SHORT PAPER

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Structural studies on bioactive compounds. Part 38.[1] Reactions of 5-aminoimidazole-4-carboxamide: synthesis of imidazo[1,5-*a*]quinazoline-3-carboxamides[†]

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5-Aminoimidazole-4-carboxamide reacts with aromatic aldehydes to afford Schiff bases which can be cyclised to imidazo[1,5-*a*]quinazoline-3-carboxamides in DMF/sodium hydride. The potassium salt of imidazo[1,5-*a*]quinazoline-3-carboxylic acid undergoes deuterium exchange in D_2O at the 1-position.

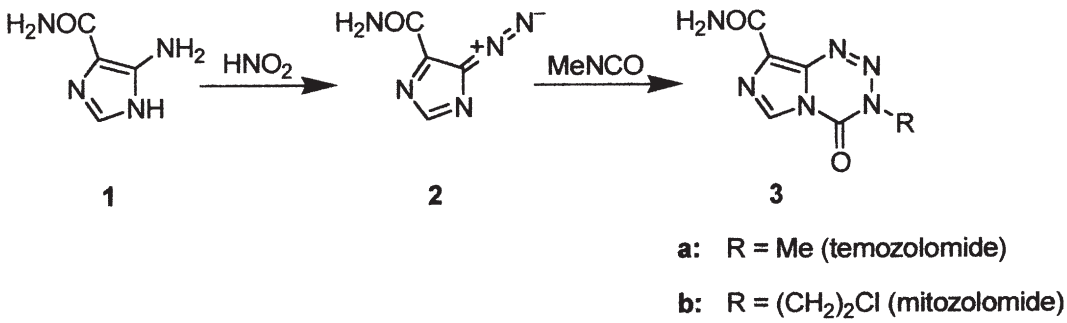
Keywords: 5-aminoimidazole-4-carboxamide, fused imidazoles, fused quinazolines, deuteriation

5-Aminoimidazole-4-carboxamide **1** is a versatile starting material for the synthesis of a variety of bicyclic heterocycles, notably purin-6(1*H*)-ones.[2] A particularly useful intermediate is the stable 5-diazoimidazole-4-carboxamide **2**, derived from **1** by nitrosation, which can be cyclised to imidazo[4,5-*d*][1,2,3]triazines[3] and imidazo[5,1-*c*][1,2,4]triazines[4] and undergoes cycloadditions with isocyanates, for example methyl and 2-chloroethyl isocyanates, to afford the antitumour imidazo[5,1-*d*][1,2,3,5]tetrazines temozolomide **3a** and its forerunner mitozolomide **3b** (Scheme 1).[5] Temozolomide is now making a significant clinical impact in the cancer therapeutic area.[6]

Transition metal-catalysed transformations of diazo compounds *via* carbenoid intermediates are well known and have been reviewed.[7] Employing reagents such as rhodium(II) acetate, cyclopropanations, additions to aromatic rings, formations of ylids, atom abstractions and bond insertions can be performed. However, simple procedures such as formation of ethers[8] which are characteristic of the decompositions of α-diazocarbonyls in alcohols, do not work with the diazoimidazole **2**. Thus, attempted decomposition of **2** in methanol or cyclohexanol with rhodium(II) acetate (2 mol. %) in THF or DMSO did not yield the expected alkoxyimidazoles **4a,b**: no nitrogen evolution occurred and only the product of intramolecular cyclisation, 2-azahypoxanthine **5**,[4] was isolated in quantitative yield (Scheme 2).

Suzuki reactions on ring *N*-protected imidazoles can be performed efficiently.[9,10] For example, 1-benzyl-4-bromo-5-methylimidazole coupled with benzeneboronic acid in the presence of tetrakis(triphenylphosphine)palladium (0) to afford the corresponding 1-benzyl-5-methyl-4-phenylimidazole (93%).[10] In the present work diazoimidazole **2** was converted into 5-bromoimidazole-4-carboxamide hydrobromide **6** with hydrobromic acid in acetic acid. (This is a more reliable synthesis and yields a fully characterised product which differs in m.p. from that reported previously).[11] However, attempted coupling of **6** with benzeneboronic acid in the presence of aqueous sodium carbonate (3.5 mol. equiv.) in refluxing DMF gave only a mixture of unreacted bromoimidazole (28%) and impure imidazole-4-carboxamide **8** (37%) (Scheme 2). This product of catalytic debromination was identified by its ^{1}H NMR spectrum, which showed weakly coupled (~ 1 Hz) signals for the imidazole H-2 and H-5 protons. Presumably, the basic conditions generate an electron-rich imidazole anion from **6** which is a poor substrate for a Suzuki reaction. Deprotonation cannot occur in the N-protected imidazoles which do couple successfully (see above).

We have shown previously that the semicarbazide **9**, prepared by ring-opening of temozolomide with ethanolic hydrazine hydrate at 25 °C, reacts with cold acetone to form the expected semicarbazone **10**; but with benzaldehyde in refluxing ethanol a semicarbazone was not formed: instead the benzylidene derivative **12a** (86%) was isolated.[11] Probably, under the reaction conditions, **9** fragments to liberate 5-aminoimidazole-4-carboxamide **1** prior to reaction with benzaldehyde since, under the same conditions **1** also gives the same benzylidene derivative **12a** (95%). By employing the commercially available hydrochloride salt of



Scheme 1 Synthesis of antitumour imidazo[5,1-*d*][1,2,3,5]tetrazines.

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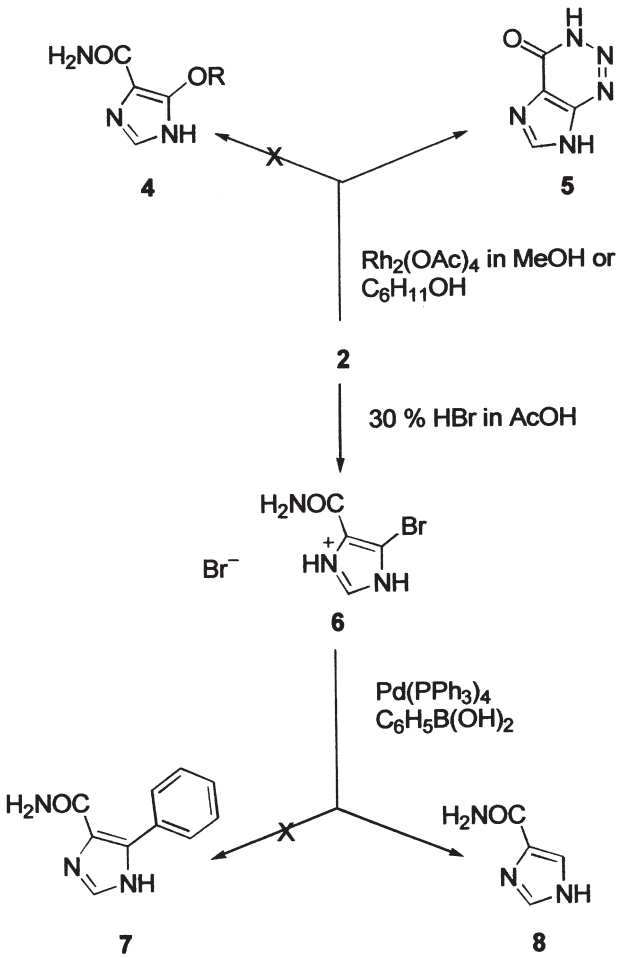
† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*



Scheme 2 Reactions of 5-diazoimidazole-4-carboxamide.

5-aminoimidazole-4-carboxamide **11** and sodium acetate trihydrate in refluxing aqueous ethanol a series of benzylidene derivatives **12a-e** were prepared from selected benzaldehydes in yields > 80% (Scheme 3). The ^{1}H NMR spectrum of the fluoro Schiff base **12d** showed a singlet at δ 9.32 for the imidazole proton and a resonance at δ 7.76 identified as the methine proton by its weak coupling to fluorine.

Attempts to effect thermal cyclisation of compounds **12b,c** to imidazo[1,5-a]quinazoline **14a** (– HNO_2 or – HCl, respectively) in a range of high-boiling solvents were unsuccessful and led only to decomposition of the substrates. The impediment to effecting this transformation lies possibly in the requirement for an *E*- to *Z*-rearrangement of the azomethine linkage prior to cyclisation. More successful to varying degrees were cyclisations of the Schiff bases **12c-d** in the presence of sodium hydride which generates the imidazole anion species **13**. Cyclisation is influenced by both temperature and the electronic influence of the 2'-substituent (Table 1). In the case of the 2′-chloro compound **12c** prolonged boiling in DMF/NaH afforded only 25% of the fluorescent (under UV) imidazoquinazoline **14a**. Following cyclisation, singlets at δ 8.99 and 9.12 are observed for the 1- and 5- (or 5- and 1-) protons of **14a**. Under similar conditions the fluoro-analogue **12d** afforded **14a** in 86% yield; at 65 °C and 25 °C yields were 61% and 0%, respectively. As expected, more reactive still was the nitro-chloro analogue **12e** which cyclised most efficiently at 65 °C, but higher temperatures led to the formation of unidentified by-products.

In an alternative approach to the synthesis of nitroimidazoquinazolines (*e.g.* **14b** or its regioisomers), **14a** was subjected to vigorous nitration conditions (90% HNO_3/concentrated H_2SO_4 at 100 °C for 24 h). The only product isolated was the carboxylic acid **15** (70%); other products, possibly nitroimidazoquinazolines, were detected (TLC). In the ^{1}H NMR spectrum of the potassium salt of **15** run in D_2O one C–H proton (δ 8.10) was observed to undergo 87% exchange in 6 days at room temperature. By analogy with deuterium exchanges in other imidazole derivatives, the structure of this product was assigned as **16**.[12]

Attempts to effect the reduction of the nitro group of Schiff base **12b** to afford amine **12f** were not successful. This amine would have been a useful precursor for azide-derived cyclisations. Thus reduction of **12b** with stannous chloride dihydrate in ethanol or ethyl acetate, or catalytic hydrogenation over palladium/charcoal, led to mixtures from which only 5-aminoimidazole-4-carboxamide **1** could be identified. With hydrazine/Raney nickel in ethanol, bis(2-aminobenzylidene)hydrazine, the azine product from the interaction of 2-aminobenzaldehyde (2 mol. equiv.) and hydrazine, was isolated (91%).[13]

In summary, this new simple two-step route to imidazo [1,5-*a*]quinazolines should be adaptable to achieve further structural diversity in a tricyclic system, derivatives of which have been reported in the patent literature to have CNS activity as anticonvulsants, anxiolytics, hypnotics, antipsychotics and antiemetics.[14,15]

Experimental

All NMR spectra were acquired on a Bruker ARX 250 instrument. Chemical shifts are referenced to the solvent as internal standard. Melting points were obtained on a Gallenkamp melting point apparatus and are uncorrected. Mass spectra were recorded on a Micromass Platform spectrometer.

Attempted synthesis of 5-alkoxyimidazole-4-carboxamides (**4**): (i) Methanol (0.18 ml) was added to a suspension of 5-diazoimidazole-4-carboxamide (**2**; 0.31 g)[16] in dry THF (30 ml) followed by rhodium (II) acetate (0.01 g) and the mixture was stirred at 25 °C under nitrogen for 76 h. ^{1}H NMR analysis of the evaporated mixture revealed it to be a mixture of starting material **2** (10%) and 2-azahypoxanthine **5** (90%) which was identical (^{1}H NMR, IR) to an authentic sample.[2]

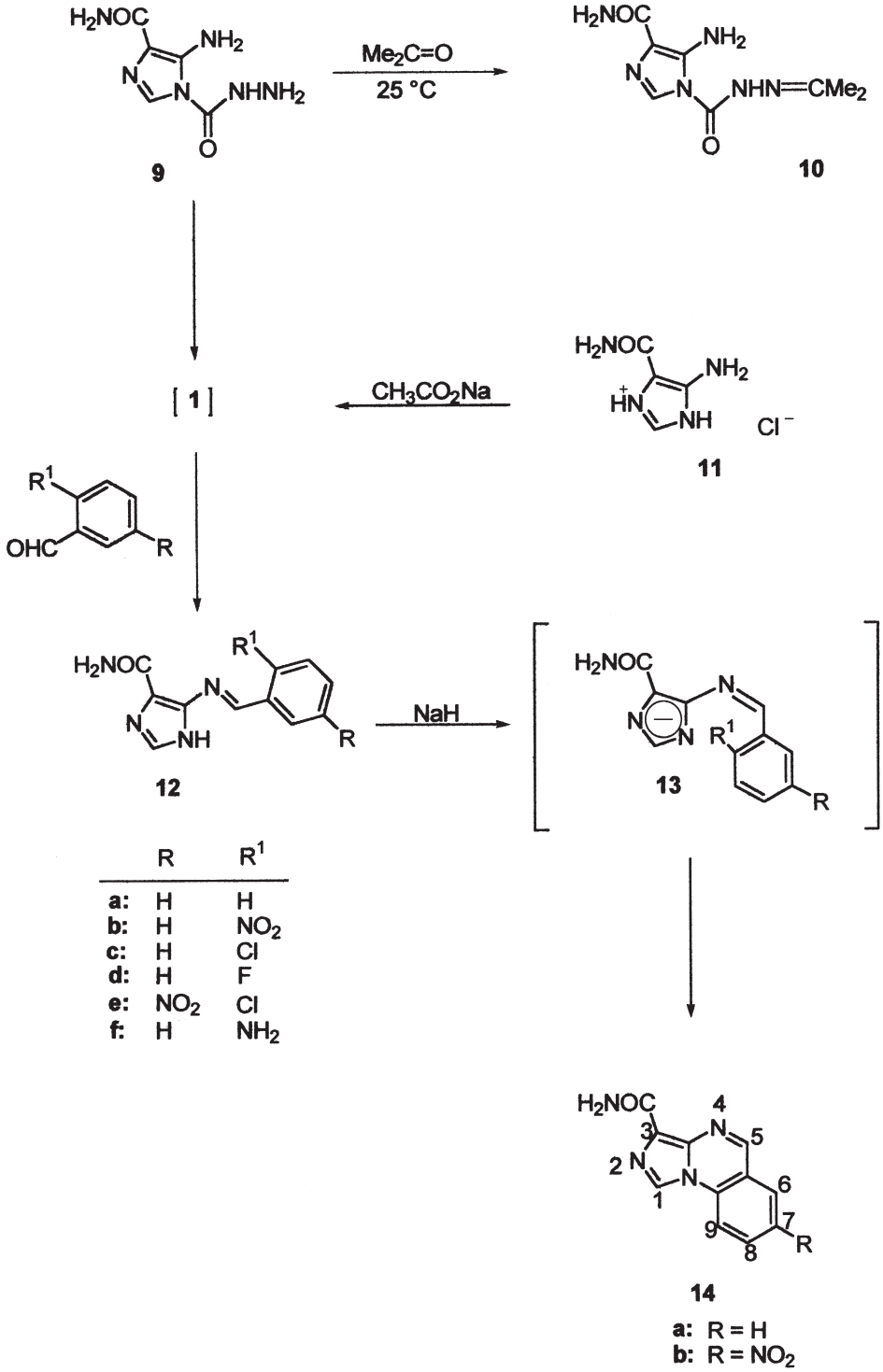
(ii) Similar reaction between **2** in DMSO (solution) or THF (suspension) with cyclohexanol in the presence of rhodium (II) acetate afforded 2-azahypoxanthine.

5-Bromoimidazole-4-carboxamide hydrobromide (**6**): A suspension of **2** (0.41 g) in acetic acid (25 ml) was treated with 30% HBr in acetic acid (9 ml) and the mixture was heated to reflux (2.5 h). The hydrobromide salt crystallised from the concentrated solution as pale brown crystals (0.44 g, 54%), m.p. 245–251 °C (Lit.,[11] 210 °C); ν_{max} (KBr) 2980, 2806, 1701, 1609, 1473, 1395, 832, 623 cm^{-1}; δ_H (DMSO-d_6) 7.21 (1H, brs, CONH), 7.71 (1H, brs, CONH), 8.13 (1H, s, H-2), 11.57 (2H, brs, protonated imidazole); δ_C (DMSO-d_6) 111.8, 124.9, 137.3, 159.6 (Found: C, 17.8; H, 1.8; N, 15.8; Br, 59.2. $C_4H_4BrN_3O$.HBr requires C, 17.7; H, 1.9; N, 15.5; Br, 59.0).

Attempted synthesis of 5-phenylimidazole-4-carboxamide (**7**): Benzeneboronic acid (0.275 g) was added to a mixture of **6** (0.55 g) and tetrakis(triphenylphosphine)palladium (0) (0.08 g) in degassed DMF (15 ml) followed by a degassed solution of Na_2CO_3 (0.765 g) in water (4 ml) and the mixture was heated to reflux under N_2 for 18 h. After removal of insoluble inorganic salts the solution was evaporated to give a gummy residue which was extracted with boiling ethyl acetate (200 ml). Saturation of this solution with HCl gas precipitated a crude mixture containing (^{1}H NMR analysis) starting material **6** (28%) and *imidazole-3-carboxamide* (**8**) (37%) (as HCl salts). Crystallisation of the mixture gave a product enriched with imidazole **8** (HCl salt) for which the following NMR signals were assigned:

δ_H (DMSO-d_6) 7.93 (1H, brs, CONH), 8.35 (1H, d, *J* 1.0 Hz, H-5), 8.56 (1H, brs, CONH), 8.22 (1H, d, *J* 1.0 Hz, H-2), 14.90 (2H, brs, protonated imidazole); δ_C (DMSO-d_6) 128.9, 135.8, 158.6.

General method for the synthesis of benzylidene derivatives of 5-aminoimidazole-4-carboxamide: A mixture of 5-aminoimidazole-4-carboxamide hydrochloride (5.0 mmol), the appropriate benzaldehyde (5.0 mmol) and sodium acetate trihydrate (4.4 mmol.)

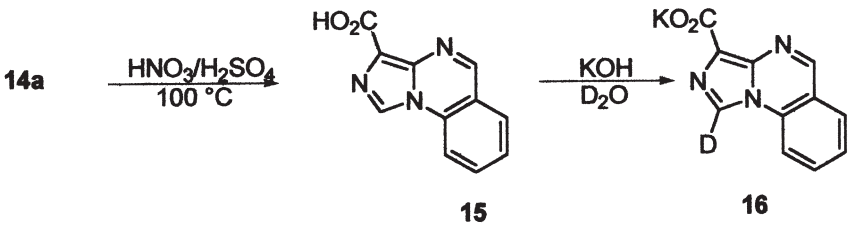


	R	R^1
a:	H	H
b:	H	NO_2
c:	H	Cl
d:	H	F
e:	NO_2	Cl
f:	H	NH_2

Scheme 3 Synthesis of imidazo[1,5-*a*]quinazolines.

was refluxed in 50% aqueous EtOH (1 h). The cooled solution deposited the benzylidene derivatives.

The following compounds were prepared: *5-(N-benzylideneamino)imidazole-4-carboxamide* (**12a**) (80%), m.p. 252 °C (decomp., from DMF) (lit.,[11] m.p. 242–245 °C); ν_{max} (KBr) 3363, 3118, 1656, 1589, 1421, 1091, 828, 685 cm^{-1}; δ_H (DMSO-d_6) 7.54 (3H, m, ArH), 7.68 (1H, brs, CONH), 7.74 (1H, s, ArC*H*=N), 7.84 (1H, brs, CONH), 7.98 (2H, m, ArH), 9.18 (1H, s, H-2), 13.06 (1H, brs, NH); δ_C (DMSO-d_6) 118.7, 128. 8, 129.0, 131.8, 135.5, 136.0, 146.8, 160.8; *m/z* (EI) 214, $C_{11}H_{10}N_4O$ requires M^+ 214; *5-[N-(2-nitrobenzylidene)amino]imidazole-4-carboxamide* (**12b**) (91%), m.p. 256 °C (decomp., from DMF); ν_{max} (KBr) 3399, 3150, 1654, 1559, 1541, 1522, 1091, 782 cm^{-1}; δ_H (DMSO-d_6) 7.53 (1H, brs, CONH), 7.78 (3H, m, CONH, ArH, ArC*H*=N), 7.87 (1H, t, *J* 7.5 Hz, ArH), 8.09 (1H, t, *J* 7.5 Hz, ArH), 8.27 (1H, t, J 7.5 Hz, ArH), 9.40 (1H, s, H-2), 13.1 (1H, brs, NH); δ_C (DMSO-d_6) 120.0, 124.6, 129.3, 130.2, 132.2, 133.6, 136.6, 146.3, 149.4, 154.1, 160.6 (Found: C, 51.9; H, 3.8; N, 27.1; M [EI], 259. $C_{11}H_9N_5O_3$ requires C, 51.0; H, 3.5; N, 27.0%; M^+ 259); *5-[N-(2-chlorobenzylidene)amino]imidazole-4-carboxamide* (**12c**) (93%), m.p. 275 °C (decomp., from DMF); ν_{max} (KBr) 3389, 3150, 1655, 1584, 1422, 1157, 837, 679 cm^{-1}; δ_H (DMSO-d_6) 7.55 (3H, m, ArH), 7.73 (2H, brs, $CONH_2$), 7.76 (1H, s, ArC*H*=N), 8.25 (1H, dd, *J* 2.0, 8.0 Hz, ArH), 9.52 (1H, s, H-2), 13.0 (1H, brs, NH); δ_C (DMSO-d_6) 119.7, 128.0, 128.6, 130.5, 132.4, 133.3, 135.3, 136.5, 146.7, 154.1, 160.8 (Found: C, 53.1; H, 3.6; N, 22.6; M [ES], 249, 251. $C_{11}H_9ClN_4O$ requires C, 53.1; H, 3.6; N, 22.5%; M^++1, 249, M^++3, 251); *5-[N-(2-fluorobenzylidene)amino]imidazole-4-carboxamide* **12d** (89%), m.p.



Scheme 4 Synthesis and deuterium exchange in potassium imidazo[1,5-*a*]quinazoline-3-carboxylate.

278 °C (decomp., from DMF); ν_{max} (KBr) 3368, 3124, 1668, 1594, 1457, 1421, 1098, 582 cm^{-1}; δ_H (DMSO-d_6) 7.38 (2H, m, ArH), 7.60 (1H, m, ArH), 7.71 (1H, brs, CONH), 7.80 (1H, brs, CONH), 7.76 (1H, d, *J* 1.0 Hz, ArC*H*=N), 8.17 (1H, m, ArH), 9.32 (1H, s, H-2), 13.0 (1H, brs, NH) (Found: C, 56.7; H, 4.1; N, 24.2; M [FAB], 233. $C_{11}H_9FN_4O$ requires C, 56.9; H, 3.9; N, 24.1%; M^++1, 233); *5-[N-(2-chloro-5-nitrobenzylidene)amino]imidazole-4-carboxamide* **12e**: (94%), m.p. 298 °C (decomp., from DMF); ν_{max} (KBr) 3407, 3181, 1678, 1586, 1530, 1350, 739, 523 cm^{-1}; δ_H (DMSO-d_6) 7.67 (1H, brs, CONH), 7.84 (1H, brs, CONH), 7.79 (1H, s, ArC*H*=N), 7.92 (1H, d, *J* 9.0 Hz, H-3'), 8.34 (1H, dd, *J* 3.0, 9.0, H-4'), 8.87 (1H, d, *J* 3.0, H-6'), 9.50 (1H, s, H-2), 12.9 (1H, brs, NH) (Found: C, 45.2; H, 3.1; N, 23.8; M [ES], 294, 296. $C_{11}H_8ClN_5O_3$ requires C, 44.8; H, 2.7; N, 23.8%; M^++1, 294, M^++3, 296).

Imidazo[1,5-a]quinazoline-3-carboxamide (**14a**): Sodium hydride (0.379 g of a 60% dispersion in mineral oil; 9.5 mmol NaH) was triturated with dry petroleum ether (30 ml) and mixed with dry DMF (60 ml). To the suspension was added *5-N-(2-fluorobenzylidene) aminoimidazole-4-carboxamide* (**12d**) (2.0 g, 8.6 mmol) and the mixture was refluxed under nitrogen for 3 h. After cooling and quenching with water (10 ml) the mixture was adjusted to neutrality with 1M-HCl. The precipitated *imidazoquinazoline* was washed with water/ethanol to furnish a yellow solid (1.56 g, 86%), m.p. 294–295 °C (decomp.) (from DMF); ν_{max} (KBr) 3436, 3154, 1665, 1612, 1548, 1424, 1228, 695 cm^{-1}; δ_H (DMSO-d_6) 7.41 (1H, brs, CONH), 7.64 (1H, brs, CONH), 7.71 (1H, t, *J* 8.0 Hz, ArH), 8.03 (1H, dt, *J* 1.0, 8.0 Hz, ArH), 8.20 (1H, dd, *J* 1.0, 8.0, ArH), 8.48 (1H, d, *J* 8.0 Hz, ArH), 8.99 (1H, s, ArH), 9.12 (1H, s, ArH); δ_C (DMSO-d_6) 116.3 (CH), 118.9 (C), 125.7 (C), 127.6 (CH), 130.4 (CH), 132.9 (C), 135.5 (CH), 136.6 (C), 153.2 (C-5), 163.9 ($CONH_2$); *m/z* (HRMS-EI) 212.0698. $C_{11}H_8N_4O$ requires 212.0698. See Table 1 for other conditions employed to synthesise **14a**.

7-Nitroimidazo[1,5-a]quinazoline-3-carboxamide (**14b**): Similarly prepared, from **12e** and sodium hydride maintained at 55–65 °C for 11 days, the *nitroimidazoquinazoline* (83%) had m.p. > 360 °C (from aq. DMF); ν_{max} (KBr) 3358, 3181, 1686, 1595, 1570, 1528, 1350, 698 cm^{-1}; δ_H (CF_3CO_2D) 9.44 (1H, d, *J* 10 Hz, H-9), 9.70 (1H, dd, *J* 3.0, 10 Hz, H-8), 9.90 (1H, d, *J* 3.0 Hz, H-6), 10.07 (1H, s, H-1/5), 10.83 (1H, s, H-5/1); δ_C (CF_3CO_2D) 116.1 (C), 118.1 (CH), 119.8 (C), 126.1)CH), 126.5 (CH), 130.6 (CH), 134.0 (C), 135.3 (C), 147.7 (C), 158.0 (CH), 159.4 ($CONH_2$) (Found: C, 51.2; H, 3.1; N, 27.0; M [ES], 358. $C_{11}H_7N_5O_3$ requires C, 51.4; H, 2.7; N, 27.2%; M^++1, 358). See Table 1 for other conditions employed to synthesise **14b**.

Imidazo[1,5-a]quinazoline-3-carboxylic acid (**15**): A solution of imidazo[1,5-*a*]quinazoline-3-carboxamide **14a** (1.0 g, 4.7 mmol) in a mixture of concentrated sulfuric acid (5 ml) and 90% nitric acid (0.5 g) was heated at 100 °C for 24 h. Dilution of the solution with ice-water furnished the yellow *carboxylic acid* (70%), m.p. 194 °C (efferv.); ν_{max} (KBr) 3401, 3160, 1705, 1603, 1549, 1317, 1175, 772 cm^{-1}; δ_H (DMSO-d_6) 7.73 (1H, t, *J* 8.0 Hz, ArH), 8.03 (1H, t, *J* 8.0 Hz, ArH), 8.21 (1H, d, *J* 8.0 Hz. ArH), 8.50 (1H, d, *J* 8.0 Hz, ArH), 9.05 (1H, s, H-5), 9.22 (1H, s, H-1); δ_C (DMSO-d_6) 115.9 (CH), 118.5 (C), 120.9 (C), 127.5 (CH), 127.6 (CH), 129.7 (CH), 132.0 (C), 135.0 (C), 137.7 (C), 154.4 (CH), 162.6 (CO_2H) (Found: C, 60.7; H, 3.7; N, 19.3. $C_{11}H_7N_3O_2$. $0.2H_2O$ requires C, 60.9; H, 3.4; N, 19.4%); *m/z* (HRMS-CI) 214.0617. $C_{11}H_8N_4O$ requires 214.0616 (M+1).

The *potassium salt* of **15**, isolated as a hydrate, had m.p. 311–313 °C (from aq. EtOH); ν_{max} (KBr) 3432, 3108, 1609, 1551, 1427, 1370, 1231, 754 cm^{-1}; δ_H (D_2O) 7.12 (1H t, *J* 7.0, ArH), 7.34 (3H, m, ArH), 8.10 (1H, s, slow exch., H-1), 8.21 (1H, s, H-5); δ_H (D_2O) 113.1 (CH), 116.6 (C), 124.8 (slow exch., C-1), 126.4 (CH), 126.8 (C), 128.2 (CH), 130.2 (C), 133.9 (CH), 134.9 (C), 151.7 (CH), 169.8 (CO_2^-) (Found: C, 46.7; H, 3.3; N, 14.6. $C_{11}H_6KN_3O_2$. $1.75H_2O$) requires C, 46.7; H, 3.4; N, 14.9%).

Table 1 Cyclisation of Schiff bases (12) to imidazo-[1,5-*a*]quinazolines (**14**) with sodium hydride – DMF

Starting material	Conditions Temp./°C	Time/h	Product	Yield/%
12c	153	30	**14a**	25
12d	25	168	**14a**	0
12d	65	100	**14a**	61
12d	153	3	**14a**	86
12e	65	264	**14b**	77
12e	100	3	**14b**	65
12e	153	0.5	**14b**	15

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