Citric Acid Catalyzed Synthesis of Dihydropyrimidinones under Solvent Free Conditions

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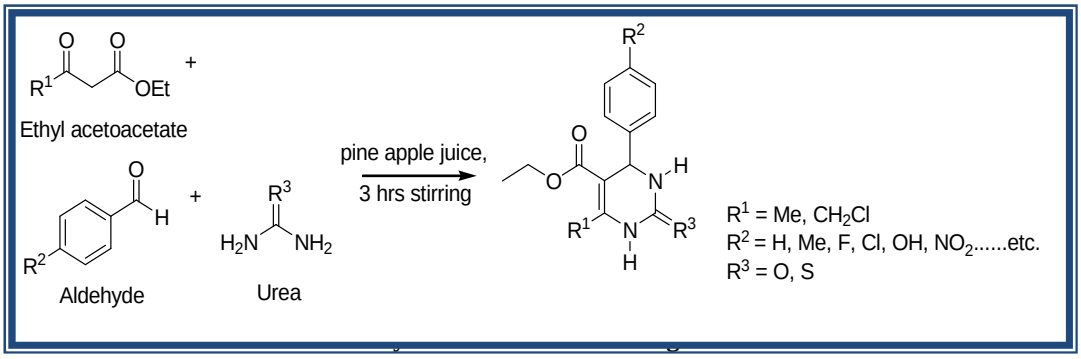
Abstract : **Multicomponent reactions (MCRs) as an inspiration to quickly design straightforward entrances to large compounds families of novel, especially the synthesis of dihydropyrimidinone via., Biginelli condensation found to have larger reaction time with poor yield using various catalysts. An efficient and greener way to three component one pot synthesis of aliphatic (acetaldehyde) and aromatic (benzaldehyde) based dihydropyrimidinone derivatives were discussed. The synthesised compounds were subjected to various spectral characterised viz., FTIR, ^{1}HNMR etc., The results of spectral studies confirmed the formation of the product. The solvent free and eco-friendly approach offers room temperature, pollution free and shorter time duration with excellent yield. The antibacterial activity among aliphatic and aromatic substituted based dihydropyrimidinone have also been compared.**
Keywords: dihydropyrimidinone; green synthesis; citrus fruits; three component one pot synthesis; spectral studies.

I. INTRODUCTION

Multicomponent reactions (MCRs) are synthetic tool for generating structurally complex molecular entities with fascinating biological properties through the formation of several carbon-carbon and carbon-heteroatom bonds in a one-pot operation and especially when these syntheses are coupled with combinatorial strategies [1]. The Italian chemist Pietro Biginelli (1893, University of Florence) for first time reported on the acid-catalyzed cyclo condensation reaction of ethyl acetoacetate, benzaldehyde, and urea [2]. The three components reaction mixture in ethanol was simply heated with a catalytic amount of HCl at reflux temperature and the product that precipitated on cooling the reaction mixture was identified as 3,4-dihydropyrimidin-2-1(H)-one. Since, the Biginelli products, DHPMs, can act as calcium channel blocker, antihypertensive agents and α-la-antagonist [3]. In general, Lewis acids including $BF_3.OEt_2$ [4], $CdCl_2$ [5] to catalyse the Biginelli reaction. The limitations of the catalysts were found in the literature viz., long reaction time, elevated reaction temperature, harsh reaction conditions, use of expensive reagents, moderate yields of the products. The present investigation focused on the utilization of extract of pineapple as natural catalyst for synthesis of dihydropyrimidinone. The formations of DHPMs were confirmed using various spectral techniques viz., FTIR and ^{1}HNMR.

II. EXPERIMENTAL

The chemicals benzaldehyde **(1),** ethylacetoacetate **(2),** Urea **(3)**, were obtained from Avra chemicals, Hyderabad and were used as such. Siliga gel (TLC and Column grade) were purchased from Merck. ^{1}H NMR (300 MHz) spectra were recorded on a Bruker Advance III 400 MHz multi nuclei solution NMR. FTIR spectra (KBr pellets) were measured on the Alpha Bruker FTIR instrument scanning the entire region of 4000 - 400 cm^{-1} with typical resolution of 1.0 cm^{-1}.



A. Synthesis of 5-ethoxycarbonyl-6-methyl-4-phenyl-3, 4-dihydro pyrimidin-2(1H) - one(4)

The equimolar quantities of benzaldehyde (1.30g, 10mmol), ethyl acetoacetate, (1.30g, 10mmol) and urea (0.6g, 10mmol), in 1ml pineapple juice were stirred for 3 hours at room temperature with monitoring by TLC. The yellow solid obtained was then recrystallized with ethanol to get fine yellow crystals of **4 (M.P 207^{0} C).** The formation of the compound have been confirmed using various spectral techniques viz., IR, NMR .

B. Synthesis of 5-ethoxycarbonyl-4, 6-dimethyl-3, 4-dihydro pyrimidin-2(1H) one (5)

The equimolar quantities of acetaldehyde (0.44g, 10mmol), ethyl acetoacetate, (1.30g, 10mmol) and urea (0.6g, 10mmol), in 1ml pineapple juice were stirred for 3 hours at room temperature with monitoring by TLC. Then the reaction mixture was filtered, washed with little water. The yellow solid obtained was then recrystallized with ethanol to get fine yellow crystals of **5 (M.P 167^{0} C)**. The formation of the compound **5** was confirmed by IR, NMR.

5-ethoxycarbonyl-6-methyl-4-phenyl-3, 4-dihydro pyrimidin-2(1H) - one (4)

IR (KBr pellet, cm^{-1}) 3236 (N-H), 1705 (C=O), 1454 (C=C)

^{1}H NMR ($CDCl_3$) δ 1.19 (t, 3H, -OCH_2CH_3), 2.3 (s, 3H, -CH_3), 3.43 (q, 2H, -OCH_2CH_3), 5.2(s, 1H, -NH), 9.2 (s, 1H, -NH), 7.2-7.7 (m, 5H, Ar-H),

5-et**hoxycarbonyl-4, 6-dimethyl-3, 4-dihydro pyrimidin-2(1H) one (5)**

IR (KBr pellet, cm^{-1}) 3234 (N-H), 1703 (C=O), 1651 (C=C)

^{1}H NMR ($CDCl_3$)	δ 1.27 (t, 3H, -OCH_2CH_3), 1.69 (s, 3H, -CH_3), 2.28 (s, 3H, -CH_3), 4.19 (q, 2H, -OCH_2CH_3), 4.43(s, 1H, -CH), 5.5 (s, 1H, -NH), 7.26 (s, 1H, -NH)

III. RESULTS AND DISCUSSION

FTIR Spectrum compound 4

The FTIR spectrum of the **4,** the intense band at 3236 cm^{-1} due to the N-H stretching viberation, the intense band at 1705 cm^{-1} are associated with stretching vibration of C=O group. The presence of medium intensity band at 1606 cm^{-1} due to stretching vibration of C=C group.

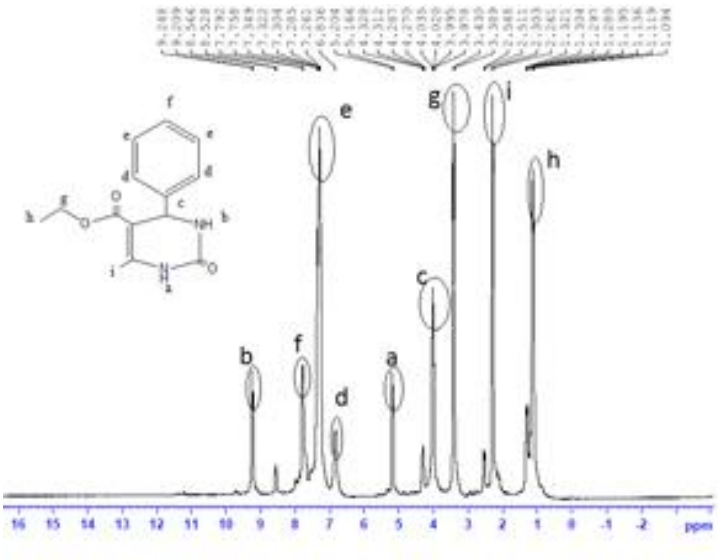


Figure 1. NMR Spectrum of compound 4

The NMR spectrum of the **4** is shown in Figure 1. A triplet at 1.19δ, equivalent to 3H, indicates the methyl protons adjacent to methylene group (-OCH_2CH_3). A singlet at 2.3δ, equivalent to 3H, indicates the methyl protons adjacent to NH and C=C. A quartet at 3.43δ, equivalent to 2H, indicates methylene protons adjacent to methyl group (-OCH_2CH_3). A singlet at 5.2δ, equivalent to 1H, indicates NH protons (a). A singlet at 9.2δ, equivalent to 1H, indicates NH protons (b). A triplet at 6.85δ, equivalent to 2H, indicates two aromatic protons in benzene ring. A multiplet at 7.2-7.7δ, equivalent to 5H, indicates aromatic protons in benzene ring. A singlet at 4.03δ, equivalent to 1H, indicates one proton adjacent to aromatic ring.

FTIR Spectrum compound 5

The FTIR spectrum of the **5** ,the intense band at 3234 cm^{-1} due to the N-H stretching viberation in a compound **5.** The intense band at 1703 cm^{-1} are associated with stretching vibration of C=O group. The presence of medium intensity band at 1651 cm^{-1} due to stretching vibration of C=C group.

NMR Spectrum of Compound 5

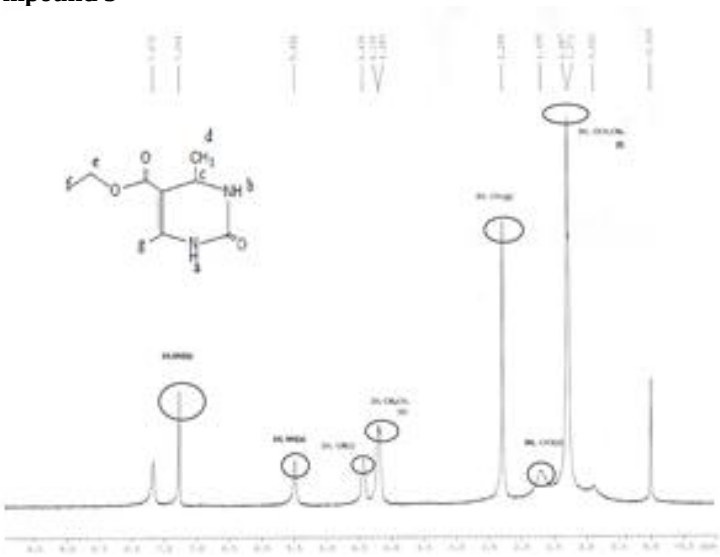


Figure 2. NMR Spectrum of compound of 5

The NMR spectrum of the **(5)** is shown in Figure 2 . The highly polar solvent $CDCl_3$ is used and TMS is used as internal standard. A triplet at 1.27δ, equivalent to 3H, indicates the methyl protons adjacent to methylene group ($-OCH_2CH_3$). A singlet at 1.69δ, equivalent to 3H, indicates the methyl protons adjacent to NH and C=C. A singlet at 2.28δ, equivalent to 3H, indicates methyl group adjacent to –CH group. A quartet at 4.19δ, equivalent to 2H, indicates methylene protons adjacent to methyl group ($-OCH_2CH_3$). A singlet at 4.43δ, equivalent to 1H, indicates CH proton adjacent to $–CH_3$ group. A singlet at 5.5δ, equivalent to 1H, indicates NH protons at position 1. A singlet at 7.26δ, equivalent to 1H, indicates NH protons at position 3.

IV. Antibacterial activity:

Table 1: Zone of inhibition for selected bacteria

S.No	Micro organisms	Compound **4**	Compound **5**	Ciprofloxacin
1.	Klebsiella pneumoniae	4 mm	10 mm	19 mm
2.	Staphylococcus aureus	4 mm	8 mm	20 mm
3.	Escherichia coli	5 mm	12 mm	24 mm

From the above Table 1,compound **4** and compound **5** showed mild zone of inhibition against ***Klebsiella pneumonia*** and ***Staphylococcus aureus***. However, both the compounds have certain influence against ***Escherichia coli*** in comparison with the model drug ciprofloxacin. While comparing the compound **4 (benzaldehyde)** and **5 (acetaldehyde),** acetaldehyde based compound found to have nice antibacterial activity than benzaldehyde based compound might be due to the basicity of acetaldehyde DHPM operated on +I effect than benzaldehyde DHPM (-I effect).

V. CONCLUSIONS

An eco -friendly and economic process for the synthesis of DHPMs by pineapple juice as catalysts have been synthesized with good yields. Formations of the compounds were confirmed using various spectral techniques. Both the compound has certain influence against the microorganism. However, acetaldehyde based DHPM has better antibacterial activity than benzaldehyde based DHPM. The solvent free approach is totally offers nonpolluting environment and avoiding the usage of toxic materials. These heterocyclic compounds find to have greater opening for the synthesis of water soluble polymers which is the further scope of the present investigation.

VI. ACKNOWLEDGEMENT

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VII.REFERENCES

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