

Green synthesis of pyrimidine derivative

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ABSTRACT

The majority of the drugs on the market today are entirely chemically synthesized in the laboratory. Several scientists had synthesized dihydropyrimidine (DHPMs) derivatives showing a wide spectrum of biological actions as antibacterials, antivirals as well as antitumor agents. This activity is principally due to presence of stereogenic carbon C4 in their structure. The current investigation is study and synthesis of dihydropyrimidinones efficiently and in high yields under mild, solvent free and eco-friendly conditions by using “Grindstone Chemistry Technique” catalyzed by $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ and Conc. HCl. The obtained products have been identified by comparison with spectral data & their melting points. The synthesis of DHPMs derivative involves a multicomponent reaction (aldehyde derivative, urea /thiourea and 1,3-dicarbonyl compounds) in presence of HCl / NH_4Cl as a catalyst. 3,4-dihydropyrimidin-2-(1H)-ones was synthesized and characterized using IR. The melting points was obtained 203 °C.

Keyword: dihydropyrimidine derivatives; Biginelli Reaction; Grindstone chemistry

1. INTRODUCTION

The original one pot synthesis of 3,4-dihydropyrimidine-2-(1H)- ones was firstly reported by Pietro Biginelli in 1893 performing the three component cyclocondensation reaction of ethyl acetoacetate, benzaldehyde and urea under Bronsted acid catalysis¹⁻². However this reaction suffers from the harsh conditions, high reaction times and frequently low yields Aryl substituted 3,4-dihydropyrimidine-2-(1H)- ones³ and their derivatives are an important class of substances in organic and medicinal chemistry.

Many synthetic methods⁴⁻⁸ for preparing these compounds have been reported including classical methods, microwave irradiation and by using Lewis acids as well as protic acids. The discovery of a new an inexpensive catalyst for the preparation of 3,4-dihydropyrimidine-2-(1H)- ones under neutral and mild conditions with high yield of prime importance. In solvent free organic reactions⁹ reagents react together in the absence of any solvent have been reviewed as a fast developing technology.

The development of new strategies for the synthesis of complex molecules is a challenging area of organic synthesis. A large number of organic reactions are typically carried out under anhydrous conditions, using volatile organic solvents like benzene which are the cause of environmental problems and also potentially carcinogenic. Hence, it is required to develop safe, practical and environmental friendly process. Many exothermic reactions can be accomplished in high yield by using a technique known as “Grindstone Chemistry” which is one of the “Green Chemistry Technique”.

Reactions are initiated by grinding, with transfer of very small amount of energy through friction. These new strategies involve catalysts such as $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$, $\text{FeCl}_3 \cdot \text{HCl}$, ZnCl_2 , CoCl_2 , $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ etc.

Several marine alkaloids possessing the dihydropyrimidione moiety have shown interesting biological activities, for instance *Batzelladine*¹⁰ alkaloid has been reported to be a potent against HIV group. In recent years, development of more economical and environmentally friendly conversion processes is gaining interest in the chemical communities.

2. EXPERIMENTAL

The chemicals used Benzaldehyde, Ethyl acetoacetate, urea, thiourea, $\text{CuCl}_2 \cdot \text{H}_2\text{O}$, hydrochloric acid were of analytical reagent grade. A mixture of Benzaldehyde, ethylacetoacetate, urea, $\text{CuCl}_2 \cdot \text{H}_2\text{O}$ and few drops of Conc. HCl was ground together for 2-5 min.

The solid mass was left overnight, then washed with cold water and purified by recrystallization from ethanol. The obtained products were identified from their spectral (IR) data and their melting point. Melting point was determined in open capillary tubes. The IR spectra were recorded on Shimadzu 435 FT- IR spectrophotometer with samples prepared as KBr palletes.

2. 1. Synthesis of 5-ethoxycarbonyl-4-phenyl-6-methyl-3,4-dihydropyrimidine-2-(1H)-one¹¹ by conventional method

A mixture of benzaldehyde(1mmol), ethyl acetoacetate(1mmol), urea/ thiourea (1mmol) and catalytic amount of HCl/ NH_4Cl was taken in round bottom flask with 30 cm³ methanol and reflux at 100 °C for 3 hrs. The progress of the reaction was monitored by TLC. The mixture was cooled to room temperature and poured in cold water.

The solid product was collected by filtration. The product was dried and recrystallised from hot alcohol to obtained the pure product. Product was characterized by melting point, IR.

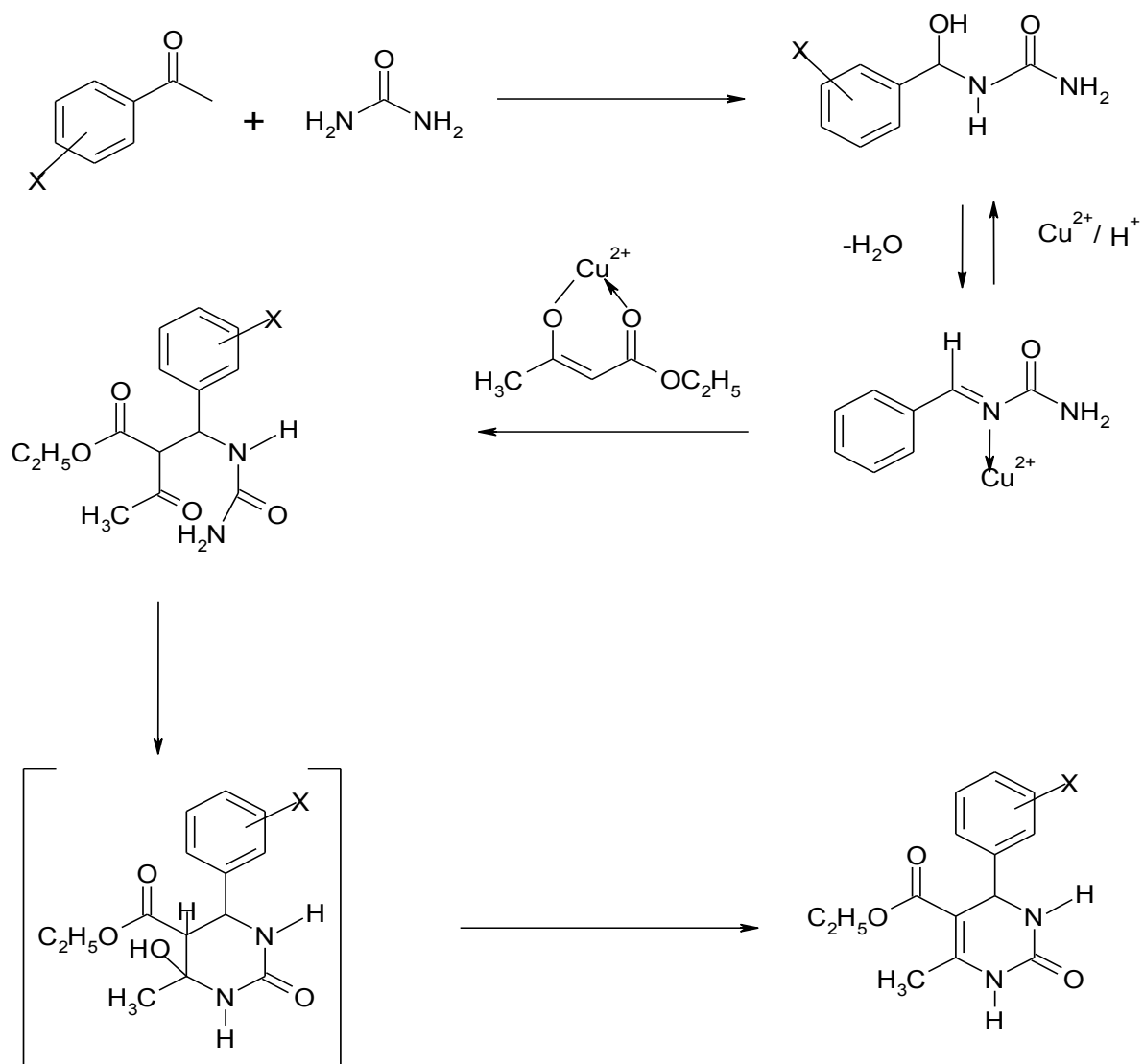
2. 2. Synthesis of 5-ethoxycarbonyl-4-phenyl-6-methyl-3,4-dihydropyrimidine-2-(1H)-one by Grindstone Chemistry

A mixture of benzaldehyde (1mmol), ethyl acetoacetate (1mmol), urea/ thiourea (1mmol) and catalytic amount of $\text{CuCl}_2 \cdot \text{H}_2\text{O}$ was ground together for 2-5 min.

The solid mass was left overnight, then washed with cold water and the product was dried and recrystallised from hot alcohol to obtained the pure product.

The progress of the reaction was monitored by TLC Product was characterized by melting point, IR.

3. REACTION



$x = \text{H} / \text{Cl} / \text{NO}_2 / \text{OMe}$

MECHANISM

4. RESULTS AND DISCUSSION

Table 1. Interpretation of IR spectra of 5-ethoxycarbonyl-4-phenyl-6-methyl-3,4-dihydropyrimidine-2-(1H)-one by conventional method.

IR range (cm ⁻¹)	Peak Intensity	Peak due to
3247.99	Sharp	N-H Stretching
3116.80	Sharp	Aromatic C-H Stretching
2980.56	Sharp	Aliphatic C-H Stretching
1725.85	Sharp	Ester
1702.16	Sharp	C=O Stretching
1650.57	Sharp	C=C Stretching
1465.18	Sharp	Asymmetric C-H bending
1270.88	Sharp	C-O Stretching
700.46	Sharp	Mono substituted benzene

Table 2. Interpretation of IR spectra of 5-ethoxycarbonyl-4-phenyl-6-methyl-3,4-dihydropyrimidine-2-(1H)-one by Grindstone Chemistry.

IR range (cm ⁻¹)	Peak Intensity	Peak due to
3288.74	Sharp	N-H Stretching
2955.04	Sharp	Aromatic C-H Stretching
2980.56	Sharp	Aliphatic C-H Stretching
1720.35	Sharp	Ester
1726.35	Sharp	C=O Stretching
1635.69	Sharp	C=C Stretching
1455.20	Sharp	Asymmetric C-H bending
1290.42	Sharp	C-O Stretching
698.2	Sharp	Mono substituted benzene

5. CONCLUSION

The preparation of 5-ethoxycarbonyl-4-phenyl-6-methyl-3,4-dihydropyrimidine-2-(1H)-one by Grindstone Chemistry shows synthesis is in good yields and in less time and also avoids problems associated with solvent use. It was found that $\text{CuCl}_2 \cdot \text{H}_2\text{O}$ works as an excellent catalyst for the one-pot three components and solvent free synthesis of dihydropyrimidione.

This technique is superior to the existing methods. Since grinding does not require solvents leading to a safe and environmental friendly synthesis solvent free approach opens up numerous possibilities for conducting rapid organic synthesis and functional group transformations more efficiently. Additionally there are distinct advantages of these solvent free reactions. It prevents pollution in organic synthesis at source.

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(Received 31 October 2013; accepted 04 November 2013)