Synthesis of 6-Cyanopurines and the Isolation and X-ray Structure of Novel 2H-Pyrroles

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(Z)-N^1-(2-Amino-1,2-dicyanovinyl)-N^2-substituted-formamidines react with dimethylformamide diethyl acetal at room temperature to give 6-cyanopurines as the major product together with novel 5-amino-2-arylimino-3,4-di[(N,N-dimethylamino)methylideneamino]-2H-pyrroles, which have been fully characterised and a single crystal X-ray analysis has been carried out on the N-phenyl derivative.

6-Cyanopurines are usually obtained by cyanide ion substitution of either 6-iodo [1], 6-tosyl- [2], 6-methylsulfonyl- [3,4] and 6-trimethylammonio [5] purine derivatives, or by dehydration of the 6-oxime derivatives with acetic anhydride [6]. The yields from these reactions are only moderate to poor. We have previously reported [7] that 6-cyanopurines can be obtained in good yields by reaction of 1-substituted-5-amino-4-(cyanoformimidoyl)-imidazoles with carboxylic acid anhydrides, but it is not always easy to isolate and handle these imidazole intermediates and we were interested in developing a simpler route to 6-cyanopurines. Previous work in our group has shown that (Z)-N^1-(2-amino-1,2-dicyanovinyl)-N^2-substituted-formamidines [8] are useful precursors to new heterocyclic compounds [8-12]. As part of our general investigations into the behaviour of these compounds we have examined the reactions of the compounds **1a-f** with dimethylformamide diethyl acetal in the expectation that this would provide a general route to 6-cyanopurines **2a-f**.

Under the conditions employed (1-3 equivalents of dimethylformamide diethyl acetal, acetonitrile, room temperature) the expected 6-cyanopurines **2a-e** were formed, but in only low to moderate yields (Table 1). In each case, the red crystalline by-products **3a,b,d,** and **e**

Table 1

Analytical and Spectroscopic Data for the Compounds 2 and 3

Compound	Yield (%)	mp (°C)	Molecular Formula	C	H	N	Cl	m/z (M+1)+ [a]	M
				Microanalytical Data (%)/ Found (Calcd)					
2a	81	205.0-205.8	$C_{13}H_9N_5$	66.4 (66.4)	3.6 (3.8)	29.5 (29.8)		236	235
2b	36	241.1-241.8	$C_{12}H_8N_6$	61.2 (61.0)	3.3 (3.4)	35.3 (35.6)		237	236
2c	28	214.6-215.6	$C_{13}H_9N_5O$	62.5 (62.2)	3.8 (3.6)	27.7 (27.9)		252	251
2d	31	220.2-221.0	$C_{12}H_6N_5Cl$	56.2 (56.4)	2.2 (2.3)	27.4 (27.4)	14.2 (13.9)	256	255
2e	53	195.2-195.9	$C_{12}H_7N_5$	65.3 (65.2)	2.9 (3.1)	31.4 (31.7)		222	221
3a	8	>170 dec	$C_{17}H_{23}N_7$	62.7 (62.8)	7.3 (7.0)	29.9 (30.2)		326	325
3b	15	>152 dec	$C_{16}H_{22}N_8$	[b]				327	326
3d	11	>157 dec	$C_{16}H_{20}N_7Cl$	56.0 (55.7)	5.5 (5.8)	28.1 (28.4)	10.4 (10.1)	346	345
3e	13	>154 dec	$C_{16}H_{21}N_7$	61.4 (61.7)	7.0 (6.8)	31.1 (31.5)		312	311
3f	36	>180 dec	$C_{17}H_{20}N_8$	60.4 (60.7)	5.7 (6.0)	33.0 (33.3)		337	336

[a] Fast atom bombardment. [b] It was not possible to obtain an analytical sample.

Table 2

^{13}C NMR Spectroscopic Data for the Compounds 2

Compound	δC (ppm) in DMSO-d_6						
	C-2	C-4	C-5	C-6	C-8	CN	
2a	152.6	152.5	129.0	135.3	149.3	114.1	131.0 (C-1'), 123.5 (C_o), 129.9 (C_m), 138.3 (C_p), 20.5 (Me)
2b	152.4	152.5	128.8	135.0	149.4	114.2	121.4 (C-1'), 113.6 (C_o), 125.1 (C_m), 149.8 (C_p)
2c	153.0	152.8	129.3	133.7	149.6	114.4	121.6 (C-1'), 156.5 (C_o), 123.9 (C_o), 121.4 (C_m), 129.9 (C_p), 113.0 (C_m), 56.2 (OMe)
2d	152.7	152.4	129.1	135.0	149.2	114.1	133.0 (C-1') [a], 125.3 (C_o), 129.6 (C_m), 132.4 (C_p) [a]
2e	153.0	152.7	129.4	133.7	149.6	114.4	135.6 (C-1'), 123.9 (C_o), 129.8 (C_m), 128.8 (C_p)

[a] These bands may be assigned to C- 1' and C_p or *vice-versa*.

were also isolated from these reactions by dry flash chromatography and the isolated yields are reported in the Scheme. In one case **1f** (R = 4-NCC$_6$H$_4$) the red compound **3f** was the only product isolated. In this case, the pyrrole **3f** is insoluble and precipitates from solution.

The molecular formulae of these red solids were established by elemental analysis and mass spectrometry (Table 1), but their ^{1}H and ^{13}C nmr were difficult to obtain

use a mixture of DMSO-d$_6$ and trifluoroacetic acid (*ca.* 10 µl TFA to 500 µl DMSO-d$_6$) to obtain acceptable spectra (Table 3).

The ^{1}H nmr spectra clearly show the presence of two dimethylamino groups in which the four methyl groups appear as separate singlets around δ 3 ppm, with two N-CH=N protons in the region δ 8.4-8.9 ppm. A single crystal X-ray structure determination on compound **3e**

Table 3

^{1}H NMR spectroscopic data for the compounds **2** and **3**

Compound	δH (ppm)	Solvent
2a	2.48 (3H, s, Me), 7.55 (2H, d, J = 8 Hz, ArH), 7.85 (2H, d, J = 8 Hz, ArH), 9.28 (1H, s, 8-H), 9.40 (1H, s, 2-H)	DMSO-d$_6$
2b	5.68 (2H, s, NH$_2$), 6.73 (2H, d, J = 8.2 Hz, ArH), 7.44 (2H, d, J = 8.2 Hz, ArH), 9.14 (1H, s, 8-H), 9.18 (1H, s, 2-H)	DMSO-d$_6$
2c	3.80 (3H, s, OMe), 7.20 (1H, m, ArH), 7.28 (1H, m, ArH), 7.62 (2H, m, ArH), 9.12 (1H, s, 8-H), 9.15 (1H,s,2-H)	DMSO-d$_6$
2d	7.81 (2H, d, J = 7.5 Hz, ArH), 8.01 (2H, d, J = 7.5 Hz, ArH), 9.25 (1H, s, 8-H), 9.41 (1H, s, 2-H)	DMSO-d$_6$
2e	7.67 (1H, m, ArH), 7.80 (2H, m, ArH), 8.00 (2H, m, ArH), 9.32 (1H, s, 8-H), 9.49 (1H, s, 2-H)	DMSO-d$_6$
3a	2.33 (3H, s, Me), 3.13 (3H, s, Me), 3.17 (3H, s, Me), 3.21 (3H, s, Me), 3.21 (3H, s, Me), 3.26 (3H, s, Me), 7.20 (2H, brs, ArH), 7.26 (2H, d, J = 7.9 Hz, ArH), 8.53 (1H, s, CH), 8.75 (1H, s, CH)	DMSO-d$_6$.TFA
3b	2.95 (6H, s, Me), 3.01 (6H, s, Me), 6.62 (2H, d, J = 7.5 Hz, ArH), 6.85 (2H, d, J = 7.5 Hz, ArH), 7.15 (<1H, brs, NH), 7.72 (<1H, brs, NH), 8.90 (1H, brs, CH)	DMSO-d$_6$
3d	3.12 (3H, s, Me), 3.18 (3H, s, Me), 3.22 (3H, s, Me), 3.28 (3H, s, Me), 7.20 (2H, brs, ArH), 7.49 (2H, d, J = 7.9 Hz, ArH), 8.46 (1H, s, CH), 8.76 (1H, s, CH)	DMSO-d$_6$.TFA
3e	3.15 (3H, s, Me), 3.20 (3H, s, Me), 3.24 (3H, s, Me), 3.30 (3H, s, Me), 7.25 (2H, m, ArH), 7.46 (2H, m, ArH), 8.46 (1H, s, CH), 8.78 (1H, s, CH)	DMSO-d$_6$.TFA
3f	3.14 (3H, s, Me), 3.21 (3H, s, Me), 3.24 (3H, s, Me), 3.31 (3H, s, Me), 7.30 (2H, d, J = 8.3 Hz, ArH), 7.91 (2H, d, J = 8.3 Hz, ArH), 8.49 (1H, s, CH), 8.80 (1H, s, CH)	DMSO-d$_6$.TFA
3h	1.92 (3H, s, Me), 1.99 (3H, s, Me), 2.91 (3H, s, Me), 2.95 (3H, s, Me), 2.99 (6H, s, Me), 8.77 (1H, s, CH), 8.97 (1H, s, CH)	DMSO-d$_6$.TFA

as only compound **3b** was sufficiently soluble in d$_6$-DMSO to obtain a ^{1}H nmr spectrum. The other compounds were insoluble in the usual nmr solvents and it was necessary to
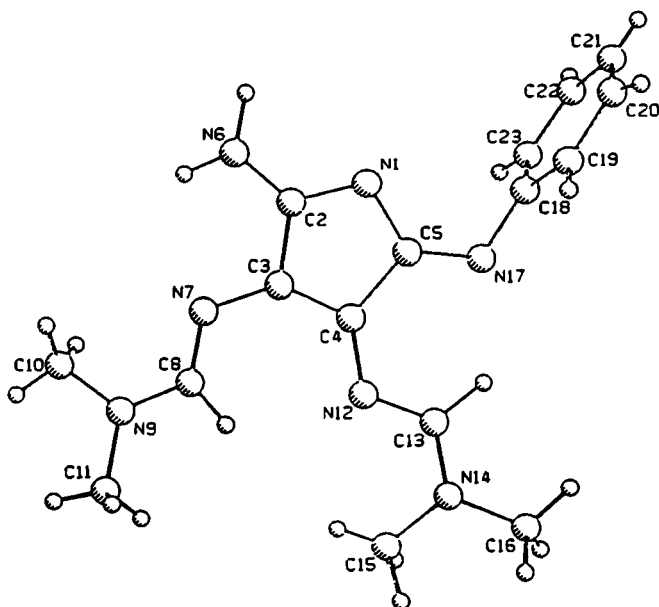

Figure 1. The X-ray crystallographic structure of **3e**, showing the number of the non-hydrogen atoms
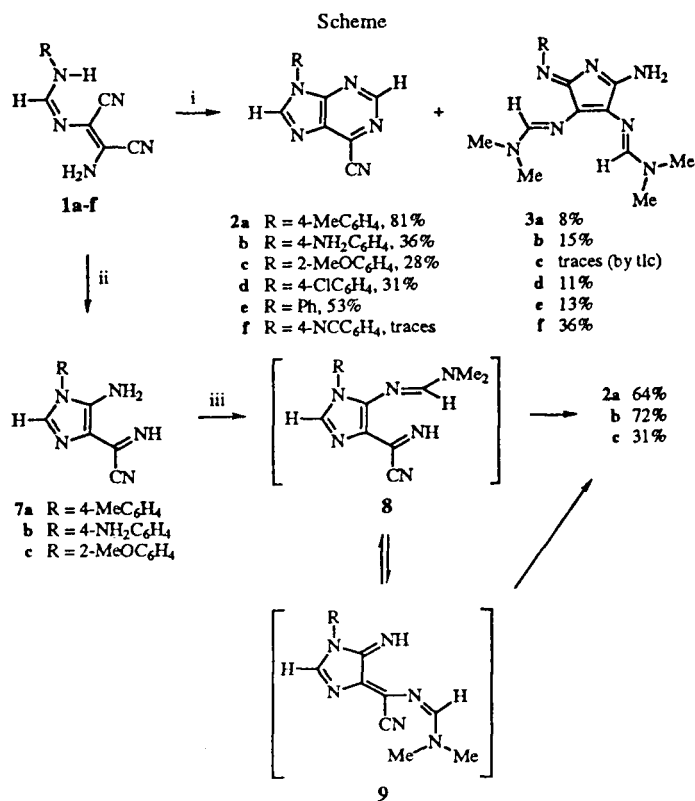
(R = Ph) established the novel structure shown in Figure 1. The molecules form centrosymmetric pairs *via* strong hydrogen bonds (see Figure 2) with N(1)-H = 1.78(8)Å. The crystal data shows that the phenyl ring is almost perpendicular to the plane of the pyrrole ring and there is little conjugation between the aromatic ring and the pyrrole ring; the bond lengths for N(17)-C(5) [1.294(5)Å] and for N(17)-C(18) [1.432(6)Å] closely approach those expected for a double and a single bond respectively.

The 2-amino substituent, on the other hand, conjugates strongly with the pyrrole ring as evidenced by the N(6)-C(2) and N(1)-C(2) bond lengths of 1.309(6) and 1.342(6)Å respectively. The amidine substituents on C(3) and C(4) are essentially planar with extensive conjugation in the N-C-N bonds. One of the *N*-methyl groups in each case [*i.e.* C(10) and C(15)] is arranged in the plane eclipsing N(7) and N(12) respectively. Both of the nitrogens N(9) and N(14) show only a very small pyramidal distortion.

There have been very few reports on the synthesis of 2*H*-pyrroles having an exocyclic C=N bond. Somewhat related compounds **4** have been isolated previously from the reaction of 2,3-diphenylfumaronitrile with guanidine [13], and the compounds **5** from 3-(α-cyanobenzylidene)-1-phenyltriazene with phenylacetonitrile in the presence of base [14], **6a** and **6b** from pentachloro-2*H*-pyrrole [15].
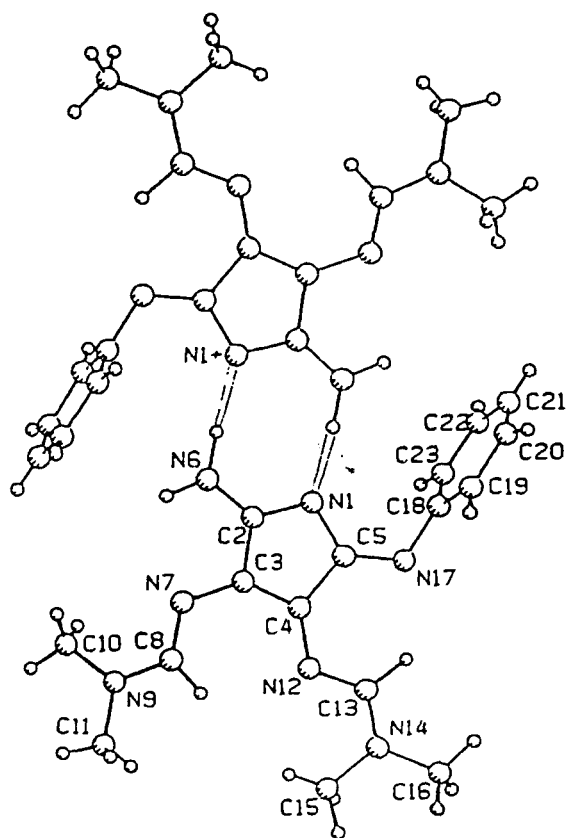
Figure 2. View of **3e** indicating hydrogen bonding.
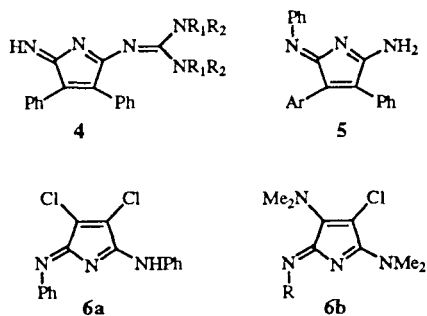
From our detailed studies of the reactions of amidines of type **1** [7,12] it seemed likely that the first step in these reactions with dimethylformamide diethyl acetal is the base catalysed cyclisation to the 1-substituted-5-amino-4-(cyanoformimidoyl)imidazoles **7** followed by reaction with dimethylformamide diethyl acetal to give an intermediate such as **8** (see Scheme). This could easily cyclise to a 6-cyanopurine. It is more difficult to see how the same intermediate might give rise to the pyrrole **3**, although one possibility might be rearrangement of **8** to **9** followed by nucleophilic opening of the imidazole ring with dimethylamine.

Scheme

2a R = 4-MeC$_6$H$_4$, 81%   3a   8%
 b R = 4-NH$_2$C$_6$H$_4$, 36%   b   15%
 c R = 2-MeOC$_6$H$_4$, 28%   c   traces (by tlc)
 d R = 4-ClC$_6$H$_4$, 31%   d   11%
 e R = Ph, 53%   e   13%
 f R = 4-NCC$_6$H$_4$, traces   f   36%

2a 64%
 b 72%
 c 31%

7a R = 4-MeC$_6$H$_4$
 b R = 4-NH$_2$C$_6$H$_4$
 c R = 2-MeOC$_6$H$_4$

[i] dimethylformamide diethyl acetal 1-3 equivalents, acetonitrile, room temperature; [ii] ethanol, 1,8-diazabicyclo[5.4.0]undec-7-ene; [iii] dimethylformamide diethyl formamide 1.5 equivalents acetonitrile.

To investigate whether this route may be feasible the known imidazoles **7a-c** were reacted with 1.5 equivalents of dimethylformamide diethyl acetal at room temperature under similar conditions to those used previously and were found to give the corresponding 6-cyanopurines **2a-c**. Compounds **2a** and **2b** were isolated in good yields (64% and 72% respectively). The reaction of imidazole **7c** was performed on a very small scale (55 mg), which may explain the poor isolated yield of **2e** (31%) considering that this was the only product detected by tlc. A careful study of these reactions showed no evidence for the formation of the red products **3a-c**. The cyanopurines were characterised by elemental analysis and spectroscopic data, and show ir spectra having no bands in the N-H region and a very weak absorption around 2200 cm^{-1} (v C≡N). This seems to be a typical feature of 6-cyanopurines previously reported in our group [7] and elsewhere [4]. It seems clear from these experiments that while compounds of type **7** and **8** do not appear to be involved in the formation of the 2H-pyrroles **3**, this pathway may account for the formation of the cyanopurines during the reactions of **1** with dimethylformamide diethyl acetal. The 2H-pyrrole derivatives isolated in this work have potential as precursors to electronic materials and we are now carrying out a more detailed investigation of the mechanism of formation of the

2H-pyrrole products in an effort to improve the yields and devise alternative methods for their synthesis. The results of these investigations will be reported in a separate paper.

Table 4
Crystallographic data for compound 3e

Formula	$C_{16}H_{21}N_7$
Mr	311.39
Crystal system	monoclinic
Space group	$PZ_{1/c}$
T/°C	23±1
λ/Å	0.71069
β	91.06(3)
a/Å	8.764(4)
b/Å	11.641(4)
c/Å	16.520(6)
U/Å³	16859(2)
Z	4
Dc/gcm⁻³	1.227
F(000)	664
μ/cm⁻¹	0.74
reflections measured	3344
Unique data observed [I>3σ(I)]	1309
R	0.049
Rw	0.060

Table 5
Selected Bond Lengths [Å] and Angles [°] for Compound 3e, with Estimated Standard Deviations in Parentheses.

atom	atom	distance	atom	atom	atom	angle
N1	C2	1.342(6)	C2	N1	C5	105.2(4)
N1	C5	1.399(5)	C3	N7	C8	118.6(4)
N6	C2	1.309(6)	C8	N9	C10	121.7(5)
N7	C3	1.395(5)	C8	N9	C11	119.5(5)
N7	C8	1.287(6)	C10	N9	C11	118.7(5)
N9	C8	1.337(6)	C4	N12	C13	119.2(4)
N9	C10	1.434(6)	C13	N14	C15	121.6(5)
N9	C11	1.448(7)	C13	N14	C16	120.1(5)
N12	C4	1.387(6)	C15	N14	C16	117.7(5)
N12	C13	1.306(6)	C5	N17	C18	117.0(4)
N14	C13	1.354(6)	N1	C2	N6	124.0(5)
N14	C15	1.450(8)	N1	C2	C3	112.3(4)
N14	C16	1.455(7)	N6	C2	C3	123.7(5)
N17	C5	1.294(5)	N7	C3	C2	117.8(4)
N17	C18	1.432(6)	N7	C3	C4	135.5(4)
C2	C3	1.475(6)	C2	C3	C4	106.6(4)
C3	C4	1.370(6)	N12	C4	C3	123.6(4)
C4	C5	1.488(6)	N12	C4	C5	131.5(4)
C18	C19	1.372(7)	C3	C4	C5	104.9(4)
C18	C23	1.373(7)	N1	C5	N17	124.5(4)
C19	C20	1.386(9)	N1	C5	C4	110.8(4)
C20	C21	1.37(1)	N17	C5	C4	124.7(4)
C21	C22	1.354(8)	N7	C8	N9	121.8(5)
C22	C23	1.384(9)	N12	C13	N14	121.0(5)
			N17	C18	C19	120.4(5)
			N17	C18	C23	120.1(5)
			C19	C18	C23	119.5(6)
			C18	C19	C20	119.7(7)
			C19	C20	C21	120.1(8)
			C20	C21	C22	120.3(7)
			C21	C22	C23	119.8(7)
			C18	C23	C22	120.6(6)

EXPERIMENTAL

The (Z)-N^1-(2-amino-1,2-dicyanovinyl)-N^2-arylformamidines and the 5-amino-1-aryl-4-(cyanoformimidoyl)imidazoles used in this work were prepared by a previously described procedure [9]. The ¹H nmr spectra were recorded on Varian Unity Plus 300 (300 MHz) or Bruker XL300 (300 MHz) instruments (with J values given in Hz), ¹³C nmr spectra (with DEPT 135) on a Bruker WP80 or XL 300 instrument, and ir spectra on a Perkin Elmer 1600 FT-IR spectrometer. Mass spectra were recorded on a Kratos Concept instrument. The melting points were measured on an Electrothermal digital melting point apparatus and are uncorrected.

Crystallography.

The crystal was mounted on glass fiber. All measurements were performed on a Rigaku AFC6S diffractometer with graphite-monochromated Mo-Kα radiation. The data were collected at a temperature of 23+/-1° using the ω scanning technique to a maximum of 2Θ values of 50.0°. The structures were solved by direct methods using MITHRIL [17] and refined by blocked-matrix least-squares based on F using TEXAN [18]. Non hydrogen atoms were refined anisotropically. Hydrogen atoms were refined isotropically. The crystallographic data for the compound 3e are shown in Tables 4 and 5.

General Procedure for the Reaction of (Z)-N^1-(2-Amino-1,2-dicyanovinyl)-N^2-arylformamidines 1a-f with Dimethylformamide Diethyl Acetal.

Dimethylformamide diethyl acetal (1.5 equivalents) was added to a suspension of amidine 1 in acetonitrile with magnetic stirring at room temperature. A homogeneous solution was formed leading to an orange solid which was filtered. The solid was solubilized in chloroform and flash chromatogaphed (Kieselgel 60) using diethyl ether or chloroform as solvents. The colourless solution obtained was concentrated in the rotary evaporator giving white crystals, identified as the corresponding 9-aryl-6-cyanopurine 2. Continuing the extraction with acetone or acetonitrile as solvents led to an orange solution which was concentrated in the rotary evaporator giving a red solid identified as the pyrrole 3.

Note: In the reaction of 1c (R = 2-MeOC₆H₄) with dimethylformamide diethyl acetal, the 6-cyanopurine (28%) was filtered directly from the reaction mixture; only traces of pyrrole 3 were detected by tlc.

Synthesis of Pyrrole 3f from Amidine 1f.

Dimethylformamide diethyl acetal (0.30 g; 2.04 mmoles) was added to a suspension of amidine 1f (0.16 g; 0.69 mmole) in acetonitrile (5 ml) with magnetic stirring. A yellow solution was obtained immediately and a yellow solid precipitated. The solid was identified by tlc as 5-amino-1-(4'-cyanophenyl)-4-(cyanoformimidoyl)imidazole by comparison with an authentic sample. The mixture was stirred at room temperature and monitored by tlc. After 3.5 months a red solid was filtered, washed with diethyl ether and identified as pyrrole 3f (0.09 g, 0.25 mmole; 36%).

General Procedure for the Reaction of 5-Amino-1-aryl-4-(cyanoformimidoyl)imidazole 7a-c with Dimethylformamide Diethyl Acetal.

Dimethylformamide diethyl acetal (1.5 equivalents) was added to a suspension of the imidazole 7 in acetonitrile under magnetic stirring at room temperature. The reaction was monitored by tlc

until all the starting material was consumed (1-2 hours). Concentradon of the reaction mixture in the rotary evaporator gave a white solid that was filtered and washed with diethyl ether. The solid was identified as the 9-aryl-6-cyanopurine 2.

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