50 (propenyl-3-C and 8-C), 135.75 (phenyl-1-C), 146.19 (2-C), 148.10 (8a-C) and 160.95 (C=O); NMR assignments were confirmed by NOESY, COSY and HMQC NMR techniques; *m/z* EI 263 (M^+, 2%), 147 (42), 121 (100), 79 (87) and 74 (26).

4-Oxo-1-[(*E*)-3-phenylprop-2-enyl]-3,4-dihyroquinazoline-2-carbonitrile 31

2-[(*E*)-3-Phenylpropeny-2-yl-ideneamino]benzamide.–A solution of anthranilamide **40** (15.21 g, 111.7 mmol) and cinnamaldehyde (14.1 cm^3, 111.7 mmol) in absolute ethanol (75 cm^3) stirred under reflux for 15 min. The resultant mixture was cooled to 0 ºC and the resultant crystals filtered and washed with light petroleum. The imine was recrystallised (MeOH) to yield 2-(3-phenylpropeny-2-yl-ideneamino)-benzamide as colourless crystals (12.77 g, 46%). The imine was reacted without further purification.

2-[(*E*)-3-Phenylpropen-2-ylamino]benzamide 44.–Sodium borohydride (1.52 g, 40.0 mmol) was added to a solution of 2-(3-phenylpropeny-2-yl-ideneamino)benzamide (10.0 g, 40.0 mmol) in methanol (70 cm^3). The reaction mixture was stirred at 45-50 ˚C for 30 min, cooled, conc. hydrochloric acid (*ca*. 5 cm^3) added and evaporated to dryness. The resultant residue was re-dissolved in diethyl ether and extracted into 2 M hydrochloric acid. The aqueous layer was basified using conc. aqueous NaOH and product extracted into DCM. The DCM fraction was dried and evaporated under reduced pressure to yield 2-[(*E*)-3-phenylpropen-2-ylamino]benzamide **44** as colourless crystals (9.44 g, 94%). (Found: 252.1261. $C_{16}H_{16}N_2O$ requires: 252.1262); δ_H(400 MHz) 3.96 (2 H, dd, *J* 5.2, 1.8, CH_2). 6.40 (1 H, dd, *J* 5.2, 8.0, propenyl-2-H), 6.71 (1 H, d, *J* 8.4, 3-C), 6.53 (1 H, d, *J* 8.0, propenyl-3-H), 6.61 (1 H, brs, NH), 7.17-7.31 (5 H, m, phenyl-3,4,5-H, 4,5-H), 7.41 (2 H, d, *J* 7.6, phenyl-2,6-H), 7.64 (1 H, dd, *J* 1.6, 8.0, 6-H) and 7.88 (1 H, brs, NH); δ_C(100 MHz) 44.0 (CH_2), 111.42 and 114.11 (3- and 5-C), 114.05 (1-C), 126.14 and 128.58 (Ph-3,5- and 2,6-C), 127.36, 127.43, 129.04, 130.26 and 132.52 (propenyl-2,3-C, 6,8-C, Ph-4-C), 136.53 (phenyl-1-C), 149.61 (2-C) and 171.67 (C=O); *m/z* 252 (M^+, 62%), 234 (39), 206 (36), 148 (16), 130 (23), 117 (100), 104 (18), 91 (70), 77 (36) and 65 (13).

4-Oxo-1-[(*E*)-3-phenylprop-2-enyl]-1,4-dihydroquinazoline-2-carboxylic acid ethyl ester 45.–Triethylamine (7.80 g, 56.11 mmol) and a catalytic quantity of DMAP were added to a solution of 2-[(*E*)-3-phenylpropen-2-ylamino]benzamide **44** (10.1 g, 40.08 mmol) and dissolved in anhydrous DCM (100 cm^3). Ethyl oxalyl chloride (4.46 cm^3, 40.08 mmol) was added drop wise with stirring and the reaction mixture was left to stir overnight. The reaction mixture was washed with dilute hydrochloric acid and the organic fraction dried and evaporated under reduced pressure. The crude residue was purified further by column chromatography using alumina as adsorbent and DCM as eluant. Analysis of the product ^{1}H NMR spectroscopy indicated that the cyclisation was incomplete. A DCM solution of the crude product was further heated under reflux in the presence of a catalytic quantity of *para*-toluenesulfonic acid for 48 h. The crude product was again purified by column chromatography as above to yield 4-oxo-1-(3-phenylpropen-2-yl)-1,4-dihydro-quinazoline-2-carboxylic acid ethyl ester **45** as a white solid (11.2 g, 83 %). [Found: 335.1398. ($C_{20}H_{18}N_2O_3$ + H) requires: 335.1396]; δ_H(400 MHz); δ_H 1.37 (3 H, t, *J* 7.0, Me), 4.53 (2 H, d, *J* 7.0, OCH_2), 4.94 (2 H, dd, *J* 5.6, 1.2, CH_2), 6.30 (1 H, dt, *J* 16.0, 5.6, propenyl-2-H), 6.63 (1 H, dd, *J* 16.0, 1.2 propenyl-3-H), 7.23-7.37 (5 H, m, phenyl-H), 7.46 (1 H, dd, *J* 7.8, 7.8, 6-H), 7.57 (1 H, dd, *J* 7.8,1.5, 8-H), 7.73 (1 H, ddd, *J* 7.8, 7.8, 1.5, 7-H) and 8.30 (1 H, dd, *J* 7.8, 1.5, 5-H); δ_C100 MHz) 13.60 (Me), 50.40 (CH_2), 63.38 (OCH_2), 116.09 (8-C), 120.85 (4a-C), 121.35 (propenyl-2-C), 126.53 and 128.65 (phenyl-2,3,5,6-C), 126.84 and 128.48 (5,6-C), 134.65, 135.25 and 135.51 (phenyl-4-C, propenyl-3-C, 7-C), 135.52 (phenyl-1-C), 139.58 (8a-C), 153.34 (2-C), 161.19 (*C*O_2Et) and 168.19 (4-C); *m/z* 328 [$(M+H)^+$, 7%), 281 (3), 261 (8), 219 (3), 207 (7), 193 (4), 117 (100) and 91 (23). NMR assignments were confirmed using NOESY, COSY and carbon-proton correlation NMR techniques. A large nOe between the cinnamyl-methylene and 8-H was measured thereby confirming the 1-*N* substitution.

4-Oxo-1-[(*E*)-3-phenylprop-2-enyl]-1,4-dihydroquinazoline-2-carboxylic acid amide 46.– Conc. aqueous ammonia solution (250 cm^3) was added to a solution of 4-oxo-1-[(*E*)-3-phenylprop-2-enyl]-1,4-dihydroquinazoline-2-carboxylic acid ethyl ester **45** (11.2 g, 33.53 mmol) in ethanol(100 cm^3) and the mixture stirred overnight at room temperature. The product was filtered to yield the amide **46** as a colourless crystals (6.84 g, 64 %), mp 204-206 ˚C [Found: 306.1242. ($C_{18}H_{12}N_3O_2$ + H) requires: 306.1243]; ν_{max}(thin film)/cm^{-1} 3331, 3195, 1681, 1629, 1606, 1589, 1357, 763, 743 and 708; δ_H(400 MHz, d_6-DMSO); 5.08 (2 H, d, *J* 4.8, CH_2), 6.44 (1 H, dt, *J* 16.0, 4.8 Hz, propenyl-2-H), 6.70 (1 H, d, *J* 16.0, propenyl-3-H), 7.38-7.21 (5 H, m, phenyl-H), 7.54 (1 H, dd, *J* 7.4, 7.4, 6-H), 7.87-7.78 (2 H, m, 7,8-H), 8.13 (1 H, d, *J* 7.8, 5-H), 8.26 (1 H, brs, NH) and 8.55 (1 H, brs, NH); δ_C100 MHz, d_6-DMSO); 49.3 (CH_2), 117.1 (8-C), 120.1 (4a-C), 123.3 (propenyl-2-C), 126.3, 126.4 and 127.3 (5,6,7-C), 126.36 and 128.0 (phenyl-2,3,5,6-C), 132.9 (phenyl-1-C), 134.3 and 135.6

(phenyl-4-C and propenyl-3-C), 139.6 (8a-C), 156.6 (2-C), 163.6 (*C*ONH$_2$) and 167.8 (4-C); *m/z* (FAB) 328 (M^++Na)(19 %), 306 (M^++H)(41), 261 (56), 220 (8), 190 (18), 117 (100), 107 (44) and 77 (61).

4-oxo-1-[(*E*)-3-phenylprop-2-enyl]-3,4-dihyroquinazoline-2-carbonitrile 31.–EDCI 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (2.00 g, 1044 mmol) was added to a solution of 4-oxo-1-[(*E*)-3-phenylprop-2-enyl]-1,4-dihydro-quinazoline-2-carboxylic acid amide **46** (1.06 g, 3.48 mmol) and HOAT (0.05 g, 0.33 mmol) in anhydrous dichloromethane (15 cm^3) and DMF (3 cm^3). The reaction mixture was heated under reflux for 18 h. The crude mixture was washed with saturated brine, dried and evaporated to dryness. The crude residue was purified by column chromatography using alumina as adsorbent and DCM:MeOH (96:4) as eluent to yield 4-oxo-1-[(*E*)-3-phenylprop-2-enyl]-3,4-dihyroquinazoline-2-carbonitrile **31** as a colourless crystals (0.36 g, 36%), mp 221-224 ˚C (Found: C, 70.3; H, 4.7; N, 13.3. $C_{18}H_{15}N_3O_2$ requires C, 70.81; H, 4.95; N, 13.76%); ν_{max}(DCM slurry)/cm^{-1} 3335, 3204, 1680, 1627, 1607, 1589, 1521, 1484 and 969 (no nitrile peak visible); δ_H(400 MHz) 5.40 (2 H, dd, *J* 1.2, 6.4, CH_2), 6.39 (1 H, dt, *J* 6.4, 16.0, propenyl 2-H), 6.72 (1 H, br d, *J* 16.0, propenyl 3-H), 7.22 (1 H, ddd, *J* 8.0, 8.0, 1.6, phenyl-*p*-H), 7.31 (2 H, ddd, *J* 8.0, 8.0. 1.6, phenyl-*m*-H), 7.37 (2 H, dd, *J* 8.0, 1.6, phenyl-*o*-H), 7.57 (1 H, ddd, *J* 0.8, 8.0, 8.0, 6-H), 7.69 (1 H, dd, *J* 0.8, 8.0, 8-H), 7.75 (1 H, ddd, *J* 1.2, 8.0, 8.0, 7-H), 8.34 (1 H, dd, *J* 1.2, 8.0, aryl 5-H, *E*), 8.24 (1 H, br s, NH or OH) and 8.53 (1 H, NH or OH). Irradiation of the peak at 5.40 have strong nOe's to 8-H and propenyl 2-and 3-H. Irradiation of 8-H gave a strong nOe with the propenyl-CH_2 and weaker nOe's with the two alkene-H's; δ_C (d_6-DMSO, 100 MHz) 50.54 (CH_2), 116.51 (8-C), 121.26 (CN), 123.35 (propenyl-2-C), 126.63 (Ph *o*-C), 127.08 (6-C), 128.37 (5-C), 128.69, (Ph *p*-C), 128.76 (Ph *m*-C), 129.10 (qC), 133.88 (propenyl 3-C), 134.54 (7-C), 135.62 (Ph 1-C), 141,16 (qC), 155.97 (qC), 163.25 (qC) and 168.56 (qC). NMR assignments were confirmed using COSY and carbon-proton correlation NMR techniques; *m/z* 261 (7%), 117 (73), 115 (100), 102 (18), 91 (56), 77 (60) and 63 (49); *m/z* (ES^+) 306 (M^++1, 22%) and 117 (100); (ES^-) 304 (88%) and 145 (100).

References

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