Research Article

A catalytic and green method for one-pot synthesis of new Hantzsch 1,4-dihydropyridines

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Abstract
A one-step procedure has been developed for the synthesis of new Hantzsch 1,4-dihydropyridines (1,4-DHPs) with high yields from four-component reaction of 4-hydroxybenzaldehyde, acetylacetone, various primary amine and barbituric acid in EtOH in the presence of 3-methyl-1-sulfonic acid imidazolium chloride {[Msim]Cl} as an acidic ionic liquid. In this work {[Msim]Cl} acts as a more efficient and green catalyst in the multicomponent reaction, leading to a simple procedure of synthesis, short reaction times, less pollution, high yields of the products, low cost of chemicals and uses less toxic solvents.

Keywords Multi-component reaction · One-pot · Green chemistry · 3-Methyl-1-sulfonic acid imidazolium chloride · 1,4-Dihydropyridines

1 Introduction

1,4-Dihydropyridines (1,4-DHPs) are one of *N*-heterocyclic, biologically active compounds and naturally occurring molecules [1, 2]. 1,4-DHPs are also considered as key starting materials to synthesize various classes of biologically and pharmacologically active compounds [3, 4]. They are used as calcium channel blockers [5], anti-inflammatory [6, 7], antiviral [8], antitumor [9], anticancer [10], analgesic activities [11]. In additions, 1,4-DHP derivatives are employed as heptatoprotective and antidiabetic agents for the treatment of cardiovascular diseases such as hypertension [12–14].

Some methods for the synthesis of 1,4-DHP derivatives have been reported in the literature. Nevertheless, these methods generally call for harsh reaction conditions, high temperature, using of expensive reagents, create wastes, long reaction time, needing strongly acidic condition, using multi-steps, need a complex synthetic route and no agreement with the green chemistry strategies [15], Therefore, facile and highly efficient synthetic methods to 1,4-DHP derivatives are highly desirable [16].

One method to address this challenge includes employing multicomponent reactions (MCRs). MCRs strategy offer a significant importance over linear-strategy synthesis due to their flexible, convergent, atomic efficient nature and provide a maximum structural complexity with a minimum number of synthetic steps [17]. Reportedly, in MCRs a wide range of catalysts has been explored in the synthesis of 1,4-DHP derivatives including L-proline [18, 19], aspartic acid [20], *p*-toluenesulfonic acid monohydrate [21–23], TiO_2 nano wires [24], phosphootungstic acid ($H_3PW_{12}O_{40}$) [25], silica-coated nano-Fe_3O_4 [26], cellulose sulfuric acid [27], chitosan supported copper(II)sulfate (CSCS) [28],

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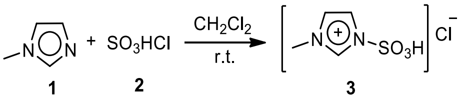
porcine pancreatic lipase [29], Magnetic dextrin nanobiomaterial [30], SO_3H-functionalized nano-MGO-D-NH_2 [31], guanidinylated chitosan magnetic nano catalyst [32], and pyrimidine-2,4-diamine (PDA)-functionalized silica-coated magnetic nanocatalyst (Fe_3O_4/SiO_2-PDA) [33]. Therefore, the discovery of new and efficient catalysts in combination with an operationally simple work up and eco-friendly conditions is highly desirable [15].

Ionic liquids have fascinated a considerable attention in the past few decades due to they have unique properties including an inexpensive, easy to prepare, environmental friendly, non-toxic catalyst for various organic synthesis, high thermal, non-hazardous, non-volatility, a simple and rapid to handle, economically viable, non-flammability, recyclability, provide a high selectivity, and can be used to dissolve a wide range of materials [34–37]. In addition, ionic liquids are used as catalyst and media in multicomponent reactions such as triethylamine-bonded sulfonic acid {[Et_3N–SO_3H]Cl} [38], [Bmim]PF_6 [39], and sulfamic acid (H_2NSO_3H) [40].

As a part of our interest with green chemistry, herein we aim to expand the application of ionic liquids in multicomponent reactions. Therefore, 3-methyl-1-sulfonic acid imidazolium chloride {[Msim]Cl}**3** was synthesized as Bronsted acidic ionic liquid (Scheme 1) and employed as an efficient catalyst for the synthesis of new 1,4-DHP derivatives **8a**–**8i** (Scheme 2).

2 Results and discussion

The optimized conditions of a model reaction were carried out from the reaction of 4-hydroxybenzaldehyde **4** (2.0 mmol), acetylacetone **5** (2.0 mmol), 4-aminomorpholine **6a** (2.0 mmol) and barbituric acid **7** (2.0 mmol) in EtOH (20 mL) in the presence of {[Msim]Cl} **3** as a catalyst at room temperature. In these optimized conditions, EtOH was found to be an excellent solvent for this reaction (Table 1, entry 5).



Scheme 1 Synthesis of {[Msim]Cl}**3**

To evaluate the efficiency of {[Msim]Cl} **3** in comparison with the reported catalysts, the model reaction was screened in some of these catalysts including L-proline, DABCO, copper, DAHP and $ZnCl_2$. Interestingly, as shown in Table 2, an efficient activity of catalysis {[Msim]Cl} **3** was observed and the desired product was collected in higher yield with a shorter reaction time.

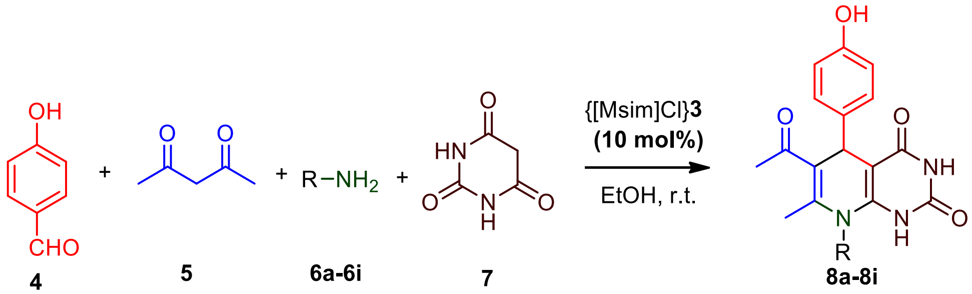
The effect of catalytic concentration was investigated on the model reaction in EtOH. Initially, at the catalytic concentration of {[Msim]Cl} **3** (5 mol%), the reaction was carried out under the same reaction time and afforded product **8a** 76% in yield (Table 2, entry 7). By increasing the amount of catalysis {[Msim]Cl} **3** from 5 to 10 mol%, the highest yield of the corresponding product **8a** was obtained (Table 2, entry 8). Increasing the catalyst loading to 15 mol%, no a significant yield was obtained at this concentration (Table 2, entry 9). As a result, 10 mol% of catalyst {[Msim]Cl} **3** was chosen in EtOH as the most appropriate conditions for the one-pot synthesis of novel 1,4-DHP derivatives **8a**–**8i** at room temperature. To evaluate the significance of {[Msim]Cl} **3** as catalyst, the model reaction was tested in the absence of {[Msim]Cl} **3** and found that no yield of corresponding product **8a** was obtained after 24 h (Table 2, entry 1).

Table 1 Effect of various organic solvents for the synthesis of 1,4-DHP derivative **8a**

Entry	Catalysis	Solvent	Temperature	Time (h)	Yield (%)
1	[Msim]Cl	Acetonitrile	r.t	10	30
2	[Msim]Cl	Methanol	r.t	2	45
3	[Msim]Cl	Methanol	50 °C	2	55
4	[Msim]Cl	Dioxane	r.t	2	22
5	[Msim]Cl	Ethanol	r.t	2	90

Reaction conditions: 4-hydroxybenzaldehyde **4** (2.0 mmol), acetylacetone **5** (2.0 mmol), 4-aminomorpholine **6a** (2.0 mmol) and barbituric acid **7** (2.0 mmol), {[Msim]Cl} **3** (10 mol%)

Scheme 2 Synthetic route of new 1,4-DHP derivatives **8a**–**8i**



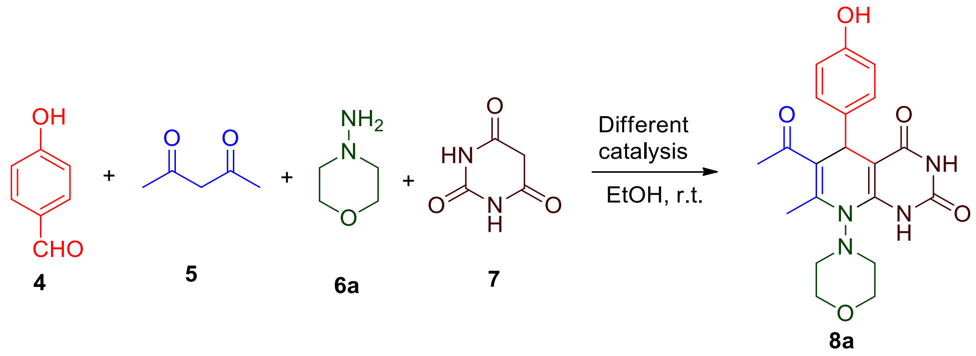
The ^{1}H and ^{13}C NMR, FT-IR and Mass spectra data of all synthesized compounds are consistent with the expected structures. The ^{1}H NMR spectra of 1,4-DHP derivatives **8a**–**8i** show a broad singlet at the lowest field for NH groups, two singles at 1.82–2.14 ppm for two CH_3 groups and a one singlet at 4.95–5.24 ppm for fused pyridine proton (CH group) at the expected region. In the ^{13}C NMR spectra of all synthesized compounds, the appearance of signals at the lowest field is due to carbon resonance of the C=O group. The other chemical shifts of ^{13}C NMR spectra were displayed in the expected regions. Also, the appearance of absorption band at 3437–3109 cm^{-1} in the FT-IR spectra of synthetic compounds (**8a**–**8i**), the characteristic of the NH groups is a good evidence in support of the expected compounds. The all synthesized 1,4-DHP derivatives **8a**–**8i** are illustrated in Table 3.

The plausible mechanism of the reaction in the presence of catalyst {[Msim]Cl} **3** is shown in Scheme 3. Initially, a nucleophilic addition of barbituric acid **A** to activated 4-hydroxybenzaldehyde **B** in the presence of catalyst {[Msim]Cl} **3** led to intermediate **C** which becomes involved in the addition reaction with acetylacetone **D** and a subsequent addition of primary amine to adduct **E** led to intermediate **F** by via losing water molecule. Ultimately, a further intramolecular cyclization of intermediate **F** led to desired compounds.

3 Experimental

All solvents and chemicals were purchased from Sigma-Aldrich. All reactions were carried out under an atmosphere of air. Melting points were recorded using a Gallenkamp melting point apparatus in capillary tubes. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV-400 (^{1}H: 400 MHz) and AV-400 (^{13}C: 100.5 Hz) spectrometer (Sheffield, UK) at room temperature in deuterated dimethyl sulfoxide and chloroform as solvent (^{1}H NMR: DMSO-d_6: δ 2.50 ppm; ^{13}C NMR: DMSO-d_6: δ 39.52 ppm, ^{1}H NMR: $CDCl_3$: δ 7.26 ppm; ^{13}C NMR: δ 77.16 ppm). For ^{1}H NMR, the completed protons of decoupling *J* are evaluated by Hz unite. Fourier Transform infrared (FT-IR) spectra were recorded on a Perkin Elmer Paragon 100 FT-IR spectrophotometer (Sheffield, UK), the recording absorbance were taken between 4000–750 cm^{-1}. High-resolution mass spectrum (HRMS) was performed by using a Micro Mass LCT operating in Electrospray mode (ES) (Sheffield, UK). All synthesized compounds were purified by flash chromatography with silica gel 60 Å (230–400 mesh). Analytical properties of TLC were performed by using plates precoated with silica gel 60 UV 255 (Merck). UV light and an alkaline aqueous solution of potassium permanganate ($KMnO_4$) were utilized to visualize all synthesized compounds.

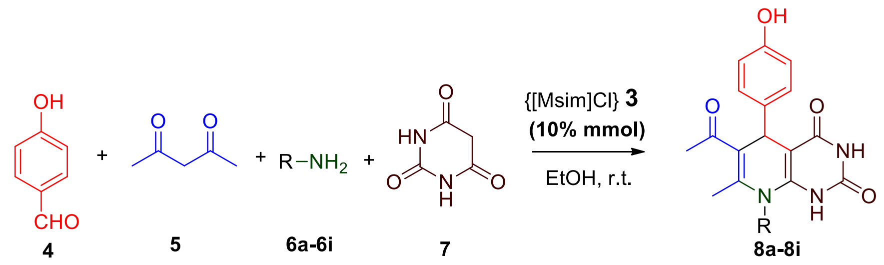
Table 2 The optimized conditions for the synthesis of 1,4-DHP derivative **8a**



Entry	Catalysis	Amount (mol%)	Temperature	Time (h)	Yield (%)^a
1	–	–	r.t	24	–
2	L-proline	10	r.t	2	55
3	DABCO	10	r.t	2	70
4	Copper	10	r.t	2	40
5	DAHP	10	r.t	2	75
6	$ZnCl_2$	10	r.t	2	67
7	[Msim]Cl	5	r.t	2	76
8	[Msim]Cl	10	r.t	2	90
9	[Msim]Cl	15	r.t	2	72

[a] Isolated pure compound

Table 3 The synthesis of 1,4-DHP derivatives **8a**–**8i** in the presence {[Msim]Cl} **3**



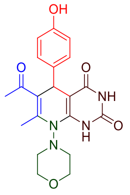
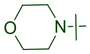
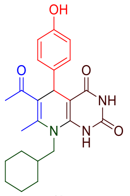
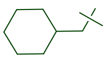
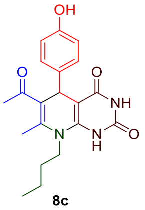
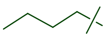
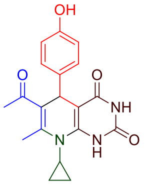
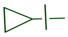
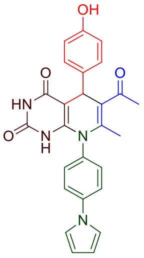
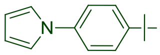
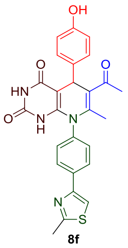
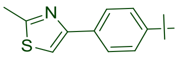
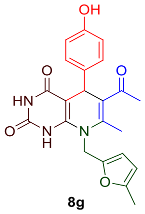
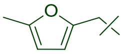
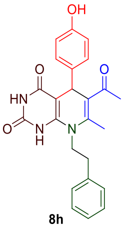
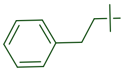
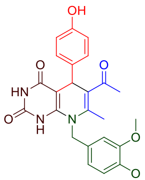
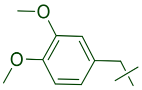
Compound	R	Molecular formula	M.p (°C)	Yield (%)
 **8a**		$C_{20}H_{22}N_4O_5$	203–204	90
 **8b**		$C_{23}H_{27}N_3O_4$	197–198	85
 **8c**		$C_{20}H_{23}N_3O_4$	180–181	93
 **8d**		$C_{19}H_{19}N_3O_4$	177–178	90
 **8e**		$C_{26}H_{22}N_4O_4$	256–257	80

Table 3 (continued)

 **8f**		$C_{26}H_{22}N_4O_4S$	267–268	82
 **8g**		$C_{22}H_{21}N_3O_5$	200–201	85
 **8h**		$C_{24}H_{23}N_3O_4$	197–198	90
 **8i**		$C_{25}H_{25}N_3O_6$	223–224	93

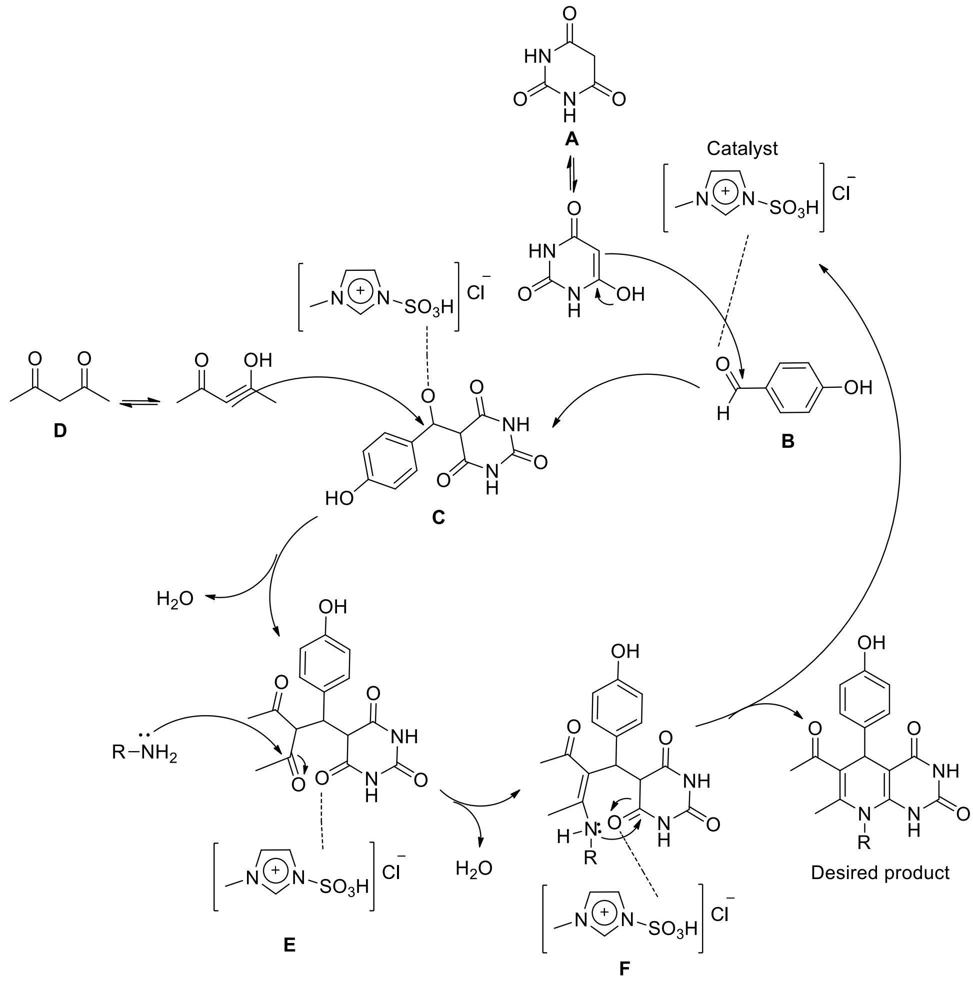
Reaction conditions: 4-hydroxybenzaldehyde **4** (2.0 mmol), acetylacetone **5** (2.0 mmol), various primary amine **6a**–**6i** (2.0 mmol) and barbituric acid **7** (2.0 mmol), {[Msim]Cl} **3** (10 mol%), EtOH (20 mL), room temperature

Synthesis of ionic liquid {[Msim]Cl} (3) To a solution of 1-methylimidazole (1.64 g, 20 mmol) dissolved in dry DCM (100 mL) in a round-bottomed flask (200 mL), chlorosulfonic acid (2.42 g, 20.8 mmol) was added. The reaction mixture was stirred for 30 min, halted for 10 min and the DCM was decanted. The resulting mixture was washed with (3 × 100 mL) DCM and dried under vacuum to afford 1.5 g (90%) {[Msim]Cl} **3** as a viscous colorless oil; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 3.87 (s, 3H, CH_3), 7.67 (d, J = 2.36 Hz, 1H, CH), 7.70 (d, J = 2.5 Hz, 1H, CH), 9.06 (s, 1H, CH), 14.22 (s, 1H, SO_3H). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 35.6 (CH_3), 120.8 (CH), 123.5 (CH), 137.5 (CH).

General method for synthesis of 1,4-DHP derivatives 8a (–8i) In a round-bottom flask (50 mL), 4-hydroxybenzaldehyde **4** (0.24 g, 2 mmol), acetylacetone **5** (0.2 g, 2 mmol), various primary amine **6a**–**6i** (2 mmol) and barbituric acid **7** (0.24 g, 2 mmol) in EtOH (20 mL) were mixed and stirred at room temperature. Ionic liquid {[Msim]Cl} **3** (0.04 g, 10 mol%) was added and the mixture was stirred at room temperature for an appropriate time 2 h. After the completion of the reaction (indicated by TLC, petroleum ether: ethyl acetate: 6:4), the resulting mixture was diluted with water (20 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated. The cured products were purified by flash chromatography to afford the titled barbituric acid derivatives.

6-Acetyl-5-(4-hydroxyphenyl)-7-methyl-8-morpholino-5,8-dihydropyrido [2,3-d pyrimidine-2,4(1H, 3H)-dione (8a) Follow general method, using 4-hydroxybenzaldehyde **4** (0.24 g, 2.0 mmol), acetylacetone **5** (0.2 g, 2.0 mmol), 4-aminomorpholine **6a** (0.2 g, 2.0 mmol) and barbituric acid **7** (0.24 g, 2.0 mmol) for 2 h. The crude compound was purified by flash chromatography (petroleum ether: ethyl acetate: 6: 4, R_f = 0.3) to give 0.18 g (90%) **8a** as a yellow solid; m.p 203–204 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 12.31 (s,

Scheme 3 Suggested mechanism for the synthesis of new 1,4-DHP derivatives **8a**–**8i**



1H, NH), 7.85 (d, *J* = 8.8 Hz, 2H, Ar–H), 7.00 (d, *J* = 8.9 Hz, 2H, Ar–H), 5.13 (s, 1H, CH), 3.83–3.79 (m, 4H, $2CH_2$), 3.12–3.01 (m, 4H, $2CH_2$), 2.06 (s, 3H, CH_3), 1.90 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 17.2 (CH_3), 25.0 (CH_3), 28.3 (CH), 49.2 (CH_2), 58.8 (CH_2), 100 (C, Ar), 114.6 (C, Ar), 124.6 (CH, Ar), 130.9 (CH, Ar), 149.3 (C=O), 160.7 (C=O), 195.2 (C=O). FT-IR (KBr, cm^{-1}): 3437 (N–H), 3037 (C–H, Ar), 2965 (C–H), 2856 (C–H), 1609 (C=O), 1568 (C=C, Ar). HR-MS (ESI$^+$): *m/z* Cald for $C_{20}H_{22}N_4O_5$ ([M + H$^+$]) 398.1600, found 398.1594.

6-Acetyl-8-(cyclohexylmethyl)-5-(4-hydroxyphenyl)-7-methyl-5,8-dihydro pyrido [2,3-d] pyrimidine-2,4(1H,3H)-dione (8b) Follow general method, using 4-hydroxybenzaldehyde **4** (0.24 g, 2.0 mmol), acetylacetone **5** (0.2 g, 2.0 mmol), cyclohexanemethylamine **6b** (0.22 g, 2.0 mmol) and barbituric acid **7** (0.24 g, 2.0 mmol) for 2 h. The crude compound was purified by flash chromatography (petroleum ether: ethyl acetate: 6: 4, R_f = 0.4) to give 0.16 g (85%) **8b** as a white solid; m.p 197–198 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 11.02 (s, 1H, NH), 7.77 (d, *J* = 8.9 Hz, 2H, Ar–H), 7.01 (d, *J* = 8.5 Hz, 2H, Ar–H), 4.99 (s, 1H, CH), 3.11 (d, *J* = 6.5 Hz, 2H, CH_2), 2.04 (s, 3H, CH_3), 1.95 (s, 3H, CH_3), 1.81–1.69 (m, 4H, CH_2), 1.27–1.16 (m, 4H, CH_2), 1.03–0.95 (m, 2H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 21.0 (CH_3), 27.2 (CH_2), 27.3 (CH_3), 29.2 (CH_2), 30.8 (CH_2), 40.2 (CH), 49.4 (CH_2), 95.6 (C), 117.9 (C, Ar), 126.8 (CH, Ar), 131.4 (CH, Ar), 163.7 (C=O), 193.3 (C=O). FT-IR (KBr, cm^{-1}): 3231 (N–H), 3010 (C–H, Ar), 2928 (C–H), 2856 (C–H), 1683 (C=O), 1546 (C=C, Ar). HR-MS (ESI$^+$): *m/z* Cald for $C_{23}H_{27}N_3O_4$ ([M + H$^+$]) 410.1456, found 410.1452.

6-Acetyl-8-butyl-5-(4-hydroxyphenyl)-7-methyl-5,8-dihydro pyrido [2,3-d] pyrimidine-2,4(1H,3H)-dione (8c) Follow general method, using 4-hydroxybenzaldehyde **4** (0.24 g, 2.0 mmol), acetylacetone **5** (0.2 g, 2.0 mmol), butylamine **6c** (0.14 g, 2.0 mmol) and barbituric acid **7** (0.24 g, 2.0 mmol) for 2 h. The crude compound was purified by flash chromatography (petroleum ether: ethyl acetate: 6: 4, R_f = 0.5) to give 0.13 g (93%) **8c** as a white solid; m.p 180–181 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 10.92 (s, 1H, NH), 7.80 (d, *J* = 3.7 Hz, 2H, Ar–H); 7.02 (d, *J* = 8.6 Hz, 2H, Ar–H), 5.02 (s, 1H, CH), 3.29 (m, 2H, CH_2), 2.06 (s, 3H, CH_3), 1.91 (s, 3H, CH_3), 1.61–1.56 (m, 2H, CH_2), 1.45–14.3 (m, 2H, CH_2), 0.94 (t, *J* = 7.3 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 13.7 (CH_3), 17.2 (CH_3), 19.9 (CH_3), 28.1 (CH_2), 31.9 (CH), 42.9 (CH_2), 58.8 (C), 95.3 (C, Ar), 116.2 (CH, Ar), 128.8 (CH, Ar), 132.4 (C), 163.7 (C, Ar), 164.8 (C=O), 191.1 (C=O), 194.4 (C=O). FT-IR (KBr, cm^{-1}): 3242 (N–H), 2862 (C–H, Ar), 2931 (C–H), 2875 (C–H), 1679 (C=O), 1592 (C=C, Ar). HR-MS (ESI^+): *m/z* Cald for $C_{20}H_{23}N_3O_4$ ([M + H^+]) 370.1350, found 370.1345.

6-Acetyl-8-cyclopropyl-5-(4-hydroxyphenyl)-7-methyl-5,8-dihydropyrido [2,3-d] pyrimidine-2,4(1H, 3H)-dione (8d) Follow general method, using 4-hydroxybenzaldehyde **4** (0.24 g, 2.0 mmol), acetylacetone **5** (0.2 g, 2.0 mmol), cyclopropylamine **6d** (0.1 g, 2.0 mmol) and barbituric acid **7** (0.24 g, 2.0 mmol) for 2 h. The crude compound was purified by flash chromatography (petroleum ether: ethyl acetate: 6: 4, R_f = 0.5) to give 0.1 g (90%) **8d** as a yellow solid; m.p 177–178 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 10.71 (s, 1H, NH), 7.81 (d, *J* = 8.7 Hz, 2H, Ar–H), 7.08 (d, *J* = 4.3 Hz, 2H, Ar–H), 5.06 (s, 1H, CH), 2.67–2.65 (m, 1H, CH), 2.13 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 0.85 (dd, *J* = 6.7, 2.2 Hz, 2H, CH_2), 0.67 (dd, *J* = 5.3, 1.6 Hz, 2H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 11.2 (CH_3), 15.1 (CH_2), 20.3 (CH_3), 25.9 (CH_2), 30.6 (CH), 40.4 (CH), 93.6 (CH, Ar), 112.8 (CH, Ar), 122.3 (C), 131.2 (C, Ar), 163.7 (C=O), 194.3 (C=O). FT-IR (KBr, cm^{-1}): 3090 (N–H), 3008 (C–H, Ar), 2921 (C–H), 2813 (C–H), 1683 (C=O), 1604 (C=C, Ar). HR-MS (ESI^+): *m/z* Cald for $C_{19}H_{19}N_3O_4$ ([M + H^+]) 354.1789, found 354.1785.

8-(4-(1H-Pyrrol-1-yl)phenyl)-6-acetyl-5-(4-hydroxyphenyl)-7-methyl-5,8-dihy dropyrido [2,3-d] pyrimidine-2,4 (1H,3H)-dione (8e) Follow general method, using 4-hydroxybenzaldehyde **4** (0.24 g, 2.0 mmol), acetylacetone **5** (0.2 g, 2.0 mmol), 4-pyrrol-1-yl-aniline **6a** (0.3 g, 2.0 mmol) and barbituric acid **7** (0.24 g, 2.0 mmol) for 2 h. The crude compound was purified by flash chromatography (petroleum ether: ethyl acetate: 6: 4, R_f = 0.3) to give 0.16 g (80%) **8e** as a yellow solid; m.p 256–257 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 12.50 (s, 1H, NH), 7.38 (d, *J* = 8.7 Hz, 1H, Ar–H), 7.19 (t, *J* = 8.4 Hz, 2H, Ar–H), 7.08 (t, *J* = 8.4 Hz, 2H, Ar–H), 6.99 (t, *J* = 2.5 Hz, 1H, CH-pyrrole), 6.74 (dd, *J* = 6.5, 2.4 Hz, 1H, CH-pyrrole), 6.38 (t, *J* = 2.4 Hz, 1H, CH-pyrrole), 5.24 (s, 1H, CH), 2.14 (s, 3H, CH_3), 2.03 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 20.5 (CH_3), 30.3 (CH_3), 41.5 (CH), 97.9 (CH, pyrrole), 109.4 (CH, pyrrole), 110.3 (C, Ar), 115.2 (C, Ar), 118.4 (CH, Ar), 122.5 (CH, Ar), 123.6 (CH, Ar), 125.9 (C, Ar), 149.5 (C=O), 160.8 (C=O), 197.6 (C=O). FT-IR (KBr, cm^{-1}): 3242 (N–H), 3066 (C–H, Ar), 2928 (C–H), 2866 (C–H), 1601 (C=O), 1570 (C=C, Ar). HR-MS (ESI^+): *m/z* Cald for $C_{26}H_{22}N_4O_4$ ([M + H^+]) 455.3222, found 455.3219.

6-Acetyl-5-(4-hydroxyphenyl)-7-methyl-8-(4-(2-methylthiazol-4-yl)phenyl)-5,8-dihydro pyrido[2,3-d] pyrimidine-2,4 (1H,3H)-dione (8f) Follow general method, using 4-hydroxybenzaldehyde **4** (0.24 g, 2.0 mmol), acetylacetone **5** (0.2 g, 2.0 mmol), 4-(2-methyl-1,3-thiazol-4-yl) aniline **6f** (0.38 g, 2.0 mmol) and barbituric acid **7** (0.24 g, 2.0 mmol) for 2 h. The crude compound was purified by flash chromatography (petroleum ether: ethyl acetate: 6: 4, R_f = 0.2) to give 0.16 g (82%) **8f** as an orange solid; m.p 267–268 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 12.55 (s, 1H, NH), 7.86 (d, *J* = 8.5 Hz, 2H, Ar–H), 7.69 (d, *J* = 8.5 Hz, 2H, Ar–H), 7.29 (d, *J* = 4.9 Hz, 2H, Ar–H), 7.16 (d, *J* = 8.4 Hz, 2H, Ar–H), 6.73 (s, 1H, CH-thiazole), 5.22 (s, 1H, CH), 2.78 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 2.05 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 20.3 (CH_3), 21.2 (CH_3), 31.8 (CH_3), 39.4 (CH), 100.2 (C, thiazole), 112.6 (C, thiazole), 114.2 (CH, Ar), 116.6 (CH, Ar), 125.3 (CH, Ar), 126.6 (C, Ar), 130.5 (C, Ar), 142.1 (C=O), 169.8 (C=O), 196.3 (C=O). FT-IR (KBr, cm^{-1}): 3225 (N–H), 3063 (C–H, Ar), 2921 (C–H), 2870 (C–H), 1606 (C=O), 1575 (C=C, Ar). HR-MS (ESI^+): *m/z* Cald for $C_{26}H_{22}N_4O_4S$ ([M + H^+]) 487.4573, found 487.4577.

6-Acetyl-5-(4-hydroxyphenyl)-7-methyl-8-((5-methylfuran-2-yl)methyl)-5,8-dihy dro pyrido[2,3-d]pyrimidine-2,4 (1H,3H)-dione (8g) Follow general method, using 4-hydroxybenzaldehyde **4** (0.24 g, 2.0 mmol), acetylacetone **5** (0.2 g, 2.0 mmol), (5-methylfuran-2-yl) methanamine **6g** (0.22 g, 2.0 mmol) and barbituric acid **7** (0.24 g, 2.0 mmol) for 2 h. The crude compound was purified by flash chromatography (petroleum ether: ethyl acetate: 6:4, R_f = 0.3) to give 0.17 g (85%) **8g** as a yellow solid; m.p 200–201 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 11.01 (s, 1H, NH), 7.79 (d, *J* = 8.7 Hz, 2H, Ar–H), 6.99 (d, *J* = 8.6 Hz, 2H, Ar–H), 6.12 (d, *J* = 3.1 Hz, 1H, furan), 5.91 (dd, *J* = 4.2, 2.2 Hz, 1H, furan), 5.08 (s, 1H, CH), 4.40 (s, 2H, CH_2), 2.08 (s, 3H, CH_3), 2.02 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 12.0 (CH_3), 16.2 (CH_3), 28.6 (CH_2), 40.8 (CH), 100.3 (CH, furan), 109.2 (CH, furan), 111.8 (CH, Ar), 117.9 (CH, Ar), 130.3 (C, Ar), 161.8 (C=O), 194.8 (C=O). FT-IR (KBr, cm^{-1}): 3109 (N–H), 3003 (C–H, Ar), 2921 (C–H), 2815 (C–H), 1683 (C=O), 1604 (C=C, Ar). HR-MS (ESI^+): *m/z* Cald for $C_{22}H_{21}N_3O_5$ ([M + H^+]) 408.8550, found 408.8545.

6-Acetyl-5-(4-hydroxyphenyl)-7-methyl-8-phenethyl-5,8-dihydropyrido [2,3-d] pyrimidine-2,4 (1H, 3H)-dione (8h) Follow general method, using 4-hydroxybenzaldehyde **4** (0.24 g, 2.0 mmol), acetylacetone **5** (0.2 g, 2.0 mmol), 2-phenylethylamine **6h** (0.24 g, 2.0 mmol) and barbituric acid **7** (0.24 g, 2.0 mmol) for 2 h. The crude compound was purified by flash chromatography (petroleum ether: ethyl acetate: 6: 4, R_f = 0.5) to give 0.18 g (90%) **8h** a white solid; m.p 197–198 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 10.92 (s, 1H, NH), 7.34–7.21 (m, 9H, Ar–H), 4.95 (s, 1H, CH), 3.49 (t, *J* = 10.3 Hz, 2H, CH_2), 2.88 (t, *J* = 7.3 Hz, 2H, CH_2), 2.01 (s, 3H, CH_3), 1.82 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 13.9 (CH_2), 16.7 (CH_3), 25.9 (CH_2), 37.3 (CH_2), 45.2 (CH), 95.8 (CH, Ar), 112.6 (CH, Ar), 124.6 (CH, Ar), 130.0 (C, Ar), 132.3 (C, Ar), 150.3 (C=O), 162.5 (C=O), 196.4 (C=O). FT-IR (KBr, cm^{-1}): 3230 (N–H), 3063 (C–H, Ar), 2926 (C–H), 2870 (C–H), 1606 (C=O), 1568 (C=C, Ar). HR-MS (ESI^+): *m/z* Cald for $C_{24}H_{23}N_3O_4$ ($[M+H^+]$) 418.2674, found 418.2673.

6-Acetyl-8-(3,4-dimethoxybenzyl)-5-(4-hydroxyphenyl)-7-methyl-5,8-dihydropyrido[2,3-d] pyrimidine-2,4(1H,3H)-dione (8i) Follow general method, using 4-hydroxybenzaldehyde **4** (0.24 g, 2.0 mmol), acetylacetone **5** (0.2 g, 2.0 mmol), 2,4-dimethoxybenzylamine **6i** (0.32 g, 2.0 mmol) and barbituric acid **7** (0.24 g, 2.0 mmol) for 2 h. The crude compound was purified by flash chromatography (petroleum ether: ethyl acetate: 6: 4, $R_f=0.2$) to give 0.18 g (93%) **8i** as a yellow solid; m.p 223–224 °C; ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 11.14 (s, 1H, NH), 7.74 (d, $J=8.6$ Hz, 1H, Ar–H), 7.09 (d, $J=8.4$ Hz, 1H, Ar–H), 6.96 (d, $J=8.7$ Hz, 2H, Ar–H), 6.44 (d, $J=7.2$ Hz, 2H, Ar–H), 5.02 (s, 1H, CH), 4.39 (s, 2H, CH_2), 3.81 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 2.04 (s, 3H, CH_3), 2.02 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 21.1 (CH_3), 28.3 (CH_3), 30.1 (CH_2), 40.3 (CH), 42.8 (OCH_3), 55.2 (OCH_3), 100.5 (CH, Ar), 106.2 (C, Ar), 112.9 (CH, Ar), 114.6 (CH, Ar), 118.6 (C, Ar), 125.4 (CH, Ar), 130.2 (C, Ar), 159.7 (C=O), 162.2 (C=O), 196.2 (C=O). FT-IR (KBr, cm^{-1}): 3088 (N–H), 3006 (C–H, Ar), 2965 (C–H), 2834 (C–H), 1683 (C=O), 1548 (C=C, Ar). HR-MS (ESI^+): *m/z* Cald for $C_{25}H_{25}N_3O_6$ ($[M+H^+]$) 464.1789, found 464.1785.

4 Conclusion

In summary, a convenient and green method was introduced for the synthesis of new 1,4-DHP derivatives by the one-pot, four-component reaction in EtOH in the presence of 3-methyl-1-sulfonic acid imidazolium chloride {[Msim]Cl}as catalyst at room temperature. Interesting properties of {[Msim]Cl} include non-toxic nature, easy to remove and offer potential advantages over conventional catalyst. This modified strategy gives increased performance for the synthesis of new 1,4-DHP derivatives. The delightful properties of this protocol include the exploitation of environmentally benign catalyst, easy work up and excellent yields of desired products. Further studies on evaluating the biological activities of these derivatives are in progress.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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