***Original Research Article***

**Eco-Friendly Synthesis of 3,4-Dihydropyrimidine-2(1H)-ones Using Ionic Liquid [Msim]Cl as a Catalyst and Development of Novel Derivatives**

**ABSTRACT**

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| The ionic liquid 3-methyl-1-sulfonic acid imidazolium chloride serves as an environmentally friendly catalyst for the efficient synthesis of 3,4-dihydropyrimidine-2(1*H*)-ones from aldehydes, β-keto esters, and urea. This method is not only eco-friendly but also produces high-purity products with excellent efficiency. Additionally, the catalyst can be recycled and reused while maintaining its effectiveness. |

***Keywords:*** *Ionic liquid, Dihydropyrimidinone, DHPM, Biginelli reaction, Green Chemistry.*

**1. INTRODUCTION**

Over the past two decades, researchers have focused on waste prevention, safer solvent design, energy efficiency, and the use of renewable feedstocks in the synthesis of organic compounds (Kurniawan et al., 2021). Integrating these principles into industrial organic chemistry presents both opportunities and challenges in achieving greener synthesis while maintaining efficiency, which calls for innovative approaches (Schaub, 2021). Strategies such as using alternative solvents and reaction media, conducting multicomponent reactions, implementing continuous processing, and ehancing process intensification have effective in improving atom economy and reducing waste (Kar et al., 2021). Additionally, environmentally friendly solvents promote quantitative synthesis and enable the efficient extraction of pure products through sustainable methods (Jiang et al., 2021).

Heterocyclic compounds account for about 80% of commercial pharmaceuticals; however, many traditional synthetic methods are not sustainable. Eco-friendly approaches, such as microwave-assisted synthesis and nanoparticle-catalyzed reactions, have emerged as efficient alternatives, providing rapid reactions and shorter reaction times (Rao et al., 2021). Additionally, ionic liquids have gained significant attention as versatile and efficient catalysts, playing a crucial role in promoting sustainable organic transformations.

Ionic liquids are composed of various cations and anions. The anions have an inorganic structure and a significantly smaller volume than the cations, which are typically larger organic compounds with positive charges. Ionic liquids remain liquid at temperatures below 100°C due to the weak interactions between the cations and anions, a result of size difference. While the structure of ionic liquid resembles that of salts, salts possess a strong crystalline structure and have melting point of around 800°C due to the strong bonds between their cations and anions. The presence of contaminants can alter the chemical and physical properties of ionic liquids, making purification necessary. The most significant pollutants in ionic liquids are halides or organic and water-based substrates, which often originate from unreacted compounds.

Ionic liquids, which are molten salts with exceptional chemical and thermal stability, have emerged as promising alternatives to traditional organic solvents, especially in renewable energy technologies (Jesus & Filho, 2022). Over the past two decades, these ionic liquids have gained prominence as clean, efficient, and environmentally friendly substitutes for volatile organic solvents. Their unique thermal, physical, chemical, and biological properties make them highly versatile for a variety of applications. Ionic liquids are extensively studied in fields such as electrochemistry, solvent engineering, catalysis, biological processes, physical chemistry, and analytical chemistry (Singh & Anthony, 2020).

Ionic liquids are used as environmentally friendly solvents and catalysts and are valuable in separation and extraction processes. They have a wide range of applications in the organic synthesis of various heterocycles, including pyrazoles (Akbarpour et al., 2022), benzothiazoles (Chen et al., 2024), tetrazoles (Aali et al., 2022), triazoles (Kumar et al., 2024), and quinazolines (Chen et al. 2022).

Heterocyclic compounds that contain a pyrimidine ring, specifically 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs), have garnered significant attention in medicinal chemistry in recent years. These compounds are particular noteworthy due to their diverse biological activities, which include antibacterial (Ramachandran et al., 2016), antifungal (Singh et al., 2008), anticancer (Sashidhara et al., 2016), anti-inflammatory, anthelmintic (Shaikh & Meshram, 2016), antihypertensive (Jain et al., 2008), anti-HIV (Kappe et al., 1997), and antimalarial properties (Chiang et al., 2009). As a result, synthesizing various 3,4-dihydropyrimidin-2(1*H*)-ones is of great importance, and the Biginelli reaction offers a straightforward method for obtaining these dihydropyrimidinones. Given the significance of the end products, extensive efforts have been dedicated to improving yields. Various catalysts have been utilized for the synthesis of dihydropyrimidin-2(1H)-ones, including Sm(ClO4)3 (Liu & Wang, 2010), Cu(OTf)2 under microwave conditions (Pasunooti et al., 2011), cerium(IV) ammonium nitrate (Sadek et al., 2010), BiCl3 (Ramalinga et al., 2001), Yb(PFO)3 (Wu et al., 2011), ammonium metavanadate (NH4VO3) (Niralwad et al., 2010), triethylammonium hydrogen sulfate (Khabazzadeh et al., 2012), La(OTf)3 (Ma et al., 2000), Fe3O4 nanoparticles (Masoud et al., 2011).

To further our research on the development of eco-friendly catalysts for organic synthesis (Deshmukh et al., 2012; Patil et al., 2013; Patil et al., 2021; Jadhav et al. 2023; Jadhav et al. 2024), we have extended the application of ionic liquid as an environmentally benign catalyst for the efficient synthesis of 3,4-dihydropyridine-2(1H)-ones from aldehydes, β-keto esters, and urea (Scheme 1).



**Scheme 1. Synthesis of 4-dihydropyrimidin-2(1*H*)-ones**

**2. EXPERIMENTAL SECTION**

**2.1 Material and Methods**

All chemicals are sourced from Merck and Sigma-Aldrich Chemical Companies and are used without any further purification. The Products are characterized by their physical constants using a DBK programmable melting point apparatus. All yields mentioned refer to the isolated products. A Bruker FTIR spectrophotometer is used for infrared (IR) spectra, while a Bruker Advance 400 MHz spectrometer is employed for 1H NMR, 13C NMR and mass spectra. The acidity of the ionic liquid is measured using pH-meter.

**2.2 General procedure for preparation of ionic liquid 3-methyl-1-sulfonic acid imidazolium chloride [Msim]Cl**

1-methylimidazole (0.410 g, 5 mmol) was dissolved in 50 mL of dry dichloromethane (CH2Cl2). To this solution, chlorosulfonic acid (0.605 g, 5.2 mmol) was added dropwise over a period of five minutes at room temperature. The mixture was stirred overnight and allowed to stand for an additional 60 minutes. The CH2Cl2 was removed by decantation. The residue was washed with 50 mL of dry CH2Cl2 and vacuum-dried to obtain [Msim]Cl, which is a viscous, colorless oil (Scheme 2).



**Scheme 2. Preparation of ionic liquid [Msim]Cl**

The formation of the ionic liquid [Msim]Cl has been confirmed through spectral characterization.

**2.2.1 Characterization of [Msim]Cl**

1H NMR (DMSO) (δ ppm) 3.848 (s, 3H, CH3), 7.623 (s, 1H), 7.673 (s, 1H), 9.048 (s, 1H), 14.391 (s, 1H)

13C NMR (DMSO-d6): 35.82, 120.08, 123.59, 136.14

In the 1H NMR spectrum of the ionic liquid [Msim]Cl, a one-proton signal appears at 14.39 ppm corresponding to the –NH group. Additionally, there are three more signals with integral ratios of 1: 2: 3 located at 9.048 ppm (1-H), 7.62-7.67 ppm (2-H), and 3.85 ppm (3H, N-CH3). The corresponding carbon signals can be observed in the 13C NMR spectrum.

 

(a) (b)

**Fig. 1. (a) 1H NMR and (b) 13C NMR spectra of ionic liquid [Msim]Cl**

**2.3 General Procedure for the Synthesis of 3, 4-dihydropyrimidin-2(1*H*)-ones Derivatives**

A solution was prepared by combining 2 mmol of urea, 1 mmol of aldehyde, and 1.5 mmol of β-keto ester in 5 mL of ethanol. To this mixture, 10 mol% of [Msim]Cl was added. The resulting mixture was stirred and heated under reflux for a specified duration, with the reaction progress monitored by thin-layer chromatography (TLC), using a solvent system of n-hexane and ethyl acetate in a 1:9 ratio. Once the reaction was complete, the solid product was recrystallized from ethanol.

Novel and unreported 3,4-dihydropyrimidin-2(1H)-one derivative (4r) was synthesized using 3,4-methylenedioxybenzaldehyde, β-keto ester, and urea in the presence of [Msim]Cl, exhibiting satisfactory spectral characteristics.

The synthesized products were identified through their physical properties and further characterized by IR, 1H NMR, and 13C NMR spectral analyses.

**2.4 Spectral data for synthesized 3, 4-dihydropyrimidin-2(1*H*)-ones derivatives**

**5-Ethoxycarbonyl-4-(4-nitrophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one.** **(4a)**

 mp 209-210°C; IR (KBr): 3222, 3112, 2977, 2913, 1724, 1698, 1629, 1598, 1292, 1211, 1087, 774 cm-1; 1H NMR δ 8.136 (s, N1-1H), 7.267-7.311 (m, 2H), 6.963-7.021 (m, 2H), 5.861 (s, N3-1H), 5.386 (s, 1H), 4.061-4.088 (m, 2H), 2.342 (s, 3H), 1.165 (t, 3H); 13C NMR (DMSO): 166.21, 162.26, 154.61, 148.52, 142.49, 133.37, 120.75, 109.25, 65.29, 58.16, 17.56, 14.85.

**5-Ethoxycarbonyl-4-(4-fluorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one.** **(4b)**

mp 180-181°C; IR (KBr): 3350, 3211, 3089, 1687, 1629 cm-1; 1H NMR (DMSO-d6): δ 8.136 (s, N1-1H), 7.267-7.311 (m, 2H), 6.963-7.021 (m, 2H), 5.861 (s, N3-1H), 5.386 (s, 1H), 4.044-4.106 (m, 2H), 2.342 (s, 3H), 1.147-1.182 (t, 3H); 13C NMR (DMSO): 165.54, 161.09, 153.33, 146.38, 139.65, 128.33, 115.52, 101.26, 60.10, 55.02, 18.64, 14.15.

**5-Ethoxycarbonyl-4-(4-hydroxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one. (4c)**

mp 199-200°C; IR (KBr): 3420, 3255, 3131, 2977, 1675, 1656, 1522 cm-1;1H NMR (DMSO-d6): δ 7.028 (s, N1-1H), 6.78-6.91 (m, 2H), 6.368-6.684 (m, 2H), 5.395 (s, N3-1H), 5.025 (br s,1H), 5.426 (s, 1H), 3.986-4.046 (m, 2H), 2.563(s, 3H), 1.184 (t, 3H); 13C NMR (DMSO): 161.23, 159.52, 150.32, 144.58, 136.87, 126.54, 114.36, 100.57, 58.39, 54.58, 17.62, 13.36.

**5-Ethoxycarbonyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one. (4d)**

mp 195-197°C; IR (KBr): 3285, 1715, 1658 cm-1; 1H NMR (DMSO-d6): δ 7.013 (s, N1-1H), 6.86-6.99 (m, 2H), 6.56-6.674 (m, 2H), 5.697 (s, N3-1H), 5.0187 (s,1H), 3.986-4.046 (m, 2H), 3.736 (s, 3H), 2.296 (s, 3H), 1.158 (t, 3H); 13C NMR (DMSO): 163.30, 160.01, 151.12, 144.38, 135.31, 128.53, 115.78, 101.41, 69.36, 55.48, 18.03, 14.84.

**5-Ethoxycarbonyl-4-(2-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one. (4e)**

mp 260-262 °C; IR (KBr): 3262, 2971, 1713, 1693, 1624 cm-1; 1H NMR (DMSO-d6) : δ 8.319 (s, N1-1H), 7.82 (d, 1H), 7.71 (m, 1H), 7.56 (m, 1H), 7.35 (d, 1H), 5.628 (s, N3-1H), 5.256 (s, 1H), 4.126-4.142 (m, 2H), 3.56 (s, 3H), 2.316 (s, 3H), 1.214 (t, 3H); 13C NMR (DMSO): 166.12,155.48,144.49, 129.23, 126.34, 121.38, 110.28, 60.12, 55.89, 47.87, 18.45, 14.02.

**5-Ethoxycarbonyl-4-(4-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one. (4f)**

mp 214-216°C; IR (KBr): 3452, 3285, 3186, 3010, 1720, 1678, 1492 cm-1; 1H NMR (DMSO-d6): δ 8.23 (s, N1-1H), 7.78 (d, 2H), 7.56 (d, 2H), 5.563 (s, N3-1H), 5.14 (s, 1H), 4.21-4.58 (m, 2H), 2.45 (s, 3H), 1.215 (t, 3H); 13C NMR (DMSO-d6): 166.5, 152.03, 150.23, 145.39, 131.28, 127.98, 125.96, 96.37, 60.28, 53.48, 18.02, 15.38.

**5-Ethoxycarbonyl-4-(3-methoxy4-hydroxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one.** **(4g)**

Mp 231-232 °C; IR (KBr): 3519, 3232, 3101, 2972, 2925, 1694, 1636, 1508 cm-1; 1H NMR (DMSO-d6: δ 7.003 (s, 1H), 6.815-6.849 (m, 3H), 6.311 (s, N1-1H), 5.593 (s, N3-1H), 5.351-5.357 (d, 1H), 5.217 (s, 1H), 4.071-4.129 (m, 2H), 3.877 (s, 3H), 2.355 (s, 3H), 1.180-1.215 (t, 3H); 13C NMR (DMSO): 165.96, 153.06, 147.69, 145.51, 136.32, 118.92, 115.29, 110.72, 100.33, 59.46, 55.83, 54.40, 18.24, 14.38.

**5-Ethoxycarbonyl-4-(2,4-dichlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one.** **(4h)**

mp 248-249°C; IR(KBr): 3360, 1658, 1631 cm-1; 1H NMR (DMSO-d6: δ 8.25 (s, N1-1H), 7.49 (s, 1H), 7.38 (d, 1H), 7.29 (d, 1H), 5.68 (s, N3-1H), 5.21 (s, 1H), 4.38-4.49 (m, 2H), 2.45 (s, 3H), 1.215 (t, 3H); 13C NMR (DMSO): 165.35, 156.44, 148.89, 140.48, 133.56, 129.65, 128.43, 127.52, 115.45, 97.26, 60.57, 51.45, 18.02, 13.96.

**5-Ethoxycarbonyl-4-(3,4-methylenedioxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one. (4i)**

 mp 187-188°C; IR(KBr): 3412, 3231, 3102, 2963, 1701, 1646, 1122, 1091 cm-1; 1H NMR (DMSO-d6): δ 8.156 (s, N1-1H), 6.717-6.810 (m, 3H), 5.939 (s, 2H), 5.763 (N3-1H), 5.316 (s, 1H), 4.057-4.116 (m, 2H), 2.340 (s, 3H), 1.168-1.203 (t, 3H); 13C NMR (DMSO): 165.87, 152.95, 147.92, 147.60, 146.73, 138.94, 119.84, 107.90, 107.16, 100.98, 100.19, 59.58, 54.52, 18.26, 14.29.

**5-Methoxycarbonyl-4-(4-nitrophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one. (4j)**

mp 236-238°C; IR (KBr): 3355, 3236, 3128, 2953, 1725, 1652, 1511 cm-1; 1H NMR (DMSO-d6) : δ 8.148 (s, N1-1H), 7.276-7.328 (m, 2H), 6.985-7.038 (m, 2H), 5.895 (N3-1H), 5.354 (s, 1H), 2.542 (s, 3H), 2.386 (s, 3H). 13C NMR (DMSO): 166.37, 162.36, 154.28, 148.32, 142.89, 133.84, 121.09, 109.56, 65.78, 57.98, 18.09.

**5-Methoxycarbonyl-4-(4-flourophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one. (4k)**

mp 191-193°C; IR (KBr): 3313, 1677, 1619 cm-1; 1H NMR (DMSO-d6): δ 7.896 (s, N1-1H), 7.185-7.213 (m, 2H), 6.696-6.786 (m, 2H), 5.697 (s, N3-1H), 5.353 (s, 1H), 2.538 (s, 3H), 2.297 (s, 3H); 13C NMR (DMSO): 165.75, 160.89, 153.89, 145.67, 140.27, 128.93, 114.28, 100.87, 60.73, 54.87, 18.18.

**5-Methoxycarbonyl-4-(4-hydroxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one**. **(4l)**

 Mp 241-244°C; 1H NMR (DMSO-d6): δ 7.056 (s, N1-1H), 6.81-6.98 (m, 2H), 6.355-6.671 (m, 2H), 5.388 (s, N3-1H), 5.019 (br s,1H), 5.478 (s, 1H), 2.586 (s, 3H), 2.184 (s, 3H); 13C NMR (DMSO): 161.83, 160.21, 150.81, 144.42, 137.04, 126.89, 115.27, 101.09, 58.12, 54.83, 17.73.

**5-Methoxycarbonyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one**. **(4m)**

mp 191-193°C; IR (KBr): 3427, 3252, 3121, 2964, 1724, 1699, 1523 cm-1; 1H NMR (DMSO-d6): δ 7.026 (s, N1-1H), 6.76-6.91 (m, 2H), 6.43-6.68 (m, 2H), 5.711 (s, N3-1H), 5.029 (s,1H), 3.753 (s, 3H), 2.596 (s, 3H), 2.158 (s, 3H); 13C NMR (DMSO): 166.28, 152.79, 147.83, 147.87, 144.56, 136.82, 119.05, 115.81, 111.19, 99.97, 59.86, 55.18, 53.48, 18.86.

**5-Methoxycarbonyl-4-(2-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one. (4n)**

mp 283-285°C; IR (KBr): 3256, 2969, 1725, 1688, 1636 cm-1; 1H NMR(DMSO-d6) : δ 8.259 (s, N1-1H), 7.78 (d, 1H), 7.68 (m, 1H), 7.44 (m, 1H), 7.29 (d, 1H), 5.656 (s, N3-1H), 5.286 (s, 1H), 3.62 (s,3H), 2.328 (s, 3H), 1.241 (s, 3H); 13C NMR (DMSO): 165.92,158.42,145.13, 130.28,125.89, 119.93, 110.87, 62.23, 55.41, 45.23, 19.38, 13.55.

**5-Methoxycarbonyl-4-(4-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one**. **(4o)**

mp 204-205°C; IR (KBr): 3428, 3256, 3189, 2889, 1725, 1678, 1502 cm-1; 1H NMR (DMSO-d6): δ 8.30 (s, N1-1H), 7.48 (d, 2H), 7.32 (d, 2H), 5.25 (d, 1H), 5.85 (s, N3-1H), 3.53 (s, 3H), 2.25 (s, 3H); 13C NMR (DMSO-d6): 165.29, 151.82, 145.21, 146.87, 130.97, 129.58, 128.25, 98.15, 60.63, 54.38, 18.82.

**5-Methoxycarbonyl-4-(3-methoxy-4-hydroxyphenyl)-6-methyl-3,4-dihydropyrimidin- 2(1H)-one. (4p)**

Mp 224-225oC; 1H NMR (DMSO-d6): δ 8.19 (s, 1H), 7.928( s, N1-1H), 6.46 (d, 1H), 6.438 (d, 1H), 6.410 (d, 1H), 5.469 (s, N3-1H),5.389 (s, 1H), 3.729 (s, 3H) 2.235 (s, 3H), 2.087 (s, 3H); 13C NMR (DMSO): 166.35, 152.86, 148.28, 146.04, 136.17, 118.70, 115.40, 110.90, 99.84, 55.86, 54.08, 50.89, 18.25.

**5-Methoxycarbonyl-4-(2,4-dichlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one. (4q)**

mp 251-253°C IR(KBr): 3389, 1680, 1644 cm-1; 1H NMR (DMSO-d6: δ 8.29 (s, N1-1H), 7.44 (s, 1H), 7.58 (d, 1H), 7.35 (d, 1H), 5.85 (s, N3-1H), 5.19 (s,1H), 2.51 (s, 3H), 1.29 (t, 3H); 13C NMR (DMSO): 165.29, 155.36, 148.89, 142.38, 133.87, 133.77, 130.45, 128.55, 1236.82, 97.89, 61.28, 52.86, 17.09.

**5-Methoxycarbonyl-4-(3,4-methylenedioxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one. (4r)**

mp 238-240 °C IR(KBr): 3414, 2964, 1702, 1640, 1125, 1090 cm-1; 1H NMR (DMSO-d6: δ 9.02 (s, N1-1H), 7.49 (s, N3-1H), 6.67-6.71 (m, 3H), 5.88 (s, 2H), 5.07 (d, 1H), 3.51 (s, 3H), 2.22 (t, 3H); 13C NMR (DMSO): 166.24, 152.72, 148.61, 147.66, 146.76, 139.03, 119.68, 108.06, 107.14, 101.09, 99.68, 54.17, 50.95, 18.29.

 

(a) (b)

**Fig. 2. (a) 1H NMR and (b) 13C NMR spectra of newly synthesized derivative 4r**

**3. RESULTS AND DISCUSSION**

To evaluate the catalytic efficiency of [Msim]Cl in synthesizing dihydropyrimidinones, we investigated its catalytic activity in a one-pot three-component condensation reaction involving an aryl aldehyde, β-ketoester and urea. For this study, we selected p-nitrobenzaldehyde (1 mmol), ethyl acetoacetate (1.5 mmol), and urea (2 mmol) as the model reaction components. The results are summarized in Table 1. We examined different amounts of the catalyst (Table 1, entries 1-7), determining that the highest yield was achieved with 10 mol% of [Msim]Cl as the catalyst (Table 1, entry 5), without the use of any solvent. Increasing the amount of catalyst beyond this did not improve the results (Table 1, entries 6, 7). Hence, 10 mol% of [Msim]Cl was established as the optimal catalytic amount. Notably, when no catalyst was used in this reaction system, the desired product was not obtained. This indicates that the ionic liquid plays a crucial role in the reaction system (Table 1, entry 1).

To enhance the yield, we investigated the effect of various solvents on the model reaction (Table 1, entries 8-11). Our findings indicated that ethanol is the most effective solvent, providing both high yields and shorter reaction times (Table 1, entry 11). In contrast, water (H2O), methanol (CH3OH), and dichloromethane (CH2Cl2) resulted in relatively lower yields (Table 1, entries 8-10).

We also examined the influence of reaction time on yield, as illustrated in (Table 1, entries 12-16). The results showed that even when the reaction time was extended to 90 minutes, the yield did not change significantly (Table 1, entry 16). Therefore, the optimal conditions identified are a 10 mol% catalyst, a reaction time 70 minutes, and ethanol as the solvent.

**Table 1. Effect of catalyst under different conditions for the model reactiona**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Entry** | **Solvent** | **Catalyst****(mol %)** | **Time****(minutes)** | **Yieldb****(%)** |
| 1 | Solvent free | None | 70 | NR |
| 2 | Solvent free | 1 | 70 | 49 |
| 3 | Solvent free | 2 | 70 | 54 |
| 4 | Solvent free | 5 | 70 | 64 |
| 5 | Solvent free | 10 | 70 | 79 |
| 6 | Solvent free | 15 | 70 | 81 |
| 7 | Solvent free | 20 | 70 | 80 |
| 8 | H2O | 10 | 70 | 70 |
| 9 | CH2Cl2 | 10 | 70 | 72 |
| 10 | CH3OH | 10 | 70 | 86 |
| 11 | C2H5OH | 10 | 70 | c95, 94, 94, 93, 92, 90 |
| 12 | C2H5OH | 10 | 40 | 76 |
| 13 | C2H5OH | 10 | 50 | 82 |
| 14 | C2H5OH | 10 | 60 | 92 |
| 15 | C2H5OH | 10 | 80 | 94 |
| 16 | C2H5OH | 10 | 90 | 94 |
| aReaction conditions: *p*-nitrobenzaldehyde (1 mmol), ethyl acetoacetate (1.5 mmol), urea (2 mmol) and catalyst in solvent (5 mL) or solvent-free ; bIsolated yield; ccatalyst was recycled six times. |

The recycling capability of [Msim]Cl was one of its most important advantages, as demonstrated in the model reaction. After the product was separated, the filtrate containing catalyst was vacuumed to remove water, allowing the catalyst to be reused directly for the next run. As shown in Table 1, the Brønsted acidic ionic liquid [Msim]Cl can be recycled at least six times without a significant loss in catalytic activity, with yields ranging from 95% to 90% (Table 1, entry 11). This indicates that ionic liquid [Msim]Cl is an efficient and recyclable catalyst for the preparation of 3,4-dihydropyrimidin-2(1*H*)-one derivatives.

The catalytic performance was evaluated in comparison to relevant studies from the literature regarding the synthesis of 5-ethoxycarbonyl-4-(4-nitrophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one. Using the acidic ionic liquid [Msim]Cl as a catalyst, our results were compared to previously reported methods (Table 2, entries 1-5) to emphasize the benefits of the current approach in synthesizing 3, 4-dihydropyrimidin-2(1*H*)-one derivatives. The findings indicate that [Msim]Cl (Table 2, entry 6) demonstrates superior efficiency compared to other catalysts.

**Table 2. The comparative synthesis of (4a) using the reported catalysts vs. [Msim]Cl**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Entry** | **Reaction and Conditions** | **Time****(minutes/hours)** | **Yield****(%)** | **Reference** |
| 1. | molten [Et3NH] [HSO4] | 80 mins | 76 | (Khabazzadeh et al., 2012) |
| 2. | FeCl3.6H2O in Ethanol | 4 hrs | 83 | (Lu & Ma, 2000) |
| 3. | NiCl2.6H2O/HCl in Ethanol | 5 hrs | 86 | (Hatkehlouei et al., 2022) |
| 4. | Neflon-Ga | 1 hr | 63 | (Prakash et al., 2012) |
| 5. | [Msim]Cl in Ethanol | 60 mins | 95 | Present work |

The new protocol was evaluated under optimized conditions using a variety of aldehydes. This method successfully yielded various substituted 3, 4-dihydropyrimidin-2(1*H*)-one derivatives with high efficiency and shorter reaction times. The results are summarized in Table 3.

**Table 3. Synthesis of 3, 4-dihydropyrimidin-2(1*H*)-ones (DHPMs) using [Msim]Cl**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Entry | Products | Time (min) | Yield(%) | Melting points (0C) |
| Observed | Reported\* |
| 4a |  | 60 | 95 | 209-210 | 208-209 |
| 4b |  | 60 | 94 | 180-181 | 180-183 |
| 4c |  | 70 | 87 | 199-200 | 200-202 |
| 4d |  | 60 | 89 | 195-197 | 196–198 |
| 4e |  | 85 | 88 | 260-262 | 262–263 |
| 4f |  | 85 | 90 | 214-216 | 215–216 |
| 4g |  | 60 | 88 | 231-232 | 232-233 |
| 4h |  | 90 | 95 | 248-249 | 249-250 |
| 4i |  | 60 | 91 | 187-188 | 186-188 |
| 4j |  | 65 | 94 | 236-238 | 235–237 |
| 4k |  | 80 | 89 | 191-193 | 193-195 |
| 4l |  | 90 | 85 | 241-244 | 242-244 |
| 4m |  | 65 | 88 | 191-193 | 194-196 |
| 4n |  | 90 | 85 | 283-285 | 284–286 |
| 4o |  | 95 | 89 | 204-205 | 205-208 |
| 4p |  | 60 | 91 | 224-225 | 225-226 |
| 4q |  | 90 | 87 | 251-153 | 252-253 |
| 4r |  | 65 | 88 | 238-240 | -- |

\* Reported Melting points (Masoud et al., 2011; Zhang et al., 2015; Rao et al., 2011; Javidi et al., 2015; Jin et al., 2004; Salehi et al. 2003; Safari & Gandomi-Ravand, 2014)

The proposed mechanism for the reaction is illustrated in Scheme 3. The reaction begins with condensation of an aldehyde and 1,3-dicarbonyl compound, resulting in the formation of carbenium ion (i). This cation is then intercepted by urea, yielding an intermediate (ii). Subsequently, cyclization of this intermediate leads to the formation of dihydropyrimidinone (4).

 

**Scheme 3. Plausible mechanism of the proposed method**

**4. CONCLUSIONS**

In conclusion, we have developed a simple and efficient one-pot method for the three-component condensation of aromatic aldehydes, urea, and either ethyl or methyl acetoacetate in ethanol. This reaction is catalyzed by the eco-friendly acidic ionic liquid 3-methyl-1-sulfonic acid imidazolium chloride. Our methodology offers several advantages: it allows for easy preparation of the catalyst, simplifies product isolation, achieves high to excellent yields, has short reaction times, and requires only a catalytic amount of [Msim]Cl. Additionally, the successful synthesis of a new derivative further illustrates the catalyst's versatility and effectiveness in facilitating the production of diverse products from various reactants.

**REFERENCES**

Aali, E., Gholizadeh, M., & Noroozi-Shad, N. (2022). 1-Disulfo-[2, 2-bipyridine]-1, 1-diium chloride ionic liquid as an efficient catalyst for the green synthesis of 5-substituted 1H-tetrazoles. Journal of Molecular Structure, 1247, 131289. <https://doi.org/10.1016/j.molstruc.2021.131289>

Akbarpour, T., Yousefi Seyf, J., Khazaei, A., & Sarmasti, N. (2022). Synthesis of pyrano [2, 3-c] pyrazole derivatives using a novel ionic-liquid based nano-magnetic catalyst (Fe3O4@ SiO2@(CH2)3NH@ CC@ Imidazole@ SO3H+ Cl−). Polycyclic Aromatic Compounds, 42(6), 3844-3864. <https://doi.org/10.1080/10406638.2021.1873152>

Chen, T., Zhang, Y., & Xu, Y. (2022). Efficient synthesis of quinazoline-2, 4 (1H, 3H)-dione via simultaneous activated CO2 and 2-aminobenzonitrile by 1-methylhydantoin anion-functionalized ionic liquid through the multiple-site cooperative interactions. ACS Sustainable Chemistry & Engineering, 10(32), 10699-10711. <https://doi.org/10.1021/acssuschemeng.2c03249>

Chen, X., Zhong, Q., Ma, X., Li, S., Sun, W., & Liu, C. (2024). Synthesis of benzothiazoles catalyzed by [Bmim] PF6 ionic liquid in solvent-free condition. Journal of Catalysis, 429, 115274. <https://doi.org/10.1016/j.jcat.2023.115274>

Chiang, A. N., Valderramos, J. C., Balachandran, R., Chovatiya, R. J., Mead, B. P., Schneider, C., et al. (2009). Select pyrimidinones inhibit the propagation of the malarial parasite, Plasmodium falciparum. Bioorganic & medicinal chemistry, 17(4), 1527-1533. <https://doi.org/10.1016/j.bmc.2009.01.024>

de Jesus, S. S., & Maciel Filho, R. (2022). Are ionic liquids eco-friendly?. Renewable and Sustainable Energy Reviews, 157, 112039. <https://doi.org/10.1016/j.rser.2021.112039>

Deshmukh, M. B., Patil, S. S., Jadhav, S. D., & Pawar, P. B. (2012). Green approach for Knoevenagel condensation of aromatic aldehydes with active methylene group. Synthetic Communications, 42(8), 1177-1183. <https://doi.org/10.1080/00397911.2010.537423>

Hatkehlouei, S. F. T., Mirza, B., & Soleimani-Amiri, S. (2022). Solvent-free one-pot synthesis of diverse dihydropyrimidinones/tetrahydropyrimidinones using biginelli reaction catalyzed by Fe3O4@ C@ OSO3H. Polycyclic Aromatic Compounds, 42(4), 1341-1357. <https://doi.org/10.1080/10406638.2020.1781203>

Jain, K. S., Bariwal, J. B., Kathiravan, M. K., Phoujdar, M. S., Sahne, R. S., Chauhan, B. S., et al. (2008). Recent advances in selective α1-adrenoreceptor antagonists as antihypertensive agents. Bioorganic & medicinal chemistry, 16(9), 4759-4800. <https://doi.org/10.1016/j.bmc.2008.02.091>

Jadhav, S. D., Patil, B. M., & Patil, S. S. (2024). An eco-friendly approach to synthesize arylmethylene bis (3-hydroxy-5, 5’-dimethyl-2-cyclohexene-1-ones) and 1, 8-dioxo-octahydroxanthenes. Research on Chemical Intermediates, 50(6), 2519-2531. <https://doi.org/10.1007/s11164-024-05274-w>

Jadhav, S. D., & Patil, S. S. (2023). Calcined eggshells as a highly efficient catalyst for the synthesis of 2-amino 4H-chromene derivatives. Research on Chemical Intermediates, 49(11), 4805-4817. <https://doi.org/10.1007/s11164-023-05109-0>

Javidi, J., Esmaeilpour, M., & Dodeji, F. N. (2015). Immobilization of phosphomolybdic acid nanoparticles on imidazole functionalized Fe3O4@ SiO2: A novel and reusable nanocatalyst for one-pot synthesis of Biginelli-type 3,4-dihydro-pyrimidine-2-(1*H*)-ones/thiones under solvent-free conditions. RSC Advances, 5(1), 308-315. <https://doi.org/10.1039/C4RA09929J>

Jiang, J., Xiao, F., He, W. M., & Wang, L. (2021). The application of clean production in organic synthesis. Chinese Chemical Letters, 32(5), 1637-1644. <https://doi.org/10.1016/j.cclet.2021.02.057>

Jin, T. S., Xiao, J. C., Chen, Y. X., & Li, T. S. (2004). Phosphotungstic acid catalysed one-pot synthesis of 5-alkoxycarbonyl-4-aryl-3, 4-dihydropyrimidin-2-ones. Journal of Chemical Research, 2004(3), 190-191. <https://doi.org/10.3184/0308234041640799>

Kappe, C. O., Fabian, W. M., & Semones, M. A. (1997). Conformational analysis of 4-aryl-dihydropyrimidine calcium channel modulators. A comparison of ab initio, semiempirical and X-ray crystallographic studies. Tetrahedron, 53(8), 2803-2816. [https://doi.org/10.1016/S0040-4020(97)00022-7](https://doi.org/10.1016/S0040-4020%2897%2900022-7)

Kar, S., Sanderson, H., Roy, K., Benfenati, E., & Leszczynski, J. (2021). Green chemistry in the synthesis of pharmaceuticals. Chemical Reviews, 122(3), 3637-3710. <https://doi.org/10.1021/acs.chemrev.1c00631>

Khabazzadeh, H., Kermani, E. T., & Jazinizadeh, T. (2012). An efficient synthesis of 3, 4-dihydropyrimidin-2 (1*H*)-ones catalyzed by molten [Et3NH][HSO4]. Arabian Journal of Chemistry, 5(4), 485-488. <https://doi.org/10.1016/j.arabjc.2010.09.015>

Kumar, A., Kumar, V., Singh, P., Tittal, R. K., & Lal, K. (2024). Ionic liquids for green synthesis of 1,2,3-triazoles: a systematic review. Green Chemistry, **26**, 3565-3594. <https://doi.org/10.1039/D3GC04898E>

Kurniawan, Y. S. ., Priyangga, K. T. A., Krisbiantoro, P. A., & Imawan, A. C. (2021). Green Chemistry Influences in Organic Synthesis : a Review. Journal of Multidisciplinary Applied Natural Science, 1(1), 1–12. <https://doi.org/10.47352/jmans.v1i1.2>

Liu, C. J., & Wang, J. D. (2010). Ultrasound-assisted synthesis of novel 4-(2-Phenyl-1, 2, 3-Triazol-4-yl)-3, 4-Dihydropyrimidin-2 (1H)-(Thio) ones catalyzed by Sm(ClO4)3. Molecules, 15(4), 2087-2095. <https://doi.org/10.3390/molecules15042087>

Lu, J., & Ma, H. (2000). Iron (III)-catalyzed synthesis of dihydropyrimidinones. Improved conditions for the Biginelli reaction. Synlett, 2000(01), 63-64. <https://doi.org/10.1055/s-2000-6469>

Ma, Y., Qian, C., Wang, L., & Yang, M. (2000). Lanthanide triflate catalyzed Biginelli reaction. One-pot synthesis of dihydropyrimidinones under solvent-free conditions. Journal of Organic Chemistry, 65(12), 3864-3868. <https://doi.org/10.1021/jo9919052>

Masoud, N. E., Hoseini, S. J., & Mohammadi, F. (2011). Fe3O4 nanoparticles as an efficient and magnetically recoverable catalyst for the synthesis of 3, 4-dihydropyrimidin-2 (1H)-ones under solvent-free conditions. Chinese Journal of Catalysis, 32(9-10), 1484-1489. [https://doi.org/10.1016/S1872-2067(10)60263-X](https://doi.org/10.1016/S1872-2067%2810%2960263-X)

Niralwad, K. S., Shingate, B. B., & Shingare, M. S. (2010). Microwave-assisted one-pot synthesis of octahydroquinazolinone derivatives using ammonium metavanadate under solvent-free condition. Tetrahedron Letters, 51(28), 3616-3618. <https://doi.org/10.1016/j.tetlet.2010.04.118>

Nishanth Rao, R., Jena, S., Mukherjee, M., Maiti, B., & Chanda, K. (2021). Green synthesis of biologically active heterocycles of medicinal importance: A review. Environmental Chemistry Letters, 19, 3315-3358. <https://doi.org/10.1007/s10311-021-01232-9>

Pasunooti, K. K., Chai, H., Jensen, C. N., Gorityala, B. K., Wang, S., & Liu, X. W. (2011). A microwave-assisted, copper-catalyzed three-component synthesis of dihydropyrimidinones under mild conditions. Tetrahedron Letters, 52(1), 80-84. <https://doi.org/10.1016/j.tetlet.2010.10.150>

Patil, B. M., Shinde, S. K., Jagdale, A. A., Jadhav, S. D., & Patil, S. S. (2021). Fruit extract of averrhoa bilimbi: A green neoteric micellar medium for isoxazole and biginelli-like synthesis. Research on Chemical Intermediates, 47, 4369-4398. <https://doi.org/10.1007/s11164-021-04539-y>

Patil, S., Jadhav, S. D., & Deshmukh, M. B. (2013). Calcined eggshell (CES): An efficient natural catalyst for Knoevenagel condensation under aqueous condition. Journal of Chemical Sciences, 125, 851-857. <https://doi.org/10.1007/s12039-013-0443-5>

Prakash, G. S., Lau, H., Panja, C., Bychinskaya, I., Ganesh, S. K., Zaro, B., et al. (2014). Synthesis of dihydropyrimidinones/thiopyrimidinones: Nafion-Ga, an efficient “green” lewis acid catalyst for the biginelli reaction. Catalysis letters, 144, 2012-2020. <https://doi.org/10.1007/s10562-014-1364-8>

Ramachandran, V., Arumugasamy, K., Singh, S. K., Edayadulla, N., Ramesh, P., & Kamaraj, S. K. (2016). Synthesis, antibacterial studies, and molecular modeling studies of 3, 4-dihydropyrimidinone compounds. Journal of chemical biology, 9, 31-40. <https://doi.org/10.1007/s12154-015-0142-4>

Ramalinga, K., Vijayalakshmi, P., & Kaimal, T. N. B. (2001). Bismuth (III)-catalyzed synthesis of dihydropyrimidinones: improved protocol conditions for the Biginelli reaction. Synlett, 2001(06), 0863-0865. <https://doi.org/10.1055/s-2001-14587>

Rao, G. D., Acharya, B. N., Verma, S. K., & Kaushik, M. P. (2011). N, N′-Dichlorobis (2, 4, 6-trichlorophenyl) urea (CC-2) as a new reagent for the synthesis of pyrimidone and pyrimidine derivatives via Biginelli reaction. Tetrahedron Letters, 52(7), 809-812. <https://doi.org/10.1016/j.tetlet.2010.12.039>

Sadek, K. U., Al-Qalaf, F., Abdelkhalik, M. M., & Elnagdi, M. H. (2010). Cerium (IV) ammonium nitrate as an efficient Lewis acid for the one-pot synthesis of 3, 4-dihydropyrimidin-2 (1H)-ones and their corresponding 2-(1H) thiones. Journal of Heterocyclic Chemistry, 47(2), 284. <https://doi.org/10.1002/jhet.259>

Safari, J., & Gandomi-Ravandi, S. (2014). Titanium dioxide supported on MWCNTs as an eco-friendly catalyst in the synthesis of 3, 4-dihydropyrimidin-2-(1H)-ones accelerated under microwave irradiation. New Journal of Chemistry, 38(8), 3514-3521. <https://doi.org/10.1039/C3NJ01618H>

Salehi, P., Dabiri, M., Zolfigol, M. A., & Fard, M. A. B. (2003). Silica sulfuric acid: an efficient and reusable catalyst for the one-pot synthesis of 3, 4-dihydropyrimidin-2 (1H)-ones. Tetrahedron Letters, 44(14), 2889-2891. [https://doi.org/10.1016/S0040-4039(03)00436-2](https://doi.org/10.1016/S0040-4039%2803%2900436-2)

Sashidhara, K. V., Singh, L. R., Shameem, M., Shakya, S., Kumar, A., Laxman, T. S., et al. (2016). Design, synthesis and anticancer activity of dihydropyrimidinone–semicarbazone hybrids as potential human DNA ligase 1 inhibitors. MedChemComm, 7(12), 2349-2363. <https://doi.org/10.1039/C6MD00447D>

Schaub, T. (2021). Efficient industrial organic synthesis and the principles of green chemistry. Chemistry–A European Journal, 27(6), 1865-1869. <https://doi.org/10.1002/chem.202003544>

Shaikh, A., & Meshram, J. (2016). Novel 1, 3, 4‐oxadiazole derivatives of dihydropyrimidinones: synthesis, anti‐inflammatory, anthelmintic, and antibacterial activity evaluation. Journal of Heterocyclic Chemistry, 53(4), 1176-1182. <https://doi.org/10.1002/jhet.2377>

Singh, O. M., Singh, S. J., Devi, M. B., Devi, L. N., Singh, N. I., & Lee, S. G. (2008). Synthesis and in vitro evaluation of the antifungal activities of dihydropyrimidinones. Bioorganic & medicinal chemistry letters, 18(24), 6462-6467. <https://doi.org/10.1016/j.bmcl.2008.10.063>

Singh, S. K., & Savoy, A. W. (2020). Ionic liquids synthesis and applications: An overview. Journal of Molecular Liquids, 297, 112038. <https://doi.org/10.1016/j.molliq.2019.112038>

Wu, M., Yu, J., Zhao, W., Wu, J., & Cao, S. (2011). One-pot synthesis of difluoromethyl-containing dihydropyrimidinones catalyzed by Yb(PFO)3 under solvent and dehydrating agent free conditions. Journal of Fluorine Chemistry, 132(3), 155-159. <https://doi.org/10.1016/j.jfluchem.2010.12.010>

Zhang, Y., Wang, B., Zhang, X., Huang, J., & Liu, C. (2015). An efficient synthesis of 3, 4-dihydropyrimidin-2 (1H)-ones and thiones catalyzed by a novel brønsted acidic ionic liquid under solvent-free conditions. Molecules, 20(3), 3811-3820. <https://doi.org/10.3390/molecules20033811>