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Simple and Efficient One Pot Solvent Free Synthesis of 3,4-Dihydropyrimidin-2(1H)-Ones and Thiones by using Ionic Liquid at Reflux Condition

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Abstract
A simple and efficient method for the one-pot Biginelli condensation reaction of aldehydes, β-dicarbonyl compounds, and urea or thiourea is developed by using ionic liquid catalyst at reflux under solvent free condition.
Keywords: Biginelli, ionic liquid, solvent free.

1. Introduction

In recent years ionic liquids have attracted extensive interest in research as environmentally benign solvents due to their favorable properties like non-inflammability, negligible vapor pressure, reusability and high thermal stability(Sheldon 2005). They have also been referred to as 'designer solvents' as their physical and chemical properties could be adjusted by a careful choice of action and anion. Combining these unique properties of ionic liquids, they are emerging as a green reaction media (catalyst + solvent) in organic synthesis. The use of ionic liquids as reaction medium may offer a convenient solution to both the solvent emission and catalytic recycling problem.

With keep these properties of IL's in mind, here we report a simple and efficient approach to the Biginelli reaction via a one-pot cyclocondensation of an aromatic aldehyde, -dicarbonyl compound, urea or thiourea as substrates using ionic liquid at solvent free and reflux conditions (Scheme 01).Dihydropyrimidinones (DHPMs) were found to possess several biological activities such as antimicrobial, antiviral, antimalarial, anticancer, antihypertensive, anti-inflammatory, calcium channel modulators, mitotic kinesin inhibitors, $_{1A}$-antagonists and neuropeptide Y(NPY) antagonists (Agrawal 2007; Rajesh 2011; Fewell 2004; Kappe 2000; Atwal 1991). The most simple and straightforward procedure, reported by Biginelli more than 100 years ago (Biginelli 1893; Dondoni 2006) involves the three component acid catalyzed condensation in one-pot, but this reaction suffers from the harsh conditions, long reaction times and frequently low yields. In the last decades, many improved procedures have been used to catalyze the Biginelli reaction, some of them include use of catalysts such as amberlyst- 15/AcOH (Yadav 2000),$HClO_4$ (Mukhopadhyay 2007),$H_3PW_{12}O_{40}$ (Mishra 2006) ,TMSCl/MeCN (Pisani 2007),PSSA/H_2O (Polshettiwar 2007),I_2/Al_2O_3 (Saxena2005),sulphated ZrO_2 (Kumar 2006),$SbCl_3$/ Al_2O_3 (Kapoor 2006),TsOH/AcOH (Tu 2003),NBS/EtOH (Hazarkhani 2004),$In(OTf)_3$ (Shanmugam 2003), ZnI_2 (Liang 2007), Fe_3O_4 and mesoporous SBA-15 (Mondal 2012), SPINOL– phosphoric acid (Xu 2012), poly(1-vinyl-3-(3-sulfopropyl) imidazolium hydrogen sulfate) (Pourjavadi 2012), chiral organocatalyst (Saha and Moorthy 2011), bioglycerol-based sulfonic acid functionalized carbon catalyst (Konkala 2012),1-methylimidazolium hydrogen sulfate in the presence of catalytic amount of chlorotrimethylsilane ([Hmim]HSO_4/TMSCl) (Kefayati 2012), perchloric acid-doped silica ($HClO_4/SiO_2$) (Narahari 2012), $MgAlCO_3$ and $CaAlCO_3$hydrotalcite (Lal 2012) and t-BuOK (Shen 2010). These available methods suffer from one or more disadvantages such as use of corrosive/expensive catalysts, inconsistent/moderate yields and organic solvents. Therefore, there is scope for exploration of synthetic methodology for synthesis of dihydropyrimidinones to achieve experimental simplicity and effectiveness. Hence here we develop an efficient and simple one pot condensation of aldehydes, -dicarbonyl compound, urea or thiourea for synthesis of 3,4-dihydropyrimidin-2(1H)-ones and thiones derivatives by using N-(4-sulfonic acid) butyl triethyl ammonium hydrogen sulphateunder solvent free condition and reflux condition (Scheme 01).

2. Experimental

2.1. Materials and Methods.

Melting points were measured in open glass capillaries on a Veego melting-point apparatus and were uncorrected. ^{1}H NMR was recorded at room temperature on a Bruker Avance II 400MHz Spectrometer (SAIF, Punjab University, Chandigarh) in $CDCl_3$ using TMS as internal standard. IR spectra (using KBr pellets) were

obtained with a Perkin Elmer Spectrum RX FTIR (SAIF, Punjab University, Chandigarh) instrument. The reactions were monitored on TLC using pre-coated plates (silica gel on aluminum, Merck). All reagents were obtained from commercial sources and used without further purification. Solvents for chromatography were distilled before use. The products were also characterized by comparison of their melting point with literature values.

2.2General procedure for synthesis of 3,4-dihydropyrimidones derivatives.

Benzaldehyde (1mmol), ethyl acetoacetate (1mmol), urea or thiourea (1.2mmol), and 0.5 gm of N-(4-sulfonic acid) butyl triethyl ammonium hydrogen sulphatewere added to a 50 ml round bottom flask. Reaction mixture was heated at 120^{o}C for the appropriate time as mentioned in Table 04. After the completion of reaction, as indicated by TLC, the reaction mixture was poured onto crushed ice and stirred for 10 to15 minutes. The yellow solid separated was filtered under suction and washed with ice-cold water. The crude reaction product thus obtained was collected and further purified by recrystallization with hot ethanol to afford pure 3,4-dihydropyrimidin-2-one/-thione. The filtrate so obtained was concentrated under reduced pressure to recover ionic liquid which could be reused in subsequent experiments.

2.3. Spectral data of compounds.

1. **5-Ethoxycarbonyl-6-methyl-4-(3-methylphenyl)-1,3-dihydropyrimidin-2-thione (4r):**

IR (KBr):υ_{max}= 3304, 1729, 1650, 1568cm^{-1}; ^{1}HNMR ($CDCl_3$):δ= 1.10 (t, J= 7.1 HZ, 3H), 2.44 (s, 3H), 2.34 (s, 3H), 4.3 (q, J=7.1 HZ, 3H), 5.27 (s, 1H), 7.1-7.3 (m,4H,Ar), 7.9 (s, 1H, NH), 8.3 (s,1H, NH) ; ^{13}CNMR ($CDCl_3$): δ= 16.1, 20.16, 23.51, 57.18, 62.29, 104.66, 124.14, 128.47, 129.72, 130.11, 137.54, 141.8, 143.1, 165.7, 175.3 ppm

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

IR (KBr):υ_{max}= 3214, 1740, 1678 cm^{-1}; ^{1}HNMR ($CDCl_3$):δ= 1.09 (t, *J* = 6.8Hz, 3H), 2.24 (s, 3H), 3.74 (s, 3H), 4.1 (q, J=6.8 HZ, 2H), 5.17 (s, 1H), 6.9-7.1(m,4H,Ar), 7.6 (s, 1H, NH), 9.2 (s,1H, NH) ; ^{13}CNMR ($CDCl_3$): δ= 14.5, 18.2,53.78, 55.47, 59.60, 99.9, 114.1, 127.8, 136.4, 148.3,158.8, 165.8ppm.

3. Result and Discussion

As our work on use of different catalyst in heterocyclic synthesis, here we use an ionic liquidN-(4-sulfonic acid) butyl triethyl ammonium hydrogen sulphate for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones and thiones derivatives under solvent free and reflux condition.

For our initial studies the effect of solvent on the reaction were studied at reflux conditions with different reaction times with model reaction of Benzaldehyde, ethylacetoacetate and urea. The best results were obtained at solvent free condition as shown in Table 01.

Table 01. Synthesis of 3,4-dihydropyrimidin-2(1H)-ones using different solvents.

Entry	Solvent used	Time in Minutes	Yield (%)
1	Chloroform	96	76
2	Ethanol	88	84
3	Water	90	82
4	Acetonitrile	120	68
5	Solvent free	75	88

However the generality of reaction was also checked with different reaction conditions by using N-(4-sulfonic acid) butyl triethyl ammonium hydrogen sulphate. The best result was obtained for reflux condition at 120^{o}C as it gives high yield at shorter reaction time summarized in Table 02. Even increase in reaction temperature from 120 to 140 the corresponding 3,4-dihydropyrimidin-2(1H)-ones gives the same yield.

Table 02. Synthesis of 3,4-dihydropyrimidin-2(1H)-ones using different reaction conditions .

Entry	Reaction condition used	Time in Minutes	Yield (%)
1	Room Temperature	120	68
2	60^{0}C	104	70
3	80^{0}C	100	70
4	100^{0}C	90	74
5	120^{0}C	75	88
6	140^{0}C	75	88

With above optimized reaction conditions, in order to study the generality of the reaction using different aldehydes containing both electron donating and electron withdrawing groups underwent the conversion smoothly and gave the products in good to excellent yields (Table 04). Similarly, we have studied the condensation of aldehyde, ethyl acetoacetate and thiourea. The reaction of thiourea proceeded at lower rate to

give S-DHPMs.

Table 03. Reuse IL for the synthesis 3,4-dihydropyrimidin-2(1H)-ones.

Cycle	Fresh	First	Second	Third	Fourth	Fifth
Yield (%)	88	88	86	83	81	78

The reuse of the catalyst is a major factor in a new synthetic green procedure. The ionic liquid can be reused after simple distillation to remove water and remaining ionic liquids was dried under vacuum and reuse for further reactions. To test this, a series of five consecutive runs of the reaction Benzaldehyde, ethylacetoacetate and urea with catalyst were carried out. The results, however, demonstrated no significant change in the activity of the catalyst. The catalyst could be reused for fourth times without significant decrease in catalytic activity (Table 03).This method offers some advantages in terms of low reaction times, simplicity of performance, low cost and use of ionic liquid as a green catalyst and solvent which follow along the line of green chemistry.

4. Conclusion

In conclusion, developed an efficient method for the synthesis of fused 3,4-dihydropyrimidin-2(1 H)-ones and thiones under solvent free conditions by using ionic liquid at reflux condition. The method offers several advantages such as catalyst reusability, high yield of product, short reaction time, simple work-up procedure and easy isolation. We believe this methodology is useful to existing methodologies for the synthesis of fused 3,4-dihydropyrimidin-2(1 H)-ones and thiones.

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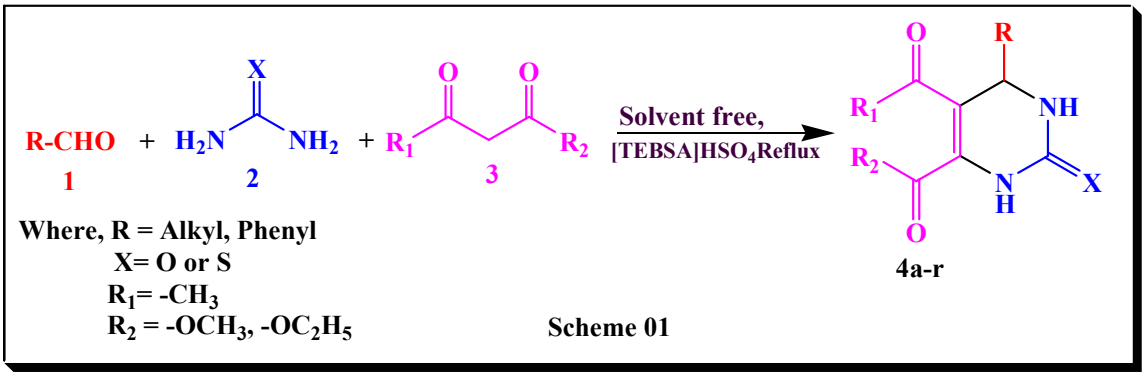

Scheme 01

Table04. Synthesis of 3,4-dihydropyrimidin-2(1H)-ones and thiones derivatives by using 1-methylimidazolium hydrogen sulfate under solvent free condition and reflux condition

Entry	**R_1**	**R_2**	**X**	**Time(Min.)**	**Yield(%)[a]**	**M.P.(^{0}C)**
a	-C_6H_5	-OEt	O	75	88	197-199
b	4-NO_2-C_6H_4	-OEt	O	90	83	198-200
c	4-Cl-C_6H_4	-OEt	O	87	90	202-204
d	4-Br-C_6H_4	-OEt	O	88	87	196-198
e	4-HO-C_6H_4	-OEt	O	96	81	214-216
f	4-OCH_3-C_6H_4	-OEt	O	65	80	198-200
g	3-NO_2-C_6H_4	-OEt	O	95	85	218-220
h	4-CH_3-C_6H_4	-OEt	O	90	78	203-205
i	2,4-$(OCH_3)_2$-C_6H_3	-OEt	O	70	84	175-177
j	-C_6H_5	-OMe	O	55	80	204-206
k	4-Cl-C_6H_4	-OMe	O	60	86	195-197
l	4-OCH_3-C_6H_4	-OMe	O	65	78	183-185
m	4-NO_2-C_6H_4	-OMe	O	65	89	214-216
n	-C_6H_5	-OEt	S	60	91	206-208
o	4-NO_2-C_6H_4	-OEt	S	120	87	110-112
p	4-CH_3-C_6H_4	-OEt	S	110	85	192-194
r	4-OCH_3-C_4H_4	-OEt	S	90	84	208-210

[a]Yields refer to the pure isolated product.

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