

An Efficient One-Pot Multi-Component Synthesis of 3,4-Dihydropyrimidin-2(1H)-ones (DHPMs) Catalyzed By Ionic Liquids

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Abstract : The syntheses of 3,4-dihydropyrimidin- 2(1H)-ones (DHPMs) by a one-pot cyclocondensation of acetoacetates, aldehydes and urea or thiourea using Ionic Liquids under Microwave-Irradiation was described. The improved Biginelli reaction not only features a simple procedure, high yields and easy purification of production, but also the recycled catalyst could be directly reused for many times while the yields of reaction would not decrease.

Keywords: Biginelli Reaction; DHPMs; Ionic Liquid; Microwave.

I. INTRODUCTION

One-pot, sequential multi-step reactions play an important role in pharmaceutical industries. Pharmacies are trying to develop green chemistry reactions. Solvent-free synthesis of complex organic structures as drugs is the dream of every pharmacy. Multi-component reaction as a powerful tool for the rapid introduction of molecular diversity is evident and developed for the generation of heterocycles which receive growing interest¹⁻³

Recently, functionalized dihydropyrimidinones have been successfully used as antihypertensive agents, calcium channel blockers, adrenergic and neuropeptide Y (NPY) antagonists.^{4,5} In addition, some alkaloids containing the dihydropyrimidine core unit which also exhibit interesting biological properties have been isolated from marine sources. Most notably, among these are the batzelladine alkaloids, which were found to be potent HIV gp-120-CD₄ inhibitors.^{6,7}

The original protocol for the synthesis of dihydropyrimidinones, reported by Biginelli in 1893, involves a one-pot reaction of benzaldehyde, ethyl acetoacetate and urea in ethanol under strongly acidic conditions such as Lewis acids,^{8,9} Bronsted acids,^{10,11} ZrCl₄,¹² zeolites¹³, silica sulfuric acid¹⁴, BF₃-OEt₂¹⁵, CuCl₂·2H₂O¹⁶, SbCl₅¹⁷, RuCl₃¹⁸, have been reported in the literature.

Organic synthesis using microwave assisted heating method is considered to be much cleaner, greener and eco friendly compared to that of conventional heating method¹⁹. The ability of MW irradiation to speed up the chemical reaction²⁰ have made us think to employ this technique (MW irradiation) as a potential tool for our green synthesis of DHPM. Large verities of "Microwave assisted Biginelli reactions" have already been well explored by researchers and well documented in literature²¹⁻²³.

In recent years, application of ionic liquids in organic synthesis have attracted considerable attention due to their special properties such as good solvating capability, wide liquid range, negligible vapor pressure, easy recycling, high thermal stability and rate enhancers.^{24,25}

Now a days, much attention has been focused on organic reactions catalyzed by ionic liquids.²⁶ In particular, ionic liquids based on imidazolium ion has been extensively employed for various organic transformations includes Diels-Alder,²⁷ Wittig,²⁸ Suzuki cross-coupling,²⁹ Hantzsch condensation.³⁰ Moreover, ionic liquids with the acidic counter ions is also found to be an efficient medium in synthetic chemistry.³¹

The field of ionic liquids has been reviewed by several authors, including Welton, Holbrey³² and Seddon.³³ The chemical behavior of Franklin acidic chloroaluminate(III) ionic liquids (where X(AlCl₃) > 0.50) is that of a powerful Lewis acid. As might be expected, it promotes reactions that are conventionally promoted by aluminum(III) chloride, without suffering the disadvantage of the low solubility of aluminum(III) chloride in many solvents. The preparation of these ionic liquids is straightforward, simply by mixing the appropriate organic halide salt with aluminum(III) chloride results in the two solids melting together to form the ionic liquid. However, this synthesis must be performed in an inert atmosphere.

Some researchers have been actively engaged in exploring new facets of ionic liquids as effective catalysts and reagents for last few years and as a part of this program we have recently introduced an acidic ionic liquid 3,3'-thionyl-1,1'-methylimidazolium chloroaluminate [tbmim]₂Cl₂/AlCl₃³⁴ as an efficient catalyst for Biginelli reaction.

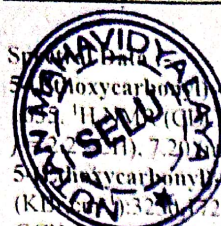
II. EXPERIMENTAL

Microwave oven (LG Smart Chef MS-255R operating at 2450 MHz having maximum out put power of 960 W) was used for microwave irradiation. ¹H NMR spectra were recorded on Mercury plus Varian at 400 MHz in CDCl₃ as a solvent and TMS as an internal standard. IR spectra were recorded on a Perkin Elmer FTIR using KBr discs. Mass spectra were recorded on Micromass Quattro II using electrospray Ionization technique.

General Procedure

A mixture of aromatic aldehydes 1(a-l) (1 mmol), Ethyl Acetoacetate 2 (1 mmol) urea/thiourea 3 (1.5 mmol) and [tbmim] was mixed properly with the help of glass rod and irradiated in a microwave oven at 360 W. The progress of the reaction was monitored by TLC (ethyl acetate: hexane, 7:3). After completion of the reaction, the reaction mixture was cooled and dichloromethane (25 mL) was added. Organic solvent was evaporated under reduced pressure and solid compound was crystallized from absolute ethanol to afford the pure corresponding Dihydropyrimidin- 2(1H)-ones (DHPMs) in excellent yields. All the products were characterized from their spectral data.

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5-(Ethoxycarbonyl)-4-phenyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one (4a). M.p. 206–208°C. IR (KBr, cm^{-1}): 3247, 1720, 1620. $^1\text{H NMR}$ (CDCl_3 , δ ppm): 1.10 (t, 3H, $J = 7.2$ Hz, OCH_2CH_3), 2.25 (s, 3H, CH_3), 3.90 (q, 2H, $J = 7.2$ Hz, OCH_2), 5.10 (d, 1H, $J = 7.2$ Hz, Ar-H), 7.21 (m, 5H, Ar-H), 7.50 (s, 1H, NH), 9.0 (s, 1H, NH).

5-(Ethoxycarbonyl)-4-(4-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (4b). M.p. 215–217°C. IR (KBr, cm^{-1}): 3247, 1720, 1620. $^1\text{H NMR}$ (CDCl_3 , δ ppm): 1.15 (t, 3H, $J = 7.09$ Hz, OCH_2CH_3), 2.44 (s, 3H, CH_3), 4.10 (q, 2H, $J = 7.10$ Hz, OCH_2CH_3), 5.77 (d, 1H, $J = 2.27$, -CH), 7.24 (d, 2H, $J = 9.22$, Ar-H), 7.8 (s, 1H, NH), 7.84 (d, 2H, $J = 9.22$, Ar-H), 9.20 (s, 1H, NH).

5-(Ethoxycarbonyl)-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (4c). M.p. 202–203°C. IR (KBr, cm^{-1}): 3240, 1735, 1630. $^1\text{H NMR}$ (CDCl_3 , δ ppm): 1.18 (t, 3H, $J = 7.15$ Hz, OCH_2CH_3), 2.40 (s, 3H, CH_3), 3.91 (s, 3H, - OCH_3), 4.10 (q, 2H, $J = 7.10$ Hz, OCH_2CH_3), 5.50 (d, 1H, $J = 2.50$ -CH), 7.0 (d, 2H, $J = 9.10$, Ar-H), 7.22 (d, 2H, $J = 9.10$, Ar-H), 7.75 (s, 1H, NH), 9.33 (s, 1H, NH).

5-(Ethoxycarbonyl)-4-(4-nitrophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (4g). M.p. 212–213°C. IR (KBr, cm^{-1}): 3245, 1735, 1620. $^1\text{H NMR}$ (CDCl_3 , δ ppm): 1.15 (t, 3H, $J = 7.02$ Hz, OCH_2CH_3), 2.35 (s, 3H, CH_3), 4.15 (q, 2H, $J = 7.02$ Hz, OCH_2CH_3), 6.07 (d, 1H, $J = 2.33$, -CH), 7.78 (d, 2H, $J = 8.88$, Ar-H), 7.85 (s, 1H, NH), 8.25 (d, 2H, $J = 8.88$, Ar-H), 9.12 (s, 1H, NH).

5-(Ethoxycarbonyl)-4-phenyl-6-methyl-3,4-dihydropyrimidin-2(1H)-thione (4i). M.p. 208–210 °C. IR (KBr, cm^{-1}): 3235, 1715, 1645, 1585, 1525. $^1\text{H NMR}$ (CDCl_3 , δ ppm): 1.12 (t, 3H, $J = 7.25$ Hz, OCH_2CH_3), 2.31 (s, 3H, CH_3), 4.18 (q, 2H, $J = 7.25$ Hz, OCH_2CH_3), 5.23 (d, 1H, $J = 2.15$ -CH), 7.38 (m, 5H, Ar-H), 7.75 (s, 1H, NH), 9.11 (s, 1H, NH).

5-(Ethoxycarbonyl)-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-thione (4j). M.p. 153–155°C. IR (KBr, cm^{-1}): 3235, 1720, 1630, 1570, 1535. $^1\text{H NMR}$ (CDCl_3 , δ): 1.18 (t, 3H, $J = 7.14$ Hz, OCH_2CH_3), 2.44 (s, 3H, CH_3), 4.23 (s, 3H, - OCH_3), 4.40 (q, 2H, $J = 7.14$ Hz, OCH_2CH_3), 5.7 (d, 1H, $J = 2.22$ -CH), 7.31 (d, 2H, $J = 8.33$, Ar-H), 7.42 (d, 2H, $J = 8.33$, Ar-H), 7.56 (s, 1H, NH), 9.25 (s, 1H, NH).

III. RESULT AND DISCUSSION

In continuation of our research work of developing methods in various organic transformations, we have developed a methodology for the synthesis of 3,4-Dihydropyrimidin- 2(1H)-ones (DHPMs) using ionic liquid, which makes use of mild catalyst under microwave-irradiation. (Scheme 1).

The reaction of benzaldehyde (1a), Ethyl acetoacetate (2) and urea (3) catalyzed by 3,3'-thionyl-1,1'-methylimidazolium chloroaluminate [tbmim] $\text{Cl}_2/\text{AlCl}_3$ under microwave-irradiation, has been considered as a standard model reaction.

We also screened a number of different catalysts on the model reaction. When the reaction was carried out in the presence of amberlite-IR 120, KH_2PO_4 , alum, acidic alumina, sulphamic acid, cellulose sulfuric acid under microwave-irradiation it gave lower yield of product even after prolonged reaction time. However, when the same reactions was conducted under microwave irradiation using ionic liquid as a catalyst it gave excellent yields of product in short reaction time (Table 1, entry 6).

Table 1. Screening of Catalysts on the Model Reaction

Entry	Catalysts	Time (min)	Yieldb(%)
1	Amberlite IR-120	15	20
1	KH_2PO_4	15	65
2	Alum	15	52
3	Acidic alumina	15	68
4	Sulphamic acid	15	54
5	Cellulose sulfuric acid	15	63
6	Ionic liquid	15	92

^aReaction of benzaldehyde, dimedone and urea in presence of ammonium metavanadate under microwave-irradiation and solvent-free condition. ^bIsolated yield.

Moreover, we investigated the effect of different microwave power settings such as 180, 360, 540 and 720 W. It was observed that, the irradiation at low power required longer time and at high power suffered from lower yield. This indicates the irradiation at 360 W gives better result (Table 2, entry 2).

Table 2. Effect of Microwave Irradiation Powers for Synthesis of 3,4-Dihydropyrimidin- 2(1H)-ones (DHPMs) 3aa

Entry	Power (W)	Time (sec)	Yield (%) ^b
1	180	70	87
2	360	50	92
2	540	40	86
2	720	30	82

^a(1 mmol) was treated with dimedone (1 mmol) and urea (1.5 mmol) in presence of ammonium metavanadate (10 mol %) under microwave irradiation. ^bIsolated yield.

After optimizing the conditions, the generality of this method was examined by the reaction of several substituted aldehydes, dimedone and urea/thiourea using ammonium metavanadate as a catalyst under microwave-irradiation, the results are shown in Table 3. We have carried out the similar reaction with various aromatic aldehydes containing electron donating or electron withdrawing functional groups at different positions but it did not show any remarkable differences in the yields of product and reaction time. It was observed that the reaction of aromatic aldehydes with urea is very fast as compared to thiourea. The results obtained in the current method are illustrated in Table 3.

Table 3. Synthesis of 3,4-Dihydropyrimidin-2(1H)-ones (DHPMs) catalyzed by 3,3'-di(4-oxo-1,2,3,4-tetrahydro-1,2,4-triazin-5-yl)chloroaluminumate [tbmm]Cl₂/AlCl₃ under microwave irradiation.

Entry	Reaction	Y	Time (min)	Yield (%)
3a	1a	O	10	91
3b	1b	O	15	89
3c	1c	O	15	89
3d	1d	O	15	88
3e	1e	O	15	88
3f	1f	O	15	88
3g	1g	O	15	88
3h	1h	O	15	88
3i	1i	S	15	88
3j	1j	S	15	88
3k	1k	S	15	88

Reaction Condition: **1** (0.4) (1 mmol), **2** (1 mmol), **3** (1.5 mmol), [tbmm]Cl₂/AlCl₃ (0.6 mmol), under microwave irradiation.

To investigate the reusability of the catalyst we performed the condensation of aromatic aldehyde (**1a**), ethyl acetoacetate **2** and urea **3** in the presence of ionic liquid [tbmm]Cl₂/AlCl₃ under microwave-irradiated. After completion, product was separated by extraction with DCM and the ionic liquid was reused as such for subsequent experiments. In view of economical and environmental friendly methodologies, recovery and reuse of the ionic liquid is highly preferable. As indicated in Table 3, recycled ionic liquid shows no loss of efficiency with regard to yield after four successive runs. Moreover, the [tbmm]Cl₂/AlCl₃ was successfully reused for four cycles without significant loss of activity.

Table 4. Synthesis of Dihydropyrimidin-2(1H)-ones (DHPMs) with Recovered Ionic Liquid [tbmm]Cl₂/AlCl₃

Cycle	Fresh	First	Second	Third	Fourth
Yield (%) ^a	91	91	89	89	88

also used yield.

IV. CONCLUSION

In conclusion, the present method is very simple, mild and efficient for the synthesis of Dihydropyrimidin-2(1H)-ones (DHPMs). In addition this protocol has advantages in terms of (i) short reaction time, (ii) high yield, (iv) easy work-up, (v) environmental friendly and (vi) recyclability of ionic liquid. We believed that, the synthesis of Dihydropyrimidin-2(1H)-ones (DHPMs) using 3,3'-di(4-oxo-1,2,3,4-tetrahydro-1,2,4-triazin-5-yl)chloroaluminumate [tbmm]Cl₂/AlCl₃ as a catalyst promoted methodology will be a valuable contribution in the field of chemistry as compare to the existing processes.

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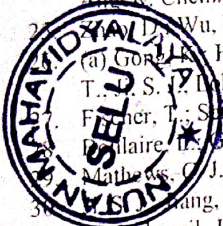
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