[PBMIM](FeCl₄)₂: AN EFFECTIVE CATALYST FOR THE ONE-POT SYNTHESIS OF 1,3-DIHYDROPYRIMIDIN-2-ONES AND THIONES UNDER SOLVENT FREE CONDITIONS

BIJAN MOMBANI GODAJDAR^{a,*}, ALI REZA KIASAT^b

^a Department of Chemistry, Islamic Azad University Omidyeh Branch, Omidyeh, Iran

^b Department of Chemistry, College of Science, Shahid Chamran University, Ahwaz, Iran

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ABSTRACT

An efficient, clean, and environmentally benign synthesis of 1,3-dihydropyrimidin-2-ones and thiones by one-pot three component reaction of substituted aromatic aldehydes, ethyl acetoacetate and urea/thiourea catalyzed by magnetic dicationic ionic liquid under solvent free conditions was described. This method provides several advantages such as environment benign, high yield, simple work up procedure and reusable catalyst. The magnetic ionic liquid could be readily separated from solution via application of an external magnet, allowing straightforward recovery and reuse.

1. INTRODUCTION

Today, one of the major goals of synthetic organic chemistry lies in the research, discovery and exploitation of environmentally friendly methods. Recently, several techniques for the efficient use of solvent free reactions and multi-component reactions (MCRs) have been developed individually but when these two wings of green chemistry can be combined, an excellent green chemistry protocol is expected.

Dihydropyrimidinones, DHPMs, and their derivatives have recently attracted universal interest because of their therapeutic and pharmacological properties such as antibacterial, antiviral, antitumor and anti-inflammatory activities.¹⁻³ Additionally due to their broad range of biological activities such as calcium blockers like the SQ-32926,⁴ betazelladine marine alkaloid nucleus,⁵ antihypertensive,⁶ β -1a adrenoceptor-selective antagonists,⁷ and antioxidant agents,⁸ have been described. The classical synthesis of DHPM is based on condensation of ethyl acetoacetate, benzaldehyde and urea or thiourea under strong acidic condition with low yields.⁹ Recently, the uses of a variety of catalysts have been reported.¹⁰⁻¹⁶ In addition; microwave,¹⁷ and ultrasound¹⁸ also reported to precede the Biginelli three component cyclocondensation reactions. However, in spite of their potential functions, many of these reported one-pot synthesis suffer from limitations such as use of expensive reagents, strong acidic conditions and long reaction times. Hence, to avoid these drawbacks, the application of milder and more efficiently approaches with higher yield are needed.

Room temperature ionic liquids (RTILs) are generally defined as salts that are liquid at or below room temperature. The combination of ammonium, pyridinium, phosphonium or imidazolium cations with various inorganic or organic anions led to a large amount of liquid salts with numerous possible applications e.g. in the field of organic synthesis, catalysis, biocatalysis, material science, chemical engineering, electrochemistry or separation processes.¹⁸ The increasing interest in RTILs is related to their possible exploitation as environmentally friendly neoteric solvents because of their vanishing vapour pressure, thermal and chemical stability, air and moisture stability, wide liquids range, solvent capability, etc.¹⁹ However the large scale application of ionic liquids is still far from realization because of their high cost and difficult recovery.

Recently, magnetic ionic liquid was discovered as a key material for «green chemistry».²⁰⁻²¹ Because magnetic ionic liquid, MIL, has both general properties of ionic liquids and strong magnetic response, the recovery system of this MIL by using a magnetic field may be easy and does not use high energy.²²

Having the above facts in mind, we wish to report a simple, convenient and efficient method for the synthesis of 1,3-dihydropyrimidin-2-ones and thiones using magnetic room temperature dicationic ionic liquid (MRTDIL) as a reusable eco-friendly magnetic catalyst in neat conditions

2. RESULTS AND DISCUSSION

1-Butyl-3-methylimidazolium tetrachloroferrate ([bmim](FeCl₄)₂) with magnetism was synthesized and first reported by Hayashi et al. in 2004.²³ Since then, the syntheses of magnetic ILs have been focused on expanding

synthesis with different alkyl chain length of imidazole cations or different magnetic metal anions. To the best of our knowledge, there is no report for the preparation of magnetic room temperature dicationic ionic liquid (MRTDIL). Scheme 1 illustrates the synthetic route for the preparation of MRTDIL synthesized and characterized in this study.

As shown in Scheme 1, the synthesis of magnetic imidazolium based dicationic room temperature ionic liquid (2a), [pbmim](FeCl₄)₂, involves two steps. First, 1, 3-dichloropropane was reacted with two equivalents of N-methylimidazole in methanol and under reflux conditions to afford dicationic RTILs in quantitative yields.²⁴ In the second step, the anions of imidazolium based dicationic room temperature ionic liquid, Cl⁻, were easily changed with FeCl₄⁻ anions by the simple mixing with FeCl₃ under neat conditions.

Scheme 1. Synthesis of [Pbmim]Cl₂ (1a), and [Pbmim](FeCl₄)₂ (2a)

Due to the paramagnetic nature of the [pbmim](FeCl₄)₂, nuclear magnetic resonance technique could not be used to confirm its structure. Instead, UV was used to characterize the [pbmim](FeCl₄)₂ structure. The UV spectrum is shown in Fig.1. [pbmim](FeCl₄)₂ spectra exhibited absorption bands in the visible region at 534, 620 and 680 nm which are characteristic for the FeCl₄⁻ anion (Fig 1).²⁵

In order to determine the most appropriate reaction conditions and evaluate the catalytic efficiency of MRTDIL, we studied the influence amount of MRTDIL and temperature on the reaction times and yields. Thus, the reaction of benzaldehyde, ethyl acetoacetate and urea at 100 °C was selected as a model reaction and different amount of catalyst were investigated. The results are illustrated in Table 1.

According to Table 1, the reaction without catalyst under solvent free conditions was performed in order to establish the true effectiveness of the catalyst. It was found that 1,3-dihydropyrimidin-2-ones was not made after 1h of heating. The best result was obtained with 1 : 1 : 3 ratios of aldehydes, ethyl acetoacetate, urea and 20 % mol of MRTDIL after 1h at 100°C.

Figure 1. Visible spectrum of [pbmim](FeCl₄)₂Table 1. Optimization of the amount MRTDIL for the synthesis of 4a^a

Entry	MRTDIL (mol %)	Time (h)	Yield(%)
1	0	1	0
2	10	1	60
3	20	1	89
4	30	1	89

^a Reaction conditions: benzaldehyde (1 mmol), ethyl acetoacetate (1 mmol), urea (3 mmol) and X % mol of MRTDIL, under solvent free conditions

The excess of urea could be easily removed by simple washing with cold deionised water. Thus, urea as an additional reagent was used to complete the reaction.

Next the effect of temperature on the rate of the reaction was studied using the reaction of benzaldehyde, ethyl acetoacetate, and urea in the presence of the optimum quantity of MRTDIL under solvent free conditions (Table 2). It was observed that the reaction did not proceed at room temperature. At 100°C, the reaction proceeded smoothly to give the corresponding product in good yield. Further increase in temperature to, 120°C had little effect on the rate of reaction. Therefore, we kept reaction temperature at 100°C as optimal temperature.

Table 2 Effect of temperature on the synthesis of 4a^a

Temperature/°C	MRTDIL (mol %)	Time (h)	Yield (%) ^b
25	20	1	0
60	20	1	55
80	20	1	66
100	20	1	89
120	20	1	90

^a Reaction conditions: benzaldehyde (1 mmol), ethyl acetoacetate (1 mmol), urea (3 mmol) and 20 % mol of MRTDIL, solvent-free

The generality of this reaction was examined using several types of aldehydes. In all cases, the reactions gave the corresponding products in good to excellent yield (Table 3, Scheme 3). A broad range of aromatic aldehydes having electron donating and electron withdrawing groups were transformed into the corresponding products in high yields. Substituent on the aromatic ring had no obviously effect on yield or reaction time under the above optimal conditions. Similarly, we have studied the condensation of aldehyde, ethyl acetoacetate and thiourea. The reaction of thiourea proceeded at lower rate to give S-DHPMs.

Scheme 2. Three-component one-pot synthesis of 1,3-dihydropyrimidin-2-(thio) ones catalyzed by [pbmim](FeCl₄)₂Table 3. [pbmim](FeCl₄)₂ catalyzed synthesis of 1,3-dihydropyrimidin-ones/thiones.

product	Ar	X	Time (h)	Yield (%) ^a	M.P (°C) Found Lit ^{ref}
4a	C ₆ H ₅	O	1	89	200-202/201-204 ²⁶
4b	4-CH ₃ O-C ₆ H ₄	O	1	83	203-205/204-206 ²⁶
4c	2-Cl-C ₆ H ₄	O	1	86	225-227/222-224 ²⁷
4d	2,4-(Cl) ₂ -C ₆ H ₃	O	1	81	250-252/246-248 ²⁶
4e	3-Br-C ₆ H ₄	O	1	88	186-188/190-192 ²⁶
4f	2,4-(OCH ₃) ₂ -C ₆ H ₃	O	1	82	173-175/175-177 ²⁶
4g	2-Furyl	O	1	88	208-210/206-208 ²⁶
4h	2-NO ₂ -C ₆ H ₄	O	1	81	205-207/203-204 ²⁶
4i	4-CH ₃ -C ₆ H ₄	O	1	89	213-214/215-217 ²⁶
4j	3-Cl-C ₆ H ₄	O	1	87	191-192/193-195 ²⁶
4k	C ₆ H ₅	S	2	85	205-208/207-209 ²⁶
4l	4-CH ₃ O-C ₆ H ₄	S	2	83	206-208/207-209 ¹²

^a Isolated yield

The success of the above reactions prompted us to investigate the recyclability of catalyst. We carried out our study by using the reaction benzaldehyde, ethyl acetoacetate and urea and under optimal conditions as a model study. After completion of the reaction (the progress of the reaction was monitored by TLC), the mixture was cooled to room temperature and the precipitated product was separated by filtration; then washed with water and dried. The solid product was crystallized from aqueous ethanol to afford the pure product. The aqueous phase was concentrated; the catalyst was separated by a strong magnetic field of 1.5T. The residue catalyst was washed with a mixed of ethyl ether and deionized water and dried in a vacuum oven at 60°C for overnight and reused in the next run. The catalyst could be reused for fourth times without significant decrease in catalytic activity (Table 4).

Table 4. Recyclability of the catalyst.

Cycle	Fresh	First	Second	Third	Fourth
Yield (%)	89	86	84	80	76

In order to show the merit of the present work in compared the results of the synthesis of 5-ethoxy carbonyl-4-phenyl-6-methyl-1,3-dihydropyrimidin-2-one (Table 3-entry 1) in the presence of montmorillonite / KSF, sulfuric acid, P₂O₅ and silica sulfuric acid with respect to the reaction times (Table 5). The yield of product in the presence of [pbmim](FeCl₄)₂ is comparable with these catalysts. However, other catalysts in Table 5 required longer reaction times than [Pbmim](FeCl₄)₂.

Table 5. Comparison of the synthesis of 4a using different catalysts

Entry	catalyst	Time (h)	Yield(%) ^b . ref
1	Montmorillonite KSF	48	82 ²⁸
2	Sulfuric acid	18	71 ⁹
3	P ₂ O ₅	4	80 ²⁹
4	Silica sulfuric acid	6	91 ³¹
5	BF ₃ .Et ₂ O/CuCl	18	71 ³⁰
6	H ₃ PMo ₁₂ O ₄₀	5	80 ³²
7	[pbmim](FeCl ₄) ₂	1	89

^a Isolated yield

3. CONCLUSIONS

In conclusion, we have successfully developed a simple and green catalytic procedure for the efficient synthesis of 1,3-dihydropyrimidin-2-ones and

thiones using MRTDIL and under solvent free conditions. MRTDIL showed remarkable reactivity as a Lewis acid reagent and considerably accelerated the reactions. MRTDIL can replace the ILs and other homogeneous catalysts with reasonable recovery and reusability and therefore ideal for industrial applications.

4. EXPERIMENTAL

4.1. General remarks. Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. ^1H & ^{13}C NMR spectra were recorded on a Bruker Advanced DPX 400 MHz instrument spectrometer using TMS as the internal standard in CDCl_3 . IR spectra were recorded on a BOMEM MB-Series 1988 FT-IR spectrometer. Aldehydes and ethylacetoacetate were purchased from Merck Company in high purity. Products were characterized by comparison of their physical and spectroscopic data with those of known samples. The purity determination of the products and reaction monitoring were accomplished by TLC on silica gel Poly Gram SILG/UV 254 plates.

4.2. Procedure for the preparation of $[\text{Pbmim}]\text{Cl}$.
1,3-Dichloropropane (1 mmol) was reacted with 1-methylimidazole (2 mmol), respectively, stirred in methanol, refluxed for 24 h, and then precipitated from ethyl acetate to obtain the required product (white solid **1a**, yield 94%). ^1H NMR of DIL (**1a**) (200 MHz, D_2O): δ 2.55 (quin, $J = 7.3$ Hz, 2H), 3.94 (s, 6H), 4.34 (t, $J = 7.3$ Hz, 4H), 7.50 (s, 2H), 7.54 (s, 2H), 8.65 (s, 2H).

4.3. Procedure for the preparation of $[\text{Pbmim}](\text{FeCl}_4)_2$ as a magnetic room temperature dicationic ionic liquid.

$[\text{Pbmim}](\text{FeCl}_4)_2$, MRTDIL, was prepared by mixing crystal powder of $[\text{Pbmim}]\text{Cl}$ (1 mmol) with anhydrous FeCl_3 (2 mmol) at room temperature for 3h, a dark brown liquid was obtained. The obtained MRTDIL was extracted with small amount of ethyl acetate. The solvent was evaporated and resulting clear brown liquid was dried in vacuum oven at 60°C for 24h. The MRTDIL was obtained in high yield.

4.4. General procedure for the preparation of 1,3-dihydropyrimidin-2-ones and thiones.

A mixture of aromatic aldehyde (1 mmol), ethyl acetoacetate (1 mmol), urea or thiourea (3 mmol) and MRTDIL (20 mol %) was heated at 100°C for an appropriate time (Table 3). After completion of the reaction (TLC), the mixture was cooled to room temperature and washed with cooled water. The solid product was crystallization from aqueous ethanol to afford the pure product. The aqueous phase was concentrated; the catalyst was separated using an external magnetic field 1.5T. The residue catalyst was washed with a mixed of ethyl ether and deionized water and dried in a vacuum oven at 60°C for overnight. The $[\text{Pbmim}](\text{FeCl}_4)_2$ was successfully reused for fourth cycles without significant decline of activity.

Products are known compounds and were characterized by comparison of spectral data and melting points with those reported in the literature.

4.4.1. Spectral data for selected compounds

5-Ethoxycarbonyl-6-methyl-4-phenyl-1,3-dihydropyrimidin-2-one (4a).
White solid,

M.P $200\text{--}202^\circ\text{C}$, IR (KBr): 3233, 1730, 1667, 1208, 670 cm^{-1} , ^1H NMR(DMSO): δ 9.20 (s, 1H, NH), 7.76 (s, 1H, NH), 7.24 (m, 5H), 5.13 (s, 1H), 3.98 (q, $J = 7.1$ Hz, 2H), 2.24 (s, 3H), 1.08 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 13.9, 17.6, 53.6, 60, 99.3, 126, 127, 128.3, 144.7, 148.3, 152.2, 165.3 ppm. Anal. Calcd. For $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_3$ (%): C, 64.60; H, 6.20; N, 10.76. Found: C, 64.16; H, 6.16; N, 10.74.

5-Ethoxycarbonyl-6-methyl-4-(3-methylphenyl)-1,3-dihydropyrimidin-2-thione

(**13**, $\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}_2\text{S}$) M.P: $204\text{--}208^\circ\text{C}$; IR (KBr): ν_{max} = 3334, 1719, 1660, 1566cm^{-1} ; ^1H NMR (CDCl_3): δ = 1.18 (t, $J = 7.1$ Hz, 3H), 2.34 (s, 3H), 2.37 (s, 3H), 4.1 (q, $J = 7.1$ Hz, 3H), 5.37 (s, 1H), 7.1–7.3 (m, 4H, Ar), 7.8 (s, 1H, NH), 8.5 (s, 1H, NH); ^{13}C NMR (CDCl_3): δ = 14.1, 18.16, 21.51, 56.11, 60.39, 102.86, 123.94, 127.47, 128.72, 129.11, 138.54, 142.3, 142.9, 165.3, 174.1 ppm

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