Synthesis of (*Z*)-*N*-(2-amino-1,2-dicyanovinyl)formamide *O*-alkyloximes and a study of their cyclization in the presence of base

Brian L. Booth,[a] Flora A. T. Costa,[b] Zahid Mahmood,[a] Robin G. Pritchard[a] and M. Fernanda Proença*[b]

[a] *Department of Chemistry, UMIST, PO Box 88, Manchester, UK M60 1QD*
[b] *Departamento de Química, Universidade do Minho, Campus de Gualtar, 4710 Braga, Portugal*

Received (in Cambridge) 17th February 1999, Accepted 17th May 1999

The title compounds (**3**) have been prepared in high yield by reaction of (*Z*)-*N*-(2-amino-1,2-dicyanovinyl)-formimidate with an alkoxyamine NH_2OR (R = CH_2Ph, Me). These compounds cyclize to the corresponding 5-amino-4-cyanoimidazoles **4** by reaction with ethanolic NaOH solution. In ethyl acetate and using DBU as a base, amidoximes **3** follow an unexpected cyclization pathway leading to a pyrimidine structure **5**. Single-crystal X-ray structures have been obtained for both the amidoxime **3a** and the pyrimidine **5a** (R = CH_2Ph). A strong intramolecular H-bond in the amidoxime structure, which was identified both in the solid state and in solution, may be responsible for the unusual cyclization pattern observed in these compounds.

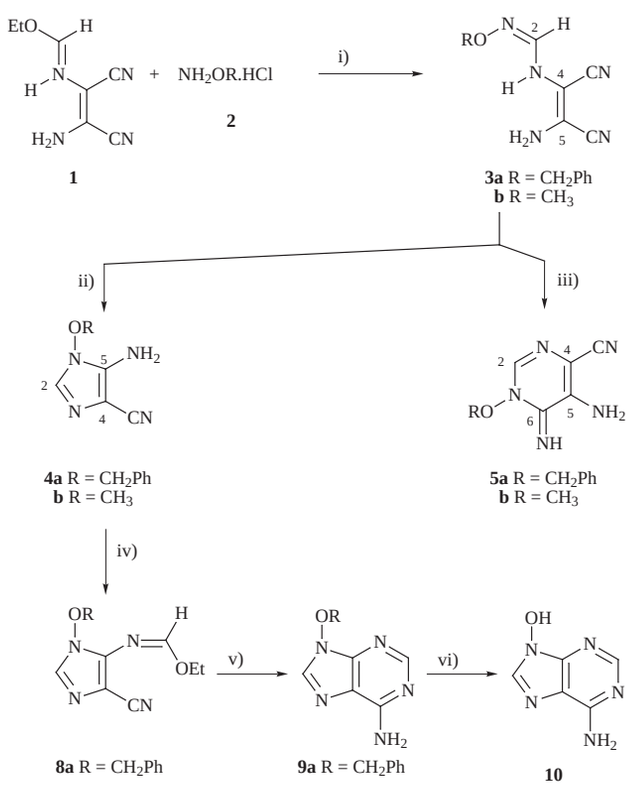
Introduction

A variety of (*Z*)-*N*-(2-amino-1,2-dicyanovinyl)formamidines[1–6] and formamidrazones[7–10] have been previously prepared in our group, and these compounds have proved to be versatile reagents in the synthesis of nitrogen heterocycles, including 6-carbamoylpurines and 1,2-dihydropurines, imidazoles, pyrroles and pyrrolo-triazepines. These results prompted us to investigate the synthesis of the corresponding *O*-alkyl-amidoximes, as they could be used as the starting material for the synthesis of *N*-alkoxypurines which are analogues of anti-cancer and anti-viral agents.[11] Considering that the imidazole ring has been traditionally obtained when the amidines or amidrazones were treated with base, similar reaction conditions were used with the amidoximes that were isolated.

Results and discussion

In a small scale reaction, the commercially available hydrochloride salt of *O*-benzylhydroxylamine was caused to react with ethyl (*Z*)-*N*-(2-amino-1,2-dicyanovinyl)formimidate leading to diaminomaleonitrile as the only product (as shown by TLC) after 5 min at room temperature in ethanolic solution. Neutralisation of the ammonium salt with either one equivalent of DBU or with 1 M aqueous sodium hydroxide solution, followed by reaction of the *O*-benzylhydroxylamine with imidate **1** gave the amidoxime **3a** in good yield (Scheme 1). When this reaction is carried out in a small volume of ethanol some diaminomaleonitrile formation is still observed, but the desired product **3a** can be obtained in 70% isolated yield after chromatography. Reaction in THF is very slow at room temperature (4 days), but a clean reaction ensues and a 97% isolated yield of pure **3a** can be obtained after simple filtration. The most effective conditions for the preparation of **3a** are to reflux an equimolar mixture of **1** and *O*-benzylhydroxylamine in diethyl ether. On cooling, the product precipitates from the ether to give a 97% yield of pure **3a** after 3 h. The first procedure was also used for the synthesis of amidoxime **3b**, which was isolated in 65% yield (Table 1).

The structure of amidoxime **3a** was confirmed by X-ray crystallography (Fig. 1). Bond angle and torsion angle analysis indicate that the amidine and diaminomaleonitrile units are



Scheme 1 *Reagents and conditions*: i, EtOH, RT, 2 h–2 days; ii, NaOH, EtOH, RT; iii, DBU, ¼ equiv.; ethyl acetate, RT; iv, Ac_2O, $CH(OEt)_3$, reflux, 16 h; v, NH_3(aq), MeOH, RT, 2 h; vi, HBr 32% in AcOH, steam bath, 3.5 h.

twisted, preventing extended conjugation [bond length N(2)–C(1) = 1.45 Å and conformation angle C(2)–C(1)–N(2)–C(10) = −140°]. The phenyl group is oriented perpendicularly to the plane of the amidine ring [conformation angle O(1)–C(9)–C(8)–C(3) = −95°] and the N(1)–C(10) and C(10)–N(2) bonds are both short (1.29 Å and 1.33 Å respectively) which is indicative of delocalized double bond character. In the solid state there is strong intramolecular bonding between O(1) and

Table 1 Microanalytical, mp and mass spectroscopic data for compounds **3**, **4** and **5**

Compound (Formula)	Mp/°C (decomp.)	Yield (%)	Found (%) (Required) C	H	N	*m/z* (EI)
3a	143–145	70[a]	59.8	4.7	29.2	241 (39.9%, M^+)
($C_{12}H_{11}N_5O$)		97[b]	(59.8)	(4.6)	(29.0)	224 (100)
		97[c]				
3b	141–142	65		165.0652		165 (16.1%, M^+)
($C_6H_7N_5O$)				(165.0651)[f]		59 (100)
4a	112–115	63[d]	61.9	4.8	25.9	214 (25.9%, M^+)
($C_{11}H_{10}N_4O$)		82[e]	(61.7)	(4.7)	(26.2)	91 (100)
4b	154–155	16	43.5	4.4	40.4	138 (40.1%, M^+)
($C_5H_6N_4O$)			(43.5)	(4.3)	(40.6)	107 (100)
5a	200–209	81	59.8	4.7	28.6	242 (100%, M + 1^+)[g]
($C_{12}H_{11}N_5O$)			(59.8)	(4.6)	(29.0)	
5b	192–194	90	43.7	4.2	42.0	165 (7.0%, M^+)
($C_6H_7N_5O$)			(43.6)	(4.2)	(42.4)	92 (100)
8	—	82	57.7	5.3	18.3	271 (100%, M + 1^+)[g]
($C_{14}H_{14}N_4O_2 \cdot H_2O$)			(58.3)	(4.9)	(18.4)	
9	165–166	80	59.8	4.5	28.7	242 (100%, M + 1^+)[g]
($C_{12}H_{11}N_5O$)			(59.8)	(4.6)	(29.0)	
10	330–331	75	39.5	3.2	46.1	152 (M + $1)^{+a}$
($C_5H_5N_5O$)			(39.7)	(3.3)	(46.8)	

[a] Using Procedure 1. [b] Using Procedure 2. [c] Using Procedure 3. [d] Using 2 M solution of KOH in ethanol. [e] Using a large excess of 1 M aqueous KOH in solution. [f] High resolution mass spectroscopy. [g] Fast atom bombardment.

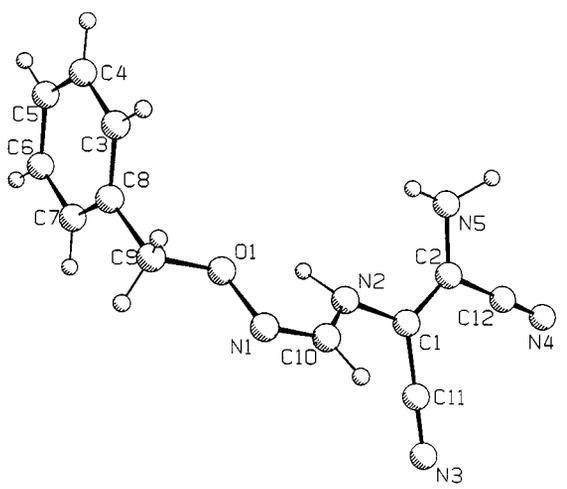


Fig. 1 X-Ray crystal structure of (*Z*)-*N*-(2-amino-1,2-dicyanovinyl) formamide *O*-benzyloxime **3a**.

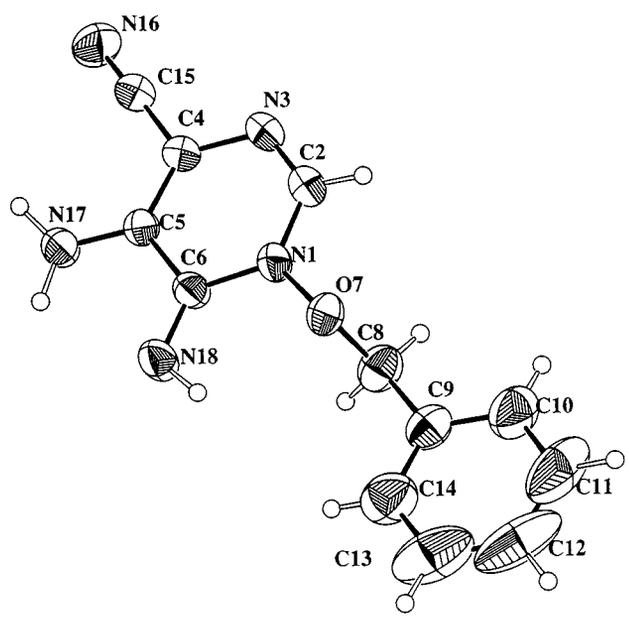


Fig. 2 X-Ray crystal structure of *N*-benzyloxy-5-amino-4-cyano-6-imino-1,6-dihydropyrimidine **5a**.

the hydrogen on N(2), responsible for a stable *Z* configuration of the amidine moiety. The bond angle N(1)–C(10)–N(2) of 125.7° is considered a typical feature of the *Z* configuration in amidines, in contrast with the *E* configuration where this bond angle is less than 124°.[12] The adjacent angles O(1)–N(1)–C(10) and C(10)–N(2)–H(2) measured 108.4° and 125° respectively.

The IR spectra of the amidoximes **3** show intense bands in the 3200–3400 cm^{-1} region (*v* NH) and both C≡N groups are visible at 2248 and 2202 cm^{-1} for **3a** and 2232 and 2213 cm^{-1} for **3b.** In the ^1H NMR spectrum, the chemical shift value for the C(2) proton is δ 6.8 ppm for **3a** and **3b**, coupling with the adjacent N–H with coupling constants of 9 Hz and 10.2 Hz respectively. This result seems to indicate that the *Z-anti* configuration is maintained in DMSO solution, in contrast with the analogous *N*-aryl amidines where the *E-syn* configuration is preferred [C(2)–H appears in the range δ 7.9–8.3 ppm and *J* CH–NH≅5 Hz].

The amidoximes **3a** and **3b** cyclized in the presence of ethanolic potassium or sodium hydroxide leading to the corresponding 5-amino-4-cyanoimidazoles **4**. Imidazole **4a** is formed after only 15 min at room temperature, precipitating out of the reaction mixture in 63% yield. The use of a large excess of 1 M aqueous KOH in this reaction affords **4a** in an improved yield of 82%. The product precipitates from solution and can be isolated by simple filtration and washing.

Imidazole **4b** is the only product in solution after almost two days at room temperature, but the solid could only be obtained after dry flash chromatography. The poor isolated yield (17%) reflects the difficulty in removing this compound from the column, even when using a large volume of diethyl ether.

When DBU was added to a solution of amidoximes **3** in ethyl acetate, a different product immediately precipitated from the reaction mixture and has been identified as the pyrimidine **5** by single crystal X-ray structure analysis of **5a**. From Fig. 2 it can be seen that the pyrimidine ring is planar and parallel to the aromatic ring. The C(6)–N(18) and C(2)–N(3) bonds are short (1.273 Å and 1.277 Å respectively) indicative of double bond character. This must be affecting the bond angles in their vicinity as C(5)–C(6)–N(1) measures 112.2°, C(6)–N(1)–C(2) measures 125.5° and N(1)–C(6)–N(3) measures 123.3° [expected for an unsubstituted pyrimidine ring: 121.3°, 115° and 129.7° respectively].[13] The IR spectra of all compounds show a

Table 2 ^{1}H NMR spectroscopic data for compounds **3**, **4** and **5**

Compound	δ([$^2H_6$]Me_2SO; 300 MHz)
3a	8.1 (d, J = 9 Hz, 1H, NH), 7.05 (s, 2H, NH_2), 6.8 (d, J = 9 Hz, 1H, CH), 5.0 (s, 2H, CH_2), 7.2–7.4 (m, 5H, Ph)
3b	8.1 (d, J = 10 Hz, 1H, NH), 7.0 (s, 2H, NH_2), 6.8 (d, J = 10 Hz, CH), 3.7 (s, 3H, CH_3)
4a	7.28 (s, 1H, CH), 6.56 (s, 2H, NH_2), 5.14 (s, 2H, CH_2), 7.4–7.51 (m, 5H, Ph)
4b	7.58 (s, 1H, CH), 6.60 (s, 2H, NH_2), 3.93 (s, 3H, CH_3)
5a	A: 7.7 (s, 1H, CH), 7.5 (s, 1H, NH), 6.6 (s, 2H, NH_2), 5.1 (s, 2H, CH_2), 7.3–7.5 (m, 5H, Ar) B: 8.1 (s, 1H, NH), 7.6 (s, 1H, CH), 6.9 (s, 2H, NH_2), 5.2 (s, 2H, CH_2), 7.3–7.5 (m, 5H, Ar) A : B, 3 : 1 ratio
5b	A: 7.9 (s, 1H, CH), 7.6 (s, 1H, NH), 6.6, (s, 2H, NH_2), 3.9 (s, 3H, CH_3) B: 8.0 (s, 1H, NH), 7.8 (s, 1H, CH), 6.9 (s, 2H, NH_2), 3.9 (s, 3H, CH_3) A : B, 5 : 1 ratio
8	8.3 (s, 1H, CH), 7.95 (s, 1H, CH), 7.36–7.45 (m, 5H, Ph), 5.22 (s, 2H, CH_2), 4.28 (q, 2H, J = 7 Hz, CH_2), 1.28 (t, 3H, CH_3)
9	8.25 (s, 1H, CH), 8.15 (s, 1H, CH), 7.25–7.38 (m, 5H, Ph), 7.2 (br s, 2H, NH_2), 5.4 (s, 2H, CH_2)

Table 3 ^{13}C NMR spectroscopic data for compounds **3**, **4** and **5**

	δ_C([$^2H_6$]Me_2SO; 75 MHz)					
Compound	C(2)	C(4)	C(5)	C(6)	CN	R
3a	140.2	94.7	120.1	—	116.5 114.8	74.4 (CH_2), 138.3, 128.5, 127.7, 127.5
3b	140.1	95.7	120.7	—	115.8 117.4	62.0 (CH_3)
4a	128.5	86.4	144.3	—	117.2	80.8 (CH_2), 133.6, 130.6, 129.9, 129.0
4b	127.2	86.1	143.7	—	117.0	67.1 (CH_3)
5a[a]	136.5	97.5	142.7	144.7	117.1	78.4 (CH_2), 130.2, 129.4, 128.7, 133.4
5b[b]	136.8	98.6	144.1	144.4	118.2	66.1 (CH_3)
8	146.3	135.9	136.4	—	119.6	18.2 (CH_3), 67.9 (CH_2), 85.7, (OCH_2), 133.9, 134.0, 134.2, 165.5 (C=N)
9	158.3	150.4	120.1	161.3	—	85.8 (CH_2), 133.7, 134.5, 134.8, 141.9, 150.0

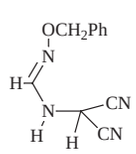
[a] Only one set of bands is visible in the spectrum. [b] The data recorded belongs to the most abundant species, A. For B, the only signal which is visible in the spectrum corresponds to C(2) at δ 138.4 ppm.

medium–strong band at 2210 cm^{-1} for the C≡N stretching vibration. The corresponding carbon atom can be identified in the ^{13}C NMR at 117.1 (**5a**) and 118.2 (**5b**) ppm. Only one set of bands is visible in the ^{13}C NMR spectrum of each compound, which is in contrast with the data registered in the ^{1}H NMR, where two sets of bands are always present in a 3 : 1 ratio (**5a**) and 5 : 1 ratio (**5b**).

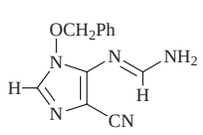
The structure of the 5-amino-4-cyano imidazoles **4** was assigned on the basis of elemental analysis and spectroscopic data. The C≡N stretching vibration is a typical feature in the IR spectrum of these compounds and corresponds to an intense band at 2215 cm^{-1} (**4a**) and 2211 cm^{-1} (**4b**). A strong band at around 1650 cm^{-1} is visible in both spectra and may be assigned to the C=N stretching vibration. In the ^{1}H NMR spectrum, the NH_2 group always shows up as a singlet in the δ 6.5–6.6 ppm region and this seems to be a typical feature of the 5-amino-4-cyanoimidazoles that have been prepared (see Table 2).[1,2,4,10] The C–H proton gives a sharp singlet at δ 7.28 (**4a**) and δ 7.58 (**4b**) ppm. All the bands in the ^{13}C NMR are sharp, with the signals for C(4) and C(5) around δ 86 and 144 ppm respectively (see Table 3).

The synthesis of imidazole **4a** has been previously reported by Watson[14] from the reaction of aminomalononitrile toluene-*p*-sulfonate and triethyl orthoformate to form the imino ether tosylate, which on reflux with an equivalent of benzyloxyamine in ether gave the product as white crystals in only 19% yield. Considering that both the melting point and spectroscopic data for this compound were different from the values now reported, the experimental procedure described in the literature was carefully reproduced. In the complex reaction mixture it was possible to identify the presence of imidazole **4a** (by TLC) and this compound was selectively isolated in less than 1% yield. The ^{1}H NMR and IR data on this compound, compare exactly with the values that were obtained in this present work for the solid isolated in the cyclization of amidine **3a** by alcoholic sodium hydroxide solution. Attempts to isolate the product previously identified as the imidazole[14] led to a complex mixture. ^{1}H NMR spectroscopic examination of the oil showed the presence of the bands assigned by Watson to the imidazole **4a**, clearly indicating that this is a different compound.

The ^{1}H NMR data reported by Watson indicate a C(2)–H proton at δ 6.84 and NH_2 protons at δ 5.00 ppm (*cf.* δ 7.28 and 6.56 ppm respectively for compound **4a**). In earlier work[1] we have described a large number of substituted 5-amino-4-cyanoimidazole derivatives and in all cases the C(2)–H proton of the imidazole ring appears within a relatively narrow range of δ 7.15 to 7.65 ppm. A chemical shift of δ 6.84 ppm is unprecedented. In contrast, the CHN_2 proton of the amidines **3a** and **3b**, which appear in the NMR spectrum at δ 6.80 ppm (see Table 2) agree well with the figure quoted by Watson.[14] For this reason, we feel that the most plausible structure for the compound isolated by Watson is the amidine **4c**, *i.e.* an isomer



4c



11

and precursor to the imidazole **4a**. The signal attributed by him to an NH_2 group could arise by the accidental equivalence of the $CH(CN)_2$ proton and the NH proton. Such an amidine might be expected to tautomerise in solution and coupling between the CH and NH protons might not be observed.

The different behaviour of the amidines **3a** and **b** in the presence of KOH and DBU requires explanation. In the presence of a relatively strong base KOH in ethanol or water there is good evidence to indicate that the amidines **3** are deprotonated to form an anion. So, for example, when NaOH (2×10^{-2} mol dm^{-3}) in ethanol was added to a solution of amidine **3a**

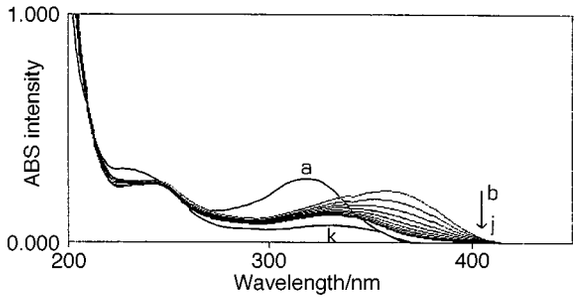


Fig. 3 Changes in the UV spectrum of amidine **3a** (1.53×10^{-5} mol dm^{-3} in ethanol, 2 cm^3) by addition of 0.25 cm^3 NaOH (2×10^{-2} mol dm^{-3}) in ethanol: (a) **3a** in the absence of base, (b) immediately after the addition of NaOH in ethanol, (b–j) spectra recorded at an interval of 10 min, (k) spectrum recorded after 24 h.

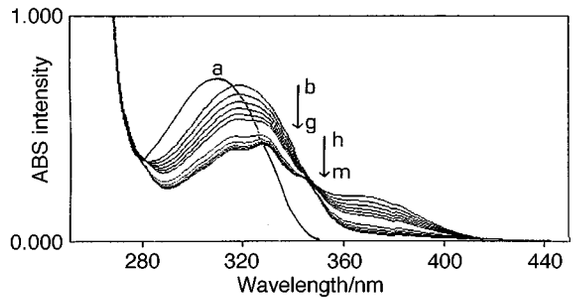
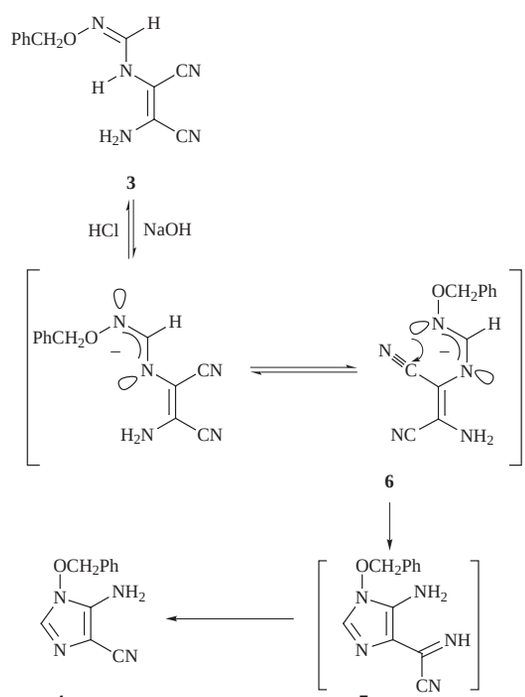


Fig. 4 Changes in the UV spectrum of amidine **3a** (4.15×10^{-5} mol dm^{-3} in ethyl acetate, 2 cm^3) by addition of DBU (10 μl): (a) **3a** in the absence of DBU, (b) immediately after the addition of 10 μl of DBU, (b–g) spectra recorded at an interval of 60 s, (h) spectrum recorded 300 s after (g), (h–m) spectra recorded at an interval of 200 s.

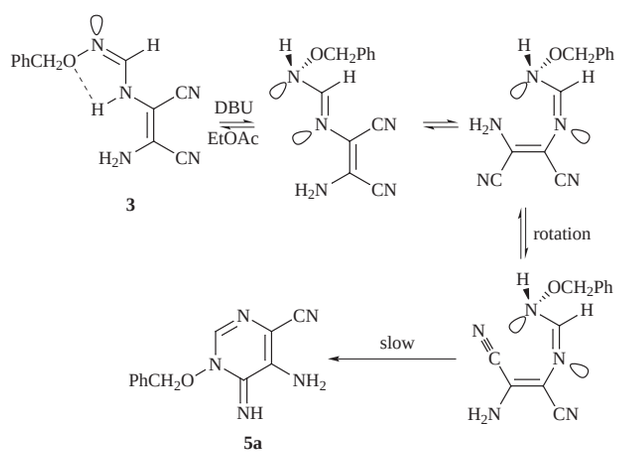
(1.53×10^{-5} mol dm^{-3}) in ethanol (2 ml) the UV absorption band with a maximum at λ_{max} (EtOH)/nm 320 (ε/dm^3 mol^{-1} cm^{-1} 17 400) for the amidine rapidly shifts to λ_{max} (EtOH)/nm 360 for the anion. This absorption band gradually loses intensity and after 24 h at room temperature the only UV signal visible is that of the imidazole **4a** λ_{max} (EtOH)/nm 240 (ε/dm^3 mol^{-1} cm^{-1} 13 800) (see Fig. 3). In a separate experiment it has been shown that the band at 360 nm for the anion reverts to the initial amidine signal at 320 nm upon addition of hydrochloric acid. It is clear from this experiment that the formation of the anion is both rapid and quantitative in the presence of HO^- ion, and that cyclisation to the unstable imidazole **7** and, hence, the isolated product **4a** is a much slower reaction. It is likely that the anion adopts the conformation shown in Scheme 2, in



Scheme 2

which the lone pair of electrons on the nitrogen atoms are in an *anti*-position to minimise repulsion.

In the presence of the weaker base DBU in ethyl acetate or diethyl ether, the concentration of the anion will be very low and cyclisation to an imidazole will be very slow. This has been demonstrated by addition of DBU (10 μl) to a solution of amidine **3a** (4.15×10^{-5} mol dm^{-3}) in ethyl acetate (2 ml). The UV absorption band with a maximum at λ_{max} (EtOAc)/nm 310 (ε/dm^3 mol^{-1} cm^{-1} 17 400) for the amidine gradually reduces in intensity (see Fig. 4) and, after 30 min at room temperature absorption bands for the pyrimidine [λ_{max} (EtOAc)/nm 328 (ε/dm^3 mol^{-1} cm^{-1} 8 000), 280 (5 200), 345 (13 800)] were the only ones observed. There was no evidence for a band at 360 nm for the anion. The fact that cyclisation to an imidazole does not occur in this case with DBU is a little surprising as DBU does still catalyse cyclisation of amidines having *N*-alkyl, -benzyl and -aryl substituents to form imidazoles of type **7** in high yields.[1,2,4,10] Perhaps, the difference of the *O*-alkyl substituent increases the basicity of amidine or the difference may be associated with the strong intramolecular H-bonding between the N–H and the O atom observed in the X-ray structure of the amidine. The formation of pyrimidine **5a** requires rotation about the C=C bond of the amidine as shown in Scheme 3 and it is not clear what role, if any, the DBU plays in accelerating this rotation. The DBU may also catalyse tautomerism in the amidine and this may play a part in determining this unusual outcome (see Scheme 3). Further work is being carried out to establish the mechanism of pyrimidine formation.



Scheme 3

Watson[14] converted his supposed **4a** into 9-hydroxyadenine **10** *via* a two step procedure involving heating with triethyl orthoformate, followed by treatment with ammonia. He identified the product of this reaction as 9-benzyloxyadenine **9a**, which was then debenzylated with 32% aqueous hydrogen bromide in glacial acetic acid to give 9-hydroxyadenine. We have repeated this sequence with our compound **4a**, and after treatment with triethyl orthoformate in glacial acetic acid the imidate intermediate **8a** was isolated and fully characterised, before treatment with ammonia to produce **9a** in 80% yield. The ^{1}H NMR spectrum of **9a** showed some significant differences from those reported by Watson.[14] In particular this can be observed in the chemical shift values of the 8-H proton and the NH_2 protons: [δ_H reported[14] (60 MHz, d_6-DMSO) 8.40 (s, 1H, 2-H), 7.40 (s, 1H, 8-H), 7.33 (s, 5H, Ph), 6.63 (s, 2 H, NH_2), 5.37 (s, 2 H, OCH_2). δ_H our work (300 MHz, d_6-DMSO) 8.25 (s,

Table 4 Crystal data and details of refinement for compounds **3a** and **5a**

Compound	**3a**	**5a**
Formula	$C_{12}H_{11}N_5O$	$C_{12}H_{11}N_5O$
M	241.26	241.26
Crystal system	tetragonal	monoclinic
Crystal size/mm	0.40 × 0.15 × 0.15	0.35 × 0.25 × 0.20
Temperature of data collection	293 K	293 K
Space group	$P42_1c$	$P2_1$
a/Å	19.028(4)	8.3838(10)
b/Å		6.6380(10)
c/Å	7.014(3)	10.580(2)
β/°		93.35(2)
U/Å^3	2540(1)	587.8(2)
Z	8	2
D_c/g cm^{-3}	1.262	1.363
F(000)	1008	252
μ/cm^{-1}	0.81	0.94
λ/Å	0.71069	0.71069
θ range for data collection/°	2–25°	2–25°
Index ranges	$0 \le h \le 22$	$-7 \le h \le 9$
	$0 \le k \le 22$	$0 \le k \le 7$
	$0 \le l \le 8$	$-12 \le l \le 12$
Measured reflections	1291	2162
Independent reflections	1291	1132 ($R_{int} = 0.019$)
Final R [$I > 2\sigma(I)$]	$R_1 = 0.047$	$R_1 = 0.034$
	$wR_2 = 0.128$	$wR_2 = 0.106$
R (all data)	$R_1 = 0.200$	$R_1 = 0.043$
	$wR_2 = 0.187$	$wR_2 = 0.115$

1H, 2-H), 8.15 (s, 1H, 8-H), 7.25–7.38 (m, 5H, Ph), 7.20 (br s, 2H, NH_2), 5.37 (s, 2H, OCH_2) ppm]. In our experience the ^{1}H NMR spectra of adenine derivatives invariably show the 8-H proton in the range of δ 8.00 to 8.40 ppm, with the 2-H proton at lower field. Watson's value of δ 7.40 is more typical of an imidazole derivative (*vide supra*). These differences can be understood if Watson's 9-benzoyladenine is, in fact, the intermediate **11** and the band he assigns to 2-H, δ 8.40 ppm, is then attributable to the formamidine proton. This structure would also explain the observed differences in the NH_2 protons. It is noticeable, that our compound **9** and Watson's compound have the same mp, and perhaps cyclisation occurs to give **9** on heating.

Debenzylation of either **9a** or, what we now believe to be **11**, result in the same compound, namely 9-hydroxyadenine implying that heating under strong acid conditions results in initial cyclisation of **11** to **9a**, prior to debenzylation.

Experimental

Ethyl (*Z*)-*N*-(2-amino-1,2-dicyanovinyl)formimidate **1** used in this work was prepared by a procedure described previously.[15]

IR spectra were recorded on a Perkin-Elmer 1600 series FTIR spectrometer, ^{1}H and ^{13}C NMR spectra on a Bruker XL 300 spectrometer and mass spectra on a GC-MS Automass 120 or on a Kratos Concept instrument.

Crystallography

Crystal data and refinement details for compounds **3a** and **5a** are presented in Table 4. Both crystals were mounted on a glass fibre. All measurements were made on a Rigaku AFC6S diffractometer employing graphite monochromated Mo-Kα radiation. The data were collected at a temperature of 23 ± 1 °C using the ω–2θ scanning technique to a maximum 2θ value of 50.0°. The structures were solved by direct methods using MITHRIL[16] and refined using DIRDIF.[17] The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined isotropically or were included in the structure factor calculation in idealized positions, and were assigned isotropic thermal parameters which were 20% greater than the equivalent B value of the atom to which they were bonded.

CCDC reference number 207/334.

See http://www.rsc.org/suppdata/p1/1999/1853 for crystallographic files in .cif format.

Synthesis of (*Z*)-*N*-(2-amino-1,2-dicyanovinyl)formamide *O*-benzyloxime (3a)

Procedure 1. A suspension of *O*-benzylhydroxylamine (1.02 g, 6.39 mmol) and DBU (156 µl, 6.39 mmol) in ethanol was stirred at room temperature until a homogeneous solution was obtained. The solvent was concentrated to low volume in the rotary evaporator and ethyl *N*-[*(Z)*-2-amino-1,2-dicyanovinyl]-formimidate (1.05 g, 6.39 mmol) was added. The mixture was stirred at room temperature for 2 h until TLC indicated that all the imidate had been consumed. The *title compound* was isolated by dry flash chromatography using diethyl ether as eluant (1.08 g, 4.48 mmol, 70%).

Procedure 2. *O*-Benzylhydroxylamine hydrochloride (2.6 g, 16.2 mmol) was neutralised with 1 M aqueous sodium hydroxide and the solution was then extracted with diethyl ether. The extract was dried ($MgSO_4$) and filtered and the solution was then added dropwise to a refluxing solution of ethyl (*Z*)-*N*-(2-amino-1,2-dicyanovinyl)formimidate (2.7 g, 16.2 mmol) in diethyl ether. After complete addition, reflux was continued for 3 h then on cooling the *title compound* precipitated as an analytically pure solid (3.8 g, 15.7 mmol, 97%).

Procedure 3. *O*-Benzylhydroxylamine (2.0 g, 16.2 mmol) and the formimidate (2.7 g, 16.2 mmol) were stirred at room temperature in dry THF (20 ml) until TLC (EtOAc–hexane, 1:1) showed complete reaction (4 days). Removal of the solvent and addition of diethyl ether gave the product (3.79 g, 15.7 mmol, 97%).

Synthesis of (*Z*)-*N*-(2-amino-1,2-dicyanovinyl)formamide *O*-methyloxime (3b)

Using Procedure 1, *O*-methylhydroxylamine hydrochloride (0.38 g, 4.60 mmol) was neutralised with DBU in ethanol and, after reduction in the volume, caused to react with the formimidate (0.75 g, 4.60 mmol) to give, after 2 days, the *title compound* (0.49 g, 3.0 mmol, 65%) isolated after flash chromatography.

Synthesis of 5-amino-4-cyano-1-benzyloxyimidazole (4a)

Procedure 1. The amidoxime **3a** (2.43g, 10 mmol) was solubilized in a 2 M solution of KOH in ethanol (20 cm^3) and the mixture was stirred at room temperature for 15 min. The brownish solid that precipitated from solution was filtered and washed with water and diethyl ether. The cream solid was identified as the *title compound* (1.36 g, 6.3 mmol, 63%) by elemental analysis and spectroscopic data.

Procedure 2. The amidoxime **3a** (3.0 g, 12.5 mmol) was added to an excess of 1 M aqueous KOH solution (120 ml) and after 5 min, the *title compound* precipitated as a white solid (2.18 g, 10.18 mmol, 74%) which was filtered, washed with diethyl ether and dried under vacuum.

Synthesis of 5-amino-4-cyano-1-methoxyimidazole (4b)

The amidoxime **3b** (0.34 g, 2.06 mmol) was solubilized in a 0.18 M solution of NaOH in ethanol (20 cm^3) and the solution was stirred at 4 °C for 17 hours and then at room temperature for 24 hours. The solid product was isolated by dry flash chromatography using diethyl ether as eluant. The cream solid was

identified as the *title compound* (0.05 g, 0.36 mmol, 17%) by elemental analysis and spectroscopic data.

Synthesis of 5-amino-1-benzyloxy-4-cyano-6-imino-1,6-dihydropyrimidine (5a)

Procedure 1. DBU (53 μl, 0.35 mmol) was added to a solution of the amidoxime **3a** (0.25 g, 1.04 mmol) in ethyl acetate (2 ml) and the solution was stirred at room temperature. After *ca*. 3 min, a cream solid started to precipitate out of solution and the suspension was stirred for a further 15 min, after which the solid was filtered and washed with diethyl ether to give **5a** (0.21 g, 0.84 mmol, 80%).

Procedure 2. A suspension of **3a** (3.0 g, 12.5 mmol) in diethyl ether (50 ml) was heated to reflux temperature and when the solution became homogeneous DBU (10 μl) was added dropwise. After 10 min the *title compound* precipitated as a white solid (1.48 g, 6.16 mmol, 74%) and was washed with cold diethyl ether and dried.

Synthesis of 5-amino-1-methoxy-4-cyano-6-imino-1,6-dihydropyrimidine (5b)

DBU (50 μl, 0.30 mmol) was added to a solution of the amidoxime **3b** (0.15 g, 0.90 mmol) in ethyl acetate (1 ml) and the solution was stirred at room temperature. After *ca*. 3 min, a cream solid started to precipitate out of solution and the suspension was stirred for a further 15 min, after which the solid was filtered and washed with diethyl ether to give **5b** (0.13 g, 0.80 mmol, 90%).

Synthesis of 1-benzyloxy-4-cyano-5-ethoxyformimidoylimidazole (8a)

Acetic anhydride (1.3 ml, 2.34 mmol) and triethyl orthoformate (4.66 ml, 2.3 mmol) were added to **4a** (0.5 g, 2.34 mmol) and the mixture was heated under reflux for 16 h. Removal of the volatiles on a rotary evaporator followed by addition of hexane to the residue gave the *title compound* as a white solid (0.52 g, 1.93 mmol, 82%).

Synthesis of 9-benzyloxyadenine (9a)

Aqueous ammonia solution (35 μl, 1.85 mmol) was added dropwise to a solution of **8a** (0.5 g, 1.85 mmol) in methanol (10 ml) and the mixture was stirred for 2 h, when the *title compound* (0.36 g, 1.49 mmol, 80%) precipitated out and was filtered, washed with diethyl ether, and dried.

Synthesis of 9-hydroxyadenine (10)

Compound **9** (0.2 g, 0.83 mmol) was added to 32% hydrogen bromide in glacial acetic acid (4 ml) and the solution was warmed on a steam bath for 3.5 h. The reaction mixture was then cooled and the hydrogen bromide salt of the *title compound* was filtered off and was washed with several portions of diethyl ether. The solid was dissolved in hot dilute aqueous ammonia solution (24 ml), treated with charcoal, filtered, and then addition of glacial acetic acid precipitated the product as white crystals (0.09 g, 75%), which were collected, washed with water, ethanol and diethyl ether, before drying under vacuum.

Acknowledgements

Thanks are due to PRAXIS XXI for a studentship award to Flora Costa (PRAXIS XXI/BD/5135/95) and to the University of Minho and the Foundation for Science and Technology, Portugal, for financial support. Thanks are also due to the ORS and the Charles Wallace Foundation for an award to Zahid Mahmood.

References

1 M. J. Alves, B. L. Booth, O. K. Al-Duaij, P. Eastwood, L. Nezhat, M. F. Proença and A. S. Ramos, *J. Chem. Res.* (*S*), 1993, 402; *J. Chem. Res.* (*M*), 1993, 2701.
2 B. L. Booth, A. M. Dias and M. F. Proença, *J. Chem. Soc.*, *Perkin Trans. 1*, 1992, 2119.
3 M. J. Alves, B. L. Booth, P. Eastwood, R. G. Pritchard and M. F. Proença, *J. Chem. Soc.*, *Chem. Commun.*, 1993, 834.
4 M. J. Alves, B. L. Booth and M. F. Proença, *J. Heterocyc. Chem.*, 1994, **31**, 345.
5 M. J. Alves, O. K. Al-Duaij, B. L. Booth, M. A. Carvalho, P. R. Eastwood and M. F. Proença, *J. Chem. Soc.*, *Perkin Trans. 1*, 1994, 3571.
6 M. J. Alves, B. L. Booth, M. A. Carvalho, R. G. Pritchard and M. F. Proença, *J. Heterocycl. Chem.*, 1997, **34**, 739.
7 M. J. Alves, B. L. Booth, A. P. Freitas and M. F. Proença, *J. Chem. Soc.*, *Perkin Trans. 1*, 1992, 913.
8 B. L. Booth, A. P. Freitas and M. F. Proença, *J. Chem. Res.* (*S*), 1993, 260; *J. Chem. Res.* (*M*), 1993, 1640.
9 B. L. Booth, A. P. Freitas and M. F. Proença, *J. Heterocycl. Chem.*, 1995, **32**, 457.
10 M. J. Alves, B. L. Booth, A. P. Freitas and M. F. Proença, *J. Chem. Soc.*, *Perkin Trans. 1*, 1992, 913.
11 (*a*) M. R. Harden, C. A. Parkin and P. G. Wyatt, *Tetrahedron Lett.*, 1988, **29**, 701; (*b*) M. R. Harden and R. L. Jarvest, *J. Chem. Soc.*, *Perkin Trans. 1*, 1990, 1705.
12 T. M. Krygowski and K. Wozniak, in *The Chemistry of Amidines and Imidates*, ed. S. Patai and Z. Rappoport, John Wiley & Sons, New York, 1991, vol. 2, p. 143.
13 D. J. Brown, in *Comprehensive Heterocyclic Chemistry*, ed. A. J. Boulton and A. McKillop, Pergamon Press, New York, 1984, vol. 3, p. 59.
14 A. A. Watson, *J. Org. Chem.*, 1977, **42**, 1610.
15 D. W. Woodward, USP 2 534 331/1950.
16 C. J. Gilmore, MITHRIL—an integrated direct methods computer program, *J. Appl. Crystallogr.*, 1984, **17**, 42.
17 P. T. Beurskens, DIRDIF: direct methods for difference structures—an automatic procedure for phase extension and refinement of difference structure factors. Technical report 1984/1 Crystallography Laboratory, Toernooiveld, 6525 Ed Nijmegan, Netherlands.

Paper 9/01332F