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REACTIONS OF 9-ARYL-6-CYANOPURINES WITH PRIMARY AMINES

Amal Al-Azmi* and K. Anita Kumari

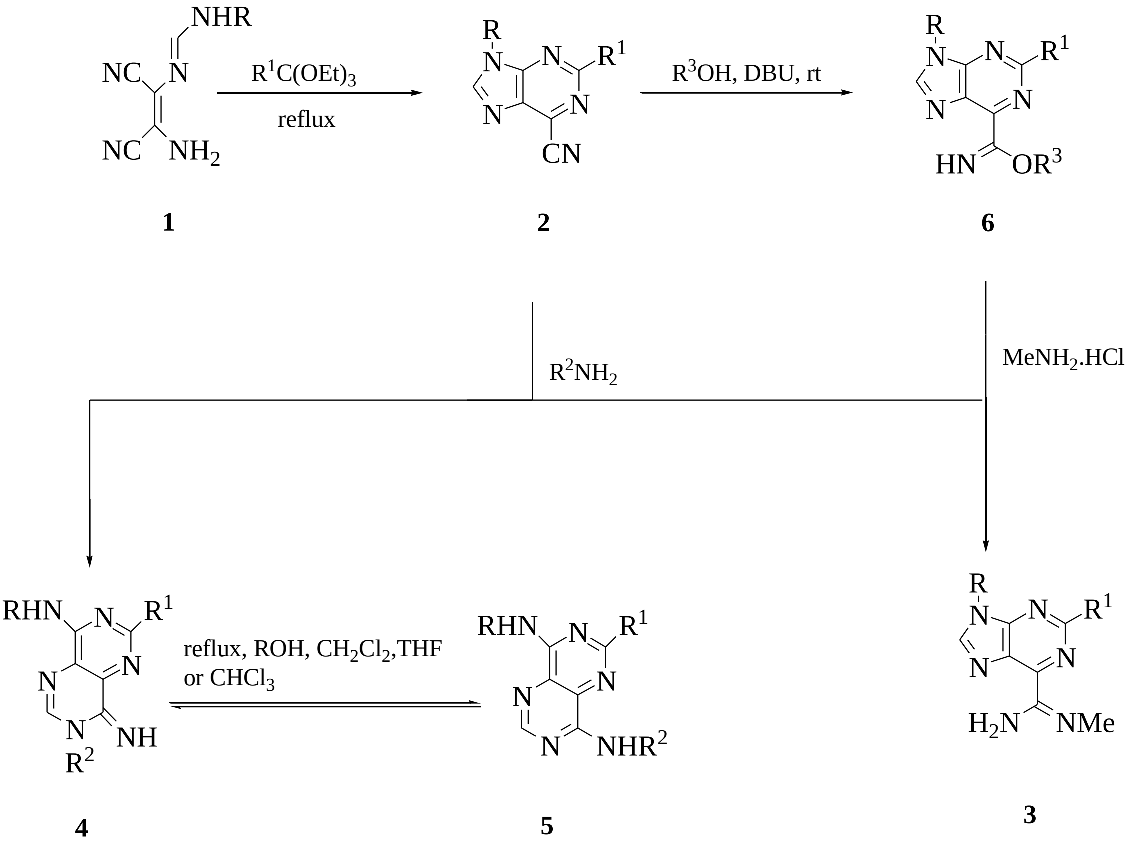
Chemistry Department, Kuwait University, P. O. Box 5969, Safat 13060, Kuwait
*Correspondent e-mail: amal.alazemi@ku.edu.kw

Abstract - Two structural isomers (9-aryl-6-cyanopurines and imidazole-4,5-dicarbonitriles) were isolated from the reaction of (*Z*)-N^1-aryl-N^2-(2-amino-1,2-dicyanovinyl)formamidines with triethyl orthoacetate or propionate. On the other hand, 9-aryl-6-cyanopurines were the only product, when triethyl orthoformate was used. The reaction of 9-aryl-6-cyanopurines with hydroxylamine hydrochloride in dichloromethane/ethanol at room temperature furnished 6-amidinopurines, while reaction with primary amines afforded pyrimido[5,4-*d*]pyrimidines. In addition, 9-aryl-6-cyanopurines reacted with hydrazine monohydrate under mild conditions to give 4-imino-N^8-arylpyrimido[5,4-*d*]pyrimidines. The latter furnished novel pyrimido[4,5-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines when refluxed with an excess of triethyl orthoesters. The new compounds were fully characterized and single crystal X-ray analyses have been carried out on 9-(4-methoxyphenyl)-9*H*-purine-6-carboximidamide and 2-methyl-1-[(*E*)-*p*-tolyliminomethyl]-1*H*-imidazole-4,5-dicarbonitrile.

INTRODUCTION

Purines continue to gain importance due to their biologically active nature. A number of reports have described several methods to synthesize various purine derivatives that played a significant role in drug development.[1-15] One of these compounds is 6-cyanopurine which has been used as a versatile reagent for the synthesis of a wide range of 6-substituted purines through the modification of the cyano group. 6-Substituted purines have been shown to have potency as antimetabolites,[16-18] antiepileptic, and antiarrhythmic agents.[19-22] The biological importance of these compounds extends to the mechanism of enzyme-mediated purine interconversion.[23] As a result, the development of selective and efficient methods for the modification of the cyano function is desirable. One of the modifications reported in the literature is the conversion of 6-cyanopurines **2** to 6-amidinopurines **3** (Scheme 1).[4-15]

Higashino *et al*. demonstrated that 6-amidinopurines **3** could be obtained in good yields when 9-aryl-6-cyanopurines **2** react with *n*-butylamine, hydrazine monohydrate, piperidine and hydroxylamine hydrochloride in methanol.[7] However, a careful investigation of these reactions showed that 6-amidinopurines **3** are formed only when hydroxylamine hydrochloride is used, while other amines afforded pyrimido[5,4-*d*]pyrimidines **4**.[6] 6-Amidinopurines **3** (some as hydrochloride salts) were also synthesized through a two-step conversion of 6-cyanopurines **2** to 6-alkoxyformimidoylpurines **6** followed by treatment with methylamine hydrochloride, whereas reactions of 6-cyanopurines **2** with other primary amines gave pyrimido[5,4-*d*]pyrimidines **4**.[4-6,15]

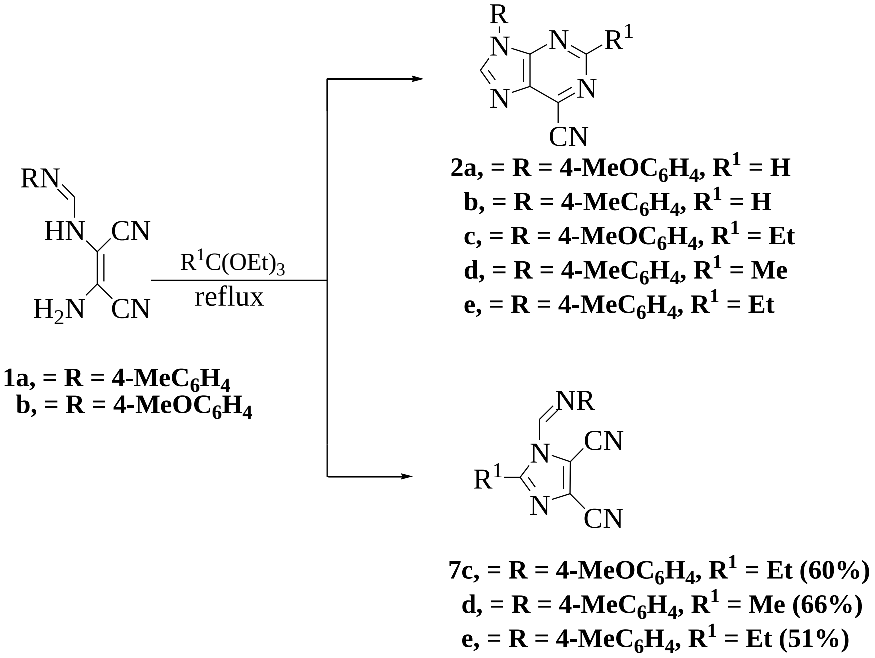


Scheme 1

Generally, direct isolation of 6-amidinopurines **3** from the reaction of 6-cyanopurines **2** with primary amines other than hydroxylamine hydrochloride has been reported to be difficult, as these reactions lead mainly to pyrimido[5,4-*d*]pyrimidines **4**.[6] So far, the reason behind the formation of either pyrimido[5,4-*d*]pyrimidines or 6-amidinopurines is still not clear. This prompted us to reinvestigate the reaction of 9-aryl-6-cyanopurines with primary amine salts under various conditions.

RESULTS AND DISCUSSION

9-Aryl-6-cyanopurines **2a,b** were prepared in good yields following the literature procedure.[4] In an attempt to prepare 2-methyl-9-(4-tolyl)-6-cyanopurine **2d** from refluxing formamidine **1a** with triethyl orthoacetate for 2 hours, a solid was formed after cooling the reaction mixture. The ^{1}H NMR analysis of the solid revealed the presence of 6-cyanopurine **2d** and another unknown compound in (2:3) ratio, respectively. X-ray analysis on the unknown product showed that the compound is 2-methyl-1-[(*E*)-*p*-tolyliminomethyl]-1*H*-imidazole-4,5-dicarbonitrile **7d** (Scheme 2 and Figure 1).



Scheme 2

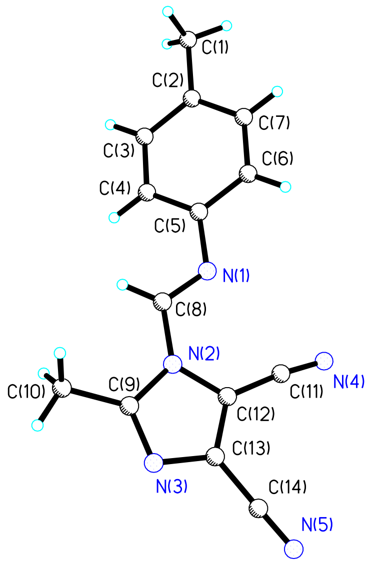
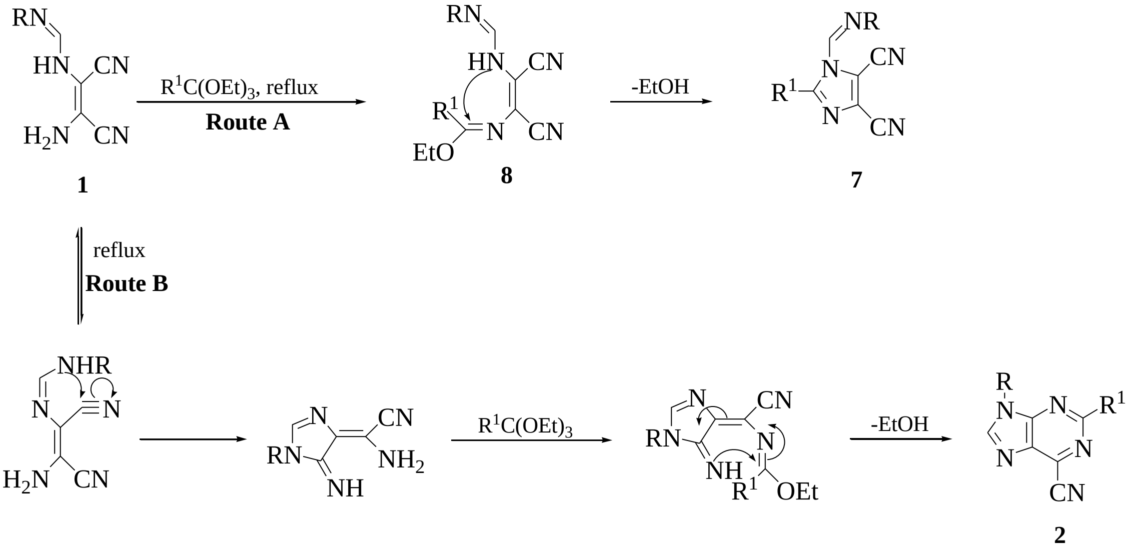


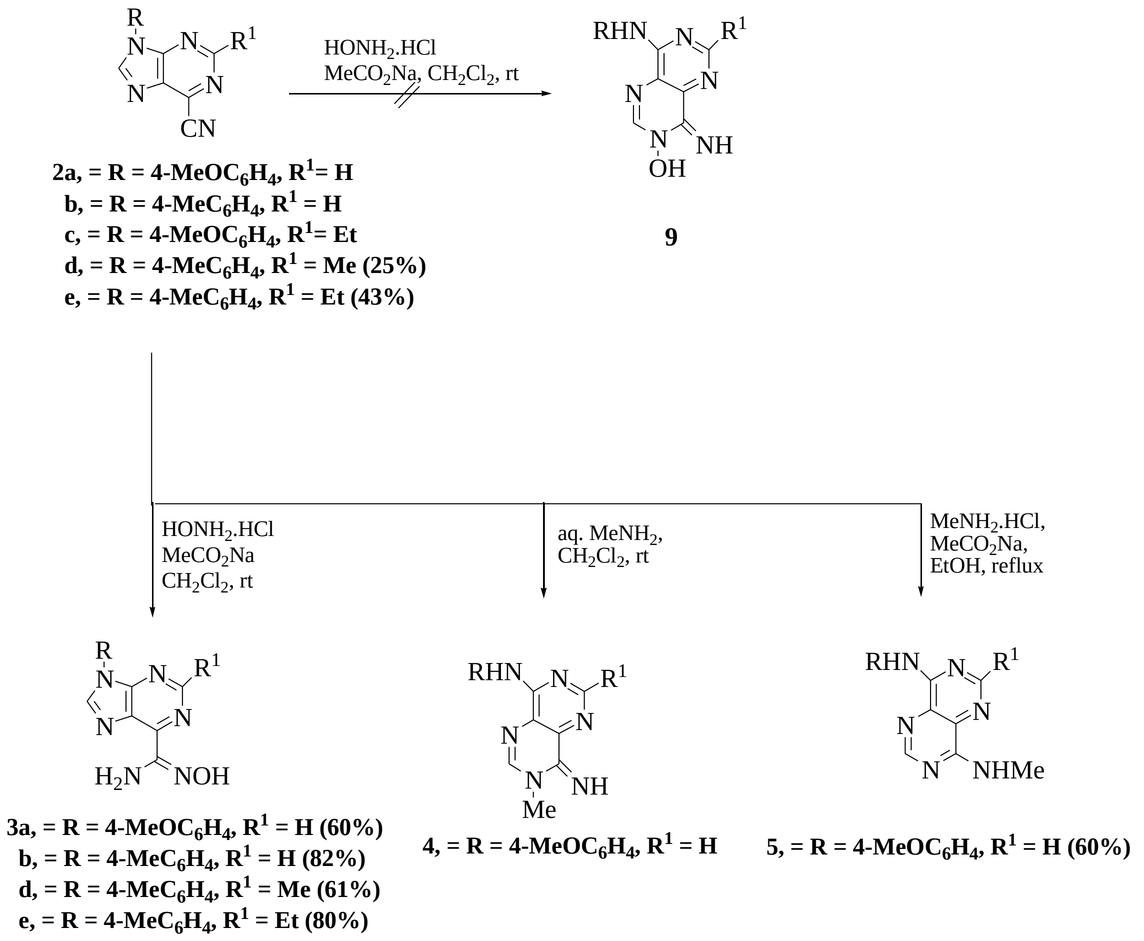
Figure 1. Molecular structure of 2-methyl-1-[(*E*)-*p*-tolyliminomethyl]-1*H*-imidazole-4,5-dicarbonitrile **7d**.

To generalise this observation, another two reactions were carried out and it was found that both formamidines **1a,b** furnished the two structural isomers, i.e. 6-cyanopurine **2c,e** and imidazole-4,5-dicarbonitrile **7c,e** when refluxed with triethyl orthopropionate. It is possible that the difference in the product of reaction of triethyl orthoformate and other orthoesters is the result of the difference in the rate of the formation of reactive oxocarbenium ion intermediates from the orthoesters. Thus, the product ratios arise from two factors stemming from alkyl groups: stabilization of an oxocarbenium intermediate and release of steric strain from the more hindered orthoesters seems to facilitate elimination of the ethoxy group to provide highly reactive species that would rapidly undergo imidation to provide **8** (Route A), which would eventually afford imidazole derivative **7**. This process is, however, unfavourable for orthoformate having no such alkyl group. As a result, formation of imidate **8** in this case becomes slow and therefore Route B is more pronounced to provide cyanopurines selectively (Scheme 3).



Scheme 3

We then turned our attention to study the reaction of 6-cyanopurines with primary amine hydrochlorides (Scheme 4). A mixture of 6-cyanopurine **2a**, hydroxylamine hydrochloride (5 equiv.), and sodium acetate (4 equiv.) in dichloromethane was stirred at room temperature. After stirring for 18 hours, TLC indicated the completion of the reaction. Formation of either of the two structural isomers, 6-amidinopurine **3a** or pyrimido[5,4-*d*]pyrimidine **9**, was expected. The ^{1}H NMR spectrum resembles the spectra of several known 6-amidinopurines derivatives reported previously.[6a] On the other hand, the ^{1}H NMR spectrum of compound **9** would be expected to show three D_2O exchangeable singlets each for one proton. This ^{1}H NMR result is more consistent with structure **3**.



Scheme 4

Further, X-ray analysis confirmed the structure of product **3a** as 9-(4-methoxyphenyl)-9*H*-purine-6-carboximidamide (Figure 2 and Figure 3).

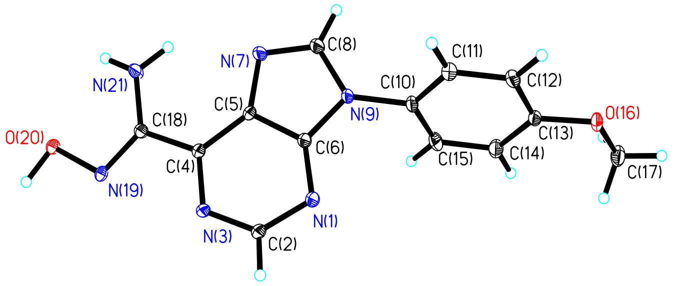


Figure 2. Molecular structure of 9-(4-methoxyphenyl)purine-6-carboximidamide **3a**.

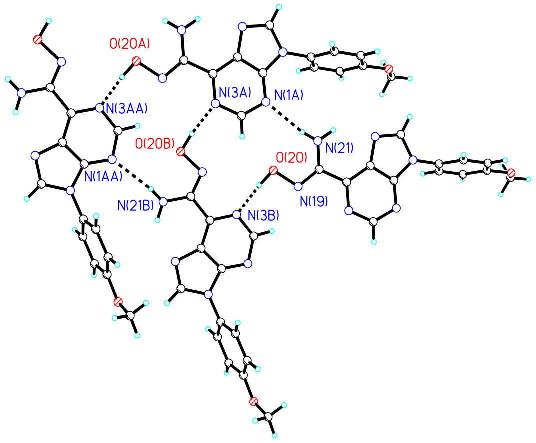


Figure 3. H-bonding in 9-(4-methoxyphenyl)-9*H*-9*H*-purine-6-carboximidamide **3a.**

Under similar reaction conditions, 9-(4-tolyl)-6-cyanopurine **2b** gave 6-amidinopurine **3b** (Scheme 4). Recently, the formation of 6-amidinopurines from the reaction of 6-cyanopurines with hydroxylamine hydrochloride and sodium acetate in refluxing methanol has been described.[6a] The use of methanol in an acidic medium was postulated to be the reason behind the conversion of the cyano group to an imidate intermediate, which facilitated the nucleophilic reaction. Isolation of 6-amidinopurines **3a,b** at room temperature, using dichloromethane as solvent, suggests that using methanol might not be crucial for an *in situ* formation of the imidate intermediate. The results obtained in this study present two important findings: Firstly, methanol does not seem to have a significant role in the formation of 6-amidinopurines, and that there might be other factors influencing the reaction pathway. And secondly, using different amine hydrochlorides, under the same conditions used to synthesize **3a,b** might afford 6-amidinopurines. Consequently, reaction of 9-aryl-6-cyanopurines with methylamine hydrochloride was investigated, in order to determine the role of acid catalysts in the formation of 6-amidinopurines directly from 6-cyanopurines.

When 6-cyanopurine **2a** was reacted with methylamine hydrochloride under the same conditions used to prepare compounds **3a,b** (Table 1, entry 5), a mixture of purine **2a** and a trace of the rearranged pyrimido[5,4-*d*]pyrimidine **4** were obtained as evidenced by ^{1}H NMR analysis. On the other hand, the 6-cyanopurine **2a** was recovered when ethanol was used. The Dimroth rearranged pyrimido[5,4-*d*]pyrimdine **5** was isolated when a mixture of 6-cyanopurine **2a**, methylamine hydrochloride (5 equiv.) and sodium acetate (4 equiv.) was refluxed in ethanol. These results indicate that neither the alcohol nor the acid catalyst are important factors in the formation of 6-amidinopurines **3** (Table 1).

Table 1. Reactions of 6-cyanopurines **2** with primary amine hydrochlorides under different conditions.

Entry	**Reactant**	**Amine/Amine.HCl**	**Solvent**	**Conditions**	**Product/yield (%)**
1	**2a (1 equiv.)**[4]	$HONH_2.HCl$ (5 equiv.)	CH_2Cl_2	$MeCO_2Na$ (4 equiv.), rt, 20 h	**3a**, 60
2	**2b (1 equiv.)**[4]	$HONH_2.HCl$ (5 equiv.)	CH_2Cl_2	$MeCO_2Na$ (4 equiv.), rt, 20 h	**3b**, 82
3	**2d (1 equiv.)**[4]	$HONH_2.HCl$ (5 equiv.)	EtOH	$MeCO_2Na$ (4 equiv.), rt, 20 h	**3d,** 61
4	**2e (1 equiv.)**	$HONH_2.HCl$ (5 equiv.)	EtOH	$MeCO_2Na$ (4 equiv.), rt, 20 h	**3e,** 80
5	**2a (1 equiv.)**	$MeNH_2.HCl$ (5 equiv.)	DCM	$MeCO_2Na$ (4 equiv.), rt, 20 h	**2a**:**4,** ratio 5:2 (^1H NMR)
6	**2a (1 equiv.)**	$MeNH_2.HCl$ (5 equiv.)	EtOH	$MeCO_2Na$ (4 equiv.), rt, 20 h	**NR**
7	**2a (1 equiv.)**	$MeNH_2.HCl$ (5 equiv.)	EtOH	$MeCO_2Na$ (4 equiv.), reflux, 3 h	**5**, 60

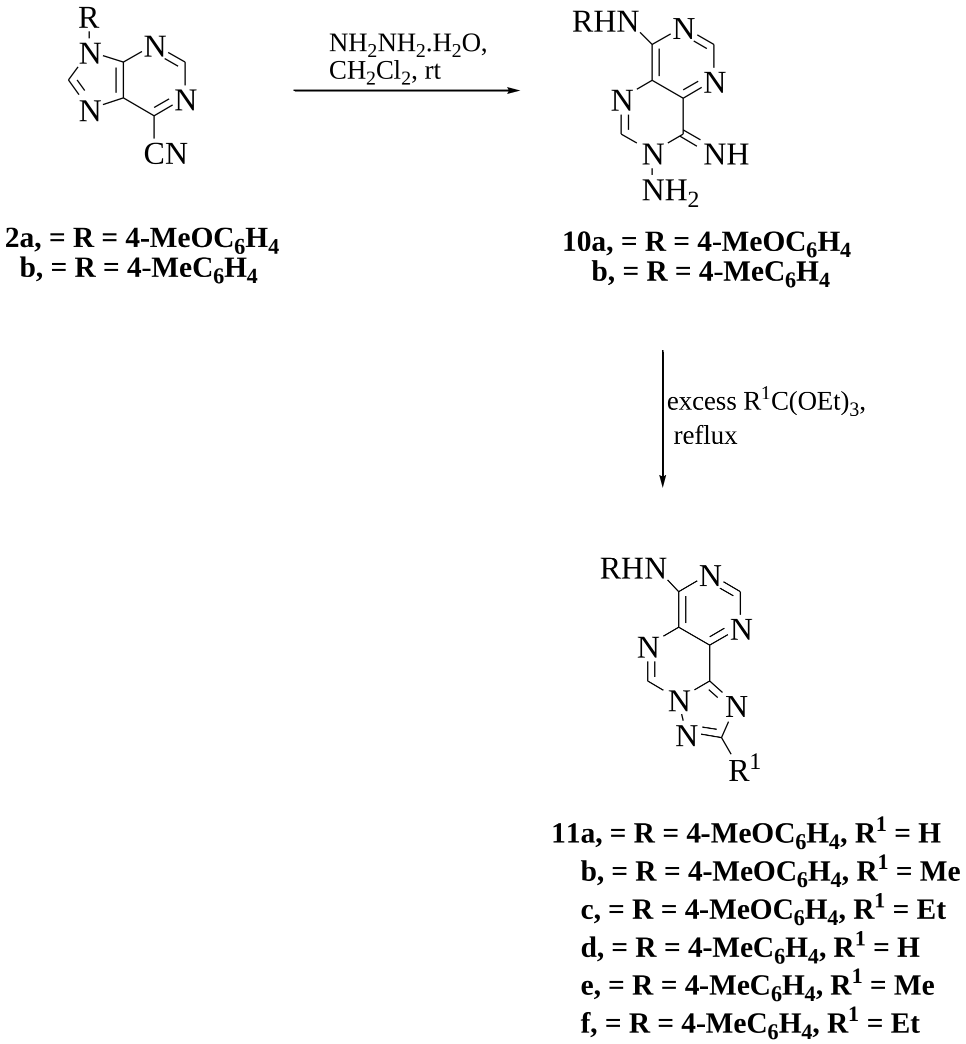
* NR = No Reaction

The reason why hydroxylamine hydrochloride behaves in a different way is not yet clear. Nevertheless, several studies carried out by Kirby and his co-workers on the nature of hydroxylamine demonstrated that this ambident α–effect nucleophile exists in its crystal structure as a mixture of equal amount of both H_3N^+OH and $H_3N^+O^-$, where $H_3N^+O^-$ is the more stable ion.[24,25a] Also, a recent study showed that hydroxylamine acts as an oxygen nucleophile.[25b]

The reaction of hydroxylamine through the oxygen site has also been noticed in both acylation and phosphorylation by other researchers.[26-28] This shows that in its reactions, hydroxylamine favours hard electrophiles. Furthermore, Kukushkin *et al.*[29] have investigated the reaction rate of hydroxylamine with nitriles and oximes, and noticed that it is more reactive towards addition to nitriles than oximes by a factor of 1.7×10^4.

It is conceivable that the two isomeric forms observed by Kirby in the solid state may also be observed in the present reaction. In addition, it has been reported previously that oxygen nucleophiles such as ethanol and methanol attack the cyano function and not the C-8 in the 6-cyanopurine.[5,6] It is possible that the C≡N function in the 6-cyanopurine is attacked by the tautomer $H_3N^+O^-$ *via* its oxygen site to form an imidate intermediate *in situ*, which would make the carbon more electrophilic. It is also possible that the buffer behaviour of the medium would allow the exchange with the acetate to furnish 6-amidinopurines **3**.

At room temperature, 6-cyanopurines **2a,b** reacted with an excess of hydrazine monohydrate in dichloromethane. After 20 hours stirring, the expected pyrimido[5,4-*d*]pyrimidines **10** precipitated from the reaction mixture in good yields (Scheme 5).



2a, = R = 4-MeOC$_6$H$_4$
b, = R = 4-MeC$_6$H$_4$

10a, = R = 4-MeOC$_6$H$_4$
b, = R = 4-MeC$_6$H$_4$

11a, = R = 4-MeOC$_6$H$_4$, R^1 = H
b, = R = 4-MeOC$_6$H$_4$, R^1 = Me
c, = R = 4-MeOC$_6$H$_4$, R^1 = Et
d, = R = 4-MeC$_6$H$_4$, R^1 = H
e, = R = 4-MeC$_6$H$_4$, R^1 = Me
f, = R = 4-MeC$_6$H$_4$, R^1 = Et

Scheme 5

The structure of pyrimido[5,4-*d*]pyrimidines **10a,b** suggests that these molecules could be utilised as precursors to synthesize novel triheterocyclic compounds, and thus opens new routes to potentially important heterocycles. Analogues of triheterocyclic compounds have been shown to be useful in cancer therapy.[30-32] In addition, the use of pyrimido[5,4-*d*]pyrimidines-based derivatives in medicine as antiviral and antitumour agents have been widely described by several authors.[8-15, 33-35] When pyrimido[5,4-*d*]pyrimidines **10a,b** were refluxed with an excess of triethyl orthoesters for 6-24 hours, bright yellow solids started to precipitate on cooling. The products **11a-f** were isolated in moderate yields.

Table 2. Reaction conditions used to synthesize compounds **10** and **11**.

Entry	Reactant	R	R^1	Reaction Conditions	Product/ yield(%)
1	**2a**	4-$MeOC_6H_4$	-	$N_2H_4.H_2O$ (5 equiv.), CH_2Cl_2, rt, 24 h	**10a** (70)
2	**2b**	4-MeC_6H_4	-	$N_2H_4.H_2O$ (5 equiv.), CH_2Cl_2, rt, 24 h	**10b** (68)
3	**10a**	4-$MeOC_6H_4$	H	excess $HC(OEt)_3$, DMF:dioxane 1:1, reflux 7 h	**11a** (52)
4	**10a**	4-$MeOC_6H_4$	Me	excess $MeC(OEt)_3$, DMF:dioxane 1:1, reflux, 24 h	**11b** (50)
5	**10a**	4-$MeOC_6H_4$	Et	excess $EtC(OEt)_3$, DMF:dioxane 1:1, reflux, 24 h	**11c** (50)
6	**10b**	4-MeC_6H_4	H	excess $HC(OEt)_3$, DMF:dioxane 1:1, reflux, 6 h	**11d** (68)
7	**10b**	4-MeC_6H_4	Me	excess $MeC(OEt)_3$, DMF:dioxane 1:1, reflux, 13 h	**11e** (57)
8	**10b**	4-MeC_6H_4	Et	excess $EtC(OEt)_3$, DMF:dioxane 1:1, reflux, 24 h	**11f** (50)

CONCLUSION

This work shows that two structural isomers i.e. 6-cyanopurines and imidazole-4,5-dicarbonitriles are formed from the reaction of (*Z*)-N^1-aryl-N^2-(2-amino-1,2-dicyanovinyl)formamidines with triethyl orthoesters. On the other hand, reaction with triethyl orthoformate afforded only 6-cyanopurines. Introducing alkyl groups was found to facilitate the formation of the imidazoles. Furthermore, generation of 6-amidinopurines from the reaction of 6-cyanopurines with hydroxylamine hydrochloride is found to be independent of both alcohol and an acidic medium, but depends on the type of nucleophile used such as an α–effect nucleophile like hydroxylamine which attacks hard electrophiles through its zwitterion $H_3N^+O^-$. Also, reaction of 6-cyanopurines with hydrazine monohydrate under mild conditions led to pyrimido[5,4-*d*]pyrimidines. These were used as intermediates to synthesize novel pyrimido[4,5-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines in moderate yields. Finally, the obtained results contribute to the synthesis of a new series of heterocyclic compounds which are potentially useful in the pharmaceutical industry.

EXPERIMENTAL

Crystal Data[36]

Compound **3a**

Chemical formula (moiety) $C_{13}H_{12}N_6O_2$, chemical formula (total) $C_{13}H_{12}N_6O_2$, formula weight 284.29, temperature 150(2) K, radiation, wavelength MoKα, 0.71073 Å, crystal system, space group monoclinic,

$P2_1/n$, unit cell parameters a = 10.586(3) Å, α = 90°, b = 8.231(2) Å, β = 92.244(5)°, c = 14.605(4) Å, γ = 90°, cell volume 1271.7(6) $Å^3$, Z 4, calculated density 1.485 g/cm^3, absorption coefficient μ 0.107 mm^{-1}, F(000) 592, crystal colour and size: colourless, 0.12 × 0.10 × 0.05 mm^3, reflections for cell refinement 2938 (θ range 2.2 to 28.2°), data collection method Bruker SMART 1K CCD diffractometer thin-slice ω scans, θ range for data collection 2.3 to 25.0°, index ranges h –12 to 12, k –9 to 9, l –16 to 17, completeness to θ = 25.0° 99.6 %, reflections collected 6603, independent reflections 2222 (R_{int} = 0.0405), reflections with $F^2>2\sigma$ 1714, absorption correction none, structure solution direct methods, refinement method Full-matrix least-squares on F^2, weighting parameters a, b 0.0690, 0.2093, data / restraints / parameters 2222 / 0 / 204, final R indices [$F^2>2\sigma$] R1 = 0.0455, wR2 = 0.1096, R indices (all data) R1 = 0.0639, wR2 = 0.1209, goodness-of-fit on F^2 1.047, extinction coefficient 0.0071(17), largest and mean shift/su 0.000 and 0.000, largest diff. peak and hole 0.30 and –0.25 e $Å^{-3}$.

Crystal Data[37]

Compound **7d**
Chemical formula (moiety) $C_{14}H_{11}N_5$, formula weight 249.28, temperature 150(2) K, radiation, wavelength MoKα, 0.71073 Å, crystal system, space group monoclinic, $P2_1/n$, nit cell parameters a = 7.1876(16) Å, α = 90°, b = 12.4551(12) Å, β = 99.085(18)°, c = 14.318(2) Å, γ = 90°, cell volume 1265.7(4) $Å^3$, Z 4, calculated density 1.308 g/cm^3, absorption coefficient 0.084 mm^{-1}, F(000) 520, crystal colour and size colourless, 0.52 × 0.40 × 0.40 mm^3, reflections for cell refinement 129 (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 –9 to 9, k –16 to 16, l –18 to 18, completeness to θ = 26.0° 99.3 % , reflections collected 13867, independent reflections, 2897 (R_{int} = 0.0224), reflections with $F^2>2\sigma$ 2426, absorption correction semi-empirical from equivalents, min. and max. transmission 0.9576 and 0.9672, structure solution direct methods, refinement method Full-matrix least-squares on F^2, weighting parameters a, 0.0418, 0.4658, data / restraints / parameters 2897 / 0 / 174, final R indices [$F^2>2\sigma$] R1 = 0.0355, wR2 = 0.0872, R indices (all data) R1 = 0.0463, wR2 = 0.0940, goodness-of-fit on F^2 1.033, largest and mean shift/su 0.000 and 0.000, largest diff. peak and hole 0.25 and –0.20 e $Å^{-3}$.

General

6-Cyanopurines **2a-c**, and pyrimido[5,4-*d*]pyrimdine **4** were prepared according to literature procedures.[4,38] ^1H NMR spectra were recorded on a Bruker DPX 400 spectrometer at 400 MHz using $CDCl_3$ or DMSO-d_6 as a solvent and 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 a RT-IR Perkin Elmer System 2000, using KBr discs 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 the synthesis of 6-cyanopurines 2d,e and imidazoles-4,5-dicarbonitrile 7c-e

Formamidines **1** (1 equiv.) were refluxed with an excess of either triethyl orthoacetate/propionate (10-15 equiv.) for 2 h. On cooling, a precipitate started to form, which was filtered and washed with petroleum ether. TLC of the precipitate showed the presence of two products (**2d** and **7d**), which were separated by column chromatography (hexane:EtOAc) (9:1). Compounds (**2c,e** and **7c,e**) were separated by recrystallization from EtOH.

2-Methyl-6-cyano-9-(4-methylphenyl)-9H-purine **2d**: white solid (0.27 g, 1.1 mmol, 25%); mp 205-208 °C [Found: accurate mass: 249.1007; m/z (EI) M$^+$ 249, 81%, 118, 100%, $C_{14}H_{11}N_5$ requires: 249.1008; M 249]; δ_H 400 MHz (DMSO-d_6, Me_4Si) 2.42 (s, 3H, CH_3), 2.76 (s, 3H, CH_3), 7.44 (d, 2H, *J* 8 Hz, ArH), 7.73 (d, 2H, *J* 8 Hz, ArH), 9.19 (s, 1H, CH); δ_C 100 MHz (DMSO-d_6, Me_4Si) 162.97, 153.68, 149.44, 138.83, 133.92, 131.60, 130.56, 129.45, 124.28, 114.83, 25.98, 21.15; ν_{max}: (KBr) 3433, 3111, 1594, 1519, 1395, 1215, 952, 811 cm^{-1}.

2-Ethyl-6-cyano-9-(4-methylphenyl)-9H-purine **2e**: colourless powder (0.83 g, 3.2 mmol, 43%); mp 125-128 °C [Found: accurate mass: 263.1164; m/z (EI) M$^+$ 263, 95%, 262, 100%, $C_{15}H_{13}N_5$ requires: 263.1165; M 263]; δ_H 400 MHz (DMSO-d_6, Me_4Si) 1.31 (t, 3H, *J* 7.6 Hz, -$CH_2\underline{CH_3}$), 2.42 (s, 3H, CH_3), 3.02 (q, 2H, *J* 7.6 Hz, -$\underline{CH_2}CH_3$), 7.45 (d, 2H, *J* 8 Hz, ArH), 7.77 (d, 2H, *J* 8 Hz, ArH), 9.20 (s, 1H, CH); δ_C 100 MHz (DMSO-d_6, Me_4Si) 166.53, 153.17, 149.00, 138.28, 133.65, 131.26, 130.11, 129.09, 123.64, 114.46, 31.75, 20.69, 12.70; ν_{max}: (KBr) 3115, 2988, 1585, 1519, 1395, 1338, 1210, 1202, 1174, 955, 824 cm^{-1}.

2-Ethyl-1-[(E)-p-methoxyphenyliminomethyl]-1H-imidazole-4,5-dicarbonitrile **7c**: light green needles (0.69 g, 2.5 mmol, 60%); mp 158-161 °C [Found: accurate mass 279.1114; m/z (EI) M$^+$ 279, 76%, 134, 100%, $C_{15}H_{13}N_5O$ requires: 279.1114; M 279]; δ_H 400 MHz (DMSO-d_6, Me_4Si) 1.27 (t, 3H, *J* 7 Hz, -$CH_2\underline{CH_3}$), 3.06 (q, 2H, *J* 7 Hz, -$\underline{CH_2}CH_3$), 3.80 (s, 3H, OCH_3), 7.04 (d, 2H, *J* 9 Hz, ArH), 7.42 (d, 2H, *J* 9

Hz, ArH), 8.94 (s, 1H, CH); δ_C 100 MHz (DMSO-d_6, Me_4Si) 159.09, 156.59, 139.86, 137.97, 123.85, 123.08, 114.73, 112.50, 109.48, 108.92, 55.57, 20.55, 10.82; ν_{max}: (KBr) 2972, 2231, 1650, 1600, 1514, 1411, 1299, 1252, 1166, 1023, 1003, 839 cm^{-1}.

2-Methyl-1-[(E)-p-tolyliminomethyl]-1H-imidazole-4,5-dicarbonitrile **7d**: light green crystals (0.80 g, 3.20 mmol, 66%); mp 183-185 °C [accurate mass Found: 249.1008; m/z (EI) M^+ 249, 73%, 118, 100%, $C_{14}H_{11}N_5$ requires: 249.1008; M 249]; δ_H 400 MHz (DMSO-d_6, Me_4Si) 2.35 (s, 3H, CH_3), 2.70 (s, 3H, CH_3), 7.29 (d, 2H, *J* 8.7 Hz, ArH), 7.31 (d, 2H, *J* 8.7 Hz, ArH), 8.88 (s, 1H, CH); δ_C 100 MHz (DMSO-d_6, Me_4Si) 152.65, 142.64, 141.31, 137.07, 129.85, 123.05, 121.93, 112.16, 109.15, 108.62, 20.61, 13.86; ν_{max}: (KBr) 3435, 2239, 2227, 1654, 1523, 1401, 1366, 1327, 1303, 1235, 966 cm^{-1}.

2-Ethyl-1-[(E)-p-tolyliminomethyl]-1H-imidazole-4,5-dicarbonitrile **7e**: off-white needles (0.56 g, 2.20 mmol, 51%); mp 155-157 °C [Anal. Calcd for $C_{15}H_{13}N_5$: C, 68.44; H, 4.94; N; 26.62; Found: C, 68.20; H, 4.85; N, 26.66; m/z (EI) M^+ 263, 76%, 118, 100%, M 263]; δ_H 400 MHz (DMSO-d_6, Me_4Si) 1.26 (t, 3H, *J* 7.4 Hz, -$CH_2\underline{CH_3}$), 2.35 (s, 3H, CH_3)3.02 (q, 2H, *J* 7.4 Hz, -$\underline{CH_2}CH_3$), 7.28 (d, 2H, *J* 8.5 Hz, ArH), 7.31 (d, 2H, *J* 8.5 Hz, ArH), 8.90 (s, 1H, CH); δ_C 100 MHz (DMSO-d_6, Me_4Si) 157.08, 143.10, 141.50, 137.60, 130.60, 123.54, 122.50, 112.77, 109.72, 109.31, 21.14, 20.88, 11.14; ν_{max}: (KBr) 3429, 2943, 2230, 1656, 1513, 1410, 1304, 1217, 938 cm^{-1}.

General procedure for the reaction of 6-cyanopurines 2a,b and d,e with hydroxylamine hydrochloride

6-Cyanopurines **2a,b** and **d,e** (1 equiv.), were dissolved/suspended in EtOH or CH_2Cl_2 (3-5 mL). While stirring, hydroxylamine hydrochloride (5 equiv.) and sodium acetate (4 equiv.) were added. The suspension was then stirred at rt, and the stirring was continued for 2-20 h, the precipitates were filtered off, and recrystallized from hot (EtOH:water) (1:1)/EtOH.

9-(4-Methoxyphenyl)-9H-purine-6-carboximidamide **3a**: colourless crystals (0.67 g, 2.40 mmol, 60%); mp 230-232 °C [Anal. Calcd for $C_{13}H_{12}N_6O_2$: C, 54.92; H, 4.220; N; 29.57. Found: C, 55.22; H, 4.39; N, 29.81; m/z (EI) M^+ 284, 60%, 254, 100%, M 284]; δ_H 400 MHz (DMSO-d_6, Me_4Si) 3.85 (s, 3H, OCH_3), 6.15 (s, 2H, NH_2), 7.17 (d, 2H, *J* 8.4 Hz, ArH), 7.78 (d, 2H, *J* 8.4 Hz, ArH), 8.92 (s, 1H, CH), 8.96 (s, 1H, CH), 10.64 (s, 1H, OH); δ_C 100 MHz (DMSO-d_6, Me_4Si) 159.98, 153.10, 152.68, 149.71, 148.93, 147.08, 131.05, 128.07, 126.54, 115.72, 56.60; ν_{max}: (KBr) 3417, 3315, 3132, 2832, 1635, 1584, 1517, 1464, 1327, 1247, 1171, 1111, 1021, 776 cm^{-1}.

9-(4-Methylphenyl)-9H-purine-6-carboximidamide **3b**: light brown crystals (0.92 g, 3.64 mmol, 82%); mp 239-240 °C [Anal. Calcd for $C_{13}H_{12}N_6O$: C, 58.20; H, 4.47; N; 31.34. Found: C, 58.24; H, 4.54; N, 31.08; m/z (EI) M^+ 268, 30%, 238, 100%, M 268]; δ_H 400 MHz (DMSO-*d*$_6$, Me_4Si) 2.41 (s, 3H, CH_3), 6.16 (s, 2H, NH_2), 7.42 (d, 2H, *J* 8 Hz, ArH), 7.77 (d, 2H, *J* 8 Hz, ArH), 8.97 (s, 1H, CH), 8.98 (s, 1H, CH), 10.5 (s, 1H, OH); δ_C 100 MHz (DMSO-*d*$_6$, Me_4Si) 152.95, 152.74, 149.71, 148.95, 146.87, 138.84, 132.75, 131.16, 131.03, 124.66, 21.69; ν_{max}: (KBr) 3440, 3335, 3161, 1630, 1584, 1519, 1461, 1380, 1327, 1215, 1106, 928, 823, 771 cm^{-1}.

6-Methyl-9-(4-methylphenyl)-9H-purine-6-carboximidamide **3d**: white powder (0.69 g, 2.4 mmol, 61%); mp 263-266 °C [Found: accurate mass: 282.1223; m/z (EI) M^+ 282, 30%, 250, 100%, $C_{14}H_{14}N_6O$ requires: 282.1223; M 282]; δ_H 400 MHz (DMSO-*d*$_6$, Me_4Si) 2.41 (s, 3H, CH_3), 2.72 (s, 3H, CH_3), 6.11 (s, 2H, NH_2), 7.42 (d, 2H, *J* 8 Hz, ArH), 7.74 (d, 2H, *J* 8 Hz, ArH), 8.85 (s, 1H, CH), 10.58 (s, 1H, OH); δ_C 100 MHz (DMSO-*d*$_6$, Me_4Si) 161.39, 153.07, 149.14, 148.03, 145.70, 138.23, 132.25, 130.47, 128.53, 124.25, 26.17, 21.12; ν_{max}: (KBr) 3482, 3371, 3270, 1649, 1580, 1520, 1396, 1334, 1231, 1205, 926, 817 cm^{-1}.

6-Ethyl-9-(4-methylphenyl)-9H-purine-6-carboximidamide **3e**: pale yellow crystals (0.9 g, 3.0 mmol, 80%); mp 235 °C [Found: accurate mass: 296.1380; m/z (EI) 262, 100%, $C_{15}H_{16}N_6O$ requires: 296.1380; M 296]; δ_H 400 MHz (DMSO-*d*$_6$, Me_4Si) 1.32 (t, 3H, *J* 7.6 Hz, $CH_2\underline{CH_3}$), 2.40 (s, 3H, CH_3), 2.96 (q, 2H, *J* 7.6 Hz, $\underline{CH_2}CH_3$), 6.11 (s, 2H, NH_2), 7.42 (d, 2H, *J* 8 Hz, ArH), 7.76 (d, 2H, *J* 8 Hz, ArH), 8.87 (s, 1H, CH), 10.60 (s, 1H, OH); δ_C 100 MHz (DMSO-*d*$_6$, Me_4Si) 164.92, 152.55, 148.71, 147.70, 145.23, 137.56, 131.96, 129.98, 128.32, 123.52, 31.88, 20.66, 12.91; ν_{max}: (KBr) 3453, 3336, 1650, 1570, 1583, 1521, 1398, 1341, 1224, 1206, 938, 914, 815 cm^{-1}.

General procedure for the synthesis of pyrimido[5,4-d]pyrimidine 5

A mixture of 6-cyanopurines **2a** (1 equiv.), methylamine hydrochloride (5 equiv.), and sodium acetate (4 equiv.), in EtOH (15 mL) was refluxed for 3 h. The precipitate was filtered off, washed with water (5 x 3 mL) and with EtOH (3 x 3 mL).

N-(4-Methoxyphenyl)-N`-methylpyrimido[5,4-d]pyrimidine-4,8-diamine **5**: cream crystals (0.67 g, 2.67 mmol, 60%); mp 185-187 °C [Anal. Calcd for $C_{14}H_{14}N_6O$: C, 59.57; H, 4.96; N; 29.78. Found: C, 59.86; H, 5.11; N, 29.95; m/z (EI) $(M)^+$ 282, 100%, M 282]; δ_H 400 MHz (DMSO-*d*$_6$, Me_4Si) 2.99 (d, 3H, *J* 4.84

Hz, NH$\underline{CH_3}$), 3.76 (s, 3H, OCH_3), 6.94 (d, 2H, *J* 9 Hz, ArH), 7.86 (d, 2H, *J* 9 Hz, ArH), 8.43 (br.q, *J* 4.8 Hz, 1H, NH), 8.47 (s, 1H, CH), 8.48 (s, 1H, CH), 9.88 (s, 1H, NH); δ_C 100 MHz (DMSO-d_6, Me_4Si) 159.91, 157.26, 156.54, 155.59, 154.61, 132.78, 132.43, 132.06, 124.01, 114.50, 56.08, 28.31; ν_{max}: (KBr) 3437, 3343, 3265, 1599, 1566, 1542, 1508, 1450, 1415, 1333, 1242, 1122, 1032, 821 cm^{-1}.

General procedure for the synthesis of pyrimido[5,4-d]pyrimidines 10a,b

6-Cyanopurines **2a,c** (1 equiv.) were dissolved in CH_2Cl_2 (3-5 mL). While stirring at rt, hydrazine monohydrate (3-5 equiv.) was added, and the mixture was stirred for 18-20 h. The formed precipitate was filtered off, and washed with CH_2Cl_2.

N8-(4-Methoxyphenyl)-4-imino-3,4-dihydropyrimido[5,4-d]pyrimidine-3,8-diamine **10a**: greenish-yellow powder (0.78 g, 2.78 mmol, 70%); mp 150-152 °C (decomp.) [Anal. Calcd for $C_{13}H_{13}N_7O$: C, 55.12; H, 4.59; N; 34.60. Found: C, 55.23; H, 4.27; N, 34.68; m/z (EI) $(M-H)^+$ 282, 100%, M 283]; δ_H 400 MHz (DMSO-d_6, Me_4Si) 3.75 (s, 3H, OCH_3), 5.80 (s, 2H, NH_2), 6.92 (d, 2H, *J* 8.9 Hz, ArH), 7.77 (d, 2H, *J* 8.9 Hz, ArH), 8.18 (s, 1H, CH), 8.32 (brs, 1H, NH), 8.48 (s, 1H, NH), 9.60 (s, 1H, CH); δ_C 100 MHz (DMSO-d_6, Me_4Si) 157.64, 157.12, 156.69, 155.97, 149.06, 139.00, 132.58, 126.34, 124.24, 114.66, 56.25; ν_{max}: (KBr) 3374, 3193, 1607, 1577, 1533, 1510, 1428, 1315, 1246, 1177, 1034, 813 cm^{-1}.

N8-(4-Methylphenyl)-4-imino-3,4-dihydropyrimido[5,4-d]pyrimidine-3,8-diamine **10b**: greenish-yellow powder (0.80 g, 3.02 mmol, 68%); mp 198-200 °C [Found: accurate mass; 267.1221; m/z (EI) (M^+) 267, 70%, 236, 100%, $C_{13}H_{13}N_7$ requires: 267.1234; M 267]; δ_H 400 MHz (DMSO-d_6, Me_4Si) 2.29 (s, 3H, CH_3), 5.96 (s, 2H, NH_2), 7.16 (d, 2H, *J* 8.2 Hz, ArH), 7.78 (d, 2H, *J* 8.2 Hz, ArH), 8.27 (s, 1H, CH), 8.56 (s, 1H, CH), 8.91 (br.s., 1H, NH), 9.73 (s, 1H, NH); δ_C 100 MHz (DMSO-d_6, Me_4Si) 157.59, 157.07, 156.39, 149.11, 138.04, 136.58, 134.38, 130.08, 127.06, 122.72, 21.50; ν_{max}: (KBr) 3434, 3353, 3263, 1638, 1603, 1556, 1531, 1421, 1188, 1036, 816 cm^{-1}.

General procedure for the synthesis of pyrimido[4,5-e][1,2,4]triazolo[1,5-c]pyrimidines 11a-f

Pyrimido[5,4-*d*]pyrimidines **10a,b** (1 equiv.) were refluxed in excess of triethyl orthoesters and a mixture of DMF/dioxane (1:1) (3 mL) for 6-24 h. The mixture was filtered while hot and crystals started to form almost immediately and were filtered off.

N-(4-Methoxyphenyl)-N-pyrimido[4,5-e][1,2,4]triazolo[1,5-c]pyrimidin-7-ylamine **11a**: greenish-yellow crystals (0.53 g, 1.83 mmol, 52%); mp 240-242 ^{o}C [accurate mass Found: 293.1030; m/z (EI) M^{+} 292, 100%, $C_{14}H_{11}N_7O$ requires: 293.1027; M 293]; δ_H 400 MHz (DMSO-*d*$_6$, Me_4Si) 3.78 (s, 3H, OCH_3), 6.97 (d, 2H, *J* 8.8 Hz, ArH), 7.81 (d, 2H, *J* 8.8 Hz, ArH), 8.75 (s, 1H, CH), 8.86 (s, 1H, CH), 9.84 (s, 1H, CH), 10.28 (s, 1H, NH); δ_C 100 MHz (DMSO-*d*$_6$, Me_4Si) 158.23, 157.75, 157.09, 156.35, 150.35, 139.99, 139.05, 132.20, 125.81, 125.01, 114.71, 56.29; ν_{max}: (KBr) 3245, 2928, 1602, 1551, 1509, 1458, 1419, 1315, 1259, 1212, 1020 831 cm^{-1}.

N-(4-Methoxyphenyl)-N-(2-methylpyrimido[4,5-e][1,2,4]triazolo[1,5-c]pyrimidin-7-yl)amine **11b**: light yellow crystals (0.54 g, 1.76 mmol, 50%); mp 258-260 ^{o}C [Anal. Calcd for $C_{15}H_{13}N_7O$: C, 58.63; H, 4.23; N; 31.92. Found: C, 58.45; H, 4.33; N, 31.55; m/z (EI) M^{+} 307, 100%, M 307]; δ_H 400 MHz (DMSO-*d*$_6$, Me_4Si) 2.62 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 6.96 (d, 2H, *J* 8.8 Hz, ArH), 7.80 (d, 2H, *J* 8.8 Hz, ArH), 8.71 (s, 1H, CH), 9.69 (s, 1H, CH), 10.18 (s, 1H, NH); δ_C 100 MHz (DMSO-*d*$_6$, Me_4Si) 165.91, 158.06, 157.67, 157.03, 150.75, 139.43, 138.35, 132.21, 125.79, 124.97, 114.68, 56.26, 15.32; ν_{max}: (KBr) 3435, 3254, 1603, 1555, 1532, 1511, 1493, 1440, 1311, 1247, 1030, 829 cm^{-1}.

N-(2-Ethylpyrimido[4,5-e][1,2,4]triazolo[1,5-c]pyrimidin-7-yl)-(4-methoxyphenyl) amine **11c**: light yellow crystals (0.56 g, 1.76 mmol, 50%); mp 228-230 ^{o}C [Anal. Calcd for $C_{16}H_{15}N_7O$: C, 59.81; H, 4.67; N; 30.52. Found: C, 59.60; H, 4.78; N, 30.49; m/z (EI) M^{+} 321, 100%, M 321]; δ_H 400 MHz (DMSO-*d*$_6$, Me_4Si) 1.38 (t, 3H, *J* 7.6 Hz, $CH_2\underline{CH_3}$), 2.96 (d, 2H, *J* 7.6 Hz, $\underline{CH_2}CH_3$), 3.77 (s, 3H, OCH_3), 6.96 (d, 2H, *J* 9.0 Hz, ArH), 7.80 (d, 2H, *J* 9 Hz, ArH), 8.72 (s, 1H, CH), 9.72 (s, 1H, CH), 10.20 (s, 1H, NH); δ_C 100 MHz (DMSO-*d*$_6$, Me_4Si) 170.46, 158.05, 157.71, 157.09, 139.53, 138.34, 132.12, 125.78, 125.00, 114.74, 80.093, 56.27, 22.72, 13.12; ν_{max}: (KBr) 3433, 3257, 1605, 1577, 1559, 1531, 1511, 1417, 1314, 1246, 1178, 1035, 826 cm^{-1}.

N-(4-Methylphenyl)-N-pyrimido[4,5-e][1,2,4]triazolo[1,5-c]pyrimidin-7-ylamine **11d**: light yellow crystals (0.70 g, 2.54 mmol, 68%); mp 262-264 ^{o}C [Found: accurate mass: 277.1071; m/z (EI) 276, 100%, M^{+} 277, 65%, $C_{14}H_{11}N_7$ requires: 277.1078; M 277]; δ_H 400 MHz (DMSO-*d*$_6$, Me_4Si) 2.32 (s, 3H, CH_3), 7.20 (d, 2H, *J* 8.3 Hz, ArH), 7.83 (d, 2H, *J* 8.3 Hz, ArH), 8.79 (s, 1H, CH), 8.87 (s, 1H, CH), 9.84 (s, 1H, CH), 10.25 (s, 1H, NH); δ_C 100 MHz (DMSO-*d*$_6$, Me_4Si) 158.15, 157.70, 156.36, 150.33, 140.08, 139.11, 136.74, 134.32, 129.97, 125.85, 123.20, 21.60; ν_{max}: (KBr) 3436, 1598, 1548, 1527, 1418, 1368, 1264, 1241, 993, 818 cm^{-1}.

N-(4-Methylphenyl)-N-(2-methylpyrimido[4,5-e][1,2,4]triazolo-[1,5-c]pyrimidin-7-yl)amine **11e**: light yellow crystals (0.62 g, 2.13 mmol, 57%); mp 253-255 °C [Anal. Calcd for $C_{15}H_{13}N_7$: C, 61.85; H, 4.46; N; 33.67; Found: C, 61.89; H, 4.51; N, 33.65; m/z (EI) M^+ 291, 70%, 290, 100%, M 291]; δ_H 400 MHz (DMSO-*d*$_6$, Me_4Si) 2.31 (s, 3H, CH_3), 3.37 (s, 3H, CH_3), 7.19 (d, 2H, *J* 8.3 Hz, ArH), 7.82 (d, 2H, *J* 8.3 Hz, ArH), 8.76 (s, 1H, CH), 9.71 (s, 1H, CH), 10.21 (s, 1H, NH); δ_C 100 MHz (DMSO-*d*$_6$, Me_4Si) 165.94, 157.99, 157.64, 150.75, 139.52, 138.43, 136.78, 134.24, 129.95, 125.83, 123.16, 21.60, 15.33; ν_{max}: (KBr) 3357, 1600, 1554, 1533, 1483, 1415, 1373, 1286, 1252, 1150, 1008, 824 cm^{-1}.

N-(2-Ethylpyrimido[4,5-e][1,2,4]triazolo[1,5-c]pyrimidin-7-yl)-(4-methylphenyl)amine **11f**: light yellow crystals (0.57 g, 1.87 mmol, 50%); mp 233-234 °C [Anal. Calcd for $C_{16}H_{15}N_7$ requires: C, 62.95; H, 4.91; N; 32.13. Found: C, 62.87; H, 5.01; N, 31.70; m/z (EI) $(M+1)^+$ 306, 100%, M 305]; δ_H 400 MHz (DMSO-*d*$_6$, Me_4Si) 1.38 (t, 3H, *J* 7.2 Hz, $CH_2\underline{CH_3}$), 2.30 (s, 3H, CH_3), 2.96 (q, 2H, *J* 7.2 Hz, $\underline{CH_2}CH_3$), 7.17 (d, 2H, *J* 8 Hz, ArH), 7.81 (d, 2H, *J* 8 Hz, ArH), 8.74 (s, 1H, CH), 9.70 (s, 1H, CH), 10.13 (s, 1H, NH); δ_C 100 MHz (DMSO-*d*$_6$, Me_4Si) 170.44, 157.18, 157.66, 150.56, 139.71, 138.24, 136.72, 134.30, 129.95, 125.79, 123.14, 22.76, 21.59, 13.12; ν_{max}: (KBr) 3435, 3356, 1601, 1554, 1532, 1483, 1415, 1305, 1260, 997, 822 cm^{-1}.

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37. Crystal data for compound **7d**: (ref. CCDC 675997) can be obtained on request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EW, UK. CCDC.
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