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Facile one-pot synthesis of pyrimido[4,5-*d*]pyrimidine-2,4-diones in Ionic Liquid and study of their antibacterial activities

Ayoob Bazgir[a], Seyyedeh Cobra Azimi*[b]

[a]*Department of Chemistry, Shahid Beheshti University, P.O. Box 1983963113, Tehran, Iran*
[b]*Young Researchers Club, Rasht Branch, Islamic Azad University, Rasht, Iran*

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ABSTRACT

A simple, novel, efficient and three-component procedure for the synthesis of pyrimido[4,5-*d*]pyrimidine-2,4-dione derivatives by the reaction of 6-amino-1,3-dimethyluracil, aldehyde and 2-benzylisothiourea hydrochloride promoted by ionic liquid 1-butyl-3-methylimidazolium bromide ([BMIm]Br) under solvent-free conditions is reported. The presented method is benefited from operational simplicity, simple workup and reusability of ionic liquid. These products were evaluated *in vitro* for their antibacterial activities.

Keywords*: Ionic liquid; Pyrimido[4,5-d]pyrimidine-2,4-dione; 6-Amino-uracil; Antibacterial activities.*

1. Introduction

Exploiting ionic liquids as solvents and catalysts have attracted much attention in the context of green synthesis [1]. Considerable attention in various fields such as chemistry, biocatalysis, separation science, material synthesis, and electrochemistry are devoted to such liquids [2]. They have several interesting properties such as excellent chemical and thermal stability, non-volatility, non-coordinating nature, good solvating capability, wide liquid range and ease of recycling. Also, they have the capability to dissolve vast ranges of organic and inorganic materials [3]. Although ionic liquids were initially introduced as an alternative green reaction medium, today they have marched far beyond this border, showing their significant role in controlling the reactions as solvent or catalysts [4-11] Pyrimidines and fused pyrimidines represent a broad class of compounds, which have received considerable attention due to their wide range of biological activities [12-15] Among them, the pyrimido[4,5-*d*]pyrimidines are an important class of annulated uracils with biological significance because of their connection with purine pteridine systems. Compounds with these ring systems have diverse pharmacological activities such as antitumour [16], antioxidant [17], hepatoprotective [18], antiviral [19], antimalarials [20], and anticancer activity [21,22]. Moreover, uracil derivatives are well known for their anti-HIV activities [23].

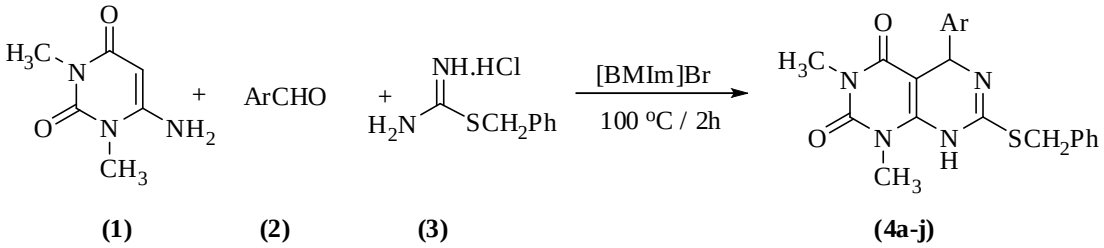
Based on the above information and due to the synthetic strategies for the construction of novel fused uracil as a biologically active pharmacophore [24-30], we have reported a novel and facile methodology for the synthesis of pyrimido[4,5-*d*]pyrimidine derivatives under [BMIm]Br ionic liquid as a promoter (Scheme 1).

2. Experimental

2.1. General

All chemicals were purchased from Merck or Fluka Chemical Companies. All products were characterized by physical data (mp), and spectral data (IR, ^{1}H NMR, ^{13}C NMR). Melting points were measured on an Electrothermal 9200 apparatus. IR spectra were obtained on a Shimadzu FTIR-8400S spectrometer. ^{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.

*Corresponding author: E-mail: tazimi_2005@yahoo.com. Tel./ Fax: +98 131 2233271.



Scheme 1. [BMIm]Br ionic liquid promoted synthesis of pyrimido[4,5-*d*]pyrimidines.

*2.2. General procedure for preparation of 1,3-dimethyl-7-(benzylthio)-5-phenyl-pyrimido[4,5-d] pyrimidine-2,4(1H,3H,5H,8H)-dione **(4a)***

A mixture of 6-amino-1,3-dimethyluracil (1 mmol), benzaldehyde (1 mmol), and 2-benzylisothiourea hydrochloride (1.5 mmol) was heated at 100 °C using 6.0 mmol (1.3 g) of [BMIm]Br as a promoter. The progress of the reaction was monitored by thin-layer chromatography (TLC). After completion of the reaction, the mixture was washed with water (2×15 mL) and then recrystallized from EtOAc/*n*-hexane (1:3) to afford the pure product (341.0 mg, 87%). The same procedure was also used for the other products listed in Table 1.

The selected spectral data

1,3-dimethyl- 7-(benzylthio)- 5-phenyl-pyrimido [4,5-*d*] pyrimidine -2,4(1*H*,3*H*,5*H*,8*H*)-dione (**4a**)**:** White Solid, m.p. 208-210 °C, IR (KBr, cm^{-1}): 3268, 1683, 1638, 1469, 1283, 1249; ^{1}H NMR (300.1 MHz, DMSO-d_6, ppm) δ: 3.09 (s, 3H), 3.43 (s, 3H), 4.35 and 4.50 (AB system, *J*= 12.8 Hz, 2H,), 5.43 (s, 1H), 7.27-7.38 (m, 10H_{arom}), 9.71 (s, 1H, NH); ^{13}C NMR (75.5 MHz, DMSO-d_6, ppm) δ: 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.

1,3-dimethyl-7-(benzylthio)-5-(4-chlorophenyl)-pyrimido [4,5-*d*]pyrimidine-2,4(1*H*,3*H*,5*H*,8*H*)-dione (**4b**): White Solid, m.p. 266-268 °C, IR (KBr, cm^{-1}): 3266, 1683, 1640, 1512, 1472, 1248; ^{1}H NMR (300.1 MHz, DMSO-d_6, ppm) δ: 3.08 (s, 3H), 3.41 (s, 3H), 4.35 (bd, 2H), 5.44 (s, 1H), 7.29-7.36 (m, 9H_{arom}), 9.72 (s, 1H, NH); ^{13}C NMR (75.5 MHz, DMSO-d_6, ppm) δ: 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.

1,3-dimethyl-7-(benzylthio)-5-(4-bromophenyl)-pyrimido [4,5-*d*]pyrimidine-2,4(1*H*,3*H*,5*H*,8*H*)-dione (**4c**): White Solid, m.p. 258-260 °C, IR (KBr, cm^{-1}): 3266, 1683, 1640, 1511, 1420; ^{1}H NMR (300.1 MHz, DMSO-d_6, ppm) δ: 3.09 (s, 3H), 3.42 (s, 3H), 4.35 and 4.50 (AB system, *J*= 13.7 Hz, 2H), 5.43 (s, 1H), 7.20-7.54 (m, 9H_{arom}), 9.71 (s, 1H, NH); ^{13}C NMR (75.5 MHz, DMSO-d_6, ppm) δ: 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.

1,3-dimethyl-7-(benzylthio)-5-(4-methylphenyl)-pyrimido 4,5-*d*]pyrimidine-2,4(1*H*,3*H*,5*H*,8*H*)-dione (**4d**): White Solid, m.p. 270-272 °C, IR (KBr, cm^{-1}): 3265, 1680, 1638, 1557, 1421; ^{1}H NMR (300.1 MHz, DMSO-d_6, ppm) δ: 2.25 (s, 3H), 3.09 (s, 3H), 3.42 (s, 3H), 4.34 and 4.49 (AB system, *J*= 13.0 Hz, 2H), 5.38 (s, 1H), 7.12-7.38 (m, 9H_{arom}), 9.67 (s, 1H, NH); ^{13}C NMR (75.5 MHz, DMSO-d_6, ppm) δ: 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.

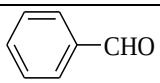
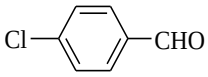
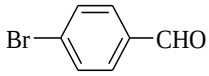
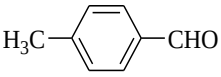
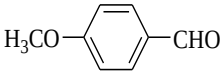
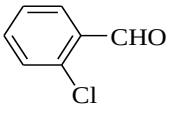
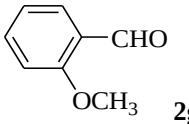
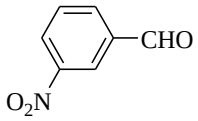
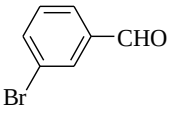
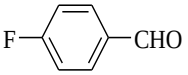
1,3-dimethyl-7-(benzylthio)-5-(4-methoxyphenyl)-pyrimido [4,5-*d*]pyrimidine-2,4(1*H*,3*H*,5*H*,8*H*)-dione (**4e**): White Solid, m.p. 234-236 °C, IR (KBr, cm^{-1}); 3273, 1683, 1639, 1512, 1470; ^{1}H NMR (300.1 MHz, DMSO-d_6, ppm) δ: 3.09 (s, 3H), 3.42 (s, 3H), 3.71 (s, 3H), 4.35 and 4.49 (AB system, *J*= 13.6 Hz, 2H), 5.36 (s, 1H), 6.86-7.40 (m, 9H_{arom}), 9.66 (s, 1H, NH); ^{13}C NMR (75.5 MHz, DMSO-d_6, ppm) δ: 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.

1,3-dimethyl-7-(benzylthio)-5-(2-chlorophenyl)-pyrimido [4,5-*d*]pyrimidine-2,4(1*H*,3*H*,5*H*,8*H*)-dione (**4f**): White Solid, m.p.138-140 °C, IR (KBr, cm^{-1}); 3207, 1693, 1632, 1472, 1286; ^{1}H NMR (300.1 MHz, DMSO-d_6, ppm) δ: 3.05 (s, 3H), 3.45 (s, 3H), 4.35 and 4.46 (AB system, *J*= 13.4 Hz, 2H), 5.84 (s, 1H), 7.30-7.39 (m, 9H_{arom}), 9.60 (s, 1H, NH); ^{13}C NMR (75.5 MHz, DMSO-d_6, ppm) δ: 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.

1,3-dimethyl-7-(benzylthio)-5-(2-methoxyphenyl)-pyrimido [4,5-*d*]pyrimidine-2,4(1*H*,3*H*,5*H*,8*H*)-dione (**4g**). White Solid, m.p. 223-225 °C, IR (KBr, cm^{-1}): 3274, 1676, 1639, 1474, 1285; ^{1}H NMR (300.1 MHz, DMSO-d_6, ppm) δ: 3.07 (s, 3H), 3.45 (s, 3H), 3.74 (s, 3H), 4.33 and 4.43 (AB system, *J*= 13.4 Hz, 2H), 5.71 (s, 1H), 6.86-7.36 (m, 9H_{arom}), 9.34 (s, 1H, NH); ^{13}C NMR (75.5 MHz, DMSO-d_6, ppm) δ: 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.

1,3-dimethyl-7-(benzylthio)-5-(3-nitrophenyl)-pyrimido [4,5-*d*]pyrimidine-2,4(1*H*,3*H*,5*H*,8*H*)-dione

Table 1. Synthesis of pyrimido[4,5-*d*]pyrimidine-2,4-diones **4a-j** [a].

Entry	Aldehyde	Product [b]	Yield (%) [c]	m.p. (°C) found	m.p. (°C) reported [d]
1	 **2a**	**4a**	87	208-210	208-210
2	 **2b**	**4b**	77	266-267	266-268
3	 **2c**	**4c**	82	259-261	258-260
4	 **2d**	**4d**	83	271-273	270-272
5	 **2e**	**4e**	80	233-235	234-236
6	 **2f**	**4f**	75	139-140	138-140
7	 **2g**	**4g**	79	222-224	223-225
8	 **2h**	**4h**	77	232-234	232-234
9	 **2i**	**4i**	75	176-178	177-179
10	 **2j**	**4j**	85	238-239	238-240

[a]Reaction time= 2 h.
[b]All products were characterized by ^{1}H NMR, ^{13}C NMR and IR spectral data and comparision of their melting points with those of authentic samples.
[c]Isolated yield.
[d]Reference 26.

(**4h**): White Solid, m.p. 232-234 ^{o}C, IR (KBr, cm^{-1}): 3244, 1681, 1639, 1527, 1473, 1350; ^{1}H NMR (300.1 MHz, DMSO-d_6, ppm) δ: 3.09 (s, 3H), 3.43 (s, 3H), 4.38 and 4.51 (AB system, *J*= 13.7 Hz, 2H), 5.66 (s, 1H), 7.26-8.15 (m, 9H$_{arom}$), 9.81 (s, 1H, NH); ^{13}C NMR (75.5 MHz, DMSO-d_6, ppm) δ: 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.

1,3-dimethyl-7-(benzylthio)-5-(3-bromophenyl)-pyrimido[4,5-*d*]pyrimidine-2,4(1*H*,3*H*,5*H*,8*H*)-dione (**4i**): White Solid, m.p. 177-179 ^{o}C, IR (KBr, cm^{-1}): 3247, 1681, 1637, 1474, 1284; ^{1}H NMR (300.1 MHz, DMSO-d_6, ppm) δ: 3.10 (s, 3H), 3.43 (s, 3H), 4.37 and 4.49 (AB system, *J*= 13.7 Hz, 2H), 5.47 (s, 1H), 7.25-7.48 (m, 9H$_{arom}$), 9.73 (s, 1H, NH); ^{13}C NMR (75.5 MHz, DMSO-d_6, ppm) δ: 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.

1,3-dimethyl-7-(benzylthio)-5-(4-fluorophenyl)-pyrimido [4,5-*d*]pyrimidine-2,4(1*H*,3*H*,5*H*,8*H*)-dione (**4j**): White Solid, m.p. 238-240 ^{o}C, IR (KBr, cm^{-1}): 3257, 1685, 1639, 1474; ^{1}H NMR (300.1 MHz, DMSO-d_6, ppm) δ: 3.09 (s, 3H), 3.43 (s, 3H), 4.35 and 4.51 (AB system, *J*= 13.7 Hz, 2H), 5.45 (s, 1H), 7.12-7.38 (m, 9H$_{arom}$), 9.71 (s, 1H, NH); ^{13}C NMR (75.5 MHz, DMSO-d_6, ppm) δ: 27.8, 29.5, 34.3, 52.2, 88.0, 115.7 (d, $^{2}J_{CF}$= 21.2 Hz), 127.8, 128.9 (d, $^{3}J_{CF}$= 8.1 Hz), 129.1, 129.2, 137.8, 140.8, 149.8, 151.9, 160.7, 161.4 (d, $^{1}J_{CF}$= 214.2 Hz), 165.1.

Table 2. Optimization of the reaction conditions [a].

Entry	Condition [b]	Catalyst	Yield (%) [c]
1	Solvent-free/ 120 °C	*p*-TSA	85 [d]
2	Solvent-free/ 100 °C	*p*-TSA	61 [d]
3	Solvent-free/ 120 °C	-	<30 [d]
4	EtOH (reflux)	*p*-TSA	<38 [d]
5	EtOH (reflux)	HCl	<35 [d]
6	Solvent-free/ 25 °C	$[BMIm]BF_4$	-
7	Solvent-free/ 100 °C	$[BMIm]BF_4$	53
8	Solvent-free/ 25 °C	[BMIm]Cl	-
9	Solvent-free/ 25 °C	[BMIm]Br	<43
10	Solvent-free/ 100 °C	[BMIm]Cl	<35
11	Solvent-free/ 100 °C	[BMIm]Br	87

[a]A mixture of 6-amino-1,3-dimethyluracil (1), benzaldehyde (2a), and 2-benzylisothiourea hydrochloride (3).
[b]Reaction time= 2 h.
[c]Isolated yield.
[d]Reference 26.

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**): White Solid, m.p. 306-308 °C, IR (KBr, cm^{-1}): 3456, 3389, 3201, 2998, 1698; ^{1}H NMR (300.1 MHz, DMSO-d_6, ppm) δ: 3.14 (s, 6H), 3.32 (s, 6H), 5.58 (s, 1H), 7.08-7.21 (m, $5H_{arom}$), 7.44 (bs, 4H, NH_2); ^{13}C NMR (75.5 MHz, DMSO-d_6, ppm) δ: 28.4, 30.4, 35.8, 86.6, 125.3, 127.0, 128.1, 140.1, 151.0, 154.7, 163.4.

1,3,7,9-tetramethyl-5-phenyl-9,10-dihydropyrido[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6,8(1*H*,3*H*,5*H*,7*H*)-tetraone (**8**): White Solid, m.p >310 °C, IR (KBr, cm^{-1}): 3500, 3389, 3200, 3000, 1780, 1740; ^{1}H NMR (300.1 MHz, DMSO-d_6, ppm) δ: 3.36 (s, 6H, $2CH_3$), 3.50 (s, 6H, $2CH_3$), 5.21 (s, 1H, CH), 7.10-7.36 (m, $5H_{arom}$), 9.06 (bs, 1H, NH).

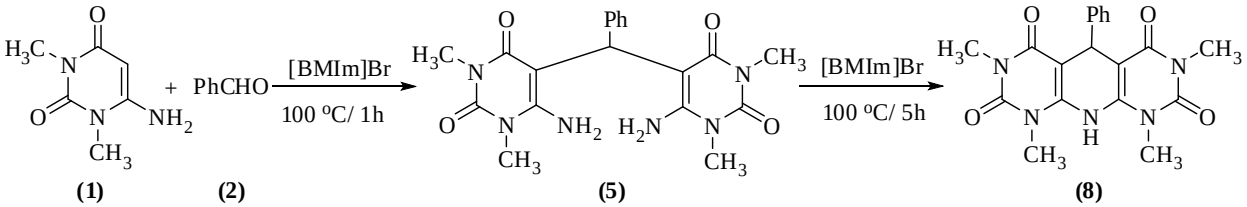
3. Results and Discussion

We first studied a reaction between 6-amino-1,3-dimethyluracil, benzaldehyde and 2-benzyl isothiourea hydrochloride by screening the reaction conditions. To determine the optimum conditions, we examined the influence of the reaction temperature, choice of solvent, and the type of IL (Table 2). Throughout the reaction, the conditions were optimized for a 100% conversion. It could be seen that the best result was obtain with 6.0 mmol (1.3 g) of [BMIm]Br at 100 °C (Table 2, Entry 11)**.** After optimizing the conditions, we next examined the generality of these conditions to other substrates using several aromatic aldehydes bearing electron-withdrawing and electron-donatingroups (Scheme 1). The results are summarized in Table 1. As indicated in Table 1, in all cases the reaction gives the products in good yields and prevents problems associated with solvent use such as cost, handling, safety and pollution. The ionic liquid is recovered from the aqueous extracts of the reaction mixtures by evaporation of water under reduced pressure. It retains almost the early activity after recovery when reused in the next successive cycles (Table 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 benzaldehyde with similar conditions to ([BMIm]Br / 100 °C) gave 5-aryl -1,3,7,9-tetramethylpyrido [2,3 *d*:6,5-*d*] dipyrimidine-2,4,6,8-tetrone **8** in 30–40% yields (Scheme 2). The structures of compounds **4a–j** were confirmed by IR, ^{1}H and ^{13}C NMR spectroscopy. The IR spectrum of compound **4a**, for example, show absorption bands at 3268, 1683 and 1638 cm^{-1} indicating the presence of N-H and C=O groups in this molecule. Aromatic protons of this compound were seen at δ 7.27-7.38 in its ^{1}H NMR spectrum resonating with proper integrals and splittings. Aliphatic region of this spectrum exhibits two singlet peaks at δ 3.09 and 3.43 arising from protons of the two methyl groups along with the characteristic sharp signal of the methine proton at

Table 3. The effect of [BMIm]Br recycling on the **4a** yield [a].

Entry	Cycle	Yield (%) [b]
1	fresh	87
2	first recycle	86
3	second recycle	84

[a]Reaction conditions: A mixture of 6-amino-1,3-dimethyluracil **1** (1.0 mmol), benzaldehyde **2a** (1.0 mmol), and 2-benzyl isothiourea hydrochloride **3** (1.5 mmol), (6.0 mmol, 1.3 g) of [BMIm]Br at 100 °C.
[b]Isolated yields.



Scheme 2. Synthesis of 1,3,7,9-tetramethyl-5-phenyl-9,10-dihydropyrido[2,3-*d*:6,5-*d'*]dipyrimidine-2,4,6,8(1*H*,3*H*,5*H*,7*H*)-tetraone in the presence of [BMIm]Br ionic liquid.

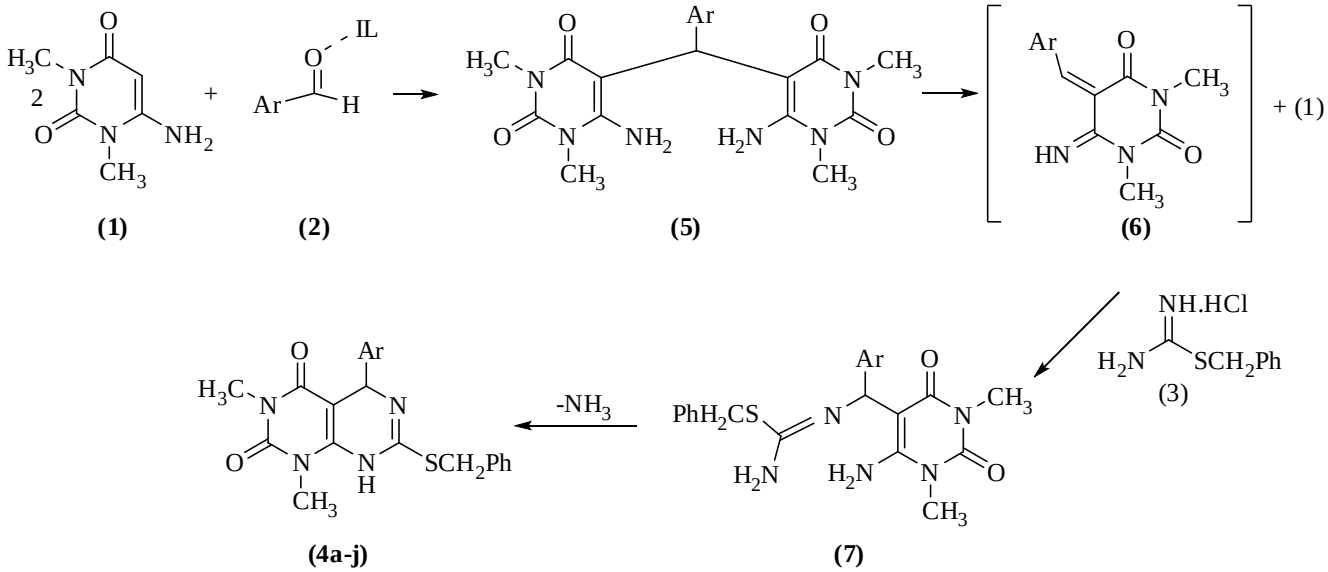
δ = 5.43 and AB system the benzylic methylene protons at δ 4.50. In addition, there is one singlet signal appeared at δ 9.71 in the spectrum accounting for the presence of the N-H group in the molecule. The ^{13}C NMR spectrum of **4a** displays 17 distinct lines with appropriate chemical shifts corresponding to the structure of this compound.

The reaction can be mechanistically considered as proceeding via the initial formation of the intermediate **5**, by in situ condensation reaction of the aldehyde with 6-amino-1,3-dimethyluracil. Then, the intermediate **5** was converted to imine **6**. The subsequent addition of 2-benzylisothiourea hydrochloride to the imine **6** followed by cyclization of the intermediate **7** resulted in the corresponding products **4a-j** and ammonia (Scheme 3).

Finally, the synthesized pyrimido[4,5-*d*]pyrimidine derivatives **4a-j** were screened for antimicrobial activity. The microorganisms used in this study were Escherichia coli ATCC 25922, Pseudomonas aeruginusa ATCC 85327 (as gram-negative bacteria), Bacillus subtilis ATCC465, and Staphylococcus aureus ATCC 25923 (as gram-positive bacteria). The minimum inhibitory concentrations (MIC) of compounds **4a-j** were determined by microdilution method [31] (Table 4). As can be seen from Table 4, good antibacterial activities were observed for most of the compounds against all species of gram-positive and gram-negative bacteria used in this study.

4. Conclusions

In this paper, we have introduced a straightforward, efficient, and cost-effective synthesis of pyrimido[4,5-*d*]pyrimidine-2,4-(1*H*,3*H*,5*H*,8*H*)-dione derivatives in the presence of ionic liquid 1-butyl-3-methylimidazolium bromide ([BMIm]Br) under solvent-free conditions. High yields, short reaction times, simplicity of operation, and easy workup are some advantages of the presented approach. Also neither additional catalyst nor solvent is necessary Almost most of the compounds exhibited good to excellent antibacterial activity against all the tested strains.



Scheme 3. Plausible mechanism for the synthesis of pyrimido[4,5-*d*]pyrimidine derivatives in the presence of [BMIm]Br ionic liquid.

Table 4. MIC (mg/mL) values of products **4a-j**.

Product	Escherichia coli	Pseudomonas aeruginus	Bacillus subtilis	Staphylococcus aureus
4a	8	32	16	64
4b	a	128	8	32
4c	4	8	16	128
4d	16	64	128	32
4e	32	16	8	64
4f	a	8	128	128
4g	16	8	16	32
4h	a	64	a	16
4i	a	16	32	128
4j	a	32	64	8
Norfloxacin	<2	20	2	16
Tetracycline	a	a	4	4

[a]Not active

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