Synthesis of 1-Substituted 5-Aminoimidazole-4-carbaldehydes and 8-Amino-1-(2-fluorobenzyl)imidazo[4',5':5,6]pyrido[2,3-*d*]pyrimidine

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Abstract: The syntheses of a number of 1-substituted 5-aminoimidazole-4-carbaldehydes **3**, by the reduction of the corresponding 5-amino-4-cyanoimidazole derivatives is reported using $LiAlH(OEt)_3$, prepared in situ from $LiAlH_4$ and ethyl acetate. The compounds of type **1** are useful intermediates for the synthesis of elongated adenine derivatives.

Key words: heterocycles, imidazoles, cyanides, aldehydes, imidazo[4',5':5,6]pyrido[2,3-*d*]pyrimidines

Although a variety of conditions have been reported [1–3] for the reduction of heterocyclic nitriles to aldehydes, to our knowledge, the only reported synthesis of 5-aminoimidazole-4-carbaldehydes **3** ($R^1 = R^2 = Me$; $R^1 = Me$, $R^2 = Ph$) is by the catalytic hydrogenation of the corresponding 4-aminoimidazole-5-carbonitriles using 10% Pd/C in dilute sulfuric acid.[4] These compounds have been shown to be useful reagents for the synthesis of imidazo[4,5-*b*]pyridine derivatives.[4]

Within our research group[5] we have developed a versatile method for the synthesis of 5-amino-4-cyanoimidazoles **2** from diaminomaleodinitrile via (*Z*)-*N*-(2-amino-1,2-dicyanovinyl)formamidines **1** and it was of some interest to explore the reduction of the 5-cyano substituent in **2** to an aminomethylene group. Apart from an isolated report by Butala[6] of the parent compound **4** ($R^1 = H$), there appears to be no general synthetic method available for this transformation, perhaps because the amines are expected to be unstable. Starting from **2a** a large number of reducing agents were tried under various conditions, but all gave tars and complex mixtures of products. However, the use of lithium aluminium hydride in anhydrous THF gave a very low yield (<1%) of a product identified by NMR spectroscopy as the carboxaldehyde **3a**. The yield of this product improved considerably when small amounts of water were added to the THF solvent, but it was difficult to control the exothermic reaction and the major product was a black tar. These preliminary results did suggest that $LiAlH(OEt)_3$ might be a more suitable reducing agent. The pioneering work of Brown and Garg[7] showed that this, and related reagents, are capable of reducing cyano groups to either an aldehyde (via the imine) or an aminomethyl group, depending upon the concentration of the reducing agent. They report that reduction is favoured in diethyl ether, rather than THF or diglyme, for aldehyde formation and they imply that the strong co-ordination of the Li^+ ion to the nitrogen atom of the initially formed imine intermediate protects it from further reduction to the aminomethyl substituent.

As compounds **2a**–**f** are completely insoluble in diethyl ether, our reactions had to be carried out in THF by adding **2** to a pre-prepared solution of $LiAl(OEt)_3$ (from $LiAlH_4$ and EtOAc) in anhydrous THF. In all cases it was found necessary to use a large excess (10 equiv) of the reducing agent to maximise the yield of the carbaldehydes **3a**–**f** (Table 1). Under these conditions reaction was complete in around 10 minutes at 0 °C and moderate to high yields of the carbaldehydes were isolated after a simple dry flash chromatography (Scheme). The products were all fully characterised by ^1H, ^{13}C NMR spectroscopy and mass spectrometry (see Tables 2– 4) and a single crystal X-ray structure was carried out on compound **3f** (Figure).

Table 1 Compounds **3a**–**f** Prepared

Imidazole (mmol)	$LiAlH_4$/ EtOAc (mmol)	THF (mL)	Temp (°C), Time (min)	Product	Yield (%)
2a (7.15)	71.5:53.6	45	0–r.t., 15	**3a**	88
2b (9.75)	71.5:53.6	45	0–r.t., 15	**3b**	88
2c (1.37)	71.5:53.6	45	0–r.t., 15	**3c**	76
2d (1.87)	71.5:53.6	45	0–r.t., 15	**3d**	67
2e (8.43)	84.3:63.3	45	0–r.t., 30	**3e**	61
2f (7.15)	23.7:9.66	25	0–r.t., 30	**3f**	70

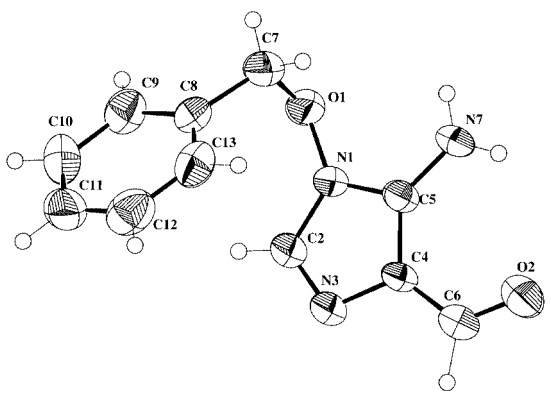

Figure X-ray crystal structure of 5-amino-1-benzyloxyimidazole-4-carbaldehyde (**3f**)

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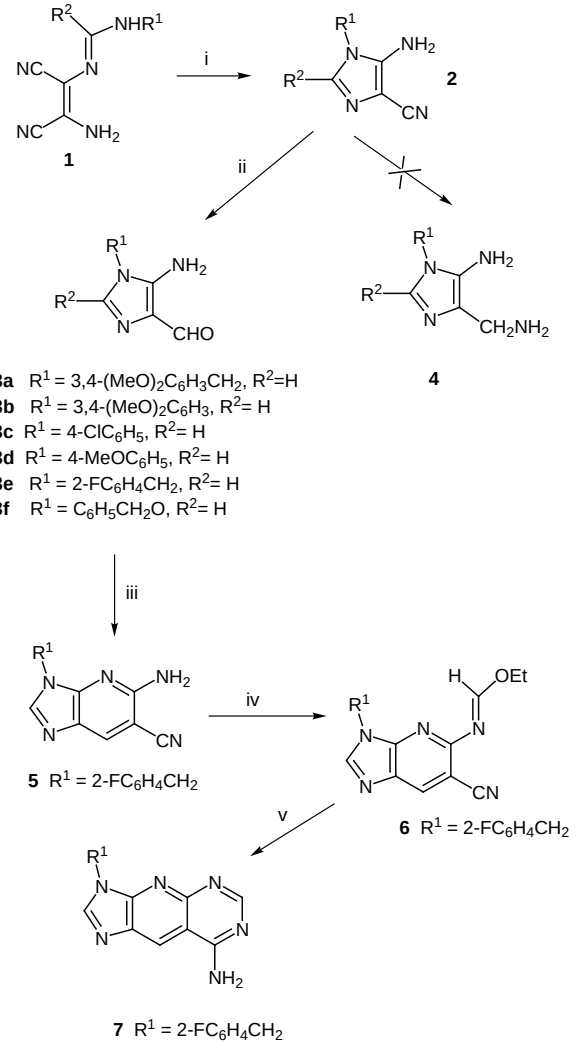

Scheme *Reagents and conditions*: (i) 1 M aq KOH, r.t.; (ii) $LiAlH_4$/EtOAc in THF (anhyd); (iii) $CH_2(CN)_2$, NaOMe in MeOH, reflux, 2.5 h; (iv) $HC(OEt)_3$, Ac_2O, reflux, 24 h; (v) NH_3, MeOH, –78 °C, 1 h

Table 2 Analytical and Mass Spectroscopic Data for Compounds **1e**, **2e**, **3a–f**, **and 5–7**

Product	Mp (°C)	MS (FAB) *m/z* (%)
1e	145	244 [(M + 1)$^+$, 100]
2e	172 (dec.)	217 (M + 1)$^+$, 81]
3a	171 (dec.)	262 [(M + 1)$^+$, 100]
3b	98 (dec.)	248 [(M + 1)$^+$, 100]
3c	170 (dec.)	222 [(M + 1)$^+$, 100]
3d	>200 (dec.)	218 [(M + 1)$^+$, 100]
3e	165 (dec.)	220 [(M + 1)$^+$, 100]
3f	110–112	218.0926 [(M + 1)$^+$, 100]; reqd. 218.0928
5	214 (dec.)	268 [(M + 1)$^+$, 60]
6	122 (dec.)	324 [(M + 1)$^+$, 74]
7	150 (dec.)	295 [(M + 1)$^+$, 100]

Table 3 ^{1}H NMR Data for Compounds **1e**, **2e**, **3a–f**, **5–7**

Product	^{1}H NMR (300 MHz, DMSO-d_6) δ, *J* (Hz)
1e	4.56 (d, 2 H, $^3J_{6,NH}$ = 5.0, H-6), 6.15 (s, 2 H, NH_2), 7.18 (m, 2 H, ArH), 7.32 (qd, 1 H, *J* = 13.3, 7.5, 2, ArH), 7.44 (td, 1 H, *J* = 8, 2, ArH), 7.73 (d, 1 H, $^3J_{5,NH}$ = 4, H-5), 8.17 (m, 1 H, NH)
2e	5.16 (s, 2 H, H-7), 6.31 (s, 2 H, NH_2), 7.05 (td, 1 H, *J* = 5, 1 Hz, ArH), 7.20 (m, 2 H, ArH), 7.37 (m, 2 H, overlapping bands, ArH and H-2)
3a	3.83 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 4.90 (s, 2 H, CH_2), 5.32 (br s, 2 H, NH_2), 6.64 (d, 1 H, *J* = 2, ArH), 6.70 (dd, 1 H, *J* = 2, 8, ArH), 6.74 (d, 1 H, *J* = 8 Hz, ArH), 7.06 (s, 1 H, H-2), 9.70 (s, 1 H, CHO)
3b	3.89 (s, 3 H, OCH_3), 3.92 (s, 3 H, OCH_3), 5.57 (br s, 2 H, NH_2), 6.83 (d, 1 H, *J* = 2, ArH), 6.91 (dd, 1 H, *J* = 2, 8, ArH), 6.98 (d, 1 H, *J* = 8, ArH), 7.11 (s, 1 H, H-2), 9.72 (s, 1 H, CHO)
3c	5.56 (br s, 2 H, NH_2), 7.12 (s, 1 H, H-2), 7.34 (d, 2 H, *J* = 8.6, ArH), 7.55 (d, 2 H, *J* = 8.6, ArH), 9.75 (s, 1 H, CHO)
3d	3.86 (s, 1 H, OCH_3), 5.52 (br s, 2 H, NH_2), 7.03 (d, 2 H, *J* = 9.1, ArH), 7.31 (s, 1 H, H-2), 7.36 (d, 2 H, *J* = 9, ArH), 9.75 (s, 1 H, CHO)
3e	5.18 (s, 2 H, H-7), 6.85 (br s, 2 H, NH_2), 7.05 (td, 1 H, *J* = 8, 1.5, H-10), 7.26 (m, 4 H, ArH + H-2), 9.47 (s, 1 H, CHO)
3f[a]	5.05 (s, 2 H, CH_2), 5.20 (br s, 2 H, NH_2), 7.42 (s, 1 H, H-2), 7.25–7.45(m, 5 H, C_6H_5), 9.55 (s, 1 H, CHO)
5	5.37 (s, 2 H, H-11), 6.76 (s, 2 H, H-7), 7.22 (m, 1 H, ArH), 8.25 (d, 2 H, overlapping bands for H-2 and H-5)
6[a]	1.45 (t, 3 H, *J* = 7.1, H-10), 4.55 (q, 2 H, *J* = 7.1, H-9), 5.44 (s, 2 H, H-11), 7.24 (m, 4 H, ArH), 8.13 (s, 1 H, H-3), 8.28 (s, 1 H, H-1) 8.32 (s, 1 H, H-8)
7	5.60 (s, 2 H, H-9), 7.20 (m, 4 H, ArH), 8.04 (br s, 2 H, H-5) 8.46 (s, 1 H, H-3), 8.77 (s, 1 H, H-1), 9.07 (s, 1 H, H-6)

[a] Measured in $CDCl_3$.

Perandones and Soto[4] have previously demonstrated the versatility of compounds of type **3** for the synthesis of imidazo[4,5-*b*]pyridine derivatives by condensation with a variety of carbonitriles, ketones and polyfunctional carbonyl compounds. We were particularly interested in the synthesis of elongated purine derivatives related to known anti-epileptic agents.[8] 6-Amino-9-benzylpurines have been reported[8] to be potent anti-epileptic agents, as well as showing anti-anginal and anti-inflammatory activity. From structure-activity relationship studies it has been established that both the 9-benzyl group (preferably 2-fluorobenzyl) and a basic group (preferably methylamino) in the 6-position are essential for activity. We are interested in exploring the dimensional restrictions of the binding sites of such drugs by extending the spatial separation of these two groups. For this reason we were interested in the synthesis of 8-amino-1-(2-fluorobenzyl)imidazo-[4',5':5,6]pyrido[2,3-*d*]pyrimidine (**7**). Such pyrido[2,3-*d*]pyrimidines have been described previously by Rams-

den et al.[9] via 5-amino-2,3-dimethyl[4,5-*b*]pyridine-6-carbonitrile, obtained in three steps from 1,2-dimethyl-5-nitroimidazole. More recently, Harris and Pendergast[10] have also prepared a number of 8-aminoimidazo[4',5':5,6]pyrido[2,3-*d*]pyrimidines from 5-aminoimidazo[4,5-*b*]pyridine-6-carbonitrile, obtained in high yield from purine by condensation with malononitrile. In our work, reaction of **3e** with malonodinitrile gave the 5-aminoimidazo[4,5-*b*]pyridine-6-carbonitrile (**5**) in 75% yield and this was converted by standard methods via **6** into **7**, which was fully characterised by spectroscopic methods (Table 2–4).

In conclusion, we have developed a new procedure for the synthesis of previously unreported 1-substituted 4-aminoimidazole-5-carbaldehydes and have shown that these can be used to prepare 5-aminoimidazo[4,5-*b*]pyridine-6-carbonitriles and extended adenine analogues. Evaluation of **7** and related compounds as anti-epileptic drugs is in progress.

Table 4 ^{13}C NMR Data for Compounds **1e**, **2e**, **3a**–**f**, **5**–**7**

Product	^{13}C NMR (300 MHz, DMSO-d_6) δ, *J* (Hz)
1e	164.5 (d, $^1J_{C\text{-}F}$ = 242.9, Ar), 154.5 (s, C-5), 134.4 (d, $^3J_{C,F}$ = 7.8, Ar), 133.3 (d, $^3J_{C,F}$ = 4.1, Ar), 129.4 (d, $^4J_{C,F}$ = 3.2, Ar), 128.3 (d, $^2J_{C,F}$ = 14.1, Ar), 121.5 (s, C-3), 120.3 (s, C-4), 119.1 (d, $^2J_{C,F}$ = 23.2, Ar), 119.1 (s, C-2), 110.1 (s, C-1), 42.1 (d, $^3J_{C,F}$ = 3.8, C-6)
2e	164.0 (d, $^1J_{C\text{-}F}$ =243.8, Ar), 152.1 (s, C-5), 136.6 (s, C-2), 134.1 (d, $^3J_{C,F}$ = 7.9, Ar), 132.6 (d, $^3J_{C,F}$ = 4.0, Ar), 128.9 (d, $^4J_{C,F}$ = 3.3, Ar), 127.4 (d, $^2J_{C,F}$ = 14.6, Ar), 121.6 (s, C-6), 119.5 (d, $^2J_{C,F}$ = 20.3, Ar), 94.5 (s, C-4), 44.9 (d, $^3J_{C,F}$ = 4.3, C-7)
3a	47.2 (C-7), 56.1 (2 × OCH_3), 110.3 (C-13), 111.7 (C-10), 119.8 (C-9), 123.3 (C-4), 126.1 (C-8), 132.9 (C-2), 146.1 (C-5), 149.8, 149.5 (C-11,12), 185.4 (C-6)
3b	56.1, 56.0 (2 × OCH_3), 108.2 (C-12), 111.6 (C-9), 117.6 (C-8), 122.1 (C-4), 125.6 (C-7), 132.2 (C-2), 145.3 (C-5), 149.7, 149.9 (C-10.11), 185.2 (C-6)
3c	132.2 (C-2), 144.6 (C-5), 154.5 (Ar) 185.6 (C-6)
3d	55.6 (OCH_3), 115.3 (Ar), 122.1 (C-4), 125.5 (C-7), 126.5 (Ar), 132.1 (C-2), 145.4 (C-5), 160.2 (Ar), 185.2 (C-6)
3e	44.2 (d, $^3J_{C,F}$ = 4.3, C-7), 119.7 (d, $^2J_{C,F}$ = 20.1, C-12), 125.6 (s, C-4), 127.6 (d, $^2J_{C,F}$ = 14.6, C-8), 128.9 ((d, $^4J_{C,F}$ = 3.2, C-10), 132.9 ((d, $^3J_{C,F}$ = 3.8, C-9), 134.1(d, $^3J_{C,F}$ = 8.0, C-11), 137.3 (s, C-2 confirmed by DEPT), 149.1 (s, C-5 confirmed by DEPT), 164.0 (d, $J_{C,F}$ = 243.9, C-13), 186.9 (s, C-6)
3f[a]	81.2 (C-7), 101.8 (C-4), 128.2, 128.4, 129.1, 129.8 (Ar), 130.1 (C-2), 141.2 (C-5), 185.6 (C-6)
6[a]	18.1 (s, C-10), 42.7 (d, $^3J_{C,F}$ = 4.0, C-11), 67.8 (s, C-9), 101.8 (s, C-3), 102.0 (s, C-4), 119.6 (d, $^2J_{C,F}$ = 20.7, C-16), 121.4 (s, C-5), 127.4 (d, $^2J_{C,F}$ = 14.6, C-12), 128.9 ((d, $^4J_{C,F}$ = 3.2, C-1-4), 134.6 (m, overlapping bands for C-13 and C-15), 135.9 (s, C-2), 151.4 (s, C-1), 151.9 (s, C-7), 160.3 (s, C-6), 164.3 (d, $J_{C,F}$ = 246.0, C-17), 164.9 (s, C-8)

[a] Measured in $CDCl_3$.

Compounds **2a**–**d**,[5] and 5-amino-4-cyano-1-benzyloxyimidazole (**2f**),[11] were prepared by procedures previously reported in the literature. ^{1}H and ^{13}C NMR spectra were recorded on a Brucker AC-300 instrument and mass spectra on a Kratos Concept 1-S instrument. IR spectra were recorded on a Perkin-Elmer 1710 FT-IR instrument.

(*Z*) –*N*^{1}-(2-Fluorobenzyl)-*N*^{2}-(amino-1,2-dicyanovinyl)formamidine (1e); Typical Procedure

2-Fluorobenzylamine (3.81 g, 30.48 mmol) was added dropwise to a suspension of pure ethyl (*Z*)-*N*-(2-amino-1,2-dicyanovinyl)formimidate (5.0 g, 30.48 mmol) in anhyd EtOH (20 mL) containing a catalytic amount of anilinium hydrochloride (0.02 g). After approximately 1 h, a pale orange solid precipitated and stirring was continued for a further 3 h when TLC confirmed that all the starting material had disappeared. The precipitate was filtered, washed with Et_2O and dried under vacuum to give 6.18 g (83%) of **1e**.

IR (KBr): 3480s (N–H), 3360s (N–H), 2240m (C≡N), 2200m (C≡N), 1640s cm^{-1} (C=N).

5-Amino-*N*^{1}-(2-fluorobenzyl)-4-cyanoimidazole (2e); Typical Procedure

A suspension of **1e** (4.0g, 16.46 mmol) in 1 M aq KOH solution (96 mL) was stirred at r.t. overnight. The white precipitate formed was filtered, washed with H_2O (5 mL) and then with Et_2O (5 mL) and dried under vacuum to give **2h** as a white solid (3.08g, 87%).

IR (KBr): 3440s (N–H), 3200s (N–H), 2220m (C≡N), 1660s cm^{-1} (C=N).

1-Substituted 5-Aminoimidazole-4-carbaldehydes 3a–f; General Procedure

A suspension of $LiAlH_4$ in anhyd THF was cooled to 0 °C. Anhyd EtOAc was added to the suspension over a period of 15 min. The mixture was then allowed to warm to r.t. and was stirred at this temperature for 1 h. Then the appropriate 5-amino-1-substituted-4-cyanoimidazole **2a**–**f** was added to the suspension over 20 min, and the mixture was stirred for a further 30 min before carefully quenching with H_2O. The mixture was extracted with $CHCl_3$ and the $CHCl_3$ layer was filtered through Celite, dried ($MgSO_4$), filtered and the solvent was evaporated to yield the title compounds, which were further purified by dry flash chromatography ($CHCl_3$–EtOH, 1:1) as eluent (Tables 1– 4).

Crystal Structure of 3f

Crystal data and refinement details for the compound **3f** are deposited with the Cambridge Crystallographic Database (CCDC 171415). The crystal was mounted on a glass fibre. All measurements were made on a Siemens R3m/v diffractometer with graphite-monochromated Mo-Kα X-radiation. The data were collected at a temperature of 23 ± 1 °C using the ω/2θ scanning technique to a maximum of 2θ values of 50.0°. The structures were solved by direct methods using MITHRIL[12] and refined using DIRDIF.[13] The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined isotropically or were included in the structure factor calculation in ideal positions, and were assigned isotropic thermal parameters which were 20% greater then the equivalent B value of the atom to which they were bonded.

5-Amino-*N*^{1}-(2-fluorobenzyl)-3*H*-imidazo[4,5-*b*]pyridine-6-carbonitrile (5)

A mixture of **3e** (0.48 g, 2.19 mmol) and malononitrile (0.14g, 2.19 mmol) in NaOMe solution (40 mg sodium in 30 mL of MeOH) was refluxed. After approximately 1 h a white solid precipitated and refluxing was continued until TLC confirmed that all the aldehyde had been consumed. The white solid was collected by filtration,

washed with H_2O followed by EtOH and dried under vacuum to give **5** (0.44g, 75%).

Ethyl *N*-[6-Cyano-3-(2-fluorobenzyl)-3*H*-imidazo[4,5-*b*]pyridine-5-yl]formimidate (6)

A mixture of **5** (0.2 g, 0.75 mmol), triethyl orthoformate (1.5 mL, 8.99 mmol, 12 mol equiv) and Ac_2O (0.42 mL, 4.49 mmol, 6 mol equiv) was refluxed for 24 h at 90 °C. After this period TLC confirmed that all the carbonitrile starting material had been consumed. The brown solution was cooled and light petroleum (bp 30–40 °C) was added dropwise to give a red precipitate. The mixture was cooled to 0 °C and was held at this temperature for several hours, before filtering off the solid, and washing it with light petroleum to give **6** (0.19 g, 79%). This was used in the next stage without further purification and no elemental analysis was obtained.

3-(2-Fluorobenzyl)-3*H*-imidazo[4',5':5,6]pyrido[2,3-*d*]pyrimidin-8-amine (7)

Compound **6** (0.185 g, 0.57 mmol) was dissolved in MeOH (100 mL) and the solution was then cooled to –76 °C before bubbling ammonia gas through the stirred solution for 1 h. After this period TLC confirmed that all the starting material had been consumed. The MeOH was removed by evaporation under reduced pressure to give the product (0.071 g, 42%) as a white solid, which was purified by washing with anhyd Et_2O (5 mL) and dried under vacuum. There was insufficient sample for elemental analysis.

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