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Microwave-promoted aluminium sulphate in PEG as a green homogeneous catalytic system to synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones

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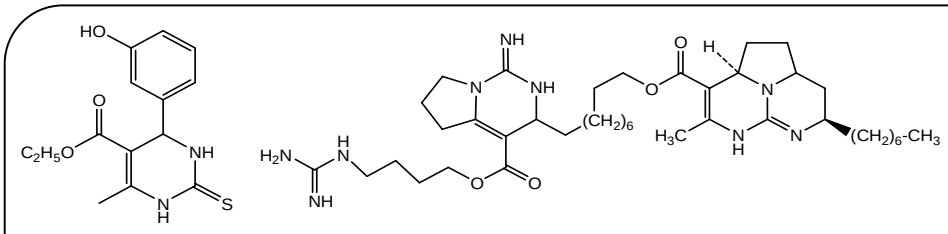
ABSTRACT

A simple, environmentally benign and highly efficient synthesis of 3, 4-dihydropyrimidin-2(1H)- (thio)one by using microwave promoted aluminium sulphate as a catalyst from aromatic aldehydes, 1, 3-dicarbonyl compounds & (thio)urea in PEG as a reaction solvent is described. Compared with the classical Biginelli reaction conditions, this new method has the advantage of excellent yield and short reaction time. The procedure is simple, rapid and high yielding. The catalyst exhibited a remarkable reactivity and is reusable up to 4 times without significant loss in yields and selectivity in PEG-400 as a solvent.

Key words: Biginelli reaction, 3, 4-dihydropyrimidin-2(1*H*)-ones, Aluminium sulphate, PEG, multicomponent reaction.

INTRODUCTION

The multicomponent one-pot reaction for the construction of C-C bond has given new way to a large variety of important compounds[1]. mainly, the Biginelli reaction is a good example of such type of multicomponent bond forming reactions [2]. The 3,4- Dihydro -1*H* pyrimidine-2- thiones/ ones (DHPMs) are among such type of organic compounds which belongs to an important class with significant therapeutic and medicinal properties [3] including antiviral, antibacterial, antitumor and anti-inflammatory properties [4]. Some of marine alkaloids having the DHPM core unit are showing interesting biological activities such as calcium channel blockers [5], antihypertensive, α-adrenergic antagonist and neuropeptide-Y- antagonist [6]. The structurally rather simple than DHPM, monastrol (**Fig.1.a**) specifically inhibits the mitotic kinesin Eg5 motor protein and considered as a new lead for the development of anticancer drugs [7]. The batzelladine alkaloids (**Fig.1.b**) containing the DHPM core unit inhibit the binding of HIV envelop protein gp-120 to human CD4 cells and therefore, are potential new leads for AIDS therapy [8], therefore the synthesis of compounds with DHPMs core unit has gained much importance.



Monastrol **(1 a)** Batzelladine **(1 b)**

Fig:- 1

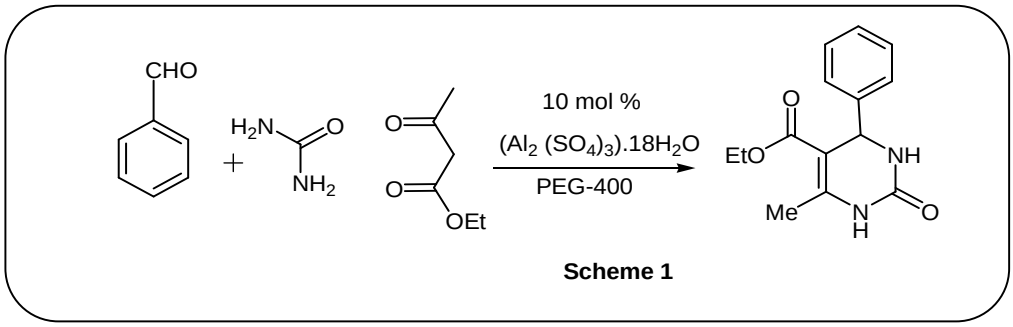
Owing to the wide range of pharmacological and biological activities, the synthesis of these compounds has become an important target in current years. The most simple and straightforward procedure first reported by Italian chemist Pietro Biginelli in 1893, it is popularly named after him i.e. Biginelli Reaction [9]. It is a direct and simple approach for the synthesis of 3,4-dihydropyrimidinones by one pot three-component cyclocondensation of β-ketoester with an aldehydes and urea under strongly acidic conditions. One major drawback of Biginelli reaction, which often suffers from low yields that are frequently encountered when using substituted aromatic or aliphatic aldehydes. This has led to development of more complex multistep strategies that produce somewhat higher overall yields but lack the simplicity of the original one pot Biginelli protocol. Therefore, Biginelli reaction continues to attract attention of researchers searching for a milder and more efficient procedure for the synthesis of DHPMs [10].

In the recent year's development of simple, safe, ecofriendly and economical synthetic routes for widely used organic compounds from the readily available reagents are one of the major challenges in academic and industrial research.

The art of performing efficient chemical transformation through multicomponent one pot condensation synthesis by a catalytic method to avoiding stoichiometric toxic reagents, large amount of solvents and expensive purification techniques represents a fundamental target of modern organic synthesis. Thus Biginelli's reaction for the synthesis of dihydropyrimidinone has received renewed interest and several improved procedures have recently been reported since last two decades. These methods have been developed using different Lewis acids such as $Yb(OTf)_3$/THF[11], $AlCl_3$ [12], $Sr(OTf)_2$ [13], $InCl_2$ [14], $InBr_3$ [15], $RuCl_3$ [16], $ZrCl_4$ [17] , $Bi(OTf)_3$ [18], $NbCl_5$ [19], BF_3 [20] as well as protic acids, such as Conc.HCl [21], $MeSO_3H$ [22], trifluoro acetic acid [23], trifluoromethane sulfonic acid [24], PEG-SO_3H [25], $ClSO_3H$ [26], as promoters, Many other catalysts including Brønsted acidic ionic liquid-promoted [27], clay [28] and also neat condition [29] procedures are also reported. Several other catalysts, such as I_2/MWI [30], TFA/THF/MWI [31] have been used to facilitate the reactions. However many of these methods are associated with harsh reaction conditions, expensive and toxic reagents, strongly acidic conditions, tedious workup, stoichiometric amount of catalyst, long reaction times, unsatisfactory yields, incompatibility with other functional groups etc. Therefore, to avoid these limitations, the discovery of a new and efficient catalyst with high catalytic activity, short reaction time, and simple work-up is of prime-interest. In this regard aluminium sulphate ($Al_2(SO_4)_3$.$18H_2O$) is used as novel catalyst for the synthesis of DHPMs.

On the other hand, the development of green and clean synthetic methods, those involving solvent-free or the use of alternative solvents such as water, ionic liquids and polyethylene glycol (PEG), has increased in recent years [32]. Solvents play an important role in mixing the ingredients to tolerate molecular interaction. Thus, the use of PEG and other alternative non-volatile solvents has been shown as an attractive approach to cleaner organic synthesis. Recently, PEG is found to be an eco-friendly and recyclable solvent for various organic transformations with unique properties such as thermal stability, commercial availability and immiscibility with a number of organic solvents. In general, PEG is an inexpensive, non-toxic and completely non-halogenated. Green synthetic routes are prime concern of the present century and current synthetic efforts are directed to achieve this goal. Certainly, there is increasing pressure on chemist to replace toxic catalyst and volatile solvents, Currently, PEG is finding extensive use in organic synthesis as it is a well-known green solvent and more suited to microwave irradiation. Also, the use of PEG under MW irradiation is reported in several organic reactions claiming green protocols [33]. Many chemists have made a great deal of effort to design environmental benign and clean synthetic procedures to replace the classical synthetic methods. Microwave heating is an eco-friendly approach and a valuable tool for synthetic

chemists because it is possible to increase the reaction rate and product yields as well as exploits a variety of factors such as milder and more efficient conditions, shorter reaction times, energy conservation, formation of purer products and waste minimization. There is an enormous growth of interest in this promising technique for promoting reactions.



Scheme 1

Most of the reported methods are associated with shortcomings like use of costly, harmful and non-reusable reagents, drastic reaction condition, long reaction time, tedious work up and use of toxic organic solvents.

Due to the low cost and easy handling of aluminium sulphate and the green nature of recyclable PEG encouraged us to combine them together and used their utility for the synthesis of DHPMs (**scheme 1**).

In continuation of our work on the development of useful synthetic methodologies for the biologically active compound synthesis [34-39] and Multicomponent [40,41] reactions, we have developed an environmentally benign and highly efficient synthesis of 3,4- Dihydro -1*H* pyrimidine-2- thiones/ones by using aluminium sulphate as a catalyst in PEG as a reaction solvent under microwave irradiation. However, to the best of our knowledge, no such recyclable Aluminium sulphate in PEG as a homogeneous catalytic system has been explored for the 3,4- Dihydro -1H pyrimidine-2- thione/ones synthesis.

MATERIALS AND METHODS

All chemicals and reagents required for the reactions were obtained from commercial sources and used without further purification. The products were characterized using ^{1}H NMR, on 300MHz spectrometer with DMSO-d_6 as a solvent and recorded in ppm relative to the tetramethylsilane as internal standard. IR spectra were recorded on a Perkin- Elmer spectrum on FTIR spectrophotometer using KBr pellets. TLC was performed on 0.25 mm E. Merck precoated silica gel plates (60 F254). All compounds are already well known in the literature. Melting points were determined in open capillary tubes and are uncorrected. For the microwave irradiation experiment described below a conventional domestic microwave oven (Kenstar, Microwave output 800W ±10%; microwave frequency 2450MHz, Videocon Industries Pvt. Ltd. India) was used.

GENERAL PROCEDURE

A mixture of aldehyde (2 mmol), 1, 3-dicarbonyl compound (2 mmol), urea/thiourea (2.4 mmol) and Aluminium sulphate (10 mol %) in 3mL PEG-400 was taken in a 10mL sealed tube and fitted in domestic microwave irradiation for a 3 min. On completion of reaction (checked by TLC), the solid product is formed in sealed tube, filtered the product from PEG-Aluminium sulphate and recrystallised by using aqueous ethanol. The PEG and catalyst was recovered and recycled without affecting the yields of the products.

The spectral data of some of the DHPMs are summarized below.

1) 5-Ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one, (4a), m.p.200-202^{o}C; IR. (KBr): 3245, 1725, 1705, 1647cm^{-1}; ^{1}H NMR (DMSO-d_6) δ: 9.12 (s, 1H). 7.66 (s, 1H). 7.28-7.16 (m, 5H), 5.10 (s, 1H), 3.94 (q, *J*=7.1 Hz, 2H), 2.18 (s, 3H), 1.04 (t, *J*=7.1 Hz, 3H).

2) 5-Ethoxycarbonyl-4-(2-chlorophenyl)-6-methyl- 3, 4-dihydropyrimidin-2(1*H*)-one, (4d) m.p. 216-218^{o}C; IR (KBr): 3225, 1710, 1643, 1560 cm^{-1}; ^{1}H NMR (DMSO-d$_6$) δ: 9.28(s,1H), 7.73 (s, 1H), 7.21-7.47 (m, 4H), 5.65 (s, 1H), 3.91 (q, *J*=7.1 Hz, 2H),2.29 (s, 1H), 1.08 (t, *J*=7.1 Hz, 3H).

3) 5-Ethoxycarbonyl-4-(4-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one, (4e) m.p. 212- 214 ^{o}C; IR (KBr): 3244, 1712, 1647, 1489 cm^{-1}; ^{1}H NMR (DMSO-d$_6$) δ: 9.20 (s, 1H), 7.76 (s, 1H), 7.40 (d, *J*=8.4 Hz, 2H), 7.27 (d, *J*=8.4 Hz, 2H), 5.11 (s, 1H), 3.96 (q, *J*=7.1 Hz, 2H), 2.23 (s, 3H), 1.06 (t, *J*=7.2Hz, 3H).

4) 5-Ethoxycarbonyl-4-(4-nitrophenyl)-6-methyl-3, 4-dihydropyrimidin-2(1*H*)-one, (4f) m.p. 206-208^{o}C; IR (KBr): 3232, 1728, 1643, 1593 cm^{-1}; ^{1}H NMR (DMSO-d$_6$) δ: 9.31 (s, 1H), 8.20 (d, *J*=8.7 Hz, 2H), 7.87 (s, 1H), 7.50 (d, *J*=8.7 Hz, 2H), 5.24 (s, 1H), 3.95 (q, *J*=7.1 Hz, 2H), 2.21 (s, 3H), 1.04 (t, *J*=7.1 Hz, 3H).

RESULTS AND DISCUSSION

Initially we made efforts to develop a catalytic system that would address the limitations of the reported acid catalyzed DHPM synthesis reactions. During the preliminary studies a model reaction employing benzaldehyde, ethyl acetoacetate and urea in the presence of aluminium sulphate as catalyst in PEG under microwave irradiation. A series of experiments were performed to optimize various reaction parameters, such as the catalyst concentration and time (Tables 1). We studied that the catalyst loadings ranging from 0 to 10 mol%; increasing the catalyst concentration from 5 to 10 mol% increased the yield of desired product to 96% (Table 1, entries 1-4). In contrast, the classical Biginelli condition (cat. HCl in EtOH, reflux, 18 h) gave 80% yield; while the yield of this reaction does not exceed more than 90% under reflux conditions in acetic acid as solvent for 3.5h reactions times.[41] The reaction was not successful in the absence of catalyst or MW irradiation.(Table 1, entries 1,5,9).

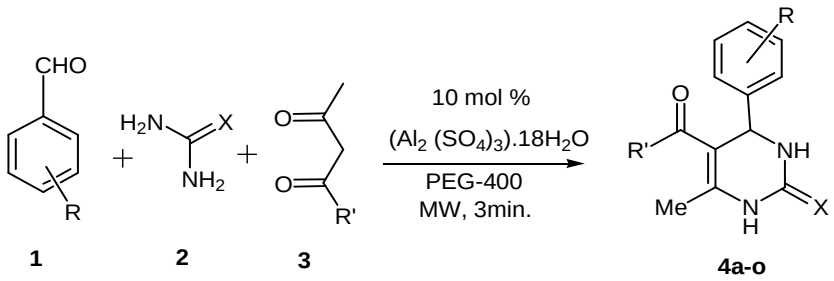
Table 1. Optimization of reaction parameters[a]

Entry	Mol % of Catalyst	Time (min.)	Yield(%)[b]
1	-	4	28
2	5	4	56
3	5	5	78
4	10	4	96
5[c]	10	150	66
6	10	5	96
7	10	3	96
8	10	2	82
9[d]	10	3	35

[a]Reaction conditions: Benzaldehyde (2 mmol), Ethyl acetoacetate (2 mmol), Urea (2.4mmol) and PEG-400 (3 mL), Microwave Irradiation. [b]Isolated yield, [c]By thermal method, [d]neat condition.

In these reactions no corrosive substances were used and no waste formation was observed. The experimental procedure for these reactions was remarkably simple and required no toxic organic solvent or inert atmosphere. We found that the transformations could be accomplished by exposing a mixture of benzaldehyde (2 mmol),ethyl acetoacetate (2 mmol), urea (2.4 mmol) and aluminium sulphate (10 mmol) in 3mL PEG-400 to MW irradiation (170 W, 100–120 °C) for 2.0–4.0 min. The reaction time was optimized at 3 min. (Table 1, entries 4,6-8).

Table 2. Substrate study for DHPM'S synthesis reaction.[a]



1 **2** **3** **4a-o**

Entry	R-	R'-	X	Yield (%)[b]
4a	H-	OEt	O	96
4b	4-HO-	OEt	O	86
4c	4-MeO-	OEt	O	88
4d	2-Cl-	OEt	O	83
4e	4-Cl-	OEt	O	96
4f	4-NO_2-	OEt	O	90
4g	3-NO_2-	OEt	O	84
4h	2-NO_2-	OEt	O	78
4i	H-	OEt	S	92
4j	4-Me-	OEt	S	88
4k	4-Cl-	OEt	S	93
4l	2-Cl-	OEt	S	83
4m	H-	Me	S	92
4n	4-NO_2-	Me	S	86
4o	4-MeO-	Me	S	82

[a]*Reaction conditions: Aldehyde (2 mmol), 1,3-Dicarbonyl Compound (2 mmol), Urea/Thiourea (2.4mmol), Aluminium sulphate (10 mol%) and PEG-400 (3 mL), Microwave Irradiation for 3 min.* [b] *Isolated yield.*

Having optimized reaction conditions in hand, we explored the substrate scope of the aluminium sulphate in PEG-400 catalyzed various aryl aldehydes containing different functional groups were investigated (**Scheme 1**). According to the above experimental section, we discovered a practical and general approach for this *Biginelli* cyclocondensation reaction using a mild catalyst hydrated aluminium sulphate, which is not only preserved the simplicity of *Biginelli's* one pot reaction but also consistently 82-96% yields of the 3,4-dihydropyrimidin-ones or thions. In order to study the generality of this procedure a series of *Biginelli* compounds were synthesized with similar operations. Most importantly, aromatic aldehydes carrying either electron donating or withdrawing substituent's afforded good yields of products, a variety of common functional group, such as alkyl, ether, halo, nitro, amino and cyano were tolerated regardless of the *meta* or *para*-position, however *ortho* substituted aryl aldehyde gave lower yields, possibly due to steric hindrance. The result of these reactions is summarized in Table 2.Additionally, We also investigated the reusability of the catalytic system and the results are described in table 3. The catalyst was separated from the reaction mixture by simple filtration technique. Then the filtrate was washed with ethyl acetate which was directly used in reusability studies.

Table: 3. Recycle Study of DHPM synthesis reactions in PEG[a]

Entry	Recycle No.	Yield(%)[b]
1	fresh	96
2	1st recycle	91
3	2nd recycle	84
4	3rd recycle	78

[a]*Reaction conditions: Benzaldehyde (2 mmol), Ethylacetoacetate (2 mmol), Urea (2.4mmol), Aluminium sulphate (10 mol%) and PEG-400 (3 mL), Microwave Irradiation for 3min.* [b] *Isolated yield*

CONCLUSION

We have developed an efficient aluminium sulphate mediated, green method for the synthesis of DHPMs by using PEG-400 as the solvent medium under microwave irradiation. The mild reaction conditions, operational simplicity, and volatile-solvent free conversion, application of a nontoxic and recyclable catalytic system, high yields and rapid formation of the products are the notable advantages of this method. These remarkable characteristics made this new protocol economically and eco-friendly attractive, inexpensive and offering the possibility of perform the reaction in the absence of toxic organic solvents.

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