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SYNTHESIS OF 6-SUBSTITUTED PURINE DERIVATIVES

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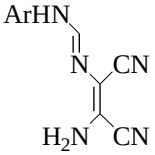
Abstract - Hydroxylamine hydrochloride reacts readily with (5-amino-1-aryl-1*H*-imidazol-4-yl)iminoacetonitriles to furnish 5-amino-1-aryl-*N*-hydroxy-1*H*-imidazole-4-carboxamidines. When a mixture of 5-amino-1-aryl-*N*-hydroxy-1*H*-imidazole-4-carboxamidine and excess of triethyl orthoesters is reacted at room temperature novel purin-6-one oximes are obtained in moderate yields. Further, reaction of formamidines and ethyl acetoacetate with DBU afforded 6-carbamoylpurines. X-Ray analysis carried out on 9-(4-methoxyphenyl)-2-methyl-9*H*-purine-6-carboxamide monohydrate confirmed its structure. Diazotization of [5-amino-1-(4-methoxyphenyl)-1*H*-imidazol-4-yl]iminoacetonitrile in the presence of an excess of sodium nitrite and concentrated HCl gave 4-carboxy-5-chloro-1-(4-methoxyphenyl)imidazolidinium chloride *via* nucleophilic aromatic substitution reaction. However, (1-aryl-5-hydroxy-1*H*-imidazol-4-yl)-iminoacetonitrile is obtained as product when (5-amino-1-aryl-1*H*-imidazol-4-yl)-iminoacetonitriles (Ar = 4-MeC_6H_4 and Ar = 4-ClC_6H_4) were the reactants. The structure of 4-carboxy-5-chloro-1-(4-methoxyphenyl)imidazolidinium chloride was also established by X-ray analysis.

INTRODUCTION

Purines are an important class of heterocycles because of their significant role as biologically active compounds.[1-12] Generally, their activity depends mainly on the type and position of substituents on the ring, and several reports in the last decade described various methods to synthesize a wide range of purine derivatives.[13-23] As a result, the search for new synthetic approaches to prepare purines with a wide variety of substituents on either or both rings is continuing. In our research group, we have been investigating the utility of both formamidines **1** and imidazoles **2** as precursors to find new facile synthetic methods to prepare novel fused nitrogen heterocycles such as imidazole derivatives, purines, 6-carbamoylpurines and pyrimido[5,4-*d*]pyrimidines. The literature reports describe many synthetic

procedures to prepare 6-substituted purines starting from either formamidines **1** or imidazoles **2**. The use of both compounds as versatile precursors to 6-substituted purines and other nitrogen heterocycles is increasing.[16-21] Conversion of the active cyanoformimidoyl unit in imidazole **2** into a new nucleophilic reactive site could be used for further transformations.



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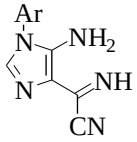

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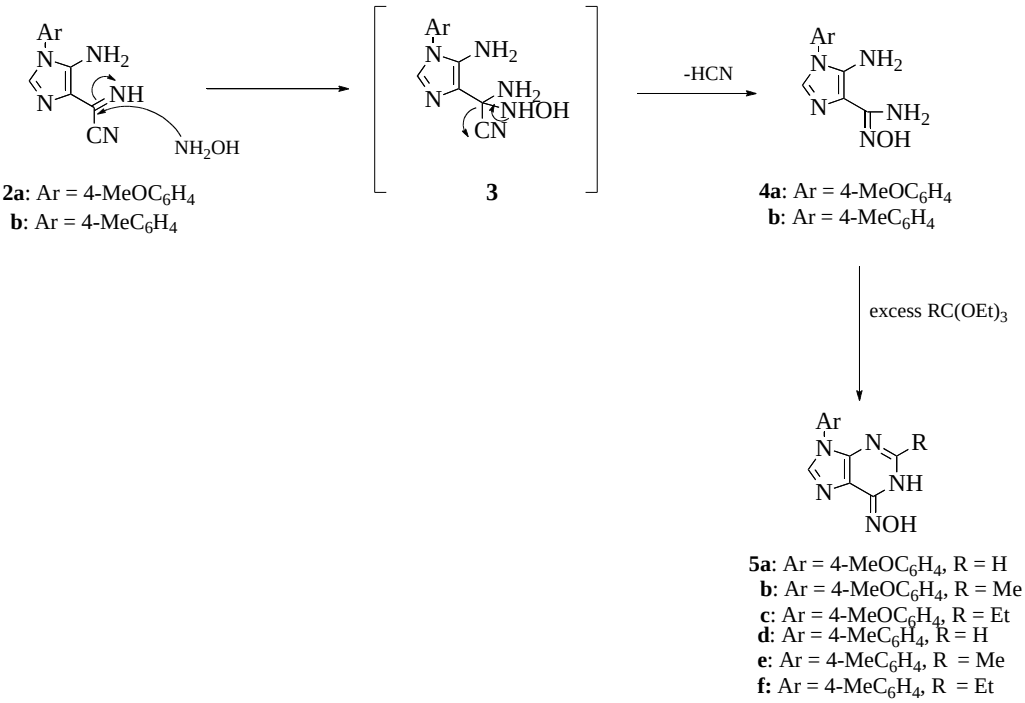
RESULTS AND DISCUSSION

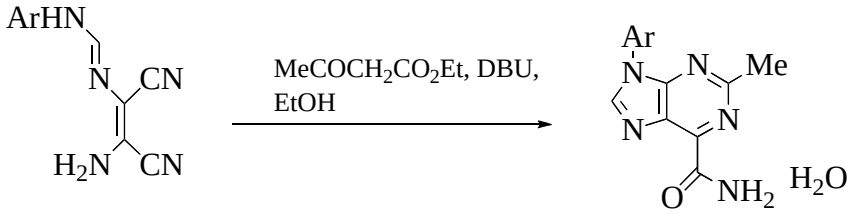
Addition of hydroxylamine hydrochloride (5 equiv.) to a suspension of (5-amino-1-aryl-1*H*-imidazol-4-yl)iminoacetonitrile **2a** (Ar = 4-$MeOC_6H_4$) or **2b** (Ar = 4-MeC_6H_4) in ethanol and stirring the mixture overnight at room temperature led to the isolation of white crystalline solids identified as 5-amino-*N*-hydroxy-1-aryl-1*H*-imidazole-4-carboxamidine **4a** (Ar = 4-$MeOC_6H_4$) and **4b** (Ar = 4-MeC_6H_4). Both imidazoles were used as intermediates and reacted with triethyl orthoesters. When a suspension of imidazole **4a** and triethyl orthoformate was refluxed, purine **5a** was isolated (48%) (**Scheme 1**). When the same reaction was carried out using triethyl orthoacetate, complete decomposition of the reaction mixture took place. However, stirring the mixture at room temperature for 18 hours afforded the product **5b** (45%). When a mixture of imidazole **4a** and an excess of triethyl orthoformate was stirred at room temperature for 18-20 hours, the yield of **5a** increased (60%).



Scheme 1

It is assumed that hydroxylamine initially adds to substrate **2** to yield intermediate **3** which then loses HCN to furnish product **4**. Similar elimination has been observed in the reaction of imidazoles **2** with phenylsulfonylacetonitrile and a catalytic amount of DBU[21] (**Scheme 1**).

In the literature, the reaction of formamidines **1** with active methylenes has been described.[22] However, to our knowledge their reaction with ethyl acetoacetate has not yet been reported. A mixture of equimolar amounts of ethyl acetoacetate and **1a** reacted in the presence of DBU to form a product for which structure **6a** was proposed (**Scheme 2**).



1a: Ar = 4-$MeOC_6H_4$
b: Ar = 4-MeC_6H_4

6a: Ar = 4-$MeOC_6H_4$
b: Ar = 4-MeC_6H_4

Scheme 2

Although the spectroscopic features of the collected needles were very similar to those of 6-carbamoylpurines,[17,19,22,23] an X-ray crystal structure analysis was carried out to confirm the structure of the product (**Figure 1**).

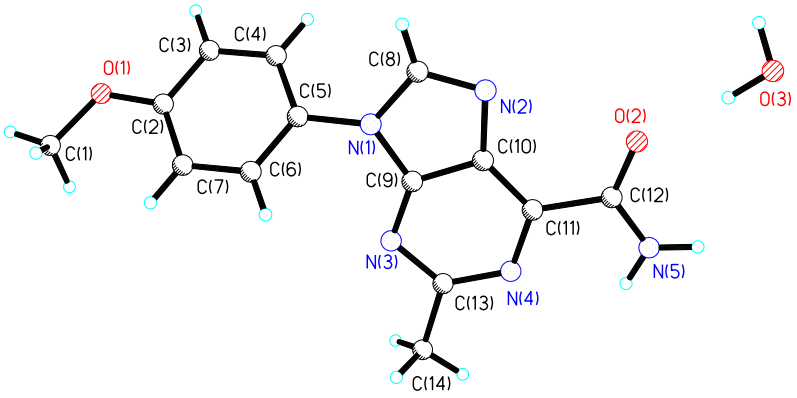
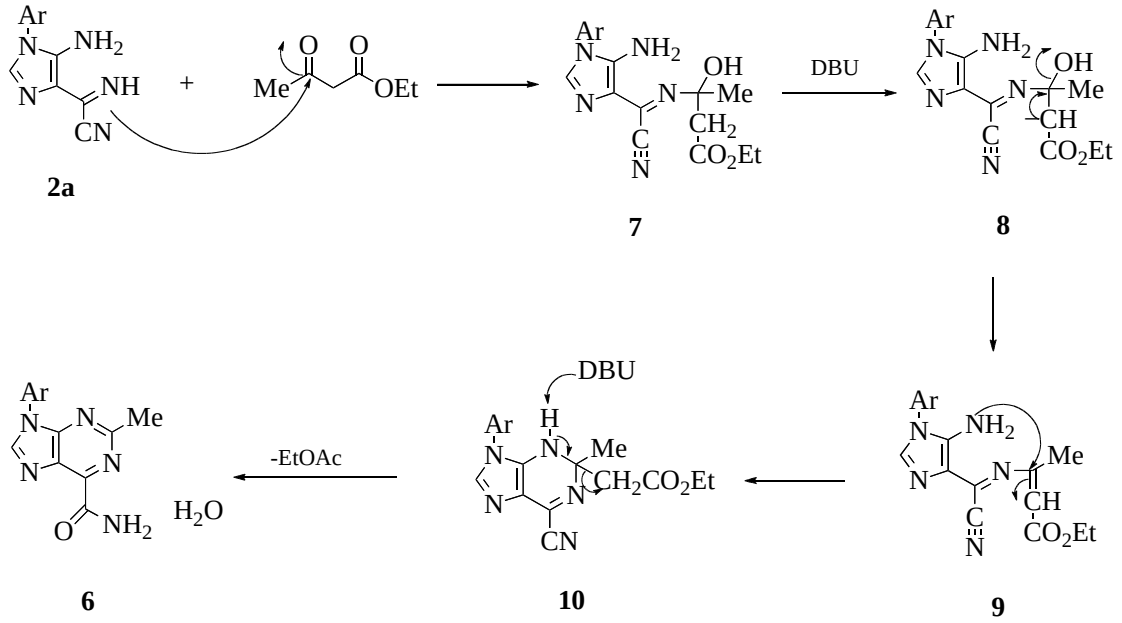


Figure 1. Molecular structure of 9-(4-methoxyphenyl)-2-methyl-9*H*-purine-6-carboxamide monohydrate **6a**

The isolation of 6-purinecarboxamide monohydrate **6a** suggests that the first step in the reaction is the conversion of formamidine **1a** to imidazole **2a**.[12] A mechanism of 6-carbamoylpurines **6** formation from imidazoles **2** has been described previously.[22,23]

Alternatively, the reaction may proceed by a nucleophilic attack of the imino function on the acetyl group. Then, an elimination of water molecule occurs to yield **9** that undergoes a rapid loss of an ethyl acetate molecule, followed by basic hydrolysis of the cyano function to furnish **6** (**Scheme 3**).



Scheme 3

An attempt to diazotize imidazole **2a** to form imidazotriazines **11** using previously described procedure, resulted only in recovering the starting material.[24] Nevertheless, when a large excess of $NaNO_2$ and concentrated HCl were used, red crystals were isolated. The ^1H NMR spectrum of the crystals revealed the presence of a singlet for one proton at δ 4.58 ppm which was D_2O exchangeable, a base peak at m/z 252 appeared in the MS, also the IR showed a band at 1712 cm^{-1} which indicates the presence of a carbonyl group. In order to establish the structure of these crystals, X-ray was carried out and showed the product to be 4-carboxy-5-chloro-1-(4-methoxyphenyl)imidazolidinium chloride **12** which resulted from a nucleophilic aromatic substitution reaction (**Figure 2**).

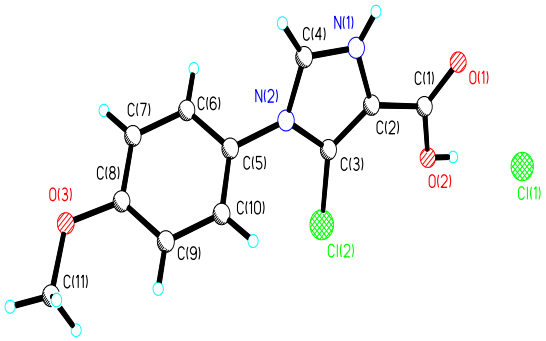
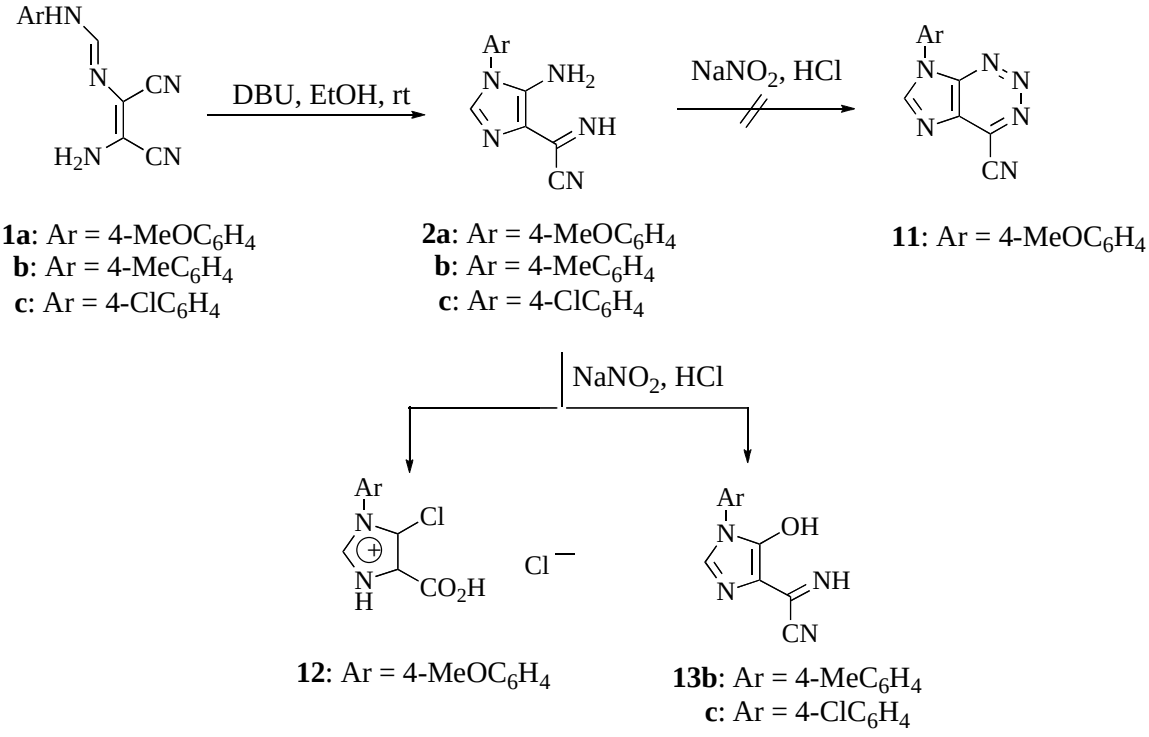


Figure 2. Molecular structure of 4-carboxy-5-chloro-1-(4-methoxyphenyl)imidazolidinium chloride **12**

Diazotization was also performed on imidazoles **2b,c** utilising the same conditions used to diazotize imidazole **2a**; small amount of red crystals were collected. The ^{1}H NMR and MS spectra of these crystals, on the other hand, showed a different pattern than expected. Careful examination of the spectroscopic analyses of the obtained crystals enabled us to identify the products to be (1-aryl-5-hydroxy-1*H*-imidazol-4-yl)iminoacetonitrile **13b** (Ar = 4-MeC_6H_4) and **13c** (Ar = 4-ClC_6H_4) (**Scheme 4**).



1a: Ar = 4-$MeOC_6H_4$
b: Ar = 4-MeC_6H_4
c: Ar = 4-ClC_6H_4

2a: Ar = 4-$MeOC_6H_4$
b: Ar = 4-MeC_6H_4
c: Ar = 4-ClC_6H_4

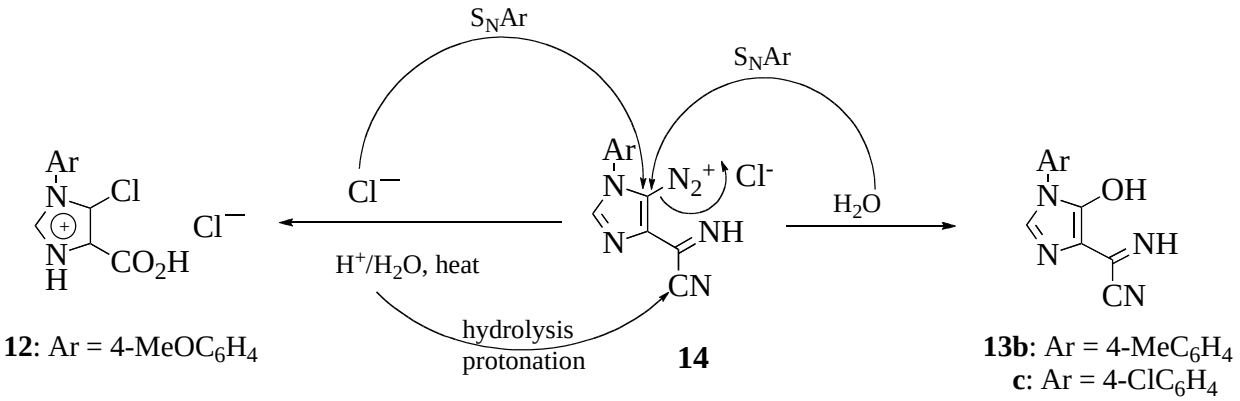
11: Ar = 4-$MeOC_6H_4$

12: Ar = 4-$MeOC_6H_4$

13b: Ar = 4-MeC_6H_4
c: Ar = 4-ClC_6H_4

Scheme 4

The yields in both reactions were low [**12** (40%), **13b** (30%) and **13c** (40%)], and all attempts to increase the yields were unsuccessful. Although the same conditions were utilised for imidazoles **2a,b** and **c**, it appears that two different S_NAr reactions operate. This might be due to the difference in the electronic effect of the methyl, chloro and methoxy substituents (**Scheme 5**).



12: Ar = 4-$MeOC_6H_4$

14

13b: Ar = 4-MeC_6H_4
c: Ar = 4-ClC_6H_4

Scheme 5

CONCLUSION

In conclusion, the reactive unit in (5-amino-1-aryl-1*H*-imidazol-4-yl)iminoacetonitrile could be converted into another reactive site simply by treating it with hydroxylamine hydrochloride. These imidazoles were shown to be valuable precursors for the synthesis of novel purines when reacted with triethyl orthoesters. In addition, reactions of formamidines with ethyl acetoacetate in the presence of DBU furnishes 6-carbamoylpurines. Also, two different S_NAr reactions took place *via* the diazotization of (5-amino-1-aryl-1*H*-imidazol-4-yl)iminoacetonitrile.

EXPERIMENTAL

General

Formamidines **1a-c** and imidazoles **2a,b** were prepared according to literature procedures.[12] Percentage yields calculated for (**4a,b, 5a-f, 6a,b, 12** and **13b,c**) are based on 1.0 g of starting material. ^{1}H NMR spectra were recorded on a Bruker DPX 400 spectrometer at 400 MHz. $CDCl_3$ or DMSO-d_6 as a solvent and tetramethylsilane (TMS) as an internal standard; chemical shifts are reported in δ units (ppm). ^{13}C NMR spectra were obtained using a Bruker DPX 400 spectrometer at 100 MHz. Mass spectra were recorded on a VG autospec Q spectrometer with a digital data output. IR was recorded on RT-IR Perkin Elmer System 2000, using KBr disc and (ν_{max}) was recorded in cm^{-1}. Melting points were determined by using a Gallenkamp melting point apparatus and are uncorrected. TLC was performed on a 0.25 mm pre-coated silica gel plates (Merck).

General procedure for preparation of Imidazole 2c

A suspension of formamidine **1c** (Ar = 4-ClC_6H_4) (5.00 mmol) and DBU (1 mL, 6.70 mmol) in EtOH was stirred at room temperature for 1 h, the solid obtained was recrystallised from a mixture of hot EtOH/H_2O.

[*5-Amino-1-(4-chlorophenyl)-1H-imidazol-4-yl*]*iminoacetonitrile* **2c**: light yellow powder (0.88 g, 3.58 mmol, 88%), mp > 200 ^{o}C (decomp.) [$C_{11}H_8N_5Cl$ requires: 245.0462; M 245. Found: accurate mass: 245.0462; m/z (EI) M^+ 245, 57%, 138, 100%]; δ_H 400 MHz (DMSO-d_6, TMS), 6.76 (s, 2H, NH_2), 7.50 (s, 1H, CH), 7.55 (m, 2H, ArH); 7.65 (m, 2H, ArH), 11.16 (s, 1H, NH); δ_C 100 MHz (DMSO-d_6, TMS), 143.91, 143.02, 133.19, 132.72, 130.01, 129.91, 126.94, 116.31, 113.32; ν_{max}: (KBr) 3444, 3298, 2226, 1631, 1580, 1538, 1489, 1393, 1305, 1246, 1172, 1088, 1051, 915, 829 cm^{-1}.

General procedure for preparation of Imidazoles 4a,b

A mixture of hydroxylamine hydrochloride (5.0 equiv.) and sodium acetate (4.0 equiv.) was added to a

suspension of imidazole **2** (1.0 equiv.) in EtOH, while stirring. The stirring was continued overnight, and the solids obtained were recrystallised from a mixture of hot EtOH/H_2O.

5-Amino-N-hydroxy-1-(4-methoxyphenyl)-1H-imidazole-4-carboxamidine **4a**: white crystalline solid (0.49 g, 1.98 mmol, 48%), mp 209-211 ^oC [$C_{11}H_{13}N_5O_2$ requires: 247.1063; M 247. Found: accurate mass: 247.1069; m/z (EI) M^+ 247, 100%]; δ_H 400 MHz (DMSO-*d*$_6$, TMS), 3.82 (s, 3H, OCH_3), 5.23 (s, 2H, NH_2), 5.42 (s, 2H, NH_2), 7.09 (d, 2H, *J* 9.2 Hz, ArH), 7.32 (s, 1H, CH), 7.41 (d, 2H, *J* 9.2 Hz, ArH), 8.97 (s, 1H, OH); δ_C 100 MHz (DMSO-*d*$_6$, TMS), 159.24, 150.69, 137.00, 130.00, 128.32, 126.49, 115.24, 112.37, 55.97; ν_{max}: (KBr) 3442, 3335, 1645, 1617, 1516, 1305, 1255, 1181, 1023, 926, 838 cm^{-1}.

5-Amino-N-hydroxy-1-(p-tolyl)-1H-imidazole-4-carboxamidine **4b**: white crystalline solid (0.74 g, 3.2 mmol, 60%), mp 225-227^oC [$C_{11}H_{13}N_5O_2$ requires: 231.1114; M 231. Found: accurate mass: 231.1115; m/z (EI) M^+ 231 100%]; δ_H 400 MHz (DMSO-*d*$_6$, TMS), 2.38 (s, 3H, CH_3), 5.27 (s, 2H, NH_2), 5.42 (s, 2H, NH_2), 7.35 (m, 5H, ArH & CH), 8.97 (s, 1H, OH); δ_C 100 MHz (DMSO-*d*$_6$, TMS), 150.18, 137.36, 136.29, 132.61, 130.14, 129.41, 124.20, 112.21, 20.63; ν_{max}: (KBr) 3434, 3396, 3313, 3180, 2846, 1633, 1581, 1514, 1490, 1447, 1322, 1194, 932 cm^{-1}.

General procedure for preparation of Purines 5a-f

A suspension of imidazoles **4** (1 equiv.), and of triethyl orthoformate/acetate or propionate (12 equiv.) was either refluxed for 2 h (**5a**), or stirred at room temperature overnight (18-20 h) (**5a-f**). The solids formed were filtered.

9-(4-Methoxyphenyl)-1,9-dihydropurin-6-one oxime **5a** (recrystallised from a mixture of hot EtOH/H_2O): white powder (0.50 g, 1.94 mmol, 48%), rt (0.62 g, 2.40 mmol, 60%), mp 274-276 ^oC (decomp.) [$C_{12}H_{11}N_5O_2$ requires: 257.0907; M 257. Found: accurate mass: 257.0907; m/z (EI) M^+ 257, 100%]; δ_H 400 MHz (DMSO-*d*$_6$, TMS), 3.84 (s, 3H, OCH_3), 7.16 (d, 2H, *J* 6.8 Hz, ArH), 7.67 (d, 2H, *J* 6.8 Hz, ArH), 8.78 (s, 1H, CH), 8.81 (s, 1H, CH), 8.94 (s, 1H, NH), 9.70 (s, 1H, OH); δ_C 100 MHz (DMSO-*d*$_6$, TMS), 159.26, 148.77, 144.70, 144.14, 143.80, 126.57, 125.52, 119.15, 114.80, 55.64; ν_{max}: (KBr) 3423, 3279, 3075, 1703, 1520, 1260, 1192, 1177, 1031, 972, 827 cm^{-1}.

9-(4-Methoxyphenyl)-2-methyl-1,9-dihydropurin-6-one oxime **5b (**recrystallised from a mixture of hot EtOH/H_2O): white powder (0.49 g, 1.80 mmol, 45%), mp 275 ^oC [$C_{13}H_{13}N_5O_2$ requires: 271.1064; M 271. Found: accurate mass: 271.1063; m/z (EI) M^+ 271, 20%, 255, 100%]; δ_H 400 MHz (DMSO-*d*$_6$, TMS), 2.70 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 7.17 (d, 2H, *J* 6.8 Hz, ArH), 7.67 (d, 2H, *J* 6.8 Hz, ArH), 8.72 (s, 1H, CH), 9.31 (s, 1H, NH), 9.91 (s, 1H, OH); δ_C 100 MHz (DMSO-*d*$_6$, TMS), 159.55, 154.20, 149.27,

143.38, 143.20, 127.27, 125.94, 118.39, 115.22, 56.04, 20.97; ν_{max}: (KBr) 3372, 3078, 3062, 1690, 1519, 1444, 1430, 1304, 1257, 1199, 1180, 1090, 1023, 840 cm^{-1}.

2-Ethyl-9-(4-methoxyphenyl)-1,9-dihydropurin-6-one oxime **5c** (recrystallised from mixture of EtOH/H_2O/acetone): white powder (0.57 g, 2.0 mmol, 50%), mp 260 ^oC (decomp.) [$C_{14}H_{15}N_5O_2$ requires: 285.1220; M 285. Found: accurate mass: 285.1220; m/z (EI) M^+ 285, 10%, 269, 100%]; δ_H 400 MHz (DMSO-*d_6*, TMS) 1.23 (t, 3H, *J* 7.2 Hz, -$CH_2\underline{CH_3}$), 3.07 (q, 2H, *J* 7.2 Hz, -$\underline{CH_2}CH_3$), 3.85 (s, 3H, OCH_3), 7.17 (d, 2H, *J* 8.8 Hz, ArH), 7.73 (d, 2H, *J* 9.2 Hz, ArH), 8.77 (s, 1H, CH), 9.31 (s, 1H, NH), 9.91 (s, 1H, OH); δ_C 100 MHz (DMSO-*d_6*, TMS), 159.62, 158.54, 149.90, 144.72, 143.82, 127.02, 125.77, 118.30, 115.22, 56.06, 26.19, 10.23; ν_{max}: (KBr) 3423, 2975, 1688, 1574, 1523, 1456, 1405, 1304, 1260, 1181, 1050, 1027, 926 cm^{-1}.

9-(p-Tolyl)-1,9-dihydropurin-6-one oxime **5d** (recrystallised from mixture of EtOH/H_2O/acetone): white powder (0.52 g, 2.15 mmol, 50%), mp 315 ^oC [$C_{12}H_{12}N_5O$ requires: 241.0958; M 241. Found: accurate mass: 241.0959; m/z (EI) M^+ 241, 100%]; δ_H 400 MHz (DMSO-*d_6*, TMS), 2.39 (s, 3H, CH_3), 7.40 (d, 2H, *J* 7.6 Hz, ArH), 7.71 (d, 2H, *J* 8.0 Hz, ArH), 8.31 (br.s, 1H, NH), 8.72 (s, 1H, CH), 8.76 (s, 1H, CH), 9.20 (s, 1H, OH); δ_C 100 MHz (DMSO-*d_6*, TMS) 148.67, 144.53, 143.51, 138.11, 131.42, 130.06, 123.54, 119.26, 56.00, 20.68, 18.59; ν_{max}: (KBr) 3327, 3209, 3113, 1696, 1520, 1494, 1391, 1345, 1245, 1193, 1092, 812 cm^{-1}.

2-Methyl-9-(p-tolyl)-1,9-dihydropurin-6-one oxime **5e** (recrystallised from mixture of EtOH/H_2O/acetone): white powder (0.51 g, 2.0 mmol, 50%), mp 275 ^oC (decomp.) [$C_{13}H_{13}N_5O$ requires: 255.1114; M 255. Found: accurate mass: 255.1114; m/z (EI) M^+ 255, 25%, 239, 100%]; δ_H 400 MHz (DMSO-*d_6*, TMS) 2.41 (s, 3H, CH_3), 2.70 (s, 3H, CH_3), 7.44 (d, 2H, *J* 8 Hz, ArH), 7.67 (d, 2H, *J* 8.4 Hz, ArH), 8.78 (s, 1H, CH), 9.35 (s, 1H, NH), 9.95 (s, 1H, OH); δ_C 100 MHz (DMSO-*d_6*, TMS), 154.40, 149.23, 143.55, 143.10, 138.33, 131.41, 130.14, 123.92, 118.23, 20.73, 20.68; ν_{max}: (KBr) 3384, 3262, 3100, 1673, 1521, 1396, 1317, 1244, 1207, 1188, 1145, 971, 814 cm^{-1}.

2-Ethyl-9-(p-tolyl)-1,9-dihydropurin-6-one oxime **5f (**recrystallised from a mixture of hot EtOH/H_2O): white powder (0.52 g, 1.93 mmol, 45%), mp 270 ^oC (decomp.) [$C_{14}H_{15}N_5O$ requires: 269.1271; M 269. Found: accurate mass: 269.1273; m/z (EI) M^+ 269, 12%, 252, 100%]; δ_H 400 MHz (DMSO-*d_6*, TMS), 1.24 (t, 3H, *J* 7.2 Hz, -$CH_2\underline{CH_3}$), 2.40 (s, 3H, CH_3), 2.99 (q, 2H, *J* 7.2 Hz, -$\underline{CH_2}CH_3$), 3.85 (s, 3H, OCH_3), 7.42 (d, 2H, *J* 8.4 Hz, ArH), 7.76 (d, 2H, *J* 8.4 Hz, ArH), 8.82 (s, 1H, CH), 9.33 (s, 1H, NH), 9.94 (s, 1H, OH); δ_C 100 MHz (DMSO-*d_6*, TMS), 157.46, 149.14, 142.93, 138.04, 131.66, 130.15, 123.38, 116.11,

79.26, 25.71, 20.71, 9.88; ν_{max}: (KBr) 3382, 3108, 1672, 1594, 1523, 1399, 1341, 1208, 1188, 1142, 968, 869, 812 cm^{-1}.

***General procedure for preparation of Purines* 6a,b**

A mixture ethyl acetoacetate (5 equiv.) and DBU (1.6 equiv.) was stirred in an ice bath. To this, a suspension of formamidines **1a** (1.00 g, 4.14 mmol), **1b** (1.00 g, 4.44 mmol) in EtOH (8 mL) was added. The stirring was continued for 2 h in an ice bath, and 18 h at room temperature. The formed precipitates were filtered off, and recrystallised from EtOH (**6a**) and a mixture of EtOH/H_2O (**6b**).

9-(4-Methoxyphenyl)-2-methyl-9H-purine-6-carboxamide monohydrate **6a**: colourless needles (0.81 g, 2.65 mmol, 65%), mp 270-273 ^oC [$C_{14}H_{15}N_5O_3$. Anal. Calcd for CHN: C, 55.81; H, 4.98; N, 23.25. Found: C, 55.85; H, 5.01; N, 23.11; m/z (EI) $(M-H_2O)^+$ 283, 100%; M 301]; δ_H 400 MHz (DMSO-d_6, TMS), 2.74 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 7.16 (d, 2H, *J* 9.8 Hz, ArH), 7.74 (d, 2H, *J* 9.8 Hz, ArH), 8.09 (s, 1H, NH), 8.38 (s, 1H, NH), 8.94 (s, 1H, CH); δ_C 100 MHz (DMSO-d_6, TMS) 164.88, 161.84, 159.49, 154.05, 148.35, 147.01, 129.54, 127.41, 126.03, 115.19, 56.04, 26.09; ν_{max}: (KBr) 3461, 3394, 3121, 1699, 1671, 1650, 1579, 1519, 1408, 1388, 1254, 1229, 1182, 1028, 956, 836 cm^{-1}.

2-Methyl-9-(p-tolyl)-9H-purine-6-carboxamide monohydrate **6b**: white solid (0.96 g, 3.36 mmol, 76%), mp 275-277 ^oC [$C_{14}H_{15}N_5O_2$ requires: accurate mass 267.1114; M 285. Found: accurate mass $(M-H_2O)$: 267.1116; m/z (EI) $(M-H_2O)^+$ 267, 45%, 224, 100%]; δ_H 400 MHz (DMSO-d_6, TMS) 2.42 (s, 3H, CH_3), 2.75 (s, 3H, CH_3), 7.44 (d, 2H, *J* 8 Hz, ArH), 7.46 (d, 2H, *J* 8.4 Hz, ArH), 8.10 (s, 1H, NH), 8.38 (s, 1H, NH), 9.01 (s, 1H, CH); δ_C 100 MHz (DMSO-d_6, TMS), 164.89, 161.89, 153.93, 148.54, 146.81, 138.35, 132.17, 130.48, 129.67, 124.19, 26.13, 21.14; ν_{max}: (KBr) 3452, 1710, 1574, 1521, 1398, 1336, 1290, 1228, 1203, 957 cm^{-1}.

General procedure for the Synthesis of imidazolidinium chloride 12 and imidazoles 13b and 13c

A suspension of imidazoles **2** (0.50 g, 2.1 mmol) and 4 N HCl (20 mL) was heated gently, and then cooled in an ice bath. A cold solution of $NaNO_2$ (2.5 g, 36.0 mmol) was then added dropwise to the imidazole suspension. After the addition, stirring was continued in an ice bath for 30-45 min. The solution was warmed up for 15 min and stirred at room temperature overnight. The solid obtained was filtered and crystallised using a mixture of (acetone/hexane) for **12** using Vapour Diffusion Technique (VDT) and acetone for **13b,c**.

4-Carboxy-5-chloro-1-(4-methoxyphenyl)imidazolidinium chloride **12**: red crystals (0.47 g, 1.60 mmol, 40%), mp 230-232 ^oC [$C_{11}H_{10}N_2O_3Cl_2$ (M-HCl). Anal. Calcd for CHN: C, 52.27; H, 3.56; N, 11.08.

Found: C, 52.34; H, 3.70; N, 11.16; requires accurate mass 252.0296, Found accurate mass (M-HCl): 252.0293; m/z (EI) $(M\text{-}HCl)^+$ 252, 100%, M 289]; δ_H 400 MHz (DMSO-d_6, TMS), 3.84 (s, 3H, OCH_3), 4.58 (s, 1H, NH), 7.13 (d, 2H, *J* 8.8 Hz, ArH), 7.46 (d, 2H, *J* 8.8 Hz, ArH), 8.25 (s, 1H, CH); δ_C 100 MHz (DMSO-d_6, TMS) 162.42, 160.50, 138.52, 128.39, 127.43, 126.57, 124.36, 115.18, 56.06; ν_{max}: (KBr), 3423, 3117, 1712, 1607, 1535, 1510, 1437, 1384, 1304, 1256, 1175, 1021, 956, 848 cm^{-1}.

[5-Hydroxy-1-(p-tolyl)-1H-imidazol-4-yl]iminoacetonitrile **13b**: red crystals (0.30 g, 1.32 mmol, 30%), mp 220 °C (decomp.) [$C_{12}H_{10}N_4O$ Anal. Calcd for CHN: C, 63.71; H, 4.42; N, 24.77; M 226. Found: C, 63.79; H, 4.56; N, 24.48; m/z (EI) $(M)^+$ 226, 100%]; δ_H 400 MHz (DMSO-d_6, TMS), 2.40 (s, 3H, CH_3), 4.58 (s, 1H, NH), 7.73 (s, 4H, Hz, ArH), 7.54 (s, 1H, CH), 7.56 (s, 1H, NH), 8.33 (s, 1H, OH); δ_C 100 MHz (DMSO-d_6, TMS) 155.47, 150.27, 138.99, 136.01, 130.39, 130.13, 125.43, 121.35, 114.82, 20.66; ν_{max}: (KBr) 3445, 3286, 1636, 1624, 1546, 1514, 1503, 1471, 1395, 1284, 1168, 922 cm^{-1}.

[1-(4-Chlorophenyl)-5-hydroxy-1H-imidazol-4-yl]iminoacetonitrile **13c**: red crystals (0.40 g, 1.62 mmol, 40%), mp > 200 °C (decomp.) [$C_{11}H_7N_4OCl$. Anal. Calcd for CHN: C, 53.54; H, 2.83; N, 22.71; M 246. Found: C, 53.30; H, 2.83; N, 22.56; m/z (EI) $(M)^+$ 246, 100%]; δ_H 400 MHz (DMSO-d_6, TMS), 7.55 (m, 3H, ArH and NH), 7.65 (m, 4H, ArH, CH & OH); δ_C 100 MHz (DMSO-d_6, TMS), 155.50, 150.39, 135.80, 133.97, 131.65, 129.97, 127.94, 121.27, 114.88; ν_{max}: (KBr) 3431, 3145, 2363, 1634, 1553, 1494, 1391, 1172, 1097m, 923 cm^{-1}.

Crystal data and structure refinement for **6a**.[25]

Chemical formula (moiety) $C_{14}H_{15}N_5O_3$, chemical formula (total) $C_{14}H_{15}N_5O_3$, formula weight 301.31, temperature 150(2) K, radiation, wavelength MoKα, 0.71073 Å, crystal system, space group monoclinic, $P2_1/c$, unit cell parameters a = 13.238(3) Å, α = 90°, b = 10.059(2) Å, β = 107.757(16)°, c = 10.7144(8) Å, γ = 90°, cell volume 1358.7(4) $Å^3$, Z 4, calculated density 1.473 g/cm^3, absorption coefficient μ 0.108 mm^{-1}, F(000) 632, crystal colour and size colourless, 0.45 × 0.40 × 0.40 mm^3, reflections for cell refinement 285 (θ range 2.5 to 27.5°), data collection method, Nonius KappaCCD diffractometer ϕ and ω scans, θ range for data collection 4.0 to 27.5°, index ranges h −17 to 17, k −13 to 12, l −13 to 13, completeness to θ = 26.0°, 99.4%, reflections collected 12996, independent reflections 3087 (R_{int} = 0.0234), reflections with $F^2>2\sigma$ 2608, absorption correction semi-empirical from equivalents, min. and max. transmission, 0.953 and 0.958, structure solution direct methods, refinement method full-matrix least-squares on F^2, weighting parameters a, b 0.0372, 0.7683, data/restraints/parameters 3087/0/ 217, final R indices [$F^2>2\sigma$] R1 = 0.0355, wR2 = 0.0840, R indices (all data) R1 = 0.0465, wR2 = 0.0910,

goodness-of-fit on F^2 1.034, largest and mean shift/su 0.000 and 0.000, largest diff. peak and hole 0.31 and –0.22 e $Å^{-3}$.

Crystal data and structure refinement for **12**.[26]

Chemical formula (moiety) $C_{11}H_{10}ClN_2O_3^+ \cdot Cl^-$, chemical formula (total) $C_{11}H_{10}Cl_2N_2O_3$, formula weight 289.11, temperature 150(2) K, radiation, wavelength MoKα, 0.71073 Å, crystal system, space group monoclinic, $P2_1/c$, unit cell parameters a = 12.3041(18) Å, α = 90°, b = 7.3244(18) Å, β = 94.266(10)°, c = 13.4882(10) Å, γ = 90°, cell volume 1212.2(4) $Å^3$, Z 4, calculated density 1.584 g/cm^3, absorption coefficient μ 0.536 mm^{-1}, F(000) 592, crystal colour and size red, 0.45 × 0.30 × 0.30 mm3, reflections for cell refinement 180 (θ range 2.5 to 27.5°), data collection method Nonius KappaCCD diffractometer ϕ and ω scans, θ range for data collection 4.1 to 27.5°, index ranges h –15 to 15, k –9 to 9, l –17 to 17, completeness to θ = 26.0° 99.5% , reflections collected 13774, independent reflections 2776 (R_{int} = 0.0278), reflections with $F^2>2\sigma$ 2340, absorption correction semi-empirical from equivalents, min. and max. transmission 0.795 and 0.855, structure solution direct methods, refinement method Full-matrix least-squares on F^2, weighting parameters a, b 0.0388, 1.1248, data/restraints/parameters 2776/0/172, final R indices [$F^2>2\sigma$] R1 = 0.0313, wR2 = 0.0861, R indices (all data) R1 = 0.0415, wR2 = 0.0929, goodness-of-fit on F^2 1.128, extinction coefficient 0.0000(12), largest and mean shift/su 0.001 and 0.000, largest diff. peak and hole 0.50 and –0.30 e $Å^{-3}$.

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25. Crystal data for compound **6a**: (ref. CCDC 695454) can be obtained on request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EW, UK. CCDC.
26. Crystal data for compound **12**: (ref. CCDC 695453) can be obtained on request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EW, UK. CCDC.