Ultrasound-assisted one-pot synthesis of dihydropyrimid-2-one/thiones catalyzed by zirconyl chloride hexahydrate

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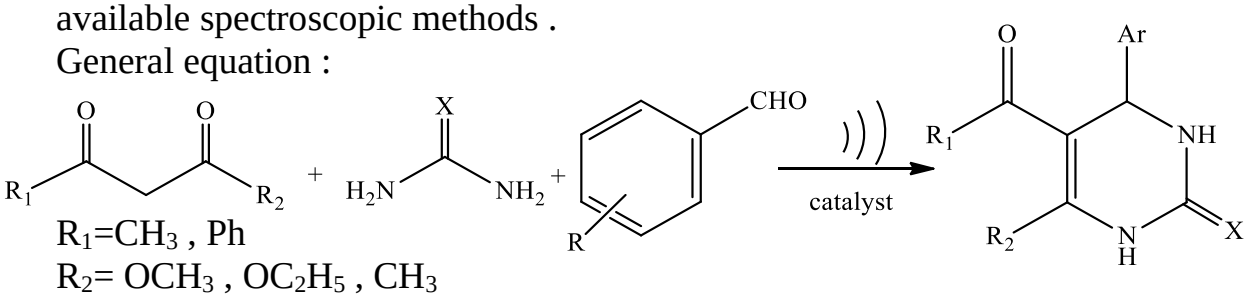
الخلاصة

حضرت معوضات مختلفة من ثنائي هيدروبريميدون وثنائي هيدروبريميدن ثايون من تفاعل بيجنيلي بين الالديهايد و1و3-ثنائي الكاربونيل مع اليوريا والثايويوريا بطريقة استخدام الامواج فوق الصوتية. هذة الطريقة تعتمد على انتقائية الحفاز المناسب(كلوريد الزركونيوم سداسي الماء) بالمقارنة مع تفاعل بيجنيلي الشائع حيث يعطي ناتج مرتفع وبطريقة عمل سهلة ووقت قصير. تم تشخيص المركبات المحضرة باستخدام الطرق الفيزياوية والطرق الطيفية .

ABSTRACT

Different substituted dihydropyrimidinones and dihydropyrimidin thiones were generated from the Biginelli reaction between aromatic aldehydes, 1,3-dicarbonyl and urea or thiourea under ultrasonic irradiation method. Compared with classical Biginelli reaction ,this method can be depending on selectivity of the suitable catalyst (zirconyl chloride hexahydrate) ,excellent yield ,easy work and short reaction time .The structure of the new compounds were confirmed by physical and available spectroscopic methods .

General equation :



R_1=CH_3 , Ph
R_2= OCH_3 , OC_2H_5 , CH_3
R=different substituents
X=O,S

Keywords: Biginelli reaction, ultrasound irradiation , green chemistry

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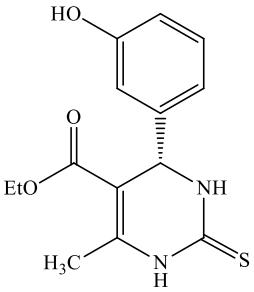
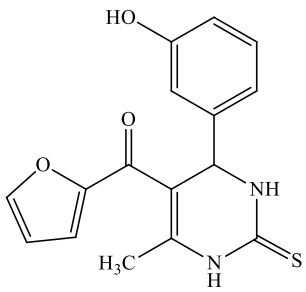
INTRODUCTION

Heterocyclic compounds have so far been synthesized mainly because of their wide range of biological activities. These compounds play an important role in medicinal chemistry, serving as key templates central to the development of numerous important therapeutic agents[1],the interest in the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones (DHPM) and their thio derivatives have received considerable attention due to their attractive pharmacological profiles. They are mostly used as calcium channel blockers1, antihypertensive agents[2], alpha-antagonists and neuropeptide antagonists. Alkaloids containing the dihydropyrimidine structure have been isolated from various marine sources which have shown some interesting biological properties[3]. The first one-pot synthesis 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. Recently, number of procedures under solvent-free conditions using $Y(NO_3)_3.6H_2O$, silica triflate lanthanide triflate, samarium diiodide and ionic liquid as catalysts have also been reported. Obviously, many of these catalysts and solvents are not at all acceptable in the context of green synthesis[4]. Human kinesin Eg5, an interesting drug target for the development of cancer chemotherapeutics. Monastrol (**1)** is the first Biginelli compound which has excellent anticancer activity, further a series of compounds for their ability to inhibit Eg5 activity has been investigated using two in vitro steady-state ATPase assays (basal and microtubule-stimulated) as well as a cell-based assay. In an attempt, another dihydropyrimidine i.e. furyl derivative **(2)** appeared more potent than monastrol by a fivefold factor. Reported compounds enastron **(3)**,dimethylenastron **(3)**, have been compared with the monastrol which are better fit of the ligand to the allosteric binding site and the addition of fluorine atoms. 12-6573LR published mainmanuscript[5]



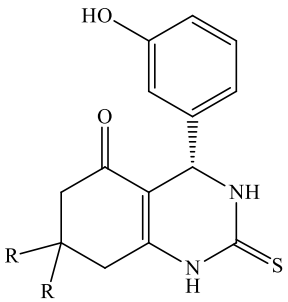
(1)

(S) Monastrol



(2)

R=H: (S)-enastron



(3)

R=Me:(S)-dimethylenastron

EXPERIMENTAL

Melting points were recorded on a Stuart melting point apparatus SMP30. IR spectra were recorded on a Perkin-Elmer FT-IR WQF-510 spectrophotometer with KBr optics. U.V. spectra were recorded on Shimadzu U.V 1650pc .

General procedure. A mixture of solution of aromatic aldehyde (0.001mole), 1,3-dicarbonyl compound , urea or thiourea (10 mmol) and zirconyl chloride hexahydrate in ethanol (15 ml) was sonicated (unisonics PTY.LTD type FXp12). 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[6][7].

RESULTS AND DISCUSSION

The reaction of 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 .The cyclocondensation proceeded smoothly to give the products in high to quantitative yields. Owing to the vibrational energy, the water bath temperature reached 25–35C^{o} under sonication. Many of the pharmacologically relevant substitution patterns on the aromatic ring could be introduced with high efficiency.

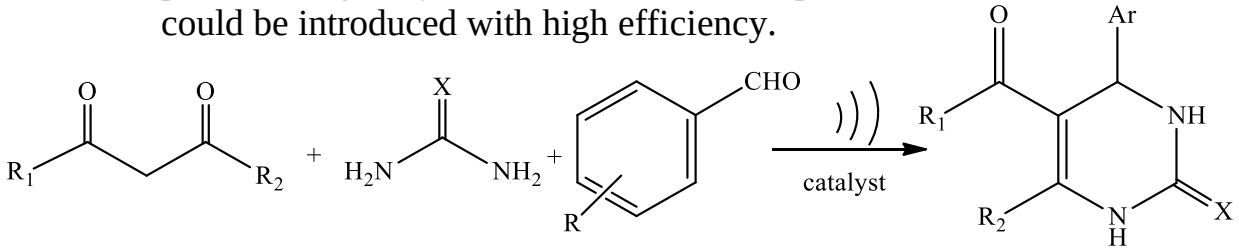


Table : Some physical properties of the prepared compounds (1-9)

Comp. No	R	R_1	R_2	X	Yield%	Color	m.p.^{o}C
1.	H	CH_3	OC_2H_5	O	63	White	195-197
2.	p-OH	CH_3	OC_2H_5	S	41	White	228-231
3.	2,4-dichloro	Ph	CH_3	O	52	White	205-208
4.	p-NO_2	Ph	CH_3	S	46.5	Yellow	223-224
5.	p-Cl	CH_3	OCH_3	O	40	Pale green	202-204
6.	p-NO_2	Ph	OC_2H_5	O	56	Orange	180-181
7.	4-dimethylamino	Ph	OC_2H_5	O	56.3	Yellow	147-148
8.	p-NO_2	CH_3	CH_3	O	81.5	Orange	180-181
9.	p-NO_2	CH_3	CH_3	S	98	Brown	104-105

Physical and Spectral data for the prepared compounds(1-9) [8,9,10,11,12]:

1- Ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate

IR (KBr) (νmax cm^{-1}) 3248, , 1726, 1701, 1647, 1599; U.V. λ_{max} ($CHCl_3$) 284.

2-Ethyl 4-(4-hydroxyphenyl)- 6-methyl-2-thioxo-1,2,3,4-tetrahydropyridimidine-5-carboxylate.

IR (KBr) (νmax cm^{-1}) 3290, 1712, 1660, 1620,1261,1198; U.V. λ_{max} ($CHCl_3$) 312.

3- 5-benzoyl-4-(2,4-dichlorophenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one

IR (KBr) (νmax cm^{-1}) 3319, 1666, 1641,1591, 1550; U.V. λ_{max} ($CHCl_3$) 318.

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

IR (KBr) (νmax cm^{-1}) 3275, 3174, 1664,1606, 1572,1523,1348,1203,1174; U.V. λ_{max} ($CHCl_3$) 328.

5- methyl4-(4-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine -5- carboxylate

IR (KBr) (νmax cm^{-1}) 3242, 3118, 1724,1703, 1649; U.V. λ_{max} ($CHCl_3$) 284.

6- ethyl4-(4-nitrophenyl)-2-oxo-6-phenyl-1,2,3,4-tetrahydropyrimidine -5- crboxylate

IR (KBr) (νmax cm^{-1}) 3311, 1734, 1670,1608, 1518,1350; U.V. λ_{max} ($CHCl_3$) 272.

7- ethyl4-(4-(dimethylamino)phenyl)-2-oxo-6-phenyl-1,2,3,4-tetrahydropyrimidine-5-crboxylate

IR (KBr) (νmax cm^{-1}) 3215, 1736, 1684,1655, 1616,1369; U.V. λ_{max} ($CHCl_3$) 344.

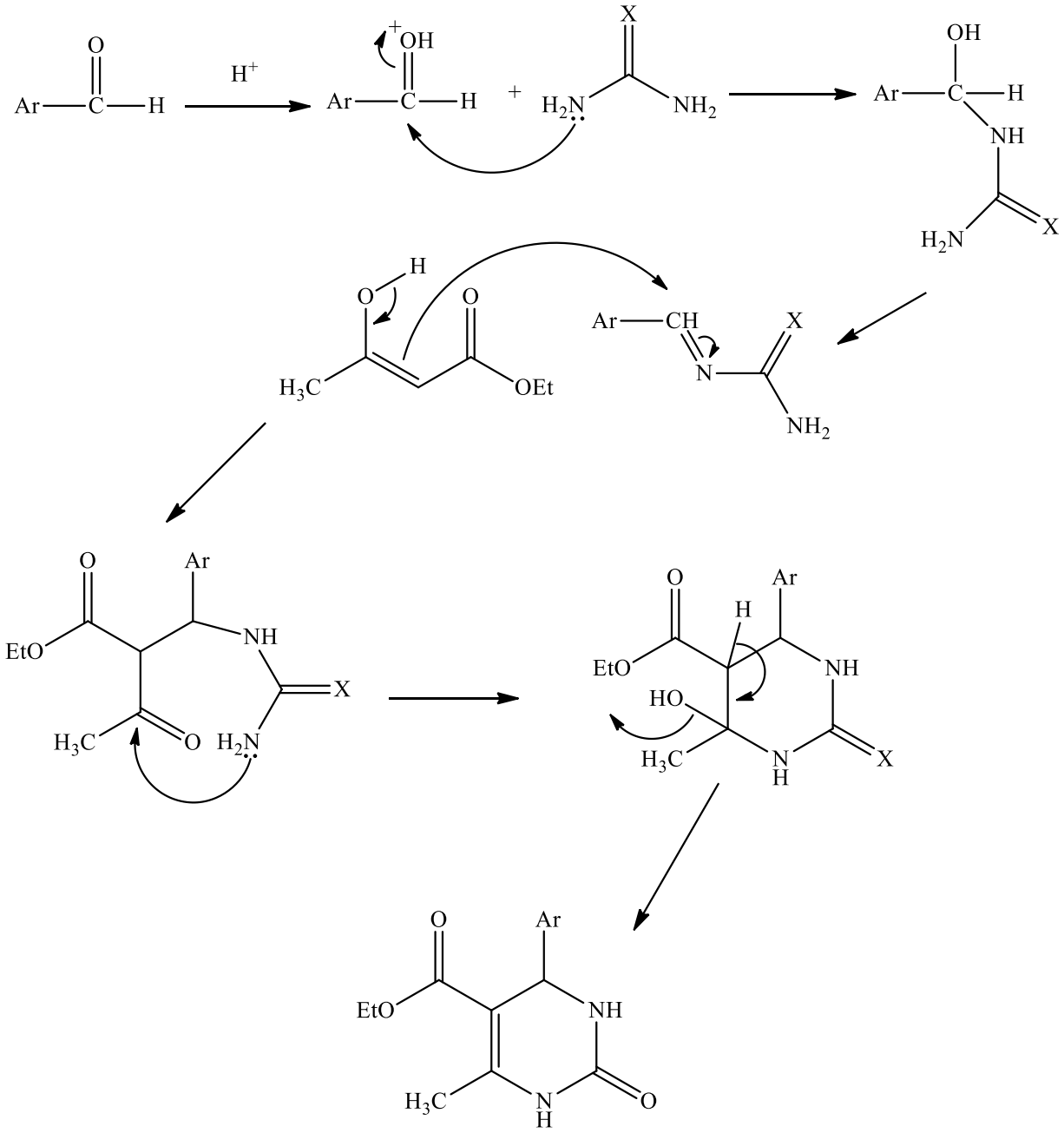
8- 5-acetyl-6-methyl- 4-(4-nitrophenyl) -3,4-dihydropyrimidin-2(1*H*)-one

IR (KBr) (νmax cm^{-1}) 3317, 1649, 1591,1547,1381; U.V. λ_{max} ($CHCl_3$) 272.

9- 1-(6-methyl-4-(4-nitrophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-yl)ethanone

IR (KBr) (νmax cm^{-1}) 3275,3178, 1612, 1589,1535,1383,1198,1142; U.V. λ_{max} ($CHCl_3$) 306.

Suggested mechanism:



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