Synthesis of 6-Cyanopurines from 5-Amino-4-(cyanoformimidoyl)-1,2-dimethylimidazole

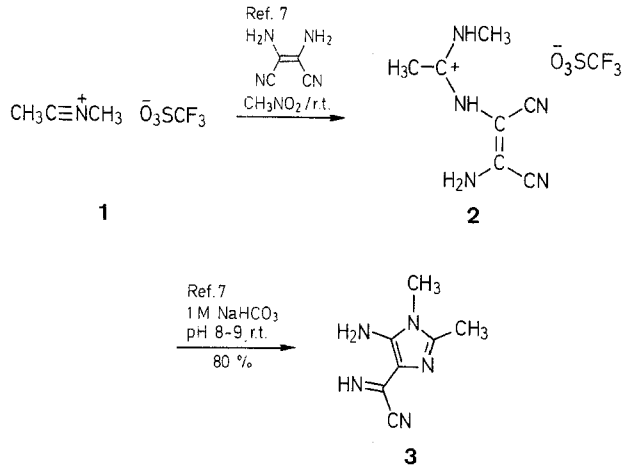
Brian L. Booth,* Ronald D. Coster, M. Fernanda J.R.P. Proença

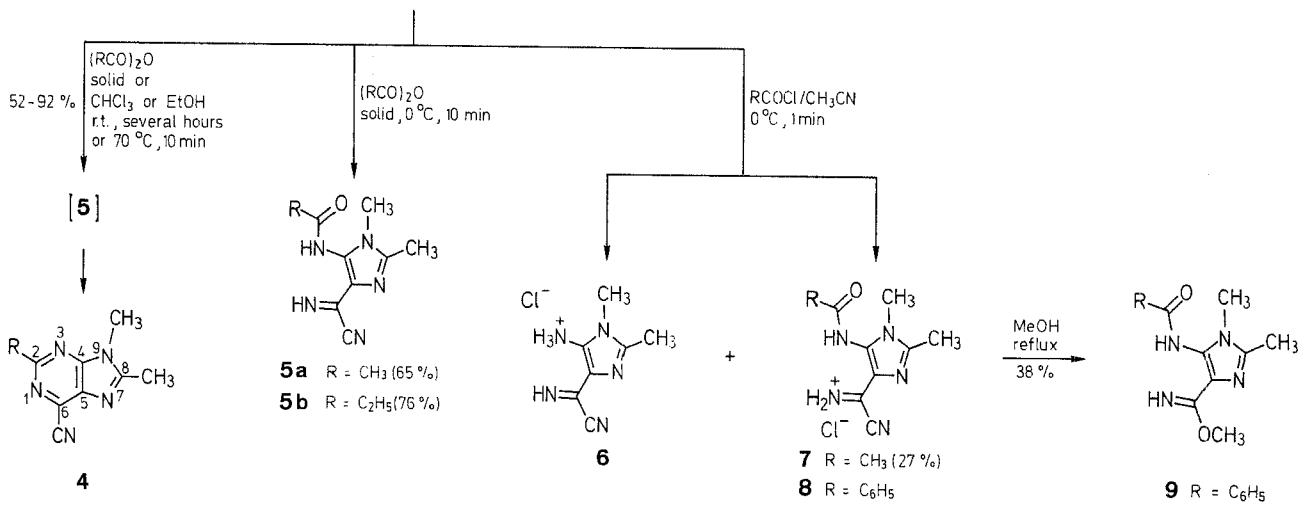
Department of Chemistry, University of Manchester Institute of Science and Technology, Manchester M60 1QD, England

Moderate to good yields of 2-substituted 6-cyano-8,9-dimethylpurines **4** have been obtained by reaction of 5-amino-4-(cyanoformimidoyl)-1,2-dimethylimidazole **(3)** with the carboxylic acid anhydrides, $(RCO)_2O$. The initial products of these reactions are the corresponding 5-carboxamido-4-(cyanoformimidoyl)-1,2-dimethylimidazoles [5-acylamino-4-(cyanoiminomethyl)-1,2-dimethylimidazoles] **5**, which can be isolated when $R = CH_3$ or C_2H_5. Acyl halides behave in a more complex manner to give mixtures of the starting material and the 5-carboxamido-4-(cyanoformimidoyl)-1,2-dimethylimidazoles as their HCl salts.

6-Cyanopurines are usually obtained by cyanide ion substitution of either 6-iodo,[1] 6-tosyl-,[2] 6-methylsulphonyl-[3] and 6-trimethylammonio[4]-purine derivatives, or by dehydration of 6-oxime derivatives with acetic anhydride.[5] The yields from these reactions are only moderate to poor, and in each case the starting materials have to be synthesised from hypoxanthines via the 6-chloropurine derivatives. Thus, the scope for the synthesis of 2,8,9-substituted-6-cyanopurines by these routes is limited. We now report a new synthesis of 6-cyanopurines by a simple three-step sequence starting from a nitrilium trifluoromethanesulphonate (triflate) salt and diaminomaleodinitrile. Part of this work has appeared in a preliminary communication.[6]

We have reported previously[7] that *N*-methylacetonitrilium triflate **1**, which is readily obtained by mixing dry acetonitrile and methyl triflate at room temperature,[8] reacts with diaminomaleodinitrile in dry nitromethane at room temperature to give the amidinium salt **2** as a 1.4:1 mixture of *cis*- and *trans*-isomers.





4	R	4	R
a	CH_3	d	$CH{=}CHCO_2H$
b	C_2H_5	e	$CH_2CH_2CO_2H$
c	CF_3		

Controlled basification of **2** to pH 8–9 with 1 M sodium carbonate affords 5-amino-4-(cyanoformimidoyl)-1,2-imidazole **3** as a pale yellow, crystalline solid in 80% yield.[7] When compound **3** is reacted with excess carboxylic anhydrides either at room temperature or on warming to 70 °C, the corresponding 6-cyanopurines **4a–e** precipitate as white, crystalline solids (Tables 1 and 2). Compounds **4d** and **e**, which are recrystallised from aqueous ethanol, are isolated as the monohydrates.

The first step in this reaction is formation of the amide **5**, which, in the cases of acetic acid and propionic anhydrides, can be isolated as orange **(5a)** and yellow **(5b)** solids, respectively (Scheme). The amides **5a, b** decompose on warming or long standing in solution to give the 6-cyanopurines **4a, b** in quantitative yield. With the other anhydrides similar amides are undoubtedly formed as unstable brown or green oils, which could not be isolated and convert rapidly into the purines.

Addition of acetyl chloride to a solution of **3** in acetonitrile either at room temperature or at 0 °C caused immediate precipitation of compound **6**, i.e. the hydrochloride salt of **3**, together with a low yield of a yellow solid, which has been tentatively identified as **7**, the hydrochloride salt of **5a**. A repeat of this reaction in the presence of triethylamine gave only a dark tar, from which the known 6-carboxamide-2,8,9-trimethylpurine[7] was isolated in 28% yield after hydrolytic work up. A similar mixture of **6** and **8** precipitated as an orange solid on addition of benzoyl chloride to a solution of **3** in acetonitrile containing triethylamine. Attempts to recrystallise this mixture from hot methanol gave only a low yield of the imidate **9**, (Scheme) identified by microanalysis, IR and MS only; the compound was insoluble in all common deuterated solvents.

An attempt to prepare **5a** by reaction between **1** and the *N*-acetyl derivative of diaminomaleodinitrile at room temperature in nitromethane appeared to give the expected amidinium salt as a dark, hard gum, but hydrolysis by addition 2 M sodium carbonate solution gave only 6-carboxamido-2,8,9-trimethylpurine in 28% yield.

Table 1. Compounds **4–9**

Product	Yield[a] (%)	mp (°C) (solvent)	Molecular Formula[b]	MS (70 eV) *m/z* (%)	UV (EtOH) λ_{max} (nm) (log ε)
4a	92	157.5–158.5 ($CHCl_3/Et_2O$)	$C_9H_9N_5$ (187.2)	187 (M^+, 100)	300 (4.02)
4b	65	119–120 (Et_2O/PE[c])	$C_{10}H_{11}N_5$ (201.2)	201 (M^+, 89.7)	300 (4.03)
4c	52	115–116 ($CHCl_3/Et_2O$)	$C_9H_6F_3N_5$ (241.1)	241 (M^+, 100)	293 (4.03)
4d	60	280 (d) (aq. EtOH)	$C_{11}H_{11}N_5O_3$ (261.2)	261 (M^+, 3.1)	304 (4.00)
4e	60	276 (d) (aq. EtOH)	$C_{11}H_{13}N_5O_3$ (263.2)	263 (M^+, 7.0)	
5a	65	137–140 (d)	–[d]	205 (M^+, 1.8); 187 (M^+-H_2O, 100)	
5b	76	90–91 (d)	–[d]	219 (M^+, 0.1); 201 (M^+-H_2O, 100)	
6	68	230–233 (d)	$C_7H_{10}ClN_5$ (199.6)	163 (M^+-HCl, 46.6)	
7	27	112–114 (d)	$C_9H_{12}ClN_5O$ (241.6)	187 (M^+-HCl $-H_2O$, 100)	
9	38	173–174 (d) (MeOH/Et_2O)	$C_{14}H_{16}N_4O_2$ (272.3)	273 ($M^+ + 1$, 22.1)	

[a] Isolated yield based on **3**.
[b] Satisfactory microanalysis obtained: C ±0.5, H ±0.3, N ±0.3.
[c] PE = petroleum ether.
[d] These compounds decomposed on recrystallization or chromatography to **4a** and **4b** respectively. No microanalytical data obtained.

Table 2. IR and ^{1}H-NMR Data of Compounds **4–9**.

Product	IR[a] ν(cm^{-1})	^{1}H-NMR ($CDCl_3$) δ, J(Hz)
4a	2230 (C≡N)	[b] *(90 MHz): 2.73 (s, 3H); 2.81* (s, 3H); 3.84 (s, 3H)
4b	2230 (C≡N)	(90 MHz): 1.40 (t, 3H, J = 7); 2.72 (s, 3H); 3.08 (q, 2H, J = 7); 3.83 (s, 3H)
4c	[c]	(90 MHz): 2.87 (s, 3H); 4.0 (s, 3H)
4d	3400 (H_2O), 3220 (OH), 1683 (C=O)	(220 MHz): 2.74 (s, 3H); 3.83 (s, 3H); 6.4 (d, 1H, J = 11); 7.05 (d, 1H, J = 11); *8.3 (br, 2H); 12.06 (s, 1H)*
4e	3360 (H_2O), 3200 (OH), 1725 (C=O)	(220 MHz): 2.63 (s, 3H); 2.83 (t, 2H, J = 7); 3.2 (br, 2H); 3.25 (t, 2H, J = 7); 3.77 (s, 3H); 12.0 (s, 1H)
5a	3245 (NH), 3162 (NH), 2200 (C≡N), 1660, 1655 (CONH)	
5b	3300 (NH), 3175 (NH), 2210 (C≡N), 1660, 1620 (CONH)	(90 MHz): 1.22 (t, 3H, J = 7); 2.33 (s, 3H); 2.45 (q, 2H, J = 7); 3.21 (s, 3H)
6	3375, 3340, 3200, 3080 (NH), 2245 (C≡N), *1680, 1640, 1630 (NH)*	(90 MHz; D_2O): 2.39 (s, 3H); 3.44 (s, 3H)
7	3220, 3100, 3040 (NH), 2220 (C≡N), 1635, 1605 (CONH)	(90 MHz, D_2O): 2.35 (s, 3H); 2.54 (s, 3H); 3.54 (s, 3H)
8	3275, 3210, 3150, 3125 (NH), 2216 (C≡N), 1650, 1620 (CONH)	
9	3300, 3225, 3150, 3050 (NH), 1665, 1645 (CONH)	

[a] KBr.
[b] ^{13}C-NMR ($CDCl_3$): δ = 14.1 (q), 25.2 (q), 28.6 (q), 113.7 (s), 127.5 (s), 132.5 (s), 154.7 (s), 158.0 (s), 161.7 (s).
[c] C≡N stretching vibration not seen.

In connection with other reactions of nitrilium triflate salts we prepared routinely the compounds [R^{1}C≡NR^2]OTf (R^1 = C_2H_5, $CH(CH_3)_2$, $C(CH_3)_3$, $C_6H_5CH_2$, CH_2=$CHCH_2$, CH_2=CH, C_6H_5, 2- and 4-$CH_3C_6H_4$; R^2 = CH_3, C_2H_5, $CH(CH_3)_2$) and several of these have been shown to react with diaminomaleodinitrile to give the corresponding 5-amino-4-(cyanoformimidoyl)imidazoles. Hence, the reaction with anhydrides described in this paper offers a useful route to a number of 9-alkyl-2,8-alkyl, vinyl or aryl substituted 6-cyanopurines.

The melting points are uncorrected. ^{1}H-NMR spectra were recorded on Perkin Elmer R32 (90 MHz) or R34 (220 MHz) instruments, and ^{13}C-NMR spectra on a Bruker WP 80 spectrometer (20.1 MHz). IR spectra were obtained on Perkin Elmer 197 or 397 instruments and high resolution mass spectra (M^+) on a Kratos MS45 spectrometer.

Acetyldiaminomaleonitrile,[9] and compound **3**[7] are prepared by previously reported procedures.

2-Substituted 6-Cyano-8,9-dimethylpurines 4; General Procedure:
The carboxylic anhydride (1–3 mL) is added to **3** (0.1 g, 0.6 mmol) either as a solid (for **4a** and **b**), a solution in $CHCl_3$ (3 mL) (for **4c**), or EtOH (1 mL) (for **4d** and **e**). The compounds **4c–e** precipitate from the solution on standing at room temperature for several hours and are purified by recrystallisation. In the case of compounds **4a** and **b** the mixtures are heated at 70 °C for 10 min on a water bath. Water (10 mL) is then added and the solutions are heated to boiling, then cooled to 0 °C, and saturated aqueous Na_2CO_3 is added to pH 9. Extraction with $CHCl_3$ (5 × 20 mL) followed by either recrystallisation (**4a**) or chromatography (**4b**; florisil, 60–100 mesh, Et_2O as eluent) gives the pure products.

5-Carboxamido-4-(cyanoformimidoyl)-1,2-dimethylimidazoles [5-Acylamino-4-(cyanoiminomethyl)-1,2-dimethylimidazoles] 5a, b; General Procedure:
When **3** (0.1 g, 0.6 mmol) is added to the anhydride (0.6 mL), and the mixture is cooled to 0 °C the product precipitates as fine needles.

Reaction Between 3 and Acetyl Chloride:
When acetyl chloride (0.5 mL) is added dropwise to a solution of **3** (0.1 g, 0.6 mmol) in dry CH_3CN at 0 °C, compound **6** (0.085 g, 0.42 mmol) precipitates immediately. The yellow mother liquor obtained after removal of **6** by filtration is cooled to 0 °C, and Et_2O (ca. 5 mL) is added to precipitate **7** (0.04 g, 0.17 mol).

Reaction Between 3 and Benzoyl Chloride:
Et_3N (0.058 g, 0.57 mmol) is added to a solution of **3** (0.1 g, 0.6 mmol) in CH_3CN (3.5 mL). On addition of benzoyl chloride (0.3 mL) to this solution an orange precipitate (0.118 g) forms immediately. This is filtered, washed with chloroform, and is found to be a mixture of **6** and **8** (IR and MS).

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(1) MacKay, L.B., Hitchings, G.H. *J. Am. Chem. Soc.* **1956**, *78*, 3511.
(2) Hayashi, E., Shimida, N., Miyashita, A. *Yakugaku Zasshi* **1976**, *96*, 1370; *C.A.* **1977**, *86*, 121295.
(3) Inoue, H., Normura, S., Ueda, T. *Nucleic Acids Symp. Ser.* **1981**, *10*, 19.
Yamane, A., Matsuda, M., Ueda, T. *Chem. Pharm. Bull.* **1980**, *28*, 150.
(4) Barlin, G.B., Young, A.C. *J. Chem. Soc. Perkin Trans. 1* **1972**, 1269.
(5) Giner-Sorolla, A. *Chem. Ber.* **1968**, *101*, 611.
(6) Booth,B.L., Proenca, M.F.J.R.P. *J. Chem. Soc. Chem. Commun.* **1981**, 788.
(7) Booth, B.L., Coster, R.D., Proenca, M.F.J.R.P. *J. Chem. Soc. Perkin Trans. 1* **1987**, 1521.
(8) Booth, B.L., Jibodu, K.O., Proenca, M.F.J.R.P. *J. Chem. Soc. Perkin Trans. 1* **1983**, 1067.
(9) Hinkel, L.E., Richards, G.O., Thomas, O. *J. Chem. Soc.* **1937**, 1432.