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AN EFFICIENT THREE-COMPONENT, ONE-POT SYNTHESIS OF NEW PYRIMIDO[4,5-*d*]PYRIMIDINE-2,4-DIONES

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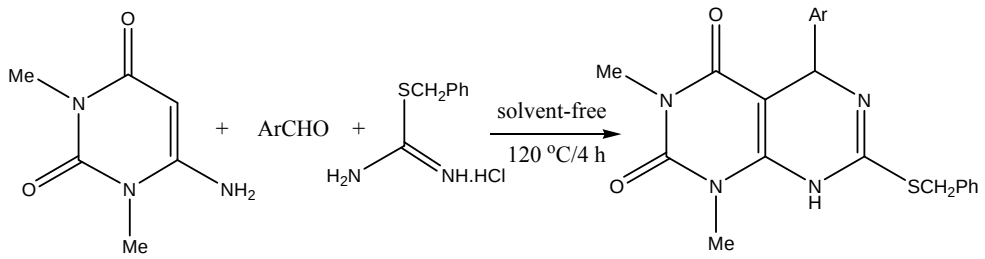
Abstract – A new pyrimido[4,5-*d*]pyrimidine-2,4-(1*H*,3*H*,5*H*,8*H*)-dione derivatives have been synthesized in good yields in a three-component, one-pot, and efficient process by condensation reaction of 6-amino-1,3-dimethyluracil, aldehyde and 2-benzylisothiourea hydrochloride under solvent-free conditions.

The importance of fused pyrimidines, common source for the development of new potential therapeutic agents,[1] is well known. Among them, the pyrimido[4,5-*d*]pyrimidines and pyrimido[2,3-*d*]pyrimidines are an important class of annelated uracils with biological significance because of their connection with purine pteridine system.[2] Numerous reports delineate the antitumor,[3] antiviral,[4] antioxidant,[5] antifungal,[6] and hepatoprotective[7] activity of these compounds. Therefore, for the preparation of these complex molecules large efforts have been directed towards the synthetic manipulation of uracils. As result, a number of reports have appeared in literature, which usually requires forcing conditions, long reaction times, and complex synthetic pathway.[8] Thus new routes for the synthesis of these molecules have attracted considerable attention in search for a rapid entry to these heterocycles.

With the emphasis on the search for atom-efficient transformations of easily available starting materials into complex organic molecules, reactions that provide maximum diversity are especially desirable. Here, multicomponent reactions[9] (MCRs) have emerged as powerful strategy. 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.[9]

Considering the above reports and in continuation of our previous works on synthesis of heterocyclic compounds,[10] herein, we wish to report an efficient, one-pot, and three-component method for the preparation of 1,3-dimethyl-7-(benzylthio)-5-arylpyrimido[4,5,*d*]pyrimidine-2,4-(1*H*,3*H*,5*H*,8*H*)-dione derivatives **4** (**Scheme 1**).



1 **2a-k** **3** **4a-k**

Scheme 1

We started to study the three-component condensation reaction by examining the conditions required for the reaction involving 6-amino-1,3-dimethyluracil (**1**), benzaldehyde (**2a**), and 2-benzylisothiourea hydrochloride (**3**) to afford the 1,3-dimethyl-7-(benzylthio)-5-phenylpyrimido[4,5,*d*]pyrimidine-2,4-(1*H*,3*H*,5*H*,8*H*)-dione (**4a**). As indicated in **Table 1**, the best result was achieved in the presence of *p*-toluenesulfonic acid (*p*-TSA) at 120 °C under solvent-free conditions (**Table 1**).

Table 1. Reaction of 6-amino-1,3-dimethyluracil (**1**), benzaldehyde (**2a**), and 2-benzylisothiourea hydrochloride (**3**) under different conditions[a]

Entry	Ar	Catalyst	Yield(%)[b]
1	solvent-free/ 120 °C	*p*-TSA	85
2	solvent-free/ 120 °C	-	<30
3	solvent-free/ 100 °C	*p*-TSA	55
4	EtOH (reflux)	*p*-TSA	<30
5	EtOH (reflux)	HCl	<30
6	MeCN	*p*-TSA	<30
7	HOAc	-	53
8	toluene	*p*-TSA	<30

[a]reaction time= 4 h. [b]isolated yield

Then, the preparation of pyrimido[4,5,*d*]pyrimidine-2,4-(1*H*,3*H*,5*H*,8*H*)-dione derivatives (**4a-k**) has been accomplished by reaction of 6-amino-1,3-dimethyluracil (**1**) with aldehyde (**2**) and 2-benzylisothiourea hydrochloride (**3**) at 120 °C under solvent-free conditions for 4 h (**Scheme 1**).

To the best of our knowledge, there are no reports in the literature for the preparation of 1,3-dimethyl-7-(benzylthio)-5-arylpyrimido[4,5,*d*]pyrimidine-2,4-(1*H*,3*H*,5*H*,8*H*)-dione derivatives (**4**) via condensation of 6-amino-1,3-dimethyluracil (**1**), aldehyde (**2**) and 2-benzylisothiourea hydrochloride (**3**).

The results are summarized in **Table 2**. The thermal solvent-free conditions are well suited for either electron-donating or electron-withdrawing substituents on the aromatic aldehydes. Good yields were

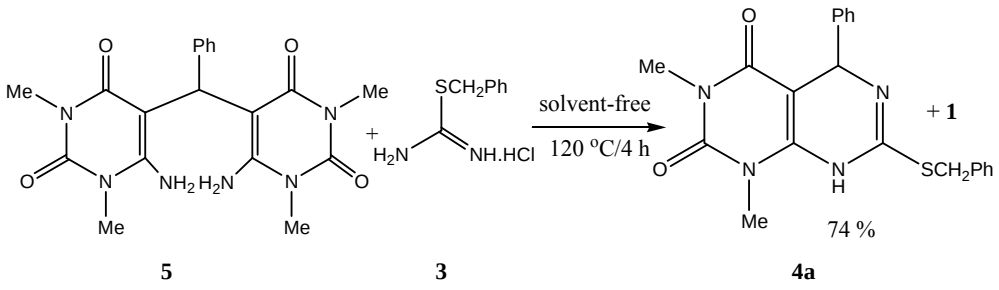
obtained using aromatic aldehydes carrying electron-donating or electron-withdrawing substituents and avoid problems associated with solvent use (cost, handling, safety and pollution).

Table 2. Synthesis of pyrimido[4,5,*d*]pyrimidine-2,4-diones[a]

Entry	Ar	Product **4**	Yield(%)[b]	MP(°C)
1	C_6H_5	**a**	85	208-210
2	4-Cl-C_6H_4	**b**	78	266-268
3	4-F-C_6H_4	**c**	74	238-240
4	4-Br-C_6H_4	**d**	81	258-260
5	4-NO_2-C_6H_4	**e**	83	251-253
6	4-Me-C_6H_4	**f**	80	270-272
7	4-MeO-C_6H_4	**g**	69	234-236
8	2-Cl-C_6H_4	**h**	73	138-140
9	2-MeO-C_6H_4	**i**	78	223-225
10	3-NO_2-C_6H_4	**j**	78	232-234
11	3-Br-C_6H_4	**k**	73	177-179

[a]reaction time= 4 h. [b]isolated yield

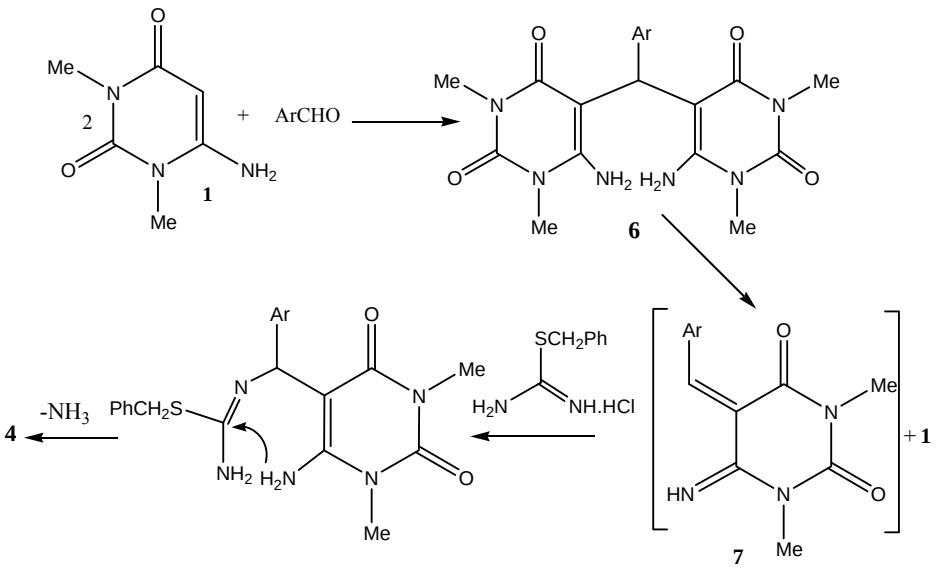
For the investigation of the reaction mechanism, it is notable that when the 6-amino-1,3-dimethyluracil (**1**), benzaldehyde (**2a**) and 2-benzylisothiourea hydrochloride (**3**) were heated for 1 h, the intermediate (**5**) was formed and which was isolated and characterized by spectroscopic methods. When intermediate (**5**) was isolated and reacted with 2-benzylisothiourea hydrochloride (**3**) under solvent-free conditions, 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**).



5 **3** **4a**

Scheme 2

According to the results, the reaction can mechanistically be considered to proceed through the intermediate (**6**) formed in situ by reaction of the aldehyde with 6-amino-1,3-dimethyluracil.[11] Then, the intermediate (**6**) was converted to imine (**7**) and the subsequent addition of the 2-benzylisothiourea hydrochloride (**3**) to the imine (**7**), followed by cyclization afforded the corresponding pyrimido[4,5,*d*]pyrimidine-2,4-(1*H*,3*H*,5*H*,8*H*)-diones (**4a-k**) and ammonia (**Scheme 3**).



Scheme 3

The structures of all compounds were confirmed by means of spectral analysis such as IR, NMR, and MS spectra. Elemental analyses of all compounds were in satisfactory agreement with the calculated values.

In summary, we have described an efficient and one-pot green synthesis for the preparation of new pyrimido[4,5,*d*]pyrimidine-2,4-(1*H*,3*H*,5*H*,8*H*)-dione derivatives in three-component cyclo-condensation reaction of 6-amino-1,3-dimethyluracil, aromatic aldehydes and 2-benzylisothiourea hydrochloride under solvent-free conditions.

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EXPERIMENTAL

Melting points were measured on an Electrothermal 9200 apparatus. IR spectra were recorded on FT-IR 102MB BOMEM apparatus. ^{1}H NMR and ^{13}C NMR spectra were determined on a BRUKER DRX-300 AVANCE spectrometer at 300.13 and 75.47 MHz, respectively. MS spectra were recorded on a Shimadzu QP 1100EX mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses were performed using a Heracus CHN-O-Rapid analyzer.

Typical procedure for the preparation of pyrimido[4,5,*d*]pyrimidine-2,4(1*H*,3*H*,5*H*,8*H*)-dione (4a-k): A mixture of 6-amino-1,3-dimethyluracil (**1**) (1 mmol), aldehyde (**2**) (1 mmol), and 2-benzylisothiourea hydrochloride (**3**) (1.5 mmol) was heated with stirring at 120 ^{o}C for 4 h. After cooling, the reaction mixture was washed with water (15 mL) and then recrystallized from EtOAc/ hexane (1:3) to afford the pure product.

Spectral data for products:

4a: mp 208-210 °C, IR (KBr) (ν_{max}, cm^{-1}): 3268, 1683, 1638; ^{1}H NMR (DMSO-d_6) δ_H: 3.09 (3H, s, CH_3), 3.43 (3H, s, CH_3), 4.35 and 4.50 (2H, AB system, J= 12.8 Hz, CH_2), 5.43 (1H, s, CH), 7.27-7.38 (10H, m, Arom.), 9.71 (1H, s, NH); ^{13}C NMR (DMSO-d_6) δ_C: 27.8, 29.5, 34.3, 52.9, 88.2, 126.8, 127.7, 128.2, 128.9, 129.0, 129.2, 137.9, 144.5, 149.7, 151.9, 160.7, 165.1. MS (m/z, %): 392 (M^+, 7), 315 (95), 91 (100). Anal. Calcd for $C_{21}H_{20}N_4O_2S$: C, 64.27; H, 5.14; N, 14.28. Found: C, 64.19; H, 5.05; N, 14.17.

4b: mp 266-268 °C, IR (KBr) (ν_{max}, cm^{-1}): 3266, 1683, 1640; ^{1}H NMR (DMSO-d_6) δ_H: 3.08 (3H, s, CH_3), 3.41 (3H, s, CH_3), 4.35 (2H, bd, CH_2), 5.44 (1H, s, CH), 7.29-7.36 (9H, m, Arom.), 9.72 (1H, s, NH); ^{13}C NMR (DMSO-d_6) δ_C: 27.8, 29.5, 34.3, 52.9, 87.8, 127.7, 128.8, 128.9, 129.0, 129.2, 132.8, 137.8, 143.4, 149.8, 151.9, 160.7, 165.2; MS (m/z, %): 426 (M^+, 9), 315 (54), 91 (100). Anal. Calcd for $C_{21}H_{19}ClN_4O_2S$: C, 59.08; H, 4.49; N, 13.12. Found: C, 58.97; H, 4.40; N, 13.04.

4c: 238-240 °C, IR (KBr) (ν_{max}, cm^{-1}): 3257, 1685, 1639; ^{1}H NMR (DMSO-d_6) δ_H: 3.09 (3H, s, CH_3), 3.43 (3H, s, CH_3), 4.35 and 4.51 (2H, AB system, J= 13.1 Hz, CH_2), 5.45 (1H, s, CH), 7.12-7.38 (9H, m, Arom.), 9.71 (1H, s, NH); ^{13}C NMR (DMSO-d_6) δ_C: 27.8, 29.5, 34.3, 52.2, 88.0, 115.7 (d, $^2J_{CF}$= 21.2 Hz) , 127.8, 128.9 (d, $^3J_{CF}$= 8.1 Hz), 129.1, 129.2, 137.8, 140.8, 149.8, 151.9, 160.7, 161.4 (d, $^1J_{CF}$= 214.2 Hz), 165.1; MS (m/z, %): 426 (M^+, 15), 315 (78), 91 (100). Anal. Calcd for $C_{21}H_{19}FN_4O_2S$: C, 61.45; H, 4.67; N, 13.65. Found: C, 61.53; H, 4.61; N, 13.74.

4d: mp 258-260 °C, IR (KBr) (ν_{max}, cm^{-1}): 3266, 1683, 1640; ^{1}H NMR (DMSO-d_6) δ_H: 3.09 (3H, s, CH_3), 3.42 (3H, s, CH_3), 4.35 and 4.50 (2H, AB system, J= 13.7 Hz, CH_2), 5.43 (1H, s, CH), 7.20-7.54 (9H, m, Arom.), 9.71 (1H, s, NH); ^{13}C NMR (DMSO-d_6) δ_C: 27.8, 29.5, 34.3, 52.4, 87.7, 121.4, 127.8, 129.0, 129.1, 129.2, 131.9, 137.8, 143.7, 149.8, 151.9, 160.7, 165.2; MS (m/z, %): 471 (M^+, 32), 315 (56), 91 (100). Anal. Calcd for for $C_{21}H_{19}BrN_4O_2S$: C, 53.51; H, 4.06; N, 11.89. Found: C, 53.46; H, 4.12; N, 11.96.

4e: mp 251-253 °C, IR (KBr) (ν_{max}, cm^{-1}): 3242, 1681, 1634; ^{1}H NMR (DMSO-d_6) δ_H: 3.08 (3H, s, CH_3), 3.43 (3H, s, CH_3), 4.36 and 4.51 (2H, AB system, J= 13.8 Hz, CH_2), 5.60 (1H, s, CH), 7.25-8.21 (9H, m, NH), 9.83 (1H, s); ^{13}C NMR (DMSO-d_6) δ_C: 27.8, 29.6, 34.4, 52.5, 87.3, 124.3, 127.8, 128.3, 129.1, 129.2, 137.7, 147.5, 149.9, 151.1, 151.9, 160.7, 165.7; MS (m/z, %): 437 (M^+, 6), 315 (25), 91 (100). Anal. Calcd for for $C_{21}H_{19}N_5O_4S$: C, 57.66; H, 4.38; N, 16.01. Found: C, 57.72; H, 4.43; N, 15.93.

4f: mp 270-272 °C, IR (KBr) (ν_{max}, cm^{-1}): 3265, 1680, 1638; ^{1}H NMR (DMSO-d_6) δ_H: 2.25 (3H, s, CH_3), 3.09 (3H, s, CH_3), 3.42 (3H, s, CH_3), 4.34 and 4.49 (2H, AB system, J= 13.0 Hz, CH_2), 5.38 (1H, s, CH), 7.12-7.38 (9H, m, Arom.), 9.67 (1H, s, NH); ^{13}C NMR (DMSO-d_6) δ_C: 21.1, 27.8, 29.5, 34.3, 52.7, 88.3, 126.7, 127.8, 129.0, 129.2, 129.5, 137.5, 137.9, 141.7, 149.7, 151.9, 160.7, 165.0; MS (m/z, %): 407 (M^++1, 78), 315 (45), 91 (100). Anal. Calcd for $C_{22}H_{22}N_4O_2S$: C, 65.00; H, 5.46; N, 13.78. Found: C, 65.09; H, 5.51; N, 13.86.

4g: mp 234-236 °C, IR (KBr) (ν_{max}, cm^{-1}): 3273, 1683, 1639; ^{1}H NMR (DMSO-d_6) δ_H: 3.09 (3H, s, CH_3), 3.42 (3H, s, CH_3), 3.71 (3H, s, CH_3), 4.35 and 4.49 (2H, AB system, *J*= 13.6 Hz, CH_2), 5.36 (1H, s, CH), 6.86-7.40 (9H, m, Arom.), 9.66 (1H, s, NH); ^{13}C NMR (DMSO-d_6) δ_C: 27.8, 29.5, 34.3, 52.4, 55.6, 88.4, 114.3, 127.7, 128.0, 129.0, 129.2, 136.9, 137.9, 149.6, 151.9, 159.3, 160.7, 164.8; MS (m/z, %): 422 (M^+, 5), 315 (53), 91 (100). Anal. Calcd for $C_{22}H_{22}N_4O_3S$: C, 62.54; H, 5.25; N, 13.26. Found: C, 62.46; H, 5.19; N, 13.17.

4h: mp 138-140 °C, IR (KBr) (ν_{max}, cm^{-1}): 3207, 1693, 1632; ^{1}H NMR (DMSO-d_6) δ_H: 3.05 (3H, s, CH_3), 3.45 (3H, s, CH_3), 4.35 and 4.46 (2H, AB system, *J*= 13.4 Hz, CH_2), 5.84 (1H, s, CH), 7.30-7.39 (9H, m, Arom.), 9.60 (1H, s, NH); ^{13}C NMR (DMSO-d_6) δ_C: 27.7, 29.5, 34.3, 50.9, 86.9, 127.7, 128.2, 128.9, 129.2, 129.9, 130.1, 130.4, 132.0, 137.9, 141.1, 150.4, 151.9, 160.4, 165.2; MS (m/z, %): 427 (M^+, 17), 391 (24), 315 (45), 91(100). Anal. Calcd for $C_{21}H_{19}ClN_4O_2S$: C, 59.08; H, 4.49; N, 13.12. Found: C, 59.14; H, 4.47; N, 13.19.

4i: mp 223-225 °C, IR (KBr) (ν_{max}, cm^{-1}): 3274, 1676, 1639; ^{1}H NMR (DMSO-d_6) δ_H: 3.07 (3H, s, CH_3), 3.45 (3H, s, CH_3), 3.74 (3H, s, OCH_3), 4.33 and 4.43 (2H, AB system, *J*= 13.4 Hz, CH_2), 5.71 (1H, s, CH), 6.86-7.36 (9H, m, Arom.), 9.34 (1H, s, NH); ^{13}C NMR (DMSO-d_6) δ_C: 27.7, 29.5, 34.2, 48.4, 55.9, 86.5, 111.8, 120.7, 127.6, 128.7, 128.9, 129.2, 129.7, 131.5, 138.1, 150.6, 152.0, 157.1, 160.5, 165.1; MS (m/z, %): 422 (M^+, 15), 331 (46), 315 (40), 91 (100). Anal. Calcd for $C_{22}H_{22}N_4O_3S$: C, 62.54; H, 5.25; N, 13.26. Found: C, 62.48; H, 5.29; N, 13.18.

4j: mp 232-234 °C, IR (KBr) (ν_{max}, cm^{-1}): 3244, 1681, 1639; ^{1}H NMR (DMSO-d_6) δ_H: 3.09 (3H, s, CH_3), 3.43 (3H, s, CH_3), 4.38 and 4.51 (2H, AB system, *J*= 13.7 Hz, CH_2), 5.66 (1H, s, CH), 7.26-8.15 (9H, m, Arom.), 9.81 (1H, s, NH); ^{13}C NMR (DMSO-d_6) δ_C: 27.8, 29.6, 34.2, 52.4, 87.3, 121.6, 123.3, 127.8, 129.0, 129.2, 130.8, 133.6, 137.8, 146.3, 148.3, 150.0, 151.9, 160.8, 165.6; MS (m/z, %): 437 (M^+, 5), 315 (53), 91 (100). Anal. Calcd for $C_{21}H_{19}N_5O_4S$: C, 57.66; H, 4.38; N, 16.01. Found: C, 57.58; H, 4.31; N, 15.94.

4k: mp 177-179 °C, IR (KBr) (ν_{max}, cm^{-1}): 3247, 1681, 1637; ^{1}H NMR (DMSO-d_6) δ_H: 3.10 (3H, s, CH_3), 3.43 (3H, s, CH_3), 4.37 and 4.49 (2H, AB system, *J*= 13.7 Hz, CH_2), 5.47 (1H, s, CH), 7.25-7.48 (9H, m, Arom.), 9.73 (1H, s, NH); ^{13}C NMR (DMSO-d_6) δ_C: 27.8, 29.5, 34.3, 52.5, 87.5, 122.2, 125.9, 127.8, 129.0, 129.2, 129.7, 131.1, 131.4, 137.8, 146.9, 149.9, 151.9, 160.7, 165.3; MS (m/z, %): 471 (M^+), 315 (32), 91 (100). *Anal*. Calcd for $C_{21}H_{19}BrN_4O_2S$: C, 53.51; H, 4.06; N, 11.89. Found: C, 53.44; H, 3.99; N, 11.81.

5: mp 306-308 °C, IR (KBr) (ν_{max}, cm^{-1}): 3456, 3389, 3201, 2998, 1698; ^{1}H NMR (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, bs, NH_2); ^{13}C NMR (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^+, 75), 242 (100), 185 (18).Anal. Calcd for $C_{19}H_{22}N_6O_4$: C, 57.28; H, 5.57; N, 21.09.

Found C, 57.35; H, 5.63; N, 21.16.

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