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BIOACTIVE SYNTHESIS OF 1-(4-PHENYL)-6-METHYL-2-THIOXO-1, 2, 3, 4-TETRAHYDROPYRIMIDINE-5-YL) ETHANONE AND PROMPTED BY TCSA

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ABSTRACT

An efficient TCSA as Bronstd acid catalyst for synthesizing bioactive compounds 1-(4-phenyl)-6-methyl-2-thioxo-1, 2, 3, 4-Tetrahydropyrimidine-5-yl) ethanone by multi-component condensation of acetylacetone, substited aryl aldehydes and thiourea catalyzed by tricholro salicylic acid. A series of compounds were synthesized, confirmed by analytical and spectral data (^{1}HNMR, ^{13}CNMR and LCMS) and examined for their antimicrobial activity.

KEYWORDS

Biginellireaction, Acetylacetonate, Substituted aromatic aldehydes, Thiourea, 1, 2, 3, 4-tetrahydropyrimidine-2-thiones, TCSA and Antimicrobial activity.

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INTRODUCTON

Medicinal chemistry was introduced as main focus on the organic synthesis and biology. It is also attains a knowledge which leads to the introduction of new therapeutic agents. Pyrimidine-2-thiones are those molecules that possible for the building blocks of DNA and RNA.

Synthesis of 6-methyl-2-thioxo-1, 2, 3, 4-tetrahydropyrimidine-5-yl) ethanone are of high interest in organic chemistry. The pyrimidine fragment is present in various biologically active compounds, many of which are used therapeutically[1-3]. Thus, much attention has been paid to derivatives of pyrimidines, including their hydrogenation products. This class of compounds possesses a wide range of biological and pharmacological properties such as antidepressant[4], calcium antagonist[5,6], antitumor[7], antitubercular[8]

anti-inflammatory[9,10], antibacterial and antifungal effects[11,12] analgesic[13,14] antioxidant[15], etc.

Nowadays, the one step methods involving three component condensation using different reagents and catalysts are popular in synthetic organic chemistry for the synthesis of heterocyclic compounds. These single step methods are more convenient as compared with two step strategies as they require shorter reaction times, product isolation easy and give higher yields and recoveries of the product.

As part of our study to design and synthesize new pyrimidine derivatives, in this letter we would like to report the synthesis of 6-amino-5cyano 4-phenyl 2-mercaptopyrimidine and its hydroxyl derivative by three-component condensation of aromatic aldehydes, malononitrile and thiourea or urea using phosphorus pent oxide in absolute ethanol under refluxing condition. The application of these compounds in pharmaceutical field prompted us to study their thermal stability's) For the complete development of a new drug, thermal analysis has many applications[16,17]. The information obtained regarding the compounds under study is useful for the initial chemical research phase[18]. In the chemical research phase, thermal analysis plays an important role. The purity of the compound, the compounds ability to be able to exist in various crystalline forms as well as to characterize polymorphs and other forms of solid state should be investigated.

MATERIAL AND METHODS

Experimental

All the chemicals and synthetic reagents were purchased from Fine chemicals and Sigma Aldrich. Reactions were performed in four necked 50mL RB. The monitoring of reaction was checkedout by Thin Layer Chromatography (TLC), silica coated aluminium plates, obtained from Merck, by using appropriate mixture of solvent. Themelting point (mp) was determined by open capillary method and was uncorrected. The product was confirmed by LCMS, ^{1}H and ^{13}C NMR spectral studies. NMR spectrum was recorded by Brucker 400MHz instrument. LCMS were recorded by positive mode, using solvents 0.1% formic acid in Acetonitrile.

General Procedure

A mixture of acetylacetonate (1.25mol), substituted aromatic aldehydes (1.2mol) and Thiourea (2.5mol) were taken in a four neck 500mL RB flask, TCSA (tricholro salylic acid) added to the above mixture. The total reaction mixture taken in RB flask carried out mechanical stirrer at 70^{o}C. The reaction mixture was checked by TLC (4:6, ethyl acetate and hexane) after all the reactation were consumed. The cruded was poured into the cooled water and added to the ethyl acetate solvent. The crude was neutralized with saturated solution of anhydrous sodium bi carbonate and separated the organic layer and distilled off under vacuums. The desired product can be separated by using column chromatography and recrystallized from ethanol.

Characterization of synthesized newly compound 1-(4-phenyl)-6-methyl-2-thioxo-1, 2, 3, 4-Tetrahydropyrimidine-5-yl) ethanone (4a)

Pale yellow solid, yield-82%, m.p-232-234^{o}C; Rf-0.450 (n-hexane: EtOAc-7:3;. ^{1}HNMR (400MHz, $CDCl_3$) δppm:9.60 (s, 1H, N-Hpyrimidine), 9.25 (s, 1H, N-Hpyrimidine), 6.59-6.49 (m, 4H, Ar-H), 5.014 (s, 2H, N-H, amine), 4.03 (s, 1H, -CH-), 2.21 (s, 3H, -$COCH_3$), 2.27 (s, 3H,-CH_3).^{13}CNMR (100MHz, $CDCl_3$) δppm: 192.27, 181.44, 158.23, 149.48, 131.76, 127.08, 115.12, 106.36, 51.93, 27.86, 18.92. LCMS (m/z):260.12. Elemental analysis: Calculated: C-59.74, H-5.79, N-16.08, Obtained: C-59.68, H-5.78, N-16.15.

1-(4-(3-Ethoxy-4-hydroxyphenyl)-6-methyl-2-thioxo-1, 2, 3, 4-Tetrahydropyrimidine-5-yl) thanone (4b)

Colourless solid, yield 86%. m.p-234-236^{o}C; Rf-0.450 (n-hexane: EtOAc-7:3^{1}HNMR (400MHz, $CDCl_3$) δppm: 9.754 (s, 1H, -OH), 9.117(s, 1H, N-H, pyrimidine), 8.817(s, 1H, N-H, pyrimidine), 6.877(d, J=8.4Hz, 1H, A-r), 6.758(d, J=8.0Hz, 1H, Ar-H), 4.211(s, 1H, -CH-), 4.059 (m, 2H, -CH_2-), 2.220 (s, 3H, -$COCH_3$), 2.125(s, 3H, -CH_3). 1.230 (t, 3H, -CH_3).^{13}CNMR (100MHz, $CDCl_3$) δppm: 191.27, 180.56, 157.68, 148.42, 146.86, 136.77, 118.54, 114.74, 112.66, 104.28, 63.95, 52.54, 27.46, 18.38, 14.37. LCMS (m/z): 307.08. Elemental

analysis: Calculated: C-59.74, H-5.79, N-16.08, Obtained: C-59.65, H-5.78, N-16.18.

1-(4-(3-ethoxy-4-methoxyphenyl)-6-methyl-2-thioxo-1, 2, 3, 4-Tetrahydropyrimidine-5-yl) ethanone (4c)

Colourless solid, yield 88%.; m.p-269-271^{o}C; Rf-0.450 (n-hexane: EtOAc-6: 4^{1}HNMR (400MHz, $CDCl_3$) δppm: 9.815 (s, 1H, N-H, pyrimidine), 9.272 (s, 1H, N-Pyrimidine), 6.978 (d, J=7.6Hz, 1H, Ar-H), 6.684 (s, 1H, Ar-H), 6.602 (d, J=8.8Hz, 1H, Ar-H), 4.108(s, 1H,-CH) 3.912-3.755 (m, 2H, -CH_2-), 3.664 (s, 3H, -OCH_3), 2.129 (s, 3H, -$COCH_3$), 2.024 (s, 3H, -CH_3), 1.228 (s, t=8.4Hz, -CH_3). ^{13}CNMR (100MHz, $CDCl_3$): δinppm: 192.53, 179.49, 157.86, 148.89, 146.76, 137.94, 118.88, 112.96, 111.84, 105.29, 63.93, 32.58, 27.14, 19.07, 14.43. LCMS (m/z): 319.51. Elemental analysis: Calculated: C-59.98, H-6.29, N-8.74, Obtained: C-59.84, H-6.28N-8.86.

1-(4-(4-aminophenyl)-6-methyl-2-thioxo-1, 2, 3, 4-Tetrahydropyrimidine-5-yl) ethanone (4d)

Yellow solid, yield-86%.; m.p-262-264^{o}C; Rf-0.450 (n-hexane: EtOAc-7:3^{1}HNMR (400MHz, $CDCl_3$) δppm: 9.860 (s, 1H, N-H, pyrimidine), 9.125 (s, 1H, N-H, pyrimidine), 7.259-6.949 (m, 4H, Ar-H), 5.014 (s, 2H, N-H, amine), 4.103 (s, 1H, -CH-), 2.221 (s, 3H, -$COCH_3$), 1.954 (s, 3H,-CCH_3). ^{13}CNMR (100MHz, $CDCl_3$): δppm: 192.27, 183.54, 158.43, 147.78, 132.56, 126.98, 114.85, 105.51, 52.33, 26.66, 17.99. LCMS (m/z): 260.25. Elemental Analysis: Calculated: C-59.74, H-5.79, N-16.08, Obtained: C-59.65, H-5.77, N-16.18.

1-(4-(4-Fluorophenyl)-6-methyl-2-thioxo-1, 2, 3, 4-Tetrahydropyrimidine-5-yl) ethanone (4e)

Pale yellow solid, yield-86%. m.p-258-260^{o}C; Rf-0.450 (n-hexane: EtOAc-7:31HNMR (400MHz, $CDCl_3$) δppm: 9.843 (s, 1H, N-H, pyridine), 9.245 (s, 1H, N-H, pyrimidine), 7.252-7.291 (m, 4H, Ar-H), 4.035 (s, 1H, -CH-), 2.114 (s, 3H, -CH_3), 2.214 (s, 3H, -COCH3). ^{13}CNMR (100MHz, $CDCl_3$): δppm: 194.51, 185.64, 162.54, 158.53, 138.56, 128.46, 115.21, 104.82, 50.47, 26.89, 17.54. LCMS (m/z): 246.46. Elemental analysis: Calculated: C-59.06, H-4.95, N-10.61, Obtained: C-58.97, H-4.93, N-10.67.

1-(4-(4-chloro phenyl)-6-methyl-2-thioxo-1, 2, 3, 4-Tetra hydro pyrimidine-5-yl) ethanone (4f)

Pale yellow solid, yield-89%.; m.p-261-263^{o}C; Rf-0.450 (n-hexane: EtOAc-7:3^{1}HNMR (400MHz, $CDCl_3$) δppm: 9.969 (s, 1H, N-H, pyridine), 9.478 (s, 1H, N-H, pyrimidine), 7.539-7.228 (m, 4H, Ar-H), 4.053 (s, 3H, -CH-), 2.135 (s, 3H, -$COCH_3$), 2.028 (s, 3H, -CH_3).^{13}CNMR (100MHz, $CDCl_3$) δppm: 195.42, 187.58, 157.62, 141.87, 132.49, 128.82, 126.74, 104.79, 50.48, 26.96, 18.73. LCMS (m/z): 280.54; Elemental analysis: Calculated: C-55.60, H-4.66, N-9.98; Obtained: C-55.57, H-4.64, N-10.07.

1-(4-(4-bromophenyl)-6-methyl-2-thioxo-1, 2, 3, 4-Tetrahydropyrimidine-5-yl) ethanone (4g)

Dark red solid, yeild-89%. m.p-257-259^{o}C; Rf-0.440 (n-hexane: EtOAc-6:4); ^{1}HNMR (400MHz, $CDCl_3$) δinppm: 9.968 (s, 1H, N-H, pyrimidine), 9.451 (s, 1H, N-H, pyrimidine), 7.884 (d, J=8.0Hz, 1H, Ar-H), 7.480 (d, J=8.4Hz, 1H, Ar-H), 7.247 (d, J=8.0Hz, 1H, Ar-H), 4.041 (s, 3H, -CH-), 2.128 (s, 3H, -$COCH_3$), 2.021 (s, 3H, -CH_3). ^{13}CNMR (100MHz, $CDCl_3$): δppm: 194.88, 191.20, 157.27, 141.36, 130.59, 128.88, 121.58, 105.65, 54.51, 27.87, 18.99. LCMS (m/z): 326.40. Elemental analysis: Calculated: C-48.01, H-4.03, N-8.61; Obtained: C-47.95, H-4.02, N-8.69.

2.2.8.4-(5-acetyl-6-methyl-2-thioxo-1, 2, 3, 4-Tetrahydropyrimidine-5-yl) benzoic acid (4h)

Pale yellow solid, yield-90%. m.p-241-243^{o}C; Rf-0.470 (n-hexane: EtOAc-6:41HNMR (400MHz, $CDCl_3$) δppm: 10.358 (s, 1H, -COOH), 9.968 (s, 1H, N-H, pyrimidine), 9.342 (s, 1H, N-H, pyrimidine), 7.578 (d, J=8.4Hz, 1H, Ar-H), 7.470 (d, J=8.8Hz, 1H, Ar-H), 7.446 (d, J=7.6Hz, 1H, Ar-H), 7.335 (d, J=8.0Hz, 1H, Ar-H), 4.547 (s, 3H, -CH-), 2.125 (s, 3H, -$COCH_3$), 2.019 (s, 3H, -CH_3). ^{13}CNMR (100MHz, $CDCl_3$): δppm: 195.63, 190.38170.74, 156.99, 148.57, 129.58, 127.46, 126.55, 104.66, 51.87, 27.15, 17.86. LCMS (m/z): 290.52. Elemental analysis: Calculated: C-57.92, H-4.86, N-9.65, Obtained: C-57.84, H-4.85, N-9.75.

Biological Activity

Anti bacterial activity

In vitro anti-bacterial activities of newly synthesized derivatives are examined against four

pathogenic bacteria strains. The result of antibiotic activity examined for the compounds. The gram (-ve) bacteria screened were *Escherichia Coli* and *Pseudomonas aeruginosa*. The gram positive bacteria screened were *S-aureas and Bacillus*.

The target compounds were used at the concentration of 250µglml and 500µglml using DMSO as a solvent the amoxylin 10µglml disc were used as a standard. The rest of the compounds were found to be moderate active against the tested micro organism.

Anti fungal activity

In vitro anti-fungal activities of new synthesized derivatives were examined by disc diffusion method against the organism of Aspergillus Niger and Candida albicans. Compared were treated at the concentrations of 500µglml and 1000µglml using DMSO as a solvent. The standard drug was used as ketoconazol 50µglml against both organisms.

RESULTS AND DISCUSSION

Chemistry

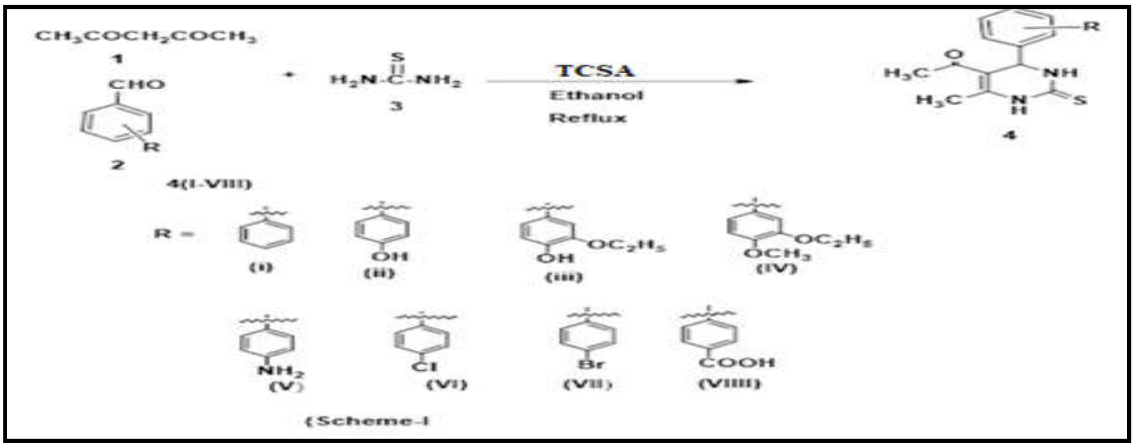
The General Procedure for the synthesis of derivatives of 1-(4-phenyl)-6-methyl-2-thioxo-1, 2, 3, 4-Tetrahydropyrimidine-5-yl) ethanone

All newly synthesized compounds can be obtained at 70^{o}C temperature. These target compounds can be obtained, we used to Bronsted acid catalyst is TCSA (tricholro salylic) in ethanol. This Bronsted acid catalyst can be used to improve the rate of reaction conditions and reaction is completed maximum 3 hours. The rate of reaction increased by using this catalyst. We used various aromatic aldehydes such as, Electron donating group and electron withdrawing group of aldehydes. Electron donating group of aldehydes react with 2-aminobenzimidazole to obtained more yield and rate of reaction increases and completion of the reaction before 30 min compared to that electron withdrawing group of aldehydes with 2-aminobenzimidazole. We are using trifluoroacetic acid, the reaction workup is easily. (Scheme No.1).

All the synthesized derivatives were examined anti-bacterial activity as well as antifungal. The aromatic aldehydes containing carboxylic group showed poor activity. The compounds having "4f and 4g" having halogens exhibited excellent activity where the compounds having "4b, 4c, 4e and 4e" showed good activity as shown in Table No.1.

Table No.1: Antimicrobial activity screening activity synthesized scaffold

S.No	Compound Code	*Zone of inhibition in (mm)					
		Bacteria				Fungi	
		S.aureus	*E.coli*	*S. typhi*	*B.substills*	*A. niger*	*C. albicans*
1	4a	04	08	06	04	08	07
2	4b	18	19	16	15	12	14
3	4c	18	19	18	19	12	13
4	4d	18	20	09	20	17	21
5	4e	17	19	17	16	15	16
6	4f	21	22	20	20	17	16
7	4g	22	17	12	20	17	16
8	4h	07	07	08	07	08	07
9	Streptomycin	25	25	22	22	-	-
10	Ketoconazole	NA	NA	NA	NA	20	20
11	DMSO	---	----	---	---	---	---



The General Procedure for the synthesis of derivatives of 1-(4-phenyl)-6-methyl-2-thioxo-1, 2, 3, 4-Tetrahydropyrimidine-5-yl) ethanone

CONCLUSION

In conclusion, we have enhanced a simple and high efficient procedure for the synthesis of 1-(4-phenyl)-6-methyl-2-thioxo-1, 2, 3, 4-Tetrahydropyrimidine-5-yl) ethanone derivatives with advantages of operational simplicity, good to high yields and use of non-toxic and commercial available catalyst viz; TCSA (tricholro salylic acid). Antimicrobial activity of titled compounds can be examined by suitable standard drugs and also acquired moderate to good active potential and yield of newly synthesised compound.

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CONFLICT OF INTEREST

We declare that we have no conflict of Interest.

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