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Research Article

Ultra Sound Assisted: One Step Cyclocondensation of Biginelli Compounds

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Abstract

Simple and improved conditions have been found to carry out the Biginelli reaction for the synthesis of 3, 4-dihydropyrimidin-2(1H) - one derivatives. This synthesis was performed in the presence of polymer nanocomposite Polyindole-Fe as catalyst. These reactions were performed under solvent free conditions cyclocondensation with ultrasound irradiation as the energy source. Compared with the classical Biginelli reaction conditions, this new method has the advantage of excellent yields (82–92%). The advantages of this novel protocol include the excellent yield, operational simplicity, short time, and the avoidance of the use of organic solvents and friendly preparation. Products were identified using physical and spectroscopic data.

Key words: 3, 4-dihydropyrimidin-2(1H) - one derivatives, Polyindole-Fe, Biginelli reaction.

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1. Introduction

Research interest in 3, 4- dihydropyrim idin-2-(1H)-ones (Biginelli compounds. DHPMs) has surged rapidly, owing to the pharmacological properties [5] associated with many derivatives of this privileged heterocyclic core. The biological activity of these Biginelli compounds includes Antiviral, Antitumor, Antibacterial and anti-inflammatory properties [10]. In addition some functionalized DHPMs have emerged as potent calcium channel blockers [9] Antihypertensive agents and neuropeptide Y (NPY), Antagonist. Several recently isolated marine alkaloids with interesting biological activity also contain the dehydropyrimidinone-5-carboxylate core. Their applications in the field of drug research have stimulated the development of wide range of synthetic methods for their preparation and chemical transformation [1]. Out of the five major bases in nucleic, three i.e (Cytosine, Uracil and Thymine) are pyrimidine derivatives, which are found in DNA and RNA [6, 8]. Because of their involvement as bases in DNA and RNA they have become very important in the world of synthetic organic chemistry[7]. The best known method for making DHPM is classical Biginelli synthesis. Although it has been

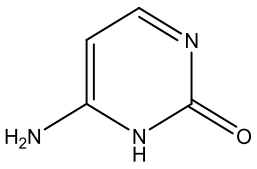
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known for more than a century, it is still the most useful method for the preparation of this class of compounds. The simple and direct method for the synthesis of DHPMs reported by Biginelli in 1893 involves a one pot condensation of an aldehyde[7]. A β-diketone and urea under strong acidic condition. However this method suffers from low yield, especially in the case of some substituted (hetero) aromatic aldehyde.

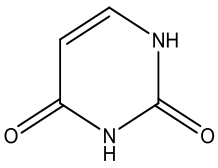
To enhance the efficiency of Biginelli reaction, various catalyst have been studied[3]. In an attempt to prepare DHPMs, different type of acidic catalyst such as NaCl, Acetic acid, Polyindole, Fe_2O_3, CNT, Citric acid Tartaric acid, C_uCl_2, $FeCl_3$, ZnBr, have been used. While the biological interest of DHPM exploded, the biginelli reaction has been the subject of high synthetic activity[4]. The major advantages of the present method are high yields, short reaction time, reducing reaction steps and purification of product [8] by non-chromatographic methods. Though conventional Biginelli involves aldehydes, urea, and ketone[2] compounds. Authors demonstrated that even active methylene compounds (1,3 dicarbonyl), Can participate in this reaction affording unconventional Biginelli compounds in excellent yields. The first Biginelli-like reaction, reported by Wang et al was conducted in CH_3CN by using aldehyde, urea and ketones[2], which remarkably broadened the Biginelli reaction. In recent years, several synthetic procedures for preparing DHPMs via a Biginelli-like reaction have been reported. The original protocol for the synthesis of dihydropyrimidinones, reported by biginelli in 1893, involves a one pot reaction of benzaldehyde, ethyl acetoacetate and urea in ethanol under strongly acidic conditions.

However, this method suffers from drawbacks such as low yields (20%-40%) of desired product, particularly in case substituted aldehydes, and loss of acid sensitive functional groups during the reaction[5]. This had led to multi-step synthetic strategies that produce somewhat better yields, but which lack of the simplicity of the original one-pot Biginelli protocol the search for more suitable preparation of dihydropyrimi dinones continues today.

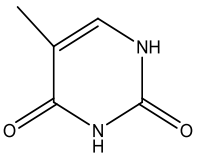
As environmental consciousness has increased in chemical research and industry, the challenge for a sustainable environment calls for clean procedures. Ultrasound has gradually been introduced in organic synthesis as a green synthetic approach over the last three decades[1]. Compared with traditional methods, this technique is more convenient and easily controlled. A large number of organic reactions can be carried out under milder conditions, in shorter reaction times and providing higher yields under ultrasonic irradiation.



Cytosine



Uracil



Thymine

2. Materials and Methods

2.1 Reagents and Chemicals

All reagents used were procured from Merck, Loba and used without further purification. Melting points were measured in open capillary tubes and

uncorrected. Unless stated otherwise, reactions were monitored by thin layer chromatography (TLC) on Merck's silica gel plates (60 F_{254}), visualizing with ultraviolet light. Column chromatography was performed on silica gel (60 - 120 mesh) using distilled hexane and ethyl acetate. Infra red spectra were recorded on a shimadzu FTIR 8310. NMR spectra were recorded on a Bruker 400 MHz spectrometer. Ultrasonicator of the technical specifications, electric supply: 230 V, Ultrasonic frequency: 33 KHz, Ultrasonic power: 100 Watt was used. Aniline monomer was distilled under reduced pressure and stored below 8°C. Poly(acrylic acid) (30% aqueous solution). All the other reagents were analytical grade.

2.2 Solvents

All the solvents like, acetone, ethyl acetate, methanol, ethanol, dioxane and petroleumether were purchased from commercial stores and were purified and dried by following standard procedures and the dried solvents were stored over 4Å molecular sieves.

2.3 Catalyst

2.3.1 Polyindole Fe

Nanoparticles have attracted much interest due to their high homogeneity, flexible process ability and tunable physical properties such as mechanical, magnetic, optical, electric and electronic properties. Polymer composite–lithium salt based systems are well studied and are promising electrolytes for battery applications. These materials have been studied extensively in recent years, not only because of their ideal features as an electrolyte, but also because of the transport mechanism, which differs sharply from that conventional fast ion conductors. It has specifically been observed that the size of dispersed particles plays a significant role in controlling the physical, electrochemical properties of Composite Polymer Electrolyte (CPE) [1,6].

Transition metal oxides such as copper oxide, iron oxide, nickel oxide and zinc oxide nanoparticles have special physicochemical properties and high specific surface area, which may be different from their atomic or bulk counterparts [7]. The dispersion of a small fraction of filler particles in the polymer electrolytes generally enhances the ionic conductivity by 1–2 orders of magnitude increases the mechanical strength, and improves the electrode= electrolyte interfacial stability quite substantially. The increase in conductivity is generally attributed either to the formation of a new kinetic path via a thin interphase layer along the interface itself, or to a concentration enhancement due to space charges in the subinterface region[10]. These features are highly preferable for electrolytes used in numerous solid state electrochemical devices, such as secondary batteries and electro chromic display devices. In the present work, LiClO4 containing polyindole–iron oxide a new CPE system was prepared and this CPE was characterized by IR, XRD, SEM and TEM. The electrical conductivity of these systems is studied by impedance spectroscopy.

2.3.2 Preparation of Polyindole-Fe

Indole (1 g) was dissolved in acetonitrile (100 ml). Sodiumdodecylsulphate (5 g) was dissolved in water (50 ml) and was added to the indole solution. Iron oxide (1 g) nanoparticles dispersed in acetonitrile (100 ml) were added the indole – SDS solution under vigorous stirring. After a few minutes, ammonium peroxydi sulphate solution (5.35 g dissolved in 100 ml acetonitrile) was added to the monomer solution and stirring continued.

The polymer nanocomposite(PNC) thus obtained was thoroughly washed twice with acetonitrile followed by distilled water to remove the unreacted monomer, ammonium peroxydisulphate and SDS. The PNC was dried in vacuum desiccator. Similarly many polyindole-iron oxide nanocomposites of different concentrations of indole (0.15, 0.3, 0.5, 0.7 and 1 g) and with iron oxide (1 g) were prepared. The resulting nanocomposite was characterized by SEM.

2.3.3 Effect of Solvent

Ethanol, methanol and chloroform were found to be effective solvents, considering the stringent environmental regulations, solvent free reactions are desired. Solvent free reaction gives yield about 90% using polyindole polymer catalyst. We have tested catalytic activity on Dihydropyrimidinone synthesis in Table 2. Polyindole catalyst, insoluble in most of the common organic solvents, it can be separated by a separation technique. Ethanol, methanol and chloroform are much better solvents in terms of yield than other tested solvents such as 2-propanol, butanol, DMF and water. While solvents like acetonitrile, DCM, THF and 1,4dioxane are moderate for this conversion using polyaniline-Fe polymer as catalyst.

2.3.4 Effect of Temperature

The activity of polyindole catalyst is tested with different reaction conditions, DHPM synthesis carried out at room temperature, sonicator (45◦C), water bath (100◦C) and oil bath (150◦C). DHPM synthesis gives good yield in a ultrasound sonicator which indicates synergistic effect of polyindole catalyst and ultra sonic irradiation as cavitations in sonicator induce very high pressure and temperature in bubbles reaction gives good yield in short reaction time.

2.3.5 Effect of Time

In order to study the effect of reaction time on DHPM yield, the reaction was studied at different reaction times in a sonicator (10, 15, 20, 25, 30, 35, 40, 45, 50, 55 and 60 min). For the model reaction of benzaldehyde (1mmol) with ethyl acetoacetate (1 mmol) and urea (1.2 mmol) in the presence of polyindole catalyst (1.5 mg) in solvent free conditions. It was observed that there is a sharp increase in the yield of product from 30 to 40 min at sonicator bath temperature (45◦C). After 40 min, the yield of the product reached a maximum level and no further increase in yield was observed.

3. Experimental

There are different types of methods for preparation of DHPM, here we used two methods i.e. Condensation method and Ultrasound method. But we found good yield in Ultrasound method for one aldehyde[5]. So we continue with same method for other aldehydes which we have listed below. Melting points were determined in open capillary tube and are uncorrected. The purity of the compounds has been checked by TLC. The IR spectra were recorded on Varian FTIR 640-IR spectrometer.1H NMR spectra were recorded on Burker 300 MHz spectrometer in CDCl3 as a solvent and TMS as a\n internal standard. Mass spectra were recorded on Thermo Polaris Q GC/MS mass Spectrometer.

3.1 Methods

3.1.1 Condensation Method

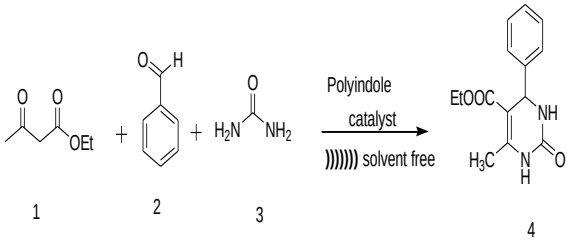
General procedure for the synthesis of 3-4 dihydropyrimidine-2-(1H)-ones:

A mixture of aldehyde (1mmole), ethyl Ethyl acetoacetate (1.1mmole), urea (1.5mmole), silica gel supported and

ethanol (10mL) was charged into a 25mL of round bottom flask. The mixture was refluxed. The reaction was monitored by TLC analysis using acetone as a eluent. After completion of the reaction, the solid materials were filtered off and the solvent (ethanol) of the filtrate was evaporated. After cooling, 20mL of water was added to the mixture and filtered. The filtrate was dissolved in hot ethanol and the insoluble materials were filtered off. Then the filtrate was concentrated and dried to obtained the corresponding 3,4-dihydropyrimidin-2-(1H)-ones (DHPMs). The crude product was crystallized from water/ethanol mixture (1:1).

3.1.2 Ultrasound heating

As environmental consciousness has increased in chemical research and industry, the challenge for a sustainable environment calls for clean procedures. Ultrasound has gradually been introduced in organic synthesis as a green synthetic approach over the last three decades. Compared with traditional methods, this technique is more convenient and easily controlled. A large number of organic reactions can be carried out under milder conditions, in shorter reaction times and providing higher yields under ultrasonic irradiation. A mixture of β dicarbonyl compound (1mmol), aldehydes (1 mmol), urea (1.2 mmol) and catalytic amount of catalyst in optimum quantity was added in the reaction vessel and reaction was performed in sonicator at 45^{o}C temprature. Reaction was monitored by thin layer chromatography (TLC). Product separates from the reaction by stirring in water to remove excess of urea and then filtered and washed with water and recrystallized from ethanol. If we take p-Nitro Benzaldehyde with Polyindole as a catalyst for synthesis of DHPM by both methods we get yield in different amount.



4. Result and Discussion

The present work describes our endeavors to develop a simple, economical and highly efficient strategy for the synthesis of dihydropirimidinones through a three component one-pot condensation of an aldehyde, ketone, and urea using poly indole as a catalyst in ethanol under reflux and Ultrasound condition. But we got good yield by Ultrasound condition.

Initialy in order to determine the optimal loading of the catalyst p-chloro benzaldehyde was combined with Ethyl acetoacetate and urea in the presence of catalyst. As a result shown in Table1, the highest yield of corresponding DHPM could be achieved using poly indole. No conversion was observed in the blank run (Without catalyst) Indicating that the presence of catalyst is necessary for the formation of dihydropirimidinones. Several 3, 4-dihydropyrimidin-2-(1H)-ones were successfully synthesized in high yield by following the above procedure. Aromatic aldehydes bearing both electron –donating and electron- withdrawing groups readily undergo the transformation, giving fair yields of corresponding Biginelli compounds. Also thiourea was used with similar success to provide the corresponding 3, 4-dihydropyrimidin-2-(1H)-thiones, which are also interest with regard to their biological activity.

Entry	Catalyst (g)	Yield (%)	Time
1	Citric Acid	56	40h
2	Malic Acid	62	82h
3	Poly Indole Fe	88	30h
4	Poly Aniline Fe	70	20h
5	Hydrochloric Acid	58	24h
6	Acetic Acid	64	6h
7	Sulfuric Acid	52	9h
8	ZnO	68	45h
9	Tartaric Acid	65	50h
10	No Catalyst	10	210h

Table 1. Model Reaction of Benzaldehyde, Ethyl acetoacetate, and urea under solvent free using different catalyst.

Entry	Solvent	Polyindole Catalyst Concentration	Yield %
1	EtOH	1mg	80%
2	EtOH	2mg	85%
3	EtOH	3mg	90%
4	EtOH	4mg	87%
5	EtOH	5mg	82%

Table 2. Shows the reusability of polyindole polymer catalyst in solvent free

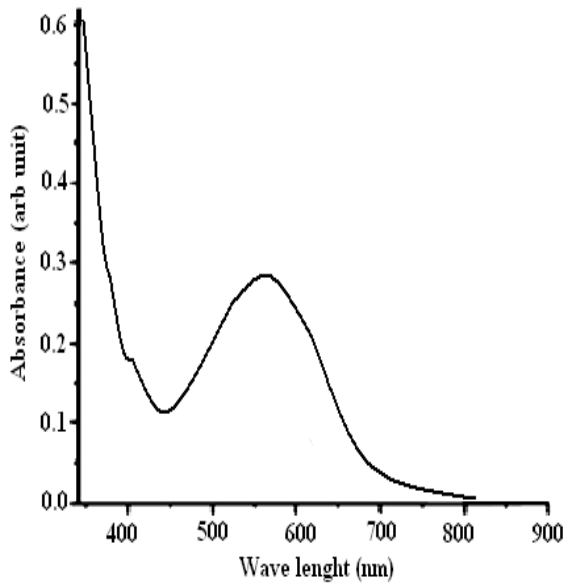


Figure 1 : U.V. of Polyindole shows with three characteristics peaks. Two peaks at 352 and 398 nm and a broad hump at 550nm.

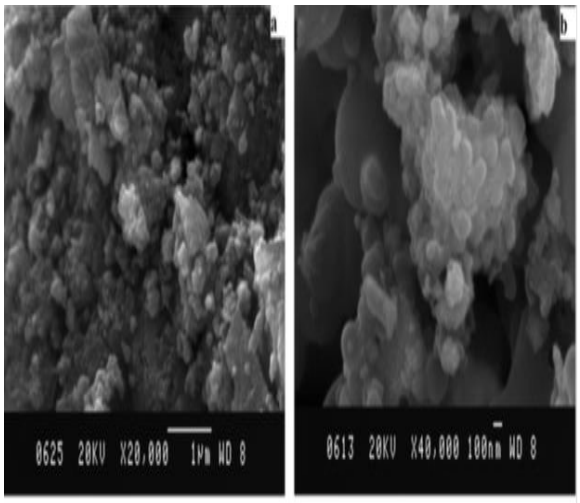


Figure 2 : SEM of Polyindole

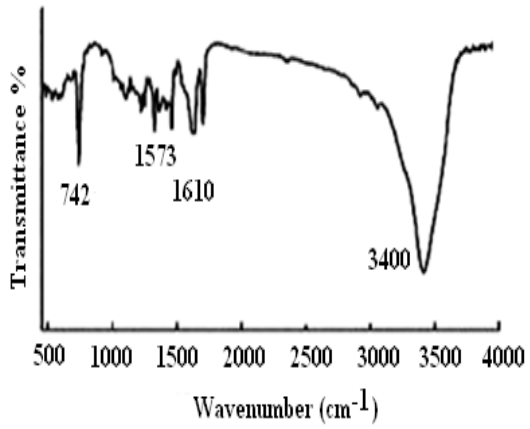
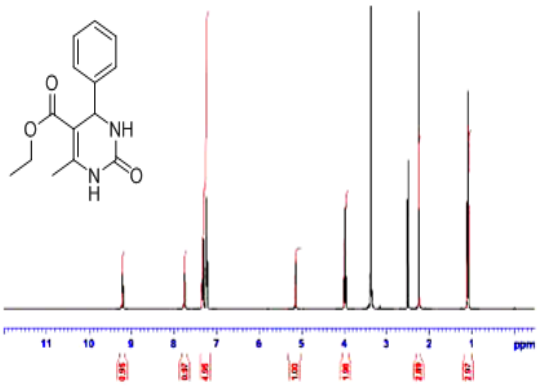


Figure 3 : IR of Polyindole

~3400 cm^{-1}	Band at indicates presence of -NH bonds.
1573 cm^{-1}	Due to stretching and deformation vibrations of -NH bond.
1610 cm^{-1}	Indicates C = C vibrations on indole ring
742 cm^{-1}	Benzene ring is not affected during polymerization of indole



5-Ethoxycarbonyl-4-(4-phenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one

^1H NMR ($CDCl_3$, 400MHz): δ 8.11(s, 1H, -NH), 5.87(s, 1H, -NH), 7.26 -7.30 (m, 5H, -C_6H_5), 5.39 (s, 1H, -CH), 4.06 (q, *J* = 6.88 Hz, 2H, - OCH_2CH_3), 1.1 (t, *J* = 6.88 Hz, 3H-OCH_2CH_3), 2.4(s,-CH_3).

IR (KBr): 3242cm^{-1}(-NH streching), 3115 cm^{-1} (-CONH), 1726 cm^{-1} (-CO ester), 1647 cm^{-1}(-CONH), 1600, 1419, 1311, 1091, 783 cm^{-}

Figure 4 : NMR of Product 1

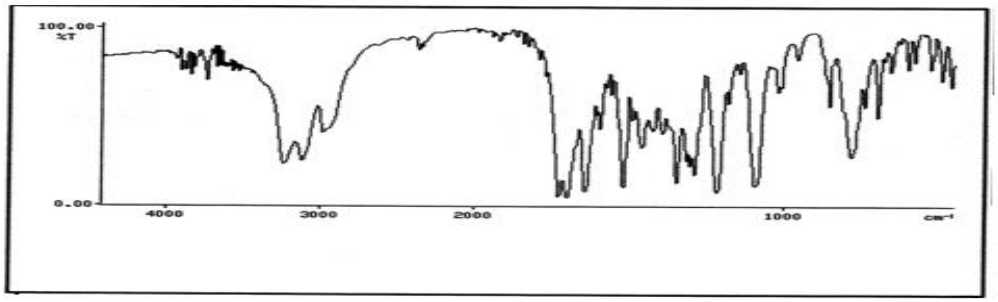


Figure 5 : IR of Product 1

5. Conclusion

We have described a simple and eco friendly method of synthesis of DHPM using polyindole as a catalyst. DHPM synthesized by using Polyindole catalyst requires short reaction time, good yield and high purity compared to other catalysts. Heterocyclic dihydropyrimidin one synthesis was successfully accomplished by using different catalysts and the results were compared with the polyindole catalyst. Preparation of a polyindole catalyst is a simple oxidative polymerization of aniline using acrylic acid as a dopant, instead of strong HCl. The Polyindole catalyst is reusable several times without any decrease in yield of DHPM. The effect of different catalysts on the yield of the DHPM was strongly influenced by the catalyst as observed from Table 1. Experimental study shows that the use of a catalytic amount of polyindole catalyst promotes cyclization under solvent free conditions in a short time, but this reaction in the absence of catalyst gives a very low yield and longer reaction time. A one pot multi-component reaction promoted by the use of polyindole catalyst and ultrasound offers easy access to synthesis of DHPMs in excellent yields. The products can be easily isolated by simple workup procedures such as filtration or by separation technique. Activity of recycled polymer (polyindole-Fe) was studied for consecutive four runs after separation of DHPM gives better yield in each run as that of fresh catalyst and again characterized by analytical methods. As a part of our efforts to the synthesis of DHPM, a variety of catalyst has been used.

6. Acknowledgement

It gives me immense pleasure to express my deep sense of gratitude to my project guide Dr. V. V. Chabukswar, Associate professor for his valuable guidance. I am also thankful to our Principal and HOD Dr. S. L. Bonde for allowing me to carry out project work and extending me all the possible infra- structural as well as instrumental facilities and enriching experience at Research Laboratory. On my personal behalf I would like to thank Kalpana Handore Mam for her constant help, encouragement and co-operation. Last but not the least I would like to thank my project colleague Mr. Harish Kale and all my friends for their help and support.

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