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Synthesis of Some Bigienelli Compounds from Thiosemicarbazide use $ZnCl_2$ as Catalyst under Solvent Free Condition

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Abstract

Synthesis of some 1-amino-5-acetyl-6-methyl-4-aryl-3,4-dihydropyrimidine-2-thione and 1-amino arylmethylidiene-5-acetyl-6- methyl-4-aryl-3,4-dihydropyrimidine-2-thione from reaction of acetyl acetone, thiosemicarbazide and aldehyde was achieved paralled synthesis of some 1-amino-5-ethoxycarbonyl-6-methyl-4-aryl-3,4-dihydropyrimidine-2-thione and 1-amino arylmethylidiene-5-ethoxycarbonyl-6-methyl-4-aryl-3,4-dihydropyrimidine-2-thione was accomplished by reaction of ethylacetoacetate, thiosemicarbazide and aldehyde, the reaction was carried out in presence of $ZnCl_2$ as catalyst, the reaction progress was followed by TLC analysis, and spectroscopic analysis (IR, VIS-UV,^{1}HNMR and ^{13}CNMR).

Keywords: Dihydropyrimidines; Schiff base.

1. Introduction

Biginelli reaction is carried out in solvent such as water [1], ionic liquids [2] ethanol [3], or methanol [4], but more recently aprotic solvent such as dioxane [5], toluene [6], acetic acid [7], or acetonitrile [8] are also use, recent ternd to provied the reaction without any solvent [9]. Bignelli reaction depend on the amount of acid catalyst in the medium [2].

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BrØnsted acids such as hydrochloric acid [10], or sulfuric acid [11] have been employed, but nowadays the used of lewis acids such as BF_3OEt_2 and CuCl [12], $LaCl_3 .7H_2O$ and $CoCl_2 .6H_2O$[13] , $FeCl_3$and $NiCl_2$ [14] $ZnCl_2$ [15] $Yb(OTf)_3$,[16], $La(OTf)_3$, $InCl_3$,[17], $InBr_3$ and $InCl_3$ [18], $In(OTf)_3$ [19], LiBr [20] are prevalent. Biginelli reaction is slow at room termperature [21] so activating by heating [6], microwave dielectric [22], ultrasound [23], IR irradiation [24], or by photochemical methods [25]. Most of the work cited in literature used ethylacetoacetate or other ß-ketoesters as dicarbonyl precursor, it is of ,interest, to test comparatively the use of ß-diketone as dicarbonyl in this work. Here in, we report the use of Biginelli reaction in construction of amino dihydropyrimidine-2- thione and aryl methylidiene amino dihydropyrimidine-2-thione with the use $ZnCl_2$ catalyst.

2. Materials and methods.

All chemicals used in this work were of analytical grade, melting point were determined by Gallenkamp melting point apparatus and were incorrect. UV- spectrophotometer model (shimadzu, Japan) the wavelength express in nm. IR spectrum (in KBr disk) is recorded using FTIR 4800s instrument model (shimadzu, Japan) the frequency are expressed in cm^{-1}. The ^{1}HNMR and^{13} CNMR record at 400MHz plus instrument model (BRUKER Germany) using DMSO as solvent the chemical schift expressed in δ ppm.

2.1 General procedure for synthesis of 1-amino-5-acetyl-6-methyl-4-aryl-3,4-dihydropyrimidine-2-thione and 1-amino arylmethylidiene-5-acetyl-6- methyl-4-aryl-3,4-dihydropyrimidine-2-thione

in a 1 litre round bottom flask equipped with a reflux condenser were placed 0.01mol of the required aromatic aldehyde , 0.01mol acetyacetone , 0.01mol thiosemicarbazide and 0.01mol zinc chloride as catalyst, the mixture was heating with stirring under reflux for 10 hours, after complete the reaction as indicate by TLC, the resulting mixture kept overnight in refrigerator and then pour in 15ml cool water with shaking to precipitate the product, the product was dissolved in hot ethanol, and allowed to preciptate and then separated into two components by TLC method using plates of alminium precoating silca gel F_{254} the solvent system are chloroform: methanol (9.2 : 0.8).

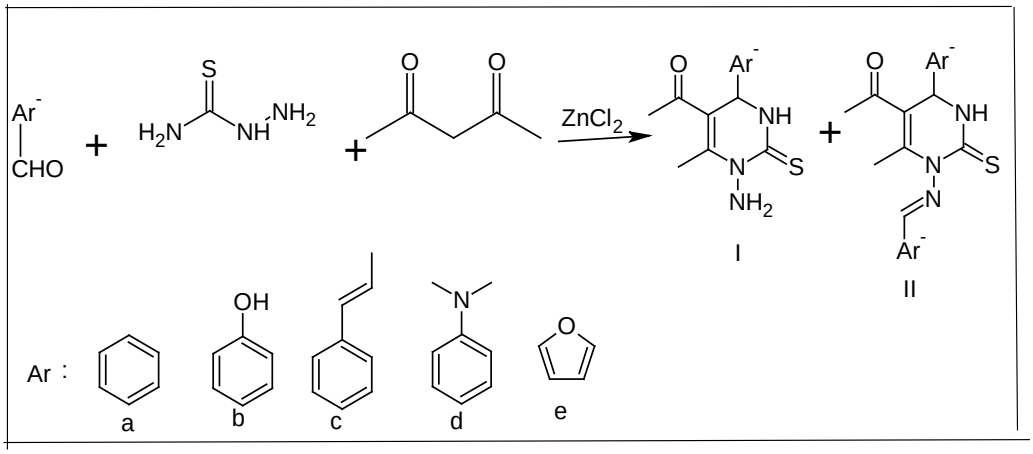

Figure 1: chemical structure of 1-amino-5-acetyl-6-methyl-4-aryl-3,4-dihydropyrimidine-2-thione and 1-amino

arylmethylidiene-5-acetyl-6- methyl-4-aryl-3,4-dihydropyrimidine-2-thione

I_a-1-amino-5-acetyl-6-methy-4-phenyl-3,4-dihydropyrimidine-2-thione: **yield** 48% **mp** < 260 °C **, UV -VIS (nm**) λmax 273.6, 265.6, 250.8, 223.2 ; **IR(KBr,cm-^{l})** : 3394.48 (N-H), 1733.89 (C=O), 1535.23 (N-H_{vs}), 1103.21 (C=S_s). **^{l}HNMR (DMSO,δ ppm**) : 3.50 (3,H,CH_3), 2.50 (3,H,CH_3), 1.35 (1,H,CH), 7.40- 8.20 (5, H, Ar).

II_a-1-amino phenyl methylidiene-5-acetyl-6-methyl-4-phenyl-3,4-dihydropyrimidine-2-thione: **yield** 47%**, mp** < 260 °C, **UV-VIS (nm)** λmax 310.4, 232.2 ; **IR(KBr,cm-^{l}**) : 3427.27(N-H), 1735.81 (C=O), 1560.30 (C=N), 1107.06 (C=S_s). **^{l}HNMR (DMSO, δ ppm)** : 3.50 (3,H,CH_3), 2.50 (3,H,CH_3), 4.10 (1,H,CH), 1.25 (1,H,CH), 7.21- 7.45 (10, H, Ar).

I_b-1-amino-5-acetyl-4-(2-hydroxy phenyl)-6-methyl-3,4-dihydropyrimidine-2-thione: **yield** 34%, **mp** < 260 °C**, UV-VIS(nm**) λmax 328.5 ;**IR(KBr,cm-^{l})**: 3741.65 (O-H), 1733.89 (C=O), 1566.09 (N-H_{vs}), 1137.92 (C=S_s). **^{l}HNMR (DMSO, δ ppm)** : 2.50 (3,H,CH_3), 3.50 (3,H,CH_3), 1.35 (1,H,CH), 8.52(1H,OH).

II_b-1-(amino[-2-hydroxy]phenyl methylidiene)-5-acetyl-4-(2-hydroxy phenyl)-6-methyl-3,4-dihydropyrimidine-2-thione : **yield** 35%**mp** < 260 °C**, UV-VIS(nm)** λmax 331.0, **IR(KBr,cm-^{l}):** 3442.70 (N-H), 1730.03 (C=O), 1569.95 (C=N_m), 1110.92 (C=S_s), **^{l}HNMR (DMSO, δ ppm)** : 2.50 (3H,CH_3), 3.50 (3H,CH_3), 1.25 (1H,CH), 1.71(1H,CH), 8.40 (`1H,OH), 6.70- 7.95. (10, H, Ar)

I_c-1-amino-5-acetyl-6-(cinnamyl)-6-methyl-3,4-dihydropyrimidine-2-thione: **yield** 37%, **mp** < 260 ° C , **UV-VIS(nm)** λmax 265.5; **IR(KBr,cm-^{l}):** 3419.56 (N-H), 1726.17 (C=O), 1591.16 (N-H_{vs}),1105.14 (C=S_s).

II_c-1-amino phenyl prop-2-en-1-ylidiene-5-acetyl-4-(cinnamyl)-6-methyl-3,4-dihydropyrimidine-2-thione**:** **yield** 37%,: **mp** < 260 °C**, UV-VIS(nm)** 266; **IR(KBr,cm-^{l}):**3446.56 (N-H), 1731.96 (C=O), 1556.45 (C=N_m), 1101.28 (C=S_s),1635.52(C=C),**^{l} HNMR (DMSO, δ ppm)** : 2.50 (3,H,CH_3) 3.50 (3,H,CH_3) 1.31 (1,H,CH) 6.85 (1H,CH) 6.9, 6.95 (1H,CH) 7.2,7.31,7.35 (1H,CH) 7.0, 7.05 (1H,CH) 7.35, - 7.95, (10, H, Ar), **^{l3}CNMR (DMSO, δ ppm)**: 39.31(1C, CH_3), 39.52(1C,CH_3), 39.73(1C,CH), 39.94(1C,C), 40.15(1C,C), 40.36(2C,CH), 40.56(1C,CH), 125.56, 127.39, 129.31 129.36 (12CAr), 136.35 (1C,CH), 139.33 (1C,CH), 145.21 (1C,C=S) 178.17(1C,C=O).

I_d-1-amino-5-acetyl-4-(4-dimethyl aminophenyl)-6-methyl-3,4-dihydropyrimidine-2-thione: **yield** 37%, **mp** < 260 ° C , **UV-VIS(nm**) λmax 355.5,236.5; **IR(KBr,cm-^{l})**: 3741.65 (N-H), 1731.96 (C=O) 1569.95 (NH_{vs}), 1110.92 (C=S_s), 1421.44(C-N),**^{l} HNMR (DMSO, δ ppm)** : 2.50 (3,H,CH_3) 3.50 (3,H,CH_3) 2.21 (1,H,CH) 2.81 (3,H,CH_3) 3.10 (3,H,CH_3) 6.65-7.05 (5, H, Ar)

II_d - 1-amino[-4-(dimethylamino)phenyl methylidiene]-5-acetyl-4-(4-dimethyl aminophenyl)-6-methyl-3,4-dihydropyrimidine-2-thione: **yield** 36%**, mp** < 260 °C**, UV-VIS(nm)** λmax 236.5 ; **IR(KBr,cm-^{l})** : 3413.77 (N-H), 1731.96 (C=O), 1517.87 (C=N) 1114.78 (C=S_s),1429.15 (C-N). **^{l}HNMR (DMSO, δ ppm)** : 2.50 (3,H,CH_3) 3.50 (3,H,CH_3) 4.10 (1,H,CH) 0.81, (1,H,CH) 3.01 (3,H,CH_3), 3.21 (3,H,CH_3), 1.30 (3,H,CH_3), 1.83 (3,H,CH_3), 6.74- 8.05 (10, H, Ar)

I_e-1-amino-5-acetyl-4-(furyl)-6-methyl-3,4-dihydropyrimidine-2-thione: **yield** 36%**, mp** < 260 °C, **UV-VIS(nm)** λmax 319.0; **IR(KBr,cm-[1])** : 3411.84 (NH), 1731.96 (C=O), 1585.38 (NH_{vs}) 1107.06 ($C=S_s$),1227.79(C-O), **[1]HNMR (DMSO, δ ppm**) : 2.50 (3,H,CH_3) 3.50 (3,H,CH_3) 1.81 (1,H,CH) 8.50 (2, H, NH_2)

II_e-1-amino[furan-2-ylmethylidiene]-5-acetyl-4-(furyl)-6-methyl-3,4-dihydropyrimidine-2-thione: **yield** 36%, **mp** < 260 °C,**UV-VIS(nm**) λmax 274.5; **IR(KBr,cm-[1])** : 3436.91 (NH), 1731.96 (C=O), 1566.09 (C=N) 1137.92 ($C=S_s$),1413.27 (C-O). **[1]HNMR (DMSO, δ ppm)** : 2.5 (3,H,CH_3), 3.50 (3,H,CH_3), 4.10 (1,H,CH), 1.70 (1,H,CH) 6.45, - 8.25 (8, H, Ar).

2.2 General procedure for synthesis of 1-amino-5-ethoxycarbonyl-6-methyl-4-aryl-3,4-dihydropyrimidine-2-thione and 1-amino arylmethylidiene-5-ethoxycarbonyl-6-methyl-4-aryl-3,4-dihydropyrimidine-2-thione

in a 1 litre round bottom flask equipped with a reflux condenser were placed 0.01mol of the required aromatic aldehyde , 0.01mol ethyl acetoacetate, 0.01mol thiosemicarbazide and 0.01mol zinc chloride as catalyst, the mixture was heated with stirring under reflux for 10 hours, after complete the reaction as indicate by TLC, the resulting mixture kept overnight in refrigerator and then pour in 15ml cool water with shaking to precipitate the product, the product was dissolved in hot ethanol, and allowed to preciptate and separated into two components by TLC method using plates of alminium precoating silca gel F_{254} the solvent system are chloroform: methanol (9.5 : 0.5).

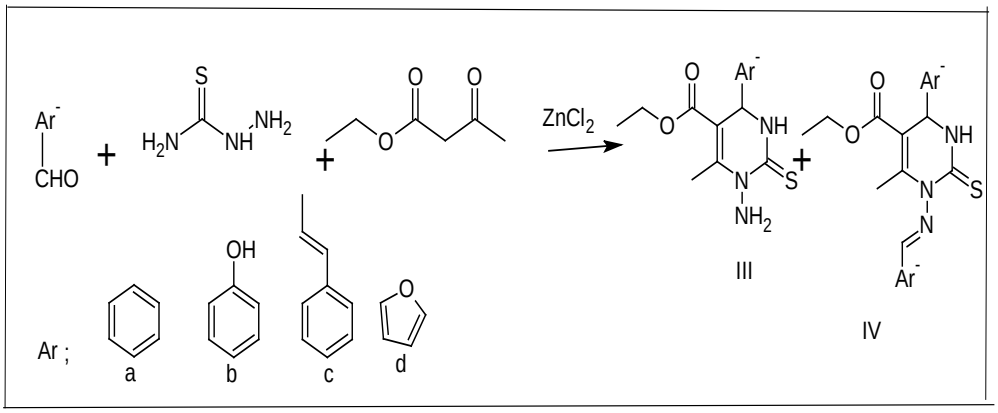

Figure 2: chemical structure of 1-amino-5-ethoxycarbonyl-6-methyl-4-aryl-3,4-dihydropyrimidine-2-thione and 1-amino arylmethylidiene-5-ethoxycarbonyl-6-methyl-4-aryl-3,4-dihydropyrimidine-2-thione

III_a -1-amino-5-ethoxycarbony-6-methy-4-phenyl-3,4-dihydropyrimidine-2-thione**: yield** 40.7% **mp** < 260 °C , **UV-VIS(nm**) λmxa 267.0,227.0 ; **IR(KBr,cm-[1])** : 3542.99 (N-H), 1706.88 (C=O) 1303.79 (C-O)1625.88 (N-H_{vs}) 1182.28($C=S_s$) **[1]HNMR (DMSO, δ ppm**) : 3.50 (3,H,CH_3) 1.01 (3,H,CH_3), 2.50 (2,H,CH_2), 2.71 (1,H,CH), 5.81(2H,NH_2), 7.01-7.81 (5, H, Ar)

IV_a -1-amino phenyl methylidiene-5-ethoxycarbony-6-methy-4-phenyl-3,4-dihydropyrimidine-2-thione: **yield** 40.6% **mp** < 260 °C**, UV-VIS(nm**) λmxa 329.0; **IR(KBr,cm-[1])** : 3400.27 (NH), 1726.17 (C=O), 1602.74 (C=N)

1371.29 (C-O)1101.85 (C=Ss). **^{1}HNMR (DMSO, δ ppm)** : 3.50 (3,H,CH_3), 1.30 (3,H,CH_3) , 2.50 (2,H,CH_2), 4.10 (1,H,CH), 3.21 (1,H,CH), 7.42- 8.25 (10, H, Ar); **^{13}CNMR (DMSO, δ ppm)**: 39.32 (1C,CH_3), 39.53 (1C,CH_3), 39.73 (1C,CH_2), 39.94 (1C,C), 40.15 (1C,C), 40.36 (1C,CH), 40.57 (1C,CH), 127.26, 129.13, 130.44, 134.75 (12C,Ar), 142.80 (1C, C=S), 185.90 (1C,C=O).

III_b - 1-amino-5-ethoxycarbony-6-methy-4-(2-hydroxy-phenyl)-3,4-dihydropyrimidine-2-thione **yield** 49%**, mp** < 260 °C**, UV-VIS(nm)** λmax 317.0; **IR(KBr,cm^{-1})** : 3446.56 (O-H), 1733.89 (C=O), 1637.45 (NH_{vs}) 1390.58 (C-O),1112.85(C=S_s) **^{1}HNMR (DMSO, δ ppm**) : 3.50 (3,H,CH_3), 1.31 (3,H,CH_3), 2.50 (2,H,CH_2), 4.10 (1,H,CH), 5.52 (2H,NH_2) 6.82- 7.53 (5, H, Ar)

IV_b -1-(amino[-2-hydroxy]phenyl methylidiene)-5-ethoxycarbonyl-4-(2-hydroxy phenyl)-6-methyl-3,4-dihydropyrimidine-2-thione: **yield** 49%**, mp** < 260 °C, **UV-VIS(nm)** λmax 331.0, 230.5; **IR(KBr,cm^{-1})** : 3444.63 (H-O)1841.88 (C=O), 1629.74 (C=N),1108.99 (C=S_s).

III_c -1-amino-5-ethoxycarbony-6-methy-4-(cinnamyl)-3,4-dihydropyrimidine-2-thione**: yield** 37.9% **mp** < 260 °C**, UV-VIS(nm)** λmax 342.0, 264.0; **IR(KBr,cm^{-1})** : 3419.56 (N-H), 1731.96 (C=O), 1587.31 (N-H_{vs}), 1415.65(C-O),1099.85 (C=S_s), **^{1}HNMR (DMSO, δ ppm**) : 3.50 (3,H,CH_3), 1.21 (3,H,CH_3), 2.50 (2,H,CH_2), 6.64 (1,H,CH), 7.00 (1,H,CH) 5.51(2,H,NH_2) 7.01-8.52 (5, H, Ar)

IV_c -1-amino phenyl prop-2-en-1-ylidiene -5-ethoxycarbony-6-methy-4-(cinnamyl)-3,4-dihydropyrimidine-2-thione: **yield** 37.9%, **mp** < 260 °C, **UV-VIS(nm**) λmax 330.0; **IR(KBr,cm^{-1})** : 3452.34 (N-H), 1637.45 (C=N),1101.28 (C=Ss), **^{1}HNMR (DMSO, δ ppm)** : 3.50 (3,H,CH_3), 1.31 (3,H,CH_3), 2.50 (2,H,CH_2), 4.10 (1,H,CH), 6.42 (1,H,CH), 7.05 (1,H,CH), 6.70(1,H,CH), 7.35 (1,H,CH), 7.38- 7.92 (10, H, Ar).

III_d-1-amino-5-ethoxycarbony-6-methy-4-(furyl)-3,4-dihydropyrimidine-2-thione: **yield** 31.4% **mp** < 260 °C**, UV-VIS(nm**) λmax 317.5, 268; **IR(KBr,cm^{-1})** : 3442.70 (N-H), 13731.96 (C=O), 1566.09 (N-H_{vs}),1139.85 (C=S_s) **^{1}HNMR (DMOS, δ ppm)** : 3.50(3,H,CH_3) , 1.32 (3,H,CH_3), 2.50 (2,H,CH_2), 4.10(1,H,CH) .

IV_d-1-amino[furan-2-ylmethylidiene]-5-ethoxycarbonyl-4-(furyl)-6-methyl-3,4-dihydropyrimidine-2-thione: **yield** 31.4% **mp** < 260 °C **, UV-VIS(nm)** λmax 255.5, 317.0, 268.0; **IR(KBr,cm^{-1})** : 3419.56 (N-H), 1647.10 (C=N), 1402.15 (C-O),1016.42 (C=S_s). **^{1}HNMR (DMSO, δ ppm** : 3.50 (3,H,CH_3) , 1.32 (3,H,CH_3) ,2.50 (2,H,CH_2), 4.15(1,H,CH)

3. Discussion

The first step in the mechanism is believed to be the condensation between the aldehydes and thiosemicarbazide in nucleophilic addition forming the iminium intermediate. The next step of formation Biginelli compound the active methylene of acetyl acetone or ethyl acetoacetate adds onto the intermediate N-acyliminium ion through its enol form produces open-chain compound which subsequently cyclized to the dihydropyrimidin-2-thione by elimination of water, the ethyl acetoacetate enol form more stable than acetyl acetone enol form due to the oxygen atom which has a higher electronegativity than carbon atom will make this resonance structure more stable, the result enol form which adduct to N-acyliminium ion to give 3,4-dihydropyrimidinthione. The

structure of synthesized compounds confirm by comparison TLC with authentic start material, the uv-absorption spectra of all synthesized compound shown that electronic transition absorption at (π-π*) and (n-π*) eg, compound -1_a - ,223.5 and 250 nm, compound-I_e - 236.5 and 355.5 nm and compound –III_c - 264.0 and 364.0nm. Also the IR data of all compounds showing strong absorption bands at frequency in cm^{-1} for N-H and C=S group, the compounds have 1-amino-5-acetyl-6-methyl-4-aryl-3,4-dihydropyrimidine-2-thione and 1-amino-5-ethoxycarbonyl-6-methyl-4-aryl-3,4-dihydropyrimidine-2-thione general structure show very strong absorption at frequency in cm^{-1} for N-H bending due to the presence of NH_2 group, the compounds have 1-amino arylmethyldiene-5-acetyl-6- methyl-4-aryl-3,4-dihydropyrimidine-2-thione and 1-amino arylmethylidene-5-ethoxycarbonyl-6-methyl-4-aryl-3,4-dihydropyrimidine-2-thione general structure show very strong absorption at frequency in cm^{-1} for C=N group.

The ^{1}HNMR confirm the structure of synthesized compounds, all the synthesized compounds show in spectrum singlet peak at δppm for protons in the position of which $3CH_3$ proton must appear with small different in δ values due to the different in the structure of every compound, and all the compounds have 1-amino-5-acetyl-6-methyl-4-aryl-3,4-dihydropyrimidine-2-thione and 1-amino arylmethylidene-5-acetyl-6-methyl-4-aryl-3,4-dihydropyrimidin2-thione general structure show two singlet peak for protons in the position of which $3CH_3$ proton must appear and all the compound have 1-amino-5-ethoxycarbonyl-6-methyl-4-aryl-3,4-dihydropyrimidin2-thione and 1-amino arylmethylidene-5-ethoxycarbonyl-6-methyl-4-aryl-3,4-dihydropyrimidin2-thione general structure show triplet peaks and quarted peaks at the position of which $3CH_3$,$2CH_2$ protons must appear resulting from spin coupling of CH_3-CH_2, the ^{13}CNMR spectrum for compound number II_c show peak at178.17 ppm for C=O and peak at 145.21 ppm for C=S, also compound number IV_a show peak at 185.90ppm for C=O and peak at 142.80 for C=S, Perform Biginelli reaction by use thiosemicarbazide as precursor leads to synthesis compounds having variety structures depend on the aldehydes use in the reaction .

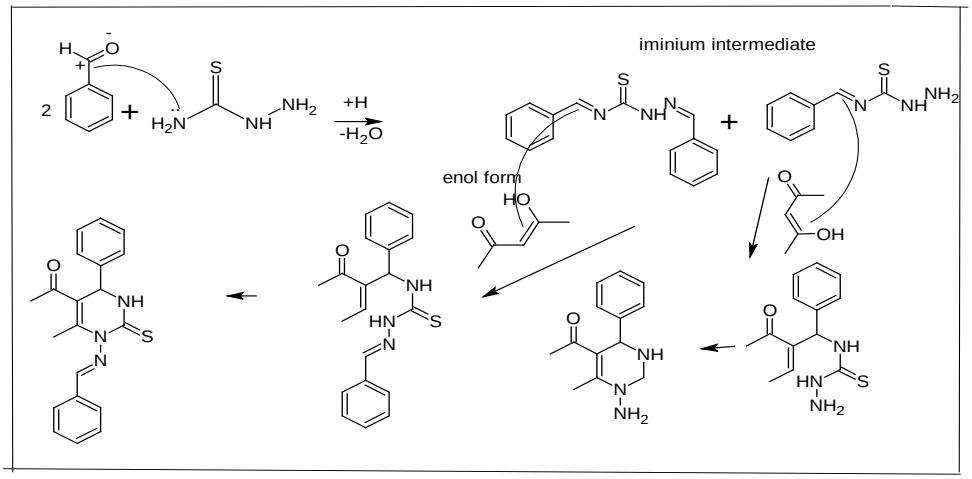

Figure 3: mechanism of the Biginelli reaction

4. Conclusion

Most published of Biginelli reaction involved urea or thiourea as one component of this reaction the modified

in this research is use thiosemicarbazide, and produced two Biginelli compounds in one reaction and one of them have N's substituted in pyrimidine ring has the structure of aldehyde use in the reaction.

References

[1] Ichiro *Suzuki*., Yuko *Suzumura*., & Kei *Takeda*. " Metal triflimide as a lewis acid catalyst for biginelli reaction in water". *Tetrahedron Letters*. 47(45), (2006) 7861-7864.

[2] Jiajian Peng & Youquan Deng. " Ionic liquid catalyzed Biginelli reaction under free-solvent condition". *Tetrahedron letter*. 42(34) (2001).5917-5919.

[3] Michal.Holden, & David Crouch. "The Biginelli reaction". *Journal of the chemical education* .78(8) (2001). 1104-1105.

[4]Lin.Haixia., Ding.Jinchang., Chen.Xianten. & Zhang.Ziyi. "An efficient synthesis of 5-alkoxycarbony-4-aryl-3,4-dihydropyrimidin-2(1H)ones catalyzed by KSF montmorillonite". *Molecular*. 5 (2000) 1240-1243.

[5] Satyajit. Saha., & Jarugu.Narasimha.Moorthy. "Enantioselective organocatalytic Biginelli reaction:dependence of the catalyst on sterics, hydrogen bonding and reinforced chairality" .*J.Org.Chem.*76(2) (2010) 396-402.

[6] Khodabakhsh.Niknam., Alieza. Hasaninejad., & Madihe. Arman. Synthesis of some new bis-3,4-dihydrpyirimdin-2(1H)ones by using silica-supported tin chloride and titanium tetrachloride. *Chinese Chemical Letters.* 21(4) (2010) 399-402.

[7] Majid. Heravi., Fatemeh.Derikvand., & Fatemeh. Bamoharram. "Acatalytic method for synthesis of Biginelli-type 3,4dihydropyrimidin-2(1H)one using12-tungstophosphoric acid". *Journal of Molecular Catalysis A:Chemical.* 242(1-2) (2005) 173-175.

[8] Gourhari. Mait., Pradip. Kundu., & Chandrani. Guin. "One –pot synthesis of dihydropyrimidinone catalyzed by Lithium Bromide:An improved procedure for the Biginelli reaction". *Tetrahedron*. 44 (13) (2003) 2757-2758.

[9] Franca. Bigi, Silvia. Cartoni, Bettina. Frullanti, Raimondo.Maggi, & Giovanni. Sartori. "A revision of the Biginelli reaction under solid acid catalysis.Solventfree synthesis of dihydropyrimidines over montmorillionite KSF". *Tetrahedron letters*. 40 (17) (1999) 3465-3468.

[10] Petro.Biginelli. "Derivati aldeiduredici degli eteri acetil-e dossal-acetico". *Gass. Chim. Ital.* 23 (1893) 360-416.

[11] Victor. Saloutin, Ya. Burgart, Olga. Kuzueva, Christian. Kappe, & Oleg. Chupakhin. " Biginelli condensations of fluorinated3-oxo esters and 1,3-diketones". *Journal of Fluorine Chemistry*. 103(1) (2000) 17-23.

[12] Alessandro. Dondoni, Alessandro. Massi, & Simona. Sabbatini . "Toward the synthesis of C-glycosylated dihydropyrimidine libraries via the three component Biginelli reaction. Anovel approach to the artificial nucleoside". *Tetrahedron Letters*. 42 (27) (2001) 4495-4497.

[13] Jin. Lu, Yinjuan. Bai, Zhenjun. Wang, Bingqin. Yang, & Huairang. Ma. "one-pot synthesis of dihydropyrimdin-2(1H)ones using Lanthanum chloride as a catalyst". *Tetrahedron Letters* , 41(47) (2000) 9075-9078.

[14] Jin. Lu, & Yinjuan. Bai. "catalysis of Biginelli reaction by ferric and nickel chloride hexahydrates. One pot synthesis of 3,4 dihydropyrimidin2(1H)ones". *Synthesis* . 4. (2002) 0466-0470.

[15] Mohamed. Pasha, Ramachandra. Swamy, & Vaderapura. Jayashankara. "one pot synthesis of 3,4 dihydropyrimidin-2(1H)ones/thiones catalyzed by zinc chloride :An improved procedure for the Biginelli reaction using microwave under solvent free conditions". *Indian journal of chemistry*. 44B. (2005) 823-826.

[16] Alessandro. Dondoni, Alessandro. Massi, & Simon. Sabbatini. "Improved synthesis and preparative scale resolution of racemic Monastrol". *Tetrahedron Letters*. 43 (34) (2002) 5913-5916.

[17] Brindaban. Ranu, Alakananda. Hajra, & Umasish. Jana. "Indium (111) chloride catalyzed one-pot synthesis of Dihydropyrimidinone by a three coupling of 1,3 dicarbonyl compounds, aldehydes and urea :An improve procedure for Biginelli reaction". *J. Org. Chem*. 65(19) (2000) 6270-6272.

[18] Nan-yan. Fu, Yao-feng. Yuan, Mei-li. Pang, Ji-toa. Wang, & Clovis. Peppe. " Indium(111)halide catalyzed preparation of ferrocene dihydropyrimidinone". *Journal of Organometalli Chemistry*. 672(1-2) (2003) 52-57.

[19] Rain. Ghosh, Swarupananda. Maiti, & Arijit. Chakraborty. " $In(OTf)_3$.-catalysed one-pot synthesis of dihydropyrimidin-2(1H)ones". *Journal of Molecular Catalysis A:Chemical*. 217(1-2) (2004) 47-50.

[20] Gourhari. Mait, Pradip. Kundu, & Chandrani. Guin."One –pot synthesis of dihydropyrimidinone catalyzed by Lithium Bromide:An improved procedure for the Biginelli reaction". *Tetrahedron*. 44 (13) (2003) 2757-2758.

[21] Wen-Jing Li., Shuai Liu., Ping He.,& Ming-Wu Ding. " New efficient synthesis of pyrimido{1,6-c}quinazolin-4-ones by a Biginelli 3CC/Staudinger/aza-Witting sequence". *Tetrahedron*. 66 (41) (2010) 8151-8159.

[22] Mazaahir. Kidwai, Shilpi. Saxena, Richa. Mohan, & R. Venkatarmanan. " Anovel one pot synthesis of nitrogen containing heterocycles: an alternate methodology to the Biginelli and Hantzsch reactions". *J. Chem. Soc. perkin tarns*. 1. (2002) 1845-1846.

[23] Xinli. Zhang, Yanping. Li, Chenjiang. Liu, & Jide. Wang. " An efficient synthesis of 4-substituted pyrazolyl-3,4dihydropyrimidin-2(1H)(thio)ones catalyst by $Mg(ClO_4)_2$ under ultrasound irradation". *Journal of*

Molecular Catalysis A: Chemical. 253(1-2) (2006) 207-211.

[24]Alexander.Stadler., & Oliver.Kappe. "Automated library generation using sequential microwave. Assisted Chemistry. Application toward the Biginelli multicomponent condensation". *J.Comb. Chem.* 3 (6) (2001) 624-630.

[25] Naser. Foroughifar. Akbar. Mobinikhaledi, & Fathinejad. Jirandehi. "Synthesis of some biginelli compounds in solvent medium using a photochemical method". *Phosphorus, sulfur and silicon and related elements.178*. (2003) 495-500.