1-Methylimidazolium Trifluoromethanesulfonate [MIM][OTf]: Recyclable Reaction Medium and Efficient Catalyst for the Synthesis of Biginelli Dihydropyrimidines

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Abstract:

Developed an efficient alternative protocol for the synthesis of 3,4-dihydropyrimidone (DHPMs) derivatives from substituted aldehydes, methyl/ethyl acetoacetate & urea/thiourea in the presence of a protic ionic liquid (PIL) - 1-Methylimidazolium trifluoromethanesulfonate [MIM][OTf]. [MIM][OTf] which acts both as a solvent as well as an efficient catalyst. This protocol offered good yield (81-96%) in very short reaction time (25-75 min.) under optimized mild reaction conditions. Reported catalyst was showed decent profitability up to five cycles. High yield, short reaction time, role of ILs as green solvent and catalyst, recyclable nature of catalyst are some key outcomes of this research work.

Keywords: *Biginelli reaction; aldehyde; β-ketoester; urea/thiourea; 3,4-dihydropyrimidin-2-(1H)-ones (DHPMs); Ionic Liquids(ILs); 1-Methylimidazolium Trifluoromethanesulfonate[MIM][OTf]; Green Chemistry; Recyclable catalyst.*

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1. Introduction

Heterocyclic chemistry is an important branch of organic chemistry accounting for nearly one-third of modern publications.[1-3] Heterocyclic compounds have vital role in our biological system. They are an integral part of many pharmacologically active molecules, natural products and nucleic acids.[4-7] Because of their diverse biological activity and pharmacological characteristics, nitrogen-containing compounds in particular are of interest.[8-9]

A unique family of useful synthetic organic reactions known as multicomponent reactions (MCRs) produces a final product by reacting one or more different starting materials in a single pot.[10] High yields, atom-/step economy, quicker reaction times, and environmental friendliness are some of the benefits of the MCR method. This method is a useful tool for creating a library of new chemical entities (NCEs) and is particularly helpful in the drug development process.[11-17] Dihydropyrimidines are the most important heterocyclic ring systems which play an important role in the synthesis of DNA and RNA. Synthetically they were synthesized using Multi-component reactions like Biginelli reaction and Hantzsch dihydropyridine. In the past decades, such Biginelli type dihydropyrimidones (DHPMs) have received a considerable amount of attention due to the interesting pharmacological properties associated with this heterocyclic scaffold (**Figure 1**).[18-35]

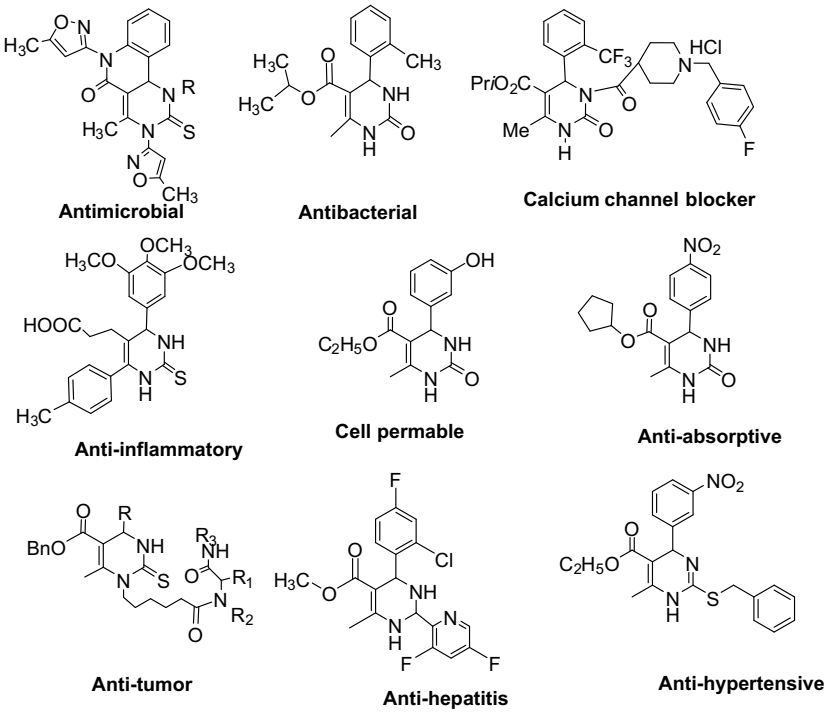


Figure 1. Pharmacological profile of dihydropyrimidinone derivatives

Because of their unique characteristics, which include low vapor pressure, excellent thermal stability, and tunable structural properties, ionic liquids (ILs) are incredibly versatile.[36-44] Very recently, there is an excellent review compiled on ionic liquid promoted Biginelli synthesis.[22] chemical biology, sophisticated organic synthesis, and energy technologies all make extensive use of 1-methylimidazolium trifluoromethanesulfonate, also known as 1-methylimidazolium triflate [MIM][OTf], a coupling activator and protic ionic liquid (PIL). This substance facilitates high-yield molecular modifications by acting as a catalyst and a dual-purpose solvent when it mediates a reaction. [45-46] To the best of our knowledge, the synthesis of DHPMs has never employed 1-methylimidazolium trifluoromethanesulfonate [MIM][OTf] both as a solvent as well as catalyst

2. Experimental

2.1 Material and Methods:

1-Methylimidazolium trifluoromethanesulfonate [MIM][OTf] or [HMIM][OTf] (CAS No: 99257-94-0) was purchased from TCI chemicals. Analytical thin layer chromatography was performed using TLC pre-coated silica gel 60 F_{254} MERCK (20x20 cm). Visualization was achieved by exposure to UV light. Organic solutions were concentrated by rotary evaporation on BUCHI-Switzerland; R-120 rotary evaporator and vacuum pump V-710. Column chromatography was performed on Merck silica gel 230-400 mesh size. ^{1}H and ^{13}C NMR spectra were recorded with Bruker 400 MHz NMR instruments. Mass spectra were recorded with Agilent LC-MS instrument. FTIR spectra were recorded from KBr disk on the FT-IR Bruker Tensor 27 spectrometer.

2.2. General Procedure for the Synthesis of 3,4-Dihydropyrimidones (DHPMs)

A mixture of the appropriate substituted benzaldehyde (1 mmol), β-keto ester (1 mmol), urea (1.5 mmol), and 1-methylimidazolium trifluoromethanesulfonate, [MIM][OTf] (10 mol%), was stirred at 120 °C for the time specified in **Table 2**. The progress of the reaction was monitored by thin-layer chromatography (TLC). After completion of the reaction, the reaction mixture was treated with cold water and extracted with ethyl acetate (10 mL X 3). The combined organic extracts were dried over anhydrous sodium sulfate (Na_2SO_4) and concentrated under reduced pressure. The resulting crude product was purified by crystallization from ethanol to afford the corresponding DHPMs derivative.

2.3. Spectral data for selected compounds

All synthesized products were purified and carried out the spectral analysis. Obtained spectral data was well coordinated with the literature and hence we confirmed the successful formation of 3,4-dihydropyrimidones under the optimized parameters.

***2.3.1. Methyl-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (Table 2, entry 4a)*: TLC (EtOAc: hexane 1:5)** R_f = 0.42; **IR:** 3332.38, 3217.38, 3115.05, 2922.34, 2364.29, 1694.99, 1665.23, 1430.8625, 1340.77, 1267.60, 1232.65,

1187.31, 1090.49, 1024.31, 798.61, 753.67, 695.93, 543.17; **^{1}H NMR (400 MHz, Chloroform-d)** δ 7.56 (s, 1H), 7.31-7.29 (m, 5H), 5.51 (s,1H), 5.39 (s, 1H), 2.61 (s, 3H), 2.34 (s, 3H); **^{13}C NMR (125 MHz, Chloroform-d):** 166.22, 153.22, 146.53, 143.67, 128.94, 128.17 128.64 101.14, 55.23, 51.42, 18.9;9 **LCMS:** Exact Mass:246.10; observed Mass: M+1=247.04.

2.3.2. Methyl-4-(4-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (Table 2, entry 4b) : **TLC (EtOAc: hexane 1:5)** R_f = 0.41;**IR:** 3329.39, 2931.75, 2356.31, 1690.41, 1635.28, 1488.68, 1424.66, 1313.79, 1223.43, 1186.85, 1092.92, 960.80, 813.96, 813.96, 757.43, 723.22, 658.11, 538.2597; **^{1}H NMR (400 MHz, Chloroform-d)** δ 8.30 (s, 1H), 7.29-7.22 (m, 4H), 6.02 (s, 1H), 5.36 (s, 1H), 2.62 (s, 3H), 2.36 (s, 3H); **^{13}C NMR (125 MHz, Chloroform-d):**166.05, 153.18, 146.73, 142.17, 133.97, 129.10, 128.08, 101.17, 55.23, 51.23, 18.99; **LCMS:** Exact Mass:280.71; observed Mass: M+1=280.92.

2.3.3. Methyl-4-(4-fluorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (Table 2, entry 4c): **TLC (EtOAc: hexane 1:5)** R_f = 0.50; **IR:** 3326.31, 3218.46, 3099.18, 2923.12, 2340.31, 1692.41, 1640.28, 1507.68, 1426.66, 1335.79, 1267.43, 1223.85, 1188.92, 1080.81, 942.12, 757.43, 723.22, 642.11, 538.04; **^{1}H NMR (400 MHz, Chloroform-d)** δ 7.78 (s, 1H), 7.29-7.26 (m, 2H), 7.01-6.89 (m, 2H), 5.67 (s, 1H), 5.38 (s, 1H), 3.63 (s, 3H), 2.34 (s, 3H); **^{13}C NMR (125 MHz, Chloroform-d)**:166.09, 163.51, 161.56, 153.09, 146.46, 139.59 128.43, 128.36, 115.88, 115.71, 101.46, 55.22, 51.39, 29.84, 29.42, 19.50; **LCMS:** Exact Mass: 264.09; observed Mass: M+1=265.00**.**

2.3.4. Methyl-4-(3-bromophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (Table 2, entry 4d): **TLC (EtOAc: hexane 1:5)** R_f = 0.50;**IR:**3502.28, 3356.45, 3309.97, 2924.10, 2334.62, 1709.14, 165.77, 1632.25, 1429.64, 1338.95, 1270.02, 1230.51, 1187.38, 1087.65, 939.57, 848.78, 723.13; **^{1}H NMR (400 MHz, Chloroform-d)** δ 8.05 (s, 1H), 7.45 (s, 1H) 7.39-7.32 (m, 2H), 7.26-7.16 (m, 2H), 6.14 (s, 1H), 5.33 (s, 1H), 3.63 (s, 3H), 2.36 (s, 3H); **^{13}C NMR (125 MHz, Chloroform-d)**:166.04, 152.51, 148.13, 146.46 130.55, 130.09, 129.58, 125.23, 122.35 99.66, 54.70, 50.92, 29.84,18.50; **LCMS:** Exact Mass:324.01; observed Mass: M+1=324.87

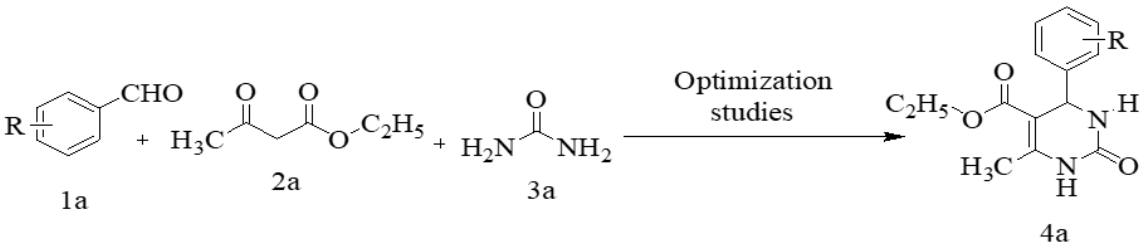
2.3.5. Methyl-6-methyl-4-(4-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (Table 2, entry. 4e): **TLC (EtOAc: hexane 1:5)** R_f = 0.50; **IR:**3362.07, 31110.04, 2945.20, 2340.43, 1713.95, 1690.51, 1637.88, 1513.91, 1411.07, 1351.32, 1297.99, 1225.16, 1092.72, 825.56, 738.23, 661.52; **^{1}H NMR (400 MHz, Chloroform-d)**δ 9.37 (s,1H), 8.22 (d, 2H, 8.5 Hz), 7.91(s,1H), 7.51 (d, 8.5 Hz, 2H,), 5.27 (s, 1H), 3.53 (s,3H), 2.26 (s, 3H); **^{13}C NMR (125 MHz, Chloroform-d)**:165.55, 151.79, 151.76, 149.62, 146.73, 127.57, 123.86, 97.97, 53.51, 50.90, 17.90, 14.07; **LCMS:** Exact Mass:291.09; observed Mass: M+1=291.94.

2.3.6. Methyl-4-(4-chloro-3-fluorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (Table 2, entry 4f): **TLC (EtOAc: hexane 1:5)** R_f = 0.50; **IR:** 3366.78, 3101.09, 2944.35, 2374.44, 2332.73, 1697.91, 1644.63, 1606.07, 1578.811, 1482.64, 1396.86, 1228.85, 1096.76, 964.75, 803.55; **^{1}H NMR (400 MHz, Chloroform-d)** δ 8.39 (s, 1H), 7.18-7.14 (m, 2H), 7.08-7.06 (m, 2H), 5.95 (s, 1H), 5.65 (s, 1H), 3.59 (s, 3H), 2.39 (s, 3H); **^{13}CNMR (125 MHz, Chloroform-d)** :165.09, 161.02, 159.03, 152.63, 149.07, 134.35 134.27, 129.36, 124.74, 116.35, 97.72, 51.15, 49.14, 18.55; **LCMS:** Exact Mass:298.05; observed Mass: M+1=298.92

3. Results and discussion

The catalytic activity of the commercially available ionic catalyst, [MIM][OTf], was investigated for the synthesis of 3,4-dihydropyrimidinones (DHPMs) using a model three-component reaction of benzaldehyde (1 mmol), ethyl acetoacetate (1 mmol), and urea (1.5 mmol) stirred at 120 °C. The optimization study was performed by systematically varying the catalyst loading, solvent and reaction temperature. The results obtained from these experiments are summarized in **Table 1.** Initially, the model reaction was examined in the absence of catalyst. At room temperature, only a trace amount of the desired product was formed even after 24 h (entry **a**), indicating that the catalyst free reaction proceeds very slowly under these conditions. Increasing the temperature to 100 °C in the absence of catalyst resulted in only 20% yield after 16 h (entry **b**). These observations demonstrate the importance of an appropriate catalytic system for achieving efficient conversion of the substrates into the corresponding DHPMs. The effect of solvent was subsequently investigated. When the reaction was carried out in ethanol under reflux without catalyst, a moderate yield of 45% was obtained after 12 h (entry **c**). In contrast, incorporation of 10 mol% of [MIM][OTf] under solvent-free conditions at 100 °C significantly improved the yield to 60% within 5 h (entry **d**). This enhancement clearly indicates the beneficial role of [MIM][OTf] in promoting the multicomponent cyclocondensation reaction. A marked improvement in product formation was observed upon increasing the reaction temperature to 120 °C.

Table 1: Optimization of reaction parameters for DHPMs synthesis



1a 2a 3a 4a

Entry	Catalyst (in mole %)	Solvent (in mL)	Temperature (in ºC)	Time (in h)	Yield (in %)
a	---	----	RT	24	Trace amount
b	----	---	100	16	20
c	---	EtOH	Reflux	12	45
d	[MIM][OTf] (10mol %)	---	100	5	60
e	**[MIM][OTf] (10 mol %)**	**---**	**120**	**1**	**95**
f	[MIM][OTf] (10 mol %)	---	150	1	80
g	[MIM][OTf] (10 mol %)	---	60	5	45
h	[MIM][OTf] (10 mol %)	---	RT	12	38
i	[MIM][OTf] (10 mol %)	EtOH	120	2	64
j	[MIM][OTf] (10 mol %)	DMF	120	5	35
k	[MIM][OTf] (10 mol %)	NMP	120	6	26
l	[MIM][OTf] (12.5 mol %)	----	120	1	82
m	[MIM][OTf] (15 mol %)	----	120	1	62
n	[MIM][OTf] (7.5 mol %)	----	120	2	84
o	[MIM][OTf] (5 mol %)	----	120	4	68

Under solvent-free conditions using 10 mol% of [MIM][OTf], the desired DHPMs was obtained in 95% yield within only 1 h (entry **e**). Thus, increasing the temperature from 100 to 120°C substantially accelerated the reaction and improved the isolated yield. The effect of reaction temperature was further evaluated using 10 mol% [MIM][OTf] under solvent-free conditions. At 150°C, the reaction afforded 80% yield after 1 h (entry **f**), whereas lowering the temperature to 60°C resulted in only 45% yield after 5 h (entry **g**). At room temperature, the reaction proceeded more slowly and provided 38% yield even after 12 h (entry **h**). These results establish that temperature has a significant influence on the reaction rate and product formation. Among the temperatures investigated, 120 °C provided the most favorable combination of reaction time and yield.

The superior performance under solvent-free conditions is also noteworthy, as the absence of an additional solvent avoids dilution of the reactants and provides a simple reaction medium. The influence of conventional organic solvents was also examined at 120 °C in the presence of 10 mol% [MIM][OTf]. When ethanol was employed, the reaction afforded only 64% yield after 2 h (entry **i**). Similarly, DMF gave 35% yield after 5 h (entry **j**), while NMP resulted in only 26% yield after 6h (entry **k**). These results clearly demonstrate that the solvent-free protocol is considerably more effective than the corresponding reactions performed in polar organic solvents. The lower yields observed in these solvents may be associated with dilution of the reactants and/or differences in the interaction of the reaction components with the ionic catalyst.

The amount of [MIM][OTf] was then optimized under the most promising solvent-free

conditions at 120 °C. Increasing the catalyst loading from 10 to 12.5 mol% did not improve the reaction outcome; instead, the yield decreased from 95% to 82% (entry **l**). A further increase to 15 mol% resulted in a still lower yield of 62% (entry **m**). These observations indicate that increasing the catalyst concentration beyond the optimum level is not advantageous for this transformation. Conversely, reducing the catalyst loading to 7.5 mol% afforded 84% yield after 2 h (entry **n**), whereas 5 mol% catalyst gave 68% yield after 4 h (entry **o**). Therefore, 10 mol% [MIM][OTf] was identified as the optimum catalyst loading, providing the highest yield within the shortest reaction time.

On the basis of the systematic optimization study, the optimum conditions for the model synthesis of DHPMs were established as benzaldehyde (1 mmol), methyl acetoacetate (1 mmol), urea (1.5 mmol), and [MIM][OTf] (10 mol%) under solvent-free conditions at 120 °C for 1 h, affording the desired product in 95% yield. The optimized conditions were selected not merely on the basis of catalyst loading but by considering the combined effects of catalyst concentration, reaction temperature, reaction medium, reaction time, and isolated yield. The optimization results also highlight the advantage of employing [MIM][OTf] under solvent-free conditions. The reaction proceeds efficiently without the use of an additional organic solvent, and the desired DHPMs is obtained in excellent yield within a comparatively short reaction time. These features make the optimized protocol operationally simple and potentially attractive for the synthesis of DHPMs derivatives.

With the optimized reaction conditions established, the scope and general applicability of the developed protocol were subsequently examined by employing a series of substituted aromatic aldehydes in the three-component synthesis of DHPMs derivatives. The substrate scope of the developed protocol was investigated using aromatic aldehydes bearing different substituents, and the results are summarized in **Table 2.** The reaction tolerated both electron-withdrawing and electron-donating substituents, affording the corresponding 2-oxo-1,2,3,4-tetrahydropyrimidine carboxylates **4a–k** in 80–96% yields. The nature of the aromatic substituent showed a noticeable influence on reaction efficiency. Electron-withdrawing substituents, particularly NO_2 and halogens, generally afforded good to excellent yields. The nitro derivative **4e** gave 96% yield within 30 min, while chloro- and fluoro-substituted derivatives **4b** and **4c** afforded 96% and 95% yields, respectively, in 1 h. The bromo derivative **4d** also furnished a high yield of 90%.

The electron-donating methoxy substituent was also well tolerated, with derivative **4j** obtained in 95% yield in only 30 min. In contrast, the hydroxy-substituted derivative **4g** gave a comparatively lower yield of 80%, indicating that the nature of the substituent can influence the reaction outcome. Disubstituted substrates also underwent the reaction efficiently: the chloro-fluoro derivative **4f** and dichloro derivative **4k** afforded 89% and 90% yields, respectively. Overall, the results demonstrate good tolerance toward diverse aromatic substituents, with no strict limitation to either electron-donating or electron-withdrawing groups. The close agreement between the experimental and reported melting points further supports the formation of the desired products.

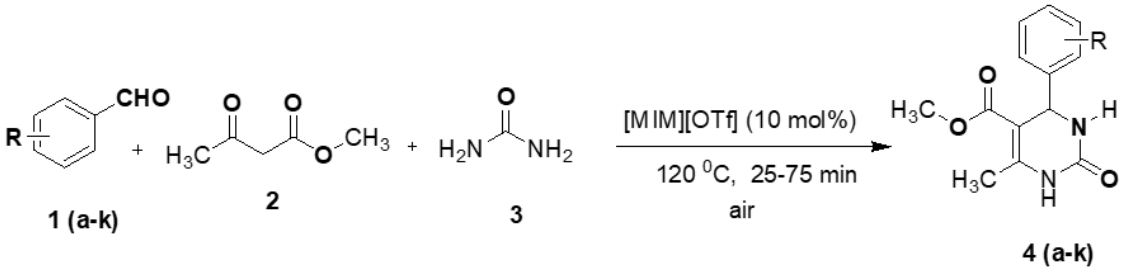
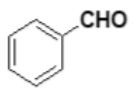
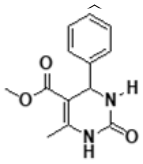
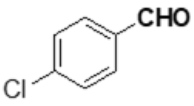
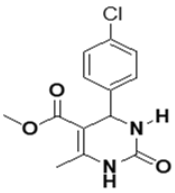
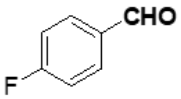
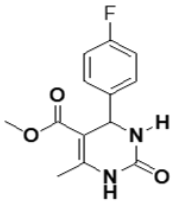
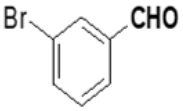
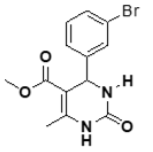
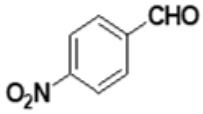
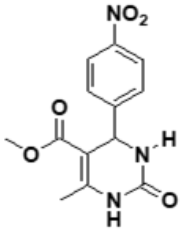
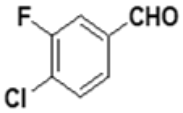
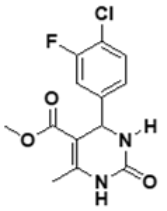
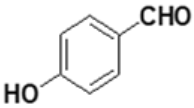
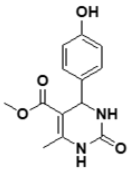
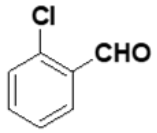
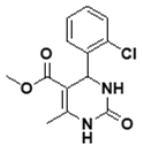
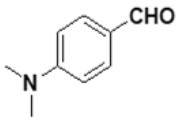
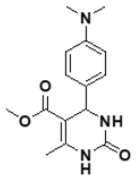
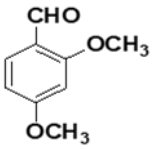
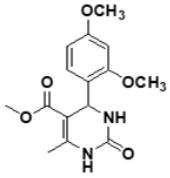
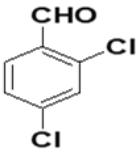
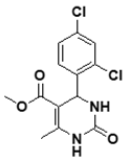


Table 2: Synthesis of 2-(Oxo)-1,2,3,4-Tetrahydropyrimidines Carboxylate Derivatives

Entry	Aldehyde (1 a-k)	Product (4 a-k)	Time	Yield (%)	mp (^{0}C)	Lit. mp (^{0}C)

4a			1 h	95	210-211	210-212
4b			1 h	96	195-196	195-196
4c			1 h	95	207-209	208–210
4d			1 h	90	214-216	215-217
4e			30 min	96	216-218	214-216
4f			1 h	89	186-188	187-188
4g			35 min	80	244-246	245-246

4h			25 min	81	248–250	248–25
4i			65 min	88	213-215	215-216
4j			30 min	95	225-227	226-228
4k			75 min	90	253-254	252-254

3.1. Probable Mechanism

Based on the obtained result and literature, the formation of the Biginelli product can be rationalized through the following probable mechanism (**Figure 2**). The ionic liquid (ILs) initially activates the carbonyl group of the aldehyde **A**, facilitating its condensation with urea **B** to generate the corresponding imine/iminium intermediate **D**. Subsequently, the β-ketoester **E** undergoes enolization to form the nucleophilic enol intermediate **F**, which attacks the electrophilic carbon of intermediate **D**, producing the open-chain ureide intermediate **G**. Intramolecular cyclization (annulation) of **G** then gives the cyclic intermediate **H**. Finally, dehydration of **H** affords the corresponding 2-oxo-1,2,3,4-tetrahydropyrimidine carboxylate (Biginelli product), with regeneration of the ionic-liquid catalyst.

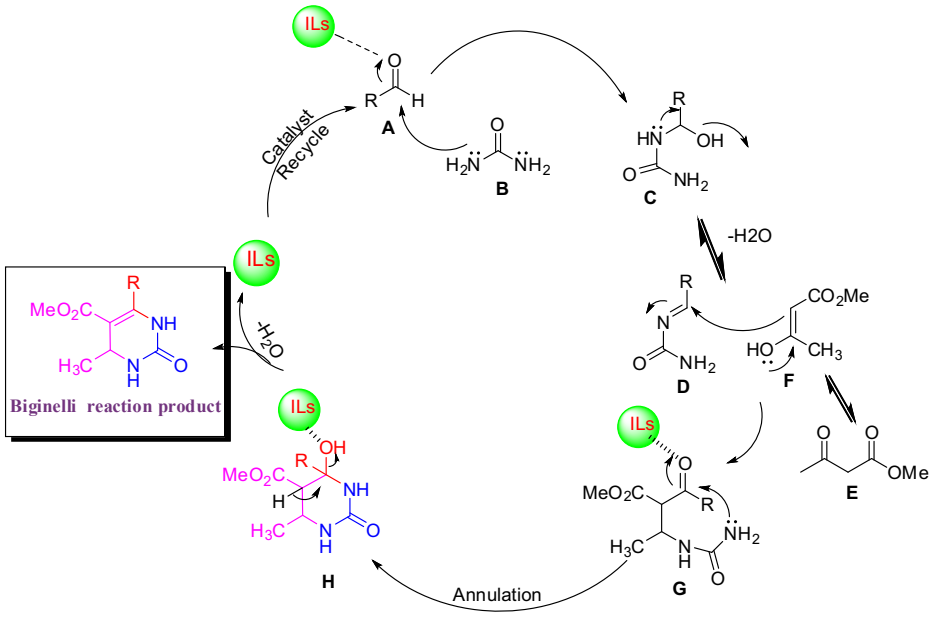


Figure 2: Probable mechanism for the [HMIM][OTf] (IL) catalyzed synthesis of DHPMs.

3.2. Recyclability of Catalyst

The recyclability of the [MIM][OTf] catalyst was evaluated using the model reaction under the optimized conditions (**Figure 3**). After completion of the reaction, as confirmed by TLC, the catalyst was recovered by rotary evaporation. The reaction filtrate was extracted with ether to remove organic residues, followed by removal of water under reduced pressure and washing with $CHCl_3$ to eliminate urea. The recovered [MIM][OTf] was subsequently reused in the model reaction. The catalyst exhibited good recyclability and retained its catalytic activity for up to five consecutive cycles, with product yields of 95, 94, 90, 86, and 78%, respectively. The gradual decrease in yield over successive cycles indicates some loss of catalytic efficiency, while the catalyst remained effective after five uses.

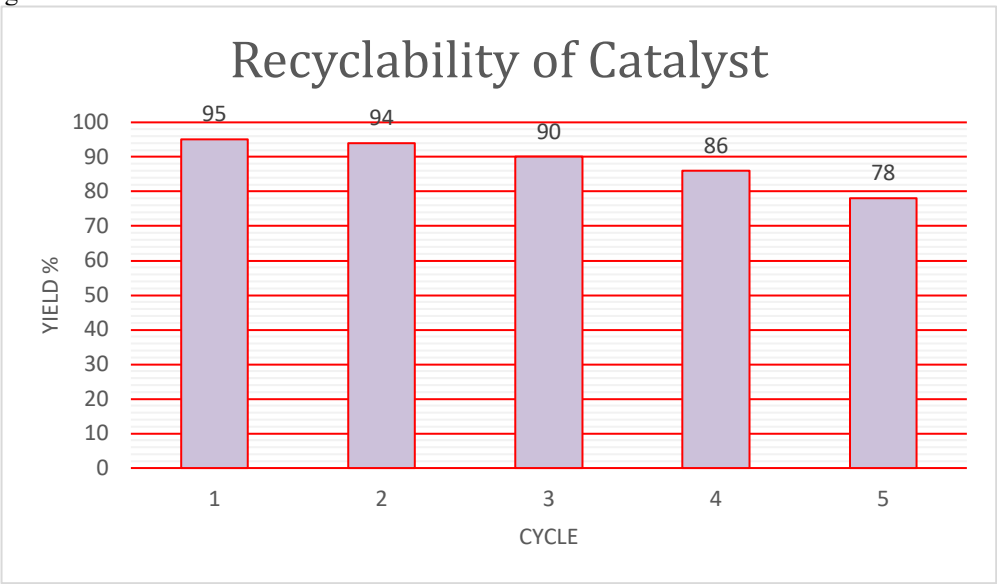


Figure 3: Study of recyclability of [MIM][OTf] catalyst.

4. Conclusion

In conclusion, an efficient [MIM][OTf]-catalyzed protocol has been developed for the synthesis of 2-oxo-1,2,3,4-tetrahydropyrimidine carboxylate derivatives through a one-pot multi-component reaction. The methodology showed good tolerance toward a range of electron-donating and electron-withdrawing aromatic substituents, affording

the desired products in 80–96% yields within relatively short reaction times. The structures of the synthesized derivatives were further supported by their melting-point data, which showed good agreement with reported values. Importantly, the [MIM][OTf] catalyst could be recovered and reused for five consecutive cycles, while maintaining appreciable catalytic activity, with yields decreasing from 95% in the first cycle to 78% in the fifth cycle. Overall, the combination of good yields, broad substrate tolerance, short reaction times, and catalyst recyclability makes this protocol a useful approach for the synthesis of 2-oxo-1,2,3,4-tetrahydropyrimidine carboxylate derivatives.

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Conflict of Interests:

The authors declare that there is no conflict of interest.

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