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A green organocatalyzed one-pot protocol for efficient synthesis of new substituted pyrimido[4,5-*d*]pyrimidinones using a Biginelli-like reaction

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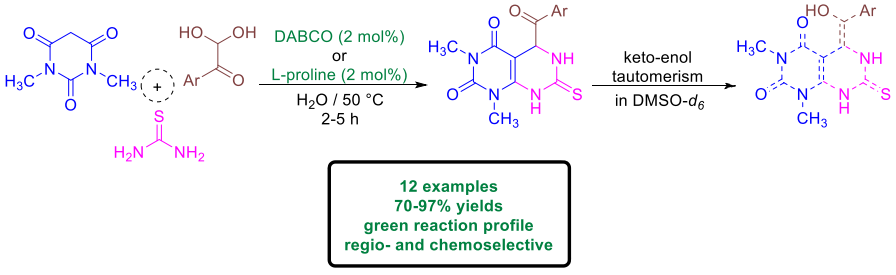
Abstract In this article, we have demonstrated a green and facile one-pot approach for the regio- and chemoselective synthesis of 5-aryloyl-1,3-dimethyl-7-thioxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione derivatives in water at 50 °C. This transformation presumably proceeds via a three-component tandem annulation of arylglyoxalmonohydrates with 1,3-dimethylbarbituric acid and thiourea in the presence of catalytic amounts of DABCO or L-proline, involving a Biginelli-like reaction.

Graphical Abstract



Ar = C_6H_5, 4-BrC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 4-$NO_2C_6H_4$, 4-$OCH_3C_6H_4$,3-BrC_6H_4, 3-$OCH_3C_6H_4$, 4-OH-3-$OCH_3C_6H_3$, 3,4-$(OCH_3)_2C_6H_3$, 2,5-$(OCH_3)_2C_6H_3$, 3,4-$(OCH_2O)C_6H_3$

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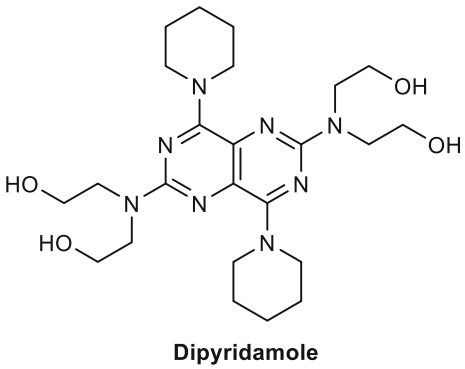
Keywords Biginelli-like reaction · Pyrimido[45-*d*]pyrimidine · Arylgylyoxalmonohydrate · Green chemistry · One-pot

Introduction

One of the main challenges in medicinal chemistry is the design and synthesis of biological compounds [1–6]. Pyrimidopyrimidines are annelated uracils that have attracted considerable interest in recent years. Dipyridamole, a 2,4,6,8-tetrasubstituted pyrimido[5,4-*d*]pyrimidine is marketed nowadays as a coronary vasodilator (Fig. 1) [7–10]. Many other derivatives have been known to display a wide range of pharmacological activities such as anti-tumor [11–13], anti-viral (as inhibitor of herpes simplex virus reactivation and viral protein synthesis) [14], anti-oxidant (as lipid peroxidation inhibitors) [15], anti-fungal [16], anti-cancer [17] and also their potent inhibitory properties with regard to the tyrosine kinase domain of epidermal growth factor receptor [18], 5-phosphoribosyl-1-pyrophosphate synthetase [19], and dihydrofolate reductase [20] have been fully demonstrated. Thus, the development of a novel, efficient, simple and environmentally friendly method for synthesis of such compounds is important.

Green chemistry has become an important and expanding research area, as it avoids the use of reagents and solvents that have a hazardous impact on the environment, and minimizes the production of waste [21–32]. One approach to achieving these aims involves the replacement of volatile organic solvents with nonvolatile solvents such as water. Water as a solvent has many advantages over conventional organic solvents, because it is cheap, readily available, non-toxic, non-polluting, and non-flammable [33–38]. Thus, the water-mediated organic synthesis is very attractive from both an economical and an environmental point of view.



Dipyridamole

Fig. 1 Structure of dipyridamole

Multi-component reactions (MCRs) are considered to be important concepts of organic chemistry. MCRs have great advantages over classical reaction strategies such as reduction of isolation and purification steps, minimization of costs, energy, time, and waste production [39–52].

The classical Biginelli reaction is a simple one-pot cyclocondensation of β-dicarbonyl compounds (especially β-ketoesters) with aldehydes and urea or thiourea in the presence of various catalysts [53–57]. In 2005, the first Biginelli-like reaction using phenylglyoxal instead of aldehyde for the synthesis of dihydropyrimidinone was reported by Balalaie [58]. Also, Karimi and co-workers expanded this chemistry to provide some novel 5-acetyl-4-aryloyl-3,4-dihydropyrimidinones via one-pot condensation of various arylglyoxals, acetylacetone and urea using tungstate sulfuric acid (TSA) or molybdate sulfuric acid (MSA) as catalyst under solvent-free conditions (Fig. 2) [59, 60].

As a part of our continuous efforts toward the development of new synthetic methods for important heterocyclic compounds [61–66], herein we report the green regio- and chemoselective synthesis of 5-aryloyl-1,3-dimethyl-7-thioxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione derivatives by one-pot, three-component Biginelli-like reaction of arylglyoxalmonohydrates with 1,3-dimethylbarbituric acid and thiourea in the presence of DABCO or L-proline as organocatalysts in water at 50 °C (Scheme 1). This new approach is a green, highly efficient, facile and atom-economical manner to generate new C–C and C–N bonds, which conserves time and energy along with avoiding hazardous solvent or catalyst.

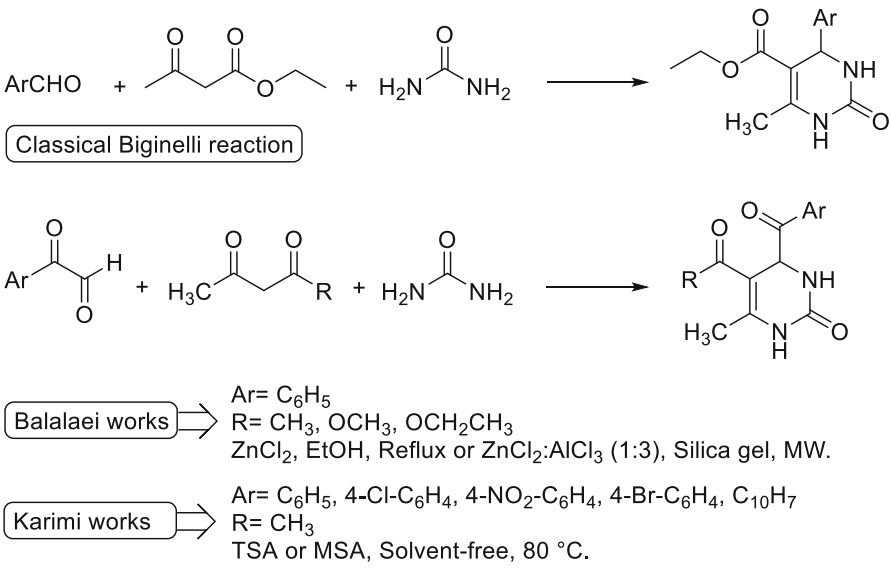
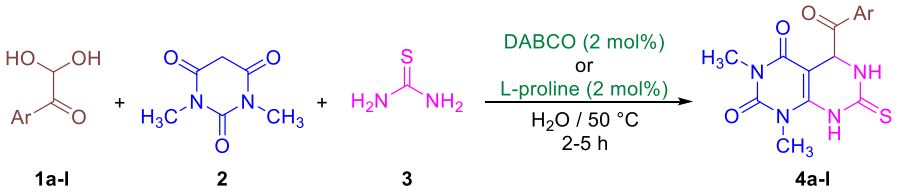


Fig. 2 Classical Biginelli and some Biginelli-like reactions for synthesis of dihydropyrimidinones



Ar = C_6H_5, 4-BrC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 4-$NO_2C_6H_4$, 4-$OCH_3C_6H_4$,3-BrC_6H_4, 3-$OCH_3C_6H_4$, 4-OH-3-$OCH_3C_6H_3$, 3,4-$(OCH_3)_2C_6H_3$, 2,5-$(OCH_3)_2C_6H_3$, 3,4-$(OCH_2O)C_6H_3$

Scheme 1 synthesis of 5-aryloyl-1,3-dimethyl-7-thioxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione derivatives

Experimental

General procedures

Melting points were determined on an Electrothermal 9200 apparatus. Infrared spectra were recorded on a Perkin Elmer Spectrum Two FT-infrared spectrophotometer, measured as KBr disks. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 MHz spectrometer at 300 and 75 MHz, respectively. Chemical shifts were measured in DMSO-d_6 as solvent relative to TMS as the internal standard. Elemental analyses were performed by using a Leco Analyzer 932.

General procedure for the synthesis of 5-aryloyl-1,3-dimethyl-7-thioxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4a–l) A mixture of arylglyoxalmonohydrates (1 mmol) and1,3-dimethylbarbituric acid (1 mmol) and thiourea (1 mmol) in the presence of DABCO (2 mol %) or L-proline (2 mol %) as organocatalysts was stirred at 50 °C in water (10 mL). After completion of the reaction, the reaction mixture was cooled to room temperature and filtered to give the crude product, which was further washed by boiling water to give pure product.

Spectral data of products

5-Benzoyl-1,3-dimethyl-7-thioxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4a) White powder; mp 321 °C (dec.); FT-IR (KBr): 3363, 3089, 2956, 2841, 1688, 1637, 1556, 1503, 1449, 1428, 1391, 1239, 762, 509 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.82 (bs, 1H, OH), 8.55 (s, 2H, 2 × NH), 7.49-7.22 (m, 5H, Ar), 3.03 (s, 6H, 2 × CH_3). ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 168.1, 161.6, 152.9, 132.0, 131.4, 129.4, 128.7, 128.4, 127.6, 119.1, 77.8, 28.1, 27.0. Anal. Calcd for $C_{15}H_{14}N_4O_3S$: C, 54.54; H, 4.27; N, 16.96. Found: C, 54.56, H, 4.28; N, 17.08.

5-(4-Bromobenzoyl)-1,3-dimethyl-7-thioxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4b) White powder; mp 324 °C (dec.); FT-IR (KBr): 3289, 3139, 2960, 1676, 1645, 1598, 1555, 1494, 1472, 1426, 1396, 1385, 829, 600, 508 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 12.74 (bs, 1H, OH), 8.57 (s, 2H, 2 × NH), 7.53 (d, J = 8.1 Hz, 2H, Ar), 7.34 (d, J = 8.1 Hz, 2H, Ar),

3.03 (s, 6H, 2 × CH_3). ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 168.0, 161.2, 152.7, 132.5, 131.0, 130.0, 129.7, 128.2, 121.3, 119.7, 78.4, 28.3, 26.9. Anal. Calcd for $C_{15}H_{13}BrN_4O_3S$: C, 44.02; H, 3.20; N, 13.69. Found: C, 44.03, H, 3.22; N, 13.80.

5-(4-Chlorobenzoyl)-1,3-dimethyl-7-thioxo-5,6,7,8-tetrahydropyrimido[4,5-*d*] pyrimidine-2,4(1*H*,3*H*)-dione (4c) White powder; mp 327 °C (dec.); FT-IR (KBr): 3384, 3289, 3128, 3079, 2985, 2950, 2746, 1695, 1673, 1641, 1591, 1554, 1493, 1434, 1396, 1245, 1092, 776, 510 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 12.72 (bs, 1H, OH), 8.55 (s, 2H, 2 × NH), 7.43 (d, J = 9 Hz, 2H, Ar), 7.39 (d, J = 9 Hz, 2H, Ar), 3.04 (s, 6H, 2 × CH_3). ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 168.1, 161.3, 152.7, 132.6, 130.7, 129.9, 129.4, 127.5, 127.4, 119.7, 78.4, 28.2, 27.0. Anal. Calcd for $C_{15}H_{13}ClN_4O_3S$: C, 49.39; H, 3.59; N, 15.36. Found: C, 49.41, H, 3.60; N, 15.45.

5-(4-Fluorobenzoyl)-1,3-dimethyl-7-thioxo-5,6,7,8-tetrahydropyrimido[4,5-*d*] pyrimidine-2,4(1*H*,3*H*)-dione (4d) White powder; mp 320 °C (dec.); FT-IR (KBr): 3362, 3094, 2955, 2840, 1684, 1642, 1621, 1559, 1515, 1435, 1389, 1351, 1236, 834, 776,509 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 12.79 (bs, 1H, OH), 8.56 (s, 2H, 2 × NH), 7.46 (t, J = 7.5 Hz, 2H, Ar), 7.18 (t, J = 8.7 Hz, 2H, Ar), 3.04 (s, 6H, 2 × CH_3). ^{13}C-NMR (75.5 MHz, DMSO-d_6): δ = 168.0, 161.5, 148.9, 139.3, 130.6, 128.5, 128.1, 118.9, 116.6, 116.3, 77.8, 28.2, 26.9. Anal. Calcd for $C_{15}H_{13}FN_4O_3S$: C, 51.72; H, 3.76; N, 16.08. Found: C, 51.69, H, 3.77; N, 16.20.

5-(4-Nitrobenzoyl)-1,3-dimethyl-7-thioxo-5,6,7,8-tetrahydropyrimido[4,5-*d*] pyrimidine-2,4(1*H*,3*H*)-dione (4e) Orange powder; mp 332 °C (dec.); FT-IR (KBr): 3352, 3109, 3067, 1701, 1640, 1597, 1582, 1536, 1513, 1439, 1337, 1245, 778, 510 cm^{-1}.^{1}H-NMR (300 MHz, DMSO-d_6): δ = 12.28 (s, 1H, OH), 8.55 (bs, 2H, 2 × NH), 8.16 (d, J = 7.8 Hz, 2H, Ar), 7.58 (d, J = 8.1 Hz, 2H, Ar), 3.03 (s, 6H, 2 × CH_3). ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 167.7, 160.9, 152.5, 146.0, 139.1, 128.7, 127.5, 124.4, 122.9, 122.6, 80.2, 28.4, 27.0. Anal. Calcd for $C_{15}H_{13}N_5O_5S$: C, 48.00; H, 3.49; N, 18.66. Found: C, 48.09, H, 3.51; N, 18.74.

5-(4-Methoxybenzoyl)-1,3-dimethyl-7-thioxo-5,6,7,8-tetrahydropyrimido[4,5-*d*] pyrimidine-2,4(1*H*,3*H*)-dione (4f) White powder; mp 305 °C (dec.); FT-IR (KBr): 3284, 3169, 2945, 2840, 2701, 1673, 1598, 1516, 1430, 1409, 1255, 1177, 829, 604 cm^{-1}.^{1}H-NMR (300 MHz, DMSO-d_6): δ = 12.74 (bs, 1H, OH), 8.58 (s, 2H, 2 × NH), 7.38 (d, J = 8.1 Hz, 2H, Ar), 6.91 (d, J = 7.8 Hz, 2H, Ar), 3.74 (s, 3H, OCH_3), 3.04 (s, 6H, 2 × CH_3). ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 168.1, 161.7, 159.4, 152.9, 132.1, 127.8, 123.4, 117.4, 114.8, 113.2, 77.4, 54.6, 28.2, 26.9. Anal. Calcd for $C_{16}H_{16}N_4O_4S$: C, 53.32; H, 4.48; N, 15.55. Found: C, 53.27, H, 4.41; N, 15.65.

5-(3-Methoxybenzoyl)-1,3-dimethyl-7-thioxo-5,6,7,8-tetrahydropyrimido[4,5-*d*] pyrimidine-2,4(1*H*,3*H*)-dione (4g) White powder; mp 311 °C (dec.); FT-IR (KBr): 3299, 3159, 2945, 2845, 1673, 1650, 1598, 1555, 1516, 1468, 1430, 1321, 1255, 1177, 604, 508 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 12.80 (bs, 1H, OH), 8.62 (s, 2H, 2 × NH), 7.26 (t, J = 8.1 Hz, 1H, Ar), 7.08 (s, 1H, Ar),7.01 (d,

$J = 7.5$ Hz, 1H, Ar),6.86 (d, $J = 8.1$ Hz, 1H, Ar), 3.67 (s, 3H, OCH_3), 3.04 (s, 6H, $2 \times CH_3$). ^{13}C-NMR (75 MHz, DMSO-d_6): $\delta = 168.1$, 161.7, 159.3, 152.9, 132.2, 131.8, 130.6, 128.6, 119.2, 118.9, 118.5, 113.5, 77.6, 56.2, 28.2, 26.9. Anal. Calcd for $C_{16}H_{16}N_4O_4S$: C, 53.32; H, 4.48; N, 15.55. Found: C, 53.25, H, 4.43; N, 15.66.

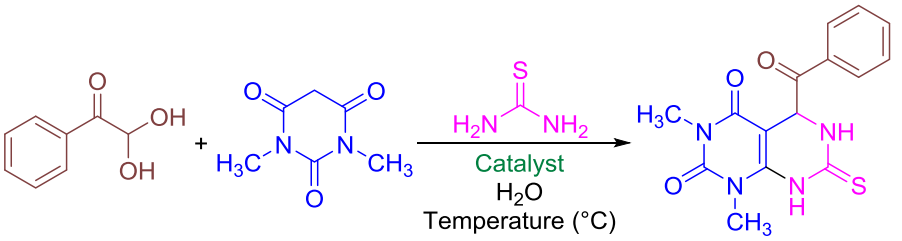
5-(3-Bromobenzoyl)-1,3-dimethyl-7-thioxo-5,6,7,8-tetrahydropyrimido[4,5-*d*] pyrimidine-2,4(1*H*,3*H*)-dione (4h) White powder; mp 328 °C (dec.); FT-IR (KBr): 3351, 3289, 3081, 3050, 2985, 2945, 1697, 1686, 1643, 1617, 1595, 1552, 1481, 1449, 1394, 1244, 790, 511 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6): $\delta = 12.80$ (bs, 1H, OH), 8.56 (s, 2H, $2 \times$ NH), 7.60 (s, 1H, Ar), 7.45 (d, $J = 7.8$ Hz, 2H, Ar), 7.40 (d, $J = 8.1$ Hz, 2H, Ar), 7.27 (t, $J = 7.5$ Hz, 1H, Ar), 6.86 (d, $J = 8.1$ Hz, 1H, Ar), 3.67 (s, 3H, OCH_3), 3.04 (s, 6H, $2 \times CH_3$). ^{13}C-NMR (75 MHz, DMSO-d_6): $\delta = 168.0$, 161.3, 152.7, 134.0, 131.9, 131.4, 130.4, 129.5, 129.2, 125.3, 121.7, 120.3, 78.5, 28.2, 27.0. Anal. Calcd for $C_{15}H_{13}BrN_4O_3S$: C, 44.02; H, 3.20; N, 13.69. Found: C, 44.06, H, 3.15; N, 13.77.

5-(4-Hydroxy-3-methoxybenzoyl)-1,3-dimethyl-7-thioxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4i) White powder; mp 304 °C (dec.); FT-IR (KBr): 3295, 3211, 2955, 1694, 1673, 1627, 1547, 1438, 1390, 1282, 1238, 1216, 778 cm^{-1}.^{1}H-NMR (300 MHz, DMSO-d_6): $\delta = 12.71$ (bs, 1H, OH), 9.28 (s, 1H, OH), 8.60 (s, 2H, $2 \times$ NH), 7.16 (s, 1H, Ar), 6.88 (d, $J = 8.4$ Hz, 1H, Ar), 6.74 (d, $J = 8.1$ Hz, 1H, Ar),3.62 (s, 3H, OCH_3), 3.04 (s, 6H, $2 \times CH_3$). ^{13}C-NMR (75 MHz, DMSO-d_6): $\delta = 168.2$, 162.0, 152.9, 147.4, 147.1, 121.8, 121.1, 119.4, 116.9, 116.1, 113.0, 111.2, 77.2, 56.5, 28.2, 27.1. Anal. Calcd for $C_{16}H_{16}N_4O_5S$: C, 51.06; H, 4.28; N, 14.89. Found: C, 50.88, H, 4.19; N, 15.01.

5-(3,4-Dimethoxybenzoyl)-1,3-dimethyl-7-thioxo-5,6,7,8-tetrahydropyrimido [4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4j) White powder; mp 322 °C (dec.); FT-IR (KBr): 3367, 3289, 3199, 1687, 1626, 1541, 1433, 1250, 1176, 809, 769, 630, 506 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6): $\delta = 12.70$ (bs, 1H, OH), 8.60 (s, 2H, $2 \times$ NH), 7.17 (s, 1H, Ar), 7.01 (d, $J = 8.1$ Hz, 1H, Ar), 6.95 (d, $J = 8.4$ Hz, 1H, Ar), 3.86 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 3.05 (s, 6H, $2 \times CH_3$).^{13}C-NMR (75 MHz, DMSO-d_6): $\delta = 168.3$, 162.0, 152.9, 149.1, 148.4, 132.6, 123.4, 117.6, 112.5, 111.4, 110.9, 110.7, 77.3, 56.4, 54.6, 28.1, 26.9. Anal. Calcd for $C_{17}H_{18}N_4O_5S$: C, 52.30; H, 4.65; N, 14.35. Found: C, 52.23, H, 4.61; N, 14.45.

5-(2,5-Dimethoxybenzoyl)-1,3-dimethyl-7-thioxo-5,6,7,8-tetrahydropyrimido [4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4k) White powder; mp 325 °C (dec.); FT-IR (KBr): 3340, 3287, 3093, 1697, 1642, 1619, 1585, 1556, 1497, 1439, 1241, 1217, 1023, 775 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6): $\delta = 12.34$ (s, 1H, OH), 8.60 (s, 2H, $2 \times$ NH), 7.10 (s, 1H, Ar), 6.98 (d, $J = 9$ Hz, 1H, Ar), 6.86 (d, $J = 6.6$ Hz, 1H, Ar), 3.73 (s, 3H, OCH_3), 3.56 (s, 3H, OCH_3), 3.00 (s, 6H, $2 \times CH_3$). ^{13}C-NMR (75 MHz, DMSO-d_6): $\delta = 167.1$, 161.8, 153.0, 150.7, 129.4, 120.3, 119.7, 116.7, 116.5, 115.0, 114.7, 112.1, 77.3, 56.5, 55.5, 28.1, 26.8. Anal. Calcd for $C_{17}H_{18}N_4O_5S$: C, 52.30; H, 4.65; N, 14.35. Found: C, 52.19, H, 4.59; N, 14.44.

Table 1 Screening of the reaction conditions

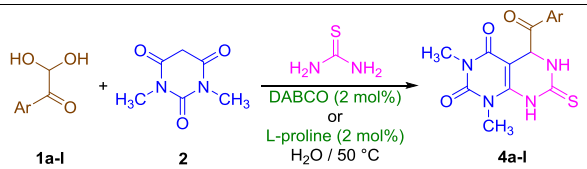


1a **2** **4a**

Entry	Catalyst (mol%)	Temperature (°C)	Time (h)	Yield (%)
1	–	50	24	50
2	DABCO (1%)	50	3	81
3	DABCO (2%)	20	24	44
4	DABCO (2%)	30	18	55
5	DABCO (2%)	40	8	70
6	**DABCO (2%)**	**50**	**3**	**85**
7	DABCO (2%)	60	3	83
8	DABCO (2%)	70	4	80
9	DABCO (2%)	80	6	77
10	DABCO (2%)	90	7	73
11	DABCO (2%)	100	8	61
12	DABCO (5%)	50	3	73
13	DABCO (10%)	50	4	61
14	DABCO (15%)	50	4	59
15	DABCO (20%)	50	5	58
16	DBN (2%)	50	3	79
17	DBN (5%)	50	3	81
18	DBN (10%)	50	4	69
19	DBN (15%)	50	4	66
20	DBN (20%)	50	5	64
21	DBU (2%)	50	3	79
22	DBU (5%)	50	3	81
23	DBU (10%)	50	4	73
24	DBU (15%)	50	4	72
25	DBU (20%)	50	5	69
26	L-proline (1%)	50	3	83
27	**L-proline (2%)**	**50**	**3**	**85**
28	L-proline (5%)	50	3	75
29	L-proline (10%)	50	3	62
30	L-proline (15%)	50	3	81
31	L-proline (20%)	50	3	79

Bold values indicate optimized reaction conditions

Table 2 Synthesis of pyrimido[4,5-*d*]pyrimidine derivatives



1a-l 2 4a-l

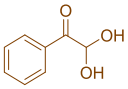
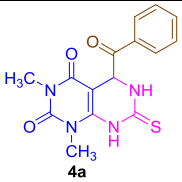
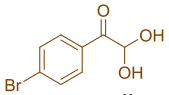
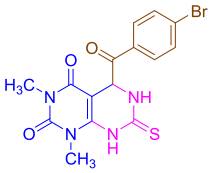
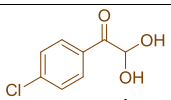
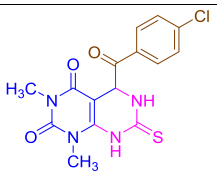
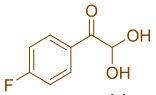
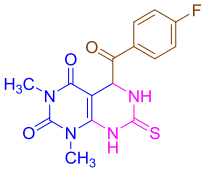
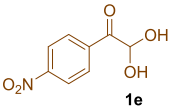
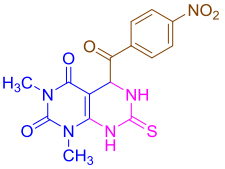
Entry	Arylglyoxal	Product	DABCO		L-proline	
			Time (h)	Yield (%)	Time (h)	Yield (%)
1	 1a	 4a	3	85	3	85
2	 1b	 4b	2	97	2	97
3	 1c	 4c	2	94	2	93
4	 1d	 4d	3	80	3	79
5	 1e	 4e	3	89	3	89

Table 2 continued

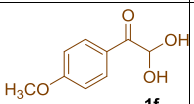
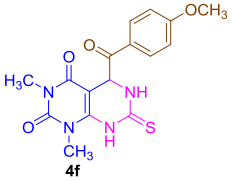
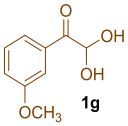
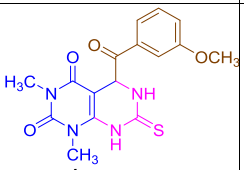
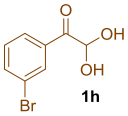
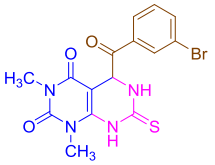
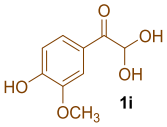
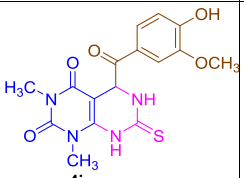
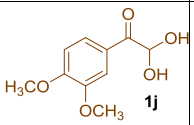
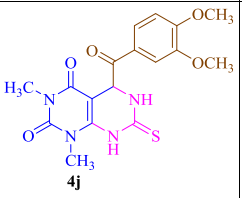
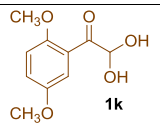
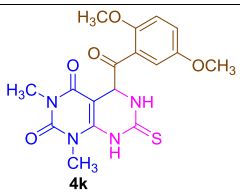
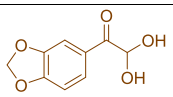
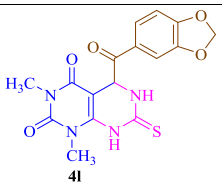
Entry	Arylglyoxal	Product	DABCO		L-proline	
			Time (h)	Yield (%)	Time (h)	Yield (%)
6	 **1f**	 **4f**	4	80	4	82
7	 **1g**	 **4g**	5	73	5	74
8	 **1h**	 **4h**	5	70	5	72
9	 **1i**	 **4i**	3	88	3	88
10	 **1j**	 **4j**	3	83	3	83

Table 2 continued

Entry	Arylglyoxal	Product	DABCO		L-proline	
			Time (h)	Yield (%)	Time (h)	Yield (%)
11	 1k	 4k	3	80	3	81
12	 1l	 4l	3	82	3	81

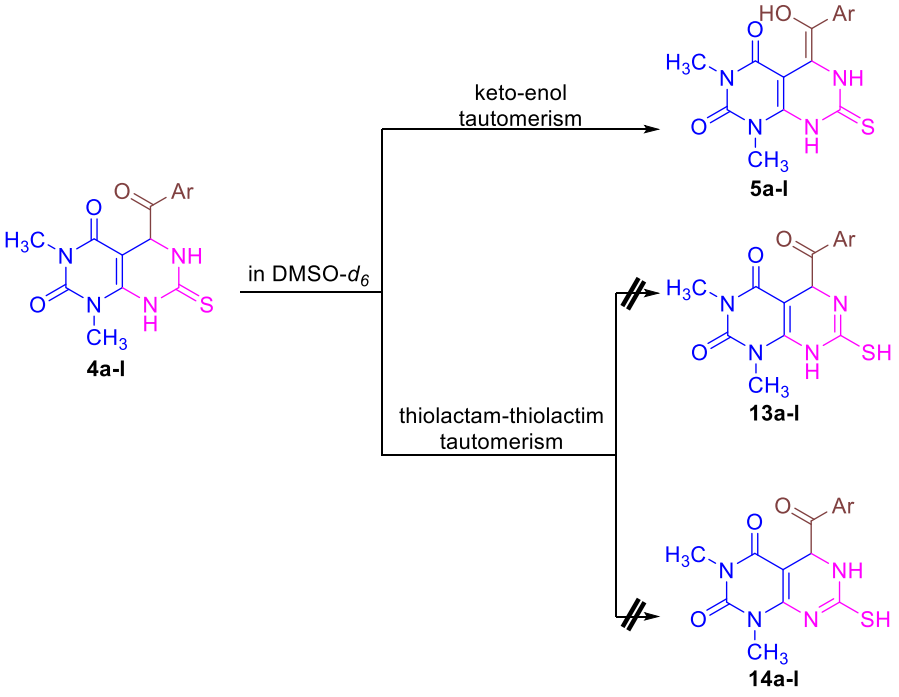
5-(Benzo[*d*] [1, 3] dioxole-5-carbonyl)-1,3-dimethyl-7-thioxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4l) White solid; mp 328 °C (dec.); FT-IR (KBr) ν_{max}: 3344, 3279, 3125, 3050, 1695, 1550, 1497, 1453, 1244, 1225, 1031, 510 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d_6): $\delta = 12.71$ (bs, 1H, OH), 8.56 (s, 2H, 2 × NH), 7.01 (s, 1H, Ar), 6.94 (d, $J = 8.7$ Hz, 1H, Ar), 6.90 (d, $J = 7.8$ Hz, 1H, Ar), 6.01 (s, 2H, CH_2), 3.04 (s, 6H, 2 × CH_3). ^{13}C-NMR (75 MHz, DMSO-d_6): $\delta = 168.1$, 161.8, 152.9, 147.4, 132.0, 124.9, 122.3, 120.8, 117.9, 109.2, 107.7, 107.2, 101.6, 77.4, 28.2, 26.9. Anal. Calcd for $C_{16}H_{14}N_4O_5S$: C, 51.33; H, 3.77; N, 14.97. Found: C, 51.11, H, 3.71; N, 15.10.

Results and discussion

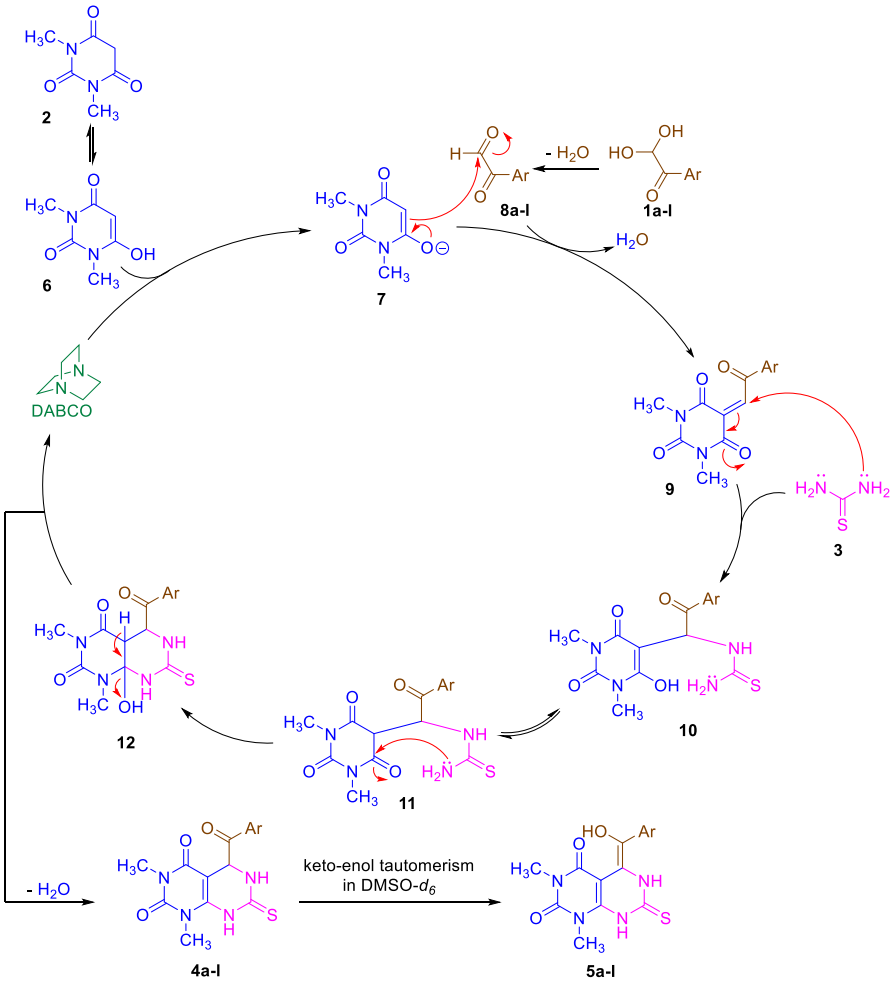
The vast biological importance of pyrimido[4,5-*d*]pyrimidine derivatives inspired us to develop a novel, highly efficient, simple and green protocol for their synthesis. For a low risk and eco-friendly process, water is used as the preferred solvent for all of the optimization experiments. The synthesis of pyrimido[4,5-*d*]pyrimidine **4a–l** was initiated by the one-pot, three-component reaction ofphenylglyoxalmonohydrate**1a**,1,3-dimethylbarbituric **2** and thiourea **3** with a molar ratio of 1:1:1 at 50 °C in water without using any catalyst. After 24 h, the expected pyrimido[4,5-*d*]pyrimidine **4a** was obtained only in 50 % yield. In further investigation, we attempted to improve the rate and yield by using various green catalysts such as 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and L-proline. Also, we checked the effect

of different ratios of catalyst loading on the reaction. Interestingly, the best result was obtained when we used DABCO (2 mol %) or L-proline (2 mol %) as catalyst (Table 1, entries 6 and 27). In order to optimize the reaction temperature, the reaction of **1a**, **2**and **3** was conducted in the presence of DABCO (2 mol %) at temperatures ranging from 20 °C to 100 °C, with an increment of 10 °C (Table 1, entries 3–11). The results showed that the reaction at 50 °C coincided with the highest yield of **4a**. Subsequently, these optimized conditions were applied for the conversion of various arylglyoxalmonohydrates into the corresponding 5-aryloyl-1,3-dimethyl-7-thioxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione derivatives **4a–l** (Table 2). The pyrimido[4,5-*d*]pyrimidine yields and reaction times were decisively affected by the electronic nature and the position of the substituent on arylglyoxalmonohydrates. The reaction time was slightly longer when the arylglyoxalmonohydrates contained the electron-donating substituents. The activity of arylglyoxalmonohydrates was higher with electron-withdrawing groups (such as *p*-Br, *p*-Cl) than that with electron-donating groups. Also, the arylglyoxalmonohydrates with meta-position substituents offered lower yields than para-position substituents.

The structure of final products were fully characterized by ^{1}H-NMR and ^{13}C-NMR, IR spectra and also elemental analysis. Noteworthy, based on spectral data, all of the obtained pyrimido[4,5-*d*]pyrimidine derivatives **4a–l** in the DMSO-d_6 solution converted to their enol forms **5a–l** via keto-enol tautomerization



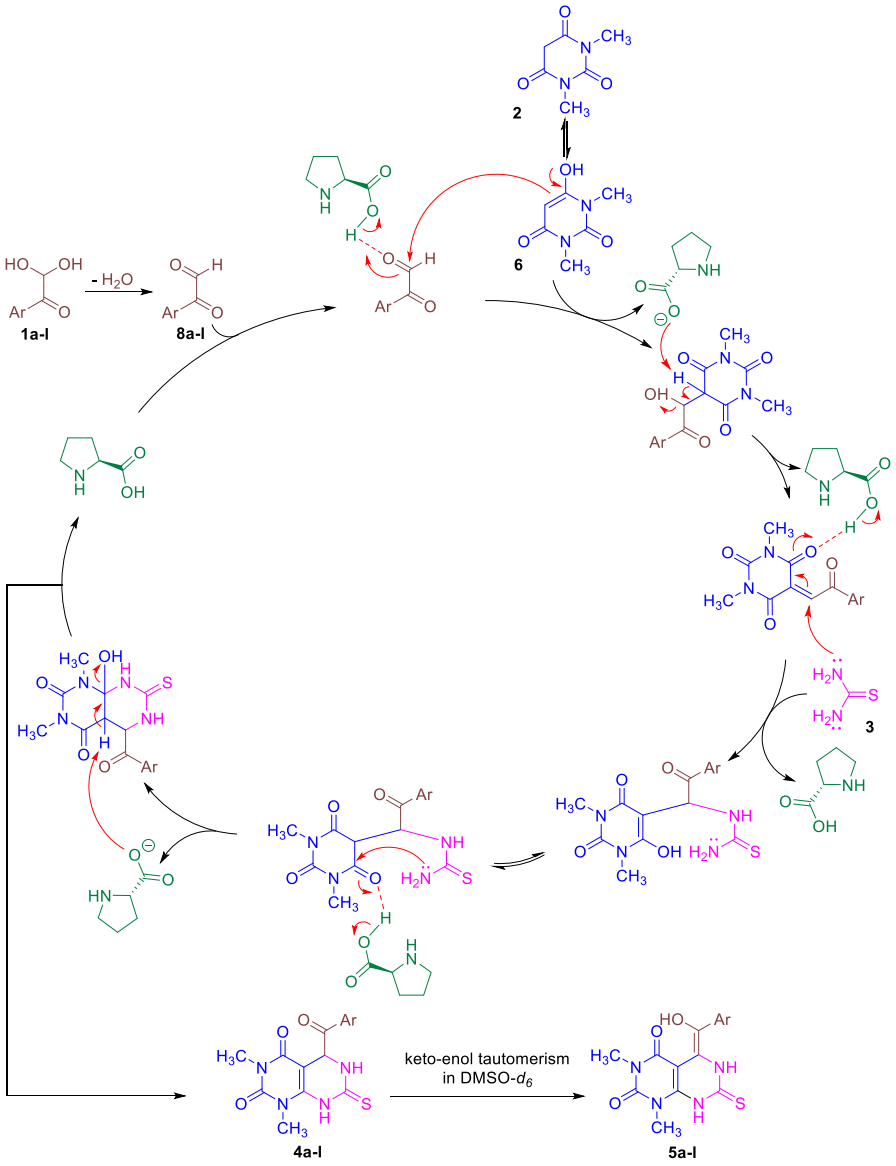
Scheme 2 Possible tautomerism of pyrimido[4,5-*d*]pyrimidine derivatives



Scheme 3 Plausible mechanism for the DABCO-catalyzed synthesis of pyrimido[4,5-*d*]pyrimidine derivatives

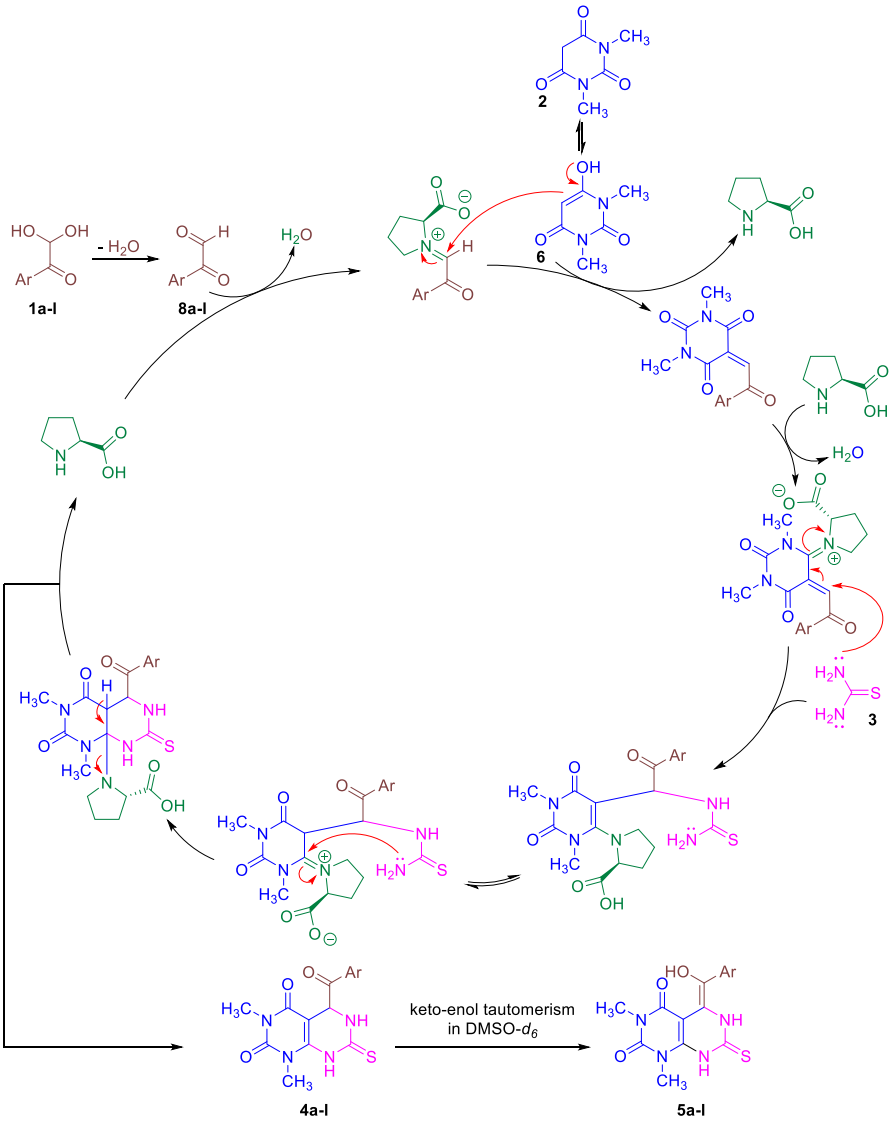
(Scheme 2). Similar to our recent reports [65, 66], the plausible explanation for the occurrence of the suggested keto-enol tautomerization is on the basis of the absence of C_5-H proton's singlet and the appearance of the OH proton's broad singlet, which can be stabilized through the formation of the favorable hydrogen-bonding with the adjacent C=O group.

Based on experimental observations, the plausible mechanism for the DABCO-catalyzed one-pot synthesis of 5-aryloyl-1,3-dimethyl-7-thioxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione derivatives is described in Scheme 3. The role of DABCO might just simply be serving as an effective general base. Initially, in the presence of DABCO, 1,3-dimethylbarbituric **2** is



Scheme 4 Suggested mechanism for the synthesis of pyrimido[4,5-*d*]pyrimidine derivatives catalyzed by L-proline (Path-A)

converted to the corresponding anionic form **7**. Then, regioselective Knoevenagel condensation of **7** with formyl group of arylglyoxal **8a–l** leads to the intermediate **9** with the elimination of water. Next, the Michael addition of thiourea **3** on the Knoevenagel adduct **9** results in the intermediate **10** and its keto-tautomers form **11**.



Scheme 5 Suggested mechanism for the synthesis of pyrimido[4,5-*d*]pyrimidine derivatives catalyzed by L-proline (Path-B)

Then, intramolecular nucleophilic attack of NH_2 to carbonyl group affords the final product **4a–l** (Scheme 3). The proposed mechanism for the synthesis of pyrimido[4,5-*d*]pyrimidine derivatives in the presence of L-proline, based on the literature [67–79], is shown in the Schemes 4 (path A) and 5 (path B).

Conclusion

In summary, we have developed a novel, green and highly efficient method for the regio- and chemoselective synthesis of 5-aryloyl-1,3-dimethyl-7-thioxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidine-2,4(1*H*,3*H*)-dione derivatives by one-pot, three-component reaction of arylglyoxalmonohydrates with 1,3-dimethylbarbituric acid and thioureacatalyzed by DABCO or L-proline as green organocatalysts. This method has advantages, such as simple operation, high regio- and chemoselectivity, mild reaction conditions, high atom-economy, easy work-up, and good to excellent yields.

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