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A novel and efficient synthesis of pyrimido[4,5-*d*]pyrimidine-2,4,7-trione and pyrido[2,3-*d*:6,5-*d*] dipyrimidine-2,4,6,8-tetrone derivatives

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Abstract—An efficient and direct procedure for the synthesis of pyrimido[4,5-*d*]pyrimidine-2,4,7-trione derivatives has been described under microwave-assisted conditions. Reaction of 6-amino-1,3-dimethyluracil with aromatic aldehydes resulted in the formation of pyrido-[2,3-*d*:6,5-*d*] dipyrimidine-2,4,6,8-tetrone derivatives.

1. Introduction

Pyrimidopyrimidines are annelated uracils that have attracted considerable interest in recent years. Their derivatives have been known to display a wide range of pharmacological activities, and their potent inhibitory properties regarding the tyrosine kinase domain of epidermal growth factor receptor,[1] 5-phosphoribosyl-1-pyrophosphate synthetase[2] and dihydrofolate reductase[3] have been fully demonstrated. Numerous reports delineate the antitumour,[4] antiviral,[5] antioxidant,[6] antifungal[7] and hepatoprotective[8] activities of these compounds. Therefore, for the preparation of these complex molecules large efforts have been directed towards the synthetic manipulation of uracils. As a result, a number of reports have appeared in the literature that usually describe forcing conditions, long reaction times and complex synthetic pathways.[9] Thus new routes for the synthesis of these molecules have attracted considerable attention allowing for a rapid entry to these heterocycles.

Multi-component reactions (MCRs) are economically and environmentally very advantageous because multi-step syntheses produce considerable amounts of waste mainly due to complex isolation procedures often involving expensive, toxic and hazardous solvents after each step. MCRs are perfectly suited for combinatorial library synthesis, and thus are finding increasing use in the discovery process for new drugs and agrochemicals.[10]

Microwave-assisted organic synthesis is an increasingly popular field as indicated by numerous publications in the past few years owing to several advantages, such as enhanced reaction rates and increase in yields under milder conditions.[11] The combination of solvent-free reaction conditions and microwave irradiation leads to large reduction in reaction times, enhancement in conversion and sometimes in selectivity with several advantages of the eco-friendly approach, termed green chemistry.[12]

Considering the above reports in conjunction with our previous work on microwave-assisted synthesis of heterocyclic compounds,[13] and pursuing our studies on multi-component reactions,[14] we wish to report a novel, efficient, one-pot and three-component method for the preparation of 5,6-dihydro-1,3-dimethyl-5-aryl pyrimido[4,5-*d*]pyrimidine-2,4,7(1*H*,3*H*,8*H*)-trione derivatives under microwave-assisted conditions. To the best of our knowledge, this paper is the first report on the synthesis of some pyrimido[4,5-*d*]-pyrimidine-2,4,7-triones with this particular regioisomeric arrangement. Of course, some related pyrimidopyrimidines with the mentioned properties have been reported.[15]

2. Results and discussion

After some preliminary experimentation, it was found that a mixture of 6-amino-1,3-dimethyluracil **1**, benzaldehyde **2a** and urea **3** in the presence of a catalytic amount of acetic acid (HOAc) afforded 5,6-dihydro-1,3-dimethyl-5-phenyl pyrimido[4,5-*d*]pyrimidine-2,4,7(1*H*,3*H*,8*H*)-trione **4a** in 87% yield under microwave-assisted conditions for 5 min (Scheme 1).

Keywords: Pyrimido[4,5-*d*]pyrimidine-trione; Microwave; Pyrido[2,3-*d*:6,5-*d*]-dipyrimidine-2,4,6,8-tetrone; Multi-component.
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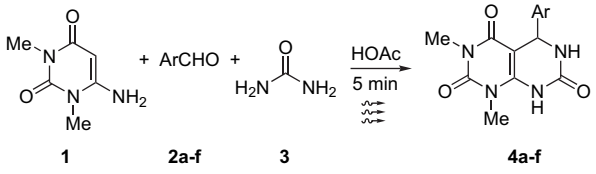


Scheme 1.

In order to find a catalyst effective for the synthesis of the pyrimido[4,5-*d*]pyrimidine-2,4,7-trione derivatives under microwave-assisted conditions, we examined this condensation reaction in the absence and the presence of several catalysts. The best results were obtained when HOAc was used (Table 1).

Table 1. Catalyst effect on the reaction[a]

Entry	Catalyst	Yields[b] (%)
1	CH_3COOH	87
2	CF_3COOH	37
3	4-Me–$C_6H_4SO_3H$	41
4	LiCl	<20
5	$ZnCl_2$	<20
6	$CuCl_2$	<20

[a] A mixture of benzaldehyde (1 mmol), urea (1.5 mmol), 6-amino-1,3-dimethyluracil (1 mmol) and catalyst (0.5 mmol) were exposure for 5 min under MW irradiation.
[b] Isolated yields.

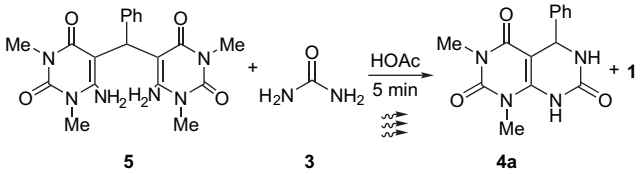
Encouraged by this success, we extended this reaction of 6-amino-1,3-dimethyluracil with a range of other aromatic aldehydes **2b–f** and urea under similar conditions (using HOAc), furnishing the respective pyrimido[4,5-*d*]pyrimidine-2,4,7-triones **4b–f** in high yields. The optimized results are summarized in Table 2. High yields were obtained using aromatic aldehydes carrying electron-donating or electron-withdrawing substituents.

Table 2. Reaction of 6-amino-1,3-dimethyluracil, aldehydes and urea under MW irradiation[a]

Product **4**	Ar	Yield[b] (%)
a	C_6H_5	87
b	4-Me–C_6H_4	86
c	4-OMe–C_6H_4	75
d	4-Cl–C_6H_4	80
e	4-F–C_6H_4	76
f	4-Br–C_6H_4	80

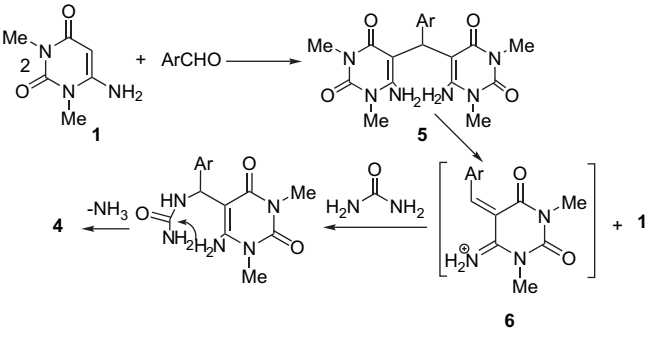
[a] With power of 900 W.
[b] Isolated yields.

For the investigation of the reaction mechanism, it is notable that when 6-amino-1,3-dimethyluracil, benzaldehyde and urea were irradiated for 1 min, the intermediate **5** was formed, which was isolated and characterized by spectroscopic methods. When intermediate **5** was isolated and reacted with urea in the presence of HOAc under microwave irradiation, the mixture of **4a** and 6-amino-1,3-dimethyluracil **1** was obtained. After purification of the reaction mixture product **4a** was obtained in good yields (Scheme 2). Replacement of urea with *N*-methyl urea afforded product **4a** in 89% yield.



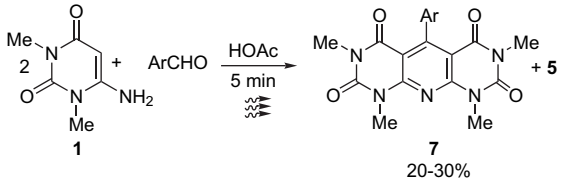
Scheme 2.

According to the results, the reaction can mechanistically be considered to proceed through the intermediate **5** formed in situ by reaction of the aldehyde with 6-amino-1,3-dimethyluracil.[16] Then, the intermediate **5** was converted to iminium cation **6** and the subsequent addition of urea to the iminium cation, followed by cyclization afforded the corresponding 5,6-dihydro-1,3-dimethyl-5-aryl pyrimido[4,5-*d*]pyrimidine-2,4,7(1*H*,3*H*,8*H*)-trione and ammonia (Scheme 3). The elimination of ammonia from urea has been reconfirmed by replacement of urea by *N*-methyl urea resulting in the same product.



Scheme 3.

During our investigation on the synthesis of pyrimido[4,5-*d*]pyrimidine-2,4,7-triones, we found that in the absence of urea, 6-amino-1,3-dimethyluracil and aromatic aldehyde using similar conditions (MW/HOAc) gave 5-aryl-1,3,7,9-tetramethylpyrido[2,3-*d*:6,5-*d*] dipyrimidine-2,4,6,8-tetrone **7** in 20–30% yields (Scheme 4).



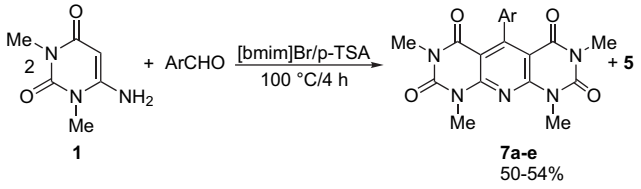
Scheme 4.

To the best of our knowledge, there are no reports in the literature for the formation of pyrido[2,3-*d*:6,5-*d*] dipyrimidine-2,4,6,8-tetrone derivatives via direct condensation of aldehydes with 6-amino-1,3-dimethyluracil. Very few methods are reported in the literature for the preparation of pyrido[2,3-*d*:6,5-*d*] dipyrimidine-2,4,6,8-tetrones.[17] These methods suffer from one or more disadvantages such as low yield, long reaction time, use of toxic solvent, harsh reaction conditions and lack of easy availability/preparation of the starting materials.

Therefore, due to the biological importance of pyridine derivatives and in order to improve the yields of pyrido-[2,3-*d*:6,5-*d*] dipyrimidine-2,4,6,8-tetrone derivatives, we

examined the reaction in different conditions. The best results were obtained in ionic liquid 1-butyl-3-methylimidazolium bromide ([bmim]Br) as solvent at 100 °C catalyzed by *p*-TSA for 4 h. Several aromatic aldehydes carrying either electron-donating or electron-withdrawing substituents reacted and gave the products **7a–e** in good yields (Table 3).

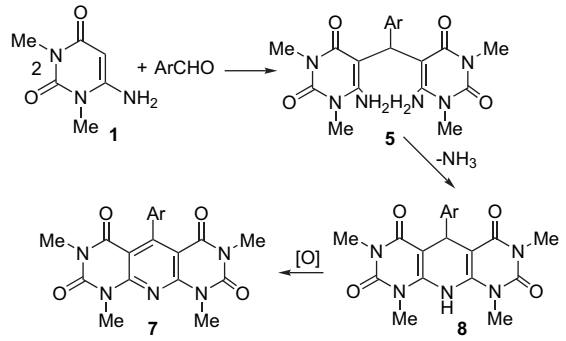
Table 3. Synthesis of pyrido[2,3-*d*:6,5-*d*] dipyrimidine-2,4,6,8-tetrone derivatives



Product **7**	Ar	Yield[a] (%)
a	C_6H_5	54
b	4-Me–C_6H_4	50
c	4-Cl–C_6H_4	52
d	4-Br–C_6H_4	53
e	4-F–C_6H_4	51

[a] Isolated yields.

The reaction can be mechanistically considered to proceed via the initial formation of the intermediate **5**, followed by the loss of a molecule of ammonia from **5** through cyclocondensation to yield intermediate **8**. The product **7** is then formed by facile air oxidation of intermediate **8** (Scheme 5).



Scheme 5.

The structures of the products **4a–f** and **7a–e** were characterized by IR, ^{1}H NMR, ^{13}C NMR and MS spectra. The structures of **4a** and **7d** were confirmed by a single-crystal X-ray analysis[18] (Figs. 1 and 2). The structure of **7d** consists of alternating stacks, linked together by some short contacts.

3. Conclusion

We have described a novel, efficient and one-pot synthesis of pyrimido[4,5-*d*]pyrimidine-2,4,7-trione derivatives via a three-component cyclocondensation reaction of 6-amino-1,3-dimethyluracil, aromatic aldehydes and urea under microwave irradiation. In addition, a novel synthesis of pyrido[2,3-*d*:6,5-*d*] dipyrimidine-2,4,6,8-tetrone derivatives by the condensation reaction of 6-amino-1,3-dimethyluracil and aromatic aldehydes in ionic liquid were introduced.

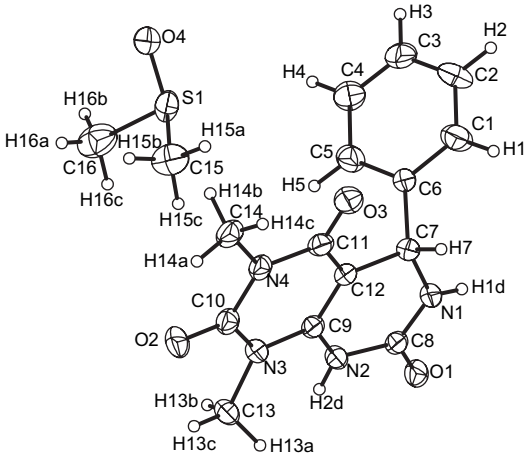


Figure 1. X-ray crystal structure of **4a**.

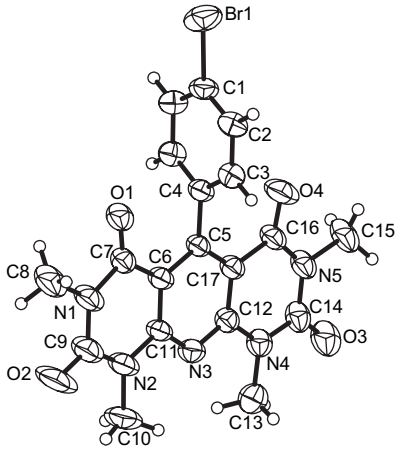


Figure 2. X-ray crystal structure of **7d**.

The novelty and synthetic usefulness of these methodologies were demonstrated by the efficient synthesis of uracil derivatives.

4. Experimental

4.1. General procedure for the preparation of 5,6-dihydro-1,3-dimethyl-5-phenyl pyrimido[4,5-*d*]pyrimidine-2,4,7(1*H*,3*H*,8*H*)-trione 4a under microwave irradiation

A mixture of 6-amino-1,3-dimethyluracil (1 mmol), benzaldehyde (1 mmol), urea (1.5 mmol) and acetic acid (0.5 mmol) in a Pyrex test tube was irradiated for 5 min at atmospheric pressure with a power of 900 W (the microwave oven was a domestic National model NN-6653 with select power levels). After cooling, the reaction mixture was washed with water (15 mL) and then recrystallized from EtOH/H_2O to afford the pure product **4a** as a white powder (87%). Mp 324 °C (dec); IR (KBr) (ν_{max}/cm^{-1}) 3321, 3112, 1687, 1654, 1636; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H 3.09 (3H, s, CH_3), 3.35 (3H, s, CH_3), 5.23 (1H, s, CH), 7.31 (5H, m, arom), 8.09 (1H, s, NH), 9.82 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ_C 27.4, 29.9, 51.6, 85.9, 126.3, 127.4, 128.3, 143.9, 145.3, 150.7, 151.8, 159.4; MS, *m*/*z* (%): 286 (M^+, 25), 242 (23), 209 (100), 152 (74),

82 (57), 51 (49). Anal. Calcd (%) for $C_{14}H_{14}N_4O_3$: C, 58.73; H, 4.93; N, 19.57. Found C, 58.66; H, 4.91; N, 19.61.

4.2. General procedure for the preparation of 5-phenyl-1,3,7,9-tetramethylpyrido[2,3-*d*:6,5-*d*] dipyrimidine-2,4,6,8-tetrone 7a in ionic liquid

A mixture of 6-amino-1,3-dimethyluracil (2 mmol), benzaldehyde (1 mmol), *p*-TSA (0.5 mmol) and ionic liquid [bmim]Br (0.3 g) was stirred at 100 °C in a pre-heated oil bath for 4 h. After cooling, the reaction mixture was washed with water (15 mL) and the solid product was filtered off. Column chromatography on silica gel using EtOAc/hexane (1:3) gave the product **7a** as a white powder (54%). Mp 254–256 °C; R_f (1:3 EtOAc/hexane) 0.74; IR (KBr) (ν_{max}/cm^{-1}) 2923, 1718, 1678, 1552; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 3.32 (6H, s, CH_3), 3.81 (6H, s, CH_3), 7.11–7.53 (5H, m, arom); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 28.6, 30.4, 105.0, 125.5, 127.8, 128.0, 137.6, 151.0, 153.4, 159.1, 160.0; MS, *m*/*z* (%): 379 (M$^+$, 98), 364 (100), 321 (85), 293 (74), 265 (87), 127 (63), 43 (71). Anal. Calcd (%) for $C_{19}H_{17}N_5O_4$: C, 60.15; H, 4.52; N, 18.46. Found C, 60.24; H, 4.59; N, 18.34.

4.2.1. 5,6-Dihydro-1,3-dimethyl-5-(4-methylphenyl) pyrimido[4,5-*d*]pyrimidine-2,4,7(1*H*,3*H*,8*H*)-trione (4b). Mp 315 °C (dec); IR (KBr) (ν_{max}/cm^{-1}) 3307, 3112, 1687, 1658; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H 2.25 (3H, s, CH_3), 3.09 (3H, s, NCH_3), 3.35 (3H, s, NCH_3), 5.19 (1H, s, CH), 7.12–7.18 (4H, m, arom), 8.04 (1H, s, NH), 9.80 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ_C 21.1, 27.9, 30.4, 51.9, 86.6, 126.7, 129.3, 137.0, 141.5, 145.7, 151.2, 152.3, 159.9; MS, *m*/*z* (%) 300 (M$^+$, 21), 209 (100), 152 (36), 109 (24), 82 (49), 55 (41). Anal. Calcd (%) for $C_{15}H_{16}N_4O_3$: C, 59.99; H, 5.37; N, 18.66. Found C, 60.12; H, 5.46; N, 18.52.

4.2.2. 5,6-Dihydro-1,3-dimethyl-5-(4-methoxyphenyl) pyrimido[4,5-*d*]pyrimidine-2,4,7(1*H*,3*H*,8*H*)-trione (4c). Mp 307 °C (dec); IR (KBr) (ν_{max}/cm^{-1}) 3350, 1684, 1666; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H 3.09 (3H, s, CH_3), 3.36 (3H, s, CH_3), 3.71 (3H, s, OCH_3), 5.18 (1H, s, CH), 6.87–7.42 (4H, m, arom), 8.03 (1H, s, NH), 9.79 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ_C 27.9, 30.4, 51.5, 55.5, 86.7, 114.1, 127.9, 136.7, 145.6, 151.2, 152.2, 159.0, 159.9; MS, *m*/*z* (%) 315 (M$^+$−1, 23), 285 (69), 209 (100), 152 (52), 82 (100). Anal. Calcd (%) for $C_{15}H_{16}N_4O_4$: C, 56.96; H, 5.10; N, 17.71. Found C, 57.07; H, 5.19; N, 17.81.

4.2.3. 5,6-Dihydro-1,3-dimethyl-5-(4-chlorophenyl) pyrimido[4,5-*d*]pyrimidine-2,4,7(1*H*,3*H*,8*H*)-trione (4d). Mp 312 °C (dec); IR (KBr) (ν_{max}/cm^{-1}) 3324, 1689, 1660, 1636; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H 3.08 (3H, s, CH_3), 3.35 (3H, s, CH_3), 5.21 (1H, s, CH), 7.34–7.36 (4H, m, arom), 8.10 (1H, s, NH), 9.86 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ_C 27.2, 29.7, 50.9, 85.2, 128.0, 128.1, 131.7, 142.6, 145.2, 150.5, 151.3, 159.2; MS, *m*/*z* (%) 321 (M$^+$, 14), 276 (26), 209 (100), 152 (30), 82 (43), 57 (28). Anal. Calcd (%) for $C_{14}H_{13}ClN_4O_3$: C, 52.43; H, 4.09; N, 17.47. Found C, 52.31; H, 4.17; N, 17.58.

4.2.4. 5,6-Dihydro-1,3-dimethyl-5-(4-fluorophenyl) pyrimido[4,5-*d*]pyrimidine-2,4,7(1*H*,3*H*,8*H*)-trione (4e). Mp 308 °C (dec); IR (KBr) (ν_{max}/cm^{-1}) 3309, 1691, 1663, 1639; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H 3.09 (3H, s, CH_3), 3.36 (3H, s, CH_3), 5.25 (1H, s, CH), 7.11–7.37 (4H, m, arom), 8.10 (1H, s, NH), 9.85 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ_C 27.9, 30.4, 51.5, 86.2, 115.5 (d, *J*=21 Hz), 128.8 (d, *J*=8.3 Hz), 145.8, 151.2, 152.1, 159.9, 161.9 (d, *J*=241 Hz); MS, *m*/*z* (%) 304 (M$^+$, 15), 260 (27), 209 (100), 152 (26), 82 (28). Anal. Calcd (%) for $C_{14}H_{13}FN_4O_3$: C, 55.26; H, 4.31; N, 18.41. Found C, 55.37; H, 4.41; N, 18.50.

4.2.5. 5,6-Dihydro-1,3-dimethyl-5-(4-bromophenyl) pyrimido[4,5-*d*]pyrimidine-2,4,7(1*H*,3*H*,8*H*)-trione (4f). Mp 307 °C (dec); IR (KBr) (ν_{max}/cm^{-1}) 3323, 1709, 1688, 1661, 1636; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H 3.07 (3H, s, CH_3), 3.34 (3H, s, CH_3), 5.21 (1H, s, CH), 7.27–7.49 (4H, m, arom), 8.11 (1H, s, NH), 9.87 (1H, s, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ_C 27.9, 30.4, 51.7, 85.8, 120.9, 129.1, 131.7, 143.8, 145.9, 151.1, 152.0, 159.9; MS, *m*/*z* (%) 365 (M$^+$, 9), 285 (14), 209 (100), 152 (30), 82 (21). Anal. Calcd (%) for $C_{14}H_{13}BrN_4O_3$: C, 46.05; H, 3.59; N, 15.34. Found C, 45.98; H, 3.49; N, 15.44.

4.2.6. 6-Amino-5-((6-amino-1,2,3,4-tetrahydro-1,3-dimethyl-2,4-dioxopyrimidin-5-yl)(phenyl)methyl)-1,3-dimethyl pyrimidine-2,4(1*H*,3*H*)-dione (5). Yield 78%. Mp 305–307 °C. IR (KBr) (ν_{max}/cm^{-1}) 3457, 3389, 3199, 2998, 1697, 1648, 1581; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H 3.14 (6H, s, CH_3), 3.32 (6H, s, CH_3), 5.58 (1H, s, CH), 7.08–7.21 (5H, m, arom), 7.44 (4H, br s, NH_2); ^{13}C NMR (75 MHz, DMSO-d_6) δ_C 28.4, 30.4, 35.8, 86.6, 125.3, 127.0, 128.1, 140.1, 151.0, 154.7, 163.4; MS, *m*/*z* (%) 398 (M$^+$, 92), 242 (100), 185 (14), 57 (23). Anal. Calcd (%) for $C_{19}H_{22}N_6O_4$: C, 57.28; H, 5.57; N, 21.09. Found C, 57.36; H, 5.64; N, 20.54.

4.2.7. 5-Methylphenyl-1,3,7,9-tetramethylpyrido[2,3-*d*:6,5-*d*] dipyrimidine-2,4,6,8-tetrone (7b). Mp 331–333 °C. IR (KBr) (ν_{max}/cm^{-1}) 2954, 1715, 1672, 1557; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.48 (3H, s, CH_3), 3.33 (6H, s, CH_3), 3.79 (6H, s, CH_3), 7.02 (2H, d, *J*=8.6 Hz, arom), 7.33 (2H, d, *J*=8.1 Hz, arom); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 21.7, 28.6, 30.5, 105.1, 125.4, 128.9, 134.6, 137.3, 151.0, 153.3, 159.1, 160.5; MS, *m*/*z* (%) 393 (M$^+$, 100), 352 (18), 335 (18), 279 (14), 115 (78), 77 (65). Anal. Calcd (%) for $C_{20}H_{19}N_5O_4$: C, 61.06; H, 4.87; N, 17.80. Found C, 60.98; H, 4.79; N, 17.87.

4.2.8. 5-Chlorophenyl-1,3,7,9-tetramethylpyrido[2,3-*d*:6,5-*d*] dipyrimidine-2,4,6,8-tetrone (7c). Mp 300–302 °C. IR (KBr) (ν_{max}/cm^{-1}) 1716, 1690, 1666, 1552; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 3.33 (6H, s, CH_3), 3.79 (6H, s, CH_3), 7.06 (2H, d, *J*=8.4 Hz, arom), 7.33 (2H, d, *J*=8.4 Hz, arom); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 28.6, 30.5, 104.9, 127.0, 128.4, 133.7, 136.0, 150.8, 153.4, 158.7, 159.1; MS, *m*/*z* (%) 413 (M$^+$, 100), 355 (16), 299 (30), 243 (14), 69 (20), 43 (65). Anal. Calcd (%) for $C_{19}H_{16}ClN_5O_4$: C, 55.15; H, 3.90; N, 16.92. Found C, 55.07; H, 3.99; N, 16.81.

4.2.9. 5-Bromophenyl-1,3,7,9-tetramethylpyrido[2,3-*d*:6,5-*d*] dipyrimidine-2,4,6,8-tetrone (7d). Mp 321–323 °C. IR (KBr) (ν_{max}/cm^{-1}) 2954, 1709, 1671, 1557; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 3.33 (6H, s, CH_3), 3.79

(6H, s, CH_3), 7.00 (2H, d, J=8.4 Hz, arom), 7.62 (2H, d, J=8.4 Hz, arom); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 28.6, 30.5, 104.9, 121.9, 127.3, 131.3, 136.5, 150.8, 153.4, 158.7, 159.1; MS, *m*/*z* (%) 458 (M^+, 100), 352 (18), 335 (18), 279 (14), 115 (78), 77 (65). Anal. Calcd (%) for $C_{19}H_{16}BrN_5O_4$: C, 49.80; H, 3.52; N, 15.28. Found C, 49.89; H, 3.56; N, 15.37.

4.2.10. 5-Fluorophenyl-1,3,7,9-tetramethylpyrido[2,3-*d*:6,5-*d*] dipyrimidine-2,4,6,8-tetrone (7e). Mp 270–272 °C. IR (KBr) (ν_{max}/cm^{-1}) 2941, 1718, 1682, 1552; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 3.33 (6H, s, CH_3), 3.80 (6H, s, CH_3), 7.06–7.27 (4H, m, arom); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 28.6, 30.5, 105.1, 115.3 (d, J=21.7 Hz), 127.3 (d, J=8.0 Hz), 133.2, 133.3, 150.9, 153.4, 159.1, 162.3 (d, J=245 Hz); MS, *m*/*z* (%) 397 (M^+, 100), 378 (26), 283 (24), 168 (97), 77 (65). Anal. Calcd (%) for $C_{19}H_{16}FN_5O_4$: C, 57.43; H, 4.06; N, 17.62. Found C, 57.50; H, 4.13; N, 17.71.

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18. *X-ray data for* ***4a***: ($C_{14}H_{14}N_4O_3$) (CH_3SOCH_3), M=364.43 g/mol, monoclinic system, space group $P2_1/c$, a=12.258(2), b=18.520(3), c=16.362(3) Å, β=109.554(14)°, V=3500.3(10) Å^3, Z=8, D_c=1.38 g cm^{-3}, μ(Mo Kα)=0.214 mm^{-1}, crystal dimension of 0.3×0.2×0.1 mm. The structure was solved by using SHELXS. The structure refinement and data reduction were carried out with SHELXL of the X-Step32 suite of programs.[19] The non-hydrogen atoms were refined anisotropically by full matrix least-squares on F^2 values to final $R1$=0.0998, $wR2$=0.2461 and S=1.080 with 475 parameters using 6642 independent reflections (θ range=1.72–25.69°). Hydrogen atoms were located from expected geometry and were not refined. Crystallographic data for **4a** have been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained, free of charge, on application to The Director, CCDC 615113, Union Road, Cambridge CB2 1EZ, UK. Fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk. *X-ray data for* ***7d***: ($C_{19}H_{16}BrN_5O_4$), M=458.27 g/mol, monoclinic system, space group $P2_1/m$, a=13.032(3), b=7.0814(15), c=13.413(3) Å, β=115.889(17)°, V=1113.6(5) Å^3, Z=2, D_c=1.36 g cm^{-3}, μ(Mo Kα)=1.88 mm^{-1}, crystal dimension of 0.35×0.32×0.20 mm. The structure was solved by using SHELXS. The structure refinement and data reduction were carried out with SHELXL of the X-Step32 suite of programs.[19] The non-hydrogen atoms were refined anisotropically by full matrix least-squares on F^2 values to final $R1$=0.0712, $wR2$=0.2116 and S=1.078 with 173 parameters using 2567 independent reflections (θ range=1.69–26.78°). Hydrogen atoms were located from expected geometry and were not refined. Crystallographic data for **7d** have been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained, free of charge, on application to The Director, CCDC 629593, Union Road, Cambridge CB2 1EZ, UK. Fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk.
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