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RESEARCH ARTICLE

EFFICIENT SYNTHESIS OF NOVEL8,8-DIMETHYL-2-(4-NITROPHENYL)-5-PHENYL-5,7,8,9-TETRAHYDRO-6H-(1,3,4)THIADIAZOLO(2,3-B)QUINAZOLIN-6-ONE CATALYZED BY $ZROCL_2$

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ABSTRACT

In this investigation, a new Lewis acid-based was synthesis of novel series of 8,8-dimethyl-2-(4-nitrophenyl)-5-phenyl-5,7,8,9-tetrahydro-6H-(1,3,4)thiadiazolo(2,3-b)quinazolin-6-one promoted by camphorsulfonic acid . The catalytic ability of camphorsulfonic acid was ascertained in the efficient synthesis of a novel array of thiadiazolo (2,3-b) quinazolin-6-one scaffolds via a one-pot three-component reaction of dimedone, substituted aromatic aldehydes, and 5-(4-nitrophenyl)-1, 3, 4-thiadiazol-2-amine under solvent ethanol conditions. This intermediate such as 5-(4-nitrophenyl)-1, 3, 4-thiadiazol-2-amine is one of the three component of this process which is nitrogen sources .This component can be obtained from 4-nitrobenzoic acid and semithiocarbazide in the presence of ethanol and con H2SO4 at reflux and among the several notable benefits of this recently established technology are its low E-factor, high reaction mass efficiency, atom economy, scalability, short reaction time, avoidance of hazardous organic solvents, and ease of enforcement.

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INTRODUCTION

One of the most important powerful useful and an efficient method for synthesis of organic molecule in a modern synthetic organic synthesis area is known multi component reactions(MCR) and have been proven to be a most elegant and continuous path way to access complex structures in a single synthetic procedure from simple construction blocks. The formation of carbon-carbon and carbon-heteroatom bonds in a single one pot allows three component reactions to reveal high atom-economy, high selectivity, and procedurally simplicity (1-2). Organic meity that have at least one heteroatom in their composition are known as heterocyclic compounds. The most prevalent ones are triple, tetragon, pentagonal, or hexagonal, and they having nitrogen, oxygen, and sulphur. There could be two distinct atoms in the Thiophene called as azoles. The nitrogen and sulphur-containing thiadiazolo ring has drawn a lot of interest due to its diversified coordination capacity towards mineral element ions, particularly in structures, biological applications, and bioactive molecules. One of the most crucial areas of research nowadays is the necessity to develop novel chemicals to address this resistance. Thiadiazolo is a multifunctional moiety displaying a broad range of biological activity (3).

The thiadiazolo moiety functions as a "two-electron donor system" and a "hydrogen binding domain." Additionally, it serves as a limited pharamacophores. For a considerable amount of time, the chemistry of heterocyclic molecules has been an intriguing area of research. One significant class of chemicals for the development of novel drugs is 1, 3, 4-thiadiazole, which has a heterocyclic nucleus. In recent decades, the synthesis of new thiadiazolo derivatives and the study of their chemical and biological behaviour have become increasingly important. Intense research in medicinal chemistry is still being done in the hunt for antiepileptic substances with more selective action and less toxicity. Significant research has been done in recent years on various classes of thiadiazolo compounds, many of which have a wide range of pharmacological properties, including antimicrobial (4-5), antioxidant (6), antifungal (7),anttuberculosis (8), Cytotoxicity (9), anticonvulsant (10) properties. The previous reports reveals that the various catalysts were applied the preparation of quinazalones such as Camphorsulfonicacid (11), phenhydramine hydrochloride-$CoCl_2 \cdot 6H_2O$ (12), Lawson's reagent (13). As part of our on-going investigation to describe an effective and workable method for the one-pot three-component synthesis of thiadiazolo(2,3-b)quinazolin-6-ones and also their derivatives via the reaction of dimedone, substituted aromatic aldehydes, and 5-substituted-1,3,4-thiadiazol-2-amines using $ZrOCl_2$ as a novel and under

solvent as a ethanol and green conditions. This is a part of our on-going research on the synthesis of novel annulated heterocycles using green and reusable catalytic systems via multicomponent strategy.

METHODS AND MATERIALS

The majority of their quire starting materials synthetic reagents and solvents are found from marketable sources and they are used without additional purification. The Thin Layer Chromatography (Silica gel coated on aluminium plates) was used to monitor reaction condition of synthesized compounds. Bruker AM400MHz and 100 MHz spectrometers were used to record the ^{1}H-NMR and ^{13}C-spectra of synthesized compounds. $CDCl_3$ was used as a solvent for recording spectrum. The Mass spectrum of the compounds was recorded by Shimadzu, LCMS-2020 to determine the Molecular weight of the compounds by LCMS method.

Preparation of 5-(4-nitrophenyl)-1, 3, 4-thiadiazol-2-amine (3): The solvent such as toluene introduced in 25mL RBF and starting material the mixture of 4-Nitro benzoic acid (0.1mol) and thiosemicarbazide (0.1mol) was dissolved in above solvent. The slowly added 30% H_2SO_4 using dropping funnel. After addition of 30% H_2SO_4 and start the reaction on the magnetic stirrer at 80^0C. The reaction continued until identifications of TLC as a mobile system polar solvent and nonpolar solvent (5:5) for the progression of reaction. The reaction cooled at 30^0C, poured into crushed ice and neutralised with a solution of $NaHCO_3$. The solution was added ethylacetae and separated organic layer. The organic layer washed with water, separated and distilled under vacuumed. Finally, desired compound get recrystallization.
Yield:94%, yellow compound; m.p(ºC):224-226;^{1}HNMR (400MHz,$CDCl_3$) δppm:8.127-7.984(m,4H, Ar-H),7.356-7.279 (m,5H,Ar-H),4.126 (s,1H,H (4)),1.845(s, 2H,CH_2),1.564(s,2H,-CH_2-), 1.094 (s,6H,$(CH_3)_2$); ^{13}CNMR (100MHz,$CDCl_3$)δppm:195.26,161.09,152.12,145.44,142.36, 139.62, 134.74,130.02,129.23, 128.55, 128.04,127.81, 125.47, 63.07, 49.54, 38.36, 30.94,26.95;LC-MS(m/z):433.52 (M+H);Molecularformule:$C_{23}H_{20}N_4O_3S$.Elemental Analysis : calculated: C- 63.87, H-4.66.N-12.9154.Obtained: C-63.80,H-4.65 ,N-12.97.

2.2.8,8-dimethyl-2-(4-nitrophenyl)-5-phenyl-5,7,8,9-tetrahydro-6H -(1,3,4)thiadiazolo(2,3-b) quinazolin-6-one(6a-6e): The mixture of 5-(4-nitrophenyl)-1, 3, 4-thiadiazol-2-amine (0.1mole), substituted aromatic aldehyde (0.1mole) and dimedone (0.1mole) are dissolved in 25mL of ethanol is taken in 50mL of four neck RBF. Initially the reaction started at RT few minutes and added catalyst such as $ZrOCl_2$. The reaction was continued at 80^0Cuntil completely consumed all reactants and also identified spot of reaction on the TLC plates as mobile system (Ethyl acetate: n-hexane). The catalyst is recovered by filtration after completion of the reaction. The mixture then neutralised with solution of $NaHCO_3$ and added the ethylacetae, separated the organic layer. This organic layer washed with water in twice, separated the ethyl acetate and distilled and vacuumed. The desired compound was recrystallized from ethanol.

8,8-dimethyl-2-(4-nitrophenyl)-5-phenyl-5,7,8,9-tetrahydro-6H-(1,3,4)thiadiazolo(2,3-b)quinazolin-6-one (6a): Yield: 86%, yellowsolid; m.p (ºC):245-247;^{1}HNMR (400MHz,$CDCl_3$)δppm:8.127-7.984(m,4H,Ar-H),7.3 56-7.279 (m,5H,Ar-H), 4.126(s,1H,H(4)), 1.845 (s,2H,CH2), 1.564 (s,2H,-CH_2-), 1.094(s,6H,$(CH_3)_2$); 13CNMR (100MHz, $CDCl_3$) δppm:195. 26,161.09, 152.12, 145.44, 142.36, 139.62, 134.74,130.02, 129.23,128. 55,128.04, 127.81, 125.47, 63.07, 49.54, 38.36, 30.94, 26.95; LC-MS (m/z):433.52 (M+H); Molecularformule: $C_{23}H_{20}N_4O_3S$. Elemental Analysis: calculated: C- 63.87, H-4.66.N-12.9154.Obtained: C-63.80,H-4.65 ,N-12.97.

5-(4-hydroxyphenyl)-8,8-dimethyl-2-(4-nitrophenyl)-5,7,8,9- tetrahydro-6H-(1,3,4)thiadi azolo(2,3-b)quinazolin-6-one (6b): Yield:88%,yellowsolid;m.p(ºC):237-239^{0}C; 1HNMR (400MHz,CDCl3)δppm:9.174(- H,s,1H),8.194-7.885 (m,4H,Ar-H), 6.946-6.783(m,4H,Ar-H),4.096(s,1H, H(4)), 2.122 (s,2H,CH2),1.674(s,2H,-CH2-),1.012(s,6H, (CH3)2); 13CNMR (100MHz,CDCl3) δppm: 194.96, 158.77, 154.65, 152.43, 148.61, 141.03, 135.14, 132.08, 129.16, 128.09, 125.66, 117.49, 62.37, 48.81, 39.04, 30.38, 28.02, 26.85;LC-MS (m/z):449.72(M+H); Molecularformule: C24 H20 N4O4S. Elemental Analysis: calculated: C- 61.60, H-4.20.N-12.49.Obtained: C-61.54,H-4.18 ,N-12.55.

5-(4-methoxyphenyl) -8,8-dimethyl-2- (4-nitrophenyl)-,7,8,9- tetrahydro-6H-(1,3,4)thiadi azolo(2,3-b)quinazolin-6-one (6c): Yield:90%, Pale yellowsolid;m.p(ºC):256-258^{0}C; 1HNMR (400MHz,CDCl3)δppm: 8.167-7.852(m,4H,Ar-H),7.192-6.845(m,4H,Ar-H),4.128(s,1H,H(4)),3.729(s,3H,-OCH3),1.945 (s,2H,-CH2),1.473(s,2H,-CH2-),1.125(s,6H, (CH3)2); 13CNMR(100MHz,CDCl3)δppm: 197.19, 159.07, 154.21, 150.03, 146.11, 140.36, 135.17, 131.24, 130.28, 127.57, 125.04, 123.44, 63.71, 54.42, 51.06, 38.55, 30.48, 28.10, 26.69;LC-MS(m/z):463.56(M+H); Molecularformule: $C_{24}H_{22}N_4O_4S$. Elemental Analysis: calculated: C- 62.32, H-4.79.N-12.11.Obtained: C-62.26,H-4.77 ,N-12.17.

8,8-dimethyl-2-(4-nitrophenyl)-5-(3,4,5-trimethoxyphenyl)-5,7,8,9-tetrahydro-6H-(1,3,4)thiadiazolo(2,3-b)quinazolin-6-one(6d): Yield: 87%, Yellowsolid;m.p(ºC):263-265^{0}C; ^{1}HNMR (400MHz,$CDCl_3$)δppm:8.244-7.814(m,4H,Ar-H),6.912-6.713(m,2H,Ar-H),4.049(s,1H,H(4)),3.784(s,3H,-OCH_3),3.595(s,3H,OCH_3),1.894(s,2H,-CH_2),1.503(s,2H,-CH_2-),1.069(s,6H,$(CH_3)_2$,^{13}CNMR(100MHz,$CDCl_3$)δppm:196.92, 160.46, 153.70, 150.13, 147.45, 140.17, 135.53, 132.04, 130.49, 129.31, 128.45, 124.60, 64.02, 59.71, 55.63, 49.81, 38.42, 29.57, 27.95,LC-MS(m/z):463.56(M+H); Molecularformule: $C_{26}H_{26}N_4O_6S$. Elemental Analysis: calculated: C- 59.76, H-5.02.N-10.72.Obtained: C-59.70,H-5.01 ,N-10.77.

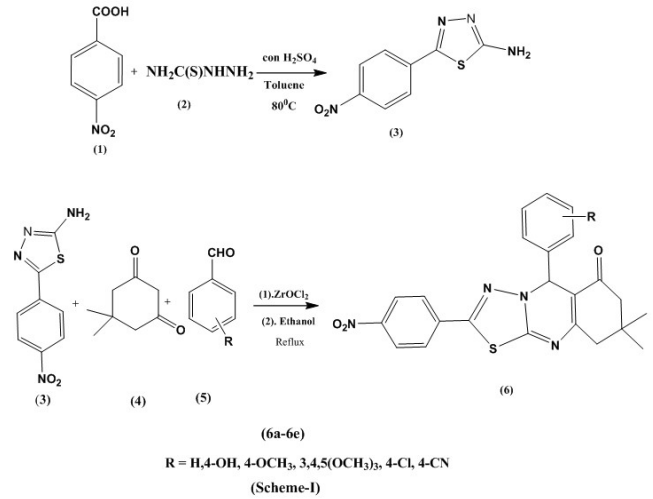
5-(4-chlorophenyl)-8,8-dimethyl-2-(4-nitrophenyl)-5,7,8,9-tetrahydro-6H-(1,3,4)thiadi azolo(2,3-b)quinazolin-6-one (6e): Yield:89%,Yellowsolid;m.p(ºC):256-258^{0}C;^{1}HNMR (400MHz,$CDCl_3$)δppm:8.273-8.042 (m,4H,Ar-H),7.352-6.950(m,4H,Ar-H),4.425(s,1H,H(4)),2.025(s,2H,-CH_2),1.514 (s,2H,-CH_2 1.028(s,3H,CH_3), 0.914(s,3H,CH_3);^{13} CNMR (100MHz,$CDCl_3$) δppm:197.21, 159.95, 152.09, 148.31, 141.03, 138.28, 134.65, 130.35, 129.46, 128.96, 128.45, 127.39,63.62, 50.46, 39.06, 28.25;LCMS (m/z):468.19(M+H); Molecularformule:$C_{23}H_{19}ClN_4O_3S$. Elemental Analysis: calculated: C- 59.16, H-4.10.N-12.00.Obtained: C-59.11,H-4.08, N-12.07

4-(8,8-dimethyl-2-(4-nitrophenyl)-6-oxo-6,7,8,9-tetrahydro-5H-(1,3,4)thiadiazolo(2,3-b) quinazolin-5-yl)benzonitrile(6f): Yield:87%,Yellowsolid;m.p(ºC):268-

270^0C;^{1}HNMR(400MHz,$CDCl_3$)δppm:8.291-8.058(m,4H,Ar-H),7.712-7.525(m,4H,Ar-H),4.346(s,1H,H(4)),2.146(s,2H,-CH_2),1.715(s,2H,-CH_2),1.108(s,3H,CH_3),0.942 (s,3H,CH_3);^{13} CNMR (100MHz,$CDCl_3$) δppm: 197.21, 161.73, 152.62, 150.02, 146.11, 142.03, 135.29, 131.15, 129.46, 128.46, 127.65, 126.06, 124.77, 117.69, 65.08, 49.15, 39.47, 30.69, 28.25;LCMS (m/z):458.72(M+H); Molecularformule: $C_{24}H_{19}N_5O_3S$. Elemental Analysis: calculated: C- 63.01, H-4.19.N-15.37.Obtained: C-62.95, H-4.12, N-15.42.

RESULTS AND DISCUSSION

In this investigation, we submitted the synthesis of novel deigned and an efficient synthesis of a series of8,8-dimethyl-2-(4-nitrophenyl)-5-phenyl-5,7,8,9-tetrahydro-6H-(1,3,4) thiadiazolo (2,3-b)quinazolin-6-one catalyzed by $ZrOCl_2$. There are various analogous can be synthesized from titled intermediate such as 5-aryl-1, 3, 4-thiadiazol-2-amines (3) combined with dimedone, substituted aromatic aldehyde to scaffold desired analogous (6a-6e) while the intermediate compound (3) obtained from 4-nitro benzoic acid (1) treated with thiosemicarbazide (2) to give the intermediate (3) in the presence of con $H_2SO_4$and toluene at 80^0C as shown in Scheme-1.



(Scheme-I)

The function of the catalyst in this investigation is the most important role synthesis of the titled derivatives. The rate of the complete reactantsconsumption,productivity development, short reaction time and utilisation of solvents, chemicals as well as temperature optimisation are dependent on catalyst. The scope of catalyst is very important performance during the mode reaction; it is very commercially availability, low cost price and easy workup. In this reaction, optimisation of the different catalyst, temperature, solvent as well as loaded catalyst applied and results shown given below. There are various transition metal catalyst was applied during this reaction at constant temperature. The entry "1" and entry "5" are most effective catalyst but generation of product ii very low, such as 49% and 60% respectively. The entry "2" and entry "3" are most effective catalyst but generation of product ii very low, such as 64% and 55% respectively. The entry "4" is powerful Lews acid catalyst that is produced excellent yield is "92". The amount of catalyst is very most important role play in this reaction, 1mmole amount of the catalyst was utilised in starting, acquired traces amount of product and gradually increasing upto 10mmol amount of the catalyst during the reaction.

Table 1. Comparison among the various catalyst synthesis of titled compound (6d)

Entry	Catalyst	Time (h)	Yield (%)
1	TiO_2	8	49
2	CuO	6	64
3	$ZnCl_2$	10	55
4	$ZrOCl_2$	3	92
5	$FeCl_3$	9	60

Hence, maximum amount yield obtained (92). Further, amount of the catalyst increased up to entry "5" and get no improvement as shown Table-2.

Table 2. Optimization amount of the catalyst ($ZrOCl_2$) for synthesis of derivatives (6d)

Entry	Catalyst (mmol)	Time (h)	Yield (%)
1	1.0	3	traces
2	2.5	3	35
3	5.0	3	59
4	10	3	92
5	15	3	92

Following the above catalyst performed during the reaction process, we proceeded to the screening of solvent effects using a variety of solvents, including H_2O, CH_3CN, EtOH, MeOH, and Toluene. Our observations are identified that the good reaction conditions are those if without the use of solvents and also the completion of the reaction as well as for the yield of the desired product compared than those obtained in any of the solvents investigated (Table-3).

Table 3. The effect of the solvent for synthesis of compound (6d)

Entry	Catalyst (mmol)	Time (h)	Yield (%)
1	H_2O	3	10
2	MeOH	3	43
3	EtOH	3	92
4	DMF	3	51
5	Toluene	3	62

In order to investigate the catalytic activity of transition metal $ZrOCl_2$, substituted aromatic aldehydes were first chosen for the reaction with benzil and ammonium acetate. Even at higher temperatures, the reaction conditions were improved to synthesis titled compounds and anefficiently in a solvent-free situation with a catalytic quantity of $ZrOCl_2$.

Table 4. The effect of the Temperature for synthesis of compound (6d)

Entry	Temperature (^{0}C)	Time (h)	Yield (%)
1	Below RT	3	20
2	RT	3	39
3	80	3	92
4	90	3	85
5	110	3	80

However, the results were not adequate. As a result, we introduced reaction catalyst to a range of solvents and conducted reactions at varying temperatures (Table-3). We were able to attain 92% of the product yield in the ethanol-lactic acid system through experiments. Next, we investigated, utilizing the improved reaction conditions, the reactant range generality of the product synthesis from various substituted aromatic aldehydes and 5-(4-nitrophenyl)-1, 3, 4-thiadiazol-2-amine.

Table 5. Antimicrobial activity screening activity synthesized scaffold

Compound Code	*Zone of inhibition in (mm)					
	Bacteria				Fungi	
	S.aureus	E.coli	S. typhi	B.substills	A. niger	C. albicans
6a	08	06	08	09	07	05
6b	13	15	12	16	09	08
6c	20	19	15	17	08	09
6d	22	20	22	21	16	17
6e	18	17	15	18	10	12
6f	12	09	10	16	14	15
streptomycin	25	25	22	22	NA	NA
fluconazole	NA	NA	NA	NA	20	20
DMSO	---	----	---	---	---	---

In order to scaffold the corresponding derivatives, imidazole 6a–6f, in good to excellent yields, the substituted aldehydes with electron-withdrawing groups (6e, 6f) and electron-donating substituents (6b, 6c, 6d) interacted easily with the 1,2- diketones (1). 8,8-dimethyl-2-(4-nitrophenyl)-5-phenyl-5,7,8,9-tetrahydro-6H-(1,3,4)thiadiazolo(2,3-b)quinazolin-6-one promoted by $ZrOCl_2$.

The catalytic ability of ZrOCl2 was ascertained in the efficient synthesis of a novel array of thiadiazolo (2,3-b) quinazolin-6-one scaffolds via a one-pot three-component reaction of dimedone, substituted aromatic aldehydes, and 5-(4-nitrophenyl)-1, 3, 4-thiadiazol-2-amine under solvent ethanol conditions. This intermediate such as 5-(4-nitrophenyl)-1, 3, 4-thiadiazol-2-amine is one of the three component of this process which is nitrogen sources .This component can be obtained from 4-nitrobenzoic acid and semithiocarbazide in the presence of ethanol and con sulphuric acid at reflux and among the several notable benefits of this recently established technology are its low E-factor, high reaction mass efficiency, atom economy, scalability, short reaction time, avoidance of hazardous organic solvents, and ease of enforcement.

BIOLOGICAL ACTIVITY

ANTI-BACTERIAL ACTIVITY: The anti-bacterial activities of newly synthesized compounds are screened against 5 pathogenic bacteria strains. The result of antibiotic activity studies for the compounds as shown in table-5. The gram negative bacteria screened were E. Coli ,P. aeruginosa. The gram positive bacteria screened were S-aureas and Bacillus .The target compounds were used at the concentration of 250 µglml and 500 µglml using DMSO as a solvent the streptomycin 10 µglml disc were used as a standard. The rest of the compounds were found to be moderate active against the tested microorganism.

ANTI-FUNGAL ACTIVITY: Anti-fungalactivity of new synthesized compounds was examined by disc diffusion method against the organism of aspergillusniger and Candida albicans 1. Compared were treated at the concentrations of 250 µglml and 500 µglml using DMSO as a solvent. The standard drug was used as ketoconazole 50 µglml against both organisms. The above table -5 represented that the result of *invitro* antimicrobial activity of the titled compounds , the various groups bearing desired derivatives such as electron withdrawing groups and electron donating groups. The derivatives 6c, 6d and 6e exhibited excellent activity against bacterial as well as fungal strains. The rest of the derivatives showed moderate activity against activity.

CONCLUSION

In summary, a one-pot, one-step, multicomponent reaction involving dimedone, substituted aromatic aldehydes, and 5-aryl-1,3,4-thiadiazol-2-amines in the presence of $ZrOCl_2$ under solvent as ethanol conditions has been developed to prepare a series of thiadiazolo(2,3-b)quinazolin-6-ones. This protocol is easy to follow, quick, convenient, and environmentally friendly. This method works well for synthesizing thiadiazolo (2,3-b)quinazolin-6-ones as well. Outstanding characteristics of this protocol include high to excellent yields, high reaction rates, the avoidance of toxic organic solvents, operational simplicity, simple catalyst separation and recycling, large-scale synthetic applicability, the formation of water as green waste, excellent atom economy, high reaction mass efficiency, and low E-factor. In addition to The derivatives 6c, 6d and 6e exhibited excellent activity against bacterial as well as fungal strains. The rest of the derivatives showed moderate activity against activity.

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