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NOVEL [DBN][HSO_4] MEDIATED FACILE AND EFFICIENT SYNTHESIS OF DIHYDROPYRIMIDO [*4, 5-D*]PYRIMIDINE DERIVATIVES

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ABSTRACT

A [DBN][HSO_4] bronsted acidic ionic liquid promoted condensation followed by cyclization protocol has been developed for the first time by a successive reaction of aldehydes, barbituric acid and urea to afford dihydropyrimido [*4,5-d*] pyrimidine derivatives in high to excellent yields under microwave irradiation (MW=240W). The ionic liquid provided the capability to allow a variability of functional groups, easy workup, short reaction times, and recyclability of the catalyst, high yields and solvent-free conditions, thus providing economic and environmental advantages.

Keywords: [DBN][HSO_4], Environmentally benign, Dihydropyrimido [*4,5-d*] pyrimidine, Multicomponent reactions, Microwave irradiation.

1. INTRODUCTION

1,4-Dihydropyridine (DHP) motif represents the heterocyclic unit of significant pharmacological competence [1]. Dipyrimido-dihydropyridines having DHPs as privileged pharmacophore provide imperative ligands for biological receptors [2]. These compounds, although described for the first time more than a century ago, have recently been recognized as vital drugs such as felodipine and amlodipine (Fig. 1) as antihypertensive
and calcium channel blockers. Moreover, DHPs also act as nicotinamide adenine dinucleotide (NADH) mimics for the reduction of carbonyl compounds and their derivatives [3]. In human body, the main metabolic route of dihydropyridine drugs involves their oxidation to pyridines catalyzed by cytochrome P450 in liver [4]. Pyrimidines represent one of the most biologically, and pharmaceutically active *N*-containing class of compounds [5]. Pyrimidine derivatives serve as antineoplastic [6], antibacterial [7], anti-HIV [8], antibiotic [9], antifungal [10], and antitubercular agents [11]. Pyrimidine bases like thymine, cytosine, and uracil are the essential building blocks of nucleic acids. Many established drugs containing a pyrimidine nucleus are reported in the literature, namely 5-fluorouracil as an anticancer drug [12], idoxuridine as an antiviral drug [13] etc. When this pyrimidine moiety is fused with different heterocycles, it results in hybrid scaffolds with improved activity. Pyrido [*2,3-d*] pyrimidines are such pyrimidine based hybrid scaffolds, which have attracted considerable attention due to their broad biological and medicinal applications [14].

Barbituric acid is one of the most important nitrogen-containing heterocyclic systems; it is found in various natural and synthesized compounds of anti-inflammatory, analgesics, anesthetics, drugs, anticancer drugs, anxiolytics, HIV/AIDS protease inhibitors, and others [15a]. Phenobarbital and Riboflavin (vitamin B_2) are vital molecules in the market having barbituric acid as one of the pharmacophores (Fig. 1) [15b]. Thus, the extension of synthetic route for the construction of this molecule using an reusable, economical, nontoxic and mild catalyst is of massive importance from the academic and industrial points of view. Even though various modes have been reported in the literature, these reactions can be accomplished under a variability of tentative conditions, and several improvements have been reported in recent years, such as Zn_2þ@KSF [16a], Fe_3O_4@SiO_2 [16b], SiO_2 composite [17] and L-proline [18] as catalysts which usually requires forcing conditions, long reaction times and complex synthetic pathways. Therefore, there is a need to develop more efficient and sustainable chemical process for the synthesis of pyrimido [4,5-d] pyrimidines.

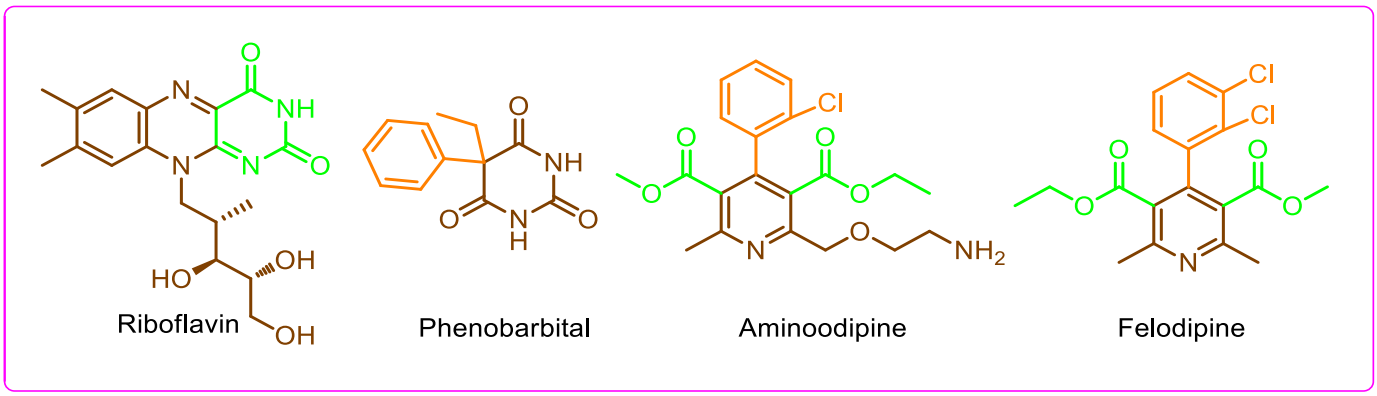


Fig. 1: Dihydropyrimido[*4,5-d*]pyrimidine incorporated bioactive molecules

Multicomponent reactions (MCRs) have received increasing attention due to their simplicity, efficiency, atom economy, short reaction times and the possibility for diversity-oriented synthesis [19]. Moreover, the incorporation of solvent-free methods in MCRs makes the process cleaner, safer and easier to perform [20]. Thus, the utilization of MCRs coupled with environmentally benign solvent-free condition is highly desirable. Owing to an extensive range of MCRs applications in different areas like the preparation of different structural scaffolds and the detection of new drugs, these types of reactions have drawn considerable attention in organic synthesis and pharmaceutical chemistry [21]. Besides, Ionic liquids (ILs) have taken the attention of the chemical community all over the globe as a green alternative option to traditional ecofriendly media for catalysis, synthesis, separation, and other several chemical tasks [22-27]. ILs include numerous exclusive properties, such as extensive liquid range, nonvolatility, low toxicity, high thermal stability, noncombustible, excellent solubility, and recyclability [28]. ILs act as "neoteric solvents" for a wide range of industrial and chemical processes. In recent times, ILs have been originating to be valuable as environmental friendly media for countless organic revolutions [29, 30]. Recently, DBN was widely used as catalysts in different research area. The combination of DBN with cation gives the formation of novel ionic liquids [31]. The large number of functionalized ILs has been considered for diverse purposes [32].

The use of microwave irradiation in combination with ILs, which has very high heat capacity, high polarity and no vapor pressure, and their high potentiality to absorb microwaves and convert them into heat energy, may accelerate the reaction very quickly. The synergy of microwave and ionic liquid in catalyst-free methodologies for the synthesis of heterocyclic compounds has attracted much interest because of the shorter reaction time, milder conditions, reduced energy consumption and higher product selectivity and yields [33].

As per our investigation, the existential of this work is to begin a rapid and efficient synthetic protocol for obtaining dihydropyrimido [*4,5-d*] pyrimidine derivatives under ecofriendly conditions. As an extension of emerging economic and efficient strategy to develop pharmaceutically and biologically significant molecules, herein, we reported synthesis of library of dihydro-pyrimido [*4,5-d*] pyrimidine derivatives promoted by synergistic effect of ionic liquid without any added catalyst in good to excellent yields.

2. EXPERIMENTAL

2.1. Material and methods

All the chemicals and solvents were purchased with high purities and used without further purification. The progress of the reaction was monitored by gas chromatography (GC) with a flame ionization detector (FID) with a capillary column (30 m 0.25 mm 0.25 lm) and thin layer chromatography (using silica gel 60 F-254 plates). The products were visualized with a 254 nm UV lamp. Products were purified by column chromatography on 100-200 mesh silica gel. The 1H NMR spectra were recorded on 400 MHz spectrometers using tetramethylsilane (TMS) as an internal standard. The ^{13}C NMR spectra were recorded at 100 MHz and chemical shifts were reported in parts per million (d) relative to tetramethylsilane (TMS) as an internal standard. Coupling constant (J) values were reported in hertz (Hz). The splitting patterns of the proton are described as s (singlet), d (doublet), dd (doublet of doublet), t (triplet), and m (multiplet) in

1H NMR spectroscopic analysis. The products were confirmed by ^{1}H and ^{13}C NMR spectroscopy analysis.

2.2. Preparation of [DBN][HSO_4]

General Procedure for the Synthesis of [DBN][HSO_4] are given in supporting information.

2.3. General Procedure for Synthesis of dihydropyrimido [4,5-d] pyrimidine derivatives (4a-l)

A mixture of aryl aldehyde (**1a**) (100 mg), barbituric acid (**2a**) (120 mg), urea (**3**) (56 mg) and ionic liquid [DBN][HSO_4] 20 mol% were kept under microwave irradiation at 280 W for 7 min. The progress of the reaction was monitored by thin layer chromatography (*n*-Hexane/EtOAc 8:2). Further, addition of ice cold water (10mL) was added and stirred for 15 min and filtered. The obtained solid was filtered, washed with cold water to remove the ionic liquid. The obtained crude compounds were recrystallized using ethanol. The synthesized compound is confirmed by MP, ^{1}H NMR and ^{13}C NMR spectra.

2.3.1. Characterization of 5-phenyl-5,6-dihydro-pyrimido[4,5-d]pyrimidine-2,4,7(1H,3H, 8H)-trione (4a)

The compound **4a** was synthesized from condensation reaction **1a, 2** and **3** as white solid; Mp: 243-244 °C; Yield 93%; 1H NMR (400 MHz, CDCL3, ppm): 11.36 (s, 1H, NH), 11.20 (s, 1H, NH), 10.25 (s, 1H, NH), 8.38 (s, 1H, NH), 7.20 (t, J = 7.8 Hz, 2H), 7.14-7.00 (m, 3H), 5.38 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.01 (C=O), 158.32 (C=O), 154.24 (C=O), 142.2 (C=C), 136.1 (Ar-C=C), 128.5 (Ar-C=C), 126.5 (Ar-C=C), 122.70 (Ar-C=C), 90.22 (Ar-C=C) and 45.36 (Ar-C).

2.3.2. Characterization of 5-(m-tolyl)-5,6-dihy-dropyrimido[4,5-d]pyrimidine-2,4,7 (1H, 3H,8H)-trione (4b)

The compound **4b** was synthesized from condensation reaction **1b, 2** and **3** as white solid; Mp: 202-204 °C; Yield: 86%; ^{1}H NMR (400 MHz, CDCl3) δ 11.50 (s, 1H, NH), 11.28 (s, 1H, NH), 10.10 (s, 1H, NH), 8.32 (s, 1H, NH), 7.12-6.94 (m, 3H), 6.82 (d, J = 6.8 Hz, 1H), 5.20 (s, 1H) and 2.25 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.1 (C=O), 159.24 (C=O), 153.26 (C=O), 141.34 (C=C), 138.25 (Ar-C=C), 128.30 (Ar-C=C), 127.54 (Ar-C=C), 123.52 (Ar-C=C), 91.35 (C=C), 52.14 (Ar-C) and 23.5 (Ar-Me).

2.3.3. Characterization of 5-(p-tolyl)-5,6-dihy-dropyrimido[4,5-d]pyrimidine-2,4,7(1H, 3H,8H)-trione (4c)

The compound **4c** was synthesized from condensation reaction **1c, 2** and **3** as white solid; Mp: 254-256 °C; Yield: 91%; ^{1}H NMR (400 MHz, CDCl3) δ 11.28 (s, 1H, NH), 11.15 (s, 1H, NH), 10.21 (s, 1H, NH), 8.24 (s, 1H, NH), 7.08 (d, J = 7.6 Hz, 2H), 6.90 (d, J = 7.5 Hz, 2H), 5.68 (s, 1H), 2.21 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.10 (C=O), 158.62 (C=O), 154.78 (C=O), 140.52 (C=C), 138.60 (Ar-C=C), 129.48 (Ar-C=C), 127.74 (Ar-C=C), 124.51 (Ar-C=C), 93.42 (C=C), 50.41 (Ar-C) and 22.12 (Ar-Me).

2.3.4. Characterization of 5-(3-methoxyphenyl)-5,6-dihydropyrimido[4,5-d]pyrimidine-2,4,7(1H,3H,8H)-trione (4d)

The compound **4d** was synthesized from condensation reaction **1d, 2** and **3** as white solid; Mp: 232-234 °C; Yield: 85%; ^{1}H NMR (400 MHz, CDCL3) δ 11.35 (s, 1H, NH), 11.08 (s, 1H, NH), 10.02 (s, 1H, NH), 8.21 (s, 1H, NH), 7.05 (t, J = 8.4 Hz, 1H), 6.79 (d, J = 6.8 Hz, 2H), 6.61 (d, J = 7.0 Hz, 1H), 5.42 (s, 1H), 3.64 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.34 (C=O), 158.20 (C=O), 153.78 (C=O), 140.68 (C=C), 138.60 (Ar-C=C), 127.75 (Ar-C=C), 125.34 (Ar-C=C), 91.30 (C=C), 55.4 (Ar-OMe) and 54.0 (Ar-C).

2.3.5. Characterization of 5-(4-methoxyphenyl)-5,6-dihydropyrimido[4,5-d]pyrimidine-2,4,7 (1H,3H,8H)-trione (4e)

The compound **4e** was synthesized from condensation reaction **1e, 2** and **3** as yellow solid; Mp: 282-284 °C; Yield: 93%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.45 (s, 1H, NH), 11.18 (s, 1H, NH), 9.95 (s, 1H, NH), 8.31 (s, 1H, NH), 7.20-7.14 (m, 2H), 7.74-7.72 (m, 2H), 5.63 (s, 1H), 3.71 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.01 (C=O), 157.91 (C=O), 154.21 (C=O), 140.52 (C=C), 139.41 (Ar-C=C), 128.25 (Ar-C=C), 127.63 (Ar-C=C), 93.21 (C=C), 55.60 (Ar-OMe) and 52.1 (Ar-C).

2.3.6. Characterization of 5-(3,4-dimethoxy-phenyl)-5,6-dihydropyrimido[4,5-d] pyri-midine-2,4,7(1H,3H,8H)-trione (4f)

The compound **4f** was synthesized from condensation reaction **1f, 2** and **3** as yellow solid; Mp: 224-226 °C;

Yield: 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.27 (s, 1H, NH), 11.19 (s, 1H, NH), 10.15 (s, 1H, NH), 8.18 (s, 1H, NH), 6.95 (s, 1H), 6.79 (td, *J* = 8.4, 4.5 Hz, 2H), 5.82 (s, 1H), 3.81 (s, 3H), and 3.76; ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.54 (C=O), 158.61 (C=O), 155.84 (C=O), 140.64 (C=C), 139.64 (Ar-C=C), 129.24 (Ar-C=C), 127.67 (Ar-C=C), 89.54 (C=C), 55.45 (Ar-OMe) and 53.71 (Ar-C).

2.3.7. Characterization of 5-(3-nitrophenyl)-5,6-dihydropyrimido[4,5-d]pyrimidine-2,4,7 (1H,3H,8H)-trione (4g)

The compound **4g** was synthesized from condensation reaction **1g, 2** and **3** as red solid; Mp: 194-196 °C; Yield: 83%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.29 (s, 1H, NH), 11.24 (s, 1H, NH), 10.28 (s, 1H, NH), 8.14 (s, 1H, NH), 8.04-7.82 (m, 2H), 7.77 (d, *J* = 6.8 Hz, 1H), 7.39 (d, *J* = 7.8 Hz, 1H), 5.78 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.91 (C=O), 159.63 (C=O), 154.23 (C=O), 140.54 (C=C), 139.61 (Ar-C=C), 130.5 (Ar-C=C), 127.51 (Ar-C=C), 92.35 (C=C) and 50.3 (Ar-C).

2.3.8. Characterization of 5-(4-nitrophenyl)-5,6-dihydropyrimido[4,5-d]pyrimidine-2,4,7 (1H,3H,8H)-trione (4h)

The compound **4h** was synthesized from condensation reaction **1h, 2** and **3** as red solid; Mp: 218-220 °C; Yield: 78%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.31 (s, 1H, NH), 11.21 (s, 1H, NH), 10.35 (s, 1H, NH), 8.21 (s, 1H, NH), 7.41 (d, *J* = 7.8 Hz, 1H), 7.31 (d, *J* = 7.6 Hz, 1H), 6.86 (t, *J* = 7.8 Hz, 1H) and 5.54 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.81 (C=O), 158.42 (C=O), 152.36 (C=O), 140.89 (C=C), 139.71 (Ar-C=C), 128.01 (Ar-C=C), 126.65 (Ar-C=C), 89.56 (C=C) and 50.3 (Ar-C).

2.3.9. Characterization of 5-(3-iodophenyl)-5,6-dihydropyrimido[4,5-d]pyrimidine-2,4,7 (1H,3H,8H)-trione (4i)

The compound **4i** was synthesized from condensation reaction **1i, 2** and **3** as white solid; Mp: 208-210 °C; Yield: 87%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.52 (s, 1H, NH), 11.29 (s, 1H, NH), 10.08 (s, 1H, NH), 8.21 (s, 1H, NH), 7.32 (d, *J* = 6.8 Hz, 2H), 7.18 (d, *J* = 6.8 Hz, 2H) and 5.62 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.45 (C=O), 157.88 (C=O), 153.23 (C=O), 141.10 (C=C), 139.21 (Ar-C=C), 129.15 (Ar-C=C), 126.53 (Ar-C=C), 91.24 (C=C) and 49.5 (Ar-C).

2.3.10. Characterization of 5-(4-bromophenyl)-5,6-dihydropyrimido[4,5-d]pyrimidine-2,4,7(1H,3H,8H)-trione (4j)

The compound **4j** was synthesized from condensation reaction **1j, 2** and **3** as pale yellow solid; Mp: 212-214 °C; Yield: 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.47 (s, 1H, NH), 11.29 (s, 1H, NH), 10.00 (s, 1H, NH), 8.11 (s, 1H, NH), 7.28 (d, *J* = 8.4 Hz, 2H), 7.14-7.08 (m, 2H), 5.84 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.44 (C=O), 157.89 (C=O), 152.32 (C=O), 141.81 (C=C), 136.52 (Ar-C=C), 128.41 (Ar-C=C), 127.14 (Ar-C=C), 90.42 (C=C) and 51.5 (Ar-C).

2.3.11. Characterization of 5-(4-chlorophenyl)-5,6-dihydropyrimido[4,5-d]pyrimidine-2,4,7(1H,3H,8H)-trione **(4k)**

The compound **4k** was synthesized from condensation reaction **1k, 2** and **3** as red solid; Mp294-296 °C; Yield: 88%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.37 (s, 1H, NH), 11.29 (s, 1H, NH), 10.09 (s, 1H, NH), 8.14 (s, 1H, NH), 7.28 (s, 1H), 7.10 (d, *J* = 7.8 Hz, 2H), 6.58 (d, *J* = 7.8 Hz, 2H), 5.69 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.44 (C=O), 157.76 (C=O), 153.67 (C=O), 140.52 (C=C), 134.41 (Ar-C=C), 128.24 (Ar-C=C), 122.63 (Ar-C=C), 88.56 (C=C) and 50.3 (Ar-C).

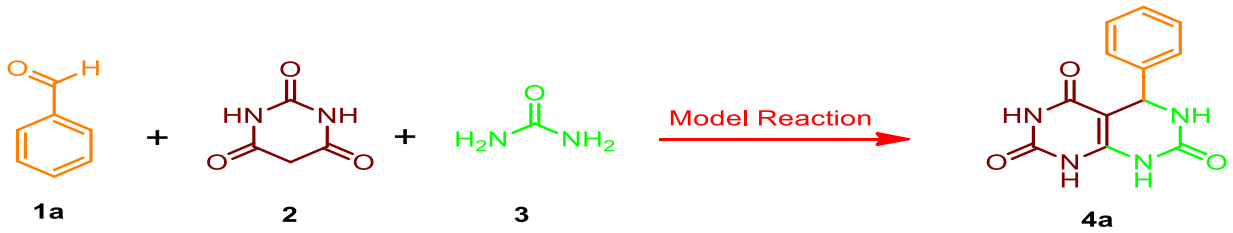
2.3.12. Characterization of 5-(4-hydroxyphenyl)-5,6-dihydropyrimido[4,5-d]pyrimidine-2,4,7(1H,3H,8H)-trione (4l)

The compound **4l** was synthesized from condensation reaction **1l, 2** and **3** as white solid; Mp: 208-210 °C; Yield: 81%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.37 (s, 1H, NH), 11.29 (s, 1H, NH), 9.90 (s, 1H, NH), 8.14 (s, 1H, NH), 7.88 (d, *J* = 7.8 Hz, 2H), 7.55 (d, *J* = 7.8 Hz, 2H), 5.46 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.51 (C=O), 158.52 (C=O), 154.21 (C=O), 141.56 (C=C), 139.24 (Ar-C=C), 130.74 (Ar-C=C), 128.98 (Ar-C=C), 92.41 (C=C) and 50.3 (Ar-C).

3. RESULTS AND DISCUSSION

3.1. Chemistry

To achieve optimized conditions protocol based on the reaction of benzaldehyde (**1a**), barbituric acid (**2**) (1 mmol) and urea (**3**) (1 mmol) as model reaction (**Scheme 1**), we checked temperatures and solvents, catalyst loading and the results of this study are summarized in Table 1.



Scheme 1: Standard model reaction

It was found that when the reaction was carried out in the nonappearance of the catalyst in ethanol, lower yield of product was perceived, after 20 min (Table 1, entry 1). To obtain the preferred product (**4a**), we tested the reaction using different catalysts such as *p*-TSA, Sulfamic acid, Sulfanilic acid, Boric acid, Citric acid, Phosphotungstic acid, Xanthan sulfuric acid, Silica sulfuric acid, CSA and [DBN][HSO_4] (Table 1, entries 2-11). Thus, room-temperature [DBN][HSO_4] as the pre-eminent catalyst was tested for this reaction. In the presence of [DBN][HSO_4], compound **4a** was isolated in 95% yield after only 8 min under the microwave irradiations. Therefore, it can be thought that [DBN][HSO_4] is green and a superior solvent and catalyst compared to the others shown in Table 1.

Table 1: Efficiency Comparison of Various Catalysts for the Synthesis of dihydro-pyrimido[*4,5-d*]pyrimidine derivatives (4a).[a]

entry	catalyst	Time (min)	Yield[b] (%)
1	-	20	35
2	*p*-TSA	20	61
3	Sulfamic acid	20	64
4	Sulfanilic acid	20	50
5	Boric acid	20	59
6	Citric acid	20	62
7	Xanthan sulfuric acid	20	57
8	Phosphotungstic acid	20	62
9	CSA	20	64
10	Silica sulfuric acid	20	8
11	[DBN][HSO_4]	7	93

*[a]Reaction conditions: benzaldehyde **1a** (100 mg), barbituric acid **2** (120 mg), urea **3** (56 mg) and [DBN][HSO_4] (20 mol%) stirred at under microwave irradiation (MW = 280 W) [b] Isolated yields. Bold values are for highlighting the good result.*

In the next step we examine the efficiency of ionic liquid [DBN][HSO_4] for the synthesis of pyrimido [4,5-d] pyrimidine derivatives. When change in concentration of [DBN][HSO_4] on model reaction suggest that much more effect on yield of final product. The catalyst loading study suggest that 20 mol% of [DBN][HSO_4] catalyst are best for the synthesis of final product in 93% yields (Table 2).

Furthermore, we also studied the power level of microwave effect on model reactions according to these study better results of the desired product when reaction carried at 280 W (Table 3, entry 3). Detailed reaction conditions are shown in Table 3.

Table 2: Effect of catalyst concentration[a]

Entry	Catalyst (mol %)	Time (min)	Yield[b] (%)
1	5	20	61
2	10	15	71
3	15	12	84
4	20	7	93
5	25	7	93

*[a]Reaction conditions: **1a** (100 mg), **2** (120 mg), (**3**) (56 mg) and [DBN][HSO_4] under microwave irradiation. [b]Isolated yield.*

Table 3: Optimization of reaction condition for the synthesis of 4a under microwave set up[a]

Entry	Power levels in Watt	Time[b] (min)	Yield[c]
1	140	20	54
2	210	15	70
3	240	10	83
4	280	7	93
5	350	7	93

*[a]Reaction conditions: **1a** (100 mg), **2** (120 mg) and **3** (56 mg) in the presence of [DBN][HSO_4] 20 mol% under microwave irradiation. [b]Reaction progress monitored by TLC. [c]Isolated yield.*

A. extremely superlative method to economic and greener preparation is recovery and recyclability of a ionic liquid. Therefore we have to check the efficiency of catalyst after recover from the reaction media during the work-up procedure. When reaction is completed, then reaction mass was pour on ice cold water to obtained fine crystal of final 2-Amino-4H-pyrans

derivatives. In the last step removal H_2O from filtrate using reduced pressure to gave viscous liquid, which is on cooling to give pure ionic liquid. Recovered catalysts were reused for next four repeated cycles without considerable loss in catalytic efficiency (Table 4).

Table 4: Reusability of [DBN][HSO_4] ionic liquid for model reaction

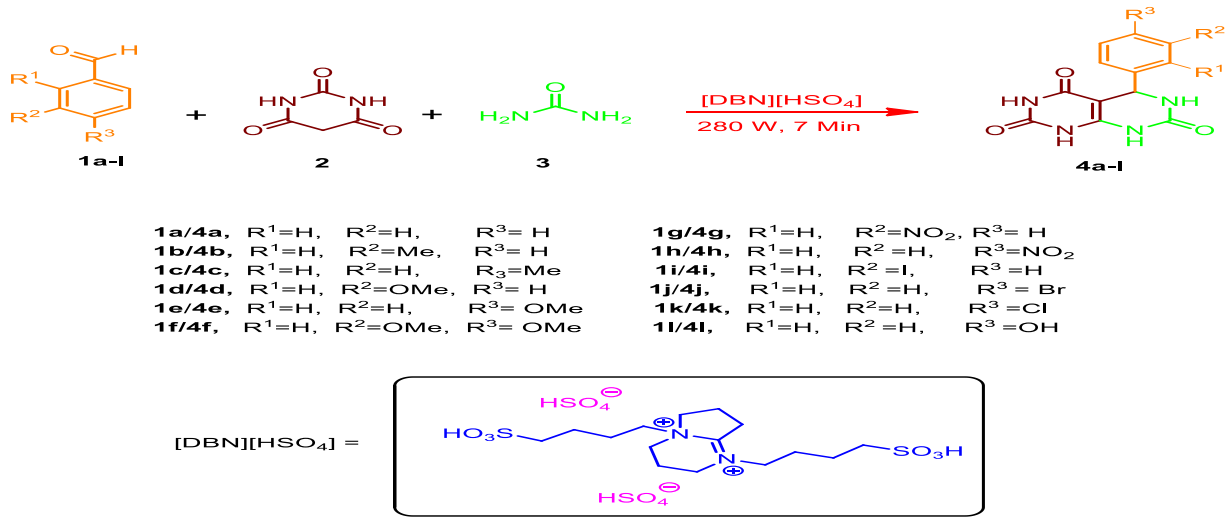
Entry	Run	Time[a] (min)	Yield[b]
1	fresh	7	93
2	2	7	93
3	3	7	85
4	4	7	83
5	5	7	80

[a]*Reaction progress monitered by TLC.* [b]*Isolated yield.*

The structure of the titled product **4a** was confirmed by ^{1}H NMR and ^{13}C NMR. In ^{1}H NMR spectra of compound **4a** exhibit four singlet bands for four -NH groups at δ 8.38, 10.25, 11.20 and 11.36 ppm suggest that NH group present in the dihydropyrimido [*4,5-d*] pyrimidine compound. The aliphatic -CH proton was shown at δ 5.38 ppm suggests that formation of cyclic ring in our final compound. In the ^{13}C NMR spectrum of compound **4a**, distinct -C=O carbonyl group observed at δ 163.01, 158.32 and 154.24 ppm. The CH peak observed at δ 45.36 ppm confirmed that formation of compound **4a**.

3.2. Plausible Reaction Mechanism

Reaction mechanism cycle for the preparation of dihydropyrimido [*4,5-d*] pyrimidine analogues employing [DBN][HSO_4] is catalyst. In first step barbituric acid activated [DBN][HSO_4] ionic liquid followed by nucleophilic attack on electron deficient benzaldehyde results in formation of intermediate **II**. In the next step, removal of water molecules from intermediates **II** with the help of [DBN][HSO_4] takes place to give intermediates **III**. In the third step intramolecular cyclization occur to give intermediates **IV**. In the last step, formation of final product **4a** achieved *via* removal of H_2O molecule and regeneration of catalyst. Detailed reaction mechanism is presented in Scheme 4.



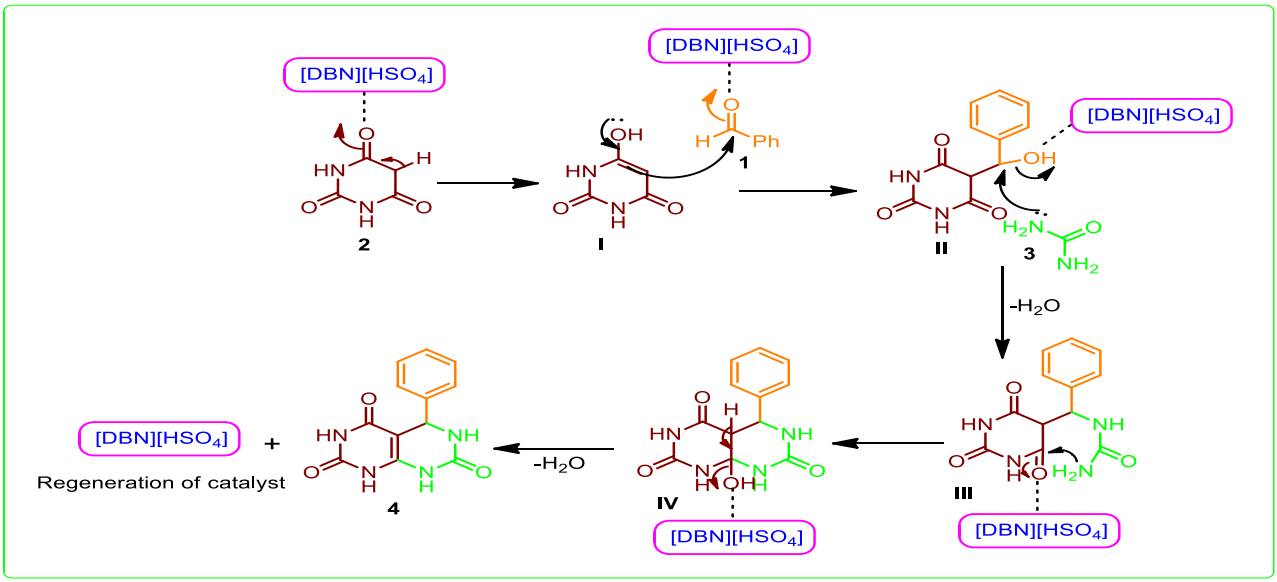
Scheme 2: Synthesis of pyrimido[4,5-d]pyrimidine derivatives (4a-l)

Table 5: [DBN][HSO_4] catalyzed synthesis of dihydropyrimido[*4,5-d*]pyrimidine derivatives[a]

Entry	Aryl aldehyde	Xanthene	Time (min)	Yield (%)[b]	Mp (°C)[c]	
					Observed	Reported
1	benzaldehyde	5-phenyl-5,6-dihydropyrimido [4,5-d]pyrimidine-2,4,7(1H,3H,8H)-trione	7	93	243-244	244-246 [34]
2	3-methyl benzaldehyde	5-(m-tolyl)-5,6- dihydro-pyrimido[4,5-d]pyrimidine-2,4,7(1H,3H,8H)-trione	7	86	202-204	-

3	4-methylbenzaldehyde	5-(p-tolyl)-5,6-dihydro-pyrimido[4,5-d]pyrimidine-2,4,7(1H,3H,8H)-trione	7	91	254-256	255-257 [35]
4	3-methoxybenzaldehyde	5-(3-methoxyphenyl)-5,6-dihydropyrimido[4,5-d]pyrimidine-2,4,7(1H,3H,8H)-trione	7	85	232-234	-
5	4-methoxybenzaldehyde	5-(4-methoxyphenyl)-5,6-dihydropyrimido[4,5-d]pyrimidine-2,4,7(1H,3H,8H)-trione	7	93	282-284	284-286 [34]
6	3,4-dimethoxybenzal-dehyde	5-(3,4-dimethoxyphenyl)-5,6-dihydropyrimido[4,5-d]pyrimidine-2,4,7(1H,3H,8H)-trione	7	90	224-226	-
7	3-nitrobenzaldehyde	5-(3-nitrophenyl)-5,6-dihydropyrimido[4,5-d]pyrimidine-2,4,7(1H,3H,8H)-trione	7	83	194-196	196-198 [36]
8	4-nitrobenzaldehyde	5-(4-nitrophenyl)-5,6-dihydropyrimido[4,5-d]pyrimidine-2,4,7(1H,3H,8H)-trione	7	78	218-220	-
9	3-iodobenzaldehyde	5-(3-iodophenyl)-5,6-dihydropyrimido[4,5-d]pyrimidine-2,4,7(1H,3H,8H)-trione	7	87	208-210	-
10	4-bromobenzaldehyde	5-(4-bromophenyl)-5,6-dihydropyrimido[4,5-d]pyrimidine-2,4,7(1H,3H,8H)-trione	7	90	212-214	210-212 [34]
11	4-chlorobenzaldehyde	5-(4-chlorophenyl)-5,6-dihydropyrimido[4,5-d]pyrimidine-2,4,7(1H,3H,8H)-trione	7	88	294-296	296-298 [37]
12	4-hydroxybenzaldehyde	5-(4-hydroxyphenyl)-5,6-dihydropyrimido[4,5-d]pyrimidine-2,4,7(1H,3H,8H)-trione	7	81	208-210	210-212 [34]

[a]*Reaction conditions: aldehydes (**1a-l**) (100 mg), barbituric acid (**2**) (120 mg), urea (**3**) (56 mg) in [DBN][HSO$_4$] 20 mol % stirred under microwave irradiations at 280 W;* [b]*isolated yields,* [c]*melting points are in good contact with those reported in the literature [34-37].*



Scheme 4: Reaction mechanism cycle for the preparation of compounds 4a

4. CONCLUSION

In conclusion, an environmental friendly and highly efficient green methodology has been established for the synthesis of functionalized dihydropyrimido [*4,5-d*] pyrimidine derivatives using an inexpensive and recoverable [DBN][HSO_4] under microwave irradiation at 280 W for 7 min. This, to the best of our knowledge, has no examples. This reaction scheme exposes a number of advantages, such as uniqueness, high atom efficiency, mild reaction conditions, clean reaction profiles, easy workup procedure and ecofriendliness. Using [DBN][HSO_4] green protocol offers advantages such as excellent yields of products, shorter reaction time period, simple procedure, preparation of catalyst and reusability of the catalyst.

Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

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