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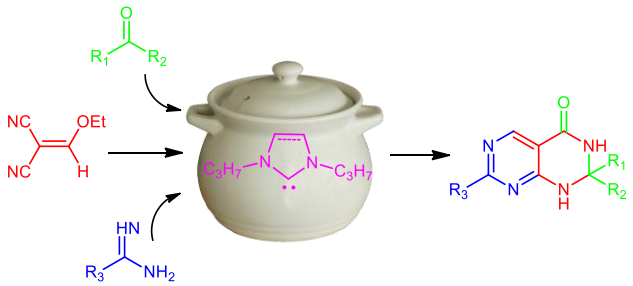

An efficient *N*-heterocyclic carbene-assisted one-pot reaction synthesis of 2,3-dihydropyrimido[4,5-*d*] pyrimidin-4(1*H*)-ones from 2-(ethoxymethylene)malononitrile, guanidines (or amidines) and ketones (or aldehyde) has been developed. The novel method provides a highly efficient synthesis of pyrimido[4,5-*d*]pyrimidine ring from materials with no heterocyclic structures. This one-pot reaction avoids complicated reagents and multiple steps.

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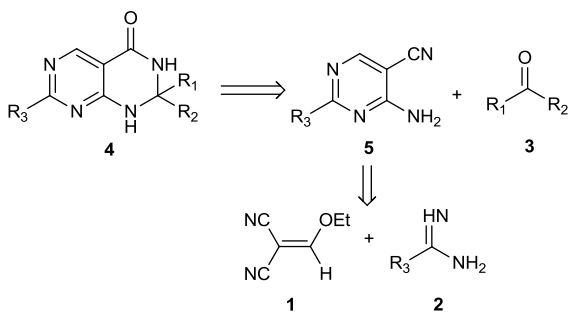
An efficient *N*-heterocyclic carbene-assisted one-pot reaction for the synthesis of 2,3-dihydropyrimido[4,5-*d*]pyrimidin-4(1*H*)-ones from 2-(ethoxymethylene)malononitrile, guanidines (or amidines) and ketones (or aldehyde) has been developed. This highly efficient method includes a series of conversions such as Michael addition, cyclisation, isomerization, aromatization, then nucleophilic attack and Dimroth rearrange. And it avoids complicated reagents and multiple steps.

Introduction

Pyrimidine and fused cyclic compounds are widely present in many natural and biologically active compounds.[1] As a subtype, pyrimidopyrimidinones possess a wide range of biological activities such as anti-inflammatory,[1] antitumor,[2] inhibitors of dihydrofolate reductase,[3] type-II kinase inhibitor,[4] tyrosine kinase inhibitor,[5] and surrogate for both T and A in duplex DNA.[6] The traditional approaches relay on multiple steps reactions,[6a, 7] such as the condensation of aldehyde and acid anhydride with 4-aminopyrimidine-5-carboxamides, which are always hydrolyzed from the corresponding *o*-aminonitriles,[8] or with the 5-aminopyrimidine-4-carbonitriles,[9] the cyclization of ethyl 5-aminopyrimidine-4-carboxylates with acrylamides,[10] the treatment of 6-aminouracil/6-amino-5,6-dihydropyrimidin-4(3*H*)-one with phosphorus oxychloride in DMF under the Vilsmeier reaction conditions.[6, 3] However, they usually suffer from drawbacks such as multistep sequences,[11] complicated reagents,[12] longer reaction time and lower yields.[3, 13]

One-pot reaction improves the efficiency of reaction. It saves time and resources, and avoids the lengthy separation and purification process of intermediate compounds.[14] *N*-heterocyclic carbenes (NHCs) as the small organic molecular catalysts have been used widely as powerful tool for the construction of complex compounds.[15] NHCs can catalyze the Benzoin condensation,[16] Stetter reaction,[17] transesterification/acylation reactions,[19c, 18] nucleophilic substitution reaction,[19] and domino reaction.[20] In our previous studies, NHC-PPIm was easily prepared *via* concentration of a 1,3-dipropylimidazolium hydroxide aqueous solution and excellent catalytic activity was found in the cyclocondensation of cyclohexanone and 2-aminobenzonitrile.[21] Inspired by this good result, especially taking into account both the synthesis of dihydropyrimidinone through PDF conversion[22] and the synthesis of 4-amino-5-cyanopyrimidine in the catalyst of base,[23] we designed a novel one-pot NHC-PPIm assisted three component heterocyclization of 2-(ethoxymethylene)malononitrile, guanidines and ketones for the synthesis of dihydropyrimido[4,5-*d*]pyrimidin-4(1*H*)-one (Scheme **1**). To the best of our knowledge, this is a first convenient method for the construction of pyrimido[4,5-*d*]pyrimidin-4(1*H*)-one core by NHC-PPIm assisted three components cyclization, and this one-pot approach is mild, inexpensive, energy efficient and avoids transition metal catalyst.

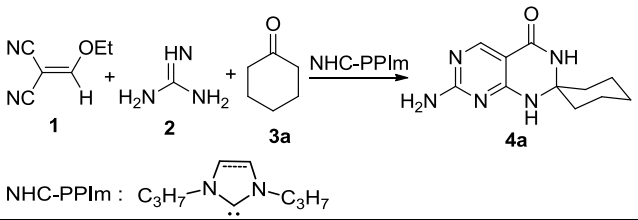


Scheme 1. The retrosynthetic design of reaction.

Results and discussion

To find the appropriate reaction conditions, we chose the reaction of 2-(ethoxymethylene)malononitrile (1.2 mmol), guanidine (1 mmol) and cyclohexanone as the model. Different reaction conditions were evaluated, and the results were summarized in Table 1. It is shown that inorganic bases and organic weak bases didn't promote this reaction (Table 1, entries 1-4). However, organic strong base could promote it easily (Table 1, entries 5-7). NHC-PPIm could promote this reaction under mild conditions, and the yield is higher in ethanol (Table 1, entries 8-11). Although higher temperature improved the reaction, NHC-PPIm was unstable at this case, so the appropriate temperature was 40°C (Table 1, entries 12-14). The amount of NHC-PPIm has a little effect on the reaction when it is more than 0.4 equivalent. So 0.4 equivalent amount of NHC-PPIm was an appropriate choice (Table 1, entries 15-18).

Table 1. Optimization of reaction conditions[a]

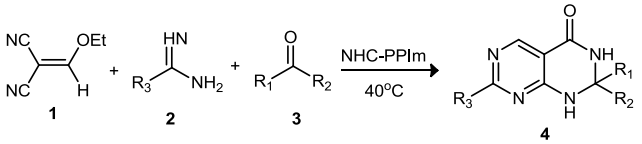


NHC-PPIm :

Entry	Solvent	NHC-PPIm (eqiv)	Time (h)	Temp (^oC)	Yield (%)[b]
1	EtOH	NaOH(1.0)	7	reflux	trace
2	EtOH	Na_2CO_3(1.0)	7	reflux	0
3	EtOH	DBU(1.0)	7	reflux	0
4	EtOH	pyridine(1.0)	7	reflux	0
5	EtOH	NaOMe(1.0)	7	reflux	79
6	EtOH	NaOEt(1.0)	7	reflux	80
7	EtOH	KOBu-*t*(1.0)	7	reflux	70
8	EtOH	NHC-PPIm(1.0)	2	25	75
9	PhMe	NHC-PPIm(1.0)	2	25	60
10	$(CH_2)_5CO$	NHC-PPIm(1.0)	2	25	72
11	H_2O	NHC-PPIm(1.0)	2	40	72
12	EtOH	NHC-PPIm(1.0)	2	40	84
13	EtOH	NHC-PPIm(1.0)	2	60	70
14	EtOH	NHC-PPIm(1.0)	2	80	49
15	EtOH	NHC-PPIm(0)	2	40	0
16	EtOH	NHC-PPIm(0.2)	2	40	42
17	EtOH	NHC-PPIm(0.4)	2	40	85
18	EtOH	NHC-PPIm(0.8)	2	40	84

[a] Reactions conditions: **1** (1.2 mmol), **2** (1 mmol), **3a** (1.2 mmol) and catalyst in solvent (10ml). [b] Isolated yields.

Table 2. NHC-PPIm-assisted three-component one-pot synthesis of 2,3-dihydropyrimido[4,5-*d*]pyrimidin-4(1*H*)-ones[a]

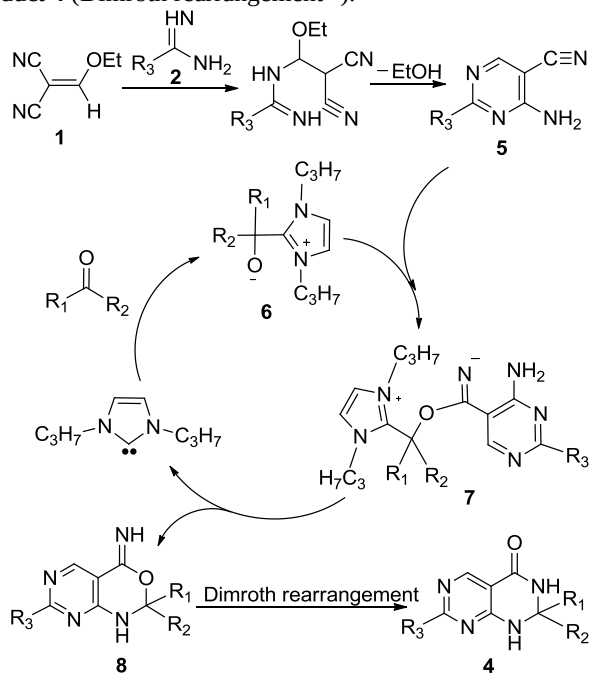


Entry	R_1	R_2	R_3	Time (h)	Product	Yield (%)[b]
1	R_1+R_2=$(CH_2)_5$		NH_2	2	**4a**	85
2	R_1+R_2=$(CH_2)_6$		NH_2	3	**4b**	81
3	CH_3	CH_3	NH_2	3	**4c**	88
4	CH_3	CH_3CH_2	NH_2	5	**4d**	87
5	CH_3	$CH_3CH_2CH_2$	NH_2	4	**4e**	92
6	CH_3CH_2	CH_3CH_2	NH_2	5	**4f**	90
7	CH_3	$(CH_3)_2CH$	NH_2	6	**4g**	82
8	CH_3	Ph	NH_2	4.5	**4h**	78
9	H	Ph	NH_2	5	**4i**	75
10	R_1+R_2=$(CH_2)_5$		$(CH_3)_2N$	2.5	**4j**	82
11	CH_3	CH_3	$(CH_3)_2N$	3	**4k**	86
12	CH_3	CH_3CH_2	$(CH_3)_2N$	6	**4l**	85
13	CH_3	$CH_3CH_2CH_2$	$(CH_3)_2N$	5	**4m**	86
14	CH_3	$(CH_3)_2CH$	$(CH_3)_2N$	5.5	**4n**	79
15	R_1+R_2=$(CH_2)_5$		PhNH	2	**4o**	91
16	R_1+R_2=$(CH_2)_6$		CH_3NH	4	**4p**	81
17	R_1+R_2=$(CH_2)_5$		C_2H_5NH	4	**4q**	86
18	CH_3	CH_3	Ph	4.5	**4r**	81
19	CH_3	CH_3	CH_3	6	**4s**	75

[a] Reactions conditions: **1** (1.2 mmol), **2** (1 mmol), **3a** (1.2 mmol) and NHC-PPIm (0.4 mmol) in ethanol (10ml). [b] Isolated yields.

With the optimal conditions in hand, a series of ketones (or benzaldehyde) and guanidines (or amidines) were investigated, and the results were summarized in Table 2. Theoretically, different carbonyl compounds had effect on this reaction because of the steric hindrance and ring tension, but all carbonyl compounds reacted with guanidine were in good yields (Table 2, entries 1-9), and partically the *N*,*N*-dimethylguanidine also gave the corresponding compounds in good yields (Table 2, entries 10-14). To expand the scope of this one-pot reaction methodology, a set of guanidines and amidines were selected and the corresponding compounds were obtained in good to excellent yields (Table 2, entries 15-19). These results illustrated the universality of NHC-PPIm and the advantages of one-pot method.

To rationalize the above results, a possible reaction mechaism is envisioned as depicted in Scheme 2. It is proposed that the 2-(ethoxymethylene)malononitrile undergoes a Michael addition reaction with guanidines (or amidines), then followed by cyclisation, isomerization and aromatization to afford intermediate 4-aminopyrimidine-5-carbonitrile **5**. The Breslow intermediate **6** nucleophilic attacks the cyano of the **5** to provide **7**. Then **7** releases NHC-PPIm and 3,1-oxazine **8** is formed, which subsequently rearranges to afford the final product **4** (Dimroth rearrangement[24]).



Scheme 2. The possible mechanism of the formation of **4**

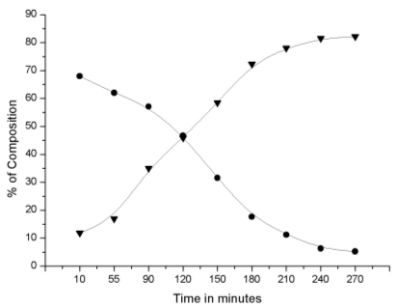


Figure 1. Percentage of intermediate and product: (●)**5j**, (▼)**4j**

In order to prove this mechanism, we tried to seperate the intermediate **5j**, and fortunately, 4-amino-2-dimethylamino-pyrimidine-5-carbonitrile (**5j**) was detected by LC after 10 minutes. As the reaction proceeded, the final product **4j** increased and the intermediate **5j** decreasd (Figure 1). the product **4j** was also obtained by the condensation of the

seperated intermediate **5j** with cyclohexanone in the same conditions in 83% yield.

All products were characterized by IR, ^{1}H NMR, ^{13}C NMR, ESI spectra, and elemental analysis. And the structure **4b** was undoubtedly confirmed by X-ray crystallographic analysis (Figure 2).[25]

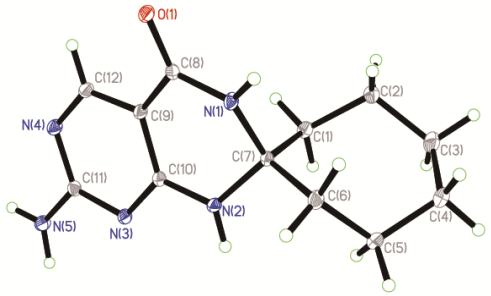


Figure 2. ORTEP representation of **4b**

Conclusions

In summary, an efficient method for combining two fairly well-known reactions into one-pot reaction and synthesizing 2,3-dihydropyrimido[4,5-*d*]pyrimidin4(1*H*)-ones was developed. It is a highly efficient method for synthesizing pyrimido[4,5-*d*]pyrimidine ring without starting from any nitrogen-containing heterocyclic compound. The reaction conducted under mild conditions and the most products deposited from the solvent when the reaction completed.

Experimental Section

General Methods: The starting materials including 2-(ethoxymethylene)malononitrile (**1**), guanidines/amidines (**2**) and ketones (**3**) are commercially available. Melting points were determined using XT4 microscope melting point apparatus (uncorrected). Infrared (IR) spectra were recorded on a Perkin Elmer FT-IR spectrophotometer with KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded at a Bruker 400 or 500 MHz spectrometer with TMS as the internal standard. Mass spectra were recorded on a ZAB-HS mass spectrometer using ESI ionization. Elemental analyses were performed on an Elementar Vario EL. The percentage of intermediate and product were determined by HPLC using an Shimadzu LC-20AT instrument with Hanbon column YWG C18.

General Procedure for the Synthesis of 4: 2-(Ethoxymethylene)malononitrile (**1**, 1.2 mmol) and guanidine/amidine (**2**, 1 mmol) were mixed in ethanol at room temperature, then ketone (**3**, 1.2 mmol) and NHC-PPIm (0.4 mmol) was added. The mixture was warmed to 40^{o}C. At the end of the reaction (TLC monitoring), the reaction mixture was cooled to room temperature. The solid was filtered and recrystallized from methanol or purified by column chromatography on silica gel (200-300 mesh silica gels) to afford pure **4a**.

4-Amino-2-(dimethylamino)pyrimidine-5-carbonitrile (5j): White solid; m.p. 217-219 ^{o}C; IR (KBr, *v*, cm^{-1}): 3424, 3390, 3336, 3203, 2215, 1661, 1602, 1555, 1529, 1487; ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 8.22 (s, 1H), 5.17 (s, 2H), 3.19 (s, 3H), 3.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 162.6, 161.6, 161.4, 117.6, 77.7, 36.4; ESI-MS (*m/z*) = 164 ([M+H]$^+$).

7'-Amino-1'*H*-spiro[cyclohexane-1,2'-pyrimido[4,5-*d*]pyrimidin]-4'(3'*H*)-one (4a): White solid; m.p. > 300 ^{o}C; IR (KBr, *v*, cm^{-1}): 3315, 3180, 2935, 2851, 1662, 1609, 1472, 1446, 1421; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 8.18 (s, 1H), 7.79 (s, 1H), 7.73 (s, 1H), 6.64 (s, 2H), 1.66-1.64 (m, 5H), 1.60-1.55 (m, 5H); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 164.7, 162.2, 161.1, 156.7, 97.6, 67.7, 38.1, 24.5, 20.7; ESI-MS (*m/z*) = 232 ([M-H]$^-$). Anal. Calcd. for $C_{11}H_{15}N_5O$: C, 56.64; H, 6.48; N, 30.02%. Found: C, 56.44; H, 6.58; N, 30.07%.

7'-Amino-1'*H*-spiro[cycloheptane-1,2'-pyrimido[4,5-*d*]pyrimidin]-4'(3'*H*)-one (4b): Light yellow solid; m.p. > 300 ^{o}C; IR (KBr, *v*, cm^{-1}): 3413, 3339, 3173, 2933, 2845, 1659, 1624, 1600, 1473, 1408; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 8.17 (s, 1H), 7.89 (s, 1H), 7.88 (s,1H), 6.61 (s, 2H), 1.87-1.84 (m, 4H), 1.4 (s, 8H); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 164.7, 162.0, 161.0, 156.7, 97.4, 71.8, 42.0, 29.4, 20.7; ESI-MS (*m/z*) = 248 ([M+H]$^+$); Anal. Calcd. for $C_{12}H_{17}N_5O$: C, 58.28; H, 6.93; N, 28.32%. Found: C, 58.14; H, 6.76; N, 28.62%.

7-Amino-2,2-dimethyl-2,3-dihydropyrimido[4,5-*d*]pyrimidin-4(1*H*)-one (4c): Yellow solid; m.p. > 300 ^{o}C; IR (KBr, *v*, cm^{-1}): 3464, 3229, 3148, 2943, 1663, 1615, 1482, 1455, 1418; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 8.18 (s, 1H), 7.77 (s, 1H), 7.75 (s, 1H), 6.68 (s, 2H), 1.37 (s, 6H);^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 164.9, 162.0, 161.0, 156.8, 97.2, 66.7, 29.9; ESI-MS (*m/z*) = 216 ([M+Na]$^+$); Anal. Calcd. for $C_8H_{11}N_5O$: C, 49.73; H, 5.74; N, 36.25%. Found: C, 49.55; H, 5.70; N, 36.36%.

7-Amino-2-ethyl-2-methyl-2,3-dihydropyrimido[4,5-*d*]pyrimidin-4(1*H*)-one (4d): Yellow solid; m.p. > 300 ^{o}C; IR (KBr, *v*, cm^{-1}): 3228, 2969, 1648, 1611, 1447; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 8.14 (s, 1H), 7.67 (s, 2H), 6.60 (s, 2H), 1.62-1.59 (m, 2H), 1.33 (s, 3H), 0.81 (t, *J* = 6.8 Hz 3H,); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 164.7, 162.0, 161.3, 156.4, 96.9, 69.2, 34.6, 29.0, 7.9; ESI-MS (*m/z*) = 206 ([M-H]$^-$); Anal. Calcd. for $C_9H_{13}N_5O$: C, 52.16; H, 6.32; N, 33.79%. Found: C, 52.22; H, 6.52; N, 33.66%.

7-Amino-2-methyl-2-propyl-2,3-dihydropyrimido[4,5-*d*]pyrimidin-4(1*H*)-one (4e): White solid; m.p. > 300 ^{o}C; IR (KBr, *v*, cm^{-1}): 3336, 3225, 3142, 2962, 1678, 1608, 1574, 1474, 1415; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 8.13 (s, 1H), 7.69 (s, 2H), 6.62 (s, 2H), 1.60-1.55 (m, 2H), 1.33 (s, 3H), 1.28 (t, *J* = 8 Hz, 2H), 0.83 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 164.7, 162.0, 161.0, 156.4, 97.0, 68.9, 44.5, 29.2, 16.4, 13.9; ESI-MS (*m/z*) = 220 ([M-H]$^-$); Anal. Calcd. for $C_{10}H_{15}N_5O$: C, 54.28; H, 6.83; N, 31.65%. Found: C, 54.38; H, 6.78; N, 31.58%.

7-Amino-2,2-diethyl-2,3-dihydropyrimido[4,5-*d*]pyrimidin-4(1*H*)-one (4f): White solid; m.p. > 300 ^{o}C; IR (KBr, *v*, cm^{-1}): 3156, 2970, 2936, 1671, 1600, 1477, 1419; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 8.11 (s, 1H), 7.54 (s, 1H), 7.49 (s,1H), 6.54 (s, 2H), 1.60-1.53 (m, 4H), 0.81 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 164.7, 162.3, 161.5, 156.1, 96.5, 79.2, 72.1, 34.2, 7.5; ESI-MS (*m/z*) = 244 ([M+Na]$^+$); Anal. Calcd. for $C_{10}H_{15}N_5O$: C, 54.28; H, 6.83; N, 31.65%. Found: C, 54.55; H, 6.72; N, 31.59%.

7-Amino-2-isopropyl-2-methyl-2,3-dihydropyrimido[4,5-*d*]pyrimidin-4(1*H*)-one (4g): White solid; m.p. > 300 ^{o}C; IR (KBr, *v*, cm^{-1}): 3416, 3173, 2970, 1657, 1605, 1566, 1482, 1414; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 8.12 (s, 1H), 7.75 (s, 1H), 7.72 (s,1H), 6.58 (s, 2H), 1.77-1.86 (m, 1H), 1.32 (s, 3H), 0.85 (d, *J* = 1.6 Hz, 3H), 0.83 (d, *J* = 2.0 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 164.7, 161.8, 161.0, 156.2, 97.1, 71.3, 38.9, 25.9, 16.6; ESI-MS (*m/z*) = 244 ([M+Na]$^+$); Anal. Calcd. for $C_{10}H_{15}N_5O$: C, 54.28; H, 6.83; N, 31.65%. Found: C, 54.42; H, 6.93; N, 31.50%.

7-Amino-2-methyl-2-phenyl-2,3-dihydropyrimido[4,5-*d*]pyrimidin-4(1*H*)-one (4h): Yellow solid; m.p. > 300 ^{o}C; IR (KBr, *v*, cm^{-1}): 3453, 3329, 1665, 1577, 1444; ^{1}H NMR (400

MHz, DMSO-d_6) (δ, ppm): 8.58 (s, 1H), 8.52 (s, 1H), 8.12 (s,1H), 7.45 (d, J = 7.6 Hz, 2H), 7.33 (t, J = 7.2 Hz, 2H), 7.22 (t, J = 7.8 Hz, 1H), 6.72 (s, 2H), 1.65 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 164.6, 163.0, 161.8, 157.2, 147.6, 128.2, 127.4, 124.7, 98.2, 69.6, 30.1; ESI-MS (m/z) = 254 ([M-H]$^-$); Anal. Calcd. for $C_{13}H_{13}N_5O$: C, 61.17; H, 5.13; N, 27.43%. Found: C, 61.34; H, 5.33; N, 27.16%.

7-Amino-2-phenyl-2,3-dihydropyrimido[4,5-*d*]pyrimidin 4(1*H*)-one (4i): White solid; m.p. > 300^{o}C; IR (KBr, v, cm^{-1}): 3464, 3299, 3090, 2938, 1673, 1643, 1606, 1565, 1475, 1420; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 8.21 (s, 1H), 8.20 (s, 1H), 8.16 (s, 1H), 7.39-7.38 (m, 4H), 7.33 (q, J = 4.4 Hz, 1H), 6.78 (s, 2H), 5.73 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 164.7, 162.2, 161.5, 156.9, 142.5, 128.4, 128.3, 126.0, 98.0, 64.9; ESI-MS (m/z) = 264 ([M+Na]$^+$); Anal. Calcd. for $C_{12}H_{11}N_5O$: C, 59.74; H, 4.60; N, 29.03%. Found: C, 59.62; H, 4.33; N, 29.23%.

7'-(Dimethylamino)-1'*H*-spiro[cyclohexane-1,2'-pyrimido [4,5-*d*]pyrimidin]-4'(3'*H*)-one (4j): White solid; m.p. > 300 ^{o}C; IR (KBr, v, cm^{-1}): 3170, 3055, 2930, 2860, 1647, 1606, 1547, 1503, 1448; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 8.25 (s, 1H), 7.85 (s, 1H), 7.80 (s, 1H), 3.00 (s, 6H), 1.68-1.57 (m, 8H), 1.34-1.25 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 163.6, 163.1, 161.4, 156.7, 97.5, 66.6, 38.7, 37.4, 25.3, 21.3; ESI-MS (m/z) = 262 ([M+H]$^+$); Anal. Calcd. For $C_{13}H_{19}N_5O$: C, 59.75; H, 7.33; N, 26.80%. Found: C, 59.81; H, 7.30; N, 26.68%.

7-(Dimethylamino)-2,2-dimethyl-2,3-dihydropyrimido[4,5-*d*] pyrimidin-4(1*H*)-one (4k): Light yellow solid; m.p. > 300 ^{o}C; IR (KBr, v, cm^{-1}): 3251, 3139, 2973, 1737, 1633, 1607, 1575, 1440; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 8.27 (s, 1H), 7.90 (s, 1H), 7.84 (s, 1H), 3.10 (s, 6H), 1.39(s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 162.9, 162.1, 160.5, 156.1, 96.4, 66.7, 36.6, 29.8; ESI-MS (m/z) = 222 ([M+H]$^+$); Anal. Calcd. For $C_{10}H_{15}N_5O$: C, 54.28; H, 6.83; N, 31.65%. Found: C, 54.41; H, 6.81; N, 31.58%.

7-(Dimethylamino)-2-ethyl-2-methyl-2,3-dihydropyrimido [4,5-*d*]pyrimidin-4(1*H*)-one (4l): White solid; m.p. 257-259 ^{o}C; IR (KBr, v, cm^{-1}): 3207, 2979, 2924, 1635, 1608, 1583, 1542, 1517, 1459; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 8.26 (s, 1H), 7.78 (s, 1H), 7.72 (s, 1H), 3.10 (s, 6H), 1.67-1.62 (m, 2H), 1.36 (s, 3H), 0.83 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 162.9, 162.3, 160.7, 155.8, 96.1, 69.3, 36.6, 34.9, 29.2, 7.9; ESI-MS (m/z) = 236 ([M+H]$^+$); Anal. Calcd. For $C_{11}H_{17}N_5O$: C, 56.15; H, 7.28; N, 29.77%. Found: C, 55.99; H, 7.32; N, 29.81%.

7-(Dimethylamino)-2-methyl-2-propyl-2,3-dihydropyrimido [4,5-*d*]pyrimidin-4(1*H*)-one (4m): White solid; m.p. 252-254 ^{o}C; IR (KBr, v, cm^{-1}): 3202, 2958, 2934, 2873, 1638, 1608, 1583, 1542, 1519, 1459; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 8.24 (s, 1H), 7.79 (s, 1H), 7.72 (s, 1H), 3.10 (s, 6H), 1.63-1.57 (m, 2H), 1.35 (s, 3H), 1.32-1.28 (m, 2H), 0.84 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 162.9, 162.1, 160.6, 155.7, 96.1, 69.0, 44.6, 36.6, 29.4, 16.5, 13.9; ESI-MS (m/z) = 250 ([M+H]$^+$); Anal. Calcd. For $C_{12}H_{19}N_5O$: C, 57.81; H, 7.68; N, 28.09%. Found: C, 57.75; H, 7.72; N, 28.21%.

7-(Dimethylamino)-2-isopropyl-2-methyl-2,3-dihydropyri-mido[4,5-*d*]pyrimidin-4(1*H*)-one (4n): Light yellow solid; m.p. 279-281 ^{o}C; IR (KBr, v, cm^{-1}): 3242, 3180, 2967, 2935, 1641, 1606, 1577, 1541, 1515, 1449, 1389; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 8.23 (s, 1H), 7.83 (s, 1H), 7.75 (s, 1H), 3.10 (s, 6H), 1.89-1.82 (m, 1H), 1.35 (s, 3H), 0.86 (d, J = 6 Hz, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 162.9, 162.0, 160.5, 155.6, 96.3, 71.5, 36.6, 26.1, 16.6; ESI-MS (m/z) = 250 ([M+H]$^+$); Anal. Calcd. For $C_{12}H_{19}N_5O$: C, 57.81; H, 7.68; N, 28.09%. Found: C, 57.61; H, 7.75; N, 28.18%.

7'-(Phenylamino)-1'*H*-spiro[cyclohexane-1,2'-pyrimido[4,5-*d*]pyrimidin]-4'(3'*H*)-one (4o): White solid; m.p. 292-294 ^{o}C; IR (KBr, v, cm^{-1}): 3200, 2923, 1647, 1594, 1574, 1531, 1498, 1443; ^{1}H NMR (500 MHz, DMSO-d_6) (δ, ppm): 9.53 (s, 1H), 8.35 (s, 1H), 8.02 (s, 1H), 7.99(s, 1H), 7.81 (d, J = 7.5 Hz, 2H), 7.28 (t, J = 7.5 Hz, 2H), 6.97 (t, J = 8.5 Hz, 1H), 1.75-1.61 (m, 8H), 1.39-1.29 (m, 2H); ^{13}C NMR (500 MHz, DMSO-d_6) (δ, ppm): 162.5, 161.9, 161.2, 156.7, 140.7, 128.9, 122.1, 120.0, 99.2, 66.6, 38.6, 24.9, 21.0; ESI-MS (m/z) = 310 ([M+H]$^+$); Anal. Calcd. For $C_{17}H_{19}N_5O$: C,66.00; H, 6.19; N, 22.64%. Found: C, 66.11; H, 6.17; N, 22.58%.

7'-(Methylamino)-1'*H*-spiro[cycloheptane-1,2'-pyrimido [4,5-*d*]pyrimidin]-4'(3'*H*)-one (4p): Yellow solid; m.p. > 300 ^{o}C; IR (KBr, v, cm^{-1}): 3253, 2929, 1655, 1595, 1530, 1461, 1380; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 8.17 (s, 1H), 8.00 (s, 1H), 7.84 (s, 1H), 7.18 (s, 1H), 2.78 (s, 3H), 1.88-1.82 (m, 4H), 1.50 (s, 8H); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 164.6, 162.6, 161.2, 156.7, 96.9, 72.3, 31.2, 30.0, 28.5, 21.3; ESI-MS (m/z) = 262 ([M+H]$^+$); Anal. Calcd. For $C_{13}H_{19}N_5O$: C, 59.75; H, 7.33; N, 26.80%. Found: C, 59.88; H, 7.31; N, 26.74%.

7'-(Ethylamino)-1'*H*-spiro[cyclohexane-1,2'-pyrimido[4,5-*d*]pyrimidin]-4'(3'*H*)-one (4q): White solid; m.p. > 300 ^{o}C; IR (KBr, v, cm^{-1}): 3195, 2935, 1633, 1587, 1517, 1454, 1432, 1389; ^{1}H NMR (500 MHz, DMSO-d_6) (δ, ppm): 8.18 (s, 1H), 7.81 (s, 1H), 7.76 (s, 1H), 7.26 (s, 1H), 3.26 (m, 2H), 1.67-1.58 (m, 8H), 1.36-1.24 (m, 2H), 1.09 (t, J = 5.4 Hz, 3H); ^{13}C NMR (500 MHz, DMSO-d_6) (δ, ppm): 164.0, 162.3, 161.3, 157.0, 97.2, 68.0, 38.6, 35.8, 25.1, 21.1, 15.3; ESI-MS (m/z) = 262 ([M+H]$^+$); Anal. Calcd. For $C_{13}H_{19}N_5O$: C, 59.75; H, 7.33; N, 26.80%. Found: C, 59.68; H, 7.32; N, 26.84%.

2,2-Dimethyl-7-phenyl-2,3-dihydropyrimido[4,5-*d*]pyrimi-din-4(1*H*)-one (4r): White solid; m.p. 282-284 ^{o}C; IR (KBr, v, cm^{-1}): 3234, 3061, 2960, 1674, 1611, 1592, 1448, 1440; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 8.65 (s, 1H), 8.61 (s, 1H), 8.34 (s, 1H), 8.32 (d, J = 2 Hz, 2H), 7.52-7.50 (m, 3H), 1.48 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 166.9, 160.9, 160.3, 154.9, 137.1, 131.1, 128.5, 128.0, 104.2, 67.2, 30.1; ESI-MS (m/z) = 255 ([M+H]$^+$); Anal. Calcd. For $C_{14}H_{14}N_4O$: C, 66.13; H, 5.55; N, 22.03%. Found: C, 66.27; H, 5.53; N, 21.98%.

2,2,7-Trimethyl-2,3-dihydropyrimido[4,5-*d*]pyrimidin-4(1*H*)-one (4s): White solid; m.p. > 300 ^{o}C; IR (KBr, v, cm^{-1}): 3190, 3050, 2923, 1684, 1613, 1555, 1424; ^{1}H NMR (400 MHz, DMSO-d_6) (δ, ppm): 8.43 (s, 1H), 8.42 (s, 1H), 8.27 (s, 1H), 2.37 (s, 3H), 1.41 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 170.6, 161.0, 159.9, 154.4, 103.3, 67.0, 30.0, 25.8; ESI-MS (m/z) = 193 ([M+H]$^+$); Anal. Calcd. For $C_9H_{12}N_4O$: C, 56.24; H, 6.29; N, 29.15%. Found: C, 56.12; H, 6.31; N, 29.21%.

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Notes and references

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† Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.
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25 Full details have been deposited the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-896461. Copies of the datacan be obtained, free of charge, on application to CCDC, 12 Union Road, CambridgeCB2 1EZ, UK (fax: +44(0)-1223336033 or e-mail: deposit@ccdc.cam.ac.uk).