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A new and efficient approach to the synthesis of 6-amidino-2-oxopurines

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The reaction of 5-amino-4-cyanoformimidoylimidazoles **1a** and **1b** with tosyl isocyanate proved to be a mild and efficient method for the synthesis of the corresponding 6-amidino-2-oxopurines **5**. These compounds, which were isolated in almost quantitative yield, rearrange in the presence of acetic acid–DMF to give a pyrimido[5,4-*d*]-pyrimidin-2-one **6**. The structure of compound **6** was confirmed by X-ray crystallography. The pathway for both reactions is discussed. Studies on the reactivity of tosyl isocyanate with imidazoles **2**, **7**, **8** and **16**, obtained from **1** by selective acylation of the amino or imino nitrogen atoms, enabled clarification of the mechanism for purine formation.

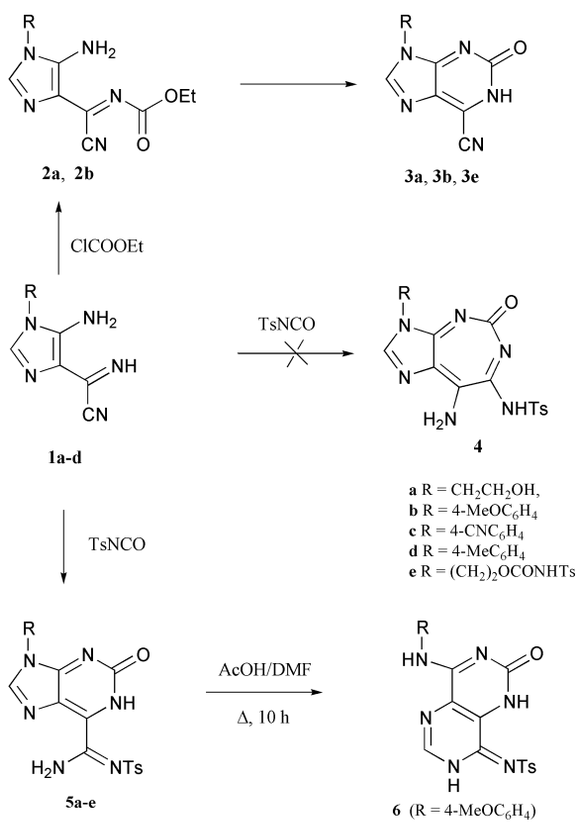
Introduction

Previous work in our research group has shown that 5-amino-4-cyanoformimidoylimidazoles **1** are versatile precursors of substituted purines. The reaction with ketones leads to 1,2-dihydro-6-carboxamidopurines and with aldehydes to the 6-carboxamidopurines.[1,2] In the presence of anhydrides, the 6-cyanopurines are formed,[3] and ethyl chloroformate leads to 6-cyano-2-oxopurines **3**.[4] We now describe the reaction of imidazoles **1** with tosyl isocyanate, which proved to be a simple and efficient method for the synthesis of 6-carboxamidino-2-oxopurines. A literature survey indicates that only a limited number of 6-carboxamidinopurines has been reported. These compounds were prepared from *N*-substituted 6-cyanopurines and 2-amino-6-cyanopurines, on treatment with a catalytic amount of sodium methoxide in methanol, followed by addition of ammonium chloride.[5] The same type of reaction was claimed to occur from 9-phenyl-6-cyanopurines after refluxing a methanolic or ethanolic solution of this compound with hydrazine, hydroxylamine, *n*-butylamine and piperidine.[6] The *N*-substituted imidazole ring has also been introduced in the 6-position of a 6-iodopurine. This reaction requires the initial formation of the imidazole anion (Li or Zn) at the 2-position, which was then coupled with a 6-iodopurine using a catalytic amount of Pd(0).[7]

Results and discussion

The reaction of imidazole **1** with a slight excess of tosyl isocyanate was carried out under a nitrogen atmosphere. The reagents were combined at 0 °C and the mixture was stirred at room temperature for a few hours. The products **5a**–**e** precipitated from the reaction mixture as yellow solid materials and were isolated by filtration in 85–99% yield (Scheme 1). This reaction is always accompanied by rapid colour and texture changes, which precede the formation of the final product. All attempts to isolate and characterise the intermediates were unsuccessful due to their instability in the solid state.

The reaction of imidazole **1** and tosyl isocyanate was previously investigated in our group and the product was initially thought to have the imidazo[4,5-*d*][1,3]diazepine structure **4** on the basis of elemental analysis and spectroscopic data, but



Scheme 1

this was subsequently shown by X-ray crystallography to be incorrect. Attempts to obtain crystals proved difficult as the compound was insoluble in most of the common organic solvents. Only by using a mixture of glacial acetic acid and DMF and allowing the solvent to evaporate slowly over a period of at least 6 months were obtained yellow needle crystals, suitable for X-ray analysis. Although this yellow solid was different from the yellow starting material according to IR, ^{1}H and ^{13}C NMR data, both structures had the same empirical formula, considering the elemental analysis results and that the

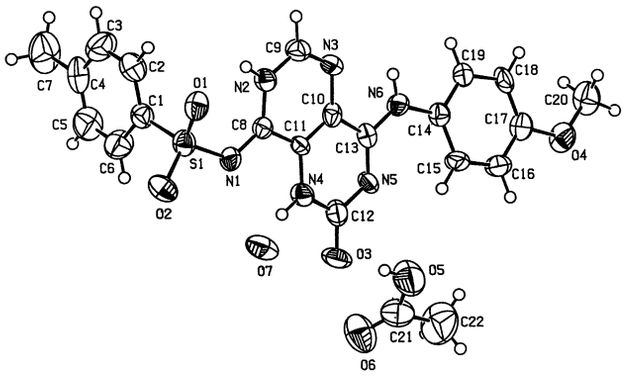
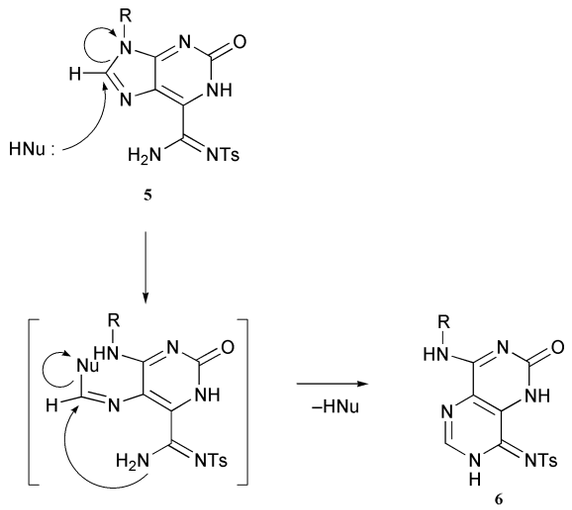


Fig. 1 *Ortep II*[14] plot of 4-(4′-methoxyphenyl)amino-8-(*N*-tosylimino)-7,8-dihydropyrimido[5,4-*d*]pyrimidin-2(1*H*)-one **6**. Displacement ellipsoids are drawn at the 50% probability level.

crystals incorporated one equivalent of acetic acid and water. The compound was identified as a pyrimido[5,4-*d*]pyrimidin-2-one **6** (R = 4-MeOC$_6$H$_4$) by X-ray diffraction (Fig. 1). Analysis of the X-ray data indicates that the tautomer which is present in the solid state shows an exocyclic double bond linking the toluene-*p*-sulfonamide substituent to the heterocyclic ring and that the three tautomerisable hydrogen atoms are located on N(2), N(4) and most likely N(6), although we cannot exclude the possibility of a mixture of protonation sites between N(6) and N(5). Bond length analysis suggests that there is no aromatic character of the fused pyrimido-pyrimidine ring due to the high double bond character of C(10)–C(11) [1.344(9) Å] and to the extended conjugation with the substituents on the ring. This conjugation is predominantly affecting the bonds: C(12)–N(5) [1.350(8) Å], N(5)–C(13) [1.320(8) Å] and C(13)–N(6) [1.333(8) Å] and also one of the amidine units N(2)–C(8) [1.339(9) Å] and C(8)–N(1) [1.318(8) Å]. The anisole ring is slightly distorted with respect to the pyrimido-pyrimidine system, which is mostly planar [torsion angles C(13)–N(6)–C(14)–C(19) = 173.1(6)°, N(2)–C(8)–C(11)–N(4) = 177.2(5)° and N(1)–C(8)–C(11)–C(10) = 176.3(6)°]. Intramolecular hydrogen bonding can be envisaged between N(4)H and N(1) [2.743(7) Å], between N(6)H and N(3) [2.728(7) Å] and also between N(2)H and O(1) [2.892(7) Å].

Further attempts to prepare compound **6** in a more convenient way included reflux for 15 h, of a solution of compound **5b** in glacial acetic acid and DMF. The pyrimido-pyrimidine **6** was isolated in only 38% yield, as a greenish-yellow solid. When ammonium acetate was added to a suspension of compound **5b** in glacial acetic acid and the mixture was refluxed for 4 h, the product precipitated on cooling and was isolated in 86% yield. Neither solid incorporates acetic acid, as evidenced by elemental analysis and spectroscopic data. The pyrimido-[5,4-*d*]pyrimidin-2-one structure **6** shows a typical carbonyl absorption in the IR spectrum at ν 1682 cm^{-1}. In the ^{1}H NMR spectrum, besides the signals for the tosyl and the aryl groups, a singlet at δ 8.26 ppm was assigned to the C–H proton. Only two N–H signals were visible at δ 10.0 and 10.1 ppm as broad singlets. In the ^{13}C NMR, it is possible to identify all the signals for the tosyl and aryl carbon atoms, but only four singlets are left for the six carbon atoms of the pyrimido-pyrimidine ring. From these, only the C–H could be assigned with certainty at δ 145.1 ppm. The three signals missing are likely to correspond to C(4a), C(8) and C(8a). These signals, which would normally be small, could disappear in the baseline due to ring tautomerism in solution. The presence of one equivalent of acetic acid in the crystals which were submitted for X-ray analysis was evident in the IR spectrum, which showed two intense bands at ν 1709 (acid C=O) and 1644 cm^{-1} (ring C=O). In the ^{1}H NMR spectrum, a singlet at δ 1.9 ppm, integrating for three protons, was assigned to the methyl group of the acetic acid molecule. In this sample, all the remaining signals showed exactly the same chemical shifts as those registered for the sample where no acetic acid was incorporated.

The formation of the pyrimido[5,4-*d*]pyrimidine **6** can be envisaged through the mechanism described in Scheme 2, by



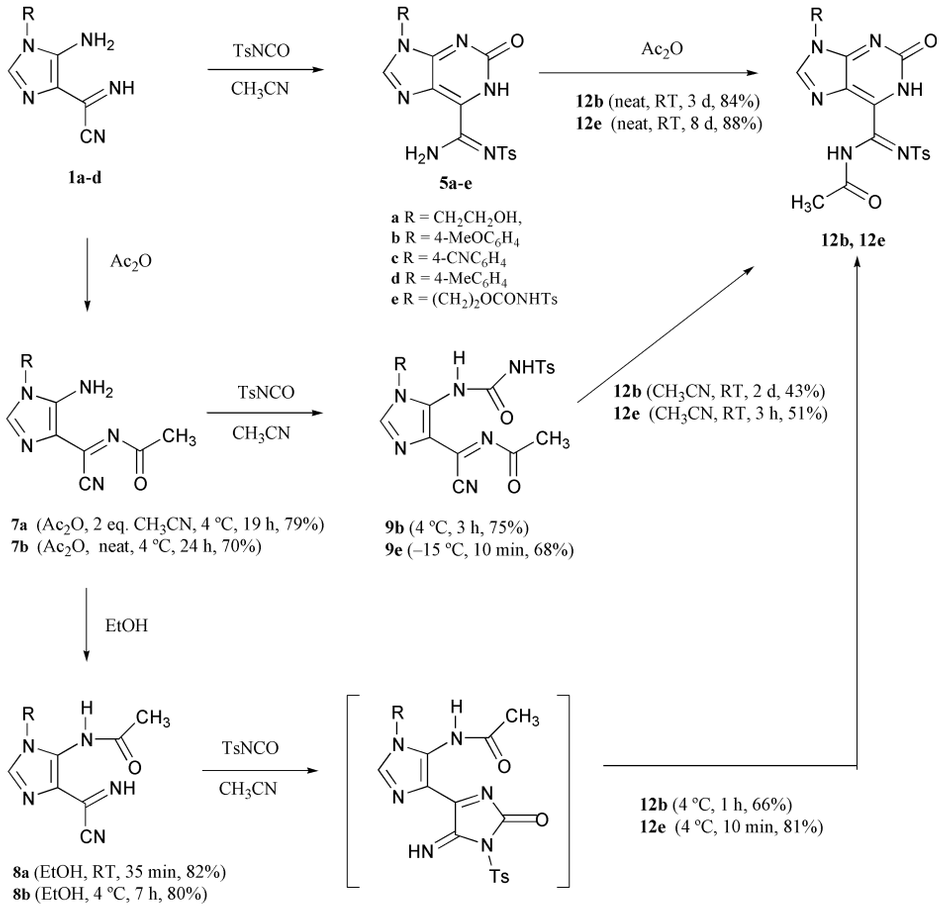
Scheme 2

rearrangement of a 6-(*N*-tosylamidino)-2-oxopurine **5** upon heating in the presence of any nucleophilic species. The structure of compound **5** is also supported by IR spectroscopy, where an intense band in the 1640–1660 cm^{-1} region can be assigned to the carbonyl stretching vibration. The stretching vibrations of the amino group are also present in the 3300–3390 cm^{-1} region. In the ^{1}H NMR, a one proton singlet at δ 8.4–9.0 ppm was assigned to the C(8)–H. The two protons of the amino group are non-equivalent leading to two broad singlets, each one integrating to less than one proton, around δ 8.7 and 9.2 ppm. This non-equivalence was attributed to conjugation within the amidine substituent and to intramolecular hydrogen bonding with the imidazole nitrogen. The ^{13}C NMR spectrum confirms the presence of the tosyl group in all the compounds. The HMBC† technique was used for compound **5b**, which enabled the identification of C(8) at δ 146.0 ppm. The signals at δ 155.8 and 126.2 ppm showed three-bond interactions with C(8)H and were assigned respectively to C(4) and C(5). All the carbon atoms of the tosyl and aryl groups were clearly identified with this technique, and the remaining carbon atoms could be assigned with certainty to C(2), C(6) and C(10).

In order to clarify the mechanism for the reaction of imidazoles **1** with tosyl isocyanate and understand the first step in the reaction sequence, both the amino and the imino nitrogen atoms were selectively protected by acetylation. The reaction of imidazoles **1** with acetic anhydride using acetonitrile as solvent, was previously reported to cause *N*-acetylation in the 5-position of the imidazole ring.[8] A recent spectroscopic analysis using the HMBC technique, indicates that the acetyl group is initially located next to the imino nitrogen atom. Compound **7**, isolated as a yellow solid, is the kinetic product, and in ethanol solution the acetyl migration leads to the thermodynamically more stable structure **8**, a white solid material (Scheme 3).

The spectroscopic characterisation of compounds **7a** and **7b** shows the presence of an intense band in the IR spectrum at ν 1647 cm^{-1} (**7a**) and ν 1670 cm^{-1} (**7b**) respectively, which can be assigned to the stretching vibration of the carbonyl group. The stretching vibration of the cyano group is not visible in the spectrum of either compound **7a** or **7b**. In the ^{1}H NMR spectrum, the methyl group is a singlet at δ 2.2 ppm and the imidazole CH is also a singlet at δ 7.48 ppm (**7a**) and δ 7.66 ppm (**7b**). The ^{13}C NMR could be registered only for compound **7a** as in DMSO solution acetyl migration is a fast process for **7b**,

† HMBC = heteronuclear multiple bond correlation.

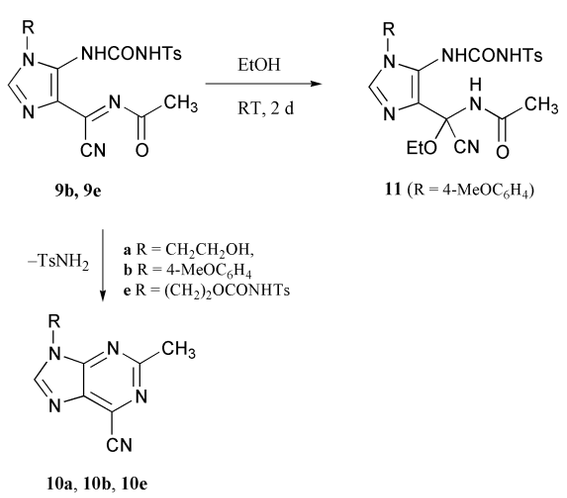


Scheme 3

leading to structure **8b**. For **7a** it is possible to identify the cyano group at δ 112.5 ppm and the CH at δ 139.8 ppm. The signal at δ 184.1 ppm was assigned to the carbonyl group. Using the HMBC technique, it is possible to detect a four-bond interaction between the methyl hydrogens and C(6) (δ 132.5 ppm). The three-bonds interaction between C(2)H, C(4) (δ 122.5 ppm) and C(5) (δ 151.5 ppm), unequivocally identifies these signals. For compounds **8**, the cyano stretching vibration is present in the IR spectrum as a weak signal at ν 2240 cm^{-1} (**8a**) and ν 2238 cm^{-1} (**8b**). The carbonyl stretching vibration is an intense band at ν 1696 cm^{-1} (**8a**) and ν 1682 cm^{-1} (**8b**). Two sets of bands (A and B) are visible for both compounds in the ^{1}H and ^{13}C NMR spectra. This may be due either to tautomerism or to intramolecular hydrogen bonding, for which two possibilities can be envisaged. In the ^{1}H NMR spectrum, the methyl group is a singlet in the δ 1.8–2.1 ppm region, and the imidazole C–H shows up in the δ 7.7–8.1 ppm region. From the HMBC spectrum, it was possible to identify C(2) in compound **8a** (δ 138.0 and 136.9 ppm), C(4) (δ 128.1 and 127.7 ppm) and C(5) (δ 129.1 and 128.6 ppm). The signal for C(4) was also confirmed by the three-bonds interaction with N–H (δ 11.4 ppm), together with the signal for the cyano group (δ 115.5 and 113.0 ppm).

The reaction of compound **7a** with tosyl isocyanate in acetonitrile, led to the isolation of the 5-ureidoimidazole **9e** in 68% yield after 10 minutes at −15 °C. The reaction of **7b** with tosyl isocyanate was carried out at 4 °C and the imidazole **9b** was isolated in 75% yield after 3 hours. Both compounds **9** show two intense bands in the IR spectrum, which can be assigned to the carbonyl stretching vibrations, at ν 1723 cm^{-1} (**9e**) and ν 1711 cm^{-1} (**9b**) for the urea and at ν 1670 cm^{-1} (**9e**) and ν 1686 cm^{-1} (**9b**) for the acetyl group. The cyano stretching vibration is a weak absorption at ν 2150 cm^{-1} (**9e**) and ν 2220 cm^{-1} (**9b**). In the ^{1}H NMR spectrum, the methyl group of the acetyl unit is a singlet at δ 2.17 ppm (**9e**) and δ 2.22 ppm (**9b**). The imidazole C–H is also a singlet at δ 7.83 ppm (**9e**) and δ 8.11 ppm (**9b**). The HMBC spectrum of **9e** identifies C(2) at δ 139.4 ppm and, as a three-bonds interaction, C(4) at δ 127.3 ppm and C(5) at δ 132.0 ppm. The carbonyl of the acetyl group could be identified at δ 182.2 ppm.

The ureido function in the 5-position of imidazoles **9** is very sensitive to hydrolysis in DMSO solution. After two days at room temperature, the starting material is no longer present. When the decomposition of **9e** is followed by ^{1}H NMR, at room temperature, the only compounds detected are toluene-*p*-sulfonamide and 6-cyano-2-methylpurine **10e**. From **9b**, toluene-*p*-sulfonamide is also formed, together with a 1 : 1 mixture of imidazole **8b** and 6-cyano-2-methylpurine **10b**. In ethanol solution, compound **9b** incorporates one equivalent of ethanol, leading to a white solid isolated in 58% yield and identified as compound **11** (Scheme 4) by elemental analysis and



Scheme 4

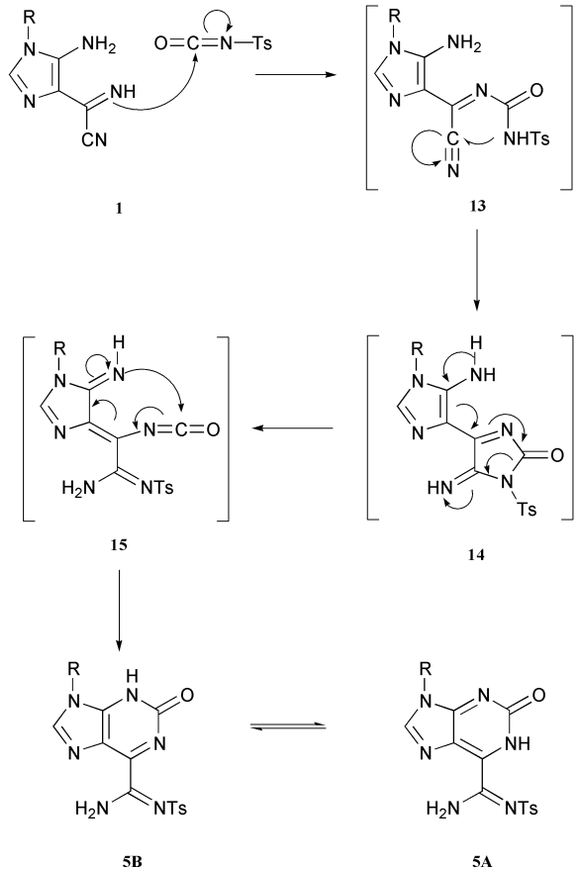
spectroscopic data. In the IR spectrum it is possible to identify an intense band at ν 1664 cm^{-1} with a shoulder at ν 1644 cm^{-1} which were assigned to the carbonyl stretching vibrations. The ^1H NMR shows a singlet for one proton at δ 7.85 ppm, typical of the imidazole structure. The HMBC technique indicates that the signal for the adjacent carbon atom [C(2)] is at δ 135.2 ppm and the three-bonds interaction enables the identification of C(4) at δ 130.5 ppm and C(5) at δ 123.1 ppm. The position of the ethoxy group is clearly indicated in the HMBC spectrum, as it is possible to identify the three-bonds interaction between the protons OCH_2 (δ 3.4 ppm) and the sp^3 carbon atom (δ 78.1 ppm). The NH signal at δ 7.95 ppm interacts with the bands at δ 123.1 ppm [C(5)] and δ 150.7 ppm (the ureido C=O). The NH signal at δ 9.06 ppm interacts with the bands at δ 78.1 ppm (the sp^3 carbon atom), δ 115.4 ppm (the CN), δ 130.5 ppm [C(4)] and δ 169.2 ppm (the acetyl C=O).

When a suspension of compounds **9e** or **9b** in dry acetonitrile was stirred at room temperature, the product isolated was the acetylated 6-amidino-2-oxopurine **12** (**12e**, 51% yield after 3 hours; **12b**, 43% yield after 2 days). When tosyl isocyanate was added to a suspension of **8a** or **8b** in acetonitrile, no intermediates were isolated, and the reaction mixture evolved directly to the same acetylated 6-amidino-2-oxopurine **12** (**12e**, 81% yield after 10 minutes at 0 °C; **12b**, 66% yield after 1 hour at 4 °C). This unexpected result prompted us to acetylate the 6-amidino-2-oxopurine **5**. When a neat mixture of purines **5e** or **5b** and acetic anhydride was stirred at room temperature, compound **12** was again the only product isolated (**12e**, 88% yield after 8 days; **12b**, 84% yield after 3 days).

The position of the acetyl group in compounds **12** was not easy to identify. These compounds showed a medium–intense band at ν 1770–1775 cm^{-1} in the IR spectrum, attributed to the stretching vibration of the carbonyl group in the acetyl unit. In the ^1H NMR spectrum of **12b**, the NH signal at δ 8.7 ppm is a sharp singlet, suggesting a strong intramolecular hydrogen bonding with N(7). In the HMBC it is possible to see the three-bond interaction of this proton with C(6) (δ 149.6 ppm). In compounds **12e** and **12b** it is also possible to see a four-bond interaction between the C–H of the methyl group and the carbon atom of the amidine function (δ 149.7 ppm for **12e** and δ 148.7 ppm for **12b**). The ^{13}C NMR spectrum also shows that the bands assigned to the ring carbon atoms are broad, indicating that tautomerism is still present. The fact that the acetyl group must be located on the amidine substituent is further supported by the reaction of the analogous 6-cyano-2-oxopurine **3b** with neat acetic anhydride. The starting material was recovered in 70% yield after 15 days at room temperature, suggesting that under these conditions, acetylation does not occur on the ring nitrogen atoms.

Considering that both *N*-acetylimidazoles **7** and **8** lead to the same acetylated purine **12** in the presence of tosyl isocyanate, then the reaction can start either at the 5-amino position or at the imino nitrogen, leading to the same product through different reaction pathways. The observation that the reaction of imidazoles **8** with tosyl isocyanate is much faster (10 minutes–1 hour) even at lower temperatures (0–4 °C), suggests that the imino nitrogen must react preferentially when both positions are free for nucleophilic attack. This indicates that the preferred pathway for the formation of purine **5** in the reaction of imidazole **1** with tosyl isocyanate, must be the one represented in Scheme 5. This mechanism requires that the intermediate **13**, initially formed, rapidly cyclises onto the adjacent cyano group. Ring opening of the imidazolone unit in structure **14** generates a reactive isocyanate function **15**, which is promptly trapped by intramolecular cyclisation with the 5-amino group. The same type of rearrangement was previously postulated for the reaction of azirines with tosyl isocyanate, where the intermediate isocyanate was isolated and characterised.[9]

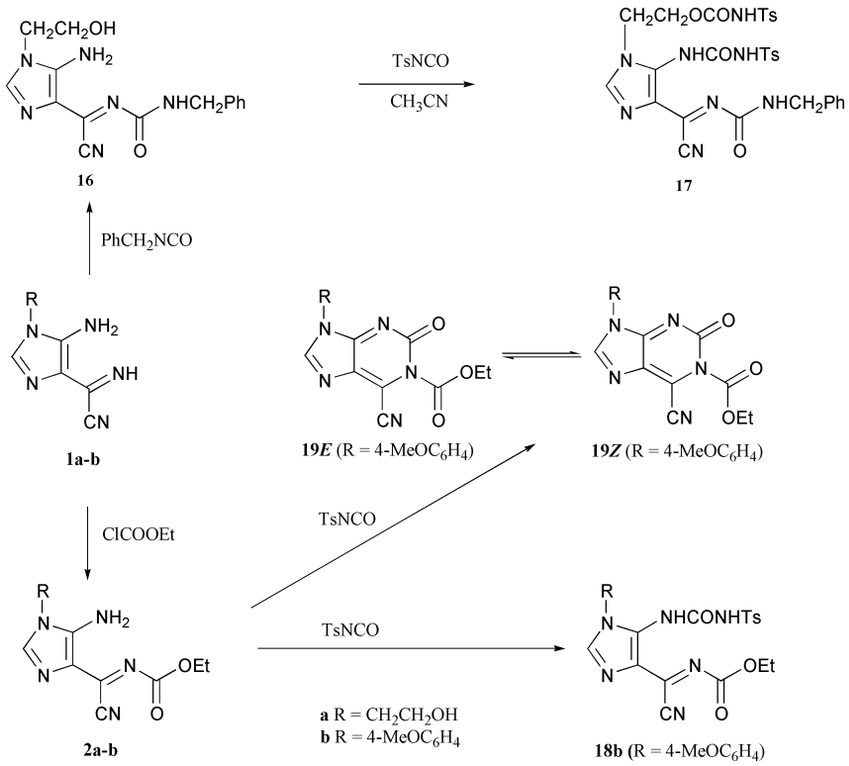
The fact that the same *N*-acetylpurine **12** is isolated either from imidazoles **7** or **8** and tosyl isocyanate or from purine **5**



Scheme 5

and acetic anhydride, indicates that the acetyl group is always incorporated in the same position of the purine structure, which must correspond to the thermodynamically stable compound. It is well known that acetyl groups can migrate both intra- and intermolecularly and this must be responsible for the facile formation of the thermodynamic product.

Other acyl groups are less prone to migration, which led us to the use of imidazoles **2** and **16** in the reaction with tosyl isocyanate (Scheme 6). Imidazoles **2** were prepared from the reaction of the appropriate 5-amino-4-cyanoformimidoylimidazole **1** with ethyl chloroformate in dry acetonitrile and pyridine. The position of the acyl group was confirmed by ^1H and ^{13}C NMR spectroscopy, using the HMBC technique for compound **2a**. Compound **2a** was isolated in 50% yield after 1 h at −15 °C, and compound **2b** was isolated in 88% yield after 24 h at 0 °C. Both compounds **2a** and **2b** were reacted with tosyl isocyanate, in dry acetonitrile and under a nitrogen atmosphere. Structure **18** could only be isolated in 40% yield from the reaction of **2b**, when the reaction mixture was kept at −4 °C for 15 min and then at room temperature for 1.5 h. When the reaction mixture was kept at room temperature for one week, under a dry atmosphere, addition of diethyl ether to the homogeneous solution led to a yellow solid identified as compound **19** (31% yield). This compound was characterised by elemental analysis and spectroscopic data. In the IR spectrum, a weak signal at ν 2232 cm^{-1} confirms the presence of the cyano group. Two equally intense bands are present in the spectrum for each carbonyl group (ν 1794 and 1767 cm^{-1} possibly for the ester carbonyl and ν 1699 and 1678 cm^{-1} for the 2-oxo group). This duplication of bands may indicate the co-existence of conformers *E* and *Z* (**19*E*** and **19*Z***) in the solid state. A similar situation was previously reported for carbimazole,[10] where two carbonyl groups are present in a comparable relative position. In this case, the two sets of bands registered in the IR spectrum of this compound were equally assigned to the *Z* and *E* conformers. In the



Scheme 6

^{1}H NMR spectrum of compound **19**, the singlet at δ 8.97 ppm was assigned to the C(8)H. In the ^{13}C NMR, the signal for C(8) was confirmed by DEPT ‡ 45 at δ 155.0 ppm. The two carbonyl carbon atoms were identified at δ 160.9 and 151.1 ppm.

The difficulties in the isolation of structure **18** are associated with the ease of hydrolysis of the ureido function, leading always to the starting material **2b** and, in part, to the 6-cyano-2-oxopurine **3b**. All attempts to follow the evolution of this compound by ^{1}H NMR either in deuterated DMSO or acetonitrile led exclusively to toluene-*p*-sulfonamide and imidazole **2b**.

Compound **17** was isolated in the reaction of imidazole **16** with 2.5 equivalents of tosyl isocyanate, in dry acetonitrile. The product precipitates out of solution as a pale yellow solid and was recovered in 51% yield. This compound is very insoluble in acetonitrile and no evolution is detected when the suspension is stirred at room temperature for 3 days. In a separate experiment, a catalytic amount of DBU was added to the previous reaction mixture and the suspension was stirred at room temperature. After 5 days, the starting material was recovered unchanged. Attempts to characterise compound **17** by NMR spectroscopy in deuterated DMSO led to complex mixtures. As soon as this compound is solubilised, a rapid evolution occurs, and it is possible to identify in the spectrum, the presence of the 6-cyano-2-oxopurine **3e** and the starting material **16**. No evidence is detected for the presence of the 6-amidino-2-oxopurine. A careful analysis of the ^{1}H and ^{13}C NMR spectra, using the HMBC technique, enables the unequivocal identification of some signals, which can be assigned to structure **17**. The imidazole C–H, at δ 7.70 ppm, shows direct interaction with the adjacent carbon, at δ 140.0 ppm and three-bonds interaction with C(4) (δ 127.1 ppm) and C(5) (δ 131.0 ppm). The assignment of C(5) is further confirmed by the three-bond interaction with the protons of the CH_2 (δ 4.38 ppm). The urea carbonyl groups show up at δ 150.5 and 160.8 ppm and the carbamate carbonyl at δ 150.6 ppm.

This study, carried out on the reaction of imidazoles **2** and **16** with tosyl isocyanate, indicates that when migration of the acyl protecting group is difficult, the formation of 6-amidino-2-oxopurine does not occur. This evidence further supports the mechanism presented for the reaction of 5-amino-4-cyanoformimidoylimidazole **1** with tosyl isocyanate, for which the first step is nucleophilic attack of the imino nitrogen on the carbon of the isocyanate function.

Experimental

The 5-amino-4-cyanoformimidoylimidazoles **1a**[2] and **1b–d**[11] used in this work were prepared by experimental procedures described previously. Cardice was obtained from Arlíquido, Portugal.

IR spectra were recorded on a Perkin-Elmer 1600 series FTIR spectrometer, ^{1}H and ^{13}C NMR spectra on a Varian Unity Plus spectrometer. Mass spectra were recorded on a GC-MS Automass 120 or on a Kratos Concept instrument. Analytical data for compounds **2**–**19** are given in Tables 1–4.

Crystallography §

The crystal was mounted on a glass fibre. All measurements were made on a CAD4 diffractometer using graphite monochromated Mo-Kα radiation. Data were collected using an $\omega/2\theta$ scanning technique up to a maximum 2θ value of 45.0° only, due to the poor diffraction power of the crystal, at room temperature. The structure was solved by direct methods using SHELXS-97[12] and refined using SHELXL-97.[13] The non-hydrogen atoms were refined anisotropically. The water hydrogen atoms could not be located reliably. The other hydrogen atoms were placed at calculated positions and refined as riding using the SHELXL-97 defaults.

Crystal data. $C_{20}H_{18}N_6SO_4$, $C_2H_4O_2$, H_2O, M = 516.54, monoclinic, a = 5.063(4) Å, b = 29.246(6) Å, c = 16.325(2) Å,

‡ DEPT = distortionless enhancements by polarisation transfer/ techniques.

§ CCDC reference number 157799. See http://www.rsc.org/suppdata/p1/b0/b010224p/ for crystallographic files in .cif or other electronic format.

Table 1 Analytical data for compounds **2**–**19**

Compound (Formula)	Mp/°C (decomp.)	Found (%) (Required) C	H	N	S	*m/z* (EI)
2a ($C_{10}H_{13}N_5O_3$)	138–141 (decomp.)	47.7 (47.8)	5.0 (5.2)	27.6 (27.9)		252 [(M + 1)$^+$, 54%][a]
2b ($C_{15}H_{15}N_5O_3$)	146–160	57.4 (57.5)	5.0 (4.8)	22.4 (22.4)		313 (M$^+$, 69%)
3a ($C_8H_7N_5O_2$)	>210 (decomp.)	46.8 (46.8)	3.4 (3.4)	33.8 (34.1)		206 [(M + 1)$^+$, 100%][a]
3b ($C_{14}H_{11}N_5O$)	>280	58.3 (58.4)	3.7 (3.4)	25.9 (26.2)		265 (M$^+$, 5%)
5a ($C_{15}H_{16}N_6O_4S$)	>243 (decomp.)	47.7 (47.9)	4.2 (4.3)	22.4 (22.3)		377 [(M + 1)$^+$, 100%][a]
5b ($C_{20}H_{18}N_6O_4S$)	>190 (decomp.)	54.6 (54.8)	4.1 (4.1)	19.2 (19.2)	7.4 (7.3)	439 [(M + 1)$^+$, 100%][a]
5c ($C_{20}H_{15}N_7O_3S$)	180–190 (decomp.)	55.1 (55.4)	3.8 (3.5)	22.3 (22.6)		434 [(M + 1)$^+$, 100%][a]
5d ($C_{20}H_{18}N_6O_3S$)	>250 (decomp.)	56.6 (56.9)	4.1 (4.3)	19.6 (19.9)		423 [(M + 1)$^+$, 100%][a]
5e ($C_{23}H_{23}N_7O_7S_2$)	228–232	47.9 (48.2)	4.0 (4.0)	17.2 (17.1)	11.5 (11.2)	574 [(M + 1)$^+$, 80%][a]
6 ($C_{20}H_{18}N_6O_3S\cdot CH_3CO_2H\cdot H_2O$)	303–307	51.2 (51.2)	4.8 (4.7)	16.5 (16.3)	6.3 (6.2)	439 [(M + 1)$^+$, 100%][a]
7a ($C_9H_{11}N_5O_2$)	>103 (decomp.)	222.0992[c] (221.0991)				222 [(M + 1)$^+$, 100%][a]
7b ($C_{14}H_{13}N_5O_2$)	124–125	59.6 (59.2)	4.6 (4.6)	25.1 (24.7)		284 (M$^+$, 100%)[b]
8a ($C_9H_{11}N_5O_2$)	>91 (decomp.)	48.9 (48.9)	5.0 (5.0)	31.4 (31.7)		222 [(M + 1)$^+$, 100%][a]
8b ($C_{14}H_{13}N_5O_2$)	163–165 (decomp.)	59.3 (59.2)	4.8 (4.6)	25.0 (24.7)		284 [(M + 1)$^+$, 100%][a]
9a ($C_{25}H_{25}N_7O_8S_2$)	125–132	54.2 (54.1)	4.5 (4.3)	16.5 (16.5)	6.3 (6.3)	616 [(M + 1)$^+$, 30%][a]
9b ($C_{22}H_{20}N_6O_5S$)	>205 (decomp.)	54.9 (55.0)	4.4 (4.2)	17.7 (17.5)	6.8 (6.7)	481 [(M + 1)$^+$, 40%][a]
10a ($C_9H_9N_5O$)	127–128	53.2 (53.2)	4.6 (4.5)	34.8 (34.5)		204 (M$^+$, 100%)[b]
10b ($C_{14}H_{11}N_5O$)	208–210	266.1045[c] (266.1042)				266 [(M + 1)$^+$, 100%][a]
11 ($C_{24}H_{26}N_6O_6S$)	174–176	54.7 (54.8)	5.1 (4.9)	16.0 (16.0)	6.2 (6.1)	527 [50%, (M + 1)$^+$][a]
12a ($C_{25}H_{25}N_7O_8S_2$)	>170 (decomp.)	48.5 (48.8)	4.3 (4.1)	15.9 (15.9)	10.4 (10.4)	616 [(M + 1)$^+$, 30%][a]
12b ($C_{22}H_{20}N_6O_5S$)	>210 (decomp.)	54.8 (55.0)	4.3 (4.2)	17.3 (17.5)	6.8 (6.7)	480.1224[c]
16 ($C_{15}H_{16}N_6O_2$)	167–169 (decomp.)	313.1414[c] (313.1413)				313 [(M + 1)$^+$, 30%][a]
17 ($C_{31}H_{30}N_8O_8S$)	229–231	707.1696[c] (707.1706)				707 [(M + 1)$^+$, 30%][a]
18 ($C_{23}H_{22}N_6O_6S$)	141–145	54.2 (54.1)	4.5 (4.3)	16.5 (16.5)	6.3 (6.3)	511 [(M + 1)$^+$, 100%][a]
19 ($C_{16}H_{13}N_5O_4$)	146–153	56.6 (56.6)	4.1 (3.9)	20.4 (20.7)		340 [(M + 1)$^+$, 80%][a]

[a] Fast atom bombardment. [b] Chemical ionisation. [c] High resolution mass spectrometry.

$U = 2404(2)$ Å^3, $\beta = 95.98(3)°$, $T = 293(2)$ K, space group P 21/c, $Z = 4$, μ(Mo-Kα) = 0.19 cm^{-1}, 1863 reflections measured, 1790 unique ($R_{int} = 0.020$) which were used in all calculations. The final $wR(F^2)$ was 0.1213 (all data).

Synthesis of 9-(2′-hydroxyethyl)-2-oxo-N^2-tosyl-2,9-dihydro-1*H*-purine-6-carboxamidine 5a

Tosyl isocyanate (1.28 ml, 8.4 mmol) was added with a microsyringe to a suspension of imidazole **1a** (0.60 g, 3.36 mmol) in dry acetonitrile (20 ml) kept with efficient stirring under a nitrogen atmosphere and in an ice–salt bath. An orange solid formed immediately and the mixture was stirred at 5 °C for 19 h. The orange solid had evolved to a yellow solid which was filtered, washed with acetonitrile and diethyl ether and identified as the purine **5e** (1.93 g, 3.36 mmol, 100%). When a suspension of **5e** (1.42 g, 2.47 mmol) in ethanol (250 ml) and water (1 ml) was refluxed for 5 h, a homogeneous solution was obtained. A solid precipitated on cooling and was filtered and washed with ethanol and diethyl ether. The product was identified as the purine **5a** (0.79 g, 2.10 mmol, 85%).

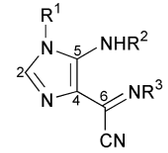
Synthesis of 9-(4′-methoxyphenyl)-2-oxo-N^2-tosyl-2,9-dihydro-1*H*-purine-6-carboxamidine 5b

Tosyl isocyanate (0.35 ml, 2.3 mmol) was added with a microsyringe to a suspension of imidazole **1b** (0.50 g, 2.09 mmol) in dry acetonitrile (10 ml) kept with efficient stirring under a nitrogen atmosphere and in an ice bath. After the addition, the mixture was stirred at room temperature, and a yellow solid started to precipitate out of solution after 30 min. The mixture was stirred at room temperature for 19 h and the solid was filtered and washed with acetonitrile and diethyl ether. The product was identified as the purine **5b** (0.86 g, 1.96 mmol, 94%).

Table 2 IR and ^{1}H NMR spectroscopic data for compounds **2**–**19**

Compound	ν_{max}/cm^{-1} (Nujol)	δ_H (300 MHz; DMSO-d_6), J/Hz
2a	3332m, 3225m, 3163m, 3068w, 1665m, 1648m, 1641s	1.25 (3H, t, *J* 7, CH_2CH_3), 3.63 (2H, t, *J* 5, CH_2O), 3.95 (2H, t, *J* 5, CH_2N), 4.15 (2H, q, *J* 7, CH_2CH_3), 5.2 (<1H, br s, OH), 7.48 (1H, s, 2-H), 8.20 (2H, s, NH_2)
2b	3425m, 3316s, 3113w, 2248m, 1675s, 1626s	1.25 (3H, t, *J* 7, CH_2CH_3), 3.82 (3H, s, OCH_3), 4.16 (2H, q, *J* 7, CH_2CH_3), 7.14 (2H, d, *J* 9, Ar), 7.46 (2H, d, *J* 9, Ar), 7.66 (1H, s, 2-H), 8.07 (br s, NH_2)
3a	3470m, 3391m, 3213s, 3143s, 1612s	3.80 (2H, t, *J* 5, CH_2O), 4.29 (2H, t, *J* 5, CH_2N), 8.61 (1H, s, 8-H)
3b	3100w, 2050w, 1614s	3.83 (3H, s, OCH_3), 7.16 (2H, d, *J* 8.9, Ar), 7.70 (2H, d, *J* 8.9, Ar), 8.89 (1H, s, 8-H), 12.6 (1H, br s, NH)
3e	3500m, 3105m, 1758s, 1615m	2.38 (3H, s, CH_3), 4.36 (4H, s, OCH_2CH_2N), 7.36 (2H, d, *J* 8.7, Ts), 7.68 (2H, d, *J* 8.7, Ts), 8.50 (1H, s, 8-H), 12.0 (<1H, br s, NH), 12.6 (<1H, br s, NH)
5a	3383m, 3316m, 3204m, 1653s, 1623s	2.37 (3H, s, CH_3), 3.72 (2H, t, *J* 5, CH_2O), 4.17 (2H, t, *J* 5, CH_2N), 5.0 (1H, t, *J* 5, OH), 7.37 (2H, d, *J* 8.7, Ts), 7.84 (2H, d, *J* 8.7, Ts), 8.41 (1H, s, 8-H), 8.66 (<1H, br s, NH), 9.19 (<1H, br s, NH), 12 (<1H, br s, NH)
5b	3370s, 3300s, 3240s, 3118m, 1658s, 1643s	2.38 (3H, s, CH_3), 3.83 (3H, s, OCH_3), 7.15 (2H, d, *J* 8.9, Ar), 7.39 (2H, d, *J* 8.7, Ts), 7.69 (2H, d, *J* 8.9, Ar), 7.87 (2H, d, *J* 8.7, Ts), 8.71 (<1H, br s, NH), 8.76 (1H, s, 8-H), 9.2 (<1H, br s, NH), 12.2 (<1H, br s, NH)
5c	3347m, 3262w, 3115w, 2234w, 1830w, 1708w, 1640s	2.38 (3H, s, CH_3), 7.47 (2H, d, *J* 8.7, Ts), 7.85 (2H, d, *J* 8.7, Ts), 8.15 (4H, q, *J* 8.7, Ar), 8.71 (<1H, br s, NH), 9.00 (1H, s, 8-H), 9.20 (<1H, br s, NH)
5d	3365s, 3298w, 3233s, 3126w, 1836w, 1737w, 1658s, 1636s	2.40 (6H, s, 2 × CH_3), 7.39 (4H, d, *J* 8.7, Ar), 7.68 (2H, d, *J* 8.7, Ar), 7.91 (2H, d, *J* 8.7, Ts), 8.71 (<1H, br s, NH), 8.79 (1H, s, 8-H), 9.21 (<1H, br s, NH), 12.20 (<1H, br s, NH)
5e	3390m, 3311m, 3113m, 1747s, 1638s, 1617s, 1600m	2.32 (3H, s, CH_3), 2.35 (3H, s, CH_3), 4.34 (4H, s, NCH_2CH_2O), 7.33 (2H, d, *J* 8.7, Ts), 7.36 (2H, d, *J* 8.7, Ts), 7.68 (2H, d, *J* 8.7, Ts), 7.86 (2H, d, *J* 8.7, Ts), 8.37 (1H, s, 8-H), 8.68 (<1H, br s, NH), 9.16 (<1H, br s, NH), 12 (<2H, br s, 2 × NH)
6	3484m, 3100m, 1709s, 1644s	2.37 (3H, s, CH_3), 3.74 (3H, s, OCH_3), 6.93 (2H, d, *J* 9.0, Ar), 7.39 (2H, d, *J* 8.7, Ts), 7.82 (2H, d, *J* 9.0, Ar), 7.95 (2H, d, *J* 8.7, Ts), 8.26 (1H, s, 7-H), 10.00 (<1H, br s, NH), 10.11 (<1H, vbr s, NH)
7a	3287m, 3158m, 3071w, 1647s, 1630s	2.22 (3H, s, CH_3), 3.63 (2H, q, *J* 5, CH_2O), 3.95 (2H, t, *J* 5, CH_2N), 4.34 (<1H, br s, OH), 7.48 (1H, s, 2-H)
7b	3402s, 3278s, 3100s, 3100w, 2235w, 1670s, 1629s	2.23 (3H, s, CH_3), 3.82 (3H, s, OCH_3), 7.44 (2H, d, *J* 8.7, Ar), 7.66 (2H, d, *J* 8.7, Ar), 7.66 (1H, s, 2-H), 8.19 (2H, br s, NH_2)
8a	3532m, 3431m, 3197s, 3121s, 3058m, 2240w, 1696s, 1624m, 1601s	A: 2.04 (3H, s, CH_3), 3.60 (2H, q, *J* 5, CH_2O), 3.79 (2H, t, *J* 5, CH_2N), 7.83 (1H, s, 2-H), 10.11 (<1H, br s, NH), 11.37 (1H, s, NH) B: 2.10 (3H, s, CH_3), 3.60 (2H, q, *J* 5, CH_2O), 3.79 (2H, t, *J* 5, CH_2N), 4.34 (<1H, br s, OH), 7.77 (1H, s, 2-H), 9.84 (<1H, br s, NH), 12.40 (1H, s, NH)
8b	3420m, 3219s, 3173m, 3102m, 2238w, 1682s, 1650w, 1602s	A: 1.97 (3H, s, CH_3), 3.80 (3H, s, OCH_3), 7.11 (2H, d, *J* 8.7, Ar), 7.35 (2H, d, *J* 8.7, Ar), 8.11 (1H, s, 2-H), 11.06 (<1H, br s, NH), 12.6 (<1H, br s, NH) B: 1.86 (3H, s, CH_3), 3.80 (3H, s, OCH_3), 7.11 (2H, d, *J* 8.7, Ar), 7.35 (2H, d, *J* 8.7, Ar), 8.02 (1H, s, 2-H), 10.63 (<1H, br s, NH)
9b	3223m, 2220w, 1711s, 1686s, 1642m, 1604s	2.22 (3H, s, $COCH_3$), 2.39 (3H, s, CH_3), 3.80 (3H, s, OCH_3), 6.94 (2H, d, *J* 8.7, Ar), 7.20 (2H, d, *J* 8.7, Ar), 7.35 (2H, d, *J* 8.1, Ts), 7.67 (2H, d, *J* 8.1, Ts), 8.11 (1H, s, 2-H), 8.82 (1H, br s, NH), 11.6 (<1H, br s, NH)
9e	3606s, 3394s, 3152m, 3093m, 2150w, 1754s, 1723s, 1670s	2.17 (3H, s, $COCH_3$), 2.37 (3H, s, CH_3), 2.39 (3H, s, CH_3), 4.37 (2H, t, *J* 5, CH_2O), 4.50 (2H, t, *J* 5, CH_2N), 7.37 (2H, d, *J* 8.3, Ts), 7.42 (2H, d, *J* 8.3, Ts), 7.77 (4H, d, *J* 8.3, 2 × Ts), 7.83 (1H, s, 2-H), 8.82 (1H, br s, NH), 12 (<2H, br s, 2 × NH)
11	3303s, 3205m, 2066w, 1664s, 1644m	0.96 (3H, t, *J* 7, CH_2CH_3), 1.90 (3H, s, $COCH_3$), 2.40 (3H, s, CH_3), 3.40 (2H, q, *J* 7, CH_2CH_3), 3.78 (3H, s, OCH_3), 6.84 (2H, d, *J* 9.0, Ar), 7.15 (2H, d, *J* 9.0, Ar), 7.36 (2H, d, *J* 8.1, Ts), 7.68 (2H, d, *J* 8.1, Ts), 7.85 (1H, s, 2-H), 7.95 (1H, s, NH), 9.06 (1H, s, NH), 11.2 (<1H, br s, NH)
10a	3273s, 3103m, 2250w	2.88 (3H, s, CH_3), 3.89 (2H, q, *J* 5, CH_2O), 4.39 (2H, t, *J* 5, CH_2N), 5.1 (1H, t, *J* 5, OH), 8.89 (1H, s, 8-H)
10b	3106w, 2245w	2.74 (3H, s, CH_3), 3.84 (3H, s, OCH_3), 7.18 (2H, d, *J* 8.7, Ar), 7.73 (2H, d, *J* 8.7, Ar), 9.11 (1H, s, 8-H)
10e	2256w, 1738s	2.39 (3H, s, CH_3), 2.72 (3H, s, CH_3), 4.39 (2H, t, *J* 5, CH_2O), 4.49 (2H, t, *J* 5, CH_2N), 7.34 (2H, d, *J* 8.7, Ts), 7.65 (2H, d, *J* 8.7, Ar), 8.73 (1H, s, 8-H)
12b	3366m, 3300m, 3147m, 1770s, 1635s	2.36 (3H, s, $COCH_3$), 2.39 (3H, s, CH_3), 3.85 (3H, s, OCH_3), 7.19 (2H, d, *J* 8.9, Ar), 7.39 (2H, d, *J* 8.0, Ts), 7.70 (2H, d, *J* 8.9, Ar), 7.87 (2H, d, *J* 8.0, Ts), 8.74 (1H, br s, NH), 9.09 (1H, s, 8-H), 9.23 (1H, br s, NH)
12e	3378m, 3236m, 3304m, 1775m, 1624s	2.36 (3H, s, CH_3), 2.38 (3H, s, $COCH_3$), 2.39 (3H, s, CH_3), 4.38 (2H, t, *J* 5, CH_2O), 4.47 (2H, t, *J* 5, CH_2N), 7.35 (2H, d, *J* 8.7, Ts), 7.47 (2H, d, *J* 8.7, Ts), 7.70 (2H, d, *J* 8.7, Ts), 7.87 (2H, d, *J* 8.7, Ts), 8.70 (<1H, br s, NH), 8.72 (1H, s, 8-H), 9.21 (<1H, br s, NH), 12.1 (<1H, br s, NH)
16	3322s, 2240s, 2240w, 1630s	3.64 (2H, br s, CH_2O), 3.94 (2H, t, *J* 5, CH_2N), 4.35 (2H, d, *J* 6, CH_2Ph), 5.07 (<1H, br s, OH), 7.27–7.33 (5H, m, Ph), 7.34 (1H, s, H2), 7.77 (1H, br s, NH), 8.35 (1H, t, *J* 6, NH)
17	3380m, 3333m, 3180m, 3100w, 2256w, 1750m, 1721s, 1679s, 1639m	2.31 (3H, s, CH_3), 2.36 (3H, s, CH_3), 4.38 (4H, s, NCH_2CH_2O), 4.41 (2H, d, *J* 6, CH_2Ph), 7.2–7.4 (9H, m, 2 × Ts, Ph), 7.6–7.8 (5H, m, 2 × Ts, H-2), 8.35 (1H, t, *J* 6, NH), 8.69 (1H, br s, NH), 12.1 (2H, br s, 2 × NH)
18	3269m, 3208m, 3142w, 2236w, 1719s, 1615m	1.29 (3H, br s, CH_3), 2.40 (3H, s, CH_3), 3.80 (3H, s, OCH_3), 4.30 (2H, br s, CH_2), 6.93 (2H, br s, Ar), 7.24 (2H, br s, Ar), 7.20 (2H, d, *J* 8.7, Ar), 7.35 (2H, d, *J* 8.1, Ts), 7.67 (2H, d, *J* 8.1, Ts), 8.11 (1H, s, 2-H), 8.60 (<1H, s, NH), 8.75 (<1H, s, NH), 11.4 (<1H, br s, NH), 11.6 (<1H, br s, NH)
19	3127w, 2232w, 1794s, 1767s, 1699s, 1678s, 1656m	1.37 (3H, t, *J* 7, CH_3), 3.82 (3H, s, OCH_3), 4.54 (2H, q, *J* 7, CH_2), 7.14 (2H, d, *J* 9, Ar), 7.63 (2H, d, *J* 9, Ar), 8.97 (1H, s, 8-H)

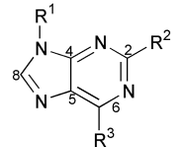
Table 3 δ_C (75 MHz, DMSO-d_6) for imidazoles **2**, **7**, **8, 9**, **16** and **17**



Compound	2-C	4-C	5-C	6-C	CN	R^1	R^2	R^3
2a	139.0	121.4	151.2	137.5	111.9	45.8, 58.7	—	12.3, 61.6, 161.2
2b	138.2	120.9	150.8	138.0	111.7	55.6, 115.1, 125.3, 127.2, 159.8	—	14.2, 61.7, 160.9
7a	139.8	122.5	151.5	132.5	112.5	46.5, 59.6	—	25.5, 184.1
7b	139.0	[a]	154.5	[a]	[a]	[a]	—	[a]
8a	A: 138.0 B: 136.9	A: 128.1 B: 127.7	A: 129.1 B: 128.6	A: 145.1 B: 142.9	A: 115.5 B: 113.0	46.4, 59.5	—	22.7, 171.0 (A), 170.1 (B)
8b	A: 138.0 B: 137.7	A: 128.8 B: 127.3	A: 129.9 B: 127.7	A: 144.7 B: 142.7	A: 112.8 B: 112.1	55.5, 114.8, 126.3, 126.5, 159.5	—	22.4, 170.3
9b	139.1	129.3	130.1	131 (br)	114.6	55.6, 114.6, 126.2, 126.4, 159.6	21.1, 127.3, 129.4, 136.7, 143.8, 150.5	24.5, 182.2
9e	139.4	127.3	132.0	130 (br)	[b]	21.1, 42.7, 63.6, 127.5, 129.8, 136.0, 144.5, 150.7	21.1, 127.4, 129.5, 136.7, 144.0, 150.5	24.4, 182.2
16	136.4	119.5	149.0	136.4	112.5	45.5, 58.9	—	43.5, 128.4, 127.4, 126.9, 139.6, 160.7
17	140	127.1	131	[b]	110.5	21.1, 42.2, 63.3, 127.5, 129.7, 136.1, 144.5, 150.6	21.1, 127.4, 129.5, 136.8, 144.3, 150.5	43.4, 127.1, 127.3, 128.5, 138.8, 160.8
18	138.5	129.3	131.8	135 (br)	110	55.5, 114.5, 126.2, 126.3, 159.6	21.1, 127.1, 129.3, 136.7, 143.8, 149.7	14.0, 63.5, 160 (br)

[a] In DMSO solution, compound **7b** evolves rapidly to compound **8b**, and most of the signals are not visible. [b] Peaks not visible in the spectrum.

Table 4 δ_C (75 MHz, DMSO-d_6) for purines **3**, **5**, **10** and **12**



Compound	2-C	4-C	5-C	6-C	8-C	R^1	R^2	R^3
3a	161.7	156.1	129.0	131.6	149.1	46.1, 58.8	—	114.3
3b	161.8	155.4	129.7	131.0	147.7	55.6, 114.7, 125.6, 126.4, 159.1	—	114.1
5a	160.2	156.5	125.8	146.6	147.5	45.7, 58.7	—	21.0, 129.3, 126.3, 139.3, 142.6, 158.8
5b	160.8	155.8	126.2	146.8 (br)	146.0	55.6, 114.7, 125.4, 126.4, 159.4	—	21.0, 129.4, 126.4, 139.4, 142.7, 158.0
5c	160.6	155.5	130.0	148.3	145.0	118.2, 127.5, 129.5, 131.0, 137.6	—	20.9, 126.3, 128.3, 139.1, 142.7, 157.9
5d	160.7	155.8	130.0	147.8	145.5	20.9, 123.3, 127.8, 131.0, 137.6	—	20.9, 142.6, 129.3, 126.3, 139.1, 157.9
5e	160.2	156.5	125.8	146 (br)	147.3	21.1, 41.8, 63.3, 127.7, 129.6, 136.1, 144.3, 150.5	—	21.0, 127.4, 129.4, 139.2, 142.8, 157.7
10a	161.7	154.8	129.3	134.0	150.6	46.3, 58.8	25.4	114.5
10b[a]	163.9	153.2	131.2	133.2	146.6	55.7, 115.3, 125.3, 126.2, 159.1	25.9	113.7
10e	161.9	153.7	128.3	132.6	150.6	21.1, 42.4, 63.6, 128.5, 129.5, 136.1, 144.2, 150.5	25.3	114.4
12b	157.9	154.9	130.4	149.6	154.6	55.6, 114.9, 125.6, 126.3, 159.3	—	20.6, 21.0, 129.4, 126.3, 139.2, 142.7, 148.7, 168.6
12e	157.7	155.4	130.0	148.7	154.2	21.0, 42.5, 63.3, 129.6, 127.3, 136.2, 144.3, 150.4	—	20.6, 21.0, 126.4, 129.4, 139.8, 142.3, 149.7, 168.6

[a] $CDCl_3$.

Synthesis of 9-(4′-cyanophenyl)-2-oxo-N^2-tosyl-2,9-dihydro-1*H*-purine-6-carboxamidine 5c

A suspension of imidazole **1c** (0.12 g, 0.51 mmol) in dry acetonitrile (15 ml) was kept at 0 °C under a nitrogen atmosphere with magnetic stirring. A solution of tosyl isocyanate (0.2 g, 1.02 mmol) in dry acetonitrile (*ca.* 1 ml) was added dropwise through the serum cap over a period of 15 min. An orange suspension was formed and this evolved to a homogeneous orange solution while still in the ice bath. Immediately after the removal of the ice bath, a pale yellow solid started to precipitate out of solution, and the mixture was stirred at room temperature for 18 hours, when the solid was filtered and washed with diethyl ether to give compound **5c** (0.22 g, 0.51 mmol, 99%).

Synthesis of 2-oxo-9-(4′-tolyl)-N^2-tosyl-2,9-dihydro-1*H*-purine-6-carboxamidine 5d

A suspension of imidazole **1c** (0.43 g, 1.91 mmol) in dry acetonitrile (15 ml) was kept at 0 °C under a nitrogen atmosphere with magnetic stirring. A solution of tosyl isocyanate (0.76 g, 3.78 mmol) in dry acetonitrile (*ca.* 2.5 ml) was added dropwise through the serum cap over a period of 30 min. The resulting orange suspension was stirred at room temperature for 4 h, when the starting material was no longer present (as evidenced by TLC). The yellow solid was filtered and washed with diethyl ether to give compound **5d** (0.77 g, 1.82 mmol, 96%).

Synthesis of 4-(4′-methoxyphenyl)amino-8-(*N*-tosylimino)-7,8-dihydropyrimido[5,4-*d*]pyrimidin-2(1*H*)-one 6b

Method A. Acetic acid (4 ml) and water (0.5 ml) were added to a solution of purine **5b** (0.16 g, 0.37 mmol) in DMF (6 ml). The mixture was refluxed for 15 h, when almost no starting material was detected on TLC. Addition of water to the cold reaction mixture led to a yellow solid which was filtered and washed with cold water, acetonitrile and diethyl ether. The product was identified as compound **6b** (0.06 g, 0.14 mmol, 38%).

Method B. Ammonium acetate (0.12 g, 1.56 mmol) was added to a suspension of purine **5b** (0.21 g, 0.48 mmol) in glacial acetic acid (10 ml). A brownish-yellow solution was obtained after refluxing the mixture for 4 h. A yellow solid precipitated on cooling and was filtered and washed with water and then with a large volume of diethyl ether. The greenish-yellow solid was identified as compound **6b** (0.18 g, 0.41 mmol, 86%). δ_C(75 MHz; DMSO-d_6; Me_4Si) 21.1 (Me), 55.3 (OMe), 113.6 (C_m, Ar), 123.9 (C_o, Ar), 127.2 (br, C_o, Ts), 129.5 (C_m, Ts), 130.8 (C_i, Ar), 138.0 (C_i, Ts), 143.5 (C_p, Ts), 145.1 (6-C), 154.0 (4-C), 156.3 (C_p, Ar), 157.6 (2-C).

Synthesis of 4-[*N*-acetyl-*C*-(cyanoformimidoyl)]-5-amino-1-(2′-hydroxyethyl)-1*H*-imidazole 7a

Acetic anhydride (0.8 ml, 0.86 g, 8.5 mmol) was added to a suspension of **1a** (0.72 g, 4.0 mmol) in acetonitrile (8 ml) and the mixture was stirred at 0–4 °C. The reaction was complete after 19 h, as the off-white solid became deep yellow. Chloroform (25 ml) and a few drops of diethyl ether were added to the suspension, which was filtered and washed with chloroform and diethyl ether to give compound **7a** (0.70 g, 3.2 mmol, 79%).

Synthesis of 4-[*N*-acetyl-*C*-(cyanoformimidoyl)]-5-amino-1-(4′-methoxyphenyl)-1*H*-imidazole 7b

A suspension of imidazole **1b** (0.33 g, 1.38 mmol) in acetic anhydride (1.0 ml) was stirred at 4 °C for 24 h, when the TLC showed the absence of the starting material. The yellow solid was filtered and washed with cold diethyl ether. The product was identified as compound **7b** (0.27 g, 0.97 mmol, 70%).

Synthesis of 5-acetamido-4-(*C*-cyanoformimidoyl)-1-(2′-hydroxyethyl)-1*H*-imidazole 8a

A suspension of **7a** (0.48 g, 2.2 mmol) in ethanol (50 ml) was stirred at room temperature. A homogeneous solution was obtained after 25 min and 10 min later, it was indicated by TLC that all the starting material had been consumed. The ethanol was partially removed in the rotary evaporator and the solid precipitated out on cooling. Ethyl acetate was added and the solid was filtered and washed with ethyl acetate and diethyl ether to give compound **8a** (0.39 g, 1.8 mmol, 82%).

Synthesis of 5-acetamido-4-(*C*-cyanoformimidoyl)-1-(4′-methoxyphenyl)-1*H*-imidazole 8b

A suspension of imidazole **7b** (0.42 g, 1.47 mmol) in ethanol (50 ml) was stirred at 4 °C for 7 h. *n*-Hexane was added to the homogeneous solution, which was concentrated in the rotary evaporator until a white solid precipitate was formed. The solid was filtered and washed with cold diethyl ether. The product was identified as compound **8b** (0.39 g, 1.17 mmol, 80%).

Reaction of 4-[*N*-acetyl-*C*-(cyanoformimidoyl)]-5-amino-1-(2′-hydroxyethyl)-1*H*-imidazole 7a with tosyl isocyanate

A suspension of imidazole **7a** (0.5 g, 2.26 mmol) in dry acetonitrile (20 ml) was kept stirring at −15 °C (slush of Cardice and ethylene glycol) under a nitrogen atmosphere. Tosyl isocyanate (0.90 ml, 5.94 mmol) was added with a microsyringe through the serum cap and the mixture was stirred at −15 °C for 10 min. The white solid was filtered rapidly, washed with acetonitrile and identified as compound **9e** (0.95 g, 1.55 mmol, 68%). The mother liquor was kept stirring at room temperature, under a nitrogen atmosphere, and after one week the white solid was filtered and washed with acetonitrile and diethyl ether. The product was identified as compound **12e** (0.34 g, 0.55 mmol, 24%).

Reaction of 4-[*N*-acetyl-*C*-(cyanoformimidoyl)]-5-amino-1-(4′-methoxyphenyl)-1*H*-imidazole 7b with tosyl isocyanate

A suspension of imidazole **7b** (0.51 g, 1.78 mmol) in dry acetonitrile (10 ml) was kept in an ice bath under a nitrogen atmosphere. Tosyl isocyanate (0.33 ml, 2.15 mmol) was added with a microsyringe through the serum cap and the mixture was stirred at 4 °C for 3 h. The deep yellow solid was filtered and washed with acetonitrile and diethyl ether. The product was identified as compound **9b** (0.64 g, 1.33 mmol, 75%).

Reaction of 4-[*N*-acetyl-*C*-(cyanoformimidoyl)]-5-(3′-tosyl-ureido)-1-(4′-methoxyphenyl)-1*H*-imidazole 9b with ethanol

A solution of imidazole **9b** (0.06 g, 0.11 mmol) in ethanol (1 ml) was stirred at room temperature for 2 days. The white solid was filtered, washed with acetonitrile and diethyl ether and identified as compound **11** (0.04 g, 0.66 mmol, 58%). δ_C(75 MHz; DMSO-d_6; Me_4Si) 14.4 (CH_2CH_3), 21.1 (Ts), 22.7 ($COCH_3$), 55.4 (OCH_3), 60.6 (CH_2CH_3), 78.1, 114.3 (C_m, Ar), 115.4 (CN), 123.1 (4-C), 126.1 (C_o, Ar), 127.1 (C_i, Ar), 127.2 (C_o, Ts), 129.4 (C_m, Ts), 130.5 (5-C), 135.2 (2-C), 136.8 (C_i, Ts), 143.8 (C_p, Ts), 150.7 (CONHTs), 159.0 (C_p, Ar), 169.2 ($CO\ CH_3$).

Synthesis of 2-oxo-9-(2′-tosylaminocarbonyloxyethyl)-N^1-acetyl-N^2-tosyl-2,9-dihydro-1*H*-purine-6-carboxamidine 12e

From 5e. A suspension of purine **5e** (0.20 g, 0.35 mmol) in acetic anhydride (2 ml) was stirred at room temperature for 8 days. The white solid was filtered and washed with acetonitrile and diethyl ether. The product was identified as **12e** (0.19 g, 0.31 mmol, 88%).

From 8a. Tosyl isocyanate (0.33 ml, 2.20 mmol) was added to a suspension of imidazole **8a** (0.22 g, 1.00 mmol) in dry

acetonitrile (20 ml) kept stirring in an ice–salt bath under a nitrogen atmosphere. A white solid immediately precipitated from the reaction mixture, which was stirred at 0 °C for a further 10 min. The solid was filtered and washed with acetonitrile and diethyl ether, but the solid was completely dry only after 2 weeks in the desiccator. The white solid was identified as the purine **12e** (0.05 g, 0.81 mmol, 81%).

From 9e. *Method A.* A suspension of **9e** (0.26 g, 0.42 mmol) in acetonitrile (10 ml) was stirred at room temperature for 3 h. The white solid was filtered and washed with acetonitrile and diethyl ether. The product was identified as compound **12e** (0.13 g, 0.21 mmol, 51%). The mother liquor was stirred at room temperature for 2 days, leading to a white solid which was identified as compound **10e** (0.04 g, 0.10 mmol, 24%).

Method B. A suspension of **9e** (0.50 g, 2.26 mmol) in dry acetonitrile (20 ml) was stirred at room temperature and under a nitrogen atmosphere. After 1 day, the white solid was filtered and washed with acetonitrile and diethyl ether. The product was identified as compound **12e** (0.34 g, 1.54 mmol, 67%).

Synthesis of 2-oxo-9-(4′-methoxyphenyl)-N^1-acetyl-N^2-tosyl-2,9-dihydro-1*H*-purine-6-carboxamidine 12b

From 5b. A suspension of purine **5b** (0.21 g, 0.47 mmol) in acetic anhydride (2 ml) was stirred at room temperature for 3 days. The white solid was filtered and washed with diethyl ether. The product was identified as **12b** (0.19 g, 0.40 mmol, 84%).

From 8b. Tosyl isocyanate (0.11 ml, 0.14 g, 0.73 mmol) was added to a suspension of imidazole **8b** (0.17 g, 0.59 mmol) in dry acetonitrile (10 ml) kept stirring in an ice bath under a nitrogen atmosphere. A deep yellow colour developed immediately and the mixture was stirred at 4 °C for 1 h. The white solid suspension was filtered and washed with acetonitrile and diethyl ether. The product was identified as the purine **12b** (0.19 g, 0.39 mmol, 66%).

From 9b. A solution of **9b** (0.13 g, 0.44 mmol) in dry acetonitrile (10 ml) was kept stirring at room temperature and under a nitrogen atmosphere for 2 days. The white solid was filtered and washed with acetonitrile and diethyl ether. The product was identified as compound **12b** (0.05 g, 0.10 mmol, 40%). An off-white solid was isolated from the mother liquor, and was identified as compound **10b** (0.05 g, 0.19 mmol, 43%).

Synthesis of 9-(4′-methoxyphenyl)-2-methyl-9*H*-purine-6-carbonitrile 10b

DBU (2 μl) was added to a suspension of imidazole **7b** (0.05 g, 0.18 mmol) in acetonitrile (1.5 ml) and the mixture was stirred at room temperature. A dark solution was obtained, from which a white solid precipitated. After 3 h, the solid was filtered and washed with acetonitrile and diethyl ether. The product was identified as compound **10b** (0.03 g, 0.13 mmol, 71%).

Synthesis of 5-amino-4-[*N*-(ethoxycarbonyl)-*C*-(cyanoformimidoyl)]-1-(2′-hydroxyethyl)-1*H*-imidazole 2a

A suspension of imidazole **1a** (0.45 g, 2.5 mmol) in dry acetonitrile (30 ml) was kept at −15 °C under a nitrogen atmosphere with magnetic stirring. Dry pyridine (0.3 ml, 3.7 mmol) was added through the serum cap followed by ethyl chloroformate (0.28 g, 2.6 mmol), which was added dropwise over a period of 30 min. As the temperature was allowed to rise slowly to room temperature a dark brown suspension developed in a clear yellow solution. The suspension was removed by filtration through glass-fibre paper and the solution was concentrated to a small volume in the rotary evaporator. Chloroform (30 ml) was added and a yellow solid precipitated after 19 h at −10 °C and was filtered and washed with chloroform. The product was identified as imidazole **2a** (0.20 g). A second crop of this compound was obtained from dry flash chromatography using acetone as eluant (0.12 g). The total isolated yield of imidazole **2a** was (0.32 g, 1.25 mmol, 50%).

Synthesis of 5-amino-4-[*N*-(ethoxycarbonyl)-*C*-(cyanoformimidoyl)]-1-(4′-methoxyphenyl)-1*H*-imidazole 2b

Dry pyridine (0.61 ml, 0.60 g, 7.59 mmol) was added to a suspension of imidazole **1b** (1.21 g, 5.0 mmol) in acetonitrile (30 ml), kept stirring in an ice bath and under a nitrogen atmosphere. Addition of ethyl chloroformate (0.58 ml, 0.66 g, 6.1 mmol) led to a homogeneous solution and 10 min later a yellow solid started to be formed. The mixture was stirred at 5 °C for 19 h, when the solid was filtered and washed with chloroform. The product was identified as compound **2b** (1.37 g, 4.39 mmol, 88%).

Synthesis of 6-cyano-9-(4′-methoxyphenyl)-9*H*-purin-2-(1*H*)-one 3b

A suspension of compound **2b** (0.61 g, 1.95 mmol) in acetonitrile (50 ml) was taken to the ultra-sound bath for 2–3 min, and then was stirred at room temperature. Addition of DBU (0.30 ml, 1.95 mmol), led to a homogeneous solution, which was stirred at room temperature for 3 days. Acetic acid (0.15 ml, 2.63 mmol) was added, and 2 h later the solvent was partially removed in the rotary evaporator. The mixture was stirred at room temperature for 19 h, and the white solid that precipitated out of the solution was filtered and washed with ethyl acetate and diethyl ether (0.18 g). Two more crops of the same compound were obtained from the mother liquor (0.14 g) and were combined to give a total yield for compound **3b** of (0.32 g, 1.20 mmol, 62%).

Reaction of 5-amino-4-[*N*-(ethoxycarbonyl)-*C*-(cyanoformimidoyl)]-1-(2′-hydroxyethyl)-1*H*-imidazole 2a with tosyl isocyanate

A suspension of imidazole **2a** (0.21 g, 0.82 mmol) in dry acetonitrile (3 ml) was kept stirring in an ice–salt bath under a nitrogen atmosphere. Tosyl isocyanate (0.36 ml, 0.47 g, 2.38 mmol) was added, leading to an orange solution. After 4 h, TLC indicated that the starting material had been consumed, leading to at least four different compounds. The mixture was stirred at room temperature for 20 h, when a second crop of tosyl isocyanate (0.1 ml, 0.13 g, 0.67 mmol) was added. After 2 days at room temperature, the yellow solid suspension was filtered and washed with acetonitrile and diethyl ether. The pale yellow solid was identified as the 6-cyano-2-oxopurine **3e** (0.02 g, 0.05 mmol, 6%). Dry flash chromatography on the mother liquor led to the isolation of toluene-*p*-sulfonamide (0.17 g), using diethyl ether as eluant. The second crop, isolated with the same eluant, was a white solid identified as ethyl *N*-tosylcarbamate (0.13 g, 0.57 mmol, 69%). The use of ethyl acetate led to a yellow solid which was a mixture of at least four components (by TLC) and was abandoned.

Reaction of 5-amino-4-[*N*-(ethoxycarbonyl)-*C*-(cyanoformimidoyl)]-1-(4′-methoxyphenyl)-1*H*-imidazole 2b with tosyl isocyanate

Method A. A suspension of imidazole **2b** (0.39 g, 1.25 mmol) in dry acetonitrile (4 ml) was kept stirring in an ice–salt bath under a nitrogen atmosphere. Tosyl isocyanate (0.38 ml, 0.50 g, 2.51 mmol) was added with a microsyringe through the serum cap and the mixture was stirred in the ice bath. After 40 min a homogeneous yellow solution was obtained, leading to a yellow solid suspension 35 min later. The mixture was stirred for a further 1.5 h when the solid was filtered and washed with acetonitrile and diethyl ether (0.06 g). A second crop of the

same compound was isolated from the mother liquor (0.20 g). The two crops were combined as they corresponded to the same product, identified as compound **18** (0.26 g, 0.51 mmol, 40%). The starting material **2b** (0.08 g, 0.27 mmol, 21%) was also recovered from the mother liquor.

Method B. A suspension of imidazole **2b** (0.21 g, 0.68 mmol) in dry acetonitrile (10 ml) was kept stirring in an ice–salt bath under a nitrogen atmosphere. Tosyl isocyanate (0.16 ml, 0.20 g, 1.02 mmol) was added with a microsyringe through the serum cap and the mixture was stirred in the ice bath for 10 min and then at room temperature. A homogeneous yellow solution was obtained and stirring was continued for one week. Addition of diethyl ether led to a yellow solid which was filtered and washed with diethyl ether. The product was identified as compound **19** (0.07 g, 0.21 mmol, 31%). δ_C(75 MHz; DMSO-d_6; Me_4Si) 13.5 ($CH_2\mathit{C}H_3$), 55.6 (OCH_3), 60.9 ($\mathit{C}H_2CH_3$), 109.1 (5-C), 114.7 (C_m, Ar), 114.5 (CN), 125.2 (C_o, Ar), 125.7 (C_i, Ar), 130.5 (6-C), 150.6 (4-C), 151.1 (COOEt), 155.0 (8-C), 159.1 (C_p, Ar), 160.9 (2-C). Dry flash chromatography on the mother liquor led to the isolation of the starting material **2b** (0.07 g, 0.23 mmol, 33%) when ethyl acetate was used as the eluant. The diethyl ether fraction gave a yellow solid (0.02 g) which proved to be a complex mixture by ^{1}H NMR, where it is possible to identify a small amount of the 2-oxo-6-cyanopurine **3b**.

Synthesis of 5-amino-4-[*N*-(benzylcarbamoyl)-*C*-(cyanoformimidoyl)]-1-(2′-hydroxyethyl)-1*H*-imidazole 16

A suspension of imidazole **1a** (0.51 g, 2.82 mmol) in dry acetonitrile (5 ml) was stirred in an ice–salt bath, under a nitrogen atmosphere. Benzyl isocyanate (0.7 ml, 0.75 g, 5.64 mmol) was added with a microsyringe through the serum cap. The mixture was kept at 0 °C for 3 days, during which time the suspension gradually developed an orange colour. The solid was filtered and washed with acetonitrile and diethyl ether, to give compound **16** as an orange solid (0.83 g, 2.67 mmol, 95%).

Reaction of 5-amino-4-[*N*-(benzylcarbamoyl)-*C*-(cyanoformimidoyl)]-1-(2′-hydroxyethyl)-1*H*-imidazole 16 with tosyl isocyanate

A suspension of imidazole **16** (0.56 g, 1.79 mmol) in dry acetonitrile (3 ml) was stirred in an ice bath, under a nitrogen atmosphere. Tosyl isocyanate (0.70 ml, 0.91 g, 4.62 mmol) was added with a microsyringe through the serum cap. The mixture was stirred at room temperature for 30 min and then at 5 °C for 19 h, when the reaction was complete as evidenced by TLC. The pale yellow solid was filtered, washed with acetonitrile and diethyl ether, and identified as compound **17** (0.64 g, 0.91 mmol, 51%).

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References

1 M. J. Alves, B. L. Booth and M. F. Proença, *J. Chem. Soc.*, *Perkin Trans. 1*, 1990, 1705; M. J. Alves, B. L. Booth, A. P. Freitas and M. F. Proença, *J. Chem. Soc.*, *Perkin Trans. 1*, 1992, 913; M. J. Alves, B. L. Booth, M. A. Carvalho, P. R. Eastwood, L. Nezhat, R. G. Pritchard and M. F. Proença, *J. Chem. Soc.*, *Perkin Trans. 2*, 1994, 1949.
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, M. A. Carvalho, R. G. Pritchard and M. F. Proença, *J. Heterocycl. Chem.*, 1997, 739.
4 B. L. Booth, A. M. Dias and M. F. Proença, *J. Heterocycl. Chem.*, 1996, 855.
5 M. Hocek, M. Masojídková, A. Holy, G. Andrei, R. Snoeck, J. Balzarini and E. De Clerck, *Collect. Czech. Chem. Commun.*, 1996, **61**, 1525.
6 T. Higashino, S. Yoshida and E. Hayashi, *Chem. Pharm. Bull.*, 1982, 4521.
7 M. Hocek, M. Masojídková and A. Holy, *Collect. Czech. Chem. Commun.*, 1997, **62**, 136.
8 M. J. Alves, B. L. Booth, M. A. Carvalho, A. M. Dias and M. F. Proença, *J. Chem. Res.* (*S*), 1996, 212; M. J. Alves, B. L. Booth, M. A. Carvalho, A. M. Dias and M. F. Proença, *J. Chem. Res.* (*M*), 1996, 1101.
9 E. Schaumann and S. Grabley, *Chem. Ber.*, 1980, **113**, 934.
10 G. Laurence, M. J. Ghomari and M. Luçon, *J. Chem. Soc.*, *Perkin Trans. 2*, 1998, 1159.
11 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; M. J. Alves, B. L. Booth, O. K. Al-Duaij, P. Eastwood, L. Nezhat, M. F. Proença and A. S. Ramos, *J. Chem. Res.* (*M*), 1993, 2701.
12 G. M. Sheldrick, SHELXS-97, Program for the solution of crystal structures, University of Göttingen, Germany, 1997.
13 G. M. Sheldrick, SHELXL-97, Program for the refinement of crystal structures, University of Göttingen, Germany, 1997.
14 G. K. Johnson, ORTEP II, Report ORNL-5138, Oak-Ridge National Laboratory, Tennessee, USA, 1976.