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Green Synthesis and Biological Effect of Some Dihydropyrimid-2-One/Thiones

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Abstract **- Different substituted dihydropyrimidinones and dihydropyrimidinthiones were synthesis under the Biginelli condensation between aromatic aldehydes , 1,3-dicarbonyl and urea or thiourea using ultrasonic irradiation method. Zirconyl chloride hexahydrate was found to be suitable catalyst to give good yield, easy work and short reaction time .The structure of the new compounds were confirmed by physical and available spectroscopic methods. A preliminary biological test for some derivatives was conducted.**

Keywords **- Biginelli reaction, ultrasound irradiation, zirconyl chloride hexahydrate biological effect.**

I. INTRODUCTION

The organic compounds of 3, 4-Dihydropyrimidin-2-(1*H*)-ones (DHPMs) and their thio derivatives have attracted global interest because of their pharmacological and therapeutic properties [1]. Such as antihypertensive agents, adrenoceptor-selective antagonists, kinesin Eg5 inhibitors [2] and posses antiviral, antitumor, antibacterial and anti-inflammatory properties. In addition some functionalized DHPMs have emerged as potent calcium channel blockers [3]. Furthermore, some of these derivatives are registered to produce wool from mites [4], used in the treatment of Trachoma [5,6], some have effect in the mitosis [7], while other has benefit in decreasing blood pressure [7]. The first one-potsynthesis of 3,4-dihydropyrimidine was reported by Biginelli in 1893. A serious drawback of the original procedure was low yield with substituted aliphatic and aromatic aldehydes. Several improved procedures have been reported using Lewis acids catalysts such as BF_3, $FeCl_3$, $InCl_3$, $BiCl_3$, $LaCl_3$, $LiClO_4$, Mn-$(OAc)_3$,CAN,in a solvent such as CH_3CN, CH_2Cl_2, or THF. Number of procedures under solvent-free conditions using Y $(NO_3)_3.6H_2O$, silica triflatelanthanidetriflate, samarium diiodide and ionic liquid as catalysts have also been reported [8]. Obviously, many of these catalysts and solvents are not at all acceptable in the context of green synthesis [8].

II. EXPEMENTAL

The incubator is from Memmert Company. The ^{1}H-NMR spectra were obtained on Bruker AC 250, and Bruker ARX 300, Bruker ARX 500. Melting points were recorded on a Stuart melting point apparatus SMP30. And are uncorrected Sonication was performed in an Unisonics PTY.LTD type FXp12. IR spectra were recorded on a Perkin-Elmer,and FT-IR WQF-510 spectrophotometer with KBr optics. U.V. spectra were recorded on Shimadzu U.V 1650pc.

General procedure

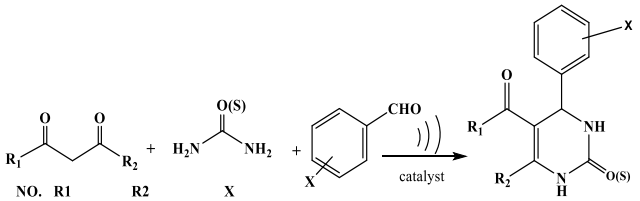
1-A mixture of aromatic aldehyde (0.001mole), 1,3-dicarbonyl compound (0.001 mole) , urea or thiourea (0.0015) and catalytic amount of zirconyl chloride hexahydrate in ethanol (15 ml) was sonicated. The reaction temperature was raised to 25-30C^o after sonication for 1/2h. On completion of the reaction, mixture was left to dry and recrystallized from hot ethanol to afford the pure product [9, 10].

2- The inhibitor effect of some synthesized compounds on bacterial growth (which is under study) are assayed by

using allergy test method (discs spread method) and depending on Bauer method and his group at 1966s. Where by prepared bacterial suspension in nutrient gravies media in concentration of 10^8 cell/cm^3 in comparison to scaling control tube, transfer (0.1 cm^3) of bacteria suspension and inoculated by using loop on the nutrient agar then incubate the plates in a degree 37 ^oC for 30 min till absorption occur. Then filter paper (Whitman No.1) of diameter 6mm saturated with prepared chemical compound. Was (by dissolving 0.01gm of chemical compound in 0.3ml of DMSO, solution in water bath in a degree 60^oC for about 20 minute for pasteurization then added this solution to 100 discs after sterilization). Then the discs are fixed by sterilized tong at the surface of inoculated plates and incubate in 37^oC for 24hr. At the end of incubation period, the compounds which effect on bacteria is under study [11].

III.RESULTS AND DISCUSSION

The reaction of substitutes benzaldehyde, 1,3-dicarbonyl and urea or thiourea in the presence of zirconyl chloride hexahydrate in ethanol under sonication resulted in the formation of dihydropyrimid-2-one/thiones as shown in scheme 1. The cyclocondensation proceeded smoothly to give afford the products in good yields. Owing to the vibrational energy of the water, the bath temperature reached 25–35^oC under sonication



NO.	R1	R2	X
1	CH_3	OC_2H_5	p-NO_2
2	CH_3	OC_2H_5	CH_2O_2*
3	CH_3	OC_2H_5	P-Cl
4	Ph	CH_3	p-$N(CH_3)_2$
5	Ph	CH_3	m-OMe
6	Ph	CH_3	CH_2O_2*
7	Ph	CH_3	p-$N(CH_3)_2$
8	CH_3	OCH_3	p-Cl
9	Ph	OC_2H_5	p-CH_3
10	CH_3	CH_3	2,4-Cl

Scheme 1

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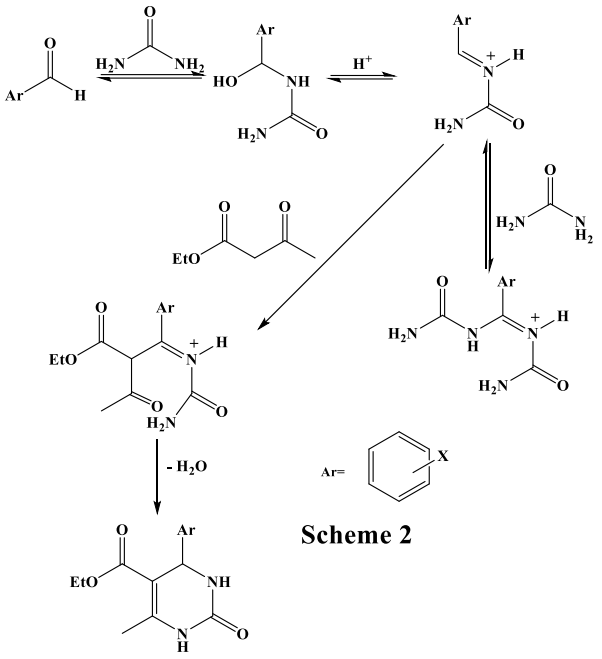
The reaction proceeded as shown in the following suggested mechanism [12] scheme 2



Scheme 2

Spectral data for the prepared compounds (1-10) [13, 14, 15, 16, and 17]

1) Ethyl 6-methyl-4-(4-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5- carboxylate

IR (KBr) (νmax cm^{-1}) 3223, 3114, 2996, 1728, 1698, 1673, 1594; ^{1}H-NMR (δ ppm): 1.2(t,2H, CH_3), 1.5(s,3H, cycloalkene), 3.4(s,1H, NH), 3.7(s,1H, ArH), 4.2(q,2H, CH_2 ester),7.5-8.4(m,4H, aromatic) .

2) Ethyl 4-(1,3-dihydroisobenzofuran-5-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate.

IR (KBr) (νmax cm^{-1}) 3200, 3160, 3080, 1715, 1652, 1640, 1551; ^{1}H-NMR (δ ppm): 1.1(t,2H, CH_3), 2.3(s,3H, CH_3), 4.1(q,1H, CH_2), 5.9(s,1H, NH), 5.6(s,2H, CH_2 ether), 6.6-7.3(m,3H, aromatic) .

3) Ethyl 4-(4-chlorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate.

IR (KBr) (νmax cm^{-1}) 3280, 3143, 3050, 1730, 1651, 1556; ^{1}H-NMR (δ ppm): 1.2(t,3H, CH_3), 2.3(s,3H, CH_3), 2.1(d,1H, NH), 4.0(q,2H, CH_2), 5.3(d,2H, CH_2 aryl),7.3(m,4H, aromatic) .

4) 5-benzoyl-4-(4-(dimethylamino)phenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one.

IR (KBr) (νmax cm^{-1}) 3346, 3261, 3020, 1700, 1678, 1650, 1593; ^{1}H-NMR (δ ppm): 2.2(s,3H, CH_3), 3.0(s,3H, CH_3), 5.6(d,1H, aryl), 6.2(s,1H, NH), 6.6-7.9(m,4H, aromatic).

5) 5-Benzoyl-4-(3-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one.

IR (KBr) (νmax cm^{-1}) 3238, 3109, 2997, 1701, 1678, 1658, 1626, 1323, 1238; ^{1}H-NMR (δ ppm): 1.7(s,3H, CH_3), 3.8(s,3H, OCH_3), 5.6(s,1H, NH), 6.1(s,1H, aryl), 6.7-7.9(m,4H, aromatic system).

6) (4-(Benzo[d][1,3]dioxol-5-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl)(phenyl)methanone.

IR (KBr) (νmax cm^{-1}) 3236, 3176, 3111, 1701, 1678, 1658, 1620, 1572, 1205, 1175, 1133, 1109; ^{1}H-NMR (δ ppm): 1.7(s,1H, NH), 2.1(s,3H, CH_3), 3.7(s,1H, aryl), 6.0(s,2H, CH_2), 6.6-7.8(m,4H, aromatic system)), 9.8(s,1H, NH).

7) (4-(4-(Dimethylamino)phenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl)(phenyl)methanone.

IR (KBr) (νmax cm^{-1}) 3284, 3174, 3112, 1614, 1591, 1292, 1196, 1171.

8) Methyl 4-(4-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate.

IR (KBr) (νmax cm^{-1}) 3294, 3228, 3036, 1721, 1698, 1643, 1573, 863; ^{1}H-NMR (δ ppm): 2.0(s,3H, CH_3), 3.3(s,3H, CH_3), 4.0(s,1H, NH), 5.1(s,1H, aryl), 7.2-7.4(m,4H, aromatic) ; U.V. λ_{max} ($CHCl_3$) 284, 232 nm .

9) Ethyl 2-oxo-6-phenyl-4-(p-tolyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate.

IR (KBr) (νmax cm^{-1}) 3346, 3288, 2985, 1726, 1676, 1625, 1593; ^{1}H-NMR (δ ppm): 1.2(t,3H, CH_3), 2.2(s,3H, CH_3), 3.8(q,2H, CH_2), 5.4(d,1H, aryl), 6.1(s,1H, NH), 7.0-7.9(m,4H, aromatic) ; U.V. λ_{max} ($CHCl_3$) 244, 252 nm

10) 5-Acetyl-4-(3,4-dichlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one.

IR (KBr) (νmax cm^{-1}) 3241, 3196, 3069, 1659, 1640, 1632, 1589, 864; ^{1}H-NMR (δ ppm): 2.1(s,3H, CH_3), 2.5(s,3H, CH_3), 5.6(s,1H, aryl), 6.2(s,2H, NH), 7.4-7.8(m,4H, aromatic) .

IV. BIOLOGICAL EFFECT FROM SOME COMPOUNDS

Some of the prepared compounds (2,4,5,10) were examined for their antibacterial activity against , E .coil , Staph. aureus and psedomonous and found to be negative.

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TABLE I

Some physical properties of the prepared compounds (1-10)

Compound Number	**R**	**R_1**	**R_2**	**X**	**Yield%**	**Color**	**m.p.^{o}C**
1	p-NO_2	CH_3	OC_2H_5	O	71	Yellow	194
2	CH_2O_2*	CH_3	OC_2H_5	O	71	Brown	181-183
3	P-Cl	CH_3	OC_2H_5	S	44	Brown	181-183
4	p-$N(CH_3)_2$	Ph	CH_3	O	63	Green	142-144
5	m-OMe	Ph	CH_3	O	82	White	192-193
6	CH_2O_2*	Ph	CH_3	S	97	Brown	191-193
7	p-$N(CH_3)_2$	Ph	CH_3	S	52	Red	240-241
8	p-Cl	CH_3	OCH_3	O	49	Pale green	202-204
9	p-CH_3	Ph	OC_2H_5	O	34	White	170-171
10	2,4-Cl	CH_3	CH_3	O	88	Yellow	226-227

*= 

TABLE II

Biological Effect From Some Compounds

Compound number	Type of bacteria		
	E. coli	Staphylococcus aureus	Pseudomonous
2	-ve	-ve	-ve
4	-ve	-ve	-ve
5	-ve	-ve	-ve
10	-ve	-ve	-ve