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GREEN CHEMISTRY APPROACH IN SYNTHESIS OF 3,4-DIHYDROPYRIMIDINONE DERIVATIVES UNDER SOLVENT-FREE CONDITIONS

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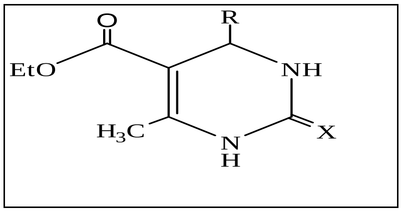
ABSTRACT: Simplify and improve conditions that have been used traditionally to carry out the conventional Biginelli reactioninvolves three-component one-pot condensation of an aldehyde, β-ketoester and urea or thiourea in ethanol under strong acidic condensation HCl for the synthesis of dihydropyrimidinone(DHPMs) and their sulphur analogue dihydropyrimidinthione derivatives which are act as (antibacterial, anti-inflamematory, antiviral, antitumor, antimalarial agents, hypnotics…. ect) by green chemistry approach. These reactions were performed by three-component condensation of different types of an aldehyde (benzaldehyde, acetaldehyde, furfural, cinnamaldehyde, and salicaldehyde), ethyl acetoacetate, and urea or thiourea at reflux temperature under solvent-free conditions without catalyst to afford the corresponding dihydropyrimidinones and dihydropyrimidinthione in excellent yields (76–96%). The advantages of this green chemistry approach the excellent yield, operational simplicity, short time, and the avoidance of the use of organic solvents and friendly preparation. Products were identified using physical and spectroscopic data (IR, ^{1}HNMR, GC. Mass, UV).

INTRODUCTION: 3,4- Dihydropyrimidinone and their sulphur analogue 3,4-Dihydropyrimidinthiones [1] are classified as heterocycles compound [2] and containing pyrimidine ring which is containing two nitrogenatoms in the six-member ring. The structure of dihydropyrimidinones and their derivatives (DHPMs) illustrated below:



R= aliphatic substituent, aromatic substituent, aromato aliphatic substituent or heterocyclic substituent. X= O or S

FIG.1: THE GENERAL STRUCTURE OF (DHPMS)

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The (DHPMs) have attracted great attention recently in synthetic organic chemistry due to their applications in the field of drug research and pharmacological and therapeutic properties such as antibacterial [3, 4], anti-inflamematory [4], antiviral [5], antitumor [6], antimalarial agents [7], hypnotics, anticonvulsant, antithyroid, antihistaminic agents , antibiotics [2] and in addition, 4-aryldihydropyrimidines have emerged antihypertensive activity as well as behaving as calcium channel blockers [8, 9] , α-antagonists and neuropeptide Y (NPY) antagonists[10].

Synthesis of dihydropyrimidinone and their thioanalogue is increasing tremendously in current years and also synthesized earlier a series of dihydropyrimidinone/thione by three component condensation of urea/thiourea [2]. The simplest and the most straightforward procedure, originally reported by Biginelli in 1893 involves three-component one-pot condensation of an aldehyde, β-ketoester and urea or thiourea [11] in ethanol under strong acidic condensation HCl [12].

Biginelli reaction is acid catalyzed cyclo-condensation reaction of ethyl acetoacetate, benzaldehyde and urea illustrated below **Fig. 2**:

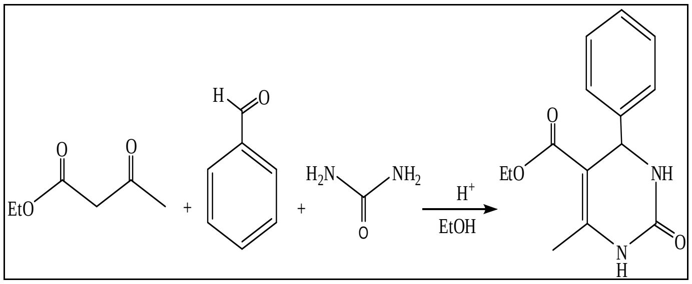


FIG. 2: BIGINELLIREACTIONETHYL ACETOACETATE, BENZALDEHYDE AND UREA

This reaction was carried out by simply heating a mixture of the three components dissolved in ethanol with a catalytic amount of hydrochloric acid at reflux temperature. The product of this novel one-pot, three components synthesis that precipitated on cooling of the reaction mixture was identified as 3,4-dihydropyrimidin-2*(1H)*one.

When the synthesis involves three-component one-pot condensation of an aldehyde, β-ketoester and thiourea will give derivative (Dihydropyrimidinthiones) act as antitumour, fungicidal, bactericidal, anti-inflammatory and antiviral activities [13].

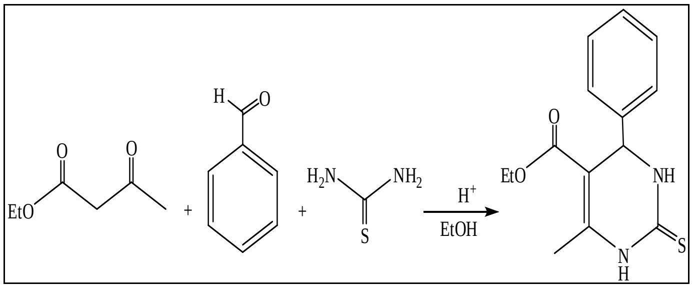


FIG.3: BIGINELLIREACTIONETHYL ACETOACETATE, BENZALDEHYDE AND THIOUREA.

The classical Biginelli reaction requires long reaction times (20 hrs), use of sulphuric acid and often suffers from low yields of products in case of substituted aromatic and aliphatic aldehydes. Multi-step synthesis produces somewhat higher yields but lacks the simplicity of original one-pot Biginelli protocol [14] **Fig.3**. Therefore, the Biginelli reaction continues to attract the attention of organic chemists interested in finding milder and more efficient procedures for the synthesis of dihydropyrimidinones[15].

The feasibility of performing multi-component reactions under solvent-free conditions could enhance their efficiency from an economic as well as ecological point of view. Thus, solvent free chemical reactions offer several advantages in preparative, simplifying work-up, formation of cleaner products, enhanced selectivity, reduction of by products, reduction in the waste produced, and much improved reaction rates (greener method).

MATERIALS AND METHODS:

Melting points were determined on a Gallenkamp melting point apparatus. UV, IR, 1H NMR, and GC-MS spectra were recorded on Shimadzu-1800UV Spectrophotometer, Shimadzu8400s FT-IR Spectrophotometer, 500MHz Brucker Spectrometer and Shimadzu GC-MS QP 2010 GC respectively. Benzaldehydes, Ethyl aceto- acetate, urea, thiourea, were all commercial products and were used without further purification. Reactions were monitored on TLC using silica gel 60 GF 254 (Merck Germany) precoted plates or coated over glass with different mobile phases.

General procedure for synthesis of 3,4- dihydropyrimidin-2(1H) ones/thiones:

A mixture of aldehyde (0.01mole), ethyl acetoacetate (0.01mole) and urea or thiourea (0.01mole) without any solvent, taken in a round bottom flask was shaken by hand for 2 minutes. The reaction mixture was then heated under reflex. With progress of the reaction a solid started to deposit. After completion of the reaction as indicated by TLC (hexane/ethyl acetate 4:1), the reaction mixture was brought to room temperature. The solid was taken out carefully with a spatula or spoon in a conical flask. The solid was washed with cold water (2 ml × 10) to remove excess of urea and then recrystallized from rectified spirit to give a pure solid product.

Ia:

5-(Ethoxy carbonyl) - 4 - (phenyl) - 6-methyl - 3,4 - dihydropyrimidin-2(1H)one:

m.p: 205-207°C; **IR (KBr, cm^{-1})**: 3318.18, 3136.35, 3015.15, 2924.20, 1742.25, 1796.95, 1212.10, 10190.60 cm^{-1}. **^{1}HNMR (DMSO, ppm)**: 1.10 (3H, t, CH_3), 2.08 (3H,s, CH_3), 4.00 (2H, q, CH_2), 5.15 (1H,d, CH), 7.24 (1H,t, H-Ar),7.33 (1H,t, H-Ar), 7.76 (1H,s, NH), 9.20 (1H,s, NH);

MS (m/z): 260,245, 231,214, 183; **UV (nm)**: 234.3, 356.7 nm.

IIa:

5-(Ethoxy carbonyl) - 4 - (phenyl) - 6-methyl - 3,4 - dihydropyrimidin-2(1H)thione:

m.p: 202-205°C; **IR (KBr, cm^{-1})**: 3328.04, 3175.51, 3105.74, 2980.39, 1671.01, 1574.77, 1197.34, 1117.57 cm^{-1}. **^{1}H-NMR (DMSO, PPm)** δ: 1.10 (3H,t, CH$_3$), 2.32 (3H, s, CH$_3$), 4.03 (2H,q, CH$_2$), 5.18 (1H,d, NH), 7.23 (1H, d, H-Ar),7.29 (1H,t, H-Ar), 7.38 (1H,t, H-Ar), 9.67 (1H,s, NH), 10.35 (1H, s, NH); **MS (m/z):**276,247, 231, 203, 199; **UV (nm):** 202.6, 307.7 nm.

IIIa:

5- (Ethoxy carbonyl) - 4, 6- dimethyl- 3, 4 - dihydropyrimidin-2(1H)one:

m.p:195-197°C; **IR (KBr, cm^{-1}):** 3212.10, 3106.50, 3015.15, 2969.65, 1698.95, 1551.50, 1106.05, 1075.75 cm^{-1}. **^{1}H-NMR (DMSO, PPm)**δ: 0.82 (3H, d, CH$_3$),1.19 (3H,t, CH$_3$), 2.18 (3H, s, CH$_3$), 3.67 (2H,q, CH$_2$), 4.75 (1H, q,NH), 8.67 (1H, s, CH); **MS (m/z):**196, 179, 150, 134, 106; **UV (nm):** 201.4, 281.6 nm.

IVb:

5- (Ethoxy carbonyl) - 4, 6- dimethyl- 3, 4 - dihydropyrimidin-2(1H)thione:

m.p: 192-195°C; **IR (KBr, cm^{-1})**: 3228.7, 2976.17, 2930.48 1719.7, 1566.94, 1098.75, 1029.09 cm^{-1}; **MS (m/z):**249, 203, 176, 146, 111, 99, 57; **UV (nm):**223.7, 293.5 nm.

Va:

5- (Ethoxy carbonyl) -4- (6-hydroxyphenyl)-6-methyl -3,4- dihydropyrimidin-2(1H)one:

m.p:105-109°C; **IR (KBr, cm^{-1})**: 3367.4, 3066.61, 2981.74, 1712.67, 1606.59, 1220.86, 1103.21 cm^{-1}. **^{1}H-NMR (DMSO, PPm)** δ: 1.5 (3H,t, CH$_3$),2.50 (3H, s, CH$_3$), 4.22 (2H, q, CH$_2$), 4.42 (1H, d, CH),6.5 (3H, m, H-Ar), 7.95 (1H, s, NH), 9.95 (1H, s, H-Ar); **MS (m/z):**275, 247, 218,205, 189, 123(2.5); **UV (nm):**211.9, 301.8 nm.

VIb:

5- (Ethoxy carbonyl) -4- (6-hydroxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)thione:

m.p:103-105°C; **IR (KBr, cm^{-1})**: 3234.48, 3201.61, 3068.53, 2979.82, 1708.81, 1105.14, 1031.85 cm^{-1}. **^{1}H-NMR (DMSO, PPm)**δ: 1.25 (3H, t, CH$_3$),2.51 (3H, s, CH$_3$), 4.15 (2H, q, CH$_2$), 4.55 (1H, d, CH),6.5-8.6 (3H, m, H-Ar), 7.91 (1H, s,NH), 9.17 (1H, s,NH), 9.68 (1H, s, H-Ar),; **MS (m/z):**293, 247,275, 218,189, 165; **UV (nm):**215.5, 304.2 nm.

VIIa:

5- (Ethoxy carbonyl) -4- (2-phenyl ethylene)-6-methyl-3,4-dihydropyrimidin-2(1H)one:

m.p:103-105°C; **IR (KBr, cm^{-1}):** 3244.69, 3115.11, 3032.67, 2977.10, 1716.06, 1651.33 1169.49, 1095.49 cm^{-1}. **^{1}H-NMR (DMSO, PPm)** δ: 1.20 (3H, t, CH$_3$),2.19 (3H, s, CH$_3$),4.08 (2H, q,CH$_2$), 4.71 (1H, d, CH), 6.17-6.20 (H,dd,=C-H), 6.33 (1H, d, H-C=), 7.23 (1H, t, H-Ar),7.41 (1H, d, H-Ar), 7.56 (1H, s,NH), 9.16 (1H, s, NH); **MS (m/z):**286, 273, 257,240,213, 183, 170; **UV (nm):** 202.6, 256.7 nm.

VIIIb:

5- (Ethoxy carbonyl) -4- (2-phenyl ethylene)-6-methyl-3, 4-dihydropyrimidin-2(1H)thione:

m.p:98-104°C; **IR (KBr, cm^{-1}):** 3181.32, 3066.67, 3026.61, 2979.39, 1705.55, 1560.00 1182.34, 1098.01 cm^{-1}. **^{1}H-NMR (DMSO, PPm)**δ: 1.20 (3H, t, CH$_3$),2.25 (3H, s, CH$_3$),4.11 (2H, q,CH$_2$), 5.75 (1H, d, CH), 6.15 (H,dd,=C-H), 6.35 (1H, d,H-C=), 7.25 (1H, t, H-Ar),7.42 (1H, d, H-Ar), 7.42 (1H, d,H-Ar), 9.49 (1H, s, NH), 10.33 (1H, s,NH); **MS (m/z):**302, 287, 273, 257,229,; **UV (nm):**201.4, 256.9 nm.

IXa:

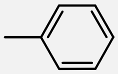
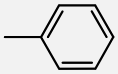
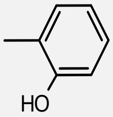
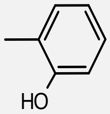
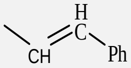
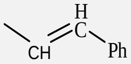
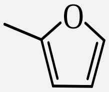
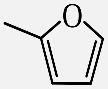
5- (Ethoxy carbonyl) -4- (2-furyl) -6- methyl - 3,4-dihydropyrimidin-2(1H)one:

m.p:191-194°C; **IR (KBr, cm^{-1}):** 3344.23, 3241.98, 3118.3, 2984.26, 1702.53, 1649.34 1146.27, 1049.57 cm^{-1}. **^{1}H-NMR (DMSO, PPm)** δ: 1.16 (3H, t, CH$_3$),2.25 (3H, s, CH$_3$),4.08 (2H, q, CH$_2$), 5.22 (1H, d, CH), 6.10 (1H, d, furyl ring), 6.35 (1H, dd, furyl ring), 7.40 (1H,dd,furyl ring),8.92 (1H, s,NH), 9.26 (1H, s, NH);**MS (m/z):**250, 233, 221,205,177; **UV (nm):**209.6, 280.4 nm.

Xb:

5-(Ethoxy carbonyl)-4-(2-furyl) -6- methyl - 3, 4-dihydropyrimidin-2(1H)thione: **m.p:**215-219°C; **IR (KBr, cm^{-1}):** 3313.85, 3178.03, 3109.3, 2989.21, 1662.10, 1574.14 1188.11, 1113.24 cm^{-1}. **^{1}H-NMR (DMSO, PPm)**δ: 1.15 (3H, t, CH$_3$),2.08(3H, s,CH$_3$),4.05(2H, q, CH$_2$), 5.24 (1H, d, CH), 6.15 (1H,d,furyl ring), 6.39 (1H,dd,furyl ring), 7.59 (1H, dd, furyl ring),9.66 (1H, s,NH), 10.42 (s, J = 4.14 Hz, 1H, NH); **MS (m/z):**266, 237, 221,209,193, 178; **UV (nm):** 234.3, 214.4 nm.

TABLE 1: REACTION CONDITIONS OF THE PREPARED DIHYDROPYRIMIDINONES/THIONES DERIVATIVES.

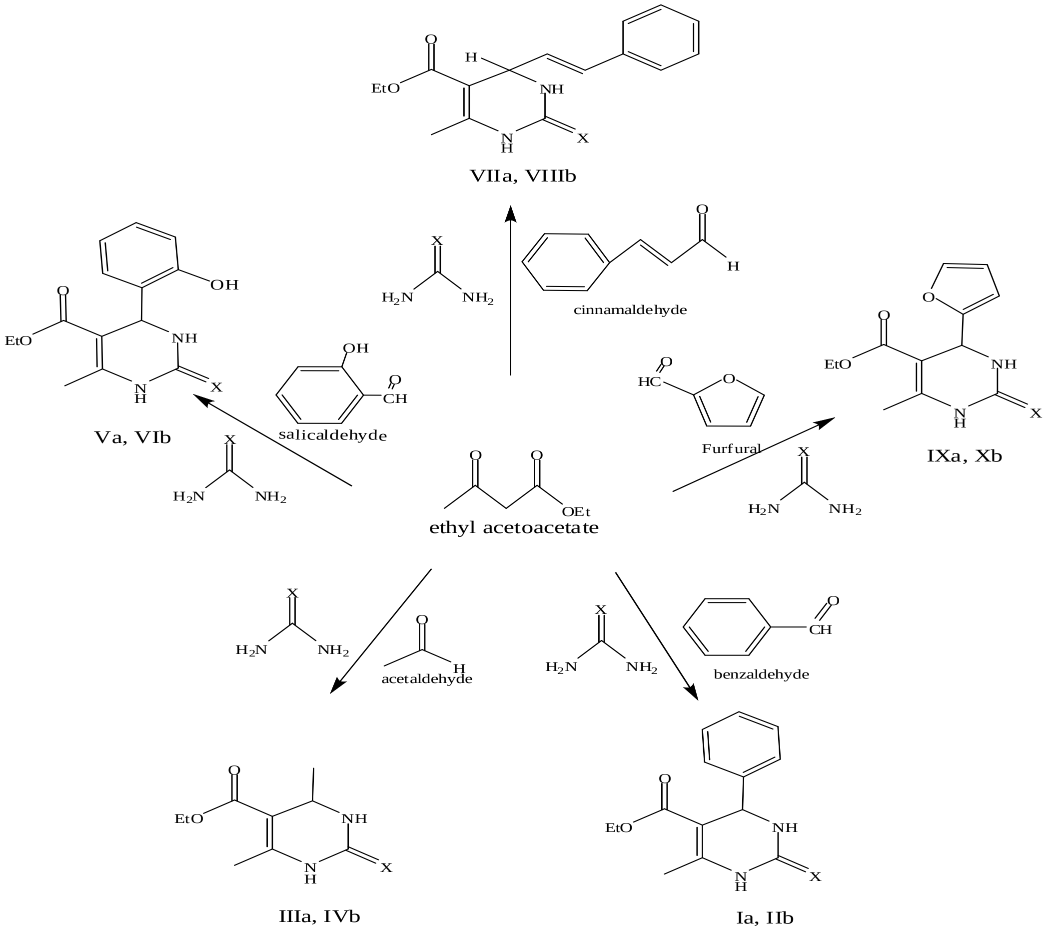
Comp.No	**R**	**X**	**Reaction Temp C°**	**Time h**	**Yield %**	**Yield gram**	**Color**	**m.p C°**
Ia		O	Reflux temperature	2	91	2.64	colorless	205-207 (lit. 203[10])
IIb		S	Reflux temperature	2	85	2.67	colorless	202-205 (lit. 205-207[1]
IIIa	$-CH_3$	O	Reflux temperature	4	40	0.94	colorless	195-197
IVb	$-CH_3$	S	Reflux temperature	4.5	31	0.78	brown	192-195
Va		O	Reflux temperature	3	83	2.60	yellow	105-109 (lit. 182-183 [15])
VIb		S	Reflux temperature	3	80	2.63	Yellow	103-105(lit.243 [16])
VIIa		O	Reflux temperature	2	89	2.75	Pale yellow	239-242 (lit. 230-233 [14])
VIIIb		S	Reflux temperature	2.5	84	2.81	Yellow	98-104 (lit. 248 [17])
IXa		O	Reflux temperature	3	78	2.21	Pale yellow	191-194 (lit. 209-211 [12])
Xb		S	Reflux temperature	3	80	2.39	Pale yellow	215-219 (lit. 186 [17])

RESULTS AND DISCUSSION:

Reaction conditions of the prepared dihydropyrimidinones/thionesderivatives in **Table 1**. The adopted method provided an excellent yields ranging from 78 to 91 % for aromatic, aromato aliphatic, and heterocyclic aldehydes in shorter reaction time of around 2-4 hours and high purity of the products as determined by chromatographic techniques. With acetaldehyde, an aliphatic aldehyde, the cross corresponding 3,4-dihydroxypyrimidinone and 3,4-dihydroxy pyrimidinthione were formed in very low yield (40-31%).

CONCLUSION: The following points can be concluded from this work: Green procedure for synthesis of 3, 4 dihydropyrimidinones and its analogues 3, 4 dihydropyrimidinthione using three-component react by condensations of an aldehyde, ethyl acetoacetate, and urea or thiourea in a one-pot operation without catalyst and free solvent is extremely useful and improved procedure for the Biginelli reaction with excellent yields in shorter reaction time with high purity of the products **Scheme1**.

Thus, this procedure of green chemistry approach in synthesis of 3,4- dihydropyrimidinones/thiones was minimized chemical hazardous, easy applied and high yields. So we recommend use our procedure as improved procedure in the synthesis of dihydropyrimidinones.



X: O, S

SCHEME 1: CHEMICAL STRUCTURE OF PREPARED DIHYDROPYRIMIDINONES/THIONESDERIVATIVES

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