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AN EFFICIENT ONE-POT SYNTHESIS OF 7, 7-DIMETHYL-4-PHENYL-2-THIOXO-2, 3, 4, 6, 7, 8- HEXAHYDRO-1H-QUINAZOLIN-5-ONES PROMOTED BRONSTED ACID

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ABSTRACT
A straight forward one pot three component synthesis of seven novel derivatives 7**,** 7-dimethyl-4-phenyl-2-thioxo-2,3,4,6,7,8-hexahydro-1H-quinazolin-5-one by a cyclocondensation of dimedone and substitutes aromatic aldehyde with thiourea in the presence of Bronsted acid trichloroacetic acid (TCSA) as a catalyst with to excellent yields. All structures of the desired compounds were evaluated by ^{1}H NMR and ^{13}C NMR spectroscopy. The antibacterial activity of some synthesized compounds was investigated against bacterial strains and fungal strains. Some of these compounds exhibited a good to significant antibacterial activity.

KEYWORDS: Dimedone,substitutedarylaldehydes,7,7-Dimethyl-4-phenyl-2-thioxo-1,2,3,4,6,7,8-hexahydro-1H-quinazolin -5-ones, TCSA, antibacterial activity.

1. INTRODUCTION

An efficient and a powerful technique in a modern synthetic organic chemistry as well as medicinally chemistry is Multi-Component Reactions (MCRs). They have emerged in synthetic organic chemistry due to their significant value features viz; the opportunity to construct desired compounds, straight forward reaction design, and atom economy and different diversity elements in a single chemical event. Exclusivity, the purification of titled derivatives resulting from MCRs. is the simple, and also another important view all organic reagents employed are utilized. MCRs, leading to interesting heterocyclic compounds scaffolds, are particularly useful for the preparative and diverse chemical libraries of 'drug-like' molecules.[1-7] Heterocyclic six membered compounds contained a hexahydroquinazolinones are of very special interests to their applications in synthetic organic chemistry as well as medicinal chemistry. They are also the basic skeleton of several biological active derivatives. The aim of the present synthesis on focus of 7, 7-Dimethyl-4-phenyl-2-thioxo-1,2,3,4,6,7,8-hexahydro-1H-quinazolin-5-ones and its analogous have considerable attracted to attention in two decades due to their potential antibacterial activity[9,10] and antioxidant such as antifungal, antibacterial, antitumor and antitubercular. The various classical methods of MCRs of Biginelli reaction involved to improve for synthesis of dimedone, substituted aromatic aldehydes and thiourea. The extension of the Biginelli reaction is employed to use by various Lewis acid catalysts.[4-6] In order to the extension of the Biginelli reaction due to expensive, harmful and are difficult to handle workup and also sluggish, require more reaction times as well as acidic conditions, give low yields and also suffered from the formation of some side products. These derivatives employed to work on the use of silica-supported reagents.[7] TMSCl has attracted our interest for the employed synthesis of the various and considerable attention as an inexpensive and readily available reagent for various organic transformations.[8]

Michael addition and cyclodehydration of dimedone with different substituted aromatic aldehyde the presence of TCSA (Scheme -1). Initially, a pilot reaction was attempted using substituted aromatic benzaldehyde (1), dime done (2) and thiourea (3) in the presence of PPh_3 without any solvent (Scheme-I).

2. METHODS AND MATERIALS

All the chemical, reagents and solvents were purchased from Merck chemicals. The melting points of titled derivatives were measured on Agrawal 535 melting point apparatus and are uncorrected. All the reactions were

checked by thin layer chromatography performed on percolated silica gel 60F254 plates. The derivatives were visualized with UV light in iodine chamber.. NMR spectra of these compounds were recorded on BRUKER 400 MHz spectrometers and ^{13}C NMR was recorded on BRUKER 100 MHz using $CDCl_3$ tetra methyl saline as internal standard. Elemental analyses were carried out in Perkin Elmer 240 CHN elemental analyzer.

2.1. GENERAL PROCEDURE FOR THE SYNTHESIS OF 7, 7-DIMETHYL-4-PHENYL-2-THIOXO-2, 3, 4, 6, 7, 8-HEXAHYDRO-1H-QUINAZOLIN-5-ONE

A mixture of substituted aromatic aldehydes (1) (1mol), dimedone (2) (1mol) and /thiourea (3) (1.5 mol) with the TCSA (5 mmol) in ethanol as a solvent taken in a beaker (capacity 25 mL). The mixture of the reaction was arranged on magnetic stirrer and reaction was continued. The completion of the reaction was examined by TLC (ethyl acetate/hexane,(4:6). The reaction mixture was extracted with ethyl acetate and neutralized with base. The organic layer then washed with water and dried over anhydrous Na_2CO_3. The Ethylacetae layer was evaporated under reduced pressure and solid compound was crystallized from absolute ethanol to lead the pure corresponding 7, 7-Dimethyl-4-phenyl-2-thioxo-2, 3, 4, 6, 7, 8-hexahydro-1H-quinazolin-5-azones and its derivatives **(4a–4h)** in good yields.

2.1.1).7, 7-Dimethyl-4-phenyl-2-thioxo-2, 3, 4, 6, 7, 8-hexahydro-1H- quinazolin-5-one (4a)

Pale yellow solid; M.p- 204-206^{0}C; Yeild-85%, ^{1}HNMR (400MHz, $CDCl_3$) δ ppm: 1.054(s, 3H,), 1.225(s, 3H), 2.245 (q, J= 12.0Hz, 2H, CH_2); 2.456(s, 2H, CH_2), 4.547 (d, J= 8.0Hz,1H, CH); 7.324-7.658 (m, 5H, Ar), 9.687(s, 1H, NH),10.145(s, 1H, NH); ^{13}CNMR (100MHz, $CDCl_3$) δ ppm: 195.69 , 173.35 , 148.05, 141.12, 128.87, 127.04, 126.71, 105.57, 53.55, 48.56, 33.54, 28.83,26.54; LCMS(m/z): 287.74 (M+H); Molecularformule.- $C_{16}H_{18}N_2OS$; Elemental analysis: Calculated: C -67.10; H- 6.33, N- 9.78; Found: C- 67.05, H- 6.30, N- 9.84.

2.1.2)4-(4-Methoxyphenyl)-7,7-dimethyl-2-thioxo-2,3,4,6,7,8-hexahydro-1H-quinazolin-5-one (4b)

Pale yellow solid Mp 217-219^{0}C; Yeild-88%, ^{1}H NMR (400MHz,$CDCl_3$)δ ppm: 0.981(s, 3H), 1.117(s, 3H), 2.229(q, J=14.2Hz, 2H, CH_2),2.570(s, 2H, CH_2), 3.778(s, 3H, OCH_3),4.718(d, J=4.4Hz, 1H, CH), 6.988(d, J=8.0Hz, 2H, Ar), 7.232(d, J=8.8Hz, 2H, Ar), 9.542(s, 1H, NH); 10.457(s, 1H, NH); ^{13}C NMR (100MHz, $CDCl_3$) δppm: 195.87, 174.54 , 158.47, 148.47, 136.59, 128.87, 115.54, 108.51, 102.54, 55.73, 52.54, 50.27, 32.41, 28.23, 27.54; LCMS (m/z): 317.59(M+H); Molecularformule: C_{17} H_{20} N_2 O_2 S: Elemental analysis: calculated C- 64.53; H- 6.37, N-8.85; Found: C- 64.46, H- 6.35; N- 8.95.

2.1.3.)4-(3-Methoxyphenyl)-7,7-dimethyl-2-thioxo-2,3,4,6,7,8-hexahydro-1H-quinazolin-5-one (4c)

Yellow solid;Mp-210-212^{0}C; Yeild-90%,^{1}HNMR (400MHz,$CDCl_3$)δppm: 0.978(s,3H), 1.254(s, 3H), 2.165(q, J=14.0Hz, 2H, CH_2), 2.557(s, 2H, CH_2), 3.770(s, 3H, OCH_3), 5.057(d, J=4.8Hz, 1H, CH), 6.826-7.254(m, 4H, Ar), 9.757(s, 1H, NH); 10.248(s, 1H, NH); ^{13}CNMR (100MHz, $CDCl_3$)δppm: 196.85, 173.87, 158.98, 148.24, 144.67, 130.25, 128.69, 119.66, 32.96,28.67, 26.76; LCMS (m/z)- 317.55; Molecularformule. C_{17} H_{20} N_2 O_2 S; Elemental analysis: calculated C- 64.53; H-6.37, N- 8.85; Found: C- 64.45, H- 6.36; N- 8.92.

2.1.4)7,7-Dimethyl-2-thioxo-4-p-tolyl-2,3,4,6,7,8-hexahydro-1H-quinazolin-5-one (4d).

Yellow compound, Mp-225- 227^{0}C; Yeild-87%, ^{1}H NMR (400MHz,$CDCl_3$) δppm: 0.955(s, 3H), 1.175(s, 3H), 2.419(q, J=12.0Hz, 2H, CH_2), 2.538(s, 2H, CH_2), 2.732(s, 3H, CH_3), 4.856(d, J=5.8Hz,1H,CH),7.224-7.624(m,4H,Ar),9.457(s,1H,NH); 10.128(s, 1H, NH);^{13}CNMR(100MHz, $CDCl_3$): δppm: 193.55, 174.44, 148.65 , 140.67, 136.72, 128.58, 126.34, 108.77, 51.53, 49.46, 32.17, 28.57, 26.21, 20.20; LCMS (m/z)-301.54; Molecularformule: C_{17} H_{20} N_2 O S: Elemental analysis: calculated; C- 67.97; H- 6.71, N- 9.32; Found: C- 67.90, H-6.71; N- 9.45.

2.1.5.)4-(4-Dimethylamino)-2-hydroxyphenyl)-7,7-dimethyl-2-thioxo-1,2,3,4,6,7,8-hexa hydro-1H-quinazolin-5(6H)- one (4e)

Brown solid; Mp-234-236^{0}C; Yeild-85%, ^{1}HNMR (400MHz,$CDCl_3$)δppm: 0.943(s,3H); 1.118(s, 3H), 2.445(q, J=16.8Hz, 2H, CH_2), 2.450(s, 2H, CH_2), 2.596(s, 6H, NMe_2), 5.124(d, J=6.4Hz, 1H, CH), 6.986-7.434 (m, 3H, Ar),9.774(s, 1H, NH),10.154(s,1H,-OH), 10.647(s, 1H, NH); ^{13}C NMR (100MHz, $CDCl_3$): δppm 195.22, 175.35,157.64,150.51, 149.92, 130.83, 125.66, 122.84, 120.03,119.05,49.62,45.37, 37.26, 28.84, 26.66, LCMS(m/z)-345.48.Molecularformule: $C_{18}H_{23}$ N_3 O_2 S; Elemental analysis: calculated: C- 62.58; H-6.71, N-12.16; Found: C- 65.54, H- 6.71; N- 12.22.

2.1.6.)4-(3-Chlorophenyl)-7,7-dimethyl-2-thioxo-2,3,4,6,7,8-hexahydro-1H-quinazolin-5-one (4f)

Yellow solid Mp: 241-243^{0}C; Yeild-88%, 1H NMR (400MHz,$CDCl_3$)δppm: 1.095(s, 3H), 1.154(s, 3H); 2.117 (q, J=12.6Hz, 2H, CH_2), 2.332(s, 2H, CH_2), 4.757 (d, J=6.4Hz, 1H, CH), 7.229-7.518(m,4H,Ar-H);9.674(s,1H,NH),10.241(s,1H,NH);^{13}CNMR((100MHz,$CDCl_3$)δppm: 196.25, 174.08, 151.22 , 141.54, 133.08, 128.81, 128.02, 126.92, 124.88, 106.55, 53.60, 48.77, 31.21, 27.55, 26.76; LCMS(m/z)- 321.55 (M+H). Molecularformule: C16H17ClN2OS; Elemental analysis: Calculated: C- 59.90; H- 5.34, N- 8.73; Found: C- 59.82, H- 5.32; N- 8.79.

2.1.7.)4-(4-Bromophenyl)-7,7-dimethyl-2-thioxo-2,3,4,6,7,8-hexahydro-1H-quinazolin-5-one (4g)
Brownredsolid; Mp-247-249^{0}C; Yeild-88%, 1HNMR (400MHz,CDCl3)δppm: 0.994(s,3H), 1.074(s,3H); 2.144(q, J=14.7Hz, 2H, CH_2); 2.290(s, 2H, CH_2), 4.751(d, J=6.4Hz, 1H, CH), 7.224 (d, J=8.0Hz, 2H, Ar), 7.334(s, J=7.8Hz, 2H, Ar-H); 9.524(s, 1H, NH), 10.137(s, 1H, NH); 13C NMR (100MHz, CDCl3) δppm: 196.27, 173.98, 147.88, 143.87, 132.65, 130.78, 128.94, 120.34,106.56, 51.58, 48.77, 30.08, 28.95, 26.06; LCMS (m/z): 366. Molecularformule Anal. Calcd for C_{16} H_{17} Br N_2 OS: Elemental analysis: calculated: C- 52.61; H- 4.69, N- 7.67; Found: C- 52.60, H- 4.69; N- 7.66.

2.1.8) 4-(4-nitrophenyl)-7, 7-dimethyl-2-thioxo-2, 3, 4, 6, 7, 8-hexahydro-1H-quinazolin-5- one (4h)
Brightyellowsolid;Mp.235-237^{0}C;Yeild-83%,^{1}HNMR(400MHz,$CDCl_3$)δppm:1.119(s,3H);1.216 (s,3H), 2.132(q, J=12.0Hz, 2H, CH_2), 2.245(s, 2H, CH_2), 4.511(d, J=8.0Hz, 1H, CH), 7.354-7.769 (m, 4H, Ar), 9.957(s, 1H, NH),10.358(s, 1H, NH); ^{13}C NMR (100MHz, $CDCl_3$) δppm: 196.56,175.28,159.58, 149.09, 145.54, 128.68,128.65, 125.28, 123.74, 105.88, 48.18, 32.56, 28.54,26.96,LCMS(m/z)-330.65(M+H); Molecularformule: $C_{16}H_{17}N_3O_3S$; Elementalanalysis: Calculated: C-57.94; H- 5.17, N- 12.68; Found: C-57.87, H- 7.16; N- 12.75.

3. ANTIBACTERIAL ACTIVITY

The antibacterial activity of the desired derivatives of 7,7-Dimethyl-4-phenyl-2-thioxo-2,3,4,6,7, 8-hexahydro-1H-quinazolin-5-ones has been evaluated ***invitro*** for its strong potent active bacterial strains, including S. aureus and Escherichia coli. The test compound's antibacterial potencies have been compared with standard drug such as Streptomycin. The ***invitro*** activities of the examined derivatives were evaluated by using agar plates containing nutrient broth for bacteria. This marked and antibacterial activity may be showed due to the quinazalones ring system and the high hydrophobic content of this family of compounds. The compounds with the quinazalones segment are more potent active against bacteria, presumably because of the strong interaction of the latter with the agar medium, which hinders their diffusion in agar medium. The antimicrobial inhibitions of test compounds are expressed as the area of zone of inhibition and summarized in Table 1.

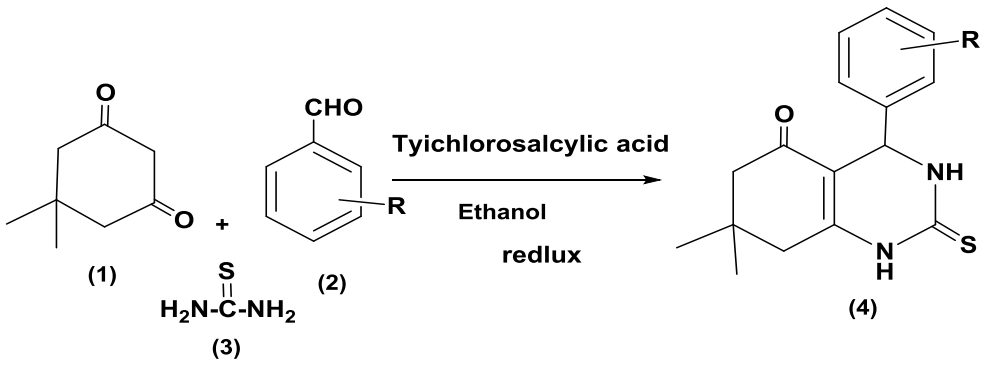
Table 1: *In vitro* antibacterial screening study of the title compounds (4a-4h).

S.No	Compound code	Zone of Inhibition (mm)					
		Gram +ve			Gram –ve		
		S.aureus			E.coli		
		100µg/ml	250 µg/ml	500 µg/ml	100µg/ml	250 µg/ml	500 µg/ml
1	**4a**	06	06	07	06	08	09
2	**4b**	14	18	18	19	19	21
3	**4c**	07	10	18	10	18	19
4	**4d**	**07**	**14**	**16**	10	15	**17**
5	**4e**	15	19	21	10	15	18
6	**4f**	12	18	21	17	22	24
7	**4g**	18	20	21	16	22	25
8	**4h**	04	11	14	12	15	16
Controlee	**DMSO**	10			10		
STD	**Streptomycin**	25	25	25	30	30	30

4. RESULTS AND DISCUSSION

Initially, we identified that the best outcome examined the reaction of substituted aryl aldehydes, dimedone, and thiourea with TCSA at refluxed with the use of ethanol as solvents (Scheme -1). This catalyst has prominent characteristic features for the reaction performance such as the shortest reaction time, an excellent product outcome, easy handling and simple work-up procedure and also purification of products by non-chromatographic methods. It is also observed that the various aromatic aldehydes having electron-releasing and withdrawing substituents in para-positions lead excelent yield of the product.

It is also performed that different substituted aromatic aldehydes contain electron-releasing or withdrawing substituents in para-positions scaffold good yield of the product. The microbial activity of the named moiety possesses EWG exhibited more active potential than the EDG of the moiety. (Table-1) The reusability of the catalyst was investigated; we have not tried this method for aliphatic aldehydes. We found that the reaction of aromatic aldehydes with electron-withdrawing groups was faster than the reaction of aldehydes with electron-donating groups.



(4a-4h)

R = H,3-OCH_3, 4-OCH_3, 4-CH_3, 2-OH-4-$N(CH_3)_2$, 4-Cl,4-Br,4-NO_2

Scheeme-1

5. CONCLUSION

In summary, We observed that this method is a convenient, economical, and environmentally for the preparation of the 7,7-Dimethyl-4-phenyl-2-thioxo-2,3,4,6,7,8- hexahydro-1H-quinazolin-5-ones derivatives in biological and medicinal most important . In conclusion, the present methodology is very attractive and important features means as minimized reaction times, good yields, and ease of product isolation. This is a simple procedure and simple solvent conditions combined with easy recovery and reuse of this catalyst make it an economically and environmentally benign process.

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