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Research Article

Three Component Coupling Green synthesis of 3, 4 dihydrtopyrimidinone derivatives under solvent free conditions by Biginelli reactions.

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ABSTRACT
A simple and precise green synthesis method that have been used to synthesis of dihydrtopyrimidinone (DHPMs) and their sulphur analogue dihydropyrimidinthione derivatives traditionally to carry out the conventional Biginelli reaction involves three-component one-pot condensation of an aldehyde, β-ketoester and urea or thiourea in ethanol under strong acidic condensation HCl. The dihydropyrimidinone (DHPMs) and their sulphur analogue dihydropyrimidinthione derivatives which are act as antibacterial, anti-inflammatory, antimalarial agents, and antiviral, antitumor, hypnotic's etc. 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 (80–95%). The advantages of this green chemistry approach the excellent yield, short time, operational simplicity, and the avoidance of the use of organic solvents and friendly preparation. Products obtained were identified using physical and spectroscopic IR, ^{1}HNMR, GC. Mass, UV, techniques.

KEYWORDS
Dihydropyrimidinones (DHPMS), Biginelli reaction, Solvent-free, One-pot synthesis.

1. INTRODUCTION

3,4-Dihydropyrimidinone and their sulphur analogue 3,4-Dihydropyrimidinthiones[1] are classified as hetero- cycles compound[2] and containing pyrimidine ring which is containing two nitrogen atoms 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

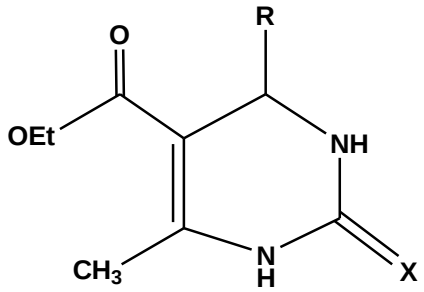

Figure 1. Structure of DHPMs

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-inflammatory [4], antiviral [5], antitumor [6], antimalarial agents [7], hypnotics, anticonvulsant, antithyroid, antihistaminic agents , antibiotics [2] and in addition, 4-aryldihy- dropyrimidines 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 thio analogue 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 involve 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 given as under.

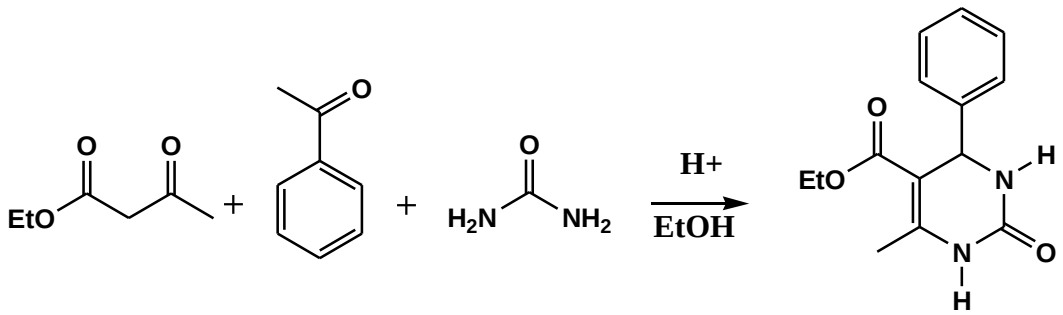

Figure 2: Biginelli reactions ethyl aceto acetate, benzaldehyde and urea.

The three components reaction was carried out by simply heating a mixture 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 antitumor, fungicidal, bactericidal, anti-inflammatory and antiviral activities [13].

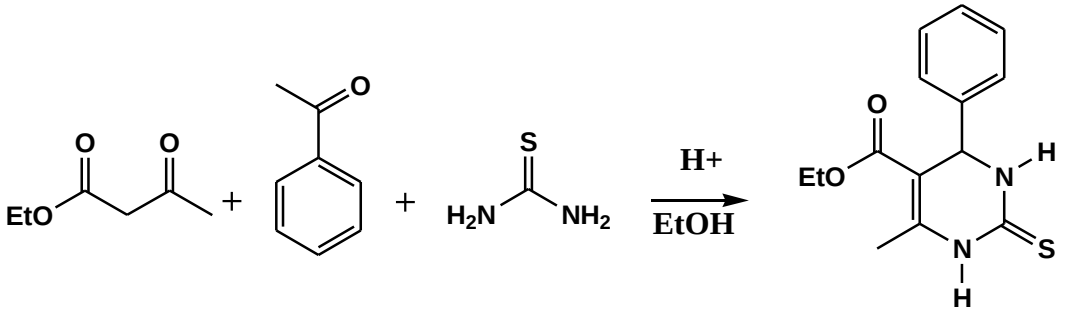

Figure 3: Biginelli reactions ethyl aceto acetate, benzaldehyde and thiourea.

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] Figure 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).

2. MATERIALS AND METHODS

The physical testing like 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, and 500MHz Brucker Spectrometer and Shimadzu GC-MS QP 2010 GC respectively. Benzaldehyde, 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) precoated plates or coated over glass with different mobile phases.

2.1. *General procedure for synthesis of 3, 4- dihy- dropyrimidin-2(1H) ones/thiones:*

A mixture of series of different 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. The completion of the reaction is checked by TLC time to time. The reaction mixture was brought to room temperature. The solid was taken out carefully in a conical flask. The different product was washed with cold water to remove excess of urea and then recrystallized from rectified spirit to give a pure solid product. The products are referred as

Compound- I,II,III,,IV,V,VI,VII,VIII and IX Reaction parameter of the prepared Dihydropyrimidinones/ Thiones derivatives and structural elucidation is as under.The compound –I 5-(Ethoxy carbonyl) - 4 - (phenyl) - 6-methyl - 3, 4 - dihydropyrimidin-2(1H) one, Compound- II 5-(Ethoxy carbonyl) - 4 - (phenyl) - 6-methyl - 3, 4 - dihydropyrimidin-2(1H) thione, Compound- III 5- (Ethoxy carbonyl) - 4, 6- dimethyl- 3, 4 - dihydropyrimidin-2(1H) one, Compound- IV, 5- (Ethoxy carbonyl) - 4, 6- dimethyl- 3, 4 - dihydropyrimidin-2(1H)thione, Compound- V,5- (Ethoxy carbonyl) -4- (6-hydroxyphenyl)-6- methyl -3, 4- dihydropyrimidin-2(1H) one, Compound- VI,5- (Ethoxy carbonyl) -4- (6-hydroxyphenyl)-6- methyl-3, 4-dihydropyrimidin-2(1H) thione, Compound VII,5- (Ethoxy carbonyl) -4- (2-phenyl ethylene)-6-methyl-3, 4-dihydropyrimidin-2(1H) one, Compound VIII, 5-(Ethoxy carbonyl)-4-(2-furyl) -6-methyl - 3, 4-dihydropyrimidin-2(1H) thione, and compound IX,5- (Ethoxy carbonyl) -4- (2-phenyl ethylene)-6-methyl-3, 4-dihydropyrimidin-2(1H) thione. The spectral characterization of few compounds are as under.

Compound- I

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); UV (nm): 233.2, 355.3 nm.MS (m/z): 261,244, 231,213, 184;

Compound- II

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); UV (nm): 203.6, 306.5 nm.MS (m/z):275,245, 231, 204, 199;

Compound- III

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); UV (nm): 202.3, 282.4 nm.MS (m/z):198, 180, 151, 133, 107;

Compound- IV

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}; UV (nm):224.7, 293.5 nm MS (m/z):250, 204, 176, 146, 112, 99, 56; .

Compound- V

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); UV (nm):212, 301.8 nm MS (m/z):276, 247, 218,205, 189, 123(2.5); .

Compound- VI

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),; UV (nm):216, 305.2 nm.MS (m/z):293, 247,275, 219,189, 166;

Compound VII

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); UV (nm): 202.6, 256.7 nm.MS (m/z):286, 273, 257,240,213, 183, 170;

Compound VIII

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); UV (nm): 235.0, 214. nmMS (m/z):267, 236, 220,209,193, 179;

Compound IX

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); UV (nm):201.4, 256.9 nm MS (m/z):302, 287, 273, 257,229 .

3. RESULTS AND DISCUSSION

Reaction conditions of the prepared dihydropyrimidinones/thiones derivatives as explained in experimental procedure. The adopted method provided an excellent yields ranging from 80 to 91 % for aromatic, aromato aliphatic, and heterocyclic aldehydes in shorter reaction time of around 2-3 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 (30%). The Green procedure for synthesis of 3, 4 dihydropyrimidinones and its analogues 3,4dihydropyrimidinthione 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 about 80 to 95% in shorter reaction time with high purity of the products synthesized as per the experimental method. Thus, this procedure of green chemistry approach in synthesis of 3, 4- dihydropyrimidinones/thiones was minimized chemical

hazardous, easy applied and high yields. The avoidance of the use of organic solvents and friendly preparation.

4. CONCLUSION

The green chemistry procedure approach in synthesis of 3, 4- dihydropyrimidinones/thiones was minimized chemical hazardous, also less environmental pollution. This indicates procedure is ecofriendly. The green procedure employed for the synthesis of all above coupling products are easy and gives better yields about 70-80%. No wastage of chemicals, no longer period of time required for the completion reaction. Procedure adopted is simple and cost effective or less cost of production. The use of organic solvents is avoided and hence friendly preparation.

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