Synthesis of 4- and 5-Disubstituted 1-Benzylimidazoles, Important Precursors of Purine Analogs

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(*Z*)-*N*-(2-amino-1,2-dicyanovinyl)-*N'*-benzylformamidine **6** has been prepared both from the reaction of benzylisonitrile with the hydrochloride salt of diaminomaleonitrile and from reaction of ethyl (*Z*)-*N*-(2-amino-1,2-dicyanovinyl)formimidate with benzylamine. Based-catalyzed cyclization of amidine **6** led to imidazoles **7** and **8** depending on the reaction conditions. Compound **7** reacts with acetone and butane-2,3-dione to give the 2,2-disubstituted-6-carbamoyl-1,2-dihydropurines **9a** and **9b** respectively. 2-Methyl-6-carbamoylpurine **12** was obtained from the reaction of imidazole **7** with pentane-2,4-dione. The same compound was observed in the ^{1}H nmr spectrum of a solution of 1,2-dihydropurine **9b** in deuteriochloroform. Benzylimidazole **7** can be acetylated with acetic anhydride leading to compound **14**. This, in solution, undergoes an acyl migration reaction to give imidazoles **15** and **17**. Imidazole **15** cyclizes in the presence of base to the corresponding 6-cyanopurine **16**. A solution of **14** in methanol is slowly converted into the 6-methoxypurine **18**, possibly *via* a methoxymidoyl intermediate. A similar intermediate **13** has been isolated from **7** in methanol.

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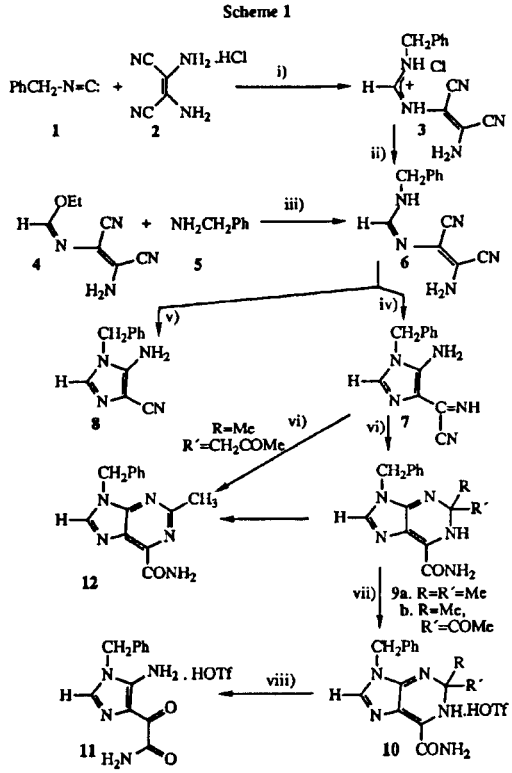
The synthesis of amidines analogous to compound **6** has been reported previously, either from reaction between *N*-methylacetonitrilium triflate and diaminomaleonitrile (DAMN) [1] or from reaction between ethyl (*Z*)-*N*-(2-amino-1,2-dicyanovinyl)formimidate **4** and ammonia [2], hydrazine monohydrate [3], or amino alcohols [4]. On treatment with base, the corresponding 5-amino-4-(cyanoformimidoyl)imidazoles can be isolated in high yield, and these have been used as precursors to 6-carbamoylpurines [1,2,3,4] 6-carbamoyl-1,2-dihydropurines [1,2,3,4] and 6-cyanopurines [5]. We now report the synthesis of amidine **6**, both from reaction of **4** with benzylamine and from the reaction of benzylisonitrile **1** and the hydrochloride salt of DAMN **2**. The use of isonitriles in the synthesis of substituted amidines is well known [6] and often the amine salt is used in such reactions [7].

5-Amino-1-benzyl-4-(cyanoformimidoyl)imidazole **7** proved to be an important intermediate not only in the preparation of new 1,2-dihydropurines and 6-carbamoylpurines but also in the synthesis of 6-methoxypurine and 6-cyanopurine derivatives.

The reaction between benzylisonitrile **1**, prepared according to a previously described procedure [8], and the hydrochloride salt of diaminomaleonitrile **2** occurs immediately at room temperature, when methanol is used as solvent. The amidinium salt **3** was isolated in 83% yield as a greenish solid which darkened progressively when exposed to the atmosphere. The corresponding amidine **6** was obtained upon neutralization of an aqueous solution of compound **3** with a saturated aqueous solution of sodium carbonate. An almost quantitative yield of amidine **6** is obtained by reaction of benzylamine **5** with ethyl (*Z*)-*N*-(2-amino-1,2-dicyanovinyl)formimidate **4** in ethanol,

Scheme 1



Reagents and conditions: i) MeOH, room temp.; ii) aq. $NaHCO_3$(sat.); iii) EtOH, anilinium chloride; iv) EtOH, KOH in EtOH (sat.) (six drops); v) aq. 1N NaOH; vi) RCOR', room temp.; vii) $CHCl_3$, HOTf (1 eq.), room temp., 15 min.; viii) $CHCl_3$, HOTf (1 eq.).

Table 1

Physical and Analytical Data

Compound	Yield (%)	mp (°C)	Molecular Formula	Found: C; H; N (%)	Requires: C; H; N (%)	ms (70ev) m/z (%)
6	98	91.5-92	$C_{12}H_{11}N_5$	64.3; 5.0; 31.1	64.0; 4.9; 31.1	226 [(M+1)$^+$, 62] 199 (100)
7	84	134-134.5	$C_{12}H_{11}N_5$	63.7; 4.8; 30.8	64.0; 4.9; 31.1	226 [(M+1)$^+$, 20] 91 (100)
9a	71	153-154 dec	$C_{15}H_{17}N_5O$	63.7; 6.0; 24.7	63.8; 5.7; 24.8	284 [(M+1)$^+$, 82] 91 (100)
9b	93	153-154 dec	$C_{16}H_{17}N_5O_2$	hrms 312.1437	hrms 312.1461	268 [(M+1)$^+$, 100]
10	85	185-188 dec	$C_{16}H_{18}N_5SF_3O_4$	43.9; 4.1; 15.9	44.3; 4.2; 16.2	285 [(M+2)$^+$, 100]
11	72	240-241 dec	$C_{13}H_{13}N_4SF_3O_5$	39.2; 3.2; 13.9	39.6; 3.3; 14.2	244 [(M-HOTf)$^+$, 11.7] 58 (100)
12	60	210-211	$C_{14}H_{13}N_5O$	62.6; 4.7; 25.9	62.9; 4.9; 26.2	268 [(M+1)$^+$, 24.5] 41 (100)
13	63	145-145.5	$C_{12}H_{14}N_4O$	62.6; 6.3; 24.3	62.6; 6.1; 24.2	231 [(M+l)$^+$, 100]
14	82	89.4-91.4	$C_{14}H_{13}N_5O$	hrms 268.1214	hrms 268.1198	268 [(M+1)$^+$, 2.6] 250 (100)
15	79	100 dec	$C_{14}H_{13}N_5O$	63.2; 4.8; 26.3	62.9; 4.9; 26.2	268 [(M+l)$^+$, 10.1] 250 (25.7)
16	88	136.4-137.7	$C_{14}H_{11}N_5$	67.8; 4.3; 27.9	67.5; 4.4; 28.1	249 [(M$^+$), 21.7] 91 (100)
17	65	120 dec	$C_{14}H_{16}N_4O_2$	62.1; 5.8; 20.6	61.8; 5.9; 20.6	273 [(M+l)$^+$, 55] 241 (100)
18	79	121-122.5	$C_{14}H_{14}N_4O$	66.4; 5.2; 22.1	66.1; 5.5; 22.0	255 [(M+l)$^+$, 100]

in the presence of a catalytic amount of anilinium hydrochloride.

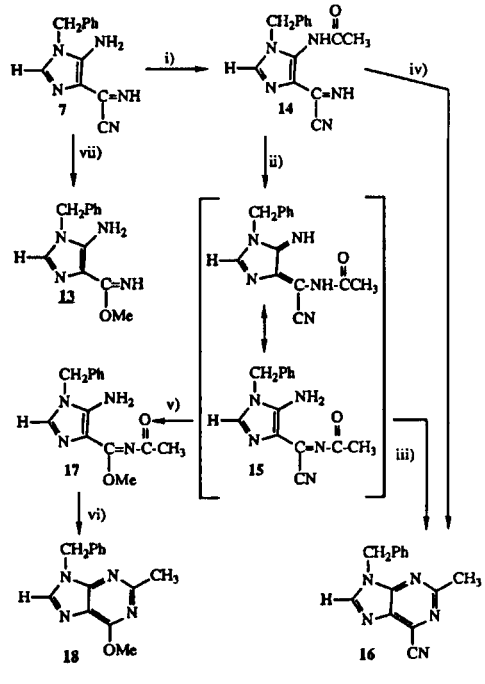
The cyclization of **6** in the presence of base led to the imidazoles **7** or **8** depending on the reaction conditions. This behavior compares with that of previously prepared amidine analogs [1,2,3,4] where both the choice of base and solvent proved to be critical to achieve selective formation of a 5-amino-4-(*C*-cyanoformimidoyl)imidazole.

A characteristic feature of imidazole **7** is a very weak C≡N stretching vibration in the ir spectrum, whereas for imidazole **8** this band is sharp and intense in the 2200 cm^{-1} region. For amidine **6**, the ir spectrum showed two intense C≡N stretching vibrations at 2210 and 2190 cm^{-1}.

Reaction of **7** with acetone and butane-2,3-dione led to the corresponding 6-carbamoyl-1,2-dihydropurines **9a** and **b** as deep orange solids in 71 and 93% yields respectively. Compound **9b** is very unstable both in solution and in the solid state and its colour gradually fades to give a white solid identified as 6-carbamoylpurine **12**. Thus, it proved impossible to obtain accurate elemental analysis data for **9b**. Nevertheless, its deep orange colour and the ir and ^{1}H nmr data, showing a singlet at δ 7.2 typical of the C_8-H of a 6-carbamoyl-1,2-dihydropurine, clearly indicate the assigned structure. In the reaction of **7** with pentane-2,4-dione the 1,2-dihydropurine intermediate could only by detected by tlc as it rapidly evolves to the 6-carbamoylpurine **12**. The ^{13}C nmr spectrum of **9a** shows two distinct sets of bands which arise from the two possible tautomeric species [3,4] present in solution. We are at present undertaking an extensive study on this phenomenon in this particular ring system [9]. The addition of one equivalent of triflic acid to compound **9a** in chloroform enabled the isolation of the triflate salt of the dihydropurine as a yellow solid **10**. Only one set of peaks is observed in the ^{13}C nmr spectrum of **10**, as protonation of N_1 nitrogen prevents tautomerism from occurring. Compound **10** rapidly hydrolyses to compound **11** in the presence of another equivalent of triflic acid.

In the presence of methanol, imidazole **7** slowly evolved to a white solid believed to have structure **13**. The empirical formula was established by elemental analysis, and mass spectroscopy shows a molecular ion at m/z 230, from which methanol is eliminated. The methoxy group is seen in the ^{1}H nmr spectrum at δ 3.9 ppm and in the in the ^{13}C nmr spectrum at δ 49.9 ppm. The absence of a C≡N stretching vibration in the ir spec-

Scheme 2



Reagents and conditions: i) $CH_3COOCOCH_3$, $CHCl_3$, room temp., 5 min.; ii) CH_3CN, 2 days, room temp.; iii) CH_3CN, DBU, room temp., 42 h.; iv) DBU, CH_3CN, 5 min., room temp.; v) MeOH, 3 h, room temp., followed by 5 days, 5°C; vi) MeOH, room temp., 3 months; vii) MeOH, room temp., 24 h.

Table 2

^{1}H NMR and IR Data for Amidine **6** and Imidazoles

Compound	IR (Nujol), ν (cm^{-1})	^{1}H NMR, δ, *J* (Hz)	Solvent
6	3425*s*, 3365*s*, 3320*s*, 2210*s*, 2190*s*, 1630*s*, 1575*s*	4.3 (2H, br *s*, NH_2), 4.5 (2H, d, *J* 6, CH_2), 5.2 (1H, br s, NH), 7.3 (5H, s, Ph), 7.9 (1H, d, *J* 4.5, CH)	$CDCl_3$ [a]
7	3323*s*, 3236*s*, 3148*s*, 3105*s*, 3019m, 1635*s*, 1580*s*, 1546*s*	5.25 (2H, *s*, CH_2), 6.9 (<2H, sl, NH_2), 7.5-7.3 (6H, m, Ph+CH), 11.0 (<1H, sl, NH)	$(CD_3)_2SO$ [b]
11	3390m, 3300*s*, 3200m, 3050m, 1710w, 1685*s*, 1618m, 1570m, 1520m	5.3 (2H, *s*, CH_2), 7.37 (5H, *s*, Ph), 8.46 (1H, *s*, CH)	CD_3OD [a]
13	3388m, 3226*s*, 3154m, 3120m, 1624*s*, 1560m, 1520m	3.9 (3H, *s*, OCH_3), 5.0 (2H, *s*, CH_2), 7.3 (6H, m, Ph+CH)	$CDCl_3$ [a]
14	3271m, 3207m, 3116*s*, 3060*s*, 2208w, 1701w, 1660*s*, 1638*s*, 1572*s*, 1545*s*,1500*s*	2.2 (3H, *s*, CH_3), 4.9 (2H, *s*, CH_2), 7.33 (6H, sl, Ph+CH)	$CDCl_3$ [a]
15	3241*s*, 3200*s*, 3205*s*, 3116w, 3050w, 1676*s*, 1652w, 1595*s*, 1534*s*, 1490*s*	2.05 (3H, *s*, CH_3), 5.15 (2H, *s*, CH_2), 7.27 (2H, m, Ph) 7.4 (3H, m, Ph), 8.05 (1H, *s*, CH), 10.2 (1H, *s*, NH), 11.5 (1H, *s*, NH)	$(CD_3)_2SO$ [b]
17	3397m, 3255*s*, 3098m, 3050m, 3031m, 1670*s*, 1646*s*, 1565m, 1550*s*, 1499m	2.15 (3H, *s*, $COCH_3$), 3.8 (3H, *s*, OCH_3), 5.1 (2H, *s*, CH_2), 7.02 (2H, m, Ph), 7.4 (3H, m, Ph), 7.85 (1H, *s*, CH), 8.2 (1H, *s*, NH), 9.8 (1H, *s*, NH)	$(CD_3)_2SO$ [b]

[a] Obtained using a 60 MHz machine. [b] Obtained using a 300 MHz machine.

Table 3

^{1}H NMR and IR Spectal Data for Dihydropurine and Purine Compounds

Compound	IR (Nujol), ν (cm^{-1})	^{1}H NMR, δ, *J* (Hz)	Solvent
9a	3310*s*, 3190*s*, 3140*s*, 2800-2000br, 1688*s*, 1615*s*, 1580w, 1530*s*	1.51 (6H, *s*, CH_3), 4.8 (2H, *s*, CH_2), 7.1 (1H, *s*, CH), 7.29 (5H, *s*, Ph)	$CDCl_3$ [a]
9b	3360m, 3320*s*, 3130m, 3090m, 1710*s*, 1642*s*, 1600m, 1580m, 1525m	1.47 (3H, *s*, CH_3), 2.19 (3H, *s*, $COCH_3$), 4.88 (2H, *s*, CH_2), 5.8-6.3 (1H, m, NH), 7.2 (1H, *s*, CH), 7.33 (5H, *s*, Ph)	$CDCl_3$ [a]
10	3350m, 3200*s*, 1730*s*, 1635*s*, 1620*s*, 1580m, 1520m	1.61 (6H, *s*, CH_3), 5.15 (2H, *s*, CH_2), 7.2.-7.4 (5H, br s, Ph), 7.96 (1H, *s*, CH)	$(CD_3)_2SO$ [a]
12	3320m, 3160w, 3100w, 1692*s*, 1620w, 1595m, 1575*s*, 1510w	2.9 (3H, *s*, CH_3), 5.5 (2H, *s*, CH_2), 7.4 (5H, *s*, Ph), 8.11 (1H, *s*, CH)	$CDCl_3$ [a]
16	3053m, 2226w, 1598m, 1574m, 1496m	2.84 (3H, *s*, CH_3), 5.6 (2H, *s*, CH_2), 7.4-7.45 (5H, m, Ph), 9.04 (1H, *s*, CH)	$(CD_3)_2SO$ [b]
18	3070w, 3021w, 1599*s*, 1585*s*	2.82 (3H, *s*, CH_3), 4.27 (3H, *s*, OCH_3), 5.45 (2H, *s*, CH_2) 7.4 (2H, m, Ph),7.5 (3H, m, Ph), 7.9 (1H, *s*, CH)	$CDCl_3$ [b]

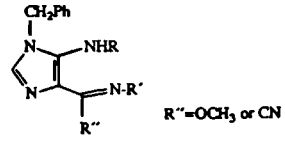
[al Obtained using a 60 MHz machine. [b] Obtained using a 300 MHz machine.

trum confirms that this group had been replaced by a methoxy group.

Reaction of compound **7** with acetic anhydride acylates the amino group in position 5 of the imidazole ring, giving compound **14** as orange crystals. On standing for 2 days in acetonitrile the orange colour gradually fades and a white solid **15** is isolated. From elemental analysis and mass spectrometric data it is apparent that compounds **14** and **15** are isomers. In the mass spectrum both show an $(M+1)^+$ ion at m/z 268, and an ion at m/z 250 corresponding to loss of a water molecule. This last ion is the base peak in the spectrum of **14** probably reflecting the ease with which this compound cyclizes to 9-benzyl-6-cyano-2-methylpurine **16**. In the spectrum of compound **15** the peak at m/z 250 is of only 25% intensity. Both compounds cyclize to **16** in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). With compound **14** reaction is complete after only 5 minutes at room temperature, while **15** requires 42 hours for complete reaction under similar conditions. On the basis of this evidence and the spectroscopic data, the orange compound **14** apparently undergoes a slow acyl migration reaction in solution to give the white solid **15**. As expected, both compounds have similar ir spectra with a strong carbonyl stretching vibration in the region 1660-1670 cm^{-1} and ν (NH) absorptions at 3100-3300 cm^{-1}. In addition, the spectrum of **14** shows a weak ν (C≡N) band at 2208 cm^{-1}, but a similar band is not present in the spectrum of **15**. The ^{1}H nmr spectra differ only in the chemical shifts of the C-2 protons [δ 7.3 for **14** and δ 8.1 for **15**], but there are significant differences in the chemical shift values for the ring carbon atoms in the ^{13}C nmr spectra.

Table 4

^{13}C NMR Chemicals Shifts [$\delta_C(CD_3)_2SO$] for Amidine **6** and for Imidazoles



Compound	R/R'	2-C	4-C	5-C	C≡N	OCH_3	6-C	R/R'	CH_2	C'	C-*ortho*	C-*meta*	C-*para*
6	-	154.4	119.2	110.1	121.1 120.2	-	-	-	47.9	142.7	131.2	132.4	131.6
7	R=H R'=H	136.4	117.6	147.2	120.3	-	148.4	-	49.8	140.4	131.3	132.7	131.7
11 [a] [b]	R=H R'=$CONH_2$	139.2	113.3	151.2	-	-	166.4	177.6	51.8	138.0	131.6	133.0	132.5
13	R=H R'=H	135.7	115.4	142.7	-	49.9	169.4	-	55.8	141.0	131.1	132.6	131.5
14 [c]	R=$COCH_3$ R'=H	142.8	116.5	136.5	120.0	-	154.8	30.3	49.8	140.0	131.2	132.8	132.0
15	R=H R'=$COCH_3$	140.0	131.6	132.2	119.5	-	149.2	174.8 26.7	51.4	141.7	131.7	132.8	132.0
17	R=H R'=$COCH_3$	139.9	129.8	132.4	-	56.4	167.9	174.3 26.5	51.4	140.7	131.5	132.7	131.8

[a] CF_3 group δ_C = 124.8, J = 320 Hz. [b] 2-C, 4-C and 5-C are broad absorptions. [c] Compound **14** decomposes during the acquisition of the spectrum. The main compound in the spectrum is **15**, comparing with the spectrum of an authentic sample of compound **15**.

Table 5

^{13}C NMR Chemical Shifts δ_C for Dihydropurines and Purines

Compound	2-C	4-C	5-C	6-C	8-C	C=O	R	C≡N	OMe	CH2	C'	C-*ortho*	C-*meta*	C-*para*
9a [b] [d]	76.1	136.0	119.4	155.3	136.3	166.7	32.0	-	-	50.0	141.0	131.3	132.7	131.5
	76.3	147.7	122.5	160.7	151.4	169.1	33.2	-	-	50.2	141.6	131.5	132.8	131.8
10 [a] [b]	75.1	155.5	119.7	149.9	147.1	162.9	30.3	-	-	50.1	139.2	131.2	133.0	132.2
12 [b]	165.4	158.0	133.0	150.0	150.8	168.4	29.7	-	-	50.6	139.6	131.6	132.6	131.9
16 [c]	162.1	152.3	131.7? 129.3?	131.7? 129.3?	146.3	-	24.7	112.6	-	46.3	133.2	126.9	127.7	127.1
18 [c]	161.0 159.2	151.5	117.8	161.0 159.2	140.0	-	24.6	-	52.7	45.8	134.3	126.5	127.7	127.0

[a] CF_3 group δ_c= 124.7, J = 324 Hz. [b] The spectrum was obtained in $(CD_3)_2SO$. [c] The spectrum was obtained in $CDCl_3$. [d] Two sets of peaks are observed due to slow tautomerism in solution.

In methanol the acetyl migration reaction appears to be much faster and stirring a suspension of **14** in this solvent at room temperature for only 1 hour gives 59% yield of **15**. When stirring is continued for a further 5 days at 5° a new white solid is isolated having structure **17**, as evidenced by the appearance of signals for a CH_3O group at δ 3.8 and δ 56.4 ppm in the ^1H and ^{13}C nmr spectra respectively. It is clear from the spectroscopic data that the *N*-acetyl group present in **15** is still present in compound **17**, but in the ^{13}C nmr spectrum the signal for C-6 is shifted downfield to 167.9 ppm as expected on replacement of a C≡N group by OMe. Cyclization of **14** to the corresponding 6-methoxypurine **18** in methanol at room temperature requires 3 months to go to completion *via* the intermediate formation of **15** and **17**.

EXPERIMENTAL

The ^1H nmr spectra were recorded on Hitachi-Perkin-Elmer R-24B (60 MHz) or Bruker XL300 (300 MHz) instruments, ^{13}C nmr spectra either on a Bruker WP80 or XL300 instrument, and

ir spectra on a Shimadzu IR-435. Mass spectra were recorded on a Kratos Concept instrument, and uv spectra on a Perkin-Elmer Lamda 15 uv/vis spectrometer. The melting points are uncorrected. Benzylisonitrile was prepared by the method described by Appel *et al* [8].

N-[(*Z*)-2-Amino-1,2-dicyanovinyl] Ammonium Chloride (**2**).

A solution of anhydrous hydrogen chloride (86 mmoles) in dioxane (17 ml) was added to a suspension of diaminomaleonitrile (8.0 g, 74 mmoles) in nitromethane (50 ml) and the mixture was stirred efficiently at room temperature for 20 minutes. The off-white solid **2** was filtered and washed with ether (8.92 g, 61.7 mmoles, 83%).

N-Benzyl-(*Z*)-*N'*-(2-amino-1,2-dicyanovinyl)formamidine (**6**).

Method A.

Benzylamine (2.62 g, 24.7 mmoles, 2.7 ml) was added to a suspension of **4** (3.62 g, 20.4 mmoles) in ethanol (20 ml) containing a catalytic amount of anilinium hydrochloride (0.01 g). The reaction flask was subjected to ultra-sound in a sonic bath for five minutes, when all the imidate had dissolved. The solution was evaporated in a rotary evaporator, chloroform was added, and the solution was concentrated again to give crystals that were washed with chloroform:petroleum ether 40-60° (1:5). The product was filtered off and identified as compound **6** (4.58 g, 20.3 mmoles, 100%).

Method B.

Benzylisonitrile (0.2 ml, 1.76 mmoles) was added in one portion to a suspension of **2** (0.25 g, 1.76 mmoles) in methanol (0.2 ml). The starting material solubilised immediately leading to a pale green solid. Dry ether (5 ml) was added to the reaction mixture and the solid was filtered and identified as *N*-benzyl-(*Z*)-*N'*-(2-amino-1,2-dicyanovinyl)formamidinium chloride (0.38 g, 1.45 mmoles, 83%). A fraction of that material (0.2 g, 0.76 mmoles) was redissolved in water (20 ml) and a saturated solution of sodium hydrogencarbonate was added dropwise until CO_2 evolution stopped. The product, identified as compound **6** (0.17 g, 0.74 mmoles, 98%) precipitated as a white solid and was washed with dry ether.

5-Amino-4-(*C*-cyanoformimidoyl)-1-benzylimidazole (**7**).

Six drops of a concentrated ethanolic solution of potassium hydroxide were added to an ethanolic solution (10 ml) of **6** (0.98 g, 4.35 mmoles). A yellow colour developed immediately giving white crystals (0.59 g). Further concentration of the filtlate gave a second crop of the product (0.23 g) leading to a total yield of **7** of 0.82 g (3.64 mmoles, 84%).

5-Amino-4-cyano-1-benzylimidazole (**8**).

A saturated solution of sodium hydrogencarbonate was added dropwise to a solution of **3** (0.55 g, 2.08 mmoles), in water (10 ml) until CO_2 evolution ceased. A white solid precipitated, and was filtered and transferred to a flask containing 1*N* aqueous sodium hydroxide solution (*ca.* 30 ml). The suspension was stirred for 40 minutes and filtered. The solid was washed with water, dissolved in chloroform (100 ml) and the solution was dried (anhydrous magnesium sulfate). The drying agent was removed by filtration and the solution concentrated on the rotary evaporator to give a white solid (0.22 g). Further concentration of the mother-liquor in the rotary evaporator led to a second crop (0.11 g) to give a total yield of **8** of 0.33 g (1.63 mmoles, 77%), mp 200.5-201° (Lit [10] mp 199-200°).

Reaction of 5-Amino-4-(*C*-cyanoformimidoyl)-1-benzylimidazole **7** with Methanol.

A suspension of **7** (1.27 g, 5.64 mmoles) in methanol (8 ml) was stirred for 24 hours at room temperature. Removal of the solvent gave a pale brown oil which was dissolved in chloroform and purified by flash chromatography (silica, chloroform eluant) to give a colourless solution. Most of the solvent was then removed on a rotary evaporator. 5-Amino-4-(methoxyformimidoyl)-l-benzylimidazole **13** crystallized as a white solid from chloroform/petroleum ether 40-60° (0.82 g, 3.57 mmoles, 63%).

Reaction of 5-Amino-4-(*C*-cyanoformimidoyl)-1-benzylimidazole **7** with Ketones.

(a) Acetone.

A solution of **7** (0.5 g, 2.22 mmoles) in acetone (7 ml) was stirred at room temperature for two days. The resulting orange solution was cooled to -20°, giving orange crystals (0.4 g) after 24 hours. Concentration of the mother liquor gave a second crop (0.03 g), leading to a total yield of **9a** of 0.43 g (1.52 mmoles, 71%).

(b) Diacetyl.

Diacetyl (0.23 g, 2.66 mmoles, 0.23 ml) was added to a suspension of **7** (0.3 g, 1.33 mmoles) in dry chloroform (1 ml). A strongly exothermic reaction occurred. All the imidazole dissolved immediately and the reaction mixture turned deep orange. Orange crystals were obtained upon cooling the reaction mixture to -20°. The compound was identified as 2-acetyl-9-benzyl-6-carbamoyl-2-methyl-1,2-dihydropurine **9b** (0.36 g, 1.23 mmoles, 93%). The compound decomposed slowly to purine **12** on standing as a solid in the open atmosphere. In solution, formation of **12** occurred rapidly as evidenced by ^{1}H nmr spectroscopy.

(c) Acetylacetone.

Acetylacetone (0.6 g, 10.6 mmoles, 1.08 ml) was added to a suspension of **7** (0.3 g, 1.33 mmoles) in chloroform (1 ml), with stirring at room temperature. After 19 hours a pale yellow solid (0.22 g) was filtered and recrystallized from chloroform/petroleum ether 40-60° giving 9-benzyl-2-methyl-6-carbamoylpurine **12** (0.2 g, 0.8 mmoles, 60%) as a white solid.

Reaction of 5-amino-4-(*C*-cyanoformimidoyl)-1-benzylimidazole **7** with Acetic Anhydride.

Acetic anhydride (1.67 g, 16.4 mmoles, 1.55 ml) was added to a suspension of **7** (0.42 g, 1.83 mmoles) in chloroform (12 ml). All the starting material dissolved in 5 minutes giving a deep yellow solution. Partial evaporation of the chloroform in a rotary evaporator (water bath 35°) followed by addition of ether gave 5-acetamido-4-(*C*-cyanoformimidoyl)-1-benzylimidazole **14** (0.36 g, 1.5 mmoles, 82%) as shiny orange crystals.

Reaction of 5-Acetamido-4-(*C*-cyanoformimidoyl)-1-benzylimidazole **14** in Acetonitrile and DBU.

DBU (50 ml, 0.3 mmole) was added to a solution of imidazole **14** (0.40 g, 1.49 mmoles) in acetonitrile (3 ml). After 5 minutes at room temperature, the deep yellow colour faded away and the acetonitrile was removed in a rotary evaporator. The dark residual oil was redissolved in ethyl acetate and the

solution was passed through a flash chromatography column. The eluate was concentrated on the rotary evaporator leading to a pale yellow oil that crystallized. After addition of diethyl ether, the solid was filtered, leading to a white solid identified as 9-benzyl-6-cyano-2-methylpurine **16** (0.33 g, 1.31 mmoles, 88%).

Reaction of 5-Acetamido-4-(*C*-cyanoformimidoyl)-1-benzylimidazole **14** in Acetonitrile.

A solution of **14** (0.41 g, 1.54 mmoles) in acetonitrile (7 ml) was stirred for 2 days, at room temperature (*ca.* 25°). The solid was filtered and washed with ethyl acetate (0.22 g). Most of the solvent was then removed from the mother liquid on the rotary evaporator, giving a second crop (0.11 g). The combined yield of 5-amino-4-[*N*-acetyl(cyanoformimidoyl)]-1-benzylimidazole **15** was 0.33 g (1.21 mmoles, 79%).

Reaction of 5-Amino-4-[*N*-acetyl-(*C*-cyanoformimidoyl)]-1-benzylimidazole **15** in Acetonitrile and DBU.

A suspension of **15** (0.32 g, 1.2 mmoles) in acetonitrile (10 ml) and DBU (90 ml, 0.5 mmole) was stirred for 42 hours at room temperature. The solution was then evaporated to dryness on the rotary evaporator, giving an oil that was dissolved in ethyl acetate and chromatographed on a small column under vacuum. The eluates were evaporated on the rotary evaporator giving crystals (0.11 g). A second crop was collected by slow evaporation of the mother liquor at room temperature (0.06 g). The combined yield of 9-benzyl-6-cyano-2-methylpurine **16** was 0.17 g (0.68 mmole, 57%).

Reaction of 5-Acetamido-4-(*C*-cyanoformimidoyl)-1-benzylimidazole **14** in Methanol.

Method A.

A suspension of **14** (0.9 g, 3.77 mmoles) in methanol (20 ml) was stirred for 1 hour at room temperature. The solution was concentrated on the rotary evaporator leading to an oil which crystallized to a white solid (0.33 g), which was filtered and washed with chloroform. A second crop was obtained from the mother liquid after concentration and addition of ether (0.2 g). The combined yield of 5-amino-4-[*N*-acetyl-(*C*-cyanoformimidoyl)]-1-benzylimidazole **15** was 0.53 g (2.0 mmoles, 59%).

Method B.

A suspension of **14** (0.67 g, 2.51 mmoles) in methanol (10 ml) was stirred for 3 hours at room temperature followed by 5 days at 5°. The solution was evaporated to dryness and the solid residue crystallized from methanol/ether to give 5-amino-4-[*N*-acetyl(*C*-methoxyformimidoyl)]-1-benzylimidazole **17** (0.49 g, 1.62 mmoles, 65%) as an off-white solid.

Method C.

A suspension of the imidazole (0.35 g, 1.31 mmoles) in methanol (4 ml) was stirred at room temperature for three months. The solvent was evaporated on the rotary evaporator and the residue dissolved in chloroform. The solution was passed through a flash silica column. The eluate was evaporated and the solid product crystallized from ether/petroleum ether 40-60° (0.10 g). A second crop (0.17 g) was collected after removing the solvents. 6-Methoxy-2-methyl-9-benzylpurine **18** was obtained in a total yield 0.27 g (1.03 mmoles, 79%), and recrystallized from ether/petroleum ether 40-60° (0.146 g, 44%).

Hydrolysis of 9-Benzyl-6-carbamoyl-2,2-dimethyl-1,2-dihydropurine **9a** with Triflic Acid.

Triflic acid (0.03 g, 0.23 mmole, 0.02 ml) was added to a suspension of **9a** (0.05 g, 0.20 mmole) in chloroform (1 ml), with magnetic stirring. After 15 minutes the yellow solid precipitate was filtered and identified as 9-benzyl-6-carbamoyl-2,2-dimethyl-1,2-dihydropurinium trifluoromethanesulphonate **10** (0.08 g, 0.17 mmole, 85%). Triflic acid (0.02 g, 0.12 mmole, 0.01 ml) was added to a suspension of 9-benzyl-6-carbamoyl-2,2-dimethyl-1,2-dihydropurinium trifluoromethanesulphonate (0.05 g, 0.12 mmole) in chloroform (3 ml), under magnetic stirring. After 15 minutes the white solid precipitate was filtered, recrystallized from methanol-ether and identified as 5-amino-4-oxamoyl-1-benzylimidazolinium trifluoromethanesulphonate **11** (0.03 g, 0.08 mmole, 72%).

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