



Synthesis and Characterization of 5-Ethoxycarbonyl-6-Methyl-4-Substituted-3,4-Dihydropyrimidin-2(1H)-One Derivatives

Neelam Vijaya Durga ^{a*}, Dr.Nallajerla Sai Krishna ^b, Saga Pavani Koteswari ^c, Marapatla Joseph Raju ^c, Kundeti Lakshmi Anitha ^c, Jakkampudi Bhargavi ^c, Namana Vijaya ^c, Sankranti Vijaya Lakshmi ^c

^a Assistant Professor, A.K.R.G. College of Pharmacy, Nallajerla, Andhra Pradesh, India 534 112

^b Principal & Professor, A.K.R.G. College of Pharmacy, Nallajerla, Andhra Pradesh, India 534 112

^c Student, A.K.R.G. College of Pharmacy, Nallajerla, Andhra Pradesh, India 534 112

ABSTRACT

The present study focuses on the synthesis of 5-ethoxycarbonyl-6-methyl-4-substituted-3,4-dihydropyrimidin-2(1H)-one derivatives through a one-pot Biginelli reaction under solvent-free conditions. These derivatives were prepared using different aromatic aldehydes containing electron-releasing and electron-withdrawing groups, ethyl acetoacetate, urea, and zinc chloride as a catalyst. The main objective of this work is to develop a simple, efficient, and environmentally friendly method for the synthesis of dihydropyrimidinone derivatives. The Biginelli reaction is an important multicomponent reaction in organic chemistry because it allows for the preparation of heterocyclic compounds from readily available starting materials in a single reaction step. In the present method, all the reactants were combined in one pot without using an additional solvent. Zinc chloride was used to promote the reaction and facilitate product formation. The solvent-free approach helps reduce solvent consumption, minimizes chemical waste, simplifies the experimental procedure, and makes the workup process easier. The method also offers the potential for shorter reaction times and favourable product yields, depending on the nature of the substituents present in the aromatic aldehydes. The synthesized compounds were isolated and purified using suitable work-up procedures. The products were characterized based on their physical properties and spectral studies to support the identification of the desired structures. The influence of electron-releasing and electron-withdrawing substituents on the aromatic ring may also be considered when evaluating the reaction outcomes. Overall, this study highlights the usefulness of the Biginelli reaction as a convenient approach for synthesizing substituted dihydropyrimidinone derivatives. The use of a one-pot procedure, zinc chloride, and solvent-free conditions provides a practical and potentially greener alternative to conventional solvent-based synthetic methods. This approach contributes to the development of efficient and environmentally responsible techniques in heterocyclic chemistry.

Keywords: Aromatic aldehydes, Biginelli reaction, electron-releasing groups, electron-withdrawing groups, urea, zinc chloride, environmentally friendly.

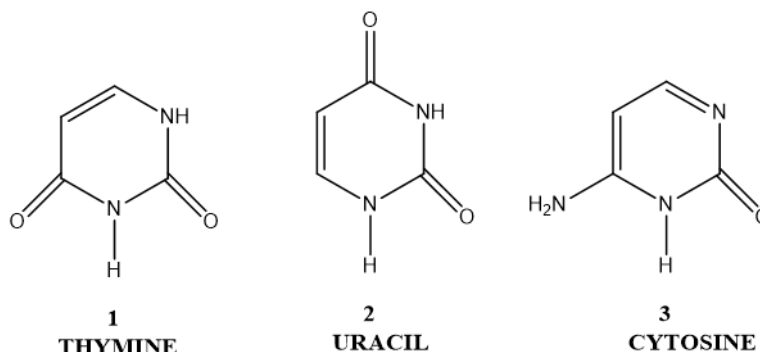
1. Introduction

Heterocyclic chemistry is a significant area of organic chemistry that accounts for over one-third of current publications[1]. Our biological system depends heavily on heterocyclic molecules. They are essential components of several naturally occurring substances, pharmacologically active compounds, and nucleic acids. Heterocyclic chemicals such as purines and pyrimidines are also found in the base pairs of DNA and RNA (guanine, cytosine, adenine, and thymine). Antitumor, antibiotic, anti-inflammatory, antidepressant, antimalarial, anti-HIV, antimicrobial, antibacterial, antifungal, antiviral, antidiabetic, herbicidal, fungicidal, and insecticidal medicines[2] are among the many therapeutic candidates that include heterocyclic compounds. Some naturally occurring compounds have been shown to have high biological activity against a variety of illnesses. For example, quinine is used as an antimalarial medication, while vinblastine and vincristine are used as anticancer agents. The pyrimidine is the most significant heterocyclic component. Pyrimidine derivatives are used in medicinal chemistry for a variety of therapeutic purposes. The existence of a pyrimidine base in thymine, cytosine, and uracil—essential building blocks of nucleic acids, DNA, and RNA[3] is one predicted explanation for their activity. Numerous chemical compounds with pyrimidine as their core nucleus were synthesized and their antihypertensive[4–6], antihyperglycemic[7], antiarrhythmic, anti-inflammatory[8], analgesic[9], antibacterial[10], anti-HIV[11], and antitubercular properties were assessed[12,13]. Scientists are drawn to creating novel dihydropyrimidine compounds because of their many medicinal qualities.

2. Dihydropyrimidinones (DHPMs)

Pyrimidinones, also known as Dihydropyrimidinones (DHPMs), are well recognized for their diverse bioactivities. As a result of their use in drug research, several synthetic techniques for their synthesis and chemical transformations have been developed. Three of the five main bases in nucleic acids are

pyrimidine derivatives, which include thymine (1) in DNA, uracil (2) in RNA, and cytosine (3) in both DNA and RNA. In the field of synthetic organic chemistry, their significance has grown due to their role as bases in DNA and RNA. In chemical and medical chemistry, aryl-substituted 3, 4-dihydropyrimidin-2(1H)-one and its derivatives constitute a significant family of compounds.



From marine sources, a number of alkaloids with the dihydropyrimidine core unit have been identified; these compounds also show intriguing biological characteristics[14]. Synthetic chemists are becoming more interested in dihydropyrimidinones and their derivatives due to their exceptional pharmacological characteristics, which include calcium channel blockers, anticancer, and anti-inflammatory effects[15–19].

3. Biginelli Reaction

The dihydropyrimidinone nucleus may be synthesized using both one-pot and multi-step methods. The Italian scientist Pietro Biginelli described a cyclocondensation process in 1893 that produced a heterocyclic system of dihydropyrimidinone (DHPM) from ethyl acetoacetate, benzaldehyde, and urea. This reaction is known as the Biginelli reaction. Currently, there are a number of broad techniques for making dihydropyrimidinones, including several solid-phase modifications[20]. The acid-catalysed cyclo-condensation reaction of urea, benzaldehyde, and ethyl acetoacetate was described by P. Biginelli in 1893. A catalytic quantity of hydrochloric acid was added to a combination of the three components dissolved in ethanol and heated to reflux temperature to initiate the reaction. This unique one-pot, three-component synthesis produced 3,4-dihydropyrimidin-2(1H)-one, which precipitated after the reaction mixture cooled. This reaction is referred to as the "Biginelli reaction", "Biginelli condensation", or "Biginelli dihydropyrimidinone synthesis[21]."

Research interest in this field is therefore increasing daily due to the vast pharmacological profile of this family of substances. As a result, more efforts are being made to create rapid, safe, and adaptable methods for their synthesis. The disadvantages of the traditional Biginelli condensation process include severe reaction conditions, lengthy reaction periods, and often low yields. As a result, multistep synthetic approaches have been developed, which offer somewhat higher yields but are not as straightforward as one-pot synthesis. Several groups have discovered innovative techniques for the synthesis of dihydropyrimidinones in recent years. Many Lewis catalysts, including ZrCl_4 [22], BiCl_3 [23], LiBr [24], $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$ [25], InCl_3 [26], $\text{Cu}(\text{OTf})_2$ [27], $\text{Zn}(\text{OTf})_2$ [28], $\text{FeCl}_3 \cdot \text{H}_2\text{O}$ [29], LiClO_4 [30], CuCl_2 [31], chloroacetic acid, and LaCl_3 as $\text{BF}_3 \cdot \text{OEt}_2$, $\text{La}(\text{OTf})_3$, $\text{Yb}(\text{OTf})_3$ silica Sulphuric acid, $\text{H}_3\text{PW}_{12}\text{O}_{40}$, and $\text{H}_3\text{PMo}_{12}\text{O}_{40}$ [32], have been developed to increase the efficiency of the Biginelli reaction. From the perspective of a synthetic chemist, some of them are quite exciting, although some disadvantages still exist. For instance, organic solvents are constantly utilised, and some catalysts are costly, complicated, or unavailable. Additionally, a lot of heavy metal salts were utilised, which somewhat contaminated the environment. There has been a lot of interest in investigating mild, fast, and high-yielding procedures at room temperature because previously published protocols often needed long reaction times and high temperatures with moderate yields. Phenylboronic acid[33], triphenylphosphine[34], phosphate ester[35], calcium fluoride[36], and ammonium carbonate in water[37] have all been used in recent findings. However, higher reaction times and the need for solvents plagued several of these methods.

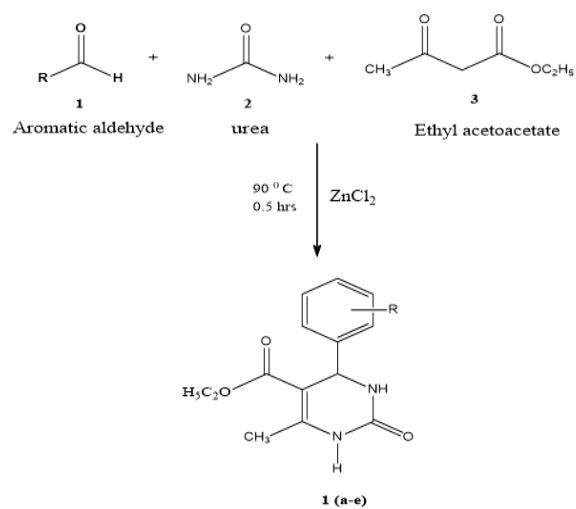
Because of the enormous biological significance of dihydropyrimidinones, it is crucial to look for catalysts that can efficiently prepare a wide range of functional dihydropyrimidinones without the need for solvents and offer a high yield in a brief reaction time.

Here, we described a solvent-free, zinc chloride-catalysed technique for making 3,4-dihydropyrimidin-2(1H)-ones. In organic processes, zinc chloride, a Lewis acid catalyst that is readily accessible and reasonably priced, is frequently utilised. We discovered that zinc chloride may catalyse Biginelli condensation without the need for a solvent throughout the investigation.

4. Materials and Instruments

Materials and reagents were purchased from commercial providers (Merck grade) and used without additional purification. Melting points were measured using electrical melting point equipment and are uncorrected. The reaction's development was tracked using TLC and Silica Gel G (Merck). IR spectra were recorded in KBr discs using a Bruker analyser.

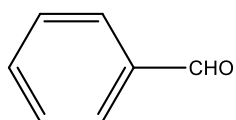
5. Experimental Work



Compound

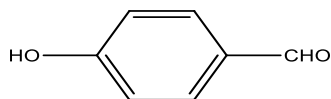
R

1a



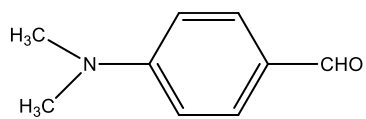
Benzaldehyde

1b



4-Hydroxy benzaldehyde

1c



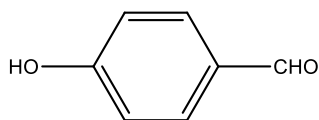
P- dimethylamino benzaldehyde

1d



P- toulaldehyde

1e



Salicylaldehyde

Procedure for synthesis of 5-Ethoxy carbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin -2-(1H)-one (1a-e)[38]

A 250 mL round-bottomed flask fitted with a reflux condenser was charged with ethyl acetoacetate (1.26 mL, 10.0 mmol), various aromatic aldehydes (1.01 mL, 10.0 mmol), urea (0.9 g, 15 mmol), and ZnCl_2 (0.136 g, 1.0 mmol). The mixture was refluxed at 90°C for 0.5 hrs. A solid mass was deposited in the flask. Completion of the reaction was monitored by TLC using silica gel G as the stationary phase and benzene, ethyl acetate (3:2) as the mobile phase. The reaction mixture was cooled and poured into crushed ice. The yellow solid separated out was filtered and washed with cold water. Purified the crude product by recrystallisation using 95% ethanol.

Synthesized compounds 5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydro pyrimidin-2(1H)-one derivatives

5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydro pyrimidin-2(1H)-one (1a)

5-ethoxycarbonyl-6-methyl-4-(4-hydroxyphenyl)-3,4-dihydropyrimidin-2(1H)-one (1b)

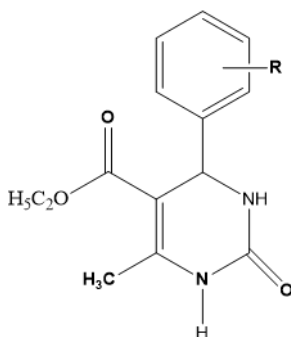
5-ethoxycarbonyl-6-methyl-4-(N, N dimethyl phenyl)-3,4-dihydropyrimidin-2(1H)-one (1c)

5-ethoxycarbonyl-6-methyl-4-(4-methylphenyl)-3,4-dihydropyrimidin-2(1H)-one (1d)

5-ethoxycarbonyl-6-methyl-4-(4-hydroxyphenyl)-3,4-dihydropyrimidin-2(1H)-one (1e)

Physical data of synthesized compounds (5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydro pyrimidin-2(1H)-one (Compound 1a-1e))

The melting points were calculated using an open-ended capillary tube and are uncorrected. TLC, with silica gel G as the stationary phase, was used to determine the purity of the compounds[39].



Compound	Molecular formula	Molecular weight (gm)	Melting point (0°C)	Percentage yield	of Reaction time(hrs.)	Rf value
1a	$\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_3$	260.2	202°C	72.05%	0.5	0.66
1b	$\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_3$	276.28	205°C	71.45%	0.5	0.87
1c	$\text{C}_{16}\text{H}_{21}\text{N}_3\text{O}_3$	303.35	211°C	76.18%	0.5	0.62
1d	$\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}_3$	274.2	219°C	70.97%	0.5	0.43
1e	$\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_3$	276.28	236°C	69.23%	0.5	0.62

❖ **Solvent System:** Benzene:Ethyl acetate (3:2)

Spectral data (IR) of Synthesized compounds (1a-1e)

5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydro pyrimidin-2(1H)-one (1a)

IR [Cm⁻¹ KBr]: 3244.09 cm⁻¹(-NH stretching); 1724.97 cm⁻¹(C = O OC₂H₅ stretching); 2978.55 cm⁻¹(-CH₃ C - H Stretching); 1649.04 cm⁻¹(C = O Stretching); 3115.83 cm⁻¹(-N - H Stretching).

5-ethoxycarbonyl-6-methyl-4-(4-hydroxyphenyl)-3,4dihydropyrimidin-2(1H)-one(1b)

IR [Cm⁻¹ KBr]: 3436.16 cm⁻¹ (-O - H Stretching); 3112.78 cm⁻¹ (-N - H Stretching); 3349.13

cm⁻¹(-N - H Stretching); 1744.31 cm⁻¹(C = O, OC₂H₅ Stretching); 2941.28 cm⁻¹(-CH₃ C - H Stretching); 1693.63 cm⁻¹(C = O Stretching).

5-ethoxycarbonyl-6-methyl-4-(4-N, N dimethyl phenyl)-3,4dihydropyrimidin-2(1H)-one (1c)

IR [Cm⁻¹ KBr]: 3244.52 cm⁻¹(-N - H Stretching); 1720.97 cm⁻¹(C = O, OC₂H₅ Stretching); 2926.23 cm⁻¹(-CH₃, C - H Stretching); 1649.62 cm⁻¹(C = O Stretching); 3115.60 cm⁻¹(-N - H Stretching).

5-ethoxycarbonyl-6-methyl-4-(4-methylphenyl)-3,4dihydropyrimidin-2(1H)-one (1d)

IR [Cm⁻¹ KBr]: 3249.84 cm⁻¹(-N - H Stretching); 1722.55 cm⁻¹(C = O, OC₂H₅ Stretching); 2981.06 cm⁻¹(-CH₃, C - H Stretching); 1649.17 cm⁻¹(C = O Stretching).

5-ethoxycarbonyl-6-methyl-4-(4-hydroxyphenyl)-3,4dihydropyrimidin-2(1H)-one(1e)

IR [Cm⁻¹ KBr]: 3234.69 cm⁻¹(-N - H Stretching); 1731.51 cm⁻¹(C = O, OC₂H₅ Stretching); 2941.52 cm⁻¹(-CH₃ C-H Stretching); 1693.05 cm⁻¹(C = O Stretching); 3084.68 cm⁻¹(-N - H Stretching).

6. Results and Discussion

Using Zinc Chloride as a catalyst, under solvent free conditions 3,4-dihydropyrimidin-2(1H)-one derivatives were synthesized in a single pot. These were created via the proper synthetic process, which involved reacting several aromatic aldehydes, urea, and a dicarbonyl molecule (ethyl acetoacetate) with zinc chloride acting as a catalyst. TLC was used to track the reaction's progress while the reactants were refluxed at 90 °C for around half an hour.

The compound's melting point was discovered to be the same as previously stated. Melting points were measured in open capillaries and are not adjusted. KBr discs were used to record IR spectra using a Bruker 300 FT-IR. On silica gel G (Merck), thin layer chromatography was carried out. Recrystallisation solvents include ethanol.

7. Conclusion

The title compounds were successfully produced in the current study without the use of a solvent and zinc chloride as a catalyst. Physical characteristics (R_f values, melting temperature, Molecular weight, Molecular formula) and spectral information (IR spectra) were used to characterize each synthesized compound. Among the compounds that were produced 5-ethoxycarbonyl-6-methyl-4-(4-N, N dimethyl phenyl)-3,4dihydropyrimidin-2(1H)-one (1c) is one of the produced compounds with a high yield percentage..

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