



ULTRASOUND-PROMOTED SYNTHESIS OF 3,4-DIHYDROPYRIMIDIN-2(1H)-ONES IN PEG

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ABSTRACT

An efficient synthesis of 3,4-dihydropyrimidin-2(1H)-one/thione by using Ultrasound promoted Aluminium sulphate as a catalyst for 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 short reaction time with good yield. The procedure is simple, rapid and high yielding. The catalyst exhibited a remarkable reactivity and is reusable.

KEY WORDS: 3,4-dihydropyrimidin-2(1H)-ones, Biginelli reaction, Aluminium sulphate, PEG, One-pot synthesis.

INTRODUCTION

The construction of C-C bond has given new way to a large variety of important compounds using the multicomponents in one pot.^[1] Biginelli reaction is a good example of such type of multicomponent C-C and C-N bond forming reaction. The use of ultrasound in chemistry offers the synthetic chemist a method of chemical activation which has broad applications and uses equipment which is relatively inexpensive. Enhancement in the reaction rates and the rates of the mass transfer due to ultrasound may be attributed to its chemical or mechanical effects or to both simultaneously, meaning that the implosion of microbubbles, i.e. cavities, results in desirable chemical effects by generation of free radicals with a great propensity for the reaction.^[2,3] The driving force for sonochemistry is cavitations and so a general requirement is that at least one of the phases of the reaction mixture should be a liquid. When laboratory research in sonochemistry began it seemed to be mainly a method of initiating intransigent reactions especially

those which depended upon the activation of metallic or solid reagents. Its development in the past 15 years however has revealed that it has far wider applicability than this and also that it presents a significant scientific challenge to understanding its underlying physical phenomenon acoustic cavitations. The ever expanding number of applications of sonochemistry in synthesis has made the subject attractive to many experimentalists and interest has spread beyond academic laboratories into industry and chemical engineering therefore the synthesis of compounds with DHPMs core unit has gained much importance. The aim of this study was to explore the impact of ultrasound application on Green Homogeneous Catalytic System to Synthesis of 3,4-Dihydropyrimidin-2(1H)-Ones . In addition, the integrated process of the UAOD in the first step and sono-Fenton treatment of generated waste-water in the second step as novel approach was studied to obtain lower sulphur content in the diesel fuel, to purify waste-water for the reuse and to achieve better overall process efficiency.^[4-6]

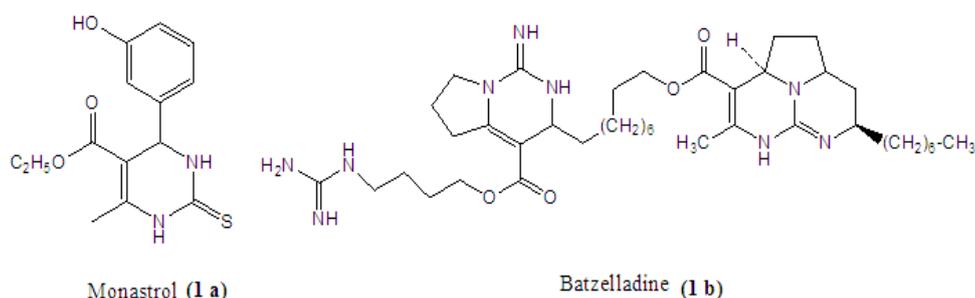
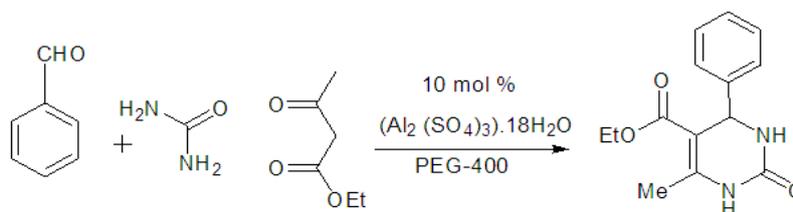


Fig:- 1

Owing to the wide range of pharmacological and biological activities, the synthesis of these compounds has become an important target in current years. In order to expand the application of ultrasound in the synthesis of heterocyclic compounds. We wish to report a general, efficient and eco-friendly method for the synthesis of DHPM's.^[8]

An increasing environmental consciousness in chemical research & industry, the challenge for a sustainable environment calls for clean procedure.^[7] Ultrasonic assisted organic synthesis as a green synthetic approach

is a powerful technique that is being used more and more to accelerate organic reactions.^[9,10] It can be extremely efficient and it is applicable to a broad range of practical synthesis. The notable features of ultrasound approach are to enhance reaction rates, formation of purer products in high yields and considered a processing aid in terms of energy conservation and waste minimization which compared with traditional methods. This technique is more convenient taking green chemistry concepts into accounts. However, the use of ultrasound in heterocyclic system is not fully explored.^[11]



Scheme 1

MATERIALS AND METHODS

All chemicals and reagents used without further purification. Some selected products were characterized using PMR 300 MHz spectrometer with DMSO- d_6 as a solvent and recorded in ppm relative to the internal TMS 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). Melting points were determined in open capillary tubes and are uncorrected. For the ultrasound irradiation experiment described below used under sonic condition at 40 KHz.

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 25mL round bottom flask and fitted in ultrasound bath (40 KHz) for a 20 min. On completion of reaction (checked by TLC), the solid product, filtered the product from PEG-Aluminium sulphate and recrystallised by using 1:1 mixture of ethanol and water. The recovery of PEG and catalyst was 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(1H)-one, (4a)**, m.p.200-202°C; IR. (KBr): 3245, 1725, 1705, 1647 cm^{-1} ; 1H 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, 2H), 2.18 (s, 3H), 1.04 (t, 3H).
- 2) **5-Ethoxycarbonyl-4-(2-chlorophenyl)-6-methyl-3, 4-dihydropyrimidin-2(1H)-one, (4c)** m.p. 216-218°C; IR (KBr): 3225, 1710, 1643, 1560 cm^{-1} ;

PMR (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, 2H),2.29 (s, 1H), 1.08 (t, 3H).

- 3) **5-Ethoxycarbonyl-4-(4-chlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one, (4d)** m.p. 212-214°C; IR (KBr): 3244, 1712, 1647, 1489 cm^{-1} ; PMR (DMSO- d_6) δ : 9.20 (s, 1H), 7.76 (s, 1H), 7.40 (d, 2H), 7.27 (d, 2H), 5.11 (s, 1H), 3.96 (q, 2H), 2.23 (s, 3H), 1.06 (t, 3H).

- 4) **5-Ethoxycarbonyl-4-(4-nitrophenyl)-6-methyl-3, 4-dihydropyrimidin-2(1H)-one, (4e)** m.p. 206-208°C; IR (KBr): 3232, 1728, 1643, 1593 cm^{-1} ; PMR (DMSO- d_6) δ : 9.31 (s, 1H), 8.20 (d, 2H), 7.87 (s, 1H), 7.50 (d, 2H), 5.24 (s, 1H), 3.95 (q, 2H), 2.21 (s, 3H), 1.04 (t, 3H).

RESULTS AND DISCUSSION

Firstly we made efforts to build up a catalytic system that would address the limitations of the previously reported acid catalyzed DHPM synthesis reactions. During the beginning study a model reaction employ benzaldehyde, ethyl acetoacetate and urea in the presence of aluminium sulphate as catalyst in PEG under ultrasound 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). The reaction was not successful in the absence of catalyst or ultrasound irradiation. (Table 1, entries 1,6,7).

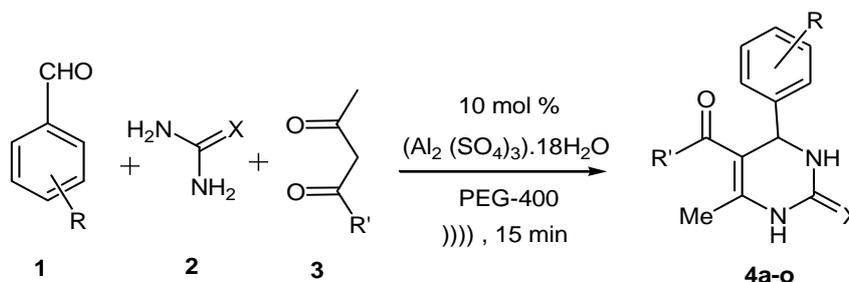
Table 1. Optimization of reaction parameters^a

Entry	Mol % of Catalyst	Time (min.)	Yield (%) ^b
1	-	10	18
2	5	10	68
3	5	15	78
4	10	15	94
5	10	10	82
6 ^c	10	150	66
7 ^d	10	15	62

^aReaction conditions: Benzaldehyde (2 mmol), Ethyl acetoacetate (2 mmol), Urea (2.4mmol) and PEG-400 (3

mL), ultrasound irradiation. ^bIsolated yield, ^c By conventional thermal method, ^d neat condition.

In these reactions no any hazardous substances was used and no waste formation was observed. The experimental procedure for these reaction was remarkably simple and requisite 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 ultrasound irradiation (40 MHz) for 10–15 min. The reaction time was optimized at 15 min. (Table 1, entries 2-4).

**Table 2. Substrate study for DHPM'S synthesis reaction.^a**

Entry	R-	R'-	X	Yield (%) ^b
4a	H-	OEt	O	94
4b	4-MeO-	OEt	O	86
4c	2-Cl-	OEt	O	83
4d	4-Cl-	OEt	O	96
4e	4-NO ₂ -	OEt	O	90
4f	3-NO ₂ -	OEt	O	86
4g	2-NO ₂ -	OEt	O	72
4h	H-	OEt	S	93
4i	4-Me-	OEt	S	87
4j	4-Cl-	OEt	S	91

^aReaction conditions: Aldehyde (2 mmol), 1,3-Dicarbonyl Compound (2 mmol), Urea/Thiourea (2.4mmol), Aluminium sulphate (10 mol%) and PEG-400 (3 mL), ultrasound irradiation for 15 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 developed a practical and general approach for this multi-component reaction using a mild catalyst aluminium sulphate, which is not only preserved the simplicity of *Biginelli's* one pot reaction but also consistently 72-96% yields of the 3,4-dihydropyrimidinones 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 and nitro 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	94
2	1 st recycle	89
3	2 nd recycle	84
4	3 rd recycle	72

^aReaction conditions: Benzaldehyde (2 mmol), Ethylacetoacetate (2 mmol), Urea (2.4mmol), Aluminium sulphate (10 mol%) and PEG-400 (3 mL), ultrasound irradiation for 15 min. ^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 ultrasound 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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