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CES Catalysed Ecofriendly Synthesis of 4-Bromo-2-Acetyl-1-Naphtholdihydropyrimidinone in PEG 400 and Study of their Antimicrobial Activity

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ABSTRACT

synthesis of 4-substituted-2-acetyl-1-naphtholdihydropyrimidinone and derivatives of some substituted dihydropyrimidinones were carried out by using ecofriendly and cheaper available green catalyst such as CES (calcinated egg cell) in environmentally benign reaction solvent medium PEG 400 in a short period of time. The structure of all synthesized compounds were confirmed by modern analytical techniques such IR and NMR. C, H, N Elemental analysis was also carried out by standard instruments.

1. INTRODUCTION

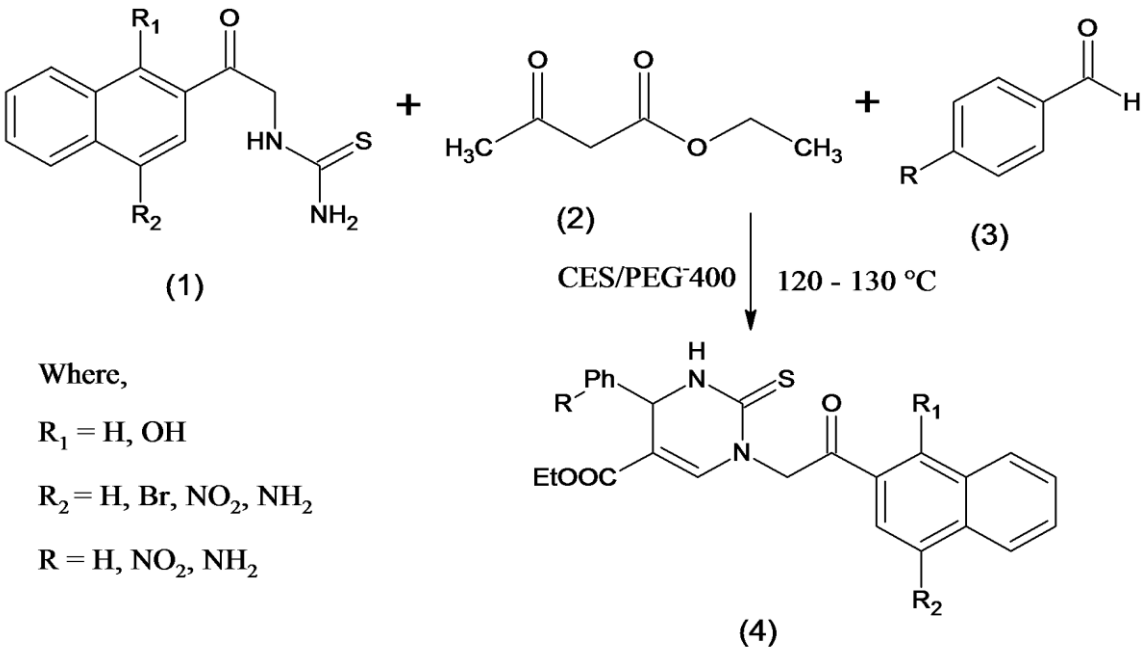
Nitrogen containing heterocyclic compounds are biologically and pharmacologically most important compounds utilized in various type of drug development processes[1]. 1, 4-Dihydropyrimidinones (DHPMs) comprise of a pyrimidine scaffold having a resemblance with the structures of nucleic acid bases found in DNA and RNA. Their involvement as bases in nucleic acids has a great significance in drug design[2]. The dihydropyrimidinones possess interesting and versatile biological activities, such as antiviral, antitumor, antibacterial, and anti-inflammatory properties as well as calcium channel modulating activity [3-4]. Recent progress in the DHPM class of anticancer agents like monastrol, an inhibitor of human kinesin Eg5[5-6], has received the attention for efficient pharmacophore variation of Biginelli DHPMs. Human kinesin Eg5 plays a crucial role in bipolar spindle generation during mitosis, inhibition of which leads to mitotic arrest and subsequent apoptotic cell death[7]. It is therefore considered as one of the promising targets in cancer chemotherapy. Racemic dihydropyrimidinone is reported to be an allosteric inhibitor of Eg5[8], and unlike taxanes, it is nontoxic to neuron cells[9-10]. More recently, they have emerged as integral backbones of several calcium blockers, antihypertensive agents, α-1a-antagonists, and neuropeptide Y (NPY) antagonists[11]. Pyrimidinone derivatives are found as core units in many marine alkaloids (batzelladine and carambine), which have been known to be potent HIV-gp-120 CD4 inhibitors[12]. Some work has also been devoted to gain insights into the structure-activity relationship in the monastrol derivative series[13]. Recently, Dennis Russowsky and coworkers described the differential effects of monastrol, oxo-monastrol and oxygenated analogs on seven human cancer cell lines[14].

Due to remarkable application of dihydropyrimidinone derivative in biological, pharmaceutical and agricultural field its synthesis has attracted many researchers and scientists. There are various methods reported in literature for the synthesis of dihydropyrimdinone. First reported synthesis of DHMP was carried out by Italian chemist before 120 years in 1891 by Pietro Biginelli, is a multiple-component chemical reaction that creates 3,4-dihydropyrimidin-2(1H)-ones from ethyl acetoacetate, an aryl aldehyde (such as benzaldehyde) and urea[15-18]. This synthesis of DHMP is now popularized as Biginelli reaction in the name of Pietro Biginelli[19-20]. Recently many reports have disclosed one-pot synthesis of variants of Biginelli-type reactions for preparation of novel DHPMs using various active methylene compounds[21-27], such as

enaminone, cyclic β-diketones, acetophenone, benzocyclic ketones and β-oxodithioesters etc., have also been developed to be carried out in the presence of a Lewis or protic acid. Dihydropyrimidinone derivative can also be synthesized by utilizing variety of catalysts such as phosphorus pentoxide-methanesulfonic acid[28], potassium ter-butoxide (t-BuOK)[29], ammonium dihydrogen phosphate[30], silica-gel[31], mesoporous molecular sieve MCM- 41[32], cyanuric chloride[33], nano-$BF_3 \cdot SiO_2$[34], silica gel supported polyphosphoric Acid[35], zirconium(IV) chloride[36], and indium(III) bromide[37]. Synthesis of DHMPs were also carried out by molecular iodine[38] by utilizing modern heating techniques such as microwave induced heating[39], solid-support[40], ionic liquids[41], Lewis acid catalysts such as LiBr[42], NH_4Cl[43].The above methods available for synthesis of dihydropyrimidinone suffer from several drawbacks mainly long reaction time. Also the solvent and catalyst used for preparation of DHMP are very hazardous to the environment. Therefore it is necessary to develop new method for synthesis of DHMPs, which comes under green chemistry parameter. Considering the above facts, authors reported the new reaction medium and green catalyst for efficient synthesis of new class of substituted derivative of DHMP.

In the present research work we report synthesis of substituted derivatives of Dihydropyrimidinone using cheap and easily available catalyst such as calcinated egg cell and non toxic solvent Polyethylene glycol-400 as an attempt to develop a method wherein green chemistry parameter will be maintained.

Accordingly the synthesis of 4-substituted-2-acetyl-1-naphtholdihydropyrimidinone (4) were carried out by the action of 1-[2-(4-Substituted-1-hydroxynaphthalen-2-yl)-2-oxoethyl] thiocarbamide (1) with ethylacetoacetate (2) and substituted banzaldehyde (3) in PEG-400 Medium using CES as a catalyst (Scheme -1)



Where,

R_1 = H, OH

R_2 = H, Br, NO_2, NH_2

R = H, NO_2, NH_2

(Scheme-1)

2. Experimental

2.1 MATERIALS AND METHODS

All chemicals used in the study were of AR grades. The melting points of all the synthesized compounds were recorded using hot paraffin bath. The Carbon and Hydrogen analysis was carried out on Carlo-Ebra 1106 analyser. Nitrogen estimation was carried out on Colman-N-analyzer-29. IR spectra were recorded on Lambda Scientific Pvt Ltd spectrometer in the range 4000-400 cm^{-1} in KBr pellets. PMR spectra were recorded on Brucker AC-500F spectrometer with TMS as internal standard using $CDCl_3$ and DMSO-d_6 as solvent. The purity of compound was checked on silica Gel-G plates by TLC with layer thickness of 0.3 mm.

2.1.1 Procedure For Synthesis of 4-Bromo-2-Acetyl-1-Naphtholdihydropyrimidinone(4a)

1-[2-(4-bromo-1-hydroxynaphthalen-2-yl)-2-oxoethyl]thiocarbamide (1a) (1.0 mmol), ethhylacetoacetate (2a), benzaldehyde (3a), 20% mmol of CES in 5ml distilled water and PEG 400 (25 mL) was taken in a 100 ml round bottom flask and refluxed the reaction mixture on oil bath for 1 hour between temperature 120^0 to 130^0C. Completion of the reaction was monitored by thin layer chromatography (N-Hexane: Ethyl acetate 90:10). The hot reaction mixture was filtered to remove the CES catalyst. The mixture was poured in to the crushed ice with constant

stirring followed by filtration and washing with distilled water. The crude product was dried and recrystallized from ethyl alcohol. The generated product (4a) was subjected to characterization in terms of Solid analysis, IR and NMR techniques. The yield of the dried crude product was found to be 0.80g (80%). Melting Point.286^{o}C Colour of compound (4a) - Yellow Colour solid Analysis: Calculated for $C_{25}H_{21}BrN_2O_4S$: C, 57.15 %; H, 4.03%; N, 5.33%; Found:C, 60.65%; H, 4.55%; N, 5.70%. IR (KBr, cm^{-1}): 3548.38cm^{-1}, 3444.24 cm^{-1}, 1288.22 cm^{-1}, 1214.93 cm^{-1}, 1697.06 cm^{-1}, 1639.20 cm^{-1}, 1022.09 cm^{-1}, 3131.83 cm^{-1}, 1450.21 cm^{-1}. NMR (500 MHz, CdCl3): δ 4.08(s, 1H, OH), δ 2.69(s, 1H, NH), δ 2.42(s, 1H, -N-CH), δ 4.29(s, 1H, COO-CH), δ 3.45(s, 1H, -C=C-H), δ 2.27 (s, 1H, CH-C=O), δ 7.26 -8.53(m, 5H,-$C_{10}H_5$)

2.1.2 Procedure For Synthesis Of 4-Nitro-2-Acetyl-1-Naphtholdihydropyrimidinone(4b)

1-[2-(4-Nitro-1-hydroxynaphthalen-2-yl)-2-oxoethyl]thiocarbamide (1b) (1.0 mmol), ethhylacetoacetate (2a), benzaldehyde (3a), 20% mmol of CES in 5ml distilled water and PEG (25 mL) was taken in a 100 ml round bottom flask and refluxed the reaction mixture on oil bath for 1 hour between temperature 120^{0} to 130^{0}C completion of the reaction was monitored by Thin layer chromatography (N-Hexane: Ethyl acetate 90:10). The hot reaction mixture was filtered to remove the CES catalyst. The mixture was poured in to the crushed ice with constant stirring filtered and washed with distilled water. The crude product was dried and recrystallized from ethyl alcohol. The generated product (4b) was subjected to characterization in terms of Solid analysis, IR and NMR techniques. The yield of the dried crude product was found to be 0.85 g (85%). Melting Point.- 296^{o}C.Colour of compound (4b) - Yellow Colour solid Analysis: Calculated for $C_{25}H_{21}N_3O_6S$: C, 61.09%; H, 4.31%; N, 8.55%. Found: C, 62.07 %; H, 5.02%; N, 8.11%. IR (KBr, cm^{-1}): 3590.81 cm^{-1}, 3436.53 cm^{-1}, 1284.36 cm^{-1}, 1214.93 cm^{-1}, 1697.05 cm^{-1}, 1643.05 cm^{-1}, 1589.06 cm^{-1},1334.50 cm^{-1}, 3100.97 cm^{-1}, 1496.49 cm^{-1}. NMR (500 MHz, CdCl3): δ 4.34 (s, 1H, OH), δ 2.87(s, 1H, NH), δ 2.42 (s, 1H, -N-CH), δ 4.29 (s, 1H, COO-CH), δ 1.33 (s, 1H, -C=C-H), δ 2.87 (s, 1H, CH-C=O), 7.27 -8.31 (m, 5H,-$C_{10}H_5$)

2.1.3 Preparation of Catalyst

Approximately 94% of a dry egg shell is calcium carbonate and has a typical mass of 5.5 grams[35]. Waste egg shells were collected and washed to remove the undesirable sticky material with plenty of water. The cleaned egg shells were placed in an oven to dry completely. The

dried egg shell was crushed in mortar and pestle to a fine powder. The powder in muffle furnace was introduced to calcinate at 900^0C. After heating 2-3 hours, thermal decomposition of Egg Shell (calcium carbonate) gives a white soft powder, calcinated egg cell (CES). The CES was subjected to characterization by XRD.

Characterization of catalyst by XRD: XRD of CES is compared with XRD of CaO which shows the formation of CaO from calcinations of egg Shell.

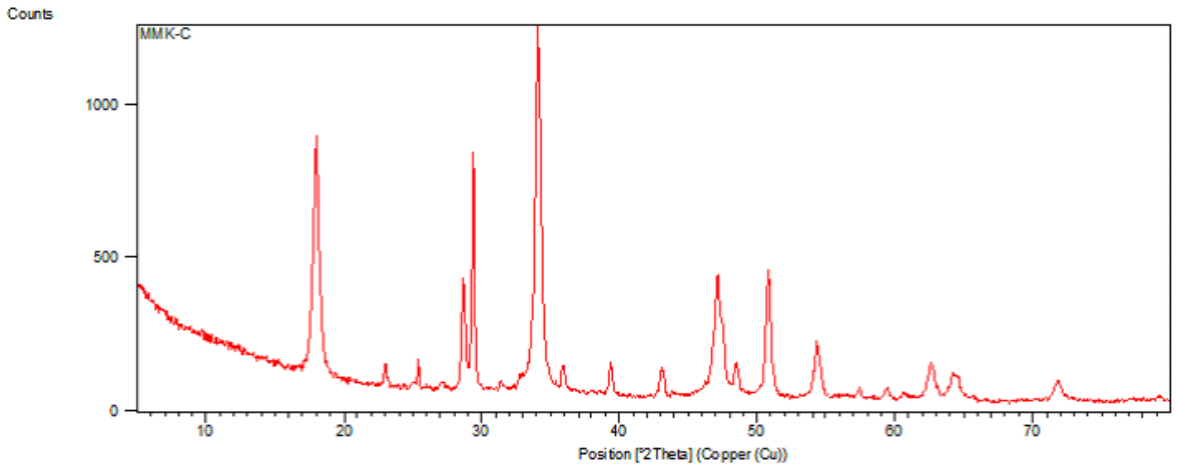


Figure 1: XRD of CaO

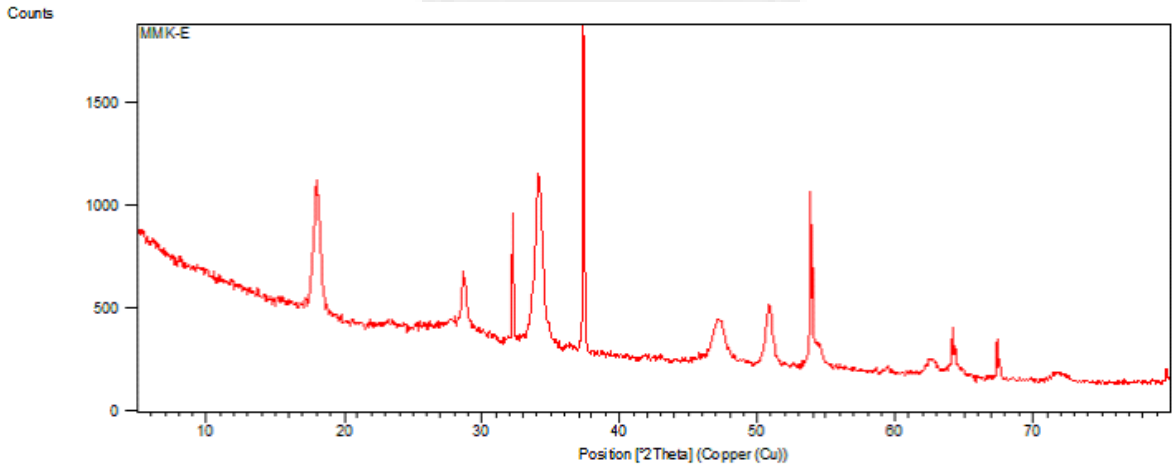


Figure 2: XRD of CES

Table: 1.1: Reaction of 1-[2-(4-bromo-1-hydroxynaphthalen-2-yl)-2oxoethyl]thiocarbamide (1a), ethtylacetoacetate (2a), benzaldehyde (3a) and CES

Sr. No.	Medium	Quantity of medium (ml)	Time Duration in Hours.	Yield (%)	M.P (^{0}C)
1.	Acetone	40	1.5	40	288
2.	Ethanol	25	12	50	288
3.	DMF	30	2	60	287
4.	PEG-400	25	1	80	288
5.	Acetic acid	30	3	65	289
6.	Isopropyl alcohol	30	3	50	287

Table: 1.2 Effect of catalyst concentration on synthesis of 4-bromo-2-acetyl-1-naphtholdihydropyrimidinone (4a)

Sr. No.	Catalyst mol %	Time Duration in hours	Yield (%)
1.	5	3	30
2.	10	2.30	45
3.	15	3	65
4.	20	1	80
5.	25	1	72
6.	50	2	60

Table 1.3 Synthesis of different dihydropyrimidinones

Sr. No.	Expt. No.	Compound	Yield % w/w??	M.P ^{0}C	Colour
1	3	4-amino-2-acetyl-1 naphtholdihydropyrimidinone (4c)	75%	283^{0}C	Dark Yellow
2	4	4-bromo-2-acetyl-1-naphtholnitrodihydropyrimidinone (4d)	80%	289^{0}C	Yellowish Brown
3	5	4-bromo-2-acetyl-1 naphtholaminodihydropyrimidinone (4e)	70%	281^{0}C	Brownish
4	6	4-nitro-2-acetyl-1-naphtholnitrodihydropyrimidinone(4f)	80%	243^{0}C	Yellow
5	7	4-nitro-2-acetyl-1-naphtholaminodihydropyrimidinone(4g)	72%	190^{0}C	Yellow
6	8	6-bromo-1-acetyl-2-naphtholdihydropyrimidinone (4h)	73%	143^{0}C	Dirty Yellow
7	9	6-nitro-1-acetyl-2-naphtholdihydropyrimidinone (4i)	75%	216^{0}C	Yellow

2.1.4 Antimicrobial Screening

From the above synthesized Dihydropyrimidinones compounds some of them were screened *in vitro* for their bactericidal activity against Gram positive bacteria (*Staphylococcus aureus*) and Gram negative bacteria (*Escherichia Coli, Salmonella typhi, Klebsiella pneumoniae* and *Shigella dysenteriae*). Further these were screened for their fungicidal activity against *Aspergillus niger* and *Candida albicans*.

The antimicrobial screening of above compounds were carried out by agar-well diffusion method. In this method the antimicrobials are allowed to diffuse out into the medium and interact in a plate freshly seeded with the test organisms. The resulting zones of inhibition will be

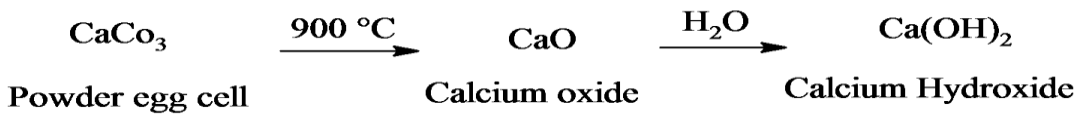
uniformly circular as there will be a confluent lawn of growth. The diameters of zone of inhibition can be measured in millimeters.

Table 1.4 Antimicrobial activities of synthesized compounds against various microbes

Compound	Activity																				
	Candida albicans			***Aspergillus niger***			***Salmonella typhi***			***Shigella dysentarie***			***Escherichia coli***			***Staphylococcus aureus***			***Klebsiella pneumoniae***		
	10 µl	20 µl	30 µl	10 µl	20 µl	30 µl	10 µl	20 µl	30 µl	10 µl	20 µl	30 µl	10 µl	20 µl	30 µl	10 µl	20 µl	30 µl	10 µl	20 µl	30 µl
4a	-	-	-	Y	Y	Y	Y	Y	Y	-	-	-	-	-	-	-	-	-	-	-	-
4b	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

3. RESULTS AND DISCUSSION

The waste Egg cell contains calcium carbonate ($CaCO_3$) and when we heat the powdered form of egg cell in muffle furnace above 900^0C it gets converted into calcium oxide (CaO). The process of conversion of calcium carbonate into calcium oxide is known as calcination and the product obtained is said to be calcinated egg cell, abbreviated as CES. Calcium oxide (CaO) in water converted in to calcium hydroxide $Ca(OH)_2$ as shown below.



This calcium hydroxide acts as a base catalyst during synthesis dihydropyrimidinone. In the present research work, synthesis of 4-bromo-2-acetyl-1-naphtholdihydropyrimidinone (4a) from 1-[2-(4-bromo-1-hydroxynaphthalen-2-yl)-2-oxoethyl] thiocarbamide (1a) Ethylacetoacetate (2a), benzaldehyde (3a) and CES as a catalyst in PEG 400 and other various medium were

carried out and the time required for completion of reaction were noted. It was observed that the time required for completion of reactions is in between 1 to 1.30 Hours. Also the method utilizes ecofriendly and biocompatible solvent PEG 400, avoiding environmentally hazardous and toxic organic solvents. . The method proposed herein proves to be advantageous over conventional methods as it reduces time duration required for completion of reaction, and maintains the green chemistry parameters. The reactions were carried out in PEG 400 mediums and in various other solvent medium it was observed that the time required to complete the reaction in Polyethylene glycol 400 medium was reduced as compared to the other medium as well as yield also increased as shown in Table 1.3

4. CONCLUSIONS

We have developed an efficient PEG promoted and CES catalyzed method for the synthesis of mono and di substituted dihydropyrimidinone with good yield. The results further demonstrated the importance of PEG promoted synthesis in terms of avoiding hazardous organic solvents and toxic catalysts. The proposed method requires comparatively short duration of reaction which meets the criteria of green chemistry.

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