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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 arylmethylidene-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 arylmethylidene-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, ¹HNMR and ¹³CNMR).

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 use of Lewis acids such as BF_3OEt_2 and CuCl [12], $\text{LaCl}_3 \cdot 7\text{H}_2\text{O}$ and $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$ [13], FeCl_3 and NiCl_2 [14], ZnCl_2 [15], $\text{Yb}(\text{OTf})_3$, [16], $\text{La}(\text{OTf})_3$, InCl_3 , [17], InBr_3 and InCl_3 [18], $\text{In}(\text{OTf})_3$ [19], LiBr [20] are prevalent. Biginelli reaction is slow at room temperature [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 β -ketoesters as dicarbonyl precursor, it is of interest, to test comparatively the use of β -diketone as dicarbonyl in this work. Here in, we report the use of Biginelli reaction in construction of amino dihydropyrimidine-2-thione and aryl methylidene 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 ^1H NMR and ^{13}C NMR record at 400MHz plus instrument model (BRUKER Germany) using DMSO as solvent the chemical shift 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 arylmethylidene-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 acetylacetone, 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 indicated 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 precipitate and then separated into two components by TLC method using plates of aluminium precoating silica gel F₂₅₄ the solvent system are chloroform: methanol (9.2 : 0.8).

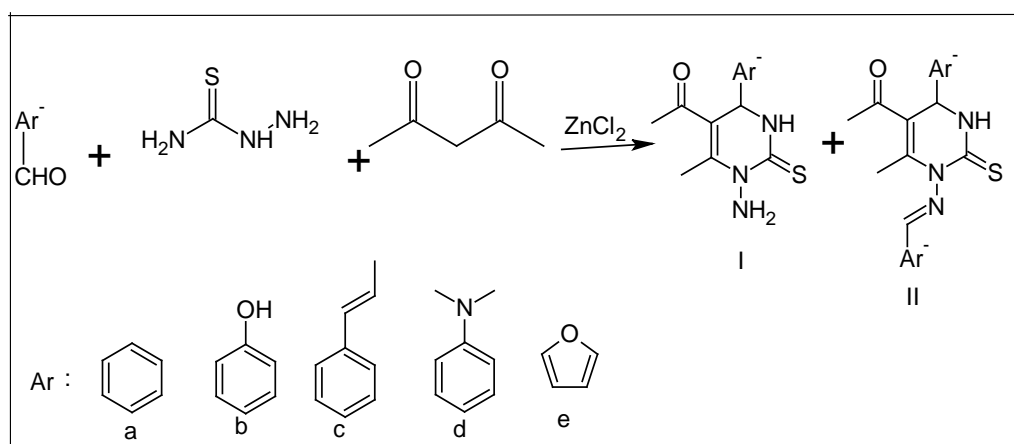


Figure 1: chemical structure of 1-amino-5-acetyl-6-methyl-4-aryl-3,4-dihydropyrimidine-2-thione and 1-amino

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

I_a-1-amino-5-acetyl-6-methyl-4-phenyl-3,4-dihydropyrimidine-2-thione: **yield** 48% **mp** < 260 °C , **UV-VIS (nm)** λ_{max} 273.6, 265.6, 250.8, 223.2 ; **IR(KBr,cm⁻¹)** : 3394.48 (N-H), 1733.89 (C=O), 1535.23 (N-H_{vs}), 1103.21 (C=S_s). **¹HNMR (DMSO, δ ppm)** : 3.50 (3,H,CH₃), 2.50 (3,H,CH₃), 1.35 (1,H,CH), 7.40- 8.20 (5, H, Ar).

II_a-1-amino phenyl methylidene-5-acetyl-6-methyl-4-phenyl-3,4-dihydropyrimidine-2-thione: **yield** 47%, **mp** < 260 °C, **UV-VIS (nm)** λ_{max} 310.4, 232.2 ; **IR(KBr,cm⁻¹)**: 3427.27(N-H), 1735.81 (C=O), 1560.30 (C=N), 1107.06 (C=S_s). **¹HNMR (DMSO, δ ppm)** : 3.50 (3,H,CH₃), 2.50 (3,H,CH₃), 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)** λ_{max} 328.5 ; **IR(KBr,cm⁻¹)**: 3741.65 (O-H), 1733.89 (C=O), 1566.09 (N-H_{vs}), 1137.92 (C=S_s). **¹HNMR (DMSO, δ ppm)** : 2.50 (3,H,CH₃), 3.50 (3,H,CH₃), 1.35 (1,H,CH), 8.52(1H,OH).

II_b-1-(amino[2-hydroxy]phenyl methylidene)-5-acetyl-4-(2-hydroxy phenyl)-6-methyl-3,4-dihydropyrimidine-2-thione : **yield** 35% **mp** < 260 °C, **UV-VIS(nm)** λ_{max} 331.0, **IR(KBr,cm⁻¹)**: 3442.70 (N-H), 1730.03 (C=O), 1569.95 (C=N_m), 1110.92 (C=S_s), **¹HNMR (DMSO, δ ppm)** : 2.50 (3H,CH₃), 3.50 (3H,CH₃), 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)** λ_{max} 265.5; **IR(KBr,cm⁻¹)**: 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-ylidene-5-acetyl-4-(cinnamyl)-6-methyl-3,4-dihydropyrimidine-2-thione: **yield** 37%, **mp** < 260 °C, **UV-VIS(nm)** 266; **IR(KBr,cm⁻¹)**: 3446.56 (N-H), 1731.96 (C=O), 1556.45 (C=N_m), 1101.28 (C=S_s), 1635.52(C=C), **¹HNMR (DMSO, δ ppm)** : 2.50 (3,H,CH₃) 3.50 (3,H,CH₃) 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), **¹³CNMR (DMSO, δ ppm)**: 39.31(1C, CH₃), 39.52(1C,CH₃), 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)** λ_{max} 355.5,236.5; **IR(KBr,cm⁻¹)**: 3741.65 (N-H), 1731.96 (C=O) 1569.95 (NH_{vs}), 1110.92 (C=S_s), 1421.44(C-N), **¹HNMR (DMSO, δ ppm)** : 2.50 (3,H,CH₃) 3.50 (3,H,CH₃) 2.21 (1,H,CH) 2.81 (3,H,CH₃) 3.10 (3,H,CH₃) 6.65-7.05 (5, H, Ar)

II_d - 1-amino[4-(dimethylamino)phenyl methylidene]-5-acetyl-4-(4-dimethyl aminophenyl)-6-methyl-3,4-dihydropyrimidine-2-thione: **yield** 36%, **mp** < 260 °C, **UV-VIS(nm)** λ_{max} 236.5 ; **IR(KBr,cm⁻¹)** : 3413.77 (N-H), 1731.96 (C=O), 1517.87 (C=N) 1114.78 (C=S_s), 1429.15 (C-N). **¹HNMR (DMSO, δ ppm)** : 2.50 (3,H,CH₃) 3.50 (3,H,CH₃) 4.10 (1,H,CH) 0.81, (1,H,CH) 3.01 (3,H,CH₃), 3.21 (3,H,CH₃), 1.30 (3,H,CH₃), 1.83 (3,H,CH₃), 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)** λ_{max} 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), **¹HNMR (DMSO, δ ppm)** : 2.50 (3,H,CH₃) 3.50 (3,H,CH₃) 1.81 (1,H,CH) 8.50 (2, H, NH₂)

II_e-1-amino[furan-2-ylmethylidene]-5-acetyl-4-(furyl)-6-methyl-3,4-dihydropyrimidine-2-thione: **yield** 36%, **mp** < 260 °C,**UV-VIS(nm)** λ_{max} 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). **¹HNMR (DMSO, δ ppm)** : 2.5 (3,H,CH₃), 3.50 (3,H,CH₃), 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 arylmethylidene-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 precipitate and separated into two components by TLC method using plates of aluminium precoating silica gel F₂₅₄ the solvent system are chloroform: methanol (9.5 : 0.5).

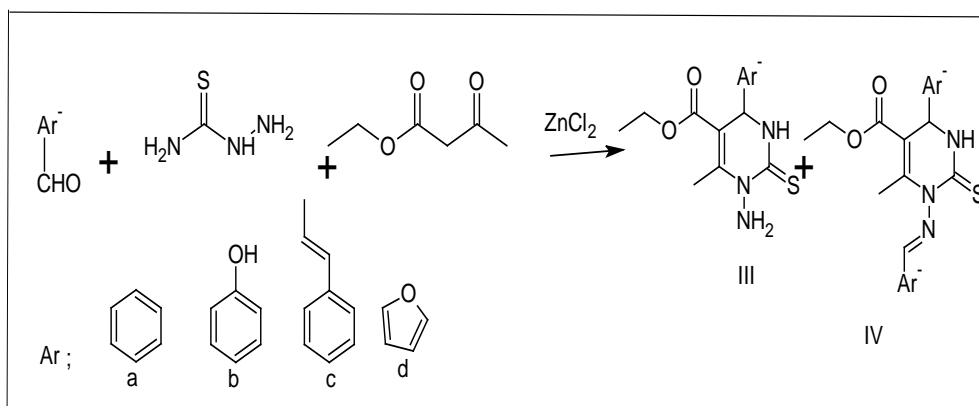


Figure 2: chemical structure of 1-amino-5-ethoxycarbonyl-6-methyl-4-aryl-3,4-dihydropyrimidine-2-thione and 1-amino arylmethylidene-5-ethoxycarbonyl-6-methyl-4-aryl-3,4-dihydropyrimidine-2-thione

III_a -1-amino-5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidine-2-thione: **yield** 40.7% **mp** < 260 °C , **UV-VIS(nm)** λ_{max} 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) **¹HNMR (DMSO, δ ppm)** : 3.50 (3,H,CH₃) 1.01 (3,H,CH₃), 2.50 (2,H,CH₂), 2.71 (1,H,CH), 5.81(2H,NH₂), 7.01-7.81 (5, H, Ar)

IV_a -1-amino phenyl methylidene-5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidine-2-thione: **yield** 40.6% **mp** < 260 °C, **UV-VIS(nm)** λ_{max} 329.0; **IR(KBr,cm⁻¹)** : 3400.27 (NH), 1726.17 (C=O), 1602.74 (C=N)

1371.29 (C-O)1101.85 (C=S_s). ¹HNMR (DMSO, δ ppm) : 3.50 (3,H,CH₃), 1.30 (3,H,CH₃), 2.50 (2,H,CH₂), 4.10 (1,H,CH), 3.21 (1,H,CH), 7.42- 8.25 (10, H, Ar); ¹³CNMR (DMSO, δ ppm) : 39.32 (1C,CH₃), 39.53 (1C,CH₃), 39.73 (1C,CH₂), 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-ethoxycarbonyl-6-methyl-4-(2-hydroxy-phenyl)-3,4-dihydropyrimidine-2-thione **yield** 49%, **mp** < 260 °C, **UV-VIS(nm)** λ_{max} 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) ¹HNMR (DMSO, δ ppm) : 3.50 (3,H,CH₃), 1.31 (3,H,CH₃), 2.50 (2,H,CH₂), 4.10 (1,H,CH), 5.52 (2H,NH₂) 6.82- 7.53 (5, H, Ar)

IV_b -1-(amino[2-hydroxy]phenyl methylidene)-5-ethoxycarbonyl-4-(2-hydroxy phenyl)-6-methyl-3,4-dihydropyrimidine-2-thione: **yield** 49%, **mp** < 260 °C, **UV-VIS(nm)** λ_{max} 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-ethoxycarbonyl-6-methyl-4-(cinnamyl)-3,4-dihydropyrimidine-2-thione: **yield** 37.9% **mp** < 260 °C, **UV-VIS(nm)** λ_{max} 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), ¹HNMR (DMSO, δ ppm) : 3.50 (3,H,CH₃), 1.21 (3,H,CH₃), 2.50 (2,H,CH₂), 6.64 (1,H,CH), 7.00 (1,H,CH) 5.51(2,H,NH₂) 7.01-8.52 (5, H, Ar)

IV_c -1-amino phenyl prop-2-en-1-ylidene -5-ethoxycarbonyl-6-methyl-4-(cinnamyl)-3,4-dihydropyrimidine-2-thione: **yield** 37.9%, **mp** < 260 °C, **UV-VIS(nm)** λ_{max} 330.0; **IR(KBr,cm⁻¹)** : 3452.34 (N-H), 1637.45 (C=N),1101.28 (C=S_s), ¹HNMR (DMSO, δ ppm) : 3.50 (3,H,CH₃), 1.31 (3,H,CH₃), 2.50 (2,H,CH₂), 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-ethoxycarbonyl-6-methyl-4-(furyl)-3,4-dihydropyrimidine-2-thione: **yield** 31.4% **mp** < 260 °C, **UV-VIS(nm)** λ_{max} 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) ¹HNMR (DMOS, δ ppm) : 3.50(3,H,CH₃), 1.32 (3,H,CH₃), 2.50 (2,H,CH₂), 4.10(1,H,CH) .

IV_d-1-amino[furan-2-ylmethylidene]-5-ethoxycarbonyl-4-(furyl)-6-methyl-3,4-dihydropyrimidine-2-thione: **yield** 31.4% **mp** < 260 °C, **UV-VIS(nm)** λ_{max} 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). ¹HNMR (DMSO, δ ppm) : 3.50 (3,H,CH₃), 1.32 (3,H,CH₃), 2.50 (2,H,CH₂), 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 ($\pi-\pi^*$) and ($n-\pi^*$) eg, compound -1_a - ,223.5 and 250 nm, compound-I_c - 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 arylmethylidene-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 ^1H NMR confirm the structure of synthesized compounds, all the synthesized compounds show in spectrum singlet peak at δ ppm 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 $3\text{CH}_3, 2\text{CH}_2$ protons must appear resulting from spin coupling of CH_3-CH_2 , the ^{13}C NMR spectrum for compound number II_c show peak at 178.17 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 .

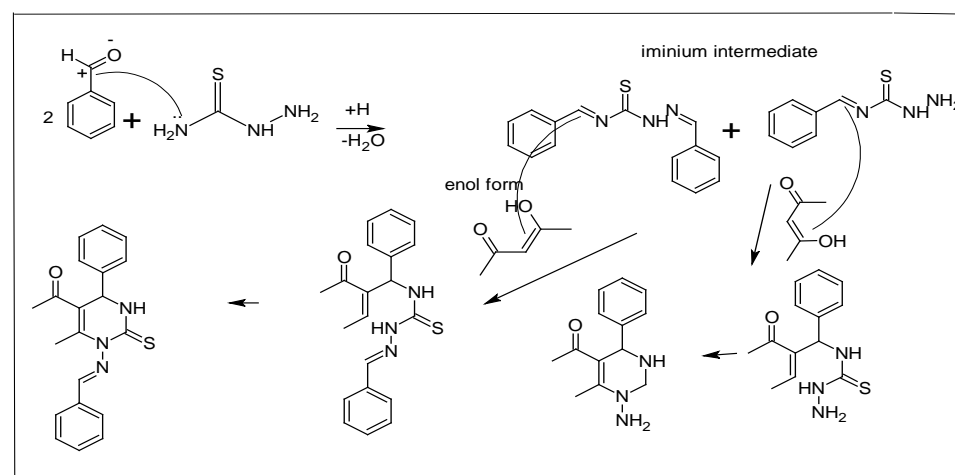


Figure 3: mechanism of the Biginelli reaction

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.

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