Facile synthesis of 6-cyano-9-substituted-9*H*-purines and their ring expansion to 8-(arylamino)-4-imino-3-methylpyrimidino-[5,4-*d*]pyrimidines

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6-Cyano-9-substituted-9*H*-purines were prepared in a high yielding, one-step process by refluxing triethyl orthoformate or triethyl orthopropionate with the corresponding (*Z*)-N^1-(aryl- or benzyl)-N^2-(2-amino-1,2-dicyanovinyl)formamidines. Attempted reaction of these cyanopurines with aqueous methylamine furnished 8-(arylamino)-4-imino-3-methylpyrimidino[5,4-*d*]pyrimidines, by attack at the imidazole ring rather than addition to the 6-cyano group. All compounds have been fully characterised by spectroscopic data and an X-ray crystal structure determination has been carried out on the 8-(4-methoxyanilino)-4-imino-3-methylpyrimidino[5,4-*d*]pyrimidine.

6-Methylamino-9-benzylpurines are reported[1] 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 and a basic group in the 6 position are essential for activity. We were interested in extending these studies to investigate the activities of 9-aryl- and, particularly, 9-benzylpurines having a strongly basic carboxamidino substituent in the 6-position.

There have been a number of previous reports of 6-amidinopurines prepared by nucleophilic attack of a primary or secondary amine on a 6-cyanopurine,[2] or by treatment of a 6-cyanopurine with a catalytic amount of sodium methoxide in methanol to form an imidate intermediate, followed by addition of ammonium chloride.[3] The yields reported by this last method are only a moderate 44–51%. 6-Cyanopurines[4–12] can be synthesised by cyanide ion substitution of 6-iodo-,[4] 6-chloro,[5–8] 6-methylsulfonyl,[9–11] 6-tosyl-[12] or 6-trimethylammonio-[13] purine derivatives, or by dehydration of the 6-oxime derivatives with acetic anhydride.[14] More recently, work in our group has established that 6-cyanopurines can also be prepared either by reaction of 1-substituted-5-amino-4-(cyanoformimidoyl)imidazoles with carboxylic acid anhydrides[15] or by the reaction of formamidines **1** with 1–3 equivalents of dimethylformamide diethyl acetal in acetonitrile.[16] Although the last reaction can give good to excellent yields in many cases, in some reactions it is not always easy to isolate the cyanopurines in a pure state due either to by-product formation or to the difficulties in handling the 5-amino-4-(cyanoformimidoyl)imidazoles.

Results and discussion

The formation of 6-cyanopurines from formamidines **1** with dimethylformamide diethyl acetal suggested the possibility that a more effective procedure might be to use trialkyl orthoformates. Consequently, the previously reported[17] formamidines **1a**–**e**, together with the previously unreported formamidines **1f**–**h**, were heated under reflux with an excess of triethyl orthoformate and were found to give the 6-cyanopurines **2a**–**h** in good yields (see Table 1) by a clean precipitation after cooling the reaction mixture to room temperature. A similar reaction of triethyl orthopropionate with **1a** gave the corresponding 2-ethyl-6-cyanopurine derivative **2i**. The reactions are summarised in Scheme 1. In the case of purines **2b**, **c** and **d** precipitation was induced by the addition of petroleum ether to the cooled solution. This reaction offers a new, simple route and high yield method for the preparation of 6-cyanopurines. As far as we are aware all of the 6-cyanopurines isolated are new compounds and they have been fully characterised by elemental analysis, IR, ^{1}H/^{13}C NMR spectroscopy and mass spectrometry and details are given in Tables 1–3.

It is clear that during this reaction, cyclisation to an imidazole intermediate must occur and it is open to question whether cyclisation occurs before reaction with the triethyl ortho-formate or -propionate (path 1), or after reaction of these reagents with the formamidine (path 2, Scheme 2). From Scheme 2 it can be seen that both pathways would lead to a common intermediate. From our extensive investigations on formamidines of type **1**[17,18] we know that cyclisation to a 5-amino-4-(cyanoformimidoyl)imidazole occurs easily under base catalysis at room temperature, and that the NH of cyanoformidoyl group reacts readily with electrophiles, such as acid anhydrides. What is less certain is whether a similar reaction can occur thermally in the absence of base and, if so, the relative rate for such a reaction. We have not carried out any kinetic investigation of this reaction and this problem remains unresolved. However, it has been established that conversion of **1a** to imidazole **3a** can be achieved in 91% yield after 3 h using our reported procedure[17] of addition of a catalytic amount of DBU to an ethanol solution at room temperature. When **3** was heated under reflux with an excess of triethyl orthopropionate for 3 h, the 6-cyanopurine **2j** was isolated in 65% yield. While this experiment does not distinguish between path 1 and path 2 it does indicate that path 1 is feasible. This observation has led to an alternative synthesis for 6-cyanopurines. Thus the acid catalysed reaction of **3a** and **3b** with triethyl orthoformate gives **2a** and **2j** respectively in 91% yields (see Scheme 1).

In an effort to prepare a 6-(*N*-methylcarboxamido)purine derivative **4** a similar procedure to that described by Higashino *et al.*[2] was followed and an equimolar quantity of 6-cyano-9-(4-methoxyphenyl)-9*H*-purine **2a** was caused to react with an excess of aqueous methylamine in dichloromethane at room

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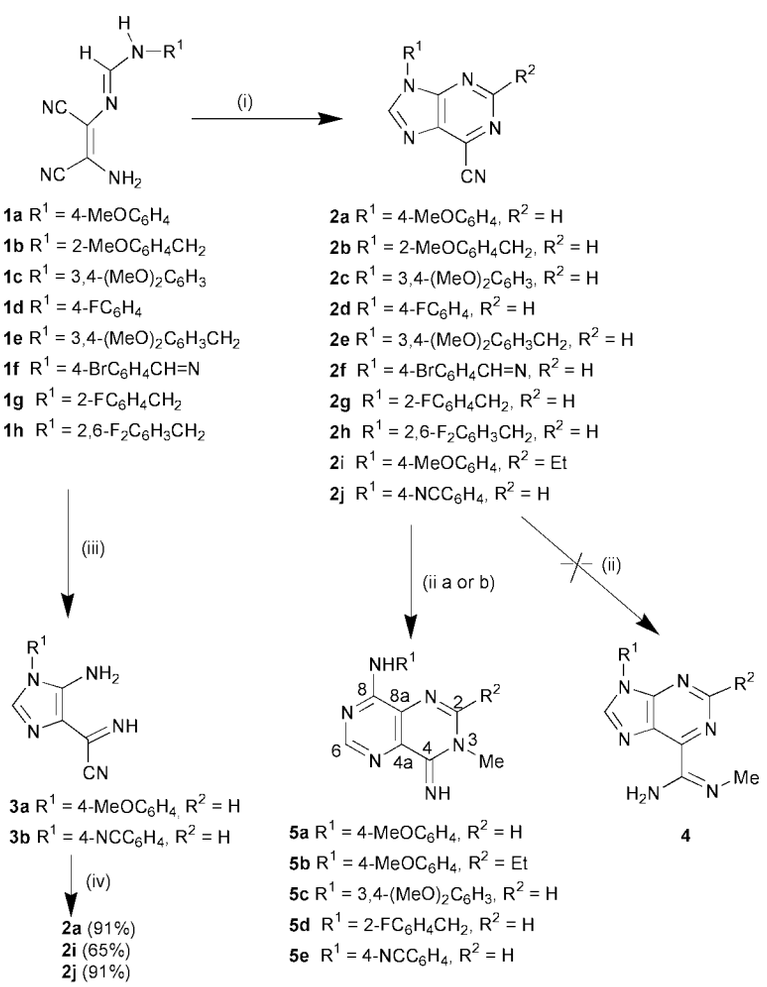
Table 1 Analytical and spectroscopic data for the compounds **1**, **2**, and **5**

Compound	Yield (%)	Mp/°C	Molecular formula	Microanalytical data (%) found (calcd)	*m/z* (M + 1)$^+$	*M*
1f	95	180–184	$C_{12}H_9N_6Br$	C, 44.9 (45.5); H, 2.6 (2.8)	317	316
1g	83	154–146	$C_{12}H_{10}N_5F$	C, 58.1 (58.3); H, 3.9 (4.1); N, 28.3 (28.8)	244	243
1h	82	115–116	$C_{12}H_9N_5F_2$	C, 54.6 (54.2); H, 3.3 (3.5), N, 26.4 (26.8)	262	261
2a	80,[a] 91[b]	178–180	$C_{13}H_9N_5O$	C, 61.6 (62.1); H, 4.0 (3.6); N, 28.5 (27.8)	252	251
2b	69	130–132	$C_{14}H_{11}N_5O$	C, 62.4 (63.2); H, 4.9 (4.2); N, 26.3 (26.4)	266	265
2c	87	160–164	$C_{14}H_{11}N_5O_2$	C, 59.0 (59.8); H, 4.4 (3.9), N, 24.8 (24.9)	282	281
2d	85	133	$C_{12}H_6N_5F$	C, 60.0 (60.2); H, 2.6 (2.5); N, 29.0 (29.3); F, 7.7 (7.9)	240	239
2e	78	152	$C_{15}H_{13}N_5O_2$	C, 61.0 (61.0); H, 4.6 (4.4); N, 23.4 (23.7)	296, 38%[c]	295
2f	91	195–198	$C_{13}H_7N_6Br$	C, 48.0 (47.8); H, 1.9 (2.1); N, 25.5 (25.7)	327	326
2g	87	104–105	$C_{13}H_8N_5F$	C, 61.6 (61.7); H, 3.4 (3.2); N, 27.7 (27.6)	254	253
2h	89	142–143	$C_{13}H_7N_5F_2$	C, 57.6 (57.6); H, 2.6 (2.6); N, 25.8 (25.8); F, 14.0 (13.6)	272	271
2i	96,[a] 65[d]	161–162	$C_{15}H_{13}N_5O$	C, 64.4 (64.5); H, 4.6 (4.6); N, 25.0 (25.0)	280	279
2j	91[b]	228–229	$C_{13}H_6N_6$	C, 63.4 (63.3); H, 2.6 (2.4); N, 33.8 (34.1)	246[f]	246
5a	86[e,h]	250	$C_{14}H_{14}N_6O$	C, 59.6 (59.5); H, 5.1 (4.9); N, 29.7 (29.7)	283	282
5b	72[e]	168–170	$C_{15}H_{16}N_6O_2$	Accurate mass 312.1338 (312.13346)[g]	313	312
5c	98[e]	180	$C_{16}H_{18}N_6O$	C, 61.1 (61.9); H, 5.8 (5.8); N, 27.7 (27.1)	311	310
5d	67[e]	190–192	$C_{14}H_{13}N_6F$	Accurate mass 284.1179 (284.11856)[g]	285	284
5e	99[e]	Above 300	$C_{14}H_{11}N_7$	C, 60.75 (60.65); H, 3.91 (3.97); N, 35.33 (35.38)	277[f]	277

[a] Method A (direct from amidine **1a**). [b] From imidazole **3** with acid catalysis. [c] (M − $C_6H_2N_5$) 100%. [d] Method B (through imidazole **3**). [e] Using $MeNH_2$ (aq) and dichloromethane. [f] By EI. [g] Despite many attempts these compounds could not be obtained analytically pure, probably due to solvent association; they were both pure by TLC (1 : 1 CH_2Cl_2–EtOAc). [h] Excess $MeNH_2$ gas in dichloromethane at 0 °C.

temperature. The reaction was monitored carefully by TLC (1 : 1 dichloromethane–ethyl acetate) and after 24 h the reaction was complete and gave a 69% yield of **5a** as a crystalline, white solid. An improved yield of **5a** (86%) was obtained by bubbling methylamine gas through a solution of **2a** in dichloromethane at 0 °C. Reactions of the cyanopurines **2i**, **c**, and **g** gave the analogous products **5b–d** also in high yields. Under the conditions of method B, compound **2j** reacts to give **5e** in 94% isolated yield after 18 h at room temperature. When this last reaction was carried out in ethanol rather than dichloromethane the rate of reaction was slower, but an improved yield of 99% of **5e** was obtained. The analytical and spectroscopic information on these products is given in Tables 1–3. The spectroscopic data showed several anomalies, which indicated that



Scheme 1 (i) Excess $HC(OEt)_3$ or $EtC(OEt)_3$ under reflux; (ii) either (a) excess $MeNH_2$ (aq) in dichloromethane at rt or (b) excess $MeNH_2$ (gas) in dichloromethane at 0 °C; (iii) cat. DBU, ethanol, rt; (iv) either (a) excess $EtC(OEt)_3$ under reflux or (b) $HC(OEt)_3$ under reflux, H^+ cat., CH_3CN at rt.

Table 2 ^{1}H NMR spectroscopic data for the compounds **1**, **2**, and **5**[a]

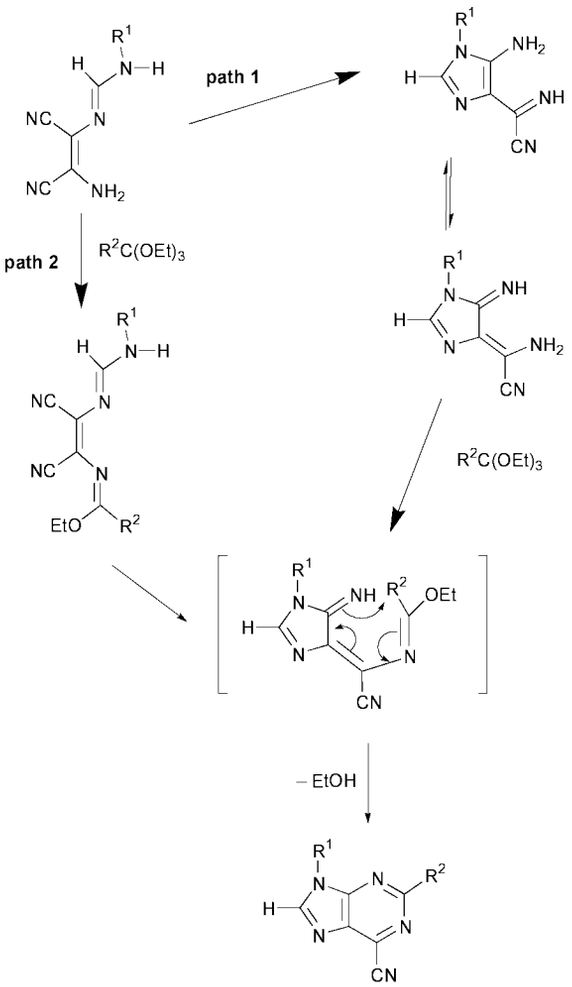
Compound	δ_H (ppm)
1f[c]	3.62 (br s, 2H, NH_2), 6.7 (br s, 1H, NH), 7.68 (d, 2H, ^3J 8.5 Hz, ArH), 7.85 (d, 2H, ^3J 8.5 Hz, ArH), 8.26 (s, 1H, CH–)
1g[d,d]	4.56 (d, 2H, $^3J_{6,NH}$ 5.0 Hz, 6-H), 6.15 (s, 2H, NH_2), 7.18 (m, 2H, ArH), 7.32 (ddd, 1H, $^3J_{H,F}$ 13.3, $^3J_{H,H}$ 7.5, $^4J_{H,H}$ 2 Hz, ArH), 7.44 (td, 1H, J 8, 2 Hz, ArH), 7.73 (d, 1H, $^3J_{5,NH}$ 4 Hz, 5-H), 8.17 (m, 1H, NH)
1h[b,d]	4.55 (d, 2H, $^3J_{5,NH}$ 5.5 Hz, 6-H), 6.44 (s, 2H, NH_2), 7.08–7.36 (m, 3H, ArH), 7.74 (d, 1H, $^3J_{5,NH}$ 3.43 Hz, 5-H), 8.18 (m, 1H, NH)
2a[c]	3.98 (s, 3H, OMe), 7.2 (d, 2H, J 8 Hz, ArH), 7.63 (d, 2H, J 8 Hz, ArH), 8.6 (s, 1H, 8-H), 9.22 (s, 1H, 2-H)
2b[c]	3.8 (s, 3H, OMe), 5.38 (s, 2H, CH_2), 6.9–7.96 (complex m, 4H, ArH), 8.3 (s, 1H, 8-H), 8.98 (s, 1H, 2-H)
2c[c]	3.98 (s, 3H, OMe), 4.00 (s, 3H, OMe), 7.00–7.20 (m, 3H, ArH), 8.5 (s, 1H, 8-H), 9.17 (s, 1H, 2-H)
2d[d]	7.45 (dd, J 9, 7.8 Hz, ArH), 7.82 (dd, J 9, 4.5 Hz, ArH), 8.5 (s, 1H, 8-H), 9.1 (s, 1H, 2-H)
2e[c]	3.86 (s, 3H, OMe), 3.90 (s, 3H, OMe), 5.45 (s, 2H, CH_2), 6.80–7.00 (m, 3H, ArH), 8.3 (s, 1H, 8-H), 9.1 (s, 1H, 2-H)
2f[b,c]	7.88 (d, 2H, J 8.2 Hz, ArH), 8.09 (d, 2H, J 8.2 Hz, ArH), 8.89 (s, 1H, 8-H), 9.00 (s, 1H, H-C=N), 9.60 (s, 1H, 2-H)
2g[b,d]	5.74 (s, 2H, CH_2), 7.11 (ddd, 1H, $^3J_{H,F}$ 9.4, $^3J_{H,H}$ 7.56, $^4J_{H,H}$ 2 Hz, ArH), 7.16 (ddd, 1H, $^4J_{H,F}$ 6, $^3J_{H,H}$ 7.56, $^4J_{H,H}$ 2 Hz, ArH), 7.36 (m, 1H, $^3J_{H,H}$ 7.56, $^3J_{H,H}$ 7.43, $^4J_{H,F}$ 5.8, $^4J_{H,H}$ 2 Hz, ArH), 7.45 (ddd, 1H, $^3J_{H,H}$ 7.43, $^3J_{H,H}$ 7.56, $^4J_{H,H}$ 2 Hz, ArH), 8.56 (s, 1H, 6-H), 9.26 (s, 1H, 2-H)
2h[b,c]	5.66 (s, 2H, CH_2), 7.14–7.46 (m, 3H, ArH), 8.37 (s, 1H, 8-H), 9.09 (s, 1H, 2-H)
2i[c]	1.25 (t, 3H, J 7.4 Hz, Me), 3.07 (q, 2H, J 7.4 Hz, CH_2), 3.83 (s, 3H, OMe), 7.08 (d, 2H, J 8 Hz, ArH), 7.56 (d, 2H, J 8 Hz, ArH), 8.36 (s, 1H, 8-H)
2j[c]	8.16 (d, 2H, J 9.0 Hz, ArH), 8.22 (d, 2H, J 9.0 Hz, ArH), 9.23 (s, 1H, 8-H), 9.46 (s, 1H, 2-H)
5a[d]	3.45 (s, 3H, NMe), 3.88 (s, 3H, OMe), 6.87 (d, 2H, J 8.5 Hz, ArH), 7.57 (d, 2H, J 8.5 Hz, ArH), 7.68 (s, 1H, 6-H), 8.18 (s, <2H, NH_2), 8.55 (s, 1H, 2-H)
5b[d]	1.34 (t, 3H, J 7.56 Hz, Me), 2.82 (q, 2H, J 7.56 Hz, CH_2), 3.42 (s, 3H, NMe), 3.76 (s, 3H, OMe), 6.87 (d, 2H, J 9.0 Hz, ArH), 7.58 (s, 1H, 6-H), 7.71 (d, 2H, J 9.0 Hz, ArH), 8.10 (s, 1H, NH), 8.44 (br s, 1H, NH)
5c[b,d]	3.45 (s, 3H, NMe), 3.85 (s, 3H, OMe), 3.90 (s, 3H, OMe), 6.80 (d, 1H, J 8.64 Hz, ArH), 7.35 (dd, 1H, J 2.34, 8.8 Hz, ArH), 7.51 (d, 1H, J 2.34 Hz, ArH), 8.14 (s, 1H, 6-H), 8.46 (br s, 1H, NH), 8.5 (s, 1H, NH), 9.43 (s, 1H, 2-H)
5d[d]	3.54 (s, 3H, NMe), 4.83 (d, 2H, J 6 Hz, CH_2), 5.60 (br s, 1H, NH), 6.80 (br s, 1H, NH), 7.35 (complex m, overlapping signals for 2H, ArH), 7.27 (m, 1H, J 1.52, ~6, 6.8 Hz, ArH), 7.39 (ddd, 1H, J 1.52, 7.47, 7.54 Hz, ArH), 7.70 (s, 1H, 6-H), 8.54 (s, 1H, 2-H)
5e[d]	3.82 (s, 3H, NMe), 7.87 (d, 2H, J 6.9 Hz, ArH), 8.25 (d, 2H, J 6.9 Hz, ArH), 8.81 (s, 1H, H-2), 8.91 (s, 1H, H-6), 10.10 (br s, 1H, NH), 10.57 (s, 1H, NH), 10.81 (s, 1H, NH)

[a] All spectra were determined in $CDCl_3$ except where stated. [b] In d_6-DMSO. [c] Determined at 300 MHz. [d] Determined at 400 MHz.

Table 3 ^{13}C NMR spectroscopic data for the compounds **1**, **2**, and **5**[a]

Compound	δ_C (ppm)
1f[d]	161.0 (6-C), 159.8 (5-C), 132.7 (Ar), 132.0 (Ar), 125.7 (Ar), 122.4 (1-C), 117.3 (4-C), 116.5 (3-C), 102.6 (2-C)
1g[b,e]	164.5 (d, $^1J_{C-F}$ 242.9 Hz, Ar), 154.5 (s, 5-C), 134.4 (d, $^3J_{C,F}$ 7.8 Hz, Ar), 133.3 (d, $^3J_{C,F}$ 4.1 Hz, Ar), 129.4 (d, $^4J_{C,F}$ 3.2 Hz, Ar), 128.3 (d, $^2J_{C,F}$ 14.1 Hz, Ar), 121.5 (s, 3-C), 120.3 (s, 4-C), 119.1 (d, $^2J_{C,F}$ 23.2 Hz, Ar), 119.1 (s, 2-C), 110.1 (s, 1-C), 42.1 (d, $^3J_{C,F}$ 3.8 Hz, 6-C)
1h[b,c]	161.6 (d, $^1J_{C,F}$ 241.8, $^3J_{C,F}$ 1.7 Hz, Ar), 161.0 (d, $^1J_{C,F}$ 239.0, $^2J_{C,F}$ 25.1 Hz, Ar), 131.6 (dd, $^3J_{C,F}$ 7.6, $^3J_{C,F}$ 7.5 Hz, Ar), 120.6 (dd, $^2J_{C,F}$ 24.4, $^2J_{C,F}$ 25.1 Hz, Ar), 119.4 (d, $^2J_{C,F}$ 24.2 Hz, Ar), 119.3 (d, $^2J_{C,F}$ 24.2 Hz, Ar), 119.1 (s, 4-C), 109.8 (s, 1-C), 100.9 (s, 1-C), 41.8 (d, $^3J_{C,F}$ 2.7 Hz, 6-C)
2a[d]	160.3 (C_p), 153.3 (2-C), 152.8 (4-C), 147.4 (8-C), 135.3 (6-C), 131.5 (5-C), 125.9 (C_i), 125.4 (C_m), 115.4 (C_o), 114.9 (CN), 55.8 (OMe)
2b[d]	160.9 (C_o), 152.1 (2-C), 150.3 (4-C), 148.1 (8-C), 133.3 (6-C), 131.2 (5-C), 129.0 (C_p), 126.9 (C_o), 122.6 (C_i), 120.5 (C_m), 114.2 (CN), 113.3 (C_m), 58.9 (OMe), 46.2 (CH_2)
2c[d]	155.4, 155.1 (C_p, C_m), 151.9 (2-C), 150.2 (4-C), 148.2 (8-C), 142.5 (C_i), 135.2 (6-C), 130.2 (5-C), 117.5 (C_o), 116.5 (C_m), 116.2 (C_o), 113.5 (CN), 53.3 (OMe), 51.2 (OMe)
2d[e]	163.5 (d, J 243 Hz, C_p), 153.3 (2-C), 152.1 (4-C), 147.0 (8-C), 135.2 (6-C), 135.0 (d, J 2.2 Hz, C_i), 131.8 (5-C), 131.5 (d, J 7.5 Hz, C_o), 121.2 (d, J 21.5 Hz, C_m), 113.4 (CN)
2e[d]	154.2, 154.4 (C_p, C_m), 152.9 (2-C), 152.2 (4-C), 148.0 (8-C), 135.0 (6-C), 132.6 (C_i), 130.7 (5-C), 126.3 (C_o), 115.6 (C_o), 115.3 (C_m), 113.7 (CN), 56.0 (OMe), 55.9 (OMe), 47.9 (CH_2)
2f[b,d]	167.8 (C=N), 152.6 (2-C), 152.4 (4-C), 147.8 (8-C), 136.5 (C_i), 134.6 (6-C), 132.7 (C_m), 129.7 (5-C), 128.3 (C_p), 124.2 (C_o), 114.3 (CN)
2g[b,e]	160.9 (d, $^1J_{C,F}$ 247.7 Hz, Ar), 153.2 (s, 2-C), 152.9 (s, 4-C), 148.1 (s, 8-C), 134.8 (s, 6-C), 131.4 (d, $^3J_{C,F}$ 8.2 Hz), 131.1 (d, $^3J_{C,F}$ 3.5 Hz, Ar), 124.9 (d, $^4J_{C,F}$ 3.7 Hz, Ar), 121.3 (d, $^2J_{C,F}$ 14.6 Hz, Ar), 116.1 (d, $^2J_{C,F}$ 21.1 Hz, Ar), 113.6 (CN), 41.9 (d, $^3J_{C,F}$ 4.1 Hz, CH_2)
2h[b,d]	162.9 (dd, $^1J_{C,F}$ 249, $^3J_{C,F}$ 7.5 Hz, Ar), 159.6 (dd, $^1J_{C,F}$ 249, $^3J_{C,F}$ 7.5 Hz, Ar), 159.0 (s, 2-C), 151.0 (s, 4-C), 132.0 (dd, $^2J_{C,F}$ 22.7, $^4J_{C,F}$ 3.8 Hz, Ar), 131.7 (dd, $^2J_{C,F}$ 22.7, $^4J_{C,F}$ 3.8 Hz, Ar), 129.3 (s, 5-C), 114.5 (CN), 112.4 (dd, $^2J_{C,F}$ 22.7, $^3J_{C,F}$ 7.5 Hz, Ar), 111.2 (t, $^2J_{C,F}$ 22.7 Hz, Ar), 42.1 (d, $^3J_{C,F}$ 3.8 Hz, CH_2)
2i[d]	160.0 (C_p), 153.6 (2-C), 152.4 (4-C), 146.6 (8-C), 135.9 (6-C), 129.1 (5-C), 125.2 (C_i), 123.8 (C_m), 115.3 (C_o), 114.9 (CN), 55.7 (OMe), 22.6 (CH_2), 11.2 (Me)
2j[b,d]	153.0 (2-C), 152.6 (4-C), 149.1 (8-C), 137.4 (Ar), 135.8 (6-C), 133.9 (Ar), 129.4 (5-C), 123.9 (Ar), 118.1 (CN), 114.1 (CN), 110.9 (Ar)
5a[e]	167.6 (8-C), 156.7 (C_p), 153.3 (4-C), 153.0 (6-C), 147.3 (2-C), 138.3 (4a-C), 131.1 (8a-C), 125.7 (C_i), 122.5 (C_o), 114.4 (C_m), 55.6 (OMe), 34.7 (NMe)
5b[e]	169.3 (8-C), 156.8 (C_p), 152.7 (4-C), 150.2 (6-C), 146.2 (2-C), 136.2 (4a-C), 131.8 (8a-C), 123.3 (C_i), 121.2 (C_o), 114.1 (C_m), 55.5 (OMe), 36.1 (NMe), 32.7 (Me), 12.5 (CH_2)
5c[b,e]	168.7 (8-C), 156.2, 155.9 (C_m, C_p), 152.2 (4-C), 151.7 (6-C), 148.5 (2-C), 141.5 (C_i), 135.5 (4a-C), 129.2 (8a-C), 116.6 (C_o), 116.3 (C_m), 115.2 (C_o), 59.5, 59.3 (2 × OMe), 39.3 (NMe)
5d[e]	166.8 (8-C), 159.3 (d, J 246.3 Hz, C_o), 153.5 (4-C), 151.4 (6-C), 147.9 (2-C), 138.4 (4a-C), 130.4 (d, J 3.4 Hz, C_o), 129.9 (8a-C), 129.8 (d, J 8.4 Hz, C_p), 125.8 (d, J 14.6 Hz, C_i), 124.7 (d, J 3.6 Hz, C_m), 116.0 (d, J 21.4 Hz, C_m), 39.1 (d, J 8.64 Hz, CH_2), 36.6 (NMe)
5e[c,e]	156.4 (4-C′), 156.3 (2-C), 155.2 (8-C), 147.0 (6-C), 142.4 (8a-C), 134.4 (C′), 132.9 (C_m), 128.7 (4a-C), 121.9 (C_o), 119.0 (CN), 106.0 (C_p)

[a] Except where stated all spectra were determined in $CDCl_3$. [b] In d_6-DMSO. [c] In d_6-DMSO–TFA. [d] Determined at 70 MHz. [e] Determined at 100 MHz.



Scheme 2 Possible mechanisms for 6-cyanopurine formation.

these products were not 6-carboxamidinopurines of type **4**. In the ^{1}H NMR spectrum (see Table 2) for the compounds **5a** and **b** there is a distinct upfield shift of the *ortho* protons of the 4-methoxyphenyl ring, when compared with the equivalent cyanopurine **2a** and this cannot be explained on the basis of minor functional group changes in the 6-position, also there are substantial changes in the chemical shifts of the heterocyclic ring protons which are unexpected. The literature on the reactions of 6-cyanopurines with amines is confusing in that, as mentioned previously, Higashino *et al.*[2] report that 9-phenyl-9*H*-purine-6-carbonitrile reacts with butylamine and piperidine to give around a 50% yield of the corresponding *N*-butyl-9-phenyl-9*H*-purine-6-carboxamidine and 9-phenyl-6-(piperidinylcarboxymidoyl)-9*H*-purine by nucleophilic attack on the cyano group. Conversely, the Robins group[11,19,20] have shown that reaction of 9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)purine-6-carbonitrile with methanolic ammonia results in attack at the imidazole ring with rearrangement to give a 4-amino-8-(β-D-ribofuranosylamino)pyrimidino[5,4-*d*]pyrimidine in unspecified yield, and a similar rearrangement in around 17% yield has been noted by Mabry *et al.*[21] during the reaction of 9-(3,5-di-*O*-benzoyl-2,2-difluoro-2-deoxy-α/β-D-ribofuranosyl)purine-6-carbonitrile with ammonium hydroxide in methanol. This follows an earlier patent by Cook and Berry[22] which describes the isolation of ribofuranosylpyrimidino[5,4-*d*]pyrimidines in 75% yield on reaction of the corresponding purine-6-carbonitrile with methanolic ammonia in a pressure vessel at 0–18 °C. Thus the product from the reaction with methylamine could be either the 6-carboxamidine derivative **4** or the pyrimidino[5,4-*d*]-pyrimidine derivative **5**. These compounds are constitutional isomers and cannot be distinguished by elemental analysis or mass spectrometry and it is difficult to distinguish between the

Table 4 Selected bond lengths (Å) and angles (°) for the compound 8-(4-methoxyanilino)-4-imino-3-methylpyrimidino[5,4-*d*]pyrimidine

Bond lengths/Å		Bond angles/°	
N(1)–C(2)	1.370(5)	C(2)–N(1)–C(6)	120.7(3)
N(1)–C(6)	1.413(4)	C(2)–N(1)–C(11)	120.5(3)
N(1)–C(11)	1.467(5)	C(6)–N(1)–C(11)	118.6(3)
N(3)–C(2)	1.277(4)	C(2)–N(3)–C(3A)	116.0(3)
N(3)–C(3A)	1.388(5)	C(8)–N(7)–C(7A)	114.0(3)
N(7)–C(8)	1.311(5)	C(8)–N(9)–C(8)	115.0(3)
N(7)–C(7A)	1.367(5)	C(10)–N(13)–C(14)	132.0(4)
N(9)–C(8)	1.360(5)	C(21)–O(20)–C(17)	119.1(5)
N(12)–C(6)	1.283(4)	N(3)–C(2)–N(1)	126.7(4)
N(13)–C(10)	1.357(5)	C(7A)–C(3A)–N(3)	123.3(3)
O(20)–C(21)	1.360(7)	C(7A)–C(3A)–C(10)	117.1(3)
O(20)–C(21)	1.360(7)	N(3)–C(3A)–C(10)	119.6(3)
O(20)–C(17)	1.361(5)	N(12)–C(6)–N(1)	118.6(3)
C(3A)–C(7A)	1.382(5)	N(12)–C(6)–C(7A)	113.7(3)
C(3A)–C(10)	1.410(5)	N(7)–C(7A)–C(3A)	122.9(3)
C(6)–C(7A)	1.458(5)	N(7)–C(7A)–C(6)	117.6(3)
C(14)–C(15)	1.386(6)	C(3A)–C(7A)–C(6)	119.5(3)
C(14)–C(19)	1.396(5)	N(7)–C(8)–N(9)	129.6(4)
C(15)–C(16)	1.381(6)	N(9)–C(10)–N(13)	120.1(3)
C(16)–C(17)	1.387(6)	N(9)–C(10)–C(3A)	121.4(4)
C(17)–C(18)	1.378(7)	N(13)–C(10)–C(3A)	118.5(3)
C(18)–C(19)	1.365(6)	C(15)–C(14)–C(19)	118.4(4)
		C(15)–C(14)–N(13)	125.1(4)
		C(19)–C(14)–N(13)	116.6(4)
		C(16)–C(15)–C(14)	120.4(5)
		C(15)–C(16)–C(17)	121.0(4)
		O(20)–C(17)–C(18)	116.3(5)
		O(20)–C(17)–C(16)	125.5(4)
		C(18)–C(17)–C(16)	118.2(4)
		C(19)–C(18)–C(17)	121.5(5)
		C(18)–C(19)–C(14)	120.6(4)

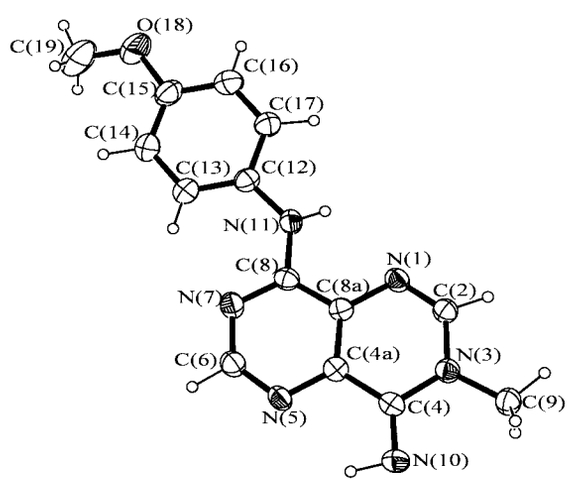
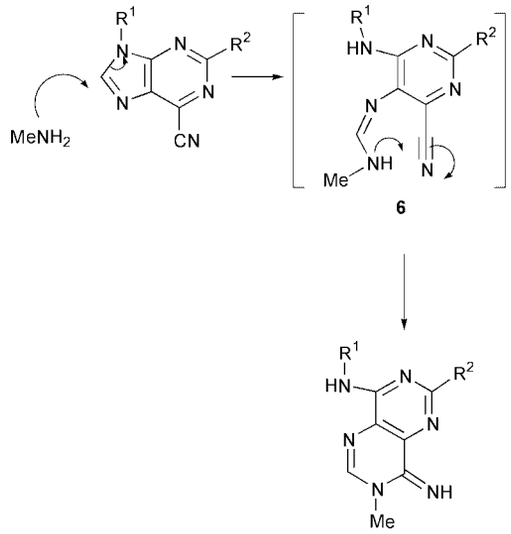


Fig. 1

two possibilities by spectroscopic methods. A single crystal X-ray structure determination on the compound **5a** confirmed that the compound was the rearrangement product 8-(4-methoxyanilino)-4-imino-3-methylpyrimidino[5,4-*d*]pyrimidine (Fig. 1, Table 4) arising by initial opening of the imidazole ring as shown in Scheme 3. Our observations lead to the conclusion that the reactions of 9-aryl-9*H*-purine-6-carbonitriles with aqueous methylamine lead invariably to the pyrimidino[5,4-*d*]-pyrimidine rearrangement products with no evidence for the formation of a 6-carboxamidinopurine derivative by nucleophilic attack on the 6-cyano group.

These results, together with the earlier work referred to above, throw into question the reports of Higashino *et al.*,[2] as it would appear unlikely that purine-6-carboxamidine derivatives can be prepared from 6-cyanopurines by direct reaction with ammonia or amine nucleophiles, although the Hocek procedure[3] *via* the imidate does appear to be a reliable method for the synthesis of 6-amidinopurines.



Scheme 3 Mechanism of formation of 8-(arylamino)-4-imino-3-methylpyrimidino[5,4-*d*]pyrimidine.

In conclusion we report a facile synthesis of 6-cyanopurines and we have established that in the case of the N^9-aryl and benzyl derivatives the reaction of a simple amine, such as methylamine, occurs by opening of the imidazole ring leading to pyrimidine[5,4-*d*]pyrimidines in good yields.

Experimental

The (*Z*)-N^1-(2-amino-1,2-dicyanovinyl)-N^2-aryl and -benzylformamidines and the 5-amino-1-aryl-4-(cyanoformimidoyl)-imidazole used in this work were prepared from previously described procedures.[16,17] ^{1}H NMR spectra were recorded on either a Bruker AC 300 or 400 spectrometer at 300 or 400 MHz respectively. ^{13}C NMR spectra were recorded on either a Bruker AC 300 or 400 spectrometer at 75 or 100 MHz respectively. Mass spectra (FAB) were recorded on a Kratos MS-45 instrument with a digital data output. Melting points were determined using a Gallenkamp melting point apparatus and are uncorrected. TLC was performed using Camlab polygram C_{245} pre-coated silica gel plates (Fluka).

Crystallography

The crystals were mounted on a glass fibre. All measurements were performed on a Rigaku AFC6S diffractometer employing graphite monochromated Cu-Kα radiation. The data were collected at a temperature of 20 ± 1 °C using the ω scanning technique to a maximum of a 2θ value of 65.17°. The structures were solved by direct methods using SHELX86[23] and refined by full-matrix least squares based on *F* using SHELX93.[24] Non-hydrogens were refined anisotropically. Hydrogen atoms were located geometrically and were refined isotropically.

Crystal data.† $C_{14}H_{14}N_6O$, M = 283.31, orthorhombic, a = 30.542(9), b = 12.114(2), c = 7.3571(10) Å, V = 2722.1(10) Å^3, space group *Pbca*, Z = 8, D_x = 1.378 g cm^{-3}. Crystal dimensions 0.35 × 0.35 × 0.02 mm^3, μ(Mo-Kα) = 0.767 mm^{-1}, 4659 reflections measured, 2317 unique (R_{int} = 0.1181) which were used in all calculations, and 1019 reflections [$I > 2\sigma(I)$]. The final $\omega R(F^2)$ was 0.1656 (all data).

Synthesis of (*Z*)-N^1-(4-bromobenzylidene)-N^2-(2-amino-1,2-dicyanovinyl)formamidrazone 1f

(*Z*)-*N*-(2-Amino-1,2-dicyanovinyl)formamidrazone[25] (2.0 g, 13.3 mmol) and 4-bromobenzaldehyde (2.44 g, 13.3 mmol) were stirred at room temperature in methanol (15 cm^3) for 50 min to give the title compound **1f** (4.0 g, 12.6 mmol, 95%) as a yellow powder.

Synthesis of (*Z*)-N^1-(2-fluorobenzyl)-N^2-(amino-1,2-dicyanovinyl)formamidine 1g

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 dry ethanol (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 hours when TLC (1 : 1 EtOAc–hexane) confirmed that all the starting material had disappeared. The precipitate was filtered, washed with diethyl ether and dried under vacuum to give **1g** (6.18 g, 25.43 mmol, 83%).

Synthesis of (*Z*)-N^1-(2,6-difluorobenzyl)-N^2-(2-amino-1,2-dicyanovinyl)formamidine 1h

Following the procedure described above 2,6-difluorobenzylamine (3.96 ml, 30.40 mmol), ethyl (*Z*)-*N*-(2-amino-1,2-dicyanovinyl)formimidate (4.98 g, 30.40 mmol) and anilinium hydrochloride (0.02 g) stirred for 18 h at room temperature in ethanol (20 ml) gave a fine, cream precipitate. This was filtered and treated as previously to give **1h** (5.07 g, 19.43 mmol, 64%).

General procedure for the reaction of (*Z*)-N^1-(2-amino-1,2-dicyanovinyl)-N^2-aryl/benzylformamidines 1a–h with triethyl ortho-formate or -propionate

Method A. Triethyl orthoformate (15.0 cm^3, 90 mmol) or triethyl orthopropionate (12.0 cm^3, 59.6 mmol) was added to the formamidines **1a**–**h** (6.0 mmol) and the resulting suspension was heated under reflux for 1.5–3 hours. The resulted brown solution was cooled to room temperature. The 6-cyanopurine products either precipitated out after cooling (**2a**, **c**, **i** and **f**) or precipitated upon addition of petroleum ether (**2b**, **d**, **e**, **g**, **h** and **j**), and the solid was filtered off under vacuum, washed with petroleum ether (bp 40–60 °C) and dried under vacuum.

Method B. Triethyl orthoformate (3 cm^3, 17.43 mmol) was added to a suspension of imidazole **3a** or **3j** (4.34 mmol) in acetonitrile (50 cm^3) and a catalytic amount of sulfuric acid (1 drop) was added. The reaction mixture was stirred at room temperature until the TLC (1 : 1 EtOAc–hexane) showed that all the starting material had been consumed. The off-white solid in suspension was filtered and washed with ethanol and diethyl ether. A second crop of the same product was isolated when the mother liquor was concentrated in the rotary evaporator.

Synthesis of 8-(arylamino)-4-imino-3-methylpyrimidino[5,4-*d*]-pyrimidines 5a–e

The cyanopurine (8.0 mmol) was dissolved in dichloromethane (20.0 cm^3) and to this, aqueous methylamine (7.0 equiv.) was added. The solution was stirred at room temperature for 24 h or until TLC (1 : 1 CH_2Cl_2–EtOAc) showed the absence of starting material. The solvent was then removed under vacuum to give a solid residue, which was washed with ethanol, to give an insoluble white solid. Isolation of the solid by filtration under vacuum, followed by washing several times with 95% ethanol (3 × 5 cm^3) gave a white powder, which could be purified by recrystallisation from hot ethanol to give white crystals.

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† CCDC reference number 167808. See http://www.rsc.org/suppdata/p1/b1/b106539b/ for crystallographic files in .cif or other electronic format.

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