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A GREENER CHEMISTRY APPROACH FOR SYNTHESIS OF 4-(4-HYDROXYPHENYL)-6-METHYL-2-OXO-1,2,3,4 TETRAHYDROPYRIMIDINE-5-CARBOXYLIC ACID ETHYL ESTER

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ABSTRACT: The objective of present research work is to provide green technique for synthesis of 4-(4-Hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester. Pyrimidine derivatives are well known in the pharmaceutical industry and exhibit to possess a broad spectrum of biological activities. Highly efficient and simple methods complying with principle of Green chemistry have been described in this manuscript for the synthesis with competent yields. As part of current studies, we here in report economical practical techniques like- microwave synthesis, mortal-pastel method (mechanochemistry) and by application of green solvents. On completion of reaction the products were characterized by IR, NMR and Mass Spectra. These methods are more convenient and reactions can be carried out in higher yield (80-96%), shorter reaction time (3-30 min) and milder conditions, without generation of pollution and safer to analyst.

INTRODUCTION: Pyrimidine moiety is an important class of nitrogen containing heterocycles and is widely used as a key building block for pharmaceutical agents. Its derivatives exhibit antifungal, analgesic, calcium antagonist and anti-inflammatory activity. In addition, several marine natural products with interesting biological activities containing pyrimidine core have recently been isolated.[1] In the past decade, dihydropyrimidine derivatives have also exhibited important pharmacological properties, as the integral backbone of several calcium channel blocker, anti hypertensive agents, alpha-la-antagonists and neuropeptide Y (NPY) antagonist.

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One of the most potent drug synthesized is 4-subsituted-1,2,3,4-tetrahydropyrimidine derivative, which has been found to be potent anti-hypertensive, calcium channel antagonist that is comparable with standard drug Nifedipine. A classical root to obtain 4-subsituted-1,2,3,4-tetra hydropyrimidine derivatives is by reaction of aldehyde, ethyl acetoacetate and urea refluxed with ethanol, hydrazine hydrate (for 24 hours) following Biginelli reaction. However, method is limited and mostly required long time.[2]

The combination of an aldehyde, β-keto ester, and urea under acid catalysis to give a dihydropyrimidine was first reported by Pietro Biginelli in 1893[3] referred to as the Biginelli reaction. The original Biginelli reaction was carried out by refluxing a mixture of the three components such as ethyl acetoacetate, benzaldehyde and urea in presence of ethanol catalyzed by small amount of HCl which often resulted in poor to moderate yields of desired products.[4] Therefore, several improved reaction protocols for the synthesis of

Biginelli compounds have been reported, either by modification of the classical one-pot Biginelli reaction, novel multi-step methods, use of combinatorial approaches or microwave irradiation techniques.[5]

In further years, improvement in Biginelli compounds is done by using different catalysts such as polyphosphate ester (PPE) [6], Bronsted acids viz. *p*-toluenesulfonic acid [7], potassium hydrogen sulphate [8], chloroacetic acid [9], titanium(IV)chloride[10], ruthenium(III)chloride [11], scandium(III)triflate[12] ,Iodine-alumina [13],Cobalt(II) acetate [14], sulphated zirconia [15] , ferric chloride hexahydrate [16], $MgBr_2$[17] , $nbcl_5$[18], Lewis acids [19, 20] viz. Yb $(OTf)_3$ [21], $InCl_3$ [22], $CuCl_2$ [23], $SnCl_2$ [24], $BF_3.OEt_2$ [25], $ZrCl_4$ [26], L-proline[19], L-proline methylester hydrochloride [27], $ZnCl_2$ [28, 29], Zinc sulphamate [30], combination catalytic system such as tin chloride-lithium chloride [31], cupric chloride-lithium chloride [32], ferric chloride/tetraethyl orthosilicates [33], Trimethylsilyl triflate [34], strontium(II)triflate [35], cadmium chloride [36], methanesulfonic acid [37], Iron(III) [38], ($AlCl_3$+KI) [39], bimetal system , $Cupy_2Cl_2$ [40], Samariumdiiodide [41]. Besides these catalysts, recently $Pb(NO_3)$[3, 42], alkaline phosphates[43, 44, 45] and sulphates [46] have been also employed.

An important area of endeavour in the development of improved catalysts with respect to green chemistry is selectivity enhancement. Basically, this means developing a catalyst that is very selective in what it does, ideally making the right product and nothing else. A highly selective catalyst increases the percentage utilization of raw material (increased percent yield) and decreases the amount of waste by-products from undesired side reactions.[47]

In light of these significances, although a variety of synthetic strategies have been developed for the preparation of tetrahydropyrimidine (THP) derivatives, despite the progress the synthesis of these compounds remains less than ideal. Thus, the development of environmentally friendly benign (*Green Chemistry*), high-yielding and clean approaches for the synthesis of THP derivatives still remains a highly desired goal in organic synthesis. Here, we try to synthesize derivatives by different efficient techniques. Although many research have been come out in this field but application of microwave in this chemical reaction have not been fully understood yet. The use of microwave irradiation in organic synthesis has become increasingly popular within the pharmaceutical and academic arenas, because it is a new enabling technology for drug discovery and development. By taking advantage of this efficient source of energy, compound libraries for lead generation and optimization can be assembled in a fraction of time required by classical thermal methods.

Kappe's group has made great contributions in the area of microwave-assisted Biginelli reactions, Kappe has published an effective Biginelli synthesis assisted by microwaves.[48] The original Biginelli reaction was carried out by refluxing a mixture of the three components such as ethyl acetoacetate, benzaldehyde and urea in presence of ethanol catalyzed by small amount of HCl [49] which often resulted in poor to variable yields of desired products (20-70%) [6]. Fabio S. Falsone and C. Oliver Kappe[6] reported a method of preparation of Ethyl-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate.

Water being the cheapest solvent, is non-toxic, and is nonhazardous. Research using water as a solvent is targeted at the development of highly productive, environmentally safe, recyclable techniques, which can be promoted to large-scale applications. In addition water is useful in biphasic processes in conjunction with other solvents. However, the cleanup of aqueous waste is still difficult and the purification requires extensive energy.[50] Mechanochemistry means mechanical breakage of intramolecular bonds by external force and must be differentiated from molecular solid-state chemistry.

Grinding, milling, shearing, scratching and polishing provide the mechanical impact for mechanochemistry.[51] The pioneering work of Toda [52] has shown that many exothermic reactions can be accomplished in high yield by just grinding solids together using mortar and pestle, a technique known as 'Grindstone Chemistry' which is one of the 'Green Chemistry Techniques'. Reactions are initiated by grinding, with the transfer of very small

amounts of energy through friction. In addition to being energy efficient Grindstone Chemistry also results in high reactivity and less waste products. Such reactions are simple to handle, reduce pollution, comparatively cheaper to operate and may be regarded as more economical and ecologically favourable procedure in chemistry. Solid-state reactions occur more efficiently and more selectively than does the solution reaction.[52]

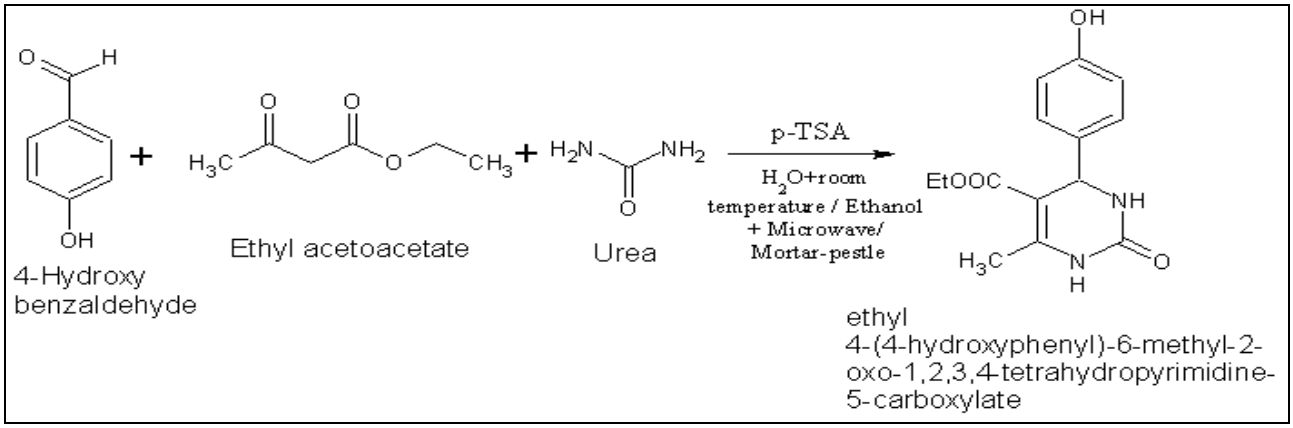
This method is superior to conventional method; since it is eco-friendly, high yielding requires no special apparatus, non-hazardous, operationally simple and convenient [53]. Here we used simple mortar and pastel for grinding purpose and microwave irradiation to complete the reaction.

Melting points of the synthesized heterocyclic compound was determined on Gallenkamp's apparatus, Model No. IC0949 and were uncorrected. The purification of synthesized compounds was performed by recrytallization with appropriate solvent system. Magic cook (Model no. 20S, Mech) Manufacturer: Whirlpool, 600W, 50 Hz frequency, 230 Volt AC with timer was used for microwave irradiation. Nuclear Magnetic Resonance spectra were recorded with Bruker-Avance-III, 400MHz, Switzerland. Infrared spectra were recorded on FTIR spectrophotometer Bruker-Tensor 27, Germany. Mass spectra were recorded in Bruker-MicrOTOFQ-II, Germany. All spectral analysis was performed in ambient condition.

Materials:

All the Chemicals and reagents used for the study were of analytical grade, 4-Hydroxybenzaldehyde, and Urea (extra pure) were procured from Lobachem, Mumbai. p-TSA (p- Toluene Sulphonic Acid, monohydrate) was procured from Rankem. Ethanol, Diethyl acetoacetate were procured from MERCK, Germany. Water used in the study was extra pure double distilled. Acetic Acid Glacial (extra pure) was procured from SDFCL, Mumbai.

General scheme for the synthesis:



4-(4-HYDROXYPHENYL)-6-METHYL-2-OXO-1,2,3,4-TETRAHYDROPYRIMIDINE-5-CARBOXYLIC ACID ETHYL ESTER

was prepared following a general reaction as stated above. The various experimental routes followed for the synthesis is as given below:

Method A: 4-Hydroxybenzaldehye (0.122 gm, 0.001 mol), Ethylacetoacetate (0.127 ml, 0.001 mol) and Urea (0.132gm, 0.002 mol) was taken in a flat bottom flask, ethanol (5 ml) as a solvent and p-TSA (0.034gm, 0.002mol) were added simultaneously to the above mixture. The mixture was irradiated for 3 minutes (30 second interval @ 20 power level). After completion of reaction, cooled reaction mass was poured on ice, solid separated was filtered, washed with water, oven dried and crude product crystallised in water and glacial acetic acid.

Method B: 4-Hydroxybenzaldehye (0.122 gm, 0.001 mol), Ethylacetoacetate (0.127 ml, 0.001 mol) and Urea (0.132gm, 0.002 mol) were taken in a flat bottom flask, water as a solvent and p-TSA (0.034gm, 0.002mol) were added simultaneously to the above mixture. The mixture was stirred vigorously at room temperature for 30 minutes. After completion of reaction, solid separated was filtered, washed with water, dried in oven and

crude product crystallised in water and glacial acetic acid.

Method C: 4-Hydroxybenzaldehye (0.122 gm, 0.001mol), Ethylacetoacetate (0.127 ml, 0.001mol), Urea (0.132gm, 0.002 mol) and p-TSA (0.034gm, 0.002mol) were taken in mortar and pestle, grounded for 4-5 minutes. This syrupy reaction mixture solidified within 15 minutes. Solid separated was filtered, washed with cold water and crude product crystallised in mixture of water and glacial acetic acid.

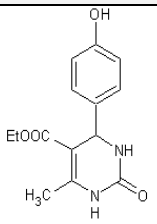
Spectroscopical studies:

IR: Characteristic IR (KBr) bands found at: 3510.63, 3150.20, 1674.20, 1596.10, 1452.33, 831.42, 776.55, 707.62, 646.66 (νmax/cm-1).

1H-NMR: (400MHz, $CDCl_3$), δ ppm 10.59, 9.78, 9.56, 9.32, 9.11, 7.64, 7.74, 7.62, 7.05, 7.03, 6.94, 6.92, 6.70, 6.69, 5.51, 5.06, 3.97, 3.95, 3.47, 2.50, 2.24, 2.07, 1.90, 1.10, 1.08.

MS (m/z): Anal.calcd for $C_{14}H_{16}N_2O_4$, 276 (calc.), 277 (exp.).

TABLE 1: COMPARISON BETWEEN TRADITIONAL SYNTHESIS AND GREEN TECHNIQUES

Sr. No.	Compound	Parameter	Traditional method	Green Techniques		
				A	B	C
1	 4-(4-Hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetra hydropyrimidine-5-carboxylic acid ethyl ester	Time Required	3-4 hrs	3 min	30 min	4-5 min
2		% Yield	71	96	80	90
3		Melting point(°C)	236-238	236	238	236

Organic reactions using water as the medium suffer from a serious disadvantage, the non-homogeneity of the reaction mixture because most of the organic chemicals are almost insoluble in water and this results in decrease in reaction rates many folds or sometimes reaction does not happen at all. This problem can be overcome by providing the activation energy to the reaction by using microwave irradiation. The microwave dielectric heating effect uses the ability of some liquids and solids to transform electromagnetic energy into heat and thereby drive chemical reactions.

This in situ mode of energy conversion has many attractions for chemists, because its magnitude depends on the properties of the molecules. This allows some control of the material's properties and may lead to reaction selectivity. There are a variety of methods for carrying out microwave-assisted organic reactions using domestic or commercial ovens; this is basically known as microwave-induced organic reaction enhancement (MORE) chemistry. Most of the published chemistry has been performed using domestic microwave ovens. The key reasons for using a device intended for heating food items to perform synthesis are that they are readily available and inexpensive.[54]

Anil Kumar Jogula et al.,[55] used Cyanuric chloride as a new catalyst for the one-pot Biginelli reaction coupling of β-ketoester, aldehydes and urea to afford the corresponding tetrahydropyrimidinones. The reaction time required was 12 hrs, with 80% yield and the melting point to be within 198-200°C. While when we synthesized the same compound viz.

4-(4-Hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester under the presence of p-TSA using 4-hydroxybezaldehye, ethyacetoacetate, ethanol and urea applying microwave irradiation, we observed a yield of 96% within 3 minutes reaction time and melting point was 236-238°C. Yadav et al.,[56] performed microwave assisted synthesis of tetrahydropyrimidinones in presence of TTSA.

They irradiated equimolar mixture (2 mmol each) of aldehyde, β-keto ester and urea or thio-urea in

acetonitrile, with catalytic amount of TTSA (3 mol%) and the contents were irradiated to microwave (450 wt) at the interval of 10 sec. They found the yield of 4-(4-Hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester to be 95% and melting point 201°C.

In the course of studies on green chemistry one of our goals has been to redesign conventional and time honoured synthetic methods and make them more eco-friendly and consistent with higher atom economy (i.e., less chemical waste). We have now come to the conclusion that the traditional procedures for many reactions are inefficient and involve unnecessary steps. Heating under reflux for several hours is logical for endothermic reactions. For exothermic reactions, however, such energy input would be superfluous.

The convenience and the time saving that results from the use of Grindstone Chemistry—for small scale as well as large scale reactions—is illustrated here in our work by describing the successful application of this technique to the multicomponent Biginelli reaction. We employed p-toluene sulfonic acid (p-TSA), an inexpensive and common organic chemical, which was an efficient catalyst for this reaction.

Bose et al.,[28] synthesized tetrahydropyrimidinone using grindstone technique and found the yield to be 95%, with melting point 236–238°C. While Sun et al.,[57] also reported the melting point of the compound to lie between 236–238°C. Ushati Das et al.,[58] also synthesized Ethyl 4-(4-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate monohydrate using 4-Hydroxy benzaldehyde, ethyl acetoacetate, urea and p-TSA in mortar and pestel (yield 95%, m.p. 509–511 K). The observations by Ushati et al.,[58] and Bose et al.,[28] were almost similar to those noted by us under solvent free conditions of grindstone technique in terms of yield (our yield 90%, m.p. 236°C) and at a reaction time of 4-5 minutes.

Ethyl-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydro pyrimidine-5-carboxylate was prepared by method reported Fabio S. Falsone and C. Oliver Kappe[6]. According to this method, A mixture of ethyl acetoacetate (0.15 mole, 19.7 gm, 99%), benzaldehyde (0.1 mole ,10.6 gm), Urea (0.1 mole, 6.0 gm) and in 250 ml ethanol was refluxed for 3 to 4 hours in presence of few drops of conc. HCl. The mixture was frozen and the product was separated, filtered and dried. It was purified by column chromatography technique and recrystallized from ethanol. The IR spectra for this compound showed a strong absorption band at 1722 for C=O cm^{-1} ester and 1HNMR spectra shows triplet-quartet pair at 1.35 and 4.28 ppm, which indicated formation of compound.[59]

Mohideen et al.,[60] synthesized Ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine – 5 - carboxylate by grounding a mixture of benzaldehyde (0.106 g, 1 mmol), ethyl acetoacetate (0.130 g, 1 mmol) and urea (0.070 g, 1.17 mmol) with four drops of *ortho* phosphoric acid for about 30 minutes. The reaction mixture was cooled for 15 minutes and poured into a beaker containing 50 ml of cold water. The precipitate obtained was filtered, washed with water and ethanol to get white solid (0.26 g, 92% yield; mp 203–204). Physiologically active tetrapyrimidinones were successfully prepared by Biginelli reaction by grinding aryl aldehydes, ethylacetoacetate and urea/ thiourea in presence of p-toluenesulphonic acid at room temperature.[28]

The Biginelli reaction is important for the preparation of dihydropyrimidine derivatives and excellent results are found for reactions carried out with microwave enhancement as observed by Hayes et al.,[61] He found that single-mode cavities offer more consistent and predictable energy distribution. Single-mode instruments produce one homogeneous, intense pocket of energy that is highly reproducible. Due to their uniform energy distribution and higher power density, these systems typically couple more efficiently with small samples.[61]

Microwave heating is able to reduce side reactions, increase yields, improve reproducibility, allow control of temperature and pressure, and even realize impossible reactions by conventional heating.[62] The practical utility of MW assisted green protocols has been realized in several synthetic operations such as protection/deprotection condensation, oxidation, reduction, rearrangement

reaction and in the synthesis of various heterocyclic systems.[63] Microwave irradiation technique leads to separation side products, which ultimately results in high yields of required products and easy workup procedure [64] as also observed by us.

In recent years, multi-component reactions have attracted the attention of organic chemists because they are more efficient and cost effective. Further, these reactions csan be carried out without isolation of the intermediates (One pot and one step synthesis) and avoid the protection deprotection strategies in the synthesis as well as time consuming purification processes. It is well known that Biginelli reaction is an acid catalyzed versatile one pot multi-component reaction for the synthesis of 3, 4-dihydropyrimidin-2(1*H*)-one / thione derivatives. The reaction occurs via formation of metal-enolate ion pairs and metal-*N*-acylimine intermediates which govern the overall progress of Biginelli reaction. The stabilization of *N*-acylium intermediate by the cation of the catalyst is the exact mechanism involved in this reaction.[65-67]

CONCLUSION: In conclusion, microwave technique is advantageous over conventional methods due to shorter reaction times, dry media (thus avoiding the use of harmful solvents), cleaner reactions, easy work up, and minimization of thermal decomposition products for synthesis of 4-(4-Hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydro pyrimidine-5-carboxylic acid ethyl ester. Compared with traditional methods, the applied methods are more convenient and reactions can be carried out in higher yield, shorter reaction time and milder conditions, without generation of pollution and safer to analyst.

It can be concluded that the microwave assisted method is an efficient, fast, simple and environment friendly method for the synthesis of a large number of organic heterocyclic molecules. In addition there is an increase in the yield. Hence it is a viable and feasible method for performing the synthesis of drug, intermediates and chemicals. However, these efforts do not mean that everything is known, and there is still a lot to learn about this fascinating and useful reaction.

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