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SYNTHESIS & CHARACTERIZATION OF SOME NEW 4-SUBSTITUTED-5-ETHOXY CARBONYL-6-METHYL-3,4-DIHYDROPYRIMIDIN-2(1*H*)-ONE DERIVATIVES

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Abstract:

4-substituted-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one derivatives were prepared by using aromatic aldehydes consists of electron releasing and electron withdrawing groups on it, ethylacetoacetate, urea and ammonium molybdate *via* one-pot reaction by using acetic acid as solvent. This method provides an eco-friendly, easy workup and gives compounds in high yield. The synthesized 4-substituted-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one derivatives were characterized by physical properties and spectral studies (IR, ^{1}H NMR).

Key words:

Biginelli pyrimidone synthesis, 3,4-dihydropyrimidin-2(1*H*)-one (DHPM), aromatic aldehydes, urea, ammonium molybdate $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$.

Introduction:

Heterocyclic chemistry is an integral part of chemical sciences and constitutes a considerable part of modern research that is occurring presently throughout the world. The chemistry of heterocyclic compounds is as logical as the chemistry of aliphatic or aromatic compounds. The study of heterocyclic systems is of great interest both from the theoretical and practical point of view. Heterocyclic compounds also play an important role in the design and discovery of new physiological/ pharmacologically active compounds.

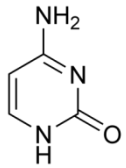
Heterocyclic systems possessing pyrimidine moiety exhibit a number of interesting biological activities such as anti-viral, anti-bacterial, anti-fungal, anti-inflammatory, analgesic, diuretic and anti-convulsant activities. A lot of works have been carried out on these derivatives and a lot of work has been carried on these compounds. It is also evident from the literature that dihydropyrimidinones are equally important in terms of pharmacological activities such as calcium channel blockers, anti-fungal, and anti-hypertensive agent [1].

Therefore, it seems promising to synthesize some new substituted 3,4-dihydropyrimidinones using the multi component one pot condensation of' Biginelli's synthesis using compounds like urea, ethylacetoacetate and aromatic aldehydes like tolualdehyde, benzaldehyde, etc. We present here our results on the design of newly substituted 3,4-dihydropyrimidinones emphasizing in particular the presence of aromatic nucleus at the 4th position of 3,4-dihydropyrimidine ring benzaldehyde, 4-chlorobenzaldehyde, 4-hydroxybenzaldehyde, 4-methoxybenzaldehyde and 2-nitrobenzaldehyde.

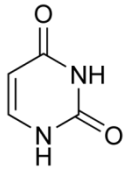
Recent progress in the DHPM class of the anti-cancer agent monastrol, an inhibitor of human kinesin has led to the attention for efficient pharmacophore variation of Biginelli DHPMs. Human kinesin plays a crucial role in bipolar spindle generation during mitosis, inhibition of which leads to mitotic arrest and subsequent apoptotic cell death. It is therefore considered as one of the promising targets in cancer chemotherapy. Racemic dihydropyrimidinone is reported to be an allosteric inhibitor of human kinesin, and unlike taxanes, it is nontoxic to neuron cells [2].

The first synthesis of dihydropyrimidinones was reported by Biginelli in 1893; however, the synthetic potential of this heterocyclic synthesis remained unexplored for quite some time. Since the late 1980's, a tremendous increase in activity has again occurred, as evident by the growing number of publications and patents on the subject. This is mainly due to the fact that the multifunctionalized

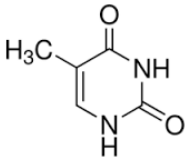
dihydropyrimidine scaffold (Biginelli compounds) represents a heterocyclic system of remarkable pharmacological efficiency. Since then several reviews on synthesis and chemical properties of pyrimidinones have been published. The search for new and efficient methods for the synthesis of pure compounds has been an active area of research in organic synthesis. From a modern point of view, Biginelli protocol is obviously very attractive for combinatorial chemistry and has been rarely used for parallel synthesis, a new avenue could be connected with an elaboration of catalytic procedures. Out of the five major bases in nucleic acids three are pyrimidine derivatives which comprises of [1] cytosine - which is found in DNA and RNA, [2] uracil - found in RNA and [3] thymine - found in DNA [3].



[1] Cytosine



[2] Uracil



[3] Thymine

Biginelli reaction/ Biginelli pyrimidone synthesis:

The Biginelli reaction is a one-pot three-component organic reaction between a β-keto ester, an aryl aldehyde and urea to produce pyrimidones under acidic conditions. This reaction begins with protonation of the aldehyde by the acid and is followed by attack of the amine from urea. Proton transfer steps then result in a protonated alcohol which leaves as water to form an N-acyliminium ion intermediate. The intermediate is then attacked by the enol form of the β-keto ester. Reaction of the other amine group to the carbonyl produces a cyclic intermediate. Proton transfer steps, the release of water, and deprotonation result in the final pyrimidone product [4,5].

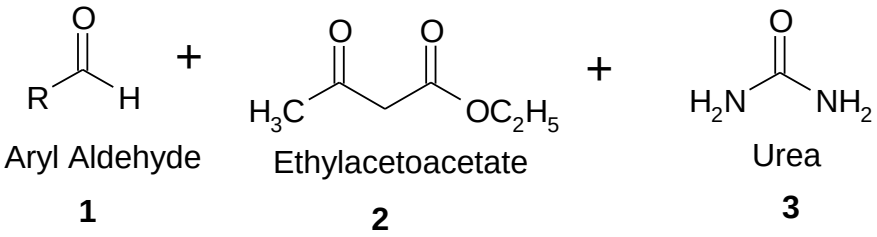
Recent studies states that 3,4-Dihydropyrimidin-2-(1*H*)-one derivatives shows various pharmacological activities such as potential calcium channel blockers [6], as active and safe tumor anti-initiating and multi-potent blocking agent[7], anti-microbial activities [8,9]. analgesic activity [10].

Aim and Objective:

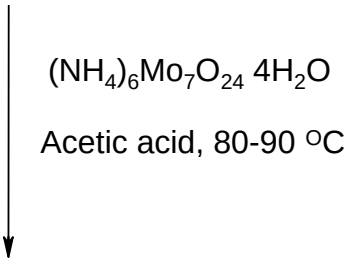
- Literature survey revealed that the chemistry and pharmacology of 3,4-dihydropyrimidin-2(1*H*)-one derivatives have been of great interest to medicinal chemists. Numerous 3,4-dihydropyrimidin-2(1*H*)-one derivatives have been synthesized and reported that they possess calcium channel blocking, antifungal, anti inflammatory and anti bacterial activities.
- Literature survey reveals that presence of substituent groups on phenyl moiety possess various biological activities.
- Our aim is to synthesize various 3,4-dihydropyrimidin-2(1*H*)-one derivatives using ammonium molybdate $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ as catalyst.
- To characterize all the synthesized compounds by physical (Molecular weight, Molecular formula, Melting point, Recrystallization, R_f value) and spectral data (^{1}H NMR, IR spectra).

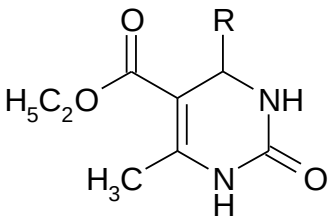
Materials and Instruments: Materials and reagents were obtained from commercial suppliers (Merck grade) and were used without further purification. Melting points were determined by using electrical melting point apparatus and are uncorrected. The progress of the reaction was monitored by TLC using Silica Gel G (Merck). IR spectra were recorded in KBr discs on a Bruker analyzer. ^{1}H NMR spectra were recorded on a Bruker (400 MHz) spectrometer (chemical shifts in γ, ppm) in DMSO using TMS as internal standard.

Experimental Work:

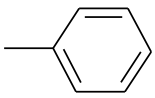
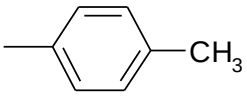
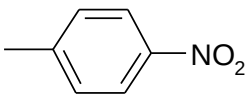
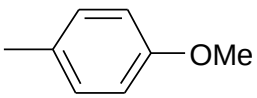
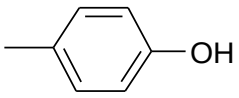
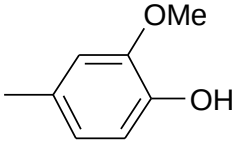


Aryl Aldehyde **1** | Ethylacetoacetate **2** | Urea **3**





4(a-f)

Compound	**R**	**Compound**	**R**
4a		4d	
4b		4e	
4c		4f	

Typical procedure for synthesis of 3,4-dihydropyrimidin -2-(1*H*)-one derivatives (4a-f): [11]

The condensation of various aromatic aldehydes (0.01 mole), ethylacetoacetate (0.01 mole), urea (0.01 mole) and ammonium molybdate (0.001 mole) in 10 ml of acetic acid was refluxed for 2 hrs. Completion of the reaction was monitored by TLC using Silica Gel G as stationary phase and benzene, ethyl acetate (3:2) as mobile phase. Cool the reaction mixture and poured onto crushed ice. The solid separated out was filtered, washed with cold water. Purify the crude product by recrystallization using 95% ethanol.

Synthesized of 3,4-dihydropyrimidin-2-(1*H*)-one derivatives:

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

5-ethoxycarbonyl-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1*H*)-one (4b)

5-ethoxycarbonyl-6-methyl-4-(4-hydroxyphenyl)-3,4-dihydropyrimidin-2(1*H*)-one (4c)

5-ethoxycarbonyl-6-methyl-4-(4-methylphenyl)-3,4-dihydropyrimidin-2(1*H*)-one (4d)

5-ethoxycarbonyl-6-methyl-4-(4-methoxyphenyl)-3,4-dihydropyrimidin-2(1*H*)-one (4e)

5-ethoxycarbonyl-6-methyl-4-(4-hydroxy-3-methoxyphenyl)-3,4-dihydropyrimidin-2(1*H*)-one (4f)

Physical characterization of the synthesized compounds:

Melting points were determined by open ended capillary tube and are uncorrected. Purity of the compounds was identified by the TLC by using silica gel G as stationary phase.

Compound	Molecular formula	Molecular weight (gm)	Melting point (˚C)	% yield	R_f value
4a	$C_{14}N_2O_3H_{16}$	260	202	74.25	0.66
4b	$C_{14}N_3O_5H_{15}$	305	210	66.33	0.58
4c	$C_{14}N_2O_4H_{16}$	276	226	77.16	0.71
4d	$C_{15}N_2O_3H_{18}$	274	216	74.31	0.62
4e	$C_{15}N_2O_4H_{18}$	290	206	66.72	0.67
4f	$C_{15}N_2O_5H_{19}$	307	198	71.52	0.65

Spectral data (IR & ^{1}H NMR) of compounds 4c & 4d:

5-ethoxycarbonyl-6-methyl-4-(4-hydroxyphenyl)-3,4-dihydropyrimidin-2(1*H*)-one (4c):

IR [Cm^{-1}, KBr]: 3492.37(OH), 3221.33(-NH), 3132.33 (-NH), 2873.76 (-CH_3), 1680.32(C=O of ester group)

^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.088-1.123 (t, *J* =14 Hz, 3H,-O-CH_2-C<u>H</u>$_3$), 2.235(Br s, 3H, -C<u>H</u>$_3$), 3.957-4.010 (q, *J* = 21 Hz 2H, O-C<u>H</u>$_2$ CH_3), 5.040-5.048 (d, *J* = 3.2 Hz, 1H, –C<u>H</u>), 7.019-7.040 (d, *J* = 8.4 Hz, 2H, H-2'& 6' Ph), 6.678-6.701 (d, *J*=9.2 Hz, 2H,H-3'& 5'Ph), 7.601 (s,1H, N<u>H</u>), 9.091 (s,1H, N<u>H</u>), 9.314 (s,1H, O<u>H</u>).

5-ethoxycarbonyl-6-methyl-4-(4-methylphenyl)-3,4-dihydropyrimidin-2(1*H*)-one (4d):

IR [Cm^{-1}, KBr]: 3410.57(-NH), 3234.13 (-NH), 2923.91 (-CH_3), 1701.13(C=O of ester group), 1640.69 (C=O)

^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.091-1.127 (t, *J* = 14 Hz, 3H,-O-CH_2-C<u>H</u>$_3$), 2.242-2.267(d, 6H, -2C<u>H</u>$_3$), 3.963-4.012 (q, *J* = 19 Hz, 2H, O-C<u>H</u>$_2$ CH_3), 5.104-5.112 (d, *J* = 3.2 Hz, 1H, –C<u>H</u>), 7.122 (d, 4H, H-2', 3', 5'& 6' Ph), 7.672 (s,1H, N<u>H</u>), 9.138 (s,1H, N<u>H</u>).

Results and Discussion:

3,4-dihydropyrimidin-2-(1*H*)-one derivatives were prepared by one-pot synthesis using ammonium molybdate as catalyst.

3,4-dihydropyrimidin-2(1*H*)-one derivatives were synthesized using the appropriate synthetic procedure i.e. reaction of aromatic aldehyde, dicarbonyl compound (ethylacetoacetate) and urea in presence of ammonium molybdate as catalyst.

The reactants aromatic aldehyde, ethylacetoacetate, urea, ammonium molybdate and acetic acid were taken and heated at refluxing temperature for 2 hr. The reactants were heated at 90^{0}C and the progress of reaction was monitored by TLC. Finally the reaction mixture was poured onto

the crushed ice and then recrystallized from ethanol. The melting point of the compound was found to be same as that of reported.

Melting points were determined in open capillaries and are uncorrected.

IR spectra were recorded in KBr discs on an Bruker (300 FT-IR)

Thin layer chromatography was performed on silica gel G (Merck).

^{1}H NMR spectra were recorded on a Bruker 400 spectrometer operating at 400.13 MHz for ^{1}H in DMSO.

Summary and Conclusion:

In the present work different aromatic aldehydes were used to prepare 3,4-dihydropyrimidin-2(1*H*)-one derivatives by cyclization with ethylacetoacetate and urea in presence of ammonium molybdate as catalyst gives good yields.

A facile method under mild conditions has been developed for the synthesis of the title compounds.

All the compounds synthesized were characterized by physically (R_f values, Melting point, Molecular weight, Molecular formula) and few compounds were characterized by spectral data (^{1}H NMR, IR spectra).

Among the synthesized compounds 5-ethoxycarbonyl-6-methyl-4-(4-hydroxy phenyl)-3,4-dihydropyrimidin-2(1*H*)-one (4c) gives high % yield.

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