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Efficient conversion of 6-cyanopurines into 6-alkoxyformimidoylpurines

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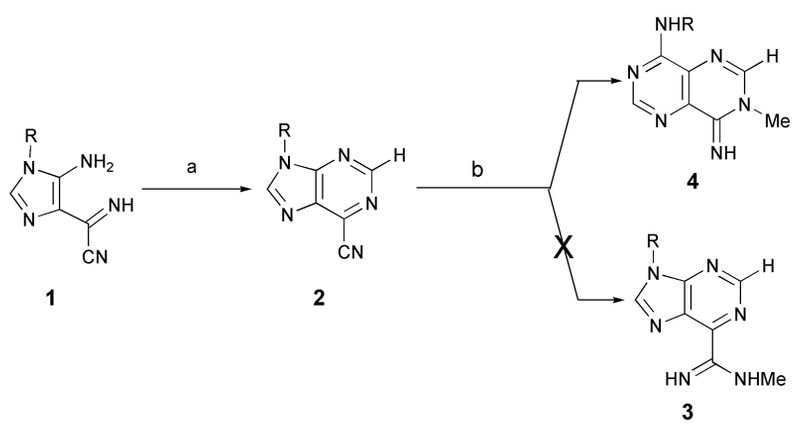
An extremely simple method for the selective synthesis of 9-aryl and 9-alkyl 6-alkoxy or 6-alkoxyformimidoylpurines from the corresponding 6-cyanopurines is described. The reaction is carried out with methanol or ethanol in the presence of DBU. At room temperature, nucleophilic attack by the primary alcohol occurs selectively on the cyano carbon atom, leading to 6-alkoxyformimidoylpurines in good yields. Heating the reaction mixture at a temperature greater than or equal to 78 °C leads to nucleophilic substitution of the substituent in the 6-position by the alkoxy group, generating the corresponding 6-alkoxypurines, also in excellent yields. The 6-alkoxyformimidoylpurines were used as intermediates in the synthesis of 6-carboxamidinopurines by reaction with methylamine (for 9-methylpurine **5a**) or methyl ammonium chloride (for 9-arylpurines **5b** and **5c**).

Introduction

In the last few decades, modified purine structures have been an important source of a wide variety of biologically active materials. The selective modification of substituents in the ring is an important approach to prepare new purine derivatives. As a consequence, the development of highly efficient methods for these synthetic transformations is potentially very useful. Recent work on the synthesis of 6-cyanopurines **2**[1] has shown that these compounds can be prepared in a simple and efficient way from 5-amino-4-(cyanoformimidoyl)imidazoles **1** and triethyl orthoformate under reflux conditions or at room temperature, in the presence of sulfuric acid (Scheme 1). Only a few reactions are described in the literature for these compounds,[2,3,4] and to our knowledge, the nucleophilic substitution of a cyano group in the 6-position of the purine ring by an alkoxy group has never been reported.

An early publication on the reactivity of 6-cyanopurines indicates that ethanol, in the presence of dry hydrogen chloride, at low temperature, converts the cyano group into an imidate function.[5] The product was isolated as the hydrochloride and its instability prevented purification and further characterization. No further successful methods have been reported for the synthesis of 6-alkoxyformimidoylpurines, although these compounds were postulated as intermediates in the synthesis of 6-amidinopurines, when 6-cyanopurines were reacted with a catalytic amount of sodium methoxide in methanol, followed by addition of ammonium chloride.[6] Unlike these compounds, 6-alkoxypurines have been known for a few decades and two major reviews have been produced about their chemistry.[7,8] Their synthesis could be envisaged through direct alkylation of the widely available oxopurines, but *N*- rather than *O*-alkylation is favored. The recent application of *O*-alkylated phosphonates and other reagents to *O*-alkylate oxopurines directly, has improved the selectivity of this synthetic method.[8] Nevertheless, almost all of the known 6-alkoxypurine derivatives have been prepared by the standard nucleophilic displacement of a halogen atom, usually chlorine. This method is only successful when alkoxides are used and the reaction temperature is kept below 100 °C. With higher temperatures, isomerization to *N*-alkyl-oxopurines occurs.[7,8] Other suitable groups have been used for nucleophilic displacement, especially the methylsulfonyl,[9] alkylthio[10,11,12] alkylseleno[13,14] or 1,2,4-triazol-4-yl[15] groups. The 6-trialkylammonium[16,17] and 6-pyridinium[18,19] salts have also been used effectively in this reaction.

In the present work, we report a simple, mild and effective method to generate 6-alkoxypurines or 6-alkoxyformimidoylpurines from 6-cyanopurines and methanol or ethanol in the presence of DBU. The isolation of 6-alkoxyformimidoylpurines obviates an important problem in the synthesis of 6-carboxamidinopurines **3** as these compounds can not be prepared from 6-cyanopurines by direct reaction with ammonia or amine



Scheme 1 *Reagents and conditions*: a) $HC(OEt)_3$; b) NH_2Me (aq), CH_2Cl_2, rt.

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Table 1

Compound	R	Reaction conditions	Yield (%)
5a	Me	16 h (rt)	94
5b	4-$MeOC_6H_4$	4 days (rt)	96
		10 h (reflux)	88
5c	4-CNC_6H_4	10 days (rt)	97
6c	4-CNC_6H_4	13 days (rt)	[a]
7a	Me	3 days (78 °C)	84
7b	4-$MeOC_6H_4$	25 h (78 °C)	76
7c	4-CNC_6H_4	17 h (78 °C)	97
8a	Me	4 h (reflux)	48
8b	4-$MeOC_6H_4$	25 h (reflux)	46
		3.5 days (rt)	
8c	4-CNC_6H_4	40 min (reflux)	82

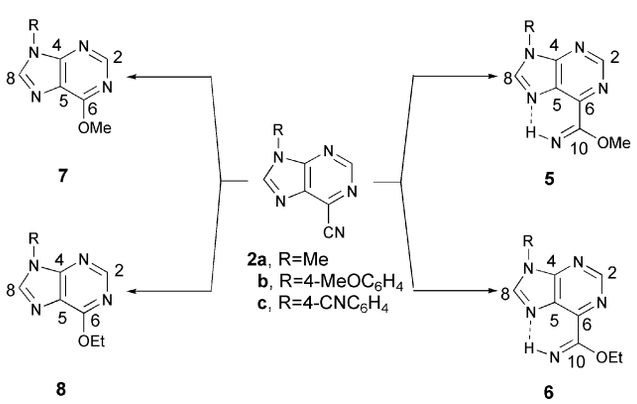
[a] The solid isolated is a mixture of **6c** and **8c** in a 1 : 1 ratio.

nucleophiles as the reactions lead invariably to pyrimido[5,4-*d*]-pyrimidine rearrangement products **4**.[1,20–23] Previous reports on the reactions of 6-cyanopurines with amines are confusing in that some authors report nucleophilic attack on the cyano group[24] while others suggest that treatment with methanolic ammonia results in attack at the imidazole ring with rearrangement to give a pyrimido[5,4-*d*]pyrimidine in unspecified yield[20–22,25,26] or 17% yield.[23] When this reaction is performed in a pressure vessel at 0–18 °C, the reported yield of rearranged product raises to 75%.[27]

These results throw into question the reports that 6-carboxamidinopurine derivatives can be prepared from 6-cyanopurines by direct reaction with ammonia or amine nucleophiles. The use of a 6-alkoxyformimidoylpurine as the starting material in the reaction with amines may solve this particular problem, leading selectively to the formation of the amidine function.[28]

Results and discussion

When a suspension of the 6-cyano-9-substituted purines **2a**–**c** in methanol was stirred at room temperature, in the presence of a catalytic amount of DBU, nucleophilic attack of the solvent occurred selectively on the cyano carbon atom and the corresponding 6-(methoxyformimidoyl)purines **5a**–**c** were isolated in excellent yields (Scheme 2; Table 1). A similar reaction has been reported previously by Rao and Revankar[29] using concentrated ammonia as the base. According to this reference, six different 9-alkyl-6-cyanopurines were combined with a large excess of aqueous ammonia and methanol, at room temperature, and only one of these compounds led to the isolation of a 6-(methoxyformimidoyl)purine in 59% yield.



Scheme 2

The reaction of 6-cyano-9-substituted purines **2a**–**c** was also carried out in ethanol, but in this case TLC on the reaction mixture indicated that a considerable amount of starting material was still present after 5 days at room temperature. In an attempt to accelerate the reaction, one equivalent of DBU was added to a suspension of purine **2c** in ethanol, and was stirred at room temperature for 13 days. The solid mixture was filtered and the ^{1}H NMR spectrum on the solid indicated the absence of starting material. The product was a mixture of compounds **6c** and **8c** in approximately 1 : 1 ratio.

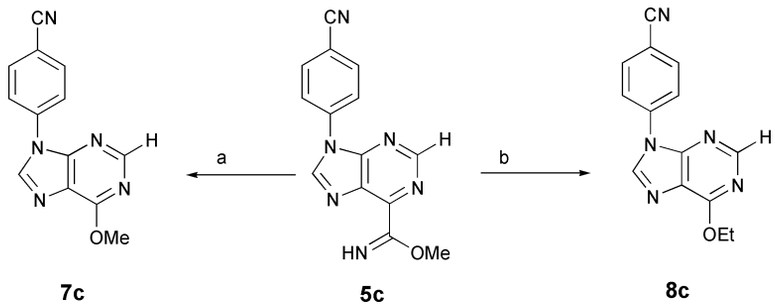
When the same reaction (**2c** and ethanol/DBU) was carried out under reflux conditions, compound **8c** was isolated in 82% yield after only 40 minutes, and no trace of the 6-(ethoxyformimidoyl)purine **6c** was detected by TLC on the reaction mixture. In this case, nucleophilic aromatic substitution occurs selectively, leading to the replacement of the substituent in the 6-position by the ethoxy group. A similar reactivity was registered when the 6-cyanopurines **2a** and **2b** were refluxed in ethanol/DBU, leading to the corresponding 6-ethoxypurines **8a** (48%) and **8b** (46%). Both 6-ethoxypurines **8a** and **8b** are very soluble in the solvent mixture, leading to comparatively low isolated yields of these products. However, the TLC indicates that a complete and clean reaction occurs in each case. The excellent isolated yield of compound **8c** results from its low solubility in the reaction mixture, a typical feature in most purines incorporating the 9-(4′-cyanophenyl) substituent.

Refluxing **2b** in methanol/DBU (catalytic amount) gave only compound **5b**, isolated in 88% yield after 10 hours; there was no evidence for the 6-methoxypurine **7b**. Considering that the difference in boiling point between these two solvents (methanol, bp 65 °C, ethanol, bp 78 °C) might be responsible for the different reactivity of **2b** in each solvent, a 1 : 8 mixture of methanol : acetonitrile was used, in order to adjust the boiling point of the solvent mixture to a value close to 78 °C. Under these experimental conditions, the evolution of **2b** occurred to give **7b** in 76% yield, after refluxing the mixture for 25 hours. Similar solvent mixtures were prepared for the reaction of **2a** and **2c** with methanol, under reflux conditions, which again led to products **7a** (84%) and **7c** (97%). The high solubility of 6-methoxypurine **7b** in the solvent mixture may again be responsible for the comparatively low isolated yield of this product, considering that no other by-products were detected by TLC. The use of a catalytic amount of DBU in the reactions with methanol (leading to **7a**–**c**) may also account for the slightly higher isolated yields of these products, when compared with the corresponding reactions to form **8a**–**c**, where one equivalent of DBU was always used.

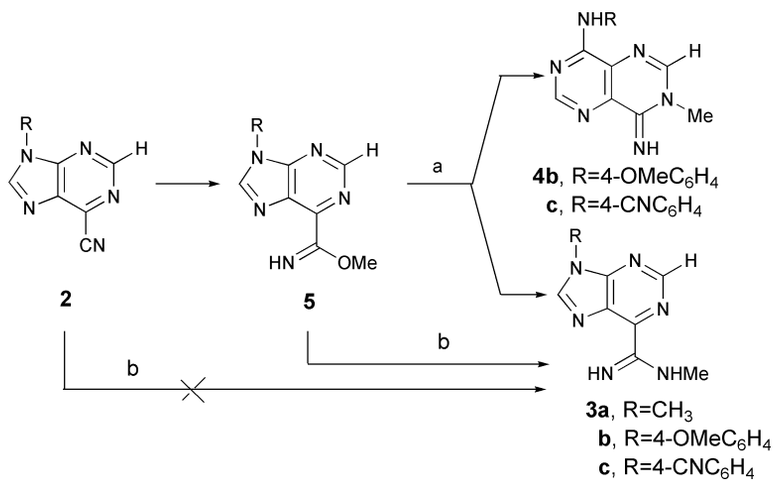
The reaction of 6-cyanopurines with methanol or ethanol leads to 6-alkoxyformimidoylpurines **5** and **6** as the kinetic products and to 6-alkoxypurines **7** and **8** under reflux conditions. Consequently, the formation of the 6-alkoxypurine could occur either from a 6-alkoxyformimidoylpurine or directly from the 6-cyanopurine used as the starting material. In order to understand the reaction mechanism, 6-(methoxyformimidoyl)-9-(4′-cyanophenyl)purine **5c** was reacted with ethanol and methanol under the same reaction conditions as those employed for the reaction with 6-cyanopurines (Scheme 3).

When compound **5c** was refluxed in ethanol, in the presence of one equivalent of DBU, no 6-ethoxypurine was detected on TLC after 40 min. After 3 h under reflux conditions, only traces of the 6-ethoxypurine were present in the reaction mixture. Purine **8c** was the major product in solution when the reflux was carried out for 27 h. A much faster reaction occurred when 6-cyanopurine **2c** was refluxed in ethanol/DBU, as the isolated yield of **8c** was 82% after 40 min. This result indicates that, although the 6-methoxyformimidate group in **5c** can be replaced by the ethoxy group, the substitution of the 6-cyano group is faster and must be the preferred pathway when **2c** is used as the starting material for this reaction.

When the 6-(methoxyformimidoyl)-9-(4′-cyanophenyl)-purine **5c** was refluxed in methanol/acetonitrile (8 : 1) in the presence of a catalytic amount of DBU, the 6-methoxypurine **7c** was formed as the only product after 20 h. This reaction time compares with that registered for the preparation of **7c** from the



Scheme 3 *Reagents and conditions*: a) MeOH; b) EtOH.



Scheme 4 *Reagents and conditions*: a) NH_2Me (aq), MeOH, rt, **3a** (98%), **4b** (86%), **4c** (detected as the major component of the crude product, by ^{1}H NMR); b) $NH_2Me.HCl$, CH_2Cl_2/MeOH, 1 : 1, **3b** (isolated as the hydrochloride 86%), **3c** (isolated as the hydrochloride, 92%).

6-cyanopurine **2c**, under similar reaction conditions (17 h). No traces of the 6-(methoxyformimidoyl)purine were detected by TLC on the reaction mixture, but in this case the comparable reaction time does not exclude the possibility of having both pathways occurring simultaneously.

A detailed spectroscopic analysis was carried out for the 6-alkoxyformimidoylpurines **5** and for the 6-alkoxypurines **7** and **8**. In the 6-alkoxyformimidoylpurines **5**, the absence of the cyano group is evident both in the IR spectrum and by ^{13}C NMR spectroscopy. The ^{13}C NMR spectrum shows, in addition, the signal for the imidate carbon atom around δ 164 ppm, as expected. The chemical shift for C-6 of the purine ring is identified in the δ 143–149 ppm region, in contrast with the corresponding signal for 6-cyanopurines, around δ 135 ppm. No major changes occur in the position of the remaining signals, indicating that the purine structure is clearly present. This is supported by the ^{1}H NMR chemical shifts for C-2(H) and C-8(H), usually slightly higher than δ 9.0 ppm. A single N–H signal is registered around δ 9.9 ppm, which reflects its highly acidic character. This signal is sharp, suggesting that a strong intramolecular H-bond maintains this proton in the vicinity of N-7, in DMSO-d_6 solution. This hydrogen bridge seems to be present also in the solid state, as a single sharp band around 3280 cm^{-1} is present in the spectra of all the compounds. A strong band in the 1630–1635 cm^{-1} region is also typical of these compounds. Compound **6c** was very insoluble in DMSO-d_6 and the ^{1}H NMR spectrum could only be obtained when 5 µl of trifluoroacetic acid were added to 500 µl of DMSO. Although the N–H signal is not observed in this spectrum, the signals for the remaining protons are very similar to those registered for the analogous compound **5c**, which was fully characterized.

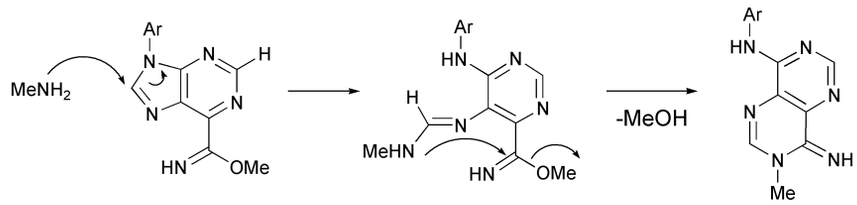
For the 6-alkoxypurines **7** and **8**, the ^{13}C NMR spectrum indicates that the purine skeleton is still present, with all the signals in the expected positions. This includes C-6, around δ 160 ppm, a chemical shift that reflects the influence of the alkoxy group. No N–H signals could be detected both in the IR and ^{1}H NMR spectra. The high chemical shifts for C-2(H) and C-8(H) (δ 8.3–9.0 ppm) are also typical of the purine ring system.

The 6-alkoxyformimidoylpurines **5a**–**c** were reacted with aqueous methylamine (7 equivalents) in methanol (Scheme 4). The 9-methylpurine **5a** led exclusively to the corresponding 6-(*N*-methylamidino)purine **3a**, isolated in 98% yield after 4 hours at room temperature and 14 hours at 4 °C. The reaction with 9-arylpurines **5b** and **5c** led to the pyrimido[5,4-*d*]pyrimidines **4b** (86% after 18 days at room temperature) and **4c** (detected in the complex reaction mixture by ^{1}H NMR on the crude product).

Under these reaction conditions, nucleophilic attack on C-8 of the purine ring in 9-arylpurines, is a favoured process compared to nucleophilic attack on the imidate function, leading to the pyrimido[5,4-*d*]pyrimidine rearrangement product **4** (Scheme 5).

In order to assist the elimination of alcohol from the imidate function in the 6-position of purines **5b** and **5c**, after nucleophilic attack by the amine, the reactions were carried out using methyl ammonium chloride (1 equivalent). Methanol and dichloromethane (1 : 1 mixture) were used as solvents, and reflux led to the formation of 6-carboxamidinopurines **3b** (86% after 2 hours) and **3c** (96% after 5 hours). When the corresponding 6-cyanopurines **2b** and **2c** were combined with methyl ammonium chloride (1.2 equivalents) under similar reaction conditions, only the starting material was isolated after refluxing the reaction mixture for 26 hours (**2b**, 87%) and 14 hours (**2c**, 84%). Previous work on the reaction of 6-cyanopurines **2b** and **2c** with aqueous methylamine indicates that pyrimido[5,4-*d*]pyrimidines **4** are the only products isolated in this process.[1]

The synthesis of 9-aryl-6-(*N*-methylamidino)purines is a delicate process and could only be achieved when the exocyclic cyano group of the 9-aryl-6-cyanopurine was transformed into



5 **4**

Scheme 5

a 6-alkoxyformimidoyl group. Addition of the amine nucleophile as the hydrochloride salt displaces the alkoxy group leading to the desired product.

Conclusion

The reaction of 6-cyanopurines with primary alcohols can occur selectively on the carbon atom of the cyano substituent, leading to 6-alkoxyformimidoylpurines **5** and **6** or on C-6 of the purine ring, with nucleophilic substitution of either the cyano or the alkoxyformimidoyl groups to give compounds **7** and **8**. Mild reaction conditions are required and the predominant pathway depends on the temperature. Nucleophilic substitution involves higher energy barriers and occurs when the temperature value reaches 78 °C. Addition to the 6-cyano substituent is kinetically controlled and occurs at room temperature. The presence of DBU was essential in both cases and the reaction is equally smooth from 9-methyl or 9-aryl-6-cyanopurines, where the aryl group is substituted by either electron-donating (OMe) or electron-withdrawing (CN) groups.

The 6-alkoxyformimidoylpurine **5a** reacts with methylamine and **5b** and **5c** react with methyl ammonium chloride leading to 6-(*N*-methylamidino)purines **3** in excellent yields. This represents the first general procedure for the synthesis of this type of 6-substituted purines and application of this method to other nucleophiles is currently in progress.

Experimental

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.

General procedure for the synthesis of 6-(methoxyformimidoyl)-purines (5)

A suspension of 6-cyanopurine **2** in methanol and DBU (20 μl, 0.05–0.06 molar equivalents) was stirred efficiently at room temperature. The reaction was followed by TLC until the starting material was no longer present; the white solid was filtered and washed with ethanol followed by diethyl ether. A second crop of the same product could usually be recovered from the mother liquor after concentration on the rotary evaporator.

9-Methyl-6-(methoxyformimidoyl)purine (5a)

Yield: 94% (1.59 mmol); mp = 175–177 °C dec; (Found: C 50.07; H 4.83; N 36.44. Calc. for $C_8H_9N_5O$: C 50.26; H 4.71; N 36.65%); ν_{max}/cm^{-1} (Nujol mull) 3278s (NH), 1635 (C=C, C=N), 1587s; δ_H (300 MHz; $(CD_3)_2SO$; Me_4Si) 9.83 (1 H, s, NH), 9.00 (1 H, s, H_2), 8.72 (1 H, s, H_8), 3.91 (3 H, s, OCH_3), 3.87 (3 H, s, NCH_3); δ_C (75 MHz; $(CD_3)_2SO$; Me_4Si) 164.4 (C_{10}), 153.7 (C_4), 151.3 (C_2), 149.1 (C_8), 143.4 (C_6), 130.5 (C_5), 53.2 (OCH_3), 29.8 (NCH_3); *m*/*z* (FAB, 70 eV) 192 $(M + H)^+$.

9-(4′-Methoxyphenyl)-6-(methoxyformimidoyl)purine (5b)

Yield: 96% (0.34 mmol); mp = 201–203 °C; (Found: C 59.38, H 4.68, N 24.91. Calc. for $C_{14}H_{13}N_5O_2$: C 59.36, H 4.59, N 24.73%); ν_{max}/cm^{-1} (Nujol mull) 3288s (NH), 1637s (C=N, C=C), 1610, 1586, 1574; δ_H (300 MHz; $(CD_3)_2SO$; Me_4Si) 9.88 (1 H, s, NH), 9.07 (1 H, s, H_8), 9.05 (1 H, s, H_2), 7.77 (2 H, d, *J* 9.0, H_m), 7.17 (2 H, d, *J* 9.0, H_o), 3.95 (3 H, s, OCH_3), 3.84 (3 H, s, OCH_3); δ_C (75 MHz; $(CD_3)_2SO$; Me_4Si) 164.2 (C_{10}), 159.0 (C_p), 153.0 (C_4), 151.8 (C_2), 147.3 (C_8), 144.3 (C_6), 130.8 (C_5), 126.7 (C_i), 125.3 (C_o), 114.6 (C_m), 55.5 (OCH_3), 53.1 (OCH_3); *m*/*z* (FAB, 70 eV) 284 $(M + H)^+$, 269 $(M + H - Me)^+$.

9-(4′-Cyanophenyl)-6-(methoxyformimidoyl)purine (5c)

Yield: 97% (2.47 mmol); mp = 253–254 °C, dec; (Found: C 60.48; H 3.37; N 30.28. Calc. for $C_{14}H_{10}N_6O$: C 60.43; H 3.60; N 30.22%); ν_{max}/cm^{-1} (Nujol mull) 3255s (NH), 2227s (CN), 1635s (C=N, C=C), 1611, 1586, 1568; δ_H (300 MHz; $(CD_3)_2SO$; Me_4Si) 9.85 (1 H, s, NH), 9.31 (1 H, s, H_8), 9.12 (1 H, s, H_2), 8.24 (2 H, d, *J* 8.7, H_m), 8.16 (2 H, d, *J* 8.7, H_o), 3.95 (3 H, s, OCH_3); δ_C (75 MHz; $(CD_3)_2SO$; Me_4Si) 164.3 (C_{10}), 153.0 (C_4), 152.2 (C_2), 148.8 (C_6), 146.7 (C_8), 137.8 (C_i), 133.8 (C_m), 123.9 (C_o), 123.4 (C_5), 118.1 (CN), 110.7 (C_p), 53.3 (OCH_3); *m*/*z* (FAB MS, 70 eV) 279 $(M + H)^+$.

Synthesis of 9-(4′-methoxyphenyl)-6-(methoxyformimidoyl)-purine 5b using reflux conditions

A suspension of 6-cyano-9-(methoxyphenyl)purine (0.08 g, 0.32 mmol) in methanol (2 cm^3) in the presence of DBU (20 μl) was refluxed for 10 h. An off-white solid was formed on cooling and the suspension was filtered and washed with diethyl ether (0.05 g). The mother liquor was concentrated on the rotary evaporator leading to a second crop of the same product (0.02 g). The two crops were combined and identified as the title compound (0.07 g, 0.25 mmol, 88%).

Synthesis of 9-(4′-cyanophenyl)-6-(ethoxyformimidoyl)purine (6c)

A suspension of 6-cyano-9-(4′-cyanophenyl)purine (0.18 g, 0.72 mmol) in ethanol (5 cm^3) was stirred at room temperature in the presence of DBU (110 μl, 0.72 mmol). The reaction mixture was stirred for 13 days, when TLC indicated that all the starting material had been consumed. The solid suspension was filtered and washed with ethanol followed by diethyl ether. The ^{1}H NMR spectrum on the solid showed that it was a mixture of the 9-(4′-cyanophenyl)-6-ethoxypurine **6c** and 9-(4′-cyanophenyl)-6-(ethoxyformimidoyl)purine **8c** in a 1 : 1 ratio (0.16 g). δ_H (300 MHz; $(CD_3)_2SO$ + CF_3CO_2D, 100 : 1; Me_4Si) for **6c** 9.28 (1 H, s, H_8), 9.14 (1 H, s, H_2), 8.23 (2 H, d, *J* 8.7, H_m), 8.10 (2 H, d, *J* 8.7, H_o), 3.47 (2 H, q, *J* 7.2, OCH_2), 1.38 (3 H, t, *J* 7.2, CH_3).

General procedure for the synthesis of 6-methoxypurines (7)

A solution of 6-cyanopurine **2** in a mixture of acetonitrile : methanol in an 8 : 1 ratio, was heated to reflux temperature. DBU (40 μl, 0.3–0.6 molar equivalents) was added and the mixture was refluxed until no starting material was present according to TLC. The orange solution was filtered through glass-fibre paper in order to eliminate dark residues in suspension. The mother liquor was concentrated to a yellow solid in the rotary evaporator. Addition of ethanol followed by diethyl ether led to

a yellow solid suspension that was filtered and washed with diethyl ether.

9-(4′-Methoxyphenyl)-6-methoxypurine (7b)

Yield: 76% (2.09 mmol); mp = 149–150 °C; (Found: C 60.85; H 4.90; N 22.02. Calc. for $C_{13}H_{12}N_4O_2$: C 60.94; H 4.69; N 21.88%); ν_{max}/cm^{-1} (Nujol mull) 1617s (C=N, C=C), 1602, 1567; δ_H (300 MHz; $(CD_3)_2SO$; Me_4Si) 8.70 (1 H, s, H_8), 8.57 (1 H, s, H_2), 7.75 (2 H, d, *J* 9.0, H_m), 7.15 (2H, d, *J* 9.0, H_o), 4.12 (3 H, s, OCH_3), 3.83 (3 H, s, OCH_3); δ_C (75 MHz; $(CD_3)_2SO$; Me_4Si) 160.5 (C_6), 158.8 (C_p), 152.0 (C_2), 151.6 (C_4), 142.8 (C_8), 127.4 (C_i), 125.5 (C_5), 125.0 (C_o), 114.6 (C_m), 55.5 (OCH_3), 54.0 (OCH_3).

9-(4′-Cyanophenyl)-6-methoxypurine (7c)

Yield: 97% (0.81 mmol); mp above 300 °C, dec; (Found: C 61.91; H 3.80; N 28.17. Calc. for $C_{13}H_9N_5O$: C 62.15; H 3.59; N 27.89%); ν_{max}/cm^{-1} (Nujol mull) 2230m (CN), 1614s (C=N, C=C), 1599, 1564; δ_H (300 MHz; $(CD_3)_2SO$; Me_4Si) 8.96 (1 H, s, H_8), 8.65 (1 H, s, H_2), 8.24 (2 H, d, *J* 9.0, H_o), 8.12 (2 H, d, *J* 9.0, H_m), 4.14 (3 H, s, OCH_3); δ_C (75 MHz; $(CD_3)_2SO$; Me_4Si) 160.7 (C_6), 152.5 (C_2), 151.4 (C_4), 142.3 (C_8), 138.4 (C_i), 133.9 (C_m), 123.3 (C_o), 121.6 (C_5), 118.3 (CN), 110.1 (C_p), 54.2 (OCH_3).

Synthesis of 9-methyl-6-methoxypurine (7a)

A solution of 6-cyano-9-methylpurine (0.14 g, 0.89 mmol) in acetonitrile (16 cm^3) with a catalytic amount of DBU (40 μl) was kept under reflux conditions, when methanol (2 cm^3) was added dropwise. The mixture was refluxed for three days, when the starting material was no longer detected by TLC. The solvent mixture was completely removed in the rotary evaporator leading to an oil. The oil was solubilized in acetonitrile and filtered through a short column (0.2 × 3 cm) of Kieselgel 60 for column chromatography (particle size less than 0.063 mm), which was than eluted with ethyl acetate (200 cm^3). The solvent was removed in the rotary evaporator leading to a cream solid. Petroleum ether was added to the solid, which was filtered and washed with petroleum ether. The product was identified as the purine **7a** (0.12 g, 0.75 mmol, 84%); mp = 141–142 °C, dec; ν_{max}/cm^{-1} (Nujol mull) 1606s (C=N, C=C), 1577; δ_H (300 MHz; $(CD_3)_2SO$; Me_4Si) 8.52 (1 H, s, H_2), 8.32 (1 H, s, H_8), 4.08 (3 H, s, OCH_3), 3.80 (3 H, s, NCH_3); δ_C (75 MHz; $(CD_3)_2SO$; Me_4Si) 160.1, 152.4, 151.4, 144.3, 120.4, 53.8, 29.7; MS (FAB) *m*/*z* (rel int) 165 (M + 1, 100). HRMS (FAB) *m*/*z* (FAB) 165.078425 ($(M + H)^+$. $C_7H_8N_4O$ requires 165.077636).

General procedure for the synthesis of 6-ethoxypurines (8)

A suspension of 6-cyanopurine **2** in ethanol and DBU (1 molar equivalent) was refluxed until no starting material was detected by TLC. A homogeneous orange solution was obtained and the solvent was concentrated in the rotary evaporator. Compounds **8b** and **8c** precipitate from the reaction mixture and were filtered and washed with diethyl ether, leading to yellow solids. For compound **8a**, an oil was obtained which was supported on silica and submitted to dry flash chromatography. The pure compound **8a** was isolated as a yellow solid using diethyl ether as eluant. The solid was filtered and washed with a mixture of diethyl ether/pet. ether 40–60.

6-Ethoxy-9-methylpurine (8a)

Yield: 48% (0.47 mmol); mp = 112–114 °C; (Found: C 53.93; H 5.72; N 31.25. Calc. for $C_8H_{10}N_4O$: C 53.93; H 5.62; N 31.46%); ν_{max}/cm^{-1} (Nujol mull) 1619m (C=N, C=C), 1600, 1582; δ_H (300 MHz; $(CD_3)_2SO$; Me_4Si) 8.50 (1 H, s, H_2), 8.31 (1 H, s, H_8), 4.57 (2 H, q, *J* 6.9, OCH_2), 3.79 (3 H, s, N_9CH_3), 1.39 (3 H, t, *J* 6.9, CH_3); δ_C (75 MHz; $(CD_3)_2SO$; Me_4Si) 159.8 (C_6), 152.4 (C_4), 151.4 (C_2), 144.2 (C_8), 120.4 (C_5), 62.4 (OCH_2), 29.7 (N_9CH_3), 14.4 (CH_3).

6-Ethoxy-9-(4′-methoxyphenyl)purine (8b)

Yield: 46% (0.37 mmol); mp = 169–172 °C; (Found: C 62.08; H 5.31; N 20.79. Calc. for $C_{14}H_{14}N_4O_2$: C 62.22; H 5.19; N 20.74%); ν_{max}/cm^{-1} (Nujol mull) 1604s (C=N, C=C), 1569, 1524; δ_H (300 MHz; $(CD_3)_2SO$; Me_4Si) 8.69 (1 H, s), 8.54 (1 H, s), 7.73 (2 H, d, *J* 8.7), 7.14 (2 H, d, *J* 8.7), 4.61 (2 H, q, *J* 6.9), 3.82 (3 H, s), 1.42 (3 H, t, *J* 6.9); δ_C (75 MHz; $(CD_3)_2SO$; Me_4Si) 160.2, 158.7, 151.9, 151.6, 142.5, 127.4, 125.2, 124.9, 114.6, 62.5, 55.4, 14.3.

9-(4′-Cyanophenyl)-6-ethoxypurine (8c)

Yield: 82% (1.14 mmol); mp above 222 °C, dec; (Found: C 63.14; H 4.35; N 26.16. Calc. for $C_{14}H_{11}N_5O$: C 63.40; H 4.15; N 26.42%); ν_{max}/cm^{-1} (Nujol mull) 2227m (CN), 1596s (C=N, C=C), 1518; δ_H (300 MHz; $(CD_3)_2SO$; Me_4Si) 8.96 (1 H, s, H_8), 8.61 (1 H, s, H_2), 8.24 (2 H, d, *J* 9.0, H_m), 8.11 (2 H, d, *J* 9.0, H_o), 4.63 (2 H, q, *J* 7.2, OCH_2), 1.43 (3 H, t, *J* 7.2, CH_3); δ_C (75 MHz; $(CD_3)_2SO$; Me_4Si) 160.4 (C_6), 152.5 (C_2), 151.5 (C_4), 142.2 (C_8), 138.5 (C_i), 133.9 (C_m), 123.2 (C_o), 121.5 (C_5), 118.3 (CN), 110.1 (C_p), 62.9 (OCH_2), 14.4 (CH_3).

Reaction of 9-(4′-cyanophenyl)-6-(methoxyformimidoyl)purine 5c with methanol

A suspension of 6-(methoxyformimidoyl)-9-(4′-cyanophenyl)-purine **5c** (0.10 g, 0.37 mmol) in acetonitrile : methanol, 8 : 1 (9 cm^3) was refluxed and the reaction was followed by TLC. After 20 h, the starting material was no longer present on TLC and the yellow solid was filtered and washed with ethanol followed by diethyl ether (0.07 g). A second crop was obtained from the mother liquor (0.01 g). The two crops were identical by TLC and were combined and identified as the 6-methoxypurine **7c** (0.08 g, 0.32 mmol, 86.5%) by comparison of the ^{1}H NMR spectrum with that of an authentic sample.

Reaction of 9-(4′-cyanophenyl)-6-(methoxyformimidoyl)purine 5c with ethanol

A suspension of 6-(methoxyformimidoyl)-9-(4′-cyanophenyl)-purine **5c** (0.10 g, 0.37 mmol) in ethanol (10 cm^3) was refluxed and the reaction was followed by TLC. After 3 h, the presence of 6-ethoxypurine could be detected on TLC and no starting material was present after 27 h. The yellow solid was filtered and washed with ethanol followed by diethyl ether giving 0.04 g of product. Two other crops were recovered from the mother liquor (0.02 g and 0.01 g). The three crops were identical by TLC and were combined and identified as the 6-ethoxypurine **8c** (0.07 g, 0.27 mmol, 73%) by comparison of the ^{1}H NMR spectrum with that of an authentic sample.

Reaction of 9-methyl-6-(methoxyformimidoyl)purine 5a with methylamine

Aqueous methylamine (0.8 cm^3 of a 40% aqueous solution, 9.24 mmol) was added to a suspension of 9-methyl-6-(methoxyformimidoyl)purine **5a** (0.25 g, 1.32 mmol) in methanol (5 cm^3), and the mixture was stirred at room temperature in a round-bottom flask equipped with a serum cap. After 4 h at room temperature, the reaction was stirred at 4 °C for another 14 h and the homogeneous solution was concentrated in the rotary evaporator. Addition of cold diethyl ether led to a suspension which was filtered and washed abundantly with diethyl ether. The white solid was identified as 9-methyl-6-(*N*-methylamidino)purine **3a** (0.25g, 1.30 mmol, 98%), mp = 105–107 °C; (Found: C 42.42; H 6.16; N 36.98. Calc. for $C_8H_{10}N_6.2H_2O$: C 42.67; H 6.22; N 37.33%); ν_{max}/cm^{-1} (Nujol mull) 3481s (NH), 3354s (NH), 3324s (NH), 3171s (NH), 3052s (NH), 1513m, 1581s; δ_H (300 MHz; $(CD_3)_2SO$; Me_4Si) 9.01 (1 H, s, H_8), 8.74 (1 H, s, H_2), 7.50 (1 H, br s, NH), 7.46 (1 H, br s, NH), 3.88 (3 H, s, N_9CH_3), 2.93 (3 H, s, NCH_3); δ_C (75 MHz; $(CD_3)_2SO$;

Me_4Si) 158.5 (C_{Am}), 153.5 (C_3), 151.1 (C_2), 148.9 (C_8), 143.7 (C_6), 129.8 (C_5), 29.9 (N_9CH_3), 28.1 ($N_{Am}CH_3$).

Reaction of 9-aryl-6-(methoxyformimidoyl)purines 5b and 5c with methylamine

Aqueous methylamine (7 molar equivalents of a 40% aqueous solution) was added to a suspension of 9-aryl-6-(methoxyformimidoyl)purine (0.20 g, 0.72 mmol for **5b** and 0.22 g, 0.80 mmol for **5c**) in methanol (5 cm^3), and the mixture was stirred at room temperature in a round-bottom flask equipped with a serum cap. The reaction was followed by TLC and the product was isolated when the starting material was no longer present. The solid suspension was filtered and washed with diethyl ether. A white solid was isolated from the reaction of **5b** and was identified as the pyrimido[5,4-*d*]pyrimidine **4b** (0.17 g, 0.62 mmol, 86%), by comparison of the ^{1}H NMR spectrum with the data described in the literature for an authentic sample.[1] A pale yellow solid was isolated from the reaction of **5c** and ^{1}H NMR indicated that the pyrimido[5,4-*d*]pyrimidine **4c** was the major component in the mixture, by comparison with the data described in the literature.[1]

General procedure for the reaction of 9-aryl-6-(methoxyformimidoyl)purines 5b and 5c with methyl ammonium chloride

A solution of methyl ammonium chloride (1 molar equivalent) in methanol (5 cm^3) was combined with a suspension of 9-aryl-6-(methoxyformimidoyl)purine in dichloromethane (5 cm^3). The mixture was refluxed until no starting material was detected by TLC (2 h for purine **5b** and 6 h for purine **5c**). The solution was concentrated in the rotary evaporator. Addition of ethanol followed by diethyl ether led to a solid which was filtered and washed with diethyl ether. Two crops of the same product were isolated and combined. The product was identified as the hydrochloride of 9-aryl-6-(*N*-methylamidino)purine (**3b**, 0.20 g, 0.64 mmol, 86% and **3c**, 0.08 g, 0.24 mmol, 92%).

9-(4′-Methoxyphenyl)-6-(*N*-methylamidino)purine hydrochloride (3b)

Mp 271–273 °C; (Found: C 48.83; H 5.23; N 24.21. Calc. for $C_{14}H_{14}N_6O.HCl.1.5H_2O$: C 48.63; H 5.21; N 24.31%); ν_{max}/cm^{-1} (Nujol mull) 3320m, 1677s, 1593s, 1523s; δ_H (300 MHz; $(CD_3)_2SO$; Me_4Si) 10.2 (2 H, br s, NH), 9.38 (1 H, s, H_8), 9.23 (1 H, s, H_2), 7.80 (2 H, d, *J* 9.0, H_m), 7.20 (2 H, d, *J* 9.0, H_o), 3.84 (3 H, s, OCH_3), 3.23 (3 H, s, CH_3); δ_C (75 MHz; $(CD_3)_2SO$; Me_4Si) 159.4 (C_p), 157.8 (C_{Am}), 153.4 (C_4), 152.1 (C_2), 149.3 (C_8), 140.3 (C_6), 131.3 (C_5), 126.3 (C_i), 125.6 (C_o), 114.9 (C_m), 55.7 (OCH_3), 30.1 (NCH_3).

9-(4′-Cyanoyphenyl)-6-(*N*-methylamidino)purine hydrochloride (3c)

Mp 230–232 °C, dec; ν_{max}/cm^{-1} (Nujol mull) 3370s, 2234m (CN), 1693m, 1651m, 1591s; δ_H (300 MHz; $(CD_3)_2SO$; Me_4Si) 10.15 (2 H, br s, NH), 9.8 (1 H, br s, NH), 9.61 (1 H, s, H_8), 9.32 (1 H, s, H_2), 8.28 (2 H, d, *J* 8.4, H_m), 8.19 (2 H, d, *J* 8.4, H_o), 3.22 (3 H, s, NCH_3); δ_C (75 MHz; $(CD_3)_2SO$; Me_4Si) 157.6 (C_{Am}), 153.2 (C_4), 152.4 (C_2), 148.7 (C_8), 140.8 (C_6), 137.5 (C_i), 134.0 (C_m), 131.7 (C_5), 124.0 (C_o) 118.2 (CN), 111.0 (C_p), 30.1 (NCH_3). MS (FAB) *m/z* (rel int) 278 (M + 1, 100). HRMS (FAB) *m/z* (FAB) 278.1165 ($(M + H)^+$. $C_{14}H_{11}N_7$ requires 278.1154).

General procedure for the reaction of 9-aryl-6-cyanopurines 2b and 2c with methyl ammonium chloride

A suspension of 9-aryl-6-cyanopurine and methyl ammonium chloride (1.2 molar equivalents) in a 1 : 1 mixture of ethanol and dichloromethane (10 cm^3) was refluxed for 26 h (**2b**) or 14 h (**2c**). The solid material precipitated on cooling and was filtered and washed with methanol followed by diethyl ether. The product was identified as the 6-cyanopurine **2b** (0.11 g, 0.43 mmol, 84%) or **2c** (0.15 g, 0.61 mmol, 87%).

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