Novel 6-substituted pyrimidines and pyrimido[5,4-*d*]pyrimidines from (2-acetamido-1,2-dicyanovinyl)ammonium chloride

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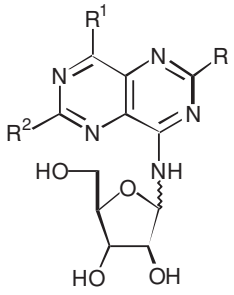
The reaction of triethyl orthoformate with 5-amino-6-ethoxy-2-methyl-4-pyrimidinecarbonitrile (**5**), available from DAMN *via* the ammonium salt **4**, afforded iminoformate **6**. The latter cyclised with aqueous ammonia or equimolar amounts of aryl/benzyl amines to give the corresponding pyrimido[5,4-*d*]pyrimidines **8, 9a–c**. Reaction with excess of aqueous ethylamine, methylamine or benzylamine caused cyclisation with substitution of an ethoxy group to give **9d–f**. Hydrolysis of compounds **8, 9a–b** under acidic conditions gave the corresponding pyrimido[5,4-*d*]pyrimidones **10**, **11a–b**. Heating **4** to reflux in THF unexpectedly formed 5-amino-6-(4-chlorobutoxy)-2-methyl-4-pyrimidinecarbonitrile (**12**) and 5-amino-2-methyl-6-oxo-1,6-dihydro-4-pyrimidinecarbonitrile (**13**). X-Ray crystallography established the structure of *N*-ethyl-*N*-(7-ethyl-8-imino-2-methyl-7,8-dihydropyrimido[5,4-*d*]pyrimidin-4-yl)amine (**9e**).

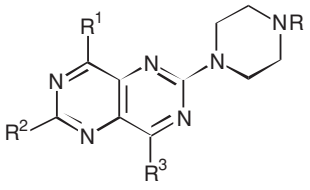
Keywords: diaminomaleonitrile, pyrimidines, pyrimidopyrimidines, tetrahydrofuran

Pyrimido[5,4-*d*]pyrimidines are biologically interesting compounds due to their structural similarity with natural products such as purines, and to their role in drug development. Several methods have been described to synthesise pyrimido[5,4-*d*]pyrimidine derivatives that have proved to have pharmaceutical applications.[1-5] Derivatives that have attracted significant attention, for instance pyrimido[5,4-*d*]pyrimidine nucleosides **1,** include those with both antitumor and antiviral properties.[6-8] Derivatives such as **2** are also known to inhibit primary and secondary drug resistance in antitumor chemotherapy.[9] These compounds sensitise drug-resistant tumor cells to antitumor agents such as daunorubicin and bleomycin.



1

R= R^1 = R^2 = H, OH, NH_2, OCH_2Ph, Cl, Br, OMe, NHMe, NMe_2;
R and $R^2 \neq$ H when R^1= NH_2



2

R^1 = R^3 = dialkylamino, pyrrolidino, or piperidino;
R^2 = dialkanolamino

Recently we have reported the formation of pyrimido[5,4-*d*]pyrimidines in the reaction of 6-cyanopurines with aqueous methylamine.[10] In addition, the hydrochloride salt **4**, which was prepared from diaminomaleonitrile (DAMN) **3**, underwent a facile rearrangement on heating in ethanol to furnish the highly functionalised 5-amino-6-ethoxy-2-methyl-4-pyrimidinecarbonitrile **5** in moderate yield.[11] This prompted us to extend this useful reaction further to synthesise novel pyrimido[5,4-*d*]pyrimidine derivatives, and to investigate the effect of various solvents on the behavior of (2-acetamido-1,2-dicyanovinyl)ammonium chloride **4**.

Results and discussion

The formation of 5-amino-6-ethoxy-2-methyl-4-pyrimidinecarbonitrile **5** on refluxing the vinylammonium salt **4** in ethanol drew attention to the possibility of using the pyrimidine **5** to prepare novel pyrimido[5,4-*d*]pyrimidines. The pyrimidine **5** was prepared following literature procedures,[11] and when this was refluxed with an excess of triethyl orthoformate the iminoformate **6** was isolated in 95% yield. The reaction of **6** with, respectively, aqueous ammonia and 4-methoxyaniline, using a catalytic amount of anilinium hydrochloride, afforded the pyrimidopyrimidines **8** and **9a**. However, the yields were poor and the products not easy to isolate in a pure state. The presence of anilinium hydrochloride has been reported to be essential for accelerating the reaction, and to reduce decomposition when amidines are targeted.[12,13] Note that the reaction of amines with iminoformate **6** is found to give purer products and higher yields without using an acidic catalyst. Therefore, the iminoformate **6** was allowed to react with aqueous ammonia, and with equimolar amounts of aryl/benzyl amines with or without a solvent, to form a series of hitherto unreported pyrimido[5,4-*d*]pyrimidines **8**, **9a–f** in good yields *via* the intermediate **7** (Scheme 1).

The ^{1}H NMR spectra of **8, 9a–c** revealed the disappearance of one of the ethoxy groups, and the IR spectra indicated the involvement of the cyano group in the reaction. These results exclude the possible exchange of the amine with the ethoxy group on the pyrimidine ring. To confirm the expected structure of the products, an X-ray crystal structure was carried out on **9e** (Fig. 1).

The crystal data indicate a high degree of aromaticity. The angles of rotation also show that both rings are planar. The structure contains two practically identical molecules linked together by hydrogen-bonding. An interesting observation comes from the bond angle of 108.3° between C(19)–N(1)–H(1), which is an unexpected angle for an sp^2 hybridised N atom, which suggests that the molecule exists mainly in a zwitterion form.[14]

On treatment of **6** with an excess of aqueous ethylamine, methylamine or benzylamine, compounds **9d–f** were formed as a result of cyclisation and replacement of the ethoxy group on the pyrimdine ring as evidenced by ^{1}H NMR spectra. It is apparent that the imidate group adjacent to the cyano group is more electrophilic due to the electron-withdrawing effect of the latter, and this is confirmed when **6** is reacted with one equivalent of amine. The formation of pyrimido[5,4-*d*]pyrimidines **9a–f** proceeds smoothly through either clean precipitation, or by addition of a mixture of petroleum ether and chloroform. The present study was extended to an investigation of the hydrolysis of the ethoxy group on the pyrimidine ring, with the possibility of preparing novel pyrimido[5,4-*d*]pyrimidones. Consequently, pyrimido[5,4-*d*]

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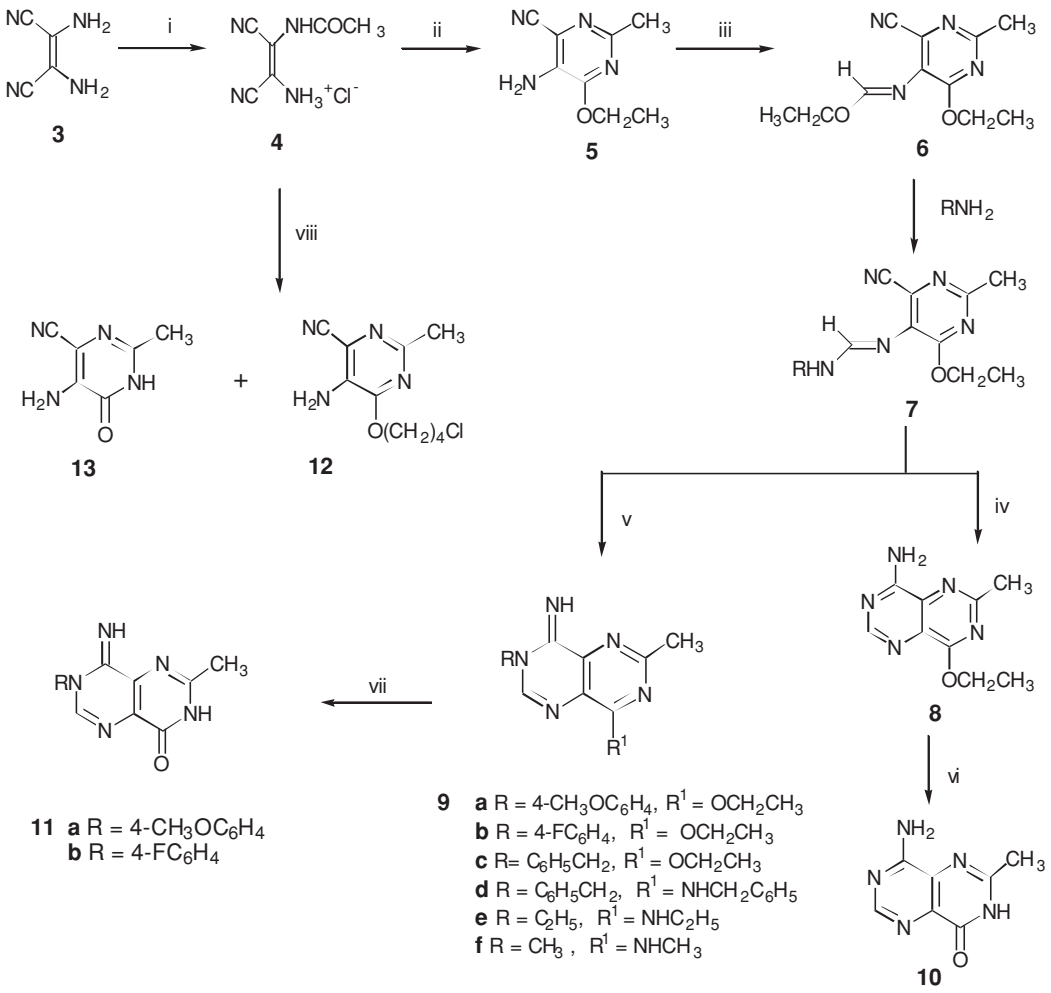


Scheme 1 (i) acetyl chloride (1 equiv.), EtOAc, r.t., 3 h; (ii) EtOH, reflux, 3–4 h; (iii) $HC(OEt)_3$ (6 equiv.), reflux, 7 h; (iv) aqueous NH_3, r.t., 3 h; (v) **9a** (1 equiv.) RNH_2, EtOH, r.t., 6 weeks; **9b** (1 equiv.) RNH_2, EtOH, r.t., 18 h; **9c** (1 equiv.) RNH_2, EtOH, r.t., 72 h; **9d**, excess RNH_2, r.t., 72 h; **9e** (20 ml) $C_2H_5NH_2$, r.t., 3 h; **9f** (20 ml) CH_3NH_2, r.t., 24 h; (vi) 1 N HCl, water, reflux, 4 h; (vii) 1 N HCl, EtOH, reflux, 3–4 h; (viii) THF, reflux, 3 h (**12**), 24 h (**13**).

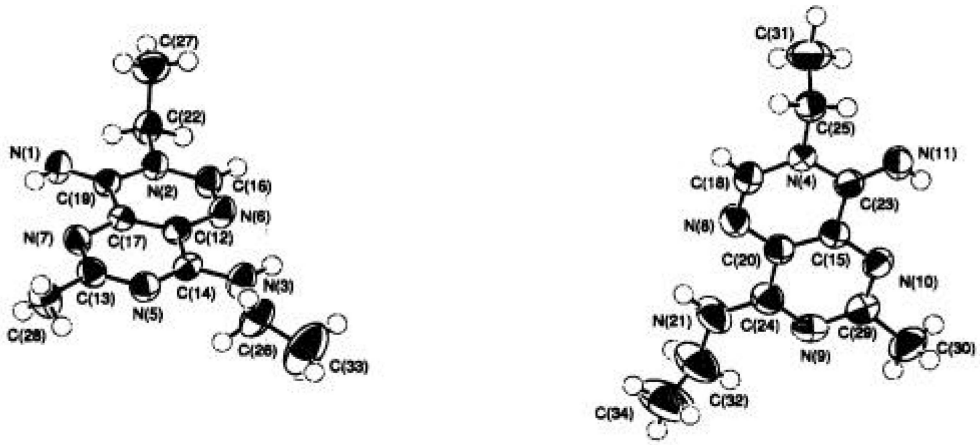
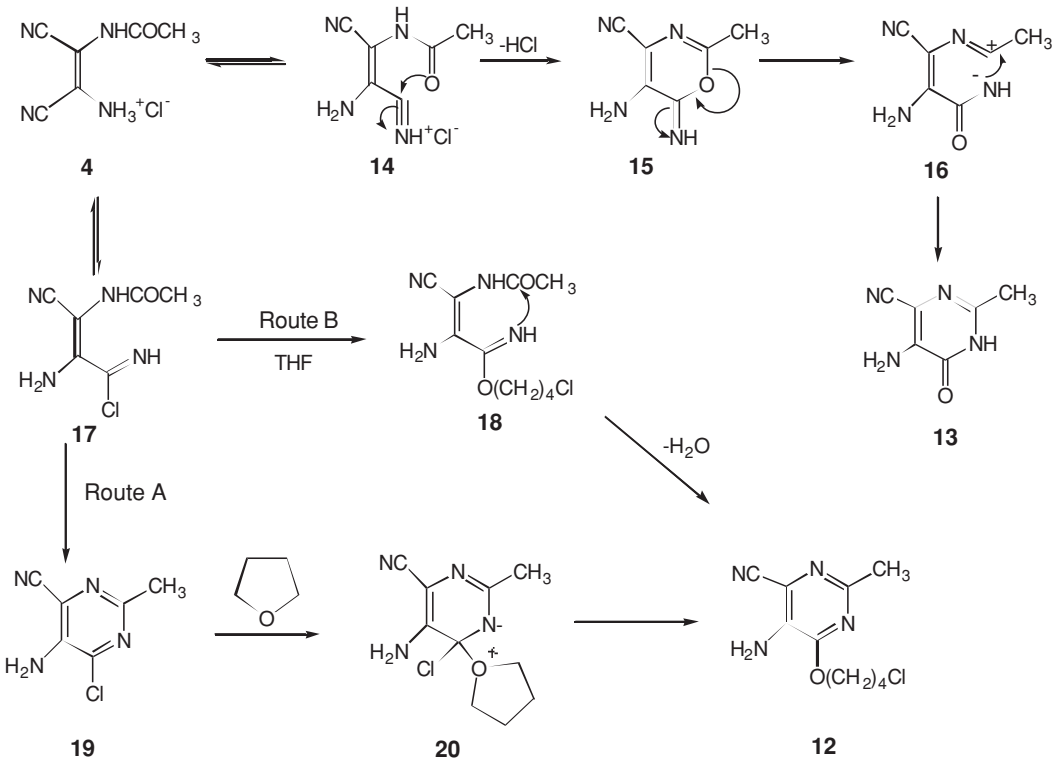


Fig. 1 X-ray crystal structure of *N*-ethyl-*N*-(7-ethyl-8-imino-2-methyl-7,8-dihydropyrimido[5,4-*d*]pyrimidin-4-yl)amine **9e**.

pyrimidines **8, 9a–b** were refluxed, respectively, in water and in ethanol under acidic conditions, to afford new pyrimido[5,4-*d*]pyrimidones **10** and **11a–b** obtained following neutralisation with aqueous NaOH. The ^{1}H NMR spectra of pyrimido[5,4-*d*]pyrimidones showed the disappearance of the ethoxy group and the appearance of a broad singlet for one proton at δ 12.6–13.3 ppm, in addition to the presence of a carbonyl group in their IR spectra at 1688–1699 cm^{-1}.

It was also of interest to prepare 6-oxopyrimidine of type **13** as a potential precursor for purine bases necessary for RNA formation. Attempts to effect the cyclisation of **4** in absence of ethanol and using various solvents such as water, *N*,*N*-dimethylformamide, dichloromethane, 1,4-dioxane, toluene and dimethyl sulfoxide has been carried out but showed no evidence of the formation of the desired 6-oxopyrimidine **13**. Instead, a mixture of several by-products was obtained,



Scheme 2 Suggested mechanisms for the formation of **12** and **13**.

and these were difficult to separate. Unexpectedly, refluxing **4** with THF gave two new products as evidenced by TLC; the R_f values of the two compounds were very close. Column chromatography of the dark brown residue gave a brownish-orange oil which was treated with a mixture of petroleum ether and chloroform, and the oil was left to stand overnight. Careful addition of dichloromethane to this mixture allowed the separation of pyrimidine **12** (orange oil, 36% yield, R_f = 0.95), and 6-oxopyrimidine **13** isolated as a yellow powder but only in low yield (15%, R_f = 0.90). The two pyrimidines were fully characterised by spectroscopic analyses. Many attempts to improve the yield of 6-oxopyrimidine **13** were unsuccessful. It seems that the 6-oxopyrimidine **13** is a by-product from this reaction, and the reason behind its interesting formation is not yet clear. On the other hand, formation of pyrimidine **13** could be the result of rotation around C1–C2 of **4** to yield intermediate **14**. The protonated species **14** is then cyclised into **15**, and the latter undergoes a Dimroth-like rearrangement *via* **16** to yield **13**. The formation of pyrimidine **12**, however, could be attributed to the formation of imidoyl chloride **17**, which then either cyclises into **19** leading through the THF reaction to the final product **12** (route A, Scheme 2), or alternatively THF initially attacks the imidoyl chloride **17**, followed by formation of **18** which is finally cyclised to **12** (route B, Scheme 2).

Conclusion

The work described in this paper shows a new route to synthesise novel pyrimido[5,4-*d*]pyrimidines from iminoformate **6** using different molar ratios of various amines. A series of highly functionalised pyrimido[5,4-*d*]pyrimidines was easily prepared from the reaction of **6** with the appropriate ratio of amine. In addition, the (2-acetamido-1,2-dicyanovinyl)ammonium chloride **4** was shown to be a valuable precursor in the synthesis of the novel 6-substituted pyrimidines **5**, **12** and **13**. Finally, the present results contribute to the preparation of new pyrimido[5,4-*d*]pyrimidine, pyrimido[5,4-*d*]pyrimidone and 6-substituted pyrimidine derivatives which can play an important role in the synthesis of natural product analogues and biologically active heterocyclic compounds.

Experimental

The (2-acetamido-1,2-dicyanovinyl)ammonium chloride **4** and 5-amino-6-ethoxy-2-methyl-4-pyrimidinecarbonitrile **5** used in this work were prepared using previously described procedures.[11] ^{1}H NMR spectra were recorded on a Bruker DPX 400 spectrometer at 400 MHz. ^{13}C NMR spectra were obtained using a Bruker DPX 400 spectrometer at 100 MHz. Chemical shifts are measured from Me_4Si. Mass spectra were recorded on a VG autospec Q spectrometer with a digital data output. UV spectra of selected compounds are listed in Table 1. Melting points were determined by using a Gallenkamp melting point apparatus. TLC was performed on a 0.25 mm pre-coated silica gel plates (Merck).

Crystallographic analysis

The crystals were mounted on a glass fibre. All measurements were performed on an ENRAF NONIUS FR 590. The data were collected at a temperature of 20±1 °C using the ω scanning technique to a maximum of a 2θ of 27.12°. The structure was solved by direct method using SIR 92 and refined by full-matrix least squares.[15] Non-hydrogen atoms were refined anisotropically. Hydrogen atoms were located geometrically and were refined isotropically.

Crystal data

$C_{11}H_{16}N_6$, M = 232.291, monoclinic, *a* = 20.1111(9), *b* = 13.5796(4), *c* = 9.2509(3) Å, v = 2470.6(2), α = γ = 90.00, β = 102.0703(10), space group: P21/c, *Z* = 8, D_x = 1.249 reflection 10122 measured, θ_{max} = 27.12 , ωR factor = 0.126. Figure 1 illustrates the structure as determined. Full data can be obtained on request from the CCDC.[14]

Ethyl-N-(4-cyano-6-ethoxy-2-methyl-5-pyrimidinyl)iminoformate (**6**): 5-Amino-6-ethoxy-2-methyl-4-pyrimidinecarbonitrile **5** (1 g, 5.6 mmol) was refluxed with triethyl orthoformate (5.6 ml, 5.0 g, 34 mmol) for seven hours until TLC (1 : 1 EtOAc : hexane) showed that all starting material has been consumed. A mixture (1 : 3) of petroleum ether (60–80) and chloroform (4 ml) was added to the reaction mixture, resulting in the precipitation of a black powder which was filtered off. The filtrate was concentrated under vacuum, until a dark brown oil is formed. On cooling, light brown crystals

Table 1 UV spectroscopic data[a] for selected compounds

Compound	λ_{max} /nm	$\log_{10}$ (ε/dm^{3}mol^{-1}cm^{-1})
5	250	4.013
6	261	4.261
8	275	4.183
9b	288	4.106
9e	306	4.195
10	277	4.158
11b	308	4.211

[a]Solvent: EtOH for compounds **5**, **10**, **11b**; $CHCl_3$ for compounds **6**, **8**, **9b**, **9e**

of **6** (1.24 g, 5.3 mmol, 95%), m.p. 37.5 °C, separated. IR (KBr): ν_{max} 2979, 2898, 1754, 1714, 1637, 1544, 1375, 1341 cm^{-1}. NMR: δ_H (400 MHz, $CDCl_3$) 1.40 (t, 6H, *J* = 7.0 Hz, 2 OCH_2CH_3), 2.58 (s, 3H, CH_3), 4.42 (q, 2H, *J* = 7 Hz, OCH_2CH_3), 4.47 (q, 2H, *J* = 7 Hz, OCH_2CH_3), 8.22 (s, 1H, CH); δ_C (100 MHz, $CDCl_3$) 163.4, 162.4, 159.9, 133.2, 131.0, 115.5, 64.1, 63.6, 25.6, 14.6, 14.3. MS: *m/z* (EI) 235 (100, M+1)$^+$. Found: C, 56.5; H, 5.9; N, 23.5; $C_{11}H_{14}N_4O_2$ requires: C, 56.4; H, 5.9; N, 23.9 %.

8-Ethoxy-6-methylpyrimido[5,4-d]pyrimidin-4-amine (**8**): Aqueous ammonia (20 ml) was added to iminoformate **6** (1 g, 4.27 mmol). After 30 min an off-white solid precipitated, and stirring was continued for three hours when TLC (1 : 1 EtOAc : hexane) confirmed the disappearance of all starting materials. The solid was filtered off, washed with water and dried to give **8** as a white powder (0.70 g, 3.37 mmol, 80%), m.p. 209 °C. IR (KBr): ν_{max} 3456, 3068, 1631, 1554, 1457, 1376, 1333, 1086, 1023 cm^{-1}. NMR: δ_H (400 MHz, $CDCl_3$) 1.54 (t, 3H, *J* = 7.0 OCH_2CH_3), 2.69 (s, 3H, CH_3), 4.65 (q, 2H, *J* = 7 Hz, OCH_2CH_3), 6.13 (brs, 1H, NH), 6.81 (brs, 1H, NH), 8.61 (s, 1H, CH); δ_C (100 MHz, $CDCl_3$) 165.5, 164.1, 160.9, 155.4, 134.6, 132.3, 64.4, 26.5, 14.6; MS: *m/z* (EI) 205 (70, M$^+$), accurate mass 205.0963; required: 205.0964. Found: C, 52.7; H, 5.0; N, 33.8; $C_9H_{11}N_5O$ requires C, 52.7; H, 5.4; N, 34.2 %.

8-Ethoxy-3-(4-methoxyphenyl)-6-methylpyrimido[5,4-d]pyrimidin-4(3H)-imine (**9a**): Iminoformate **6** (0.25 g, 1.1 mmol) and 4-methoxyaniline (0.135 g, 1.1 mmol) in ethanol (10 ml) was stirred at room temperature for 6 weeks. During this period the reaction mixture was gently heated once for one hour on a water bath at 50–60 °C. The product **9a**, a light green solid (0.22 g, 0.71 mmol, 64%), was filtered and washed with petroleum ether. M.p. 136 °C. IR (KBr): ν_{max} 3339, 2833, 1608, 1555, 1510, 1455, 1338, 1230, 1058, 829 cm^{-1}. NMR: δ_H (400 MHz, $CDCl_3$) 1.55 (t, 3H, *J* = 7 Hz OCH_2CH_3), 2.74 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 4.67 (q, 2H, *J* = 7 Hz, OCH_2CH_3), 6.97 (d, 2H, *J* = 8.7 Hz, ArH), 7.77 (d, 2H, *J* = 8.7 Hz, ArH), 8.73 (s, 1H, CH), 8.80 (s, 1H, NH); δ_C (100 MHz, d_6–DMSO) 165.8, 163.8, 157.1, 156.9, 155.6, 135.7, 132.2, 132.1, 124.8, 114.9, 64.3, 56.2, 26.9, 15.1. MS: *m/z* (EI) 311, (100, M$^+$). Found: C, 61.6; H, 5.5; N, 22.4; $C_{16}H_{17}N_5O_2$ requires C, 61.7; H, 5.5; N, 22.5%.

8-Ethoxy-3-(4-fluorophenyl)-6-methylpyrimido[5,4-d]pyrimidin-4(3H)-imine (**9b**): Iminoformate **6** (1 g, 4.27 mmol) was dissolved in ethanol (4 ml), and 4-fluoroaniline (0.4 ml, 0.47 g, 4.27 mmol) was added and the mixture was stirred for 18 h. A white precipitate formed which was filtered, washed with petroleum ether and dried to give **9b** (0.85 g, 2.8 mmol, 67%), m.p. 238 °C. IR (KBr): ν_{max} 3429, 2998, 1628, 1557, 1381, 1345, 1102, 837 cm^{-1}. NMR: δ_H (400 MHz, $CDCl_3$) 1.52 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3), 2.69 (s, 3H, CH_3), 4.63 (q, *J* = 7.2 Hz, 2H, OCH_2CH_3), 7.24 (t, $^3J_{H,H}$ = $^3J_{F,H}$ = 8.4 Hz, 2H, ArH), 7.29 (s, 1H, NH), 7.42 (dd, $^3J_{H,H}$ = 9, $^4J_{F,H}$ = 4.6 Hz, 2H, ArH), 7.80 (s, 1H, CH); δ_C (100 MHz, d_6-DMSO) 165.8, 164.1 (d, $^1J_{F-C}$ = 247 Hz), 156.9, 155.3, 147.2, 142.4, 135.0, 130.1 (d, $^3J_{F-C}$ = 8.8 Hz), 125.3, 117.4 (d, $^2J_{F-C}$ = 22.8 Hz), 64.3, 26.5, 14.9. MS: *m/z* (EI) 299 (76, M$^+$) 298 [100, (M–H)$^+$], Found: C, 60.5; H, 4.9; N, 23.5; $C_{15}H_{14}FN_5O$ requires C, 60.2; H, 4.7; N, 23.4 %.

3-Benzyl-8-ethoxy-6-methyl-3,4-pyrimido[5,4-d]pyrimidin-4-imine (**9c**): A mixture of iminoformate **6** (0.25 g, 1.07 mmol) and benzylamine (0.12 ml, 0.12 g, 1.1 mmol) in ethanol was stirred at room temperature for 72 h. The solvent was evaporated and a mixture of petroleum ether (60–80) and chloroform (1 : 1) (3 ml) was added. On trituration, a white precipitate was obtained which was filtered off and dried to give **9c** (0.21 g, 0.71 mmol, 67%), m.p. 131 °C. IR (KBr): ν_{max} 3289, 2989, 1628, 1597, 1551, 1450, 1384, 1344, 1163, 1083, 740 cm^{-1}. NMR: δ_H (400 MHz, $CDCl_3$) 1.49 (t, *J* = 7 Hz, 3H, OCH_2CH_3), 2.66 (s, 1H, CH_3), 4.5 (q, *J* = 7 Hz, 2H, OCH_2CH_3), 5.2 (s, 2H, CH_2), 7.33 (m, 5H, ArH), 7.8 (s, 1H, CH), 8.7 (s, 1H, NH); δ_C (100 MHz, $CDCl_3$) 165.7, 165.6, 156.1, 147.7, 142.2, 135.8, 129.5, 128.7, 128.3, 125.6, 64.4, 51.6, 26.5, 14.8. MS: *m/z* (EI) 296 [15, (M+1)$^+$], 295 (70, M$^+$), 294 [100, (M-1)$^+$]. Found: C, 65.0, H, 5.7; N, 23.3; $C_{16}H_{17}N_5O$ requires C, 65.0; H, 5.7; N, 23.7 %.

N-Benzyl-N-(7-benzyl-8-imino-2-methyl-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)amine (**9d**): A mixture of iminoformate **6** (0.1 g, 0.43 mmol), and benzylamine (1.2 ml, 1.2 g, 11.0 mmol) was stirred at room temperature. After 72 h a precipitate started to form on the sides of the flask and TLC showed the completion of the reaction. A mixture of petroleum ether (60–80) and chloroform (1 : 1) (3 ml) was then added. Trituration afforded **9d** as a white powder (0.13 g, 0.36 mmol, 85%), m.p. 140 °C. IR (KBr): ν_{max} 2996, 1597, 1478, 1468, 1383, 1215, 1112, 1059, 745 cm^{-1}. NMR: δ_H (400 MHz, $CDCl_3$) 2.58 (s, 3H, CH_3), 4.82 (s, 2H, CH_2), 4.83 (s, 2H, CH_2), 7.05 (brs, 1H, NH), 7.18 (brs, 1H, NH), 7.34 (m, 10H, 2 ArH), 8.47 (s, 1H, CH); δ_C (100 MHz, $CDCl_3$) 164.8, 159.1, 154.3, 138.5, 138.4, 132.3, 131.4, 130.1, 129.4, 129.3, 129.1, 128.5, 128.4, 128.2, 45.1, 30.2, 27.0. MS: *m/z* (EI) 356, (100, M$^+$). Found: C, 70.5, H, 5.6; N, 23.2; $C_{21}H_{20}N_6$ requires C, 70.7; H, 5.6; N, 23.5 %.

N-Ethyl-N-(7-ethyl-8-imino-2-methyl-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)amine (**9e**): Aqueous ethylamine (20 ml) was added to iminoformate **6** (1 g, 4.27 mmol). After 3h stirring TLC showed complete disappearance of **6** and the appearance of the product **9e** with an unidentified dark line. The solvent was evaporated and the precipitate was washed with a mixture of (3 : 1) petroleum ether (60–80) and chloroform. The precipitate was filtered off and recrystallised from dichloromethane to give white crystals **9e** (0.72 g, 3.1 mmol, 73%), m.p. 145 °C. IR (KBr): ν_{max} 3249, 2974, 1586, 1565, 1381, 1177, 1146 cm^{-1}. NMR: δ_H (400 MHz, $CDCl_3$) 1.28 (t, *J* = 7.2 Hz, 3H, $NHCH_2CH_3$), 1.41 (t, *J* = 7.1 Hz, 3H, $NHCH_2CH_3$), 2.57 (s, 3H, CH_3), 3.57 (dt, *J* = 14, 7.2 Hz, 2H, $NHCH_2CH_3$), 4.08 (q, *J* = 7.1, 2H, CH_2), 6.29 (brs, 1H, $NHCH_2CH_3$ slow exchange with D_2O), 7.65 (s, 1H, CH), 8.50 (s, 1H, NH); δ_C (100 MHz, $CDCl_3$) 166.3, 159.3, 156.3, 145.8, 138.2, 123.5, 44.4, 36.6, 26.9, 15.2, 14.3. MS: accurate mass, found: 232.1428 *m/z* (EI) (M$^+$) 232 (100); $C_{11}H_{16}N_6$ requires M$^+$ = 232.1431.

N-(8-Imino-2,7-dimethyl-7,8-dihydropyrimido[5,4-d]pyrimidin-4-yl)-N-methylamine (**9f**): Aqueous methylamine (20 ml) was added to iminoformate **6** (1 g, 4.27 mmol). After 24 h stirring the solvent was evaporated and the remaining solid was washed with a mixture of petroleum ether (60–80) and chloroform (3 : 1). The residual solid was recrystallised from ethanol to furnish **9f** as white needles (0.72 g, 3.12 mmol, 73%), m.p. 186 °C. IR (KBr): ν_{max} 3346, 2905, 1582, 1389, 1246, 1146 cm^{-1}. NMR: δ_H (400 MHz, $CDCl_3$) 2.5 (s, 3H, CH_3), 3.17 (s, 3H, CH_3), 3.23 (s, 3H, CH_3), 6.7 (brs, 1H, NH), 6.8 (brs, 1H, NH), 8.4 (s, 1H, CH); δ_C (100 MHz, $CDCl_3$) 164.7, 159.8, 159.7, 154.3, 132.1, 129.8, 30.2, 27.8, 27.0. MS: accurate mass, found (M+1)$^+$ 205.1200, *m/z* (EI) 204 (100, M$^+$), $C_9H_{12}N_6$ requires (M+H)$^+$ = 205.1196.

8-Amino-2-methyl-3,4-dihydropyrimido[5,4-d]pyrimidin-4-one (**10**): Pyrimidopyrimidine **8** (0.25 g, 1.22 mmol) was refluxed in a mixture of water (15 ml) and 1N HCl (4 ml) for four hours. On neutralising the reaction mixture with 1N NaOH a white precipitate started to form. The precipitate was filtered off and washed with cold water followed by drying to give the pyrimidopyrimidinone **10** (0.16 g, 0.90 mmol, 74%). m.p. >300 °C. IR (KBr): ν_{max} 3465, 2956, 1694, 1612, 1572, 1493, 1340, 1212 cm^{-1}. NMR: δ_H (400 MHz, d_6-DMSO) 2.45 (s, 3H, CH_3), 8.6 (s, 1H, CH), 9.1 (s, 1H, NH), 9.5 (s, 1H, NH), 13.3 (s, 1H, NH); δ_C (100 MHz, d_6-DMSO) 160.7, 159.6, 158.0, 147.2, 139.8, 138.9, 21.7. MS: accurate mass, found 177.0650; *m/z* (EI) 177 (100, M$^+$). $C_7H_7N_5O$ requires M$^+$ = 177.0651.

8-Imino-7-(4-methoxyphenyl)-2-methyl-7,8-dihydropyrimido[5,4-d]pyrimidin-4(3H)-one (**11a**): Pyrimidopyrimidine **9a** (0.25 g, 0.80 mmol) was refluxed in a mixture of ethanol (15 ml) and 1N HCl (4 ml) for 4 h. Neutralisation of the reaction mixture resulted in the precipitation of a pale green precipitate. This was filtered and washed with cold water and dried to furnish **11a** (0.19 g, 0.68 mmol, 84%), m.p. >250 °C. IR (KBr): ν_{max} 3362, 1688, 1569, 1243, 1034, 830 cm^{-1}. NMR: δ_H (400 MHz, d_6-DMSO) 2.51 (s, 3H, CH_3), 3.76 (s, 3H, OCH_3), 6.94 (d, *J* 6.8, 2H, ArH), 7.77 (m, 2H, ArH), 8.46 (s, 1H, CH), 9.42 (s, 1H, NH), 12.6 (brs, 1H, NH); δ_C (100 MHz, d_6-DMSO) 160.9, 157.5, 156.7, 156.4, 155.2, 139.7, 132.7, 132.4, 124.3, 114.6, 56.2, 22.4. MS: accurate mass, found 283.1013; *m/z* (EI) 283 (100, M$^+$). $C_{14}H_{13}N_5O_2$ requires: 283.1019; M$^+$ = 283.1019.

7-(4-Fluorophenyl)-8-imino-2-methyl-7,8-dihydropyrimido[5,4-d]pyrimidin-4(3H)-one (**11b**): Pyrimidopyrimidine **9b** (0.25 g, 0.84 mmol) was refluxed in a mixture of ethanol (15 ml) and 1N HCl (4 ml) for three hours. Neutralisation of the reaction mixture furnished a pale yellow precipitate. Washing with cold water followed by drying

afforded **11b** (0.13 g, 0.50 mmol, 57%), m.p. >300 °C. IR (KBr): ν_{max} 3356, 2889, 1694, 1568, 1533, 1421, 1212, 836 cm^{-1}. NMR: δ_H (400 MHz, d_6-DMSO) 2.43 (s, 3H, CH_3), 7.19 (t, $^3J_{H,H}$ = $^3J_{F,H}$ 8.9 Hz, 2H, ArH), 7.90 (dd, $^3J_{H,H}$ = 8.9, $^4J_{F,H}$ = 5 Hz, 2H, ArH), 8.52 (s, 1H, CH), 9.62 (s, 1H, NH, exchanged with D_2O), 12.7 (brs, 1H, NH); δ_C (100 MHz, d_6-DMSO) 160.9, 160.6 (d, $^1J_{F-C}$ = 239 Hz), 157.5, 156.6, 155.0, 139.9, 135.9 (d, $^4J_{F-C}$ = 2.5 Hz), 132.8, 124.6 (d, $^3J_{F-C}$ = 7.8 Hz), 116.2 (d, $^2J_{F-C}$ = 22.2 Hz), 22.4. MS: *m/z* (EI) 271 (90, M^+), 270, [100, $(M-1)^+$]. Found: C, 57.6; H, 3.8; N, 25.5, $C_{13}H_{10}FN_5O$ requires C, 57.6; H, 3.7; N, 25.8 %.

5-Amino-6-(4-chlorobutoxy)-2-methyl-4-pyrimidinecarbonitrile (**12**) *and 5-amino-2-methyl-6-oxo-1,6-dihydro-4-pyrimidinecarbonitrile* (**13**): (2-Acetamido-1,2-dicyanovinyl)ammonium chloride **4** (1.0 g, 5.36 mmol) was refluxed with THF (15 ml). The reaction was monitored by TLC (3 : 1 EtOAc: hexane). After 3 h, the TLC indicated the presence of a new product, R_f = 0.95. Heating was continued for another 24 h, when the TLC showed that all the starting material had disappeared, with the appearance of a second product, R_f = 0.90. The solvent was removed and the dark residue was chromatographed (3 : 1, EtOAc : hexane). A brownish-orange oil containing both compounds was collected, and to this a mixture of petroleum ether and chloroform was added. The whole mixture was allowed to stand overnight, during which an oily precipitate was formed. Careful addition of minimum amount of dichloromethane dissolved the orange oil **12** (0.47 g, 1.95 mmol, 36%) leaving a yellow precipitate **13** (0.12 g, 0.80 mmol, 15%).

6-(4-Chlorobutoxy) compound (**12**): IR (KBr): ν_{max} 3460, 3353, 2922, 2226, 1626, 1560, 1491, 1272, 1046, 800 cm^{-1}. NMR: δ_H (400 MHz, $CDCl_3$) 1.94 (m, 4H, $2CH_2$), 2.49 (s, 3H, CH_3), 3.62 (t, *J* = 6.2, 2H, CH_2Cl), 4.4 (m, 4H, NH_2 and OCH_2); δ_C (100 MHz, $CDCl_3$) 158.5, 156.6, 132.4, 118.0, 115.3, 66.6, 44.8, 29.4, 26.3, 25.1. MS: accurate mass, found: 240.0772, *m/z* EI/CI 241 [100, $(M+1)^+$]. $C_{10}H_{13}ClN_4O$ requires M^+ 240.0772; M = 240.

6-Oxo compound (**13**): M.p. 255 °C IR (KBr): ν_{max} 3432, 3327, 2877, 2214, 1686, 1611, 1437, 1303, 1011, 800 cm^{-1}. NMR: δ_H (400 MHz, d_6-DMSO) 2.1 (s, 3H, CH_3), 6.3 (s, 2H, NH_2), 12.5 (s, 1H, NH); δ_C (100 MHz, d_6-DMSO) 158.2, 145.9, 141.1, 117.9, 105.5, 21.2. MS: accurate mass, found: 150.0535, *m/z* EI/CI 151, [100, $M+1)^+$]. $C_6H_6N_4O$ requires M^+ 150.0536; M = 150.

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14 Crystal data for **9e** (ref. CCDC 265721) can be obtained on request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EW, UK.