Synthesis of Biginelli reaction products using a heterogeneous catalyst and their characterization.

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Abstract :

P . Biginelli reported the synthesis of functionalized 3,4-dihydropyrimidine-2-(1H)-ones (DHPMS) via three component condensation of an aromatic aldehyde, urea and ethylacetoacetate. We have synthesized the heterogeneous catalyst first and using this heterogeneous catalysts we have synthesized several Biginelli products. The products has been characterized by FT-NMR, FT-IR and BET.

Keywords: Biginelli products, heterogeneous catalyst.

1. Introduction :

In the past decade, this multicomponent reaction has experienced a remarkable revival, mainly due to the interesting pharmacological properties associated with this dihydropyrimidine scaffold.

The classical three-component Biginelli condensation is usually carried out in alcoholic solution containing a few drops of concentrated hydrochloric or sulfuric acid as catalyst, although other systems such as THF/HCl, dioxane/HCl, or acetic acid/HCl have also been employed. Multicomponent reactions (MCRs) occupy an outstanding position in organic and medicinal chemistry for their high degree of atom economy, applications in combinatorial chemistry, and diversity-oriented synthesis.[1,2,3,4,5,6,7] Ionic Liquids Liu Zuliang and coworkers used cheap and reusable task-specific ionic liquids that bear an alkanesulfonic acid group in an acyclic trialkylammonium cation were found to be effective catalysts for synthesizing 3,4-dihydropyrimidine-2-(1H)-ones via the one-pot three-component Biginelli reaction. The satisfactory results were obtained with good yields, short reaction time and simplicity in the experimental procedure. The catalysts could be recycled and reused six times without noticeably decrease in the catalytic activity. [8] Zlotin, S.G. et al reported the synthesis of dihydropyrimidinones by condensation of aromatic (heteroaromatic) aldehydes with 1,3-dicarbonyl compounds under the 1-butyl-3methylimidazolium tetrafluoroborate ([Bmim][BF4]) ionic liquid-piperidinium acetate catalytic system (0.2 equiv. of each component) in the absence of a solvent affords, depending on the structures of the reagents, 2-arylidene

derivatives of methyl acetoacetate and acetylacetone, diethyl 2,4-bis(trifluoroacetyl)-3-phenylpentanedioate, or dimethyl 2aryl-4-hydroxy-6-oxocyclohexane-1,3-dicarboxylates. The reactions of the resulting 2arylidene derivatives with O-methylisourea in the [Bmim][BF4] ionic liquid produced methyl 2-methoxy-4-methyl-6-aryldihydropyrimidine-5-carboxylates and 1-(2-methoxy4-methyl-6-phenyldihydropyrimidin-5-yl)ethanone (mixtures of 3,6- and 1,6-dihydro isomers), which were transformed into the corresponding 3,4-dihydropyrimidin-2(1H)one derivatives. [9]

2. Experimental

2.1. Synthesis of heterogeneous catalyst:

Preparation of the heterogeneous catalyst was done using basically two components, first is thiomaleic anhydride and the second one in silica gel. Silica gel (1 gram) and thiophene (0.35 gram) were mixed thoroughly in ethyl acetate, placed in a round bottom flask. The mixture was reflux for 3–4 h. After complete conversion of the ketones, reactions were monitored by TLC and the activity of catalyst was maintained at P-4 the mixture was cooled to room temperature. Dichloromethane (20–30 ml) was added and heated for 3–5 min. The excess undoped was removed by filtration. The filtrate was concentrated and the solid residue was separated from ethanol to afford final product. The catalyst was recycled by washing ethyl acetate (20 ml) on solid remaining on the filter followed by drying in an oven at 50 ˚C for 2 h, which can be reusable for another reaction run.

2.1.1. Preparation of ethyl 4-(3-nitrophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate

Process: Take 2 gm 2-nitrobenzaldehyde in Round Bottom add 1 gm of thiourea in and add 10 ml ethylacetoacetate add absolute assolvent. Put Round Bottom on stirrer with condensation assembly. Stir the mixture until all solid are dissolve. Add 0.26 gm of catalyst then give stirring for 35 min then filter it. Collect the product in a petri dish to keep at room temperature to dry. Finally we get crystals. These crystals were recrystallized (if required) and the dried product is collected in plastic pouch. This product is further characterized by Melting point analysis, NMR spectroscopy and FTIR spectroscopy.. Figure 1 shows reactant, possible product and photograph of the obtained crystals.

2.1.2. Preparation of Ethyl 4-(3-hydroxypheneyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate

Process: Take 2 gm 4-hydroxybenzaldehyde in Round Bottom add 1 gm of thiourea in and add 10 ml ethylacetoacetate add absolute assolvent. Put Round Bottom on stirrer with condensation assembly. Stir the mixture until all solid are dissolve. Add 0.26 gm of catalyst then give stirring for 25 min then filter it.

Collect the product in a petri dish to keep at room temperature to dry. Finally we get crystals. These crystals were recrystallized (if required) and the dried product is collected in plastic pouch. This product is further characterized by Melting point analysis, NMR spectroscopy and FTIR spectroscopy. Figure 2 shows reactant, possible product and photograph of the obtained crystals.

2.1.3. Preparation of 4-(3,5-dichloro-2-formylphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate

Process: Take 2 gm 2-4-Dichlorobenzaldehyde in Round Bottom add 1 gm of thiourea in and add 10 ml ethylacetoacetate add absolute as solvent. Put Round Bottom on stirrer with condensation assembly. Stir the mixture until all solid are dissolve. Add 0.26 gm of catalyst then give stirring for 45 min then filter it. Collect the product in a petri dish to keep at room temperature to dry. Finally we get crystals. These crystals were recrystallized (if required) and the dried product is collected in plastic pouch. This product is further characterized by Melting point analysis, NMR spectroscopy and FTIR spectroscopy. Figure 3 shows reactant, possible product and photograph of the obtained crystals.

2.1.4..Preparation of 1-(6-methyl-4-phynyle-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl)ethanone

Process: Take 2 gm benzaldehyde in Round Bottom add 1 gm of thiourea in and add 10 ml ethylacetoacetate add absolute assolvent. Put Round Bottom on stirrer with condensation assembly. Stir the mixture until all solid are dissolve. Add 0.26 gm of catalyst then give stirring for 35 min then filter it. Collect the product in a petri dish to keep at room temperature to dry. Finally we get crystals. These crystals were recrystallized (if required) and the dried product is collected in plastic pouch. This product is further characterized by Melting point analysis, NMR spectroscopy and FTIR spectroscopy. Figure 4 shows reactant, possible product and photograph of the obtained crystals.

2.1.5.Preparation of ethyl 4-(2-formyl-3-hydroxyphenyl)-2-tioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate

Process: Take 2 gm salisaldehyde in Round Bottom add 1 gm of thiourea in and add 10 ml ethylacetoacetate add absolute assolvent. Put Round Bottom on stirrer with condensation assembly. Stir the mixture until all solid are dissolve. Add 0.26 gm of catalyst then give stirring for 45 min then filter it. Collect the product in a petri dish to keep at room temperature to dry. Finally we get crystals. These crystals were recrystallized (if required) and the dried product is collected in plastic pouch. This product is further characterized by Melting point analysis, NMR spectroscopy and FTIR spectroscopy. Figure 5 shows reactant, possible product and photograph of the obtained crystals.

2.1.6.Preparation of(E)-methyl 6-methyl-2-oxo-4-(-3-(4-oxobut-2-en-l-yl)-Phenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate

Process: Take 2 gm cinnamaldehyde in Round Bottom add 1 gm of thiourea in and add 10 ml ethylacetoacetate add absolute assolvent. Put Round Bottom on stirrer with condensation assembly. Stir the mixture until all solid are dissolve. Add 0.26 gm of catalyst then give stirring for 45 min then filter it. Collect the product in a petri dish to keep at room temperature to dry. Finally we get crystals. These crystals were recrystallized (if required) and the dried product is collected in plastic pouch. This product is further characterized by Melting point analysis, NMR spectroscopy and FTIR spectroscopy. Figure 6 shows reactant, possible product and photograph of the obtained crystals.

2.1.7.Preparation of methyl 4-(3-fluorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate

Process: Take 2 gm Fluorobenzaldehyde in Round Bottom add 1 gm of thiourea in and add 10 ml ethylacetoacetate add absolute assolvent. Put Round Bottom on stirrer with condensation assembly. Stir the mixture until all solid are dissolve. Add 0.26 gm of catalyst then give stirring for 35 min then filter it. Collect the product in a petri dish to keep at room temperature to dry. Finally we get crystals. These crystals were recrystallized (if required) and the dried product is collected in plastic pouch. This product is further characterized by Melting point analysis, NMR spectroscopy and FTIR spectroscopy. Figure 7 shows reactant, possible product and photograph of the obtained crystals.

Results :

2.1.1. Ethyl 4-(3-nitrophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate

^{1}H NMR Chemical Shift Value δ PPM 1.20 (3H, s); 2.3 (2H, t);4.03 (1H, d);4.14 (Ar-H, s); 7.69 (Ar-H, s);7.70(Ar-H, m);8.16(Ar-H, d);8.22(Ar-H, m);8.23(N-H of Pyrimidine, s); 8.25 (N-H of Pyrimidine, s).

FTIR cm^{-1} 3160 (O-H stretching) ,1701; C-O(carbonyl) 1524(ethyl fragments, 1243 (C-O stetching) 728cm-1 (Disubstituted benzene).

Yield of the product: 2.36 grams

Melting point of the product: 170 ^{o}C.

2.1.2. Ethyl 4-(3-hydroxypheneyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate

^{1}H NMR Chemical Shift Value δ PPM 1.21 (3H, s); 2.3 (2H, t);2.5 (1H, d);6.72 (Ar-H, s); 6.73 (Ar-H, s);6.9(Ar-H, m);7.1 (Ar-H, d);7.2(Ar-H, m);8.27(N-H of Pyrimidine, s); 9.79 (N-H of Pyrimidine, s);10.73(O-H of Pyrimidine, s).

FTIR cm^{-1}.3129 (O-H stretching) ,1718; C-O(carbonyl) 1576 (ethyl fragments, 1282 (C-O stetching) 833 cm^{-1} (Disubstituted benzene).

Yield of the product: 2.56 grams

Melting point of the product: 185^{o}C

2.1.3. 4-(3,5-dichloro-2-formylphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate

^{1}H NMR Chemical Shift Value δ PPM 2.27 (2H, t);3.60(1H, d);5.13(Ar-H, s); 7.53 (Ar-H, s);7.69(Ar-H, m));7.56(N-H of Pyrimidine, s); 9.06 (N-H of Pyrimidine, s);10.56(O-H of Pyrimidine, s).

FTIR cm^{-1}3162 (O-H stretching) ,1606; C-O(carbonyl) 1408(ethyl fragments, 1080 (C-O stetching) 728 cm^{-1} (Disubstituted benzene).

Yield of the product:1.86 grams

Melting point of the product: 190^{o}C

2.1.4. 1-(6-methyl-4-phynyle-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl)ethanone

^{1}H NMR Chemical Shift Value δ PPM3162 (O-H stretching) ,1606; C-O(carbonyl) 1408(ethyl fragments, 1080 (C-O stetching) 728 cm^{-1} (Disubstituted benzene).

FTIR cm^{-1}3144 (O-H stretching) ,1701; C-O(carbonyl) 1407 (ethyl fragments, 1079 (C-O stetching) 728 cm^{-1} (Disubstituted benzene).

Yield of the product: 1.90 grams

Melting point of the product: 195 ^{o}C

2.1.5. Ethyl 4-(2-formyl-3-hydroxyphenyl)-2-tioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate.

^{1}H NMR Chemical Shift Value δ PPM 1.16 (3H, s);4.08 (2H, t);4.16 (1H, d);6.93 (Ar-H, s);7.03 (Ar-H, s);7.10(Ar-H, m);7.36 (Ar-H, d);9.14(N-H of Pyrimidine, s); 9.73 (N-H of Pyrimidine, s);16.43(O-H of Pyrimidine, s).

FTIR cm^{-1}3149 (O-H stretching) ,1738; C-O(carbonyl) 1604(ethyl fragments, 1407 (C-O stetching) 728 cm^{-1} (Disubstituted benzene.

Yield of the product: 1.98 grams

Melting point of the product: 180 ^{o}C

2.1.6.(E)-methyl 6-methyl-2-oxo-4-(-3-(4-oxobut-2-en-l-yl)-Phenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate

^{1}H NMR Chemical Shift Value δ PPM 2.27 (3H, s); 3.33 (2H, t);3.60 (1H, d);5.11 (Ar-H, s);5.98 (Ar-H, s);7.21(Ar-H, S);7.21 (Ar-H, d);7.27(Ar-H,d);7.47(Ar-H,d)7.56(Ar-H,d)7.56(N-H of Pyrimidine, s); 9.06 (N-H of Pyrimidine, s);9.68(O-H of Pyrimidine, s).

FTIR cm^{-1}3151 (O-H stretching) ,1736; C-O(carbonyl) 1604 (ethyl fragments, 1243 (C-O stetching) 728 cm^{-1} (Disubstituted benzene).

Yield of the product: 2.36 grams

Melting point of the product: 175 ^{o}C

2.1.7.Methyl 4-(3-fluorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate

^{1}H NMR Chemical Shift Value δ PPM 2.27 (3H, s);3.60 (2H, d);5.11 (1H,m);6.97 (Ar-H,d);7.04 (Ar-H, s);7.09(Ar-H, d);7.36 (Ar-H, d);7.56(N-H of Pyrimidine, s); 9.06 (N-H of Pyrimidine, s).

FTIR cm^{-1}3155 (O-H stretching) ,11602; C-O(carbonyl) 1407 (ethyl fragments, 1228 (C-O stetching) 728 cm^{-1} (Disubstituted benzene).

Yield of the product: 2.48 grams

Melting point of the product: 185 ^{o}C

3.Conclusion

The reaction was selective for aromatic aldehydes for thiourea and ethyl acetoacetate. The neat silica gel had shown 587.31 m^2/g high surface area which is better to prepare a good heterogeneous catalysis. Formed catalyst show good BET surface area with the value of 409.65 m^2/g. This value of surface area of the obtained catalyst is lower than the neat silica material which confirms that the compound thiomaleic anhydride is sufficiently doped in the pores of silica material. This heterogeneous catalyst recycling is very easy and was recycled for three times with 80% retention of its capacity. This catalyst is found promising for Biginelli reaction as the obtained products yield was comparable with previous reports and these products were formed in lesser period of time compare to literature findings. The obtained Biginelli products clearly show their corresponding FTIR and 1HNMR spectra which confirms the extraction of the final products from reaction mixtures with purity.

4.References:

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Legends to Figure :

Figure 1.

Shows reactant, possible product and photograph of the obtained crystals of ethyl 4-(3-nitrophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate.

Figure 2.

Shows reactant, possible product and photograph of the obtained crystals of Ethyl 4-(3-hydroxypheneyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate.

Figure 3.

Shows reactant, possible product and photograph of the obtained crystals of 4-(3,5-dichloro-2-formylphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate.

Figure 4.

Shows reactant, possible product and photograph of the obtained crystals of 1-(6-methyl-4-phynyle-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl)ethanone.

Figure 5.

Shows reactant, possible product and photograph of the obtained crystals of ethyl 4-(2-formyl-3-hydroxyphenyl)-2-tioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate.

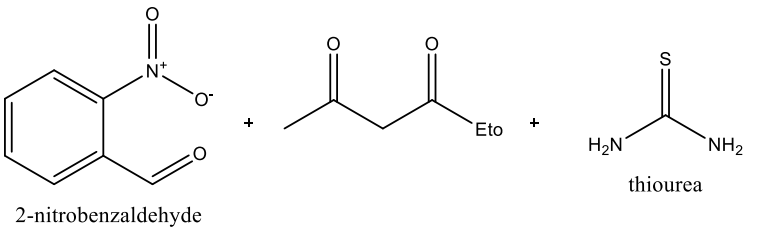
Figure 6.

Shows reactant, possible product of (E)-methyl 6-methyl-2-oxo-4-(-3-(4-oxobut-2-en-l-yl)-Phenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate.

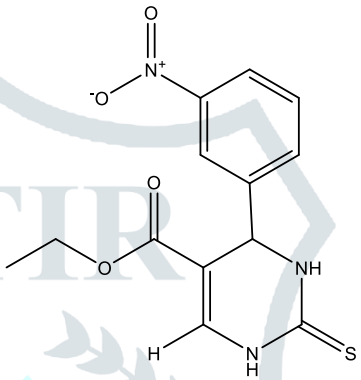
Figure 7.

Shows reactant, possible product of methyl 4-(3-fluorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate.

Figure 1

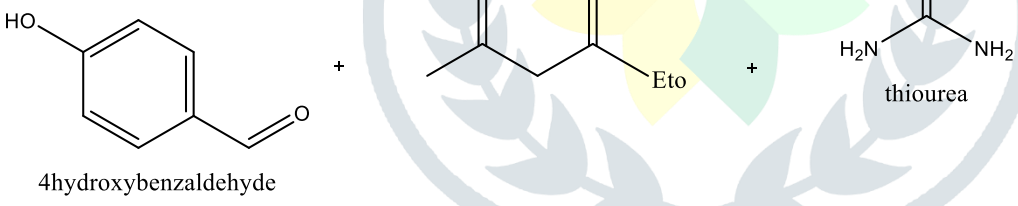


2-nitrobenzaldehyde thiourea

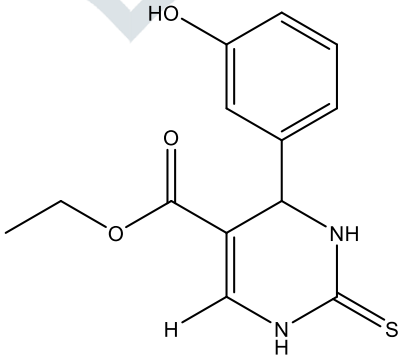


ethyl 4-(3-nitrophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate

Figure 2

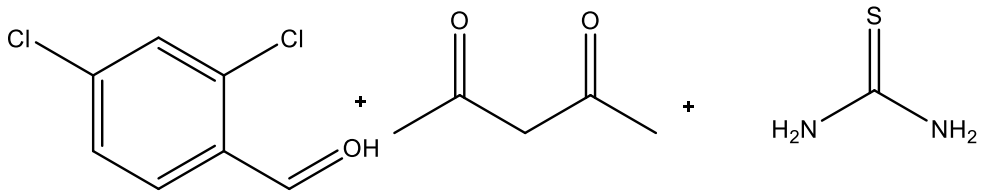


4hydroxybenzaldehyde thiourea

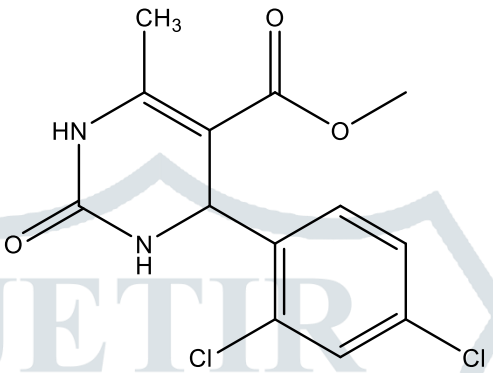


ethyl 4-(3-hydroxyphenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate

Figure 3

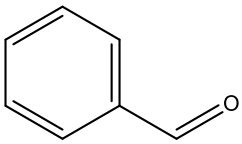


2,4-dichloro benzaldehyde

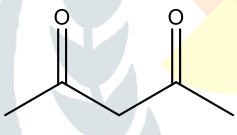


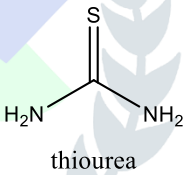
methyl 4-(2,4-dichlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate

Figure 4

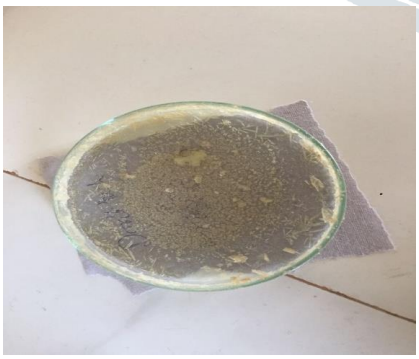


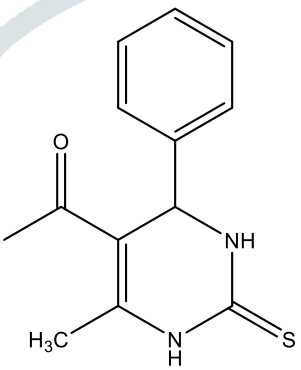
benzaldehyde





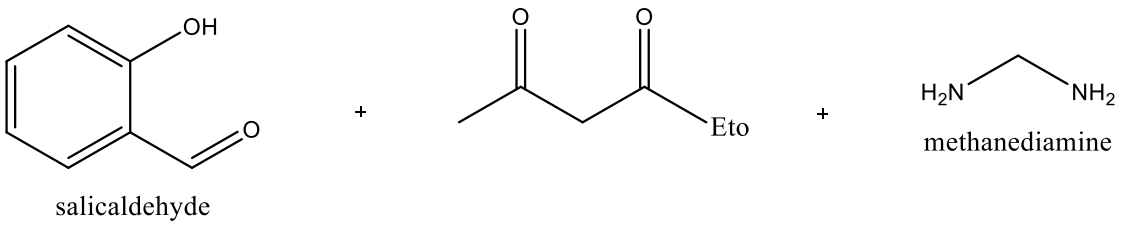
thiourea



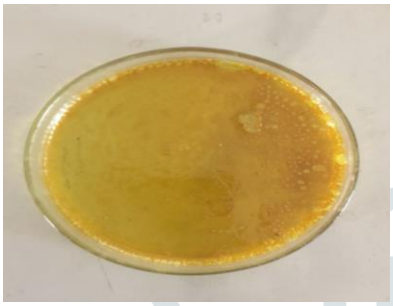


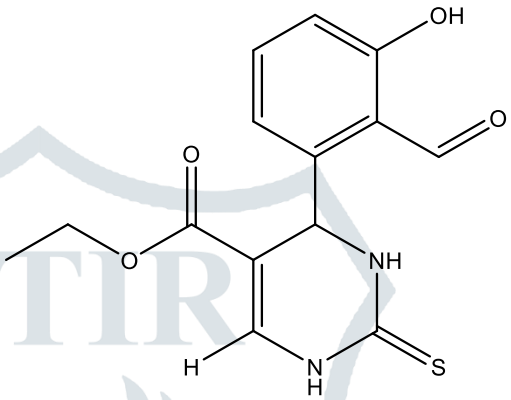
1-(6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl)ethan-1-one

Figure 5



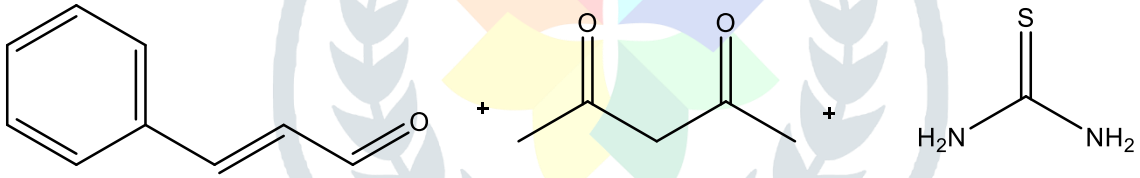
salicaldehyde methanediamine



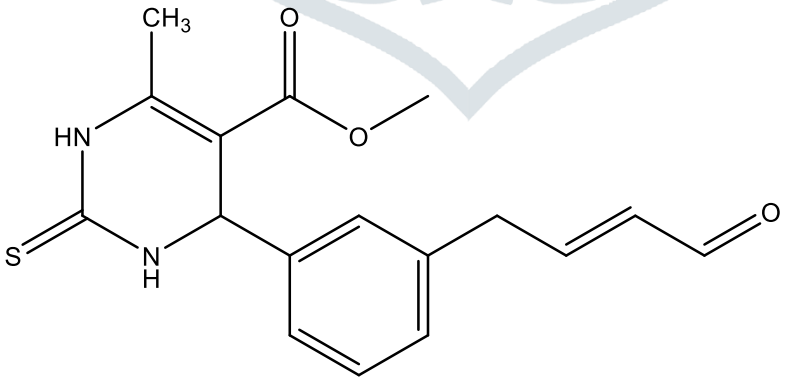


ethyl 4-(2-formyl-3-hydroxyphenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate

Figure 6

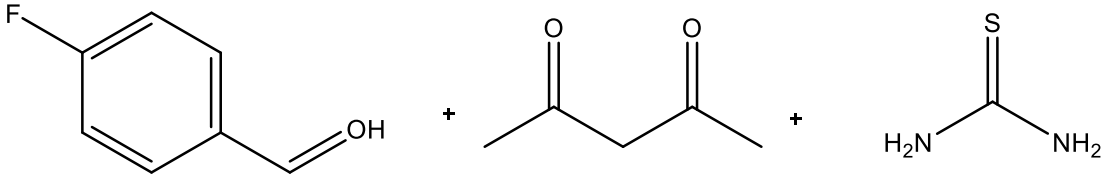


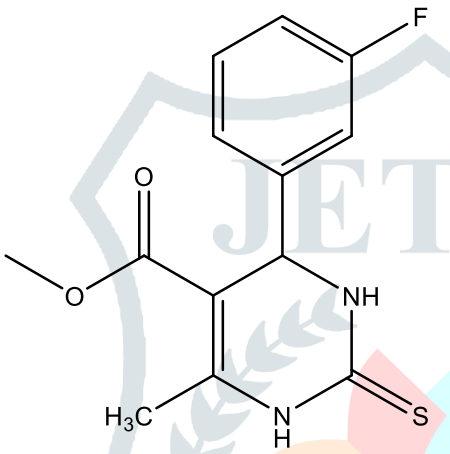
cinnamaldehyde



methyl (*E*)-6-methyl-4-(3-(4-oxobut-2-en-1-yl)phenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate

Figure 7





methyl 4-(3-fluorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate