

Comparative study of chemical synthesis of pyrimidine derivatives by using Grindstone chemistry Technique and Conventional method

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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 steriogenic carbon C4 in their structure. The current investigation is comparative study of chemically synthesis of two DHPMs derivatives by Biginelli Reaction using conventional method and grindstone chemistry technique. The synthesis of DHPMs derivative involves a multicomponent reaction (aldehyde derivative, urea /thiourea and 1,3-dicarbonyl compounds) in presence of HCl / NH₄Cl as a catalyst. Two derivative viz. 3,4-dihydropyrimidin-2-(1H)-ones and 3,4-dihydropyrimidin-2-(1H)-thiones were synthesized and characterized using IR. The melting points were obtained are 208 °C and 210 °C respectively. “Grindstone Chemistry Technique” catalyzed by CuCl₂·2H₂O and Conc. HCl. gave more yield, solvent free and ecofriendly. The obtained products have been identified by comparison with spectral data & their melting points. This study will help to develop easy protocol for the synthesis of many more DHPMs derivative with high yield.

Keyword: dihydropyrimidine derivatives; Biginelli Reaction; Grindstone chemistry

1. INTRODUCTION

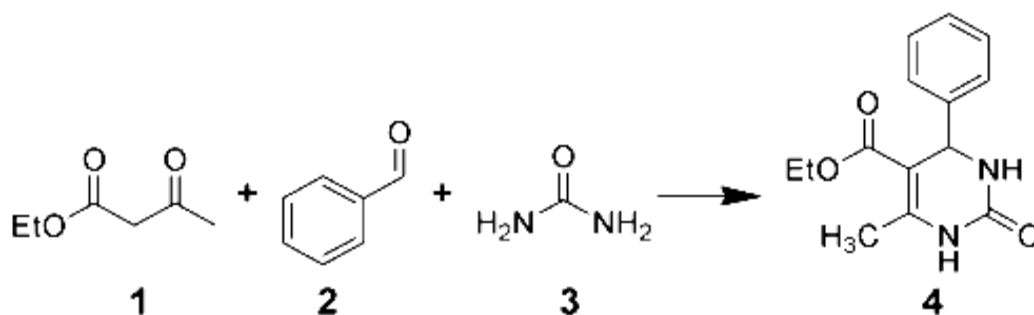
The original one pot synthesis of 3,4-dihydropyrimidine-2-(1H)-ones was firstly reported by Pietro Biginelli in 1893 performing the three component cyclocondensation reaction of ethyl acetoacetate, benzaldehyde and urea under Bronsted acid catalysis¹⁻². However this reaction suffers from the harsh conditions, 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. 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".

2. EXPERIMENTAL

The chemicals used Benzaldehyde, Ethyl acetoacetate, urea, thiourea, methanol, ethanol, ammonium chloride, hydrochloric acid were of analytical reagent grade. Methods used for synthesis of 3,4-dihydropyrimidine-2-(1H)-ones and their derivatives are conventional method and Grindstone chemistry Technique. Melting points were determined in open capillary tubes on a Buchi 530 melting point apparatus. The IR spectra were recorded on Shimadzu 435 FT- IR spectrophotometer with samples prepared as KBr palletes.

Biginelli Reaction



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

A mixture of benzaldehyde (1 mmol), ethyl acetoacetate (1 mmol), urea/ thiourea (1 mmol) and catalytic amount of HCl/NH₄Cl was taken in round bottom flask with 30 cm³ methanol and reflux at 60 °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, 1H NMR, IR.

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

A mixture of benzaldehyde (1 mmol), ethylacetoacetate (1 mmol), urea/thiourea (1 mmol) and catalytic amount of CuCl₂·2H₂O was ground together for 2-5 min. The solid mass was left over 20 min, washed with cold water. The product was dried and recrystallized from hot alcohol to obtained the pure product. The progress was monitored by TLC. The Product was characterized by melting point, IR.

3. 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 Technique.

IR range (cm ⁻¹)	Peak Intensity	Peak due to
3288.78	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
1313.89	Sharp	C-N Stretching
1290.42	Sharp	C-O Stretching
698.20	Sharp	Mono substituted benzene

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

IR range (cm ⁻¹)	Peak Intensity	Peak due to
3330.38	Sharp	N-H Stretching
2981.25	Sharp	Aliphatic C-H Stretching
1673.67	Sharp	C=O Stretching
1575.38	Sharp	C=C Stretching
1466.42	Sharp	Asymmetric C-H bending
1371.61	Sharp	C=N Stretching
1284.56	Sharp	C=S Stretching
1178.47	Sharp	C-O Stretching
724.25	Sharp	Mono substituted benzene

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

IR range (cm ⁻¹)	Peak Intensity	Peak due to
3329.99	Sharp	N-H Stretching
2981.34	Sharp	Aliphatic C-H Stretching
1674.51	Sharp	C=O Stretching
1575.70	Sharp	C=C Stretching
1467.04	Sharp	Asymmetric C-H bending
1371.62	Sharp	C=N Stretching
1284.69	Sharp	C=S Stretching
1120.61	Sharp	C-O Stretching
724.32	Sharp	Mono substituted benzene

5-ethoxycarbonyl-4-phenyl-6-methyl-3,4-dihydropyrimidine-2-(1H)-one prepared was confirmed by IR spectra. Interpretations of these spectra's were carried out in Table 1 and 2. It was also confirmed by NMR spectra. (DMSO-d-6) δ : 1.09 (t, 3H, J = 7.1 Hz, -OCH₂CH₃) 2.25 (s, 3H, CH₃), 3.97 (q, 2H, J = 7.1 Hz, -OCH₂), 5.05 (d, 1H, J = 2.15 Hz, -CH), 7.28 (m, 5H, Ar-H), 7.75 (s, 1H, NH), 9.20 (s, 1H, NH).

Melting point was observed at 208 °C. 5-ethoxycarbonyl-4-phenyl-6-methyl-3,4-dihydropyrimidine-2-(1H)-thione prepared was confirmed by IR spectra. Interpretations of these spectra's were carried out in Table 3 and 4. Melting point was observed at 210 °C.

Table 5. Comparison for Ketone derivative.

Method	conventional	Grindstone
Benzaldehyde (ml)	2.5	2.5
Ethyl acetoacetate (ml)	2.4	2.4
Urea (gm)	2.50	2.500
Thiourea (gm)	-	-
Dil. HCl (ml)	4.0	-
CuCl ₂ ·2H ₂ O (ml)	-	1.000
Time(min)	180	20
Crude Yield (gm)	1.732	2.3
Purified Yield (gm)	1.560	2.1
Melting point (°C)	208	208

Table 6. Comparison for thione derivative.

Method	conventional	Grindstone
Benzaldehyde (ml)	2.5	2.5
Ethyl acetoacetate (ml)	2.6	2.6
Urea (gm)	--	--
Thiourea (gm)	2.0	2.0
Dil. HCl (ml)	4.0	-
CuCl ₂ ·2H ₂ O (ml)	-	1.000
Time (min)	73	20
Crude Yield (gm)	1.710	1.77
Purified Yield (gm)	1.6698	1.70
Melting point (°C)	210	210

4. CONCLUSION

The preparation of 5-ethoxycarbonyl-4-phenyl-6-methyl-3,4-dihydropyrimidine-2-(1H)-one/ thione by conventional and Grindstone chemistry Technique shows that by comparing the yield obtained with respect to time, the product obtained by Grindstone chemistry Technique is in good yields and in less time and also avoids problems associated with solvent use. It was found that $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ work 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. Synthesis by solvent free approach opens up numerous possibilities for conducting rapid organic synthesis and functional transformation 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 19 April 2014; accepted 27 April 2014)