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Nano catalysed Biginelli type reaction in green reaction media

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Green chemical approach has been developed by using ionic liquid [MIM-H] CCl_3 and TiO_2 nanoparticles (NPs) for the synthesis of 3,4-dihydropyrimidine-2(1*H*)-one (DHPMs) derivatives **4a-r**. The formed compounds have been characterised by IR, ^1H and ^{13}C NMR and mass spectrometry.

Keywords: Biginelli reaction, green approach, multicomponent, ionic liquid, nanoparticles

Biginelli reaction is well established reaction for the synthesis of heterocyclic compounds in synthetic organic chemistry for last few years[1-3]. This reaction is continuously in research attention due to significant role of 3,4-dihydropyrimidine-2(1*H*)-one (DHPMs) compound as therapeutic agents. The compound DHPM is nitrogen containing heterocycle and is very important in the field of medicinal chemistry, it has wide range of biological[4,5] activities such as antibacterial[6], antihypertensive activity[7,8], antifungal[9], antiviral[10], anticancer[11], antidiabetic[12] and many other biological properties. A three component reaction of aromatic aldehyde, urea and β-ketoester occur and produce 3,4-dihydropyrimidine-2(1*H*)-one (DHPMs) by different methods[13-19].

Many methods have been reported for the preparation of DHPM derivatives and Pietro Biginelli in 1893 was the first researcher who has synthesized this compound in a single step. To obtain the compound 3,4-dihydropyrimidine-2(1*H*)-one (DHPMs) the reaction was carried out simply by heating the mixture of three components in ethanol with catalytic amount of HCl but this provides only low to moderate yield of desired product. Feng Xu and co-workers[20] (2008) have synthesized the DHPM compound by aromatic aldehyde, β-ketoester and urea in presence of $CuCl_2.5H_2O$, Luciana M. Ramos and co-workers[21] (2012) synthesized the compound by using aldehyde, urea and 1,3-diketone in presence of strong lewis acid catalyst, Min Wang and coworkers[22] (2014) synthesized DHPM compound by using aromatic aldehyde, aromatic ketone and urea in presence of catalyst [$SnCl_4.5H_2O$] and many other methods were reported, but these methods had many drawbacks such as use of organic solvent, high reaction time, low product yield, expensive reaction work up and use of harmful chemicals which are responsible for the environmental pollution.

In short most of above reported methods includes harsh reaction conditions for the synthesis of 3,4-dihydropyrimidine-2(1*H*)-one (DHPMs) derivatives through Biginelli type reactions but recently, the environment friendly techniques have also been developed in synthetic organic chemistry such as green chemistry. The replacement of organic solvent by the green solvent has been increased in synthetic organic chemistry in the most of the industrial field because of its green characteristics like non-flammability, high thermal stability, high chemical stability, low vapor pressure and recycling of ionic liquid[23-26]. The advantages of ionic liquid has been confirmed by enhancing reactivity and selectivity in many examples therefore the use of the green solvent is the demand of today's chemistry[27].

Many researchers had synthesized the useful products by this reaction in good quantity but the generation of waste by products was neglected which was responsible for environmental pollution, therefore to minimize the waste and keep the environment healthy various methods have been developed and one of them is the use of TiO_2 **(NPs)** as a heterogeneous catalyst. In the present article we have used TiO_2 NPs as a heterogeneous catalyst because it provides large surface area to adsorbed the reactant which leads to

the fast reaction rates and it has high stability, low cost and safety towards human as well as environment.

We have synthesized compounds with better yield in shorter time by using ionic liquid {[MIM-H] CCl_3} as a green solvent in place of organic solvent and TiO_2 as a heterogeneous catalyst. The compound 3,4-dihydropyrimidine-2(1*H*)-one (DHPMs) was synthesized by a one pot process which involves the following reaction (Scheme I).

The ionic liquid used in the reaction 1-methyl- 3-hydro-1*H*-imidazol-3-ium trichloromethanide {[MIM-H] CCl_3} was synthesized by following reaction (Scheme II).

Results and Discussion

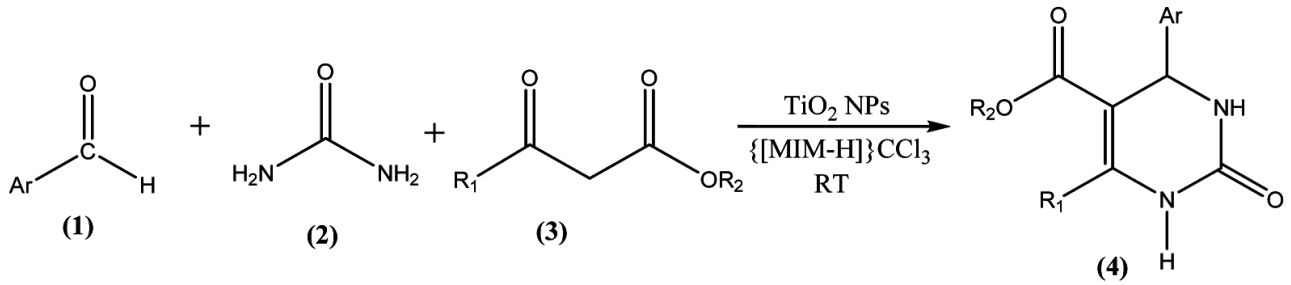
We have synthesized eighteen different DHPM derivatives and their structures were confirmed by spectral analysis. The carbonyl group of NH-CO (amide) was observed at 1670-1700 cm^{-1}, CO bond of ketonic group in β-ketoester observed at 1730-1750 cm^{-1} and C=C stretching peak of aromatic ring observed at 1620-1650 cm^{-1}. Appearence of NH streaching peak at cm^{-1} confirmed the formation of ionic liquid appears. In ^1H NMR spectra amide proton observed at 5-8 ppm. The proton attached to methylene (-CH_2) was observed at 4-6 ppm. The proton of phenyl ring were observed at 6-7.3 ppm. The proton of (-CH_3) group attached to oxygen of ether **(4d, 4j, 4p)** was observed at 3.5-4.0 ppm. In ionic liquid CH_3 proton appear at 3.56 ppm. In mass spectra the molecular ion peaks were observed according to their molecular weight.

As shown in Table I, the best results were obtained when the reaction was occurred in 1.0 mL of {[MIM-H] CCl_3 as a green solvent and TiO_2 (1 mol%) as a catalyst at RT. Whereas product yield was not obtained in absence of catalyst even after 1 hour at RT and 100ºC.

Effect of polarity of organic solvent v/s green solvent on the reaction

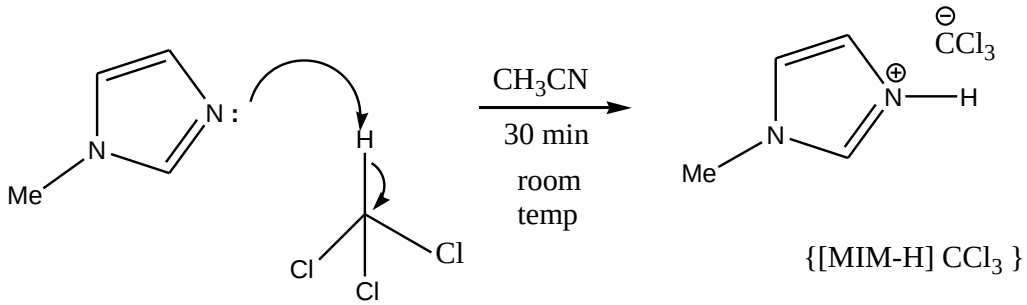
Reaction of aromatic aldehyde, urea and β-ketoester, in presence of different solvent like H_2O, C_2H_5OH, CH_3CN, CH_2Cl_2, *etc.* has been observed at RT, but in presence of green solvent better yield was obtained as compared to organic solvent (Table II and Table III).

As Biginelli reaction is three component reaction, aromatic aldehyde, β-ketoester and urea, this reaction is expected to proceed in following manner,



Reaction Conditions: Aldehyde **1** (1 mmol), urea **2** (1 mmol), ester **3** (1 mmol), TiO_2 (**NPs**) catalytic amount, **IL** (1 mL), stirring at RT, time 2-4 h

Scheme I — Biginelli type reaction



Scheme II — Preparation of Ionic liquids

Table I — Effect of amount of catalyst and temperature on the reaction conditions for compound **(4d)**

S.No.	Amount of TiO_2 NPs (mol%)	Temperature (°C)	Time (min)	Yield (%)
1	0.1	RT	80	–
2	0.1	100°C	80	–
3	0.2	RT	80	–
4	0.2	100°C	80	–
5	0.3	RT	60	–
6	0.3	100°C	60	–
7	0.5	RT	40	59
8	0.5	100°C	40	59
9	1	RT	5	94
10	1	100°C	5	94
11	2	100°C	5	94
12	5	100°C	5	94

Table II — Effect of solvent on reaction conditions

S.No.	Solvent	Time (min)	Yield (%)
1	CH_2Cl_2	30	77
2	CH_3CN	15	90
3	C_2H_5OH	10	94
4	H_2O	10	94
5	Ionic liquid	5	94

nucleophilic attack of urea at carbonyl carbon of aromatic aldehyde to yield iminium ion as an intermediate and this iminium ion further reacted with β-ketoester and finally it gave DHPM compound by the removal of water (Scheme III).

Reusability of {[MIM-H] CCl_3} ionic liquid

At the end of the reaction, ethyl acetate was added to the reaction mixture to separate the reactant and product. The reaction mixture was washed with water to separate product and catalyst (the product is soluble in ethyl acetate and catalyst is soluble in water). Layer was formed between water and product, water containing ionic liquid was separated from the product and it was again reused for other reaction after removing water.

Experimental Section

The chemicals for synthesis were purchased from Alfa Asear and Sigma Aldrich and used without further purification. The homogeneity of synthesized compound was monitored by thin layer chromatography (TLC) and visualized by UV chamber. The IR spectra were recorded in KBr on Shimadzu 8400S FTIR spectrophotometer in cm^{-1}. The ^1H and ^{13}C NMR were recorded on Jeol resonance spectrometer in $CDCl_3$/DMSO-d_6 using TMS as an internal standard at 300 MHz and 100 MHz. Chemical shifts were measured in δ (ppm). Mass spectra were recorded on Jeol SX 102/DA 600 using Argon/Xenon gas.

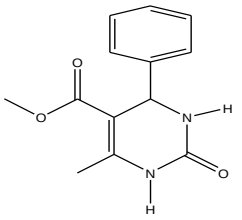
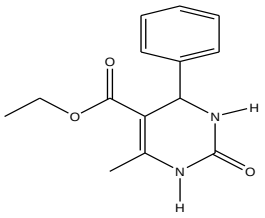
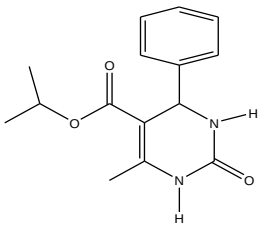
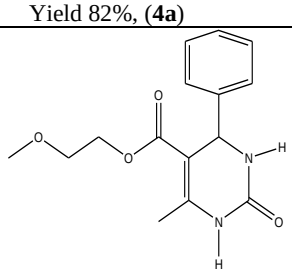
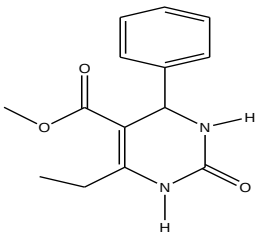
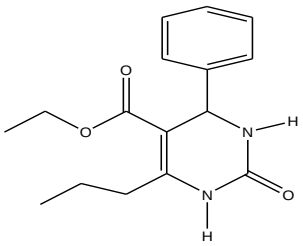
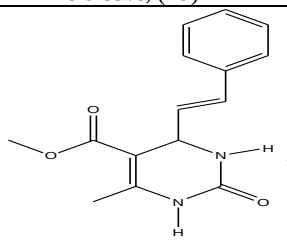
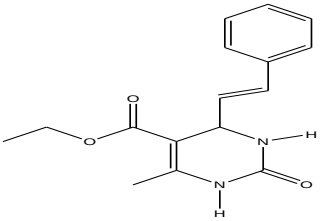
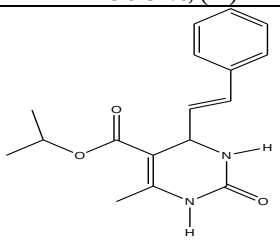
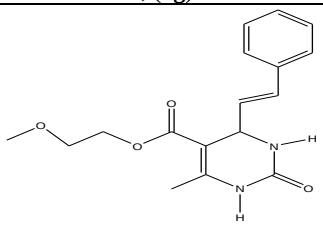
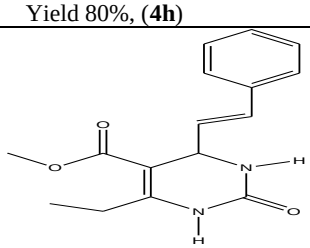
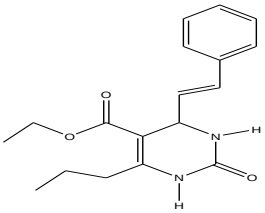
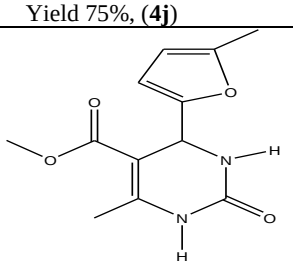
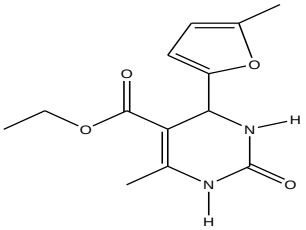
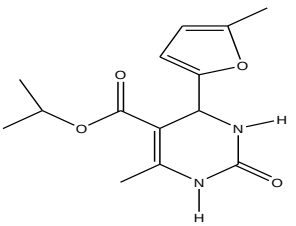
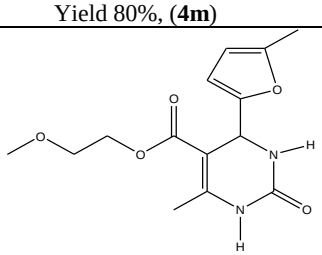
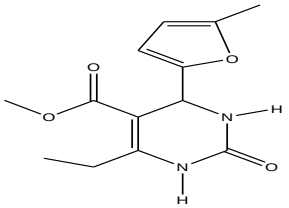
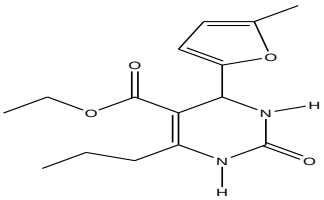
General process for the synthesis of ionic liquid: **1-methyl-3-hydro-1*H*- imidazole-3-ium trichloromethanide {[MIM-H] CCl_3}**

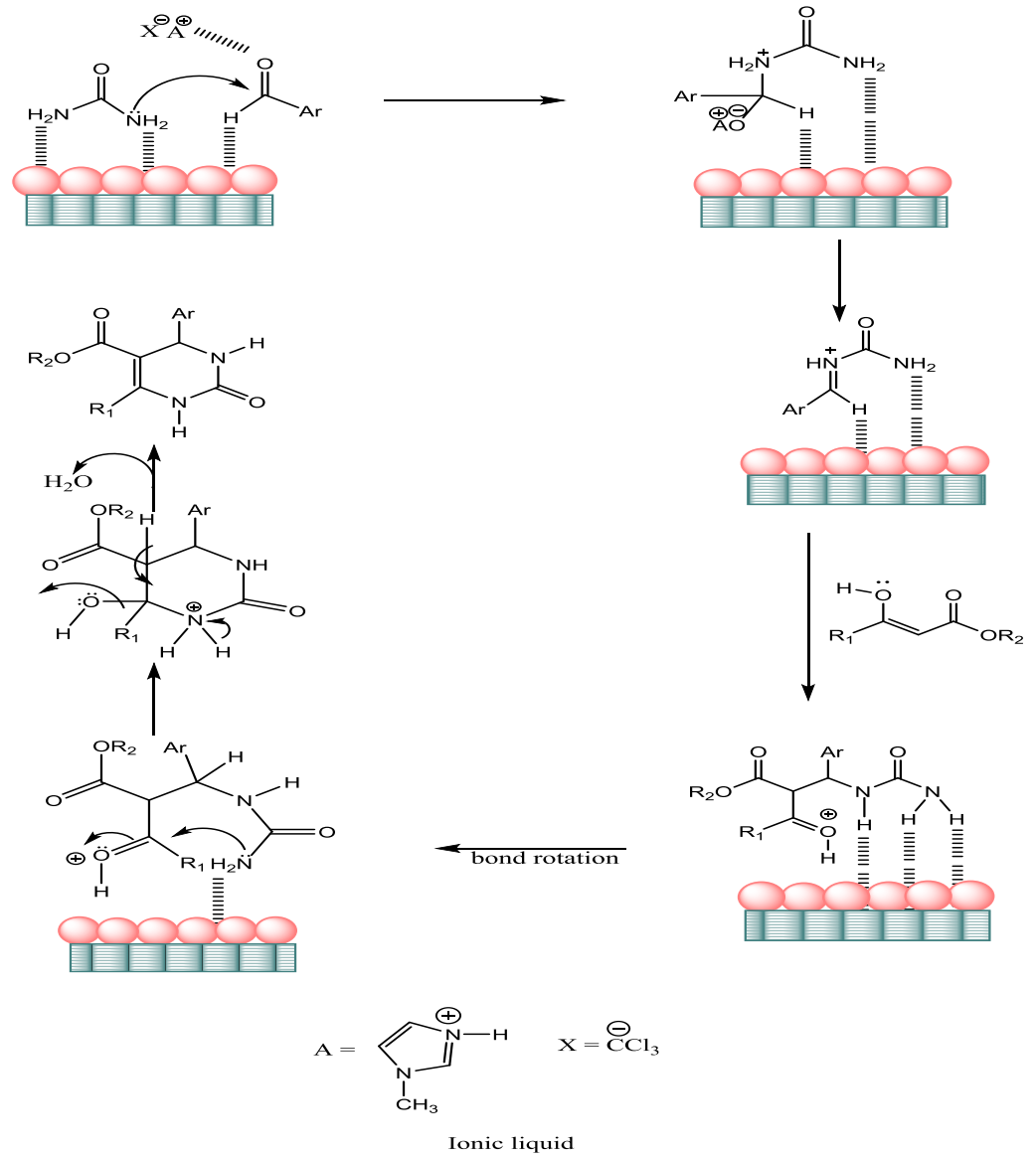
Round bottom flask of 50 mL having 1-methylimidazole (3 mmol) have been taken, CH_3CN (5 mL), chloroform (3 mmol) were added to the reaction mixture and stirred it at RT for 30 min. After completion of the reaction solvent was removed by distillation, the product was dried at 80-100ºC for 120 min (Scheme II).

General method for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-one (DHPM) derivatives

A mixture of aromatic aldehyde **1** (1 mmol), β-ketoester **3** (1 mmol) and urea **2** (1 mmol) was taken in round bottom flask,TiO_2 NPs (1 mol%) as a catalyst and 1-methyl-3-hydro-1*H*-imidazol-3-ium trichloromethanide {[MIM-H] CCl_3} ionic liquid (1.0 mL) as a green solvent were added in the reaction mixture, the reaction mixture was magnetically stirred at RT. The progress of reaction was monitored by TLC as a disappearance of reactants, after completion of procedure ethyl acetate (10 mL) was added to the reaction mixture and refluxed for next 10 min, and then washed with water (10 mL), finally the reaction mixture was recrystallized from ethanol. In this work, ionic liquid was recycled and reused without loss of its catalytic activity.

Table III — Structures of compounds with their yield

		
Yield 82%, (**4a**)	Yield 87%, (**4b**)	Yield 65%, (**4c**)
		
Yield 89%, (**4d**)	Yield 80%, (**4e**)	Yield 84%, (**4f**)
		
Yield 78%, (**4g**)	Yield 80%, (**4h**)	Yield 72%, (**4i**)
		
Yield 75%, (**4j**)	Yield 80%, (**4k**)	Yield 84%, (**4l**)
		
Yield 80%, (**4m**)	Yield 82%, (**4n**)	Yield 70%, (**4o**)
		
Yield 5%, (**4p**)	Yield 80%, (**4q**)	Yield 85%, (**4r**)



Scheme III — Proposed mechanism for the synthesis

Methyl 1,2,3,4-tetrahydro-6-methyl-2-oxo-4-phenylpyrimidine-5-carboxylate, 4a: Brown solid. IR (KBr): 3320 and 3315 (NH str.), 1727 (COOR), 1694 and 1663 cm^{-1} (C=O str.); ^1H NMR (300 MHz, DMSO-d_6): δ 9.5 (s, 1H, NH-3), 7.85 (s, 1H, NH-1), 7.22-7.43 (m, 5H, Ar-H) 5.22 (s, 1H, CH), 2.58 (s, 3H, OCH_3), 2.33 (s, 3H, CH_3); ^{13}C NMR (100 MHz, CD_3COCD_3): δ 164, 156, 137.5, 128, 108, 50.2, 42.8, 17.5. Anal. Calcd for $C_{13}H_{14}N_2O_3$: C, 69.48; H, 6.61; N, 5.4. Found: C, 68.97; H, 6.21; N, 5.78%.

Ethyl 1,2,3,4-tetrahydro-6-methyl-2-oxo-4-phenylpyrimidine-5-carboxylate, 4b: Brown solid. IR (KBr): 3320 and 3315 (NH str.), 1725 (COOR), 1695 and 1665 cm^{-1} (C=O str.); ^1H NMR (300 MHz, DMSO-d_6): δ 1.04 (t, 3H, OCH_2CH_3), 2.31 (s, 3H, CH_3), 3.95 (q, 2H, OCH_2CH_3), 5.20 (s, 1H, CH),7.21-7.42 (m, 5H, Ar-H), 7.86 (s, 1H, NH-1) 9.50 (s, 1H, NH-3), 3.8 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, CD_3COCD_3): δ 167, 155, 146.3, 143, 129.2, 125.5,123, 100.3, 60,54.4, 17.8, 14. Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.14; H, 7.12; N, 4.96%.

Isopropyl 1,2,3,4-tetrahydro-6-methyl-2-oxo-4-phenylpyrimidine-carboxylate, 4c: Brown solid. IR (KBr): 3323 and 3313 (NH str.), 1730 (COOR), 1694 and 1665 (C=O str.), 1440 cm^{-1} (C-C str.); ^1H NMR (300 MHz, DMSO-d_6): δ 9.5 (s, 1H, NH-3), 7.86 (s, 1H, NH-1), 7.21-7.44 (m, 5H, Ar- H), 5.21 (s, 1H,

CH), 4.15 (m, 1H, -CH-), 2.34 (s, 3H, CH_3), 1.34 (d, 6H, CH_3); ^{13}C NMR (100 MHz, CD_3COCD_3): δ 165, 157.3, 139.2, 128.6, 106.4,68.8, 43,22, 17.45. Anal. Calcd for $C_{15}H_{18}N_2O_3$: C, 75.25; H, 7.80; N, 5.16. Found: C, 75.84; H,7.12; N, 4.96%.

2-Methoxy ethyl 1,2,3,4-tetrahydro-6-methyl-2-oxo-4-phenylpyrimidine-5-carboxylate, 4d: Brown solid. IR (KBr): 3440 (NH), 1750 (COOR), 1685 cm^{-1} (CONH); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.4-7.15 (m, 5H, Ar-H), 6.16 (s, 2H,NH), 4.32 (t, 2H, -CH_2-), 3.6 (t, 2H, -CH_2-) 3.2 (s, 3H, CH_3) 1.7 (s, 3H, CH_3); ^{13}C NMR (100 MHz, CD_3COCD_3): δ 165.2, 156.6, 140, 128.2, 105.8, 72, 67.2, 54,42.6, 17.3. Anal. Calcd for $C_{15}H_{18}N_2O_4$: C, 71.06; H, 7.37; N, 4.87. Found: C, 70.45; H,7.68; N, 4.13%.

Methyl 1,2,3,4-tetrahydro-6-ethyl-2-oxo-4-phenylpyrimidine-5-carboxylate, 4e: Brown solid. IR (KBr): 3450 (NH), 1745 (COOR), 1680 (CONH), 1445 cm^{-1} (C-C str.); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.54-7.12 (m, 5H, Ar-H), 6.18 (s, 2H, NH), 3.8 (s, 3H, -CH_3), 2.1 (m, 2H,- CH_2-)1.04 (t, 3H, CH_3); ^{13}C NMR (100 MHz, CD_3COCD_3): δ 165.7, 156.3, 142, 127.5, 107.2, 52, 43, 30,9. Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 74.68; H, 7.44; N, 5.44. Found: C, 73.79; H, 7.03; N, 5.15%.

Ethyl 1,2,3,4-tetrahydro-2-oxo-4-phenyl-6-propyl-pyrimidine-5-carboxylate, 4f: Brown solid. IR (KBr): 3455 (NH), 1755 (COOR), 1685 (CONH), 1450 cm^{-1} (C-C str.); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.47-7.08 (m, 5H, Ar-H), 6.13 (d, 2H, NH), 4.1 (Q, 2H, -CH_2-), 1.9 (t, 2H,- CH_2-)1.34 (m, 3H, - CH_2-), 1.24 (t,3H, CH_3), 1.0 (t, 3H, CH_3); ^{13}C NMR (100 MHz, CD_3COCD_3): δ 163.9, 155, 144.5,105.4, 60, 42.9, 34.3, 17.4, 14, 13.5. Anal. Calcd for $C_{16}H_{19}N_2O_3$: C, 75.76; H, 8.12; N, 4.91. Found: C, 75.13; H, 7.82; N, 5.10%.

Methyl 1,2,3,4-tetrahydro-6-methyl-2-oxo-4-styryl-pyrimidine-5-carboxylate, 4g: Brown solid. IR (KBr): 3445 (NH), 1750 (COOR), 1680 cm^{-1} (CONH); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.52-7.02 (m, 5H, Ar-H), 6.13 (d, 2H, NH), 5.8 (d, 1H, -CH-), 3.72 (s, 3H,- CH_3-) 1.7 (s, 3H,- CH_3-); ^{13}C NMR (100 MHz, CD_3COCD_3): δ 164.8, 156.7, 137.5, 126.4, 124.2, 108, 50.7, 49, 17.2. Anal. Calcd for $C_{15}H_{16}N_2O_3$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.12; H, 6.97; N, 5,56%.

Ethyl 1,2,3,4-tetrahydro-6-methyl-2-oxo-4-styryl-pyrimidine-5-carboxylate, 4h: Brown solid. IR (KBr): 3460 (NH), 1755 (COOR), 1690 cm^{-1} (CONH); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.49-7.10 (m, 5H, Ar-H), 6.10 (d, 2H, NH), 5.87 (d, 1H, -CH-), 4.0 (Q, 2H,- CH_2-)1.69 (s, 3H,- CH_3-), 1.3 (t, 3H, CH_3); ^{13}C NMR (100 MHz, CD_3COCD_3): δ 165.1, 156.9, 139.5, 126.8, 124.3, 106.3, 59.7, 49. 2, 17, 13.8. Anal. Calcd for $C_{16}H_{18}N_2O_3$: C, 72.22; H, 7.07; N, 4.68. Found: C, 73.11; H, 7.34; N, 5.13%.

Isopropyl 1,2,3,4-tetrahydro-6-methyl-2-oxo-4-styryl-pyrimidine-5-carboxylate, 4i: Brown solid. IR (KBr): 3465 (NH), 1740 (COOR), 1700 cm^{-1} (CONH); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.50- 7.12 (m, 5H, Ar-H), 6.0 (d, 2H, NH), 5.89 (d, 1H, -CH-), 4.3 (m, 1H,- CH-) 1.72 (s, 3H,- CH_3-), 1.34 (d, 6H, CH_3); ^{13}C NMR (100 MHz, CD_3COCD_3) 165.3, 157, 139.2, 126.5,124.1,106.5, 69.1, 49. 0, 22, 17.2. Anal. Calcd for $C_{17}H_{19}N_2O_3$: C, 72.82; H, 7.40; N, 4.47. Found: C, 72.23; H, 7.16; N, 4.14%.

2-Methoxy ethyl 1,2,3,4-tetrahydro-6-methyl-2-oxo-4-styryl-pyrimidine-5-carboxylate, 4j: Brown solid. IR (KBr): 3435 (NH), 1740 (COOR), 1695 cm^{-1} (CONH); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.5-7.06 (m, 5H, Ar-H), 5.89 (d, 2H, NH), 5.92 (d, 1H, -CH-), 4.32 (t, 2H,- CH_2-) 3.63 (t, 2H,- CH_2-), 3.22 (s, 3H, CH_3) 1.71 (s, 3H,- CH_3-); ^{13}C NMR (100 MHz, CD_3COCD_3): δ 165, 156.6, 139.2, 126.9, 124.1, 106.2, 72, 67.7, 53.7 49. 1, 17.3. Anal. Calcd for $C_{17}H_{20}N_2O_4$: C, 76.72; H, 7.80; N, 4.71. Found: C, 76.24; H, 7.28; N, 4.37%.

Methyl 1,2,3,4-tetrahydro-6-methyl-2-oxo-4-styryl-pyrimidine-5-carboxylate, 4k: Brown solid. IR (KBr): 3445 (NH), 1750 (COOR), 1705 cm^{-1} (CONH); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.52- 7.03 (m, 5H, Ar-H), 6.01(d, 2H, NH), 5.92 (d, 1H, -CH-), 3.76 (s, 3H, CH_3), 2.1 (Q, 2H, - CH_2-), 1.03 (t, 3H,CH_3); ^{13}C NMR (100 MHz, CD_3COCD_3): δ 165.3, 156.3, 142.2, 127, 124.2, 107.2, 51,49. 3,25, 9. Anal. Calcd for $C_{16}H_{18}N_2O_3$: C,76.29; H,7.48; N,4.94. Found: C,75.89; H, 7.16; N, 4.24%.

Ethyl 1,2,3,4-tetrahydro-2-oxo-6-propyl-4-styryl-pyrimidine-5-carboxylate, 4l: Brown solid. IR (KBr): 3465 (NH),1760 (COOR), 1710 cm^{-1} (CONH); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.50- 7.03 (m, 5H, Ar-H), 6.04(d, 2H, NH), 5.90 (d, 1H, -CH-), 4.18 (Q, 2H,- CH_2-), 1.95 (t, 2H, - CH_2-), 1.36 (Q, 2H,-CH_2-), 1.3 (t, 3H, CH_3), 0.96 (t, 3H, CH_3); ^{13}C NMR (100 MHz, CD_3COCD_3): δ 165.1, 156.3, 144.6, 127, 124.2, 105.2, 60, 49. 3, 34.5, 17.5, 14, 13.7. Anal. Calcd for $C_{18}H_{22}N_2O_3$: C, 77.14; H, 8.09; N, 4.50. Found: C, 76.82; H, 7.89; N, 4.13%.

Methyl 1,2,3,4-tetrahydro-6methyl-4-(5-methyl-furan-2-yl)-2-oxo-pyrimidine-5-carboxylate, 4m: Brown solid. IR (KBr): 3470 (NH), 3000 (C-H_{str}), 1750 (COOR), 1700 (CONH), 1650 (C=C), 1150 cm^{-1} (C-O); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.2 (d, 1H, CH-), 6.15- 1.45 (d, 2H, Ar-H), 6.0 (d, 2H, NH), 3.78 (s, 3H,CH_3) 2.19 (s, 3H, CH_3), 1.69 (s, 3H, CH_3); ^{13}C NMR (100 MHz, CD_3COCD_3): δ 165, 156.8, 150.6, 137.7, 108.1, 106.2, 51, 16.7. Anal. Calcd for $C_{12}H_{14}N_2O_4$: C, 68.00; H, 6.93; N,5.66. Found: C, 67.76; H, 6.37; N, 5.25%.

Ethyl 1,2,3,4-tetrahydro-6-methyl-4-(5-methyl-furan-2-yl)-2-oxo-pyrimidine-5- carboxylate, 4n: Brown solid. IR (KBr): 3455 (NH), 2970 (C-H_{str}), 1755(COOR), 1695 (CONH), 1620 (C=C), 1170 cm^{-1} (C-O); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.18 (d, 1H, CH-), 6.17- 1.42 (d, 2H, Ar-H), 6.02 (d, 2H, NH), 4.2 (Q, 3H, CH_3), 2.2 (s, 3H,CH_3) 1.71 (s,3H,CH_3), 1.32 (t,3H,CH_3); ^{13}C NMR (100 MHz, CD_3COCD_3): δ 165.2, 157, 150.7, 139.5, 106.4, 60,51, 16.5, 13.8. Anal. Calcd for $C_{13}H_{16}N_2O_4$: C, 68.94; H, 7.33; N,5.36. Found: C, 68.43; H, 7.12; N, 5.20%.

Isopropyl 1,2,3,4-tetrahydro-6-methyl-4-(5-methyl-furan-2-yl)-2-oxo-pyrimidine-5-carboxylate, 4o: Brown solid. IR (KBr): 3480 (NH), 3050 (C-H_{str}), 1755 (COOR), 1720 (CONH), 1630 (C=C), 1170 cm^{-1} (C-O); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.21 (d, 1H, CH-), 6.18- 1.46 (d, 2H, Ar-H), 6.04(d, 2H, NH), 4.32 (m, 1H, -CH-), 2.17 (s, 3H, CH_3) 1.72 (s, 3H, CH_3), 1.35 (d,6H,CH_3); ^{13}C NMR (100 MHz, CD_3COCD_3): δ 165.4, 156.8, 150.9, 138.9, 106.6, 70,51, 22,16.7. Anal. Calcd for $C_{14}H_{18}N_2O_4$: C, 69.79; H, 7.69; N,5.09. Found: C, 69.47; H, 7.27, N, 4.97%.

2-Methoxy ethyl 1,2,3,4-tetrahydro-6-methyl-4-(5-methyl-furan-2-yl)-2-oxo-pyrimidine-5-carboxylate, 4p: Brown solid. IR (KBr): 3490 (NH),3070 (C-H_{str}), 1755 (COOR),1715 (CONH), 1650 (C=C), 1200 (C-O), 1100 and 1220 cm^{-1} (C-O-C); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.24 (d, 1H, CH-), 6.18- 1.46 (d, 2H, Ar-H), 6.0(d, 2H, NH), 4.34 (t, 2H, -CH_2-), 3.67 (t,2H,-CH_2-),3.25 (s,3H, CH_3), 2.17 (s,3H,CH_3), 1.72 (s, 3H, CH_3); ^{13}C NMR (100 MHz,CD_3COCD_3): δ 165.7, 157.4, 150.7, 139.3, 106.6, 72.2, 67.4, 53.7, 51, 17.2. Anal. Calcd for $C_{14}H_{18}N_2O_5$: C, 65.96; H, 7.27; N, 4.81. Found: C, 65.45; H, 5.57; N, 4.46%.

Methyl 1,2,3,4-tetrahydro-6-ethyl-4-(5-methyl-furan-2-yl)-2-oxo-pyrimidine-5-carboxylate, 4q: Brown solid. IR (KBr): 3495 (NH), 3090 (C-H_{str}), 1755 (COOR), 1710 (CONH), 1650 (C=C), 1220 (C-O), 1090 and 1230 cm^{-1} (C-O-C); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.21 (d, 1H, CH-), 6.15- 1.45 (d, 2H, Ar-H), 6.02 (d, 2H, NH), 3.76 (s, 3H, CH_3), 2.18 (s, 3H, CH_3) 2.1 (Q, 2H,-CH_2-)1.04 (t, 3H, CH_3); ^{13}C NMR (100 MHz, CD_3COCD_3): δ 165, 156.8, 150.6, 142.5, 107.3, 106.2.50.8, 51.3, 24.48.7. Anal. Calcd for $C_{13}H_{16}N_2O_4$: C, 64.96; H, 6.91; N,5.05. Found: C, 65.10; H, 6.28; N, 4.67%.

Ethyl 1,2,3,4-tetrahydro4-(5-methyl-furan-2-yl)-2-oxo-6-propyl-pyrimidine-5-carboxylate, 4r: Brown solid. IR (KBr): 3470 (NH), 3100 (C-H_{str}), 1750 (COOR), 1700 (CONH), 1650 (C=C), 1200 (C-O), 1080 and 1250 cm^{-1} (C-O-C); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.2 (d, 1H, CH-), 6.18-1.46 (d, 2H, Ar-H), 6.01 (d, 2H, NH), 4.2 (q, 2H, -CH_2-), 2.18 (s, 3H, CH_3), 2.0 (t, 2H, -CH_2-), 1.38 (m, 2H, -CH_2-), 1.3 (t, 3H, CH_3), 1.0 (t,3H,CH_3); ^{13}C NMR (100 MHz, CD_3COCD_3): δ 165.4, 156.8, 150.7, 144.5, 105.1, 59.8, 51.2, 33.8, 17.5, 14.0, 13.6. Anal. Calcd for $C_{15}H_{20}N_2O_4$: C, 70.56; H, 8.01; N, 4.85. Found: C, 70.16; H, 7.65; N, 4.56%.

Conclusion

A new and simple modified series of 3,4-dihydropyrimidin-2(1*H*)-one DHPM compounds has been synthesized using green approach. This approach employs readily available ionic liquid as a green solvent and TiO_2 NPs as a catalyst. The yield of the products in Biginelli protocol can be increased by 60-70% as compared to earlier reported methods. Therefore, this single step procedure for the synthesis of DHPM derivatives is superior in its simplicity and higher yields as compared to other alternative multistep syntheses that are already reported.

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