***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 Brønsted acidic ionic liquid 3-methyl-1-sulfonic acid imidazolium chloride, [Msim]Cl, serves as an environmentally friendly catalyst for the efficient synthesis of 3,4-dihydropyrimidine-2(1*H*)-ones from the aromatic aldehydes, β-keto esters, and urea. This method is not only eco-friendly, but also produces high-purity products with excellent efficiency. The synthesized compounds were further characterized by using spectroscopic techniques, such as IR, 1H NMR and 13C NMR spectroscopy. The proposed method offers additional advantages such as operational simplicity, shorter reaction times, and mild reaction conditions. Additionally, the catalyst exhibits good recyclability. These features collectively highlight the feasibility and sustainability of this ionic liquid catalyzed system in the organic synthesis. |

***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). A quantum chemical investigation of the oxidation process of 1,4-dihydropyrimidine has also been reported recently (Shyshkina & Desenko, 2024). As a result, synthesizing various 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 five 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)

 

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

The proposed mechanism for the reaction is illustrated in Scheme 3. The reaction begins with the condensation of an aldehyde and a 1,3-dicarbonyl compound. The acidic nature of [Msim]Cl, activates the carbonyl group of aldehyde by protonation. This protonation enhances the electrophilicity of the carbonyl carbon, promoting the formation of a carbenium ion intermediate (i). This carbenium ion is then intercepted by urea, forming an intermediate (ii) through nucleophilic addition. The acidic ionic liquid further aids this step by stabilizing the developing positive charge and facilitating proton transfer. Subsequently, cyclization of this intermediate leads to the formation of dihydropyrimidinone (4).

**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.

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1. Grammarly

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