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ONE POT SYNTHESIS 7, 7-DIMETHYL-4-PHENYL-2-THIOXO-2, 3,4,6,7, 8- HEXAHYDRO-1H-QUINAZOLIN-5-ONES PROMOTED BY $ZROCL_2$ AND STUDY OF BIOEVLUATION

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ABSTRACT

A simple and an efficient method for the Synthesis of derivatives 7**,** 7-dimethyl-4-phenyl-2-thioxo-2, 3, 4, 6, 7, 8-hexahydro-1H-quinazolin-5-one from dimedone and substituted aromatic aldehydes with thiourea in the presence of $ZrOCl_2$ catalyst and an excellent yields under reflux through condensation followed by cyclization of the desired products. All structures of derivatives were confirmed by ^{1}H NMR and ^{13}C NMR spectroscopy. In addition to study of the Bioevluation of desired compounds.

KEYWORDS: Dimedone, substitutedaryialdehydes, 7, 7-Dimethyl-4-phenyl-2-thioxo-1, 2, 3, 4, 6, 7, 8-hexahydro-1H-quinazolin-5-ones, $ZrOCl_2$, Bioevluation.

1. INTRODUCTION

Multi component reaction (MCRs) is a most powerful and efficient tool in a modern synthetic organic chemistry. The advantages this type of reaction in synthetic organic chemistry and the valuable characteristics such as the establishment of the desired compounds, straight forward reaction, design as well as atom economy and the purification of target products from MCRs is also simple, leading to interesting heterocyclic moiety and are also particularly useful for the construction ‘drug-like ‘molecules.[1-3] The special interest of six membered heterocyclic compounds, hexahydroquinazolinone are preparing in medicinal chemistry and synthetic organic chemistry. The main focus on synthesis of derivatives of 7, 7-Dimethyl-4-phenyl-2-thioxo-1, 2, 3, 4, 6, 7, 8-hexahydro-1H-quinazolin-5-ones have considerable attracted to attention in

recent years due to their potential antibacterial activity[4] and antioxidant such as antifungal, antibacterial, antitumor and antitubercular. With wide applications including anticonvulsant,[5] sedative, tranquilizer, analgesic,[6] antimicrobial,[8] anesthetic,[9] anticancer,[10] antihypertensive,[11] anti-inflammatory,[12] diuretic[13] andmusclerelaxantproperties.[14] (Scheme -1). Initially, a pilot reaction was attempted using substituted aryl aldehyde (1), dime done (2) and thiourea (3) in the presence of $ZrOCl_2$ as Lews catalyst (Scheme-I).

2. METHODS AND MATERIALS

All the chemical and reagents and solvents were purchased from Merck chemicals**.** The Aggarwal 535 melting point apparatus is used for the determination to mesurening temperature of various newly synthesized compounds and are uncorrected. All the reactions were checked by thin layer chromatography performed on percolated silica gel (Merck chemicals). Compounds were visualized with UV light in iodine chamber. NMR spectra of these compounded 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.

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) (1 mol), dimedone (2) (1 mol) and thiourea (3) (1.5 mol) with the Lews acid catalyst such as $ZrOCl_2$ with solvent taken in a beaker in 50 mL and The total mixture fitted on magnetic stirrer and reaction was proceeding. The completion of the reaction was monitored by TLC (ethyl acetate/hexane (4:6). The reaction mixture was then extracted with ethyl acetate and the catalyst was separated by the filtration. The organic layer then washed with water and dried over anhydrous Na_2CO_3. Organic solvent 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; Mp. 214-216^0 C; Yeild-84%, ^{1}HNMR (400MHz, $CDCl_3$), δ ppm:1.114(s, 3H, CH_3); 1.121(s, 3H, CH_3); 2.128 (q, J=8.0Hz, 2H, CH_2); 2.258(s, 2H, CH_2); 4.654 (d, J=7.65Hz,1H, CH); 7.112-7.328 (m, 5H, Ar); 9.471(s, 1H, NH); 10.262(s, 1H, NH); ^{13}CNMR

(100MHz, $CDCl_3$): δ ppm: 194.77, 170.07, 147.58, 141.45, 128.29, 127.76, 125.148, 102.44, 51.65, 49.88, 32.56, 28.50, 27.64; LCMS(m/z): 286.45; Molecularformule: C_{16} H_{18} N_2OS.

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; Mp 237-239^{0}C; Yeild-90%, ^{1}H NMR (400MHz,$CDCl_3$)δ ppm**:** 0.955(s, 3H, CH_3); 1.047(s, 3H, CH_3); 2.118(q, J=8.6.2Hz, 2H, CH_2); 2.4651(s, 2H, CH_2); 3.757(s, 3H, OCH_3), 4.324(d, J=7.2Hz, 1H, CH); 6.882(d, J=8.6Hz, 2H, Ar); 7.242(d, J=8.8Hz, 2H, Ar); 9.758(s, 1H, NH); 10.223(s, 1H, NH); ^{13}C NMR (100MHz, $CDCl_3$): δppm: 195.54, 172.08, 158.52, 147.68, 137.81, 128.18, 115.82, 107.57, 100.58, 55.29, 52.14, 50.04, 32.29, 28.09, 26.98; LCMS (m/z): 317.25; Molecularformule: C_{17} H_{20} N_2 O_2 S.

2.1.3 4-(3-ethoxy-4-hydroxyphenyl)-7,7-dimethyl-2-thioxo-1,2,3,4,6,7,8-hexahydro-1H-quina zolin-5-one (4c)

Pale-yellow; Mp: 254-256^0 C; Yeild-87%, ^{1}HNMR (400MHz,$CDCl_3$)δppm: 0.997(s, 3H, CH_3); 1.211(s, 3H, CH_3);1.255(t,3H,CH_3); 2.146(q,2H,-CH_2-),2.654(q, =9.2.1Hz, 2H, CH_2); 2.939(s, 2H, CH_2); , 4.622(d, J=8.06Hz, 1H, CH); 6.970-7.251(m,34H, Ar);9.633(s,1H,-OH); 9.873(s, 1H, NH); 10.326(s, 1H, NH); ^{13}CNMR (100MHz, $CDCl_3$): δppm: 190.59, 172.56, 158.54,147.58,146.53,139.58,135.55,120.56,118.53,115.65,101.04,60.09,50.84,47.58,36.19,30.56, 26.34, 13.57.; LCMS (m/z)- 365.22(M-H). Molecularformule. C_{18} H_{22} N_2 O_3 S.

2.1.4 4-(4-Dimethylamino)-2-hydroxyphenyl)-7,7-dimethyl-2-thioxo-1,2,3,4,6,7,8-hexahydro-1H -quinazolin-5(6H)- one (4d)

Pale-yellow; Mp- 254-256^{0}C; Yeild-90%, ^{1}HNMR (400MHz,$CDCl_3$)δppm: 1.105(s,3H, CH_3); 1.115(s, 3H, CH_3); 2.261(q, J=7.2Hz, 2H, CH_2); 2.336(s, 2H, CH_2); 2.674(s, 6H, NMe_2), 4.894(d, J=8.2Hz, 1H, CH); 7.029-7.229 (m, 3H, Ar); 9.654(s, 1H, NH);10.324 (s,1H,-OH),10.356 (s,1H,NH); ^{13}CNMR (100MHz,$CDCl_3$): δppm195.59, 172.32, 158.56, 151.26, 149.52, 131. 54, 126.57, 122.69, 121.54, 120.85, 49.28, 46.53, 38.16, 28.48, 26.49, LCMS(m/z)-345.48.Molecular formula: $C_{18}H_{23}$ N_3 O_2 S.

2.1.5 4-(4-Chlorophenyl)-7,7-dimethyl-2-thioxo-2,3,4,6,7,8-hexahydro-1H-quinazolin-5-one (4e)

Pale-yellow; MP: 241-243^{0}C; Yeild-88%, ^{1}H NMR (400MHz,$CDCl_3$)δppm: 0.944(s, 3H, CH_3); 1.114(s, 3H, CH_3); 2.119 (q, J=7.2Hz, 2H, CH_2); 2.240(s, 2H, CH_2); 5.017 (d, J=6.8Hz, 1H, CH); 7.236-7.515 (m,4H,Ar); 9.574 (s,1H,NH); 10.234(s,1H,NH); ^{13}CNMR

((100MHz,$CDCl_3$) δppm: 196.51, 174.02, 150.37, 141.54, 132.20, 129.07, 128.53, 127.64, 125.58, 104.54, 52.28, 50.26, 32.57, 28.29, 25.26CMS (m/z) 321.64. Molecularformule $C_{16}H_{17}ClN_2OS$.

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

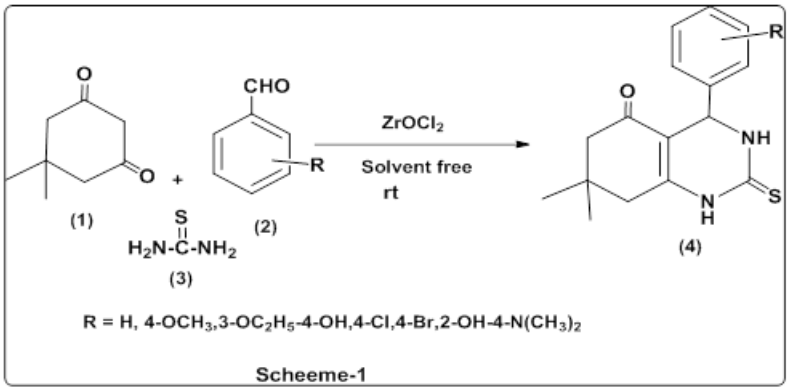
Pale-yellow; Mp 256=258^{0}C; Yeild-94%, ^{1}HNMR (400MHz,$CDCl_3$)δppm: 0.898(s, 3H, CH3); 1.029(s, 3H, CH3); 2.014(q, J=6.8Hz, 2H, CH_2); 2.135(s, 2H, CH_2); 5.208(d, J=8.0Hz, 1H, CH); 7.220 (d, J=8.4Hz, 2H, Ar); 7.544(s, J=7.6Hz, 2H, Ar); 9.712(s, 1H, NH); 10.223(s, 1H, NH); ^{13}C NMR (100MHz, $CDCl_3$): δ 195.2, 173.2, 147.04, 141.07, 132.77, 130.42, 128.98, 121.25, 104.56, 52.20, 49.0, 32.44, 28.96, 25.89; LCMS (m/z): 366.16. Molecularformule $C_{16}H_{17}BrN_2OS$.

2.1.7 4-(4-nitrophenyl)-7, 7-dimethyl-2-thioxo-2, 3, 4, 6, 7, 8-hexahydro-1H-quinazolin-5- one (4g)

Pale-yellow: Mp. 225-227^{0}C; Yeild-88%, ^{1}HNMR (400MHz,$CDCl_3$)δppm: 1.112(s,3H, CH3); 1.189(s, 3H, CH_3); 2.219(q, J=8.0Hz, 2H, CH_2); 2.334(s, 2H, CH_2); 5.015(d, J=7.6Hz, 1H, CH); 7.305-7.720 (m, 4H, Ar);9.641(s, 1H, NH); 10.201(s, 1H, NH); ^{13}C NMR (100MHz, $CDCl_3$): δppm194.91.175.02, 160.82, 150.49, 145.59, 129.66, 128.05, 126.58, 125.44, 103.58, 50.28, 34.26, 28.51, 27.44, LCMS(m/z)-330.25 . Molecularformule: $C_{16}H_{17}N_3O_3S$.

3. RESULTS AND DISCUSSION

We observed that the important result in investigated the reaction of substituted aryl aldehydes, dimedone and thiourea in the presence of Lews acid catalyst under solvent free conditions at room temperature (Scheme -1). The advantages this catalyst used for in the reaction, which is response carried out easy work-up, the low reaction time, good yields, and purification of titled compound by non-chromatographic methods. It is also identified that various substituted aryl aldehydes containing electron withdrawing and electron-releasing substituents in para-positions lead better yield than that of ortho substituents. Therefore, we observed that the reaction of aryl aldehydes having electron-withdrawing groups was faster rate of reaction as compared to the reaction of aldehydes possessing electron realsing groups. The reusability of this catalyst was investigated; we have not tried this method for aliphatic aldehydes. The antimicrobial activity of titled compounds possesses EWG exhibited more active potent than the EDG of the meity (Table-I).



Scheeme-1

Antibacterial activity

The antimicrobial activity of the titled compounds enhancedviz; The 7,7-Dimethyl-4-phenyl-2-thioxo-2,3,4,6,7, 8- hexahydro-1H-quinazolin-5-ones and its derivatives have being screened in vitro for its bacterial strains such as, E.coli, P. aeruginosa, B. substilis, B. megaterium, A. niger and C.albicans. The test compound was screened using agar plates containing in nutrient broth for bacteria in vitro activities. The test compound was screened against each microbial species.[9-12] The antibacterial potencies of the test compound have being compared with Streptomycin. The antimicrobial inhibitions of test compound are expressed as the area of zone of inhibition and summarized in Table-I. This marked and antibacterial activity may be due to the presence of high hydrophobic content of this family of compounds and the quinazalones ring system. The compounds containing the quinazalones segment are more active against bacteria. Presumptively due to the strong interaction of the later with the agar medium, this hinders their diffusion in agar medium.

Table I: In vitro antibacterial screening study of the title compounds 4(a-f).

Entry	Zone of Inhibition against(mm)					
	E. Coli	P. Aeruginosa	B. Substills	B. Megaterium	Angier	C. albicans
4a	08	10	09	10	10	12
4b	15	15	21	25	10	12
4c	20	21	22	20	16	17
4d	19	18	20	20	14	15
4e	14	12	18	18	11	14
4f	10	14	21	16	14	13
DMSO	10			10		
Streptomycin	25	25	25	25		
Ketonozole					22	22

4. CONCLUSION

In conclusion, an efficient catalyst for the synthesis of series of titled compounds. The present methodology is very attractive features such as reduced reaction times, good yields, ease of product isolation. This is a simple procedure and solvent free conditions combined with easy recovery and reuse of this $ZrOCl_2$ as Lews acid catalyst make this method economically and environmentally benign process. We believe that this procedure is convenient, economic and ecofriendly for the synthesis of The 7,7-Dimethyl-4-phenyl-2-thioxo-2,3,4,6,7, 8- hexahydro-1H-quinazolin-5-ones derivatives of biological and medicinal importance.

5. ACKNOWLEDGEMENTS

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