Efficient conversion of 6-cyanopurines into 6-alkoxyformimidoyl-purines

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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 methyamine (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 has shown that these compounds can be prepared in a simple and efficient way from 5-amino-4-(cyanoformimidoyl)imidazoles and tri-ethyl 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, 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. 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. Unlike these compounds, 6-alkoxypurines have been known for a few decades and two major reviews have been produced about their chemistry.

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. 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-alkoxopurines occurs. Other suitable groups have been used for nucleophilic displacement, especially the methyl-sulfonyl, alkylthio, alkylseleno, 1,2,4-triazol-4-yl or 1,2,4-triazol-4-yl groups. The 6-trialkylammonium 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 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)$_2$; b) NH$_3$Me (aq), CH$_2$Cl$_2$, rt.

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nucleophiles as the reactions lead invariably to pyrimido[5,4-d]-pyrimidine rearrangement products. Previous reports on the reactions of 6-cyanopurines with amines are confusing in that some authors report nucleophilic attack on the cyano group 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 or 17% yield. When this reaction is performed in a pressure vessel at 0–18 °C, the reported yield of rearranged product raises to 75%. These results throw into question the reports that 6-carboxyaminopurine 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.

Results and discussion

When a suspension of the 6-cyano-9-substituted purines in methanol was stirred at room temperature, in the presence of a catalytic amount of DBU, nucleophilic attack 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-ethoxyxpurine was detected on TLC after 40 minutes. After 3 hours under reflux conditions, only traces of the 6-ethoxyxpurine 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 minutes. 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-methoxyxpurine 7c was formed as the only product after 20 hours. This reaction time compares with that registered for the preparation of 7c from the

Table 1

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>Reaction conditions</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a</td>
<td>Me</td>
<td>16 h (rt)</td>
<td>94</td>
</tr>
<tr>
<td>5b</td>
<td>4-MeOC&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;2&lt;/sub&gt;N</td>
<td>4 days (rt)</td>
<td>96</td>
</tr>
<tr>
<td>5c</td>
<td>4-CNC&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;N</td>
<td>10 days (rt)</td>
<td>97</td>
</tr>
<tr>
<td>6c</td>
<td>4-CNC&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;N</td>
<td>3 days (rt)</td>
<td>97</td>
</tr>
<tr>
<td>7a</td>
<td>Me</td>
<td>3 days (78 °C)</td>
<td>84</td>
</tr>
<tr>
<td>7b</td>
<td>4-MeOC&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;2&lt;/sub&gt;N</td>
<td>25 h (78 °C)</td>
<td>76</td>
</tr>
<tr>
<td>7c</td>
<td>4-CNC&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;N</td>
<td>17 h (78 °C)</td>
<td>97</td>
</tr>
<tr>
<td>8a</td>
<td>Me</td>
<td>4 h (reflux)</td>
<td>48</td>
</tr>
<tr>
<td>8b</td>
<td>4-MeOC&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;2&lt;/sub&gt;N</td>
<td>25 h (reflux)</td>
<td>46</td>
</tr>
<tr>
<td>8c</td>
<td>4-CNC&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;N</td>
<td>40 min (reflux)</td>
<td>82</td>
</tr>
</tbody>
</table>

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

The reaction of 6-cyanopurines with methanol or ethanol leads to 6-alkoxyformimidoylpurines as the starting material in the reaction with amines and may solve this particular problem, leading selectively to the formation of the amidine function.

![Scheme 2](image-url)
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 

\[ \delta_{\text{C}} \]

signals in the expected positions. This includes C-6, around 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 

\[ ^1H \text{NMR} \] spectra. The high chemical shifts for C-2(H) and C-8(H) are typical of the purine ring system.

The synthesis of 9-aryl-6-cyanopurines is a favoured process compared to nucleophilic attack on the imidate function, leading to the pyrimido[5,4-d]pyrimidines 4b (86% after 5 hours) and 4c (96% after 5 hours). When the corresponding 6-cyanopurines 2b and 2c were reacted with aqueous methylamine, 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 methanol indicated that pyrimido[5,4-d]pyrimidines 4 are the only products isolated in this process.

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...
a 6-alkoxyformimidoyl group. Addition of the amine nucleophile as the hydrochloride salt displaces the alkoy 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 kinetically controlled and occurs at room temperature. The reaction of 6-cyanopurines with primary alcohols can occur 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. 1H and 13C NMR spectra were 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% (0.59 mmol); mp = 175–177 °C dec; (Found: C 50.07; H 4.83; N 36.44. Calc. for C10H12N2O: C 50.26; H 4.71; N 36.65%; 1H NMR): δ (Nujol mull) 3278 (NH), 1635 (C=C, C=N), 1587; δ (300 MHz; CD3SO3H): 9.83 (1 H, s, NH), 9.00 (1 H, s, H2), 8.72 (1 H, s, H2), 3.91 (3 H, s, OCH3), 3.87 (3 H, s, NCH3); δ (75 MHz; CD3SO3H): 164.4 (C2), 153.7 (C2), 151.3 (C2), 149.1 (C3), 144.3 (C4), 130.5 (C5), 53.2 (OCH3), 29.8 (NCH3); 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 C16H15N2O2: C 59.36, H 4.59, N 24.73%); 1H NMR: 3288 (NH), 1673s (C=N, C=C), 1610, 1586, 1574; δ (300 MHz; CD3SO3H): 9.88 (1 H, s, NH), 9.07 (1 H, s, H4), 9.05 (1 H, s, H2), 7.77 (2 H, d, J 9.0, H2), 7.17 (2 H, d, J 9.0, H2), 3.95 (3 H, s, OCH3), 3.84 (3 H, s, OCH3); δ (75 MHz; CD3SO3H): 164.2 (C2), 159.0 (C5), 153.0 (C5), 151.8 (C2), 147.3 (C2), 144.3 (C2), 130.8 (C3), 126.7 (C5), 125.3 (C5), 114.6 (C2), 55.5 (OCH3), 53.1 (OCH3); m/z (FAB, 70 eV) 284 (M + H)+, 269 (M + H – Me)+.

Synthesis of 9-(4'-Cyano)phenyl)-6-(methoxyformimidoyl)purine (5c)

Yield: 97% (2.47 mmol); mp = 253–254 °C; dec; (Found: C 60.48; H 3.37; N 30.22%; 1H NMR): δ (Nujol mull) 3255 (NH), 2273s (CN), 1635s (C=C, C=N), 1611, 1586, 1568; δ (300 MHz; CD3SO3H): 9.85 (1 H, s, NH), 9.31 (1 H, s, H4), 9.12 (1 H, s, H2), 8.24 (2 H, d, J 8.7, H2), 8.16 (2 H, d, J 8.7, H2), 3.95 (3 H, s, OCH3); δ (75 MHz; CD3SO3H): 164.3 (C3), 153.0 (C2), 152.2 (C2), 148.8 (C4), 146.7 (C2), 137.8 (C2), 133.8 (C2), 123.9 (C3), 123.4 (C1), 118.1 (CN), 110.7 (C5), 53.3 (OCH3); m/z (FAB MS, 70 eV) 279 (M + H)+.

Synthesis of 9-(4'-Methoxyphenyl)-6-(methoxyformimidoyl)purine (6c)

A suspension of 6-cyano-9-(methoxyphenyl)purine (0.08 g, 0.32 mmol) in methanol (2 cm3) 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'-Cyano)phenyl)-6-(ethoxyformimidoyl)purine (8c)

A suspension of 6-cyano-9-(4'-cyano)phenyl)purine (0.18 g, 0.18 g, 0.72 mmol) in ethanol (5 cm3) was stirred at room temperature in the presence of DBU (20 µl) 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 1H NMR spectrum on the solid showed that it was a mixture of the 9-(4’-cyano)phenyl)-6-ethoxypurine 6c and 9-(4’-cyano)phenyl)-6-(ethoxyformimidoyl)purine 8c in a 1 : 1 ratio (0.16 g).

δ (300 MHz; CD3SO3H + CF3CO2D, 100 : 1; Me2Si) for 6c 9.28 (1 H, s, H4), 9.14 (1 H, s, H2), 8.23 (2 H, d, J 8.7, H2), 8.10 (2 H, d, J 8.7, H2), 3.47 (2 H, q, J 7.2, OCH2), 1.38 (3 H, t, J 7.2, CH2).

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'-Methoxy)-6-methoxypurine (7b)**

Yield: 76% (2.09 mmol); mp = 149–150 °C; (Found: C 60.85; H 4.90; N 22.02. Calc. for C₈H₉N₂O₂: C 60.94; H 4.69; N 21.88%).

**6-Ethoxy-9-methylpurine (8a)**

δ (300 MHz; (CD₃)₂SO; MeSO) 8.70 (1 H, s, H₈), 8.57 (1 H, s, H₂), 7.75 (2 H, d, J 9.0, H₈), 7.15 (2 H, d, J 9.0, H₂), 4.12 (3 H, s, OCH₃), 3.83 (3 H, s, OCH₃); δc (75 MHz; (CD₃)₂SO; MeSO) 160.5 (C₈), 158.8 (C₈), 152.0 (C₈), 151.6 (C₈), 142.8 (C₈), 127.4 (C₈), 125.5 (C₈), 114.6 (C₈), 55.5 (OCH₃), 54.0 (OCH₃).

**9-(4'-Cyano)-6-methoxypurine (7c)**

Yield: 97% (0.81 mmol); mp above 300 °C; (Found: C 61.91; H 3.80; N 28.17. Calc. for C₈H₉N₂O₂: C 62.15; H 3.59; N 27.89%).

**61.91; H 3.80; N 28.17. Calc. for C₈H₉N₂O₂: C 62.15; H 3.59; N 27.89%.)**

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

A solution of 6-cyano-9-methylpurine (0.14 g, 0.89 mmol) in acetonitrile (16 cm³) with a catalytic amount of DBU (40 μl) was kept under reflux conditions, when methanol (2 cm³) 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 then eluted with ethyl acetate (200 cm³). 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%).

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

A suspension of 6-cyano-9-methylpurine 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 C₈H₉N₂O₂: C 53.93; H 5.62; N 31.46%).

**6-Ethoxy-9-(4'-methoxy)purine (8b)**

Yield: 46% (0.37 mmol); mp = 169–172 °C; (Found: C 62.08; H 5.31; N 20.74%).

**6-Ethoxy-9-(4'-cyano)purine (8c)**

Yield: 82% (1.14 mmol); mp above 222 °C; (Found: C 63.14; H 4.35; N 26.16. Calc. for C₈H₉N₂O₂: C 63.40; H 4.15; N 26.42%).

A suspension of 6-(methoxymethyl)imidazolyl)-5-carboxylic acid was recovered 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 1H NMR spectrum with that of an authentic sample.

**Reaction of 9-(4'-cyano)-6-(methoxymethyl)imidazolyl)purine 5c with methanol**

A suspension of 6-(methoxymethyl)imidazolyl)-9-(4'-cyano)purine 5c (0.10 g, 0.37 mmol) in acetonitrile : methanol, 8 : 1 (9 cm³) 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 1H NMR spectrum with that of an authentic sample.

**Reaction of 9-(4'-cyano)-6-(methoxymethyl)imidazolyl)purine 5c with ethanol**

A suspension of 6-(methoxymethyl)imidazolyl)-9-(4'-cyano)purine 5c (0.10 g, 0.37 mmol) in ethanol (10 cm³) 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 identified by TLC and were combined and identified as the 6-ethoxypurine 8e (0.07 g, 0.27 mmol, 73%) by comparison of the 1H NMR spectrum with that of an authentic sample.

**Reaction of 9-methyl-6-(methoxymethyl)imidazolyl)purine 5a with methylene**

Aqueous methylene (0.8 cm³ of a 40% aqueous solution, 9.24 mmol) was added to a suspension of 9-methyl-6-(methoxymethyl)imidazolyl)purine 5a (0.25 g, 1.32 mmol) in methanol (5 cm³), 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 1 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-(9-methylamino)methoxy)purine 3a (0.25 g, 1.30 mmol, 98%).

**Reaction of 9-methyl-6-(methoxymethyl)imidazolyl)purine 5a with methanol**

A suspension of 6-(methoxymethyl)imidazolyl)-9-(4'-cyano)purine 5c (0.10 g, 0.37 mmol) in ethanol (10 cm³) 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 identified by TLC and were combined and identified as the 6-ethoxypurine 8e (0.07 g, 0.27 mmol, 73%) by comparison of the 1H NMR spectrum with that of an authentic sample.

**Reaction of 9-methyl-6-(methoxymethyl)imidazolyl)purine 5a with methylene**

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Me₂Si 158.5 (C₄₉), 153.5 (C₇), 151.1 (C₇), 148.9 (C₇), 143.7 (C₄), 129.8 (C₉), 29.9 (NCH₃), 28.1 (N₉₆CH₃).

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 cm³), 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 ¹H 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 ¹H NMR indicated that the pyrimido[4,5-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 cm³) was added to a suspension of 9-aryl-6-(methoxyformimidoyl)purine in dichloromethane (10 cm³). 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. Two crops of the same product were isolated and combined. The product was identified as the hydrochloride of 9-aryl-6-(N-methylamino)purine 3b (0.20 g, 0.64 mmol, 86%) and 3c (0.08 g, 0.24 mmol, 92%).

9-(4'-Methoxyphenyl)-6-(N-methylamino)purine hydrochloride (3b)

Mp 271–273 °C; Found: C 48.83; H 5.23; N 24.21, Calc. for C₁₆H₁₄N₂O.HCl.1.5H₂O: C 48.63; H 5.21; N 24.31%; v max/cm⁻¹ (Nujol Mull) 3320m, 1673m, 1593s, 1524s; δ H NMR indicated that the pyrimido[5,4-d]pyrimidine 4b (0.11 g, 0.43 mmol, 84%) or 2e (0.15 g, 0.61 mmol, 87%).

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References