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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 CUI_2

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ABSTRACT

In this study, a 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 was synthesized using a novel Lewis acid-based method with CuI_2 as a catalyst. CuI_2 catalytic potential was determined by a one-pot three-component reaction involving dimedone, substituted aromatic aldehydes, and 5-(4-nitrophenyl)-1, 3, 4-thiadiazol-2-amine in the presence of ethanol as a solvent, which produced an array of new thiadiazolo (2,3-b) quinazolin-6-one scaffolds. This component can be produced by refluxing 4-nitrobenzoic acid and semithiocarbazide with ethanol and sulphuric acid present. This recently developed technology offers a number of noteworthy advantages, including a low E-factor, high reaction mass efficiency, atom economy, scalability, short reaction time.

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INTRODUCTION

Heterocyclic compounds are organic compounds containing one or more heteroatom's in their composition. The most common ones, which are composed of nitrogen, oxygen, and sulphur, are tetragon, pentagonal, hexagonal, and triple. The thiophene, also known as as azoles, may include two different atoms. Due to its versatile coordination capacity towards mineral element ions, the nitrogen and sulphur-containing thiadiazolo ring has attracted a lot of attention, especially in structures, biological applications, and bioactive compounds. In light of the remaining three isomers, the isomer 1, 3, 4-thiadiazole assumes a significantly greater significance. In this field of modern chemistry, the identification, isolation, and purification of active compounds from plant, animal, and microbe tissues as well as from their fermentation products has generated interest and drawn attention from researchers across the globe.

Because these substances have lately been included to the blood pressure equation and are useful as antiseptics, anti-inflammatory, antifungal, and antiviral medicines, it is believed that they are biologically effective. The need to discover new compounds to combat this resistance is currently one of the most important areas of research. A versatile moiety with a wide variety of biological action is thiadiazolo. The thiadiazolo moiety serves as both a "hydrogen binding domain" and a "two-electron donor system." It also functions as a restricted pharamacophores. The chemistry of heterocyclic compounds has been a fascinating field of study for quite some time. With a heterocyclic nucleus, 1, 3, 4-thiadiazole is an important class of compounds for the development of new medications. The creation of novel thiadiazolo compounds and the investigation of their chemical and biological properties have grown in significance in recent years. The search for antiepileptic drugs with less toxicity and more selective activity continues to be a focus of intense medicinal chemistry research.

Many classes of thiadiazolo compounds have been the subject of extensive research in recent years; these compounds have a wide range of pharmacological properties, such as antimicrobial (2-5), antioxidant (6), anti-tuberculosis (7), anticonvulsant (8), antidiabetic (9,10), analgesic and anti-inflammatory (11,12) properties. The different catalyst can be applied fotsunthesis of dithiazole derivatives such as Lawson's reagent" (13) carbocationiccatalytic (14), Camphorsulfonicacid (15), phenhydramine hydrochloride-CoCl2·6H2O (16). As part of our ongoing research, we are describing an efficient and feasible one-pot three-component synthesis of thiadiazolo(2,3-b)quinazolin-6-ones and also their derivatives through the reaction of dimedone, substituted aromatic aldehydes, and 5-substituted-1,3,4-thiadiazol-2-amines using CuI_2 as a novel solvent under green conditions and ethanol as a solvent. This is a portion of our ongoing study on the multicomponent strategy for the green and reusable catalytic system synthesis of new annulated heterocycles.

METHODS AND MATERIALS

The recently synthesized derivatives were subjected to ^{1}HNMR and ^{13}C NMR spectra (400 MHz and 100 MHz) on AVANCE Brucker NMR in $CDCl_3$, with the melting points of the newly preparative derivatives measured by open capillary method using Agrawal thermometer and spots visualized under UV-light. The starting materials of the reaction, such as reagents and solvents, were commercially obtained from SRL chemicals and Merck chemicals of India and were not further purified prior to use. The molecular weight of the derivatives can be assessed by mass spectrometry.

Preparation of 5-(4-nitrophenyl)-1, 3, 4-thiadiazol-2-amine (3): The solvent such as DMF introduced in 25mL RBF and starting material the mixture of 4-Nitro benzoic acid (1mol) and thiosemicarbazide (1mol) was dissolved in above solvent. The slowly added 40% H_2SO_4 using dropping funnel. After addition of 40% 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:92%,yellowcompound;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: 194.27,161.25,151.84,146.04, 141.87, 138.65,135.72,13 0.02,129.58, 128.32,128.14, 127.68,124.87, 64.77,50.54, 37.36,29.94,26.95; LCMS(m/z): 434.26(M+2); Molecularformule: $C_{23}H_{20}N_4O_3S$.Elemental Analysis : Calculated: C- 63.87, H-4.66.N-12.91.Obtained: C-63.82,H-4.64 ,N-12.98.

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 (1mole), substituted aromatic aldehydes (1mole) and dimedone (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 CuI_2. The reaction was continued at 70^0Cuntil completely consumed, all reactants and also identified spot of reaction on the TLC plates as mobile system (Ethyl acetate: n-hexane = 4:6). 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:84%,yellowsolid;m.p(ºC):214-216;^{1}HNMR(400MHz,$CDCl_3$)δppm:8.132-7.957(m, 4H,Ar-H),7.387-7.278(m,5H,Ar-H),4.154(s,1H,H(4)),1.864 (s,2H,CH_2),1.517 (s,2H,-CH_2-), 1.047(s,6H,$(CH_3)_2$); ^{13}CNMR(100MHz,$CDCl_3$)δppm:193.44,162.88,153.87,146.87 ,142.38, 138.55,135.57, 131.77,129.56, 128.54,128.12, 127.54,124.47,64.87,48.54,38.15,30.94,26.95;LCMS(m/z):433 .57(M+H); Molecularformule: $C_{23}H_{20}N_4O_3S$. Elemental Analysis:calculated:C- 63.86, H-4.65.N-12.90.Obtained: C-63.87,H-4.64 ,N-12.98.

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:87%;yellowsolid;m.p(ºC):230-232^{0}C;^{1}HNMR (400MHz,$CDCl_3$)δppm:9.125(-OH,s, 1H),8.175-7.880 (m,4H,Ar-H),6.940-6.782(m,4H,Ar-H),4.074 (s,1H,H (4)),2.128(s,2H,CH_2), 1.675(s,2H,-CH_2-),1.214 (s,6H, $(CH_3)_2$);^{13}CNMR (100MHz,$CDCl_3$) δppm:195.44,157.76, 153.65, 151.78, 147.98, 142.24, 134.54, 131.87, 129.55, 128.74, 125.65, 117.47, 62.16, 49.55,39.26, 30.87, 28.46, 26.81;LC-MS(m/z): 449.72 (M+H); Molecularformule: $C_{24}H_{20}N_4O_4S$. 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)-5,7,8,9-tetrahydro-6H-(1,3,4) thiadi azolo(2,3-b)quinazolin-6-one (6c): Yield:90%, Pale Yellow solid; m.p(ºC):226-228^{0}C; ^{1}HNMR (400MHz,$CDCl_3$)δppm: 8.176-7.864 (m,4H,Ar-H),7.194-6.847(m,4H,Ar-H),4.124 (s,1H,H (4)), 3.721(s,3H,-OCH_3),1.887 (s,2H, -CH_2),1.468(s,2H,-CH_2-),1.120 (s,6H,$(CH_3)_2$);^{13} CNMR (100MHz,$CDCl_3$)δppm: 196.46, 158.84, 153.54, 151.58, 145.57, 142.76, 134.85, 132.05, 130.28, 127.65, 125.44, 123.78, 64.89, 54.41,51.76,39.87, 30.41, 28.45, 26.84;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.

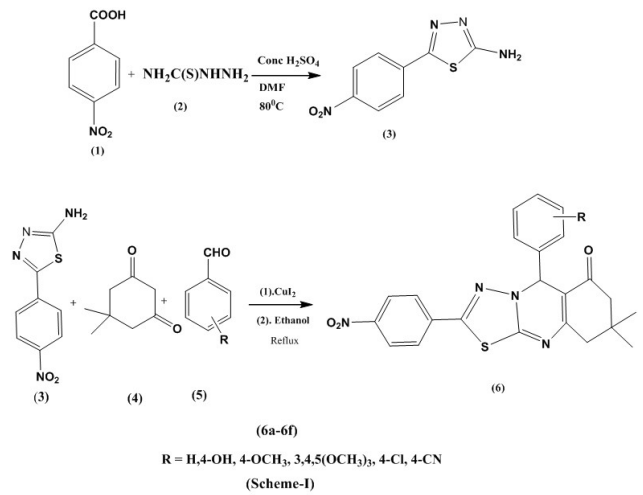
8,8-dimethyl-2-(4-nitrophenyl)-5-(3,4,5-trimethoxyphenyl)-5,7,8,9-tetrahydro-6H-(1,3,4)thiadiazolo(2,3-b)quinazolin-6-one(6d): Yield:85%,Yellowsolid;m.p(ºC):260-262^{0}C;^{1}HNMR (400MHz,$CDCl_3$)δppm:8.245-7.816(m, 4H,Ar-H), 6.911-6.714(m,2H,Ar-H),4.049(s,1H,H(4)), 3.784(s,3H,-OCH3),3.595(s,3H, OCH_3),1.894(s,2H,-CH_2),1.503 (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.

5.5-(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:88%,Yellowsolid;m.p(ºC):236-238^{0}C;^{1}HNMR(400MHz,$CDCl_3$)δppm:8.258-8.025 (m,4H,Ar-H),7.350-6.958(m,4H,Ar-H),4.368(s,1H,H(4)),2.041(s,2H,-CH_2),1.523(s,2H,-CH_2-1.029(s,3H,CH_3),0.947 (s,3H,CH_3);^{13}CNMR (100MHz,$CDCl_3$) δppm:196.88, 158.54, 152.18, 148.58, 141.48, 138.24, 134.66, 130.38, 129.77, 128.88, 128.44, 127.84,63.78, 50.44, 39.66, 28.87;LCMS (m/z):468.58(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

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:84%,Yellowsolid;m.p(ºC):245-247^{0}C;^{1}HNMR (400MHz,$CDCl_3$)δppm:8.278-8.045(m, 4H,Ar-H),7.745-7.522(m,4H,Ar-H),4.340(s,1H,H (4)),2.144 (s,2H,-CH_2),1.718(s,2H,-CH_2), 1.104 (s,3H,CH_3), 0.912(s,3H,CH_3);^{13}CNMR(100MHz,$CDCl_3$) δppm: 197.66, 162.78, 153.78, 150.06, 146.51, 142.06, 136.78, 130.86, 129.47, 128.64, 127.55, 126.09, 124.78, 117.65, 65.04,49.18,39.47, 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 ofaseriesof8,8-dimethyl-2-(4-nitrophenyl)-5-phenyl-5,7,8,9- tetrahydro-6H (1,3,4) thiadiazolo (2,3-b)quinazolin-6-one catalyzed by CuI_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 aldehydesto scaffold desired analogous (6a-6e) while the intermediate compound (3) obtained from 4-nitro benzoic acid (1) treated with thiocemicarbazide (2) to give the intermediate (3) in the presence of con $H_2SO_4$and toluene at 80^{0}C as shown in Scheme-1.



(6a-6f)

R = H,4-OH, 4-OCH_3, 3,4,5(OCH_3)$_3$, 4-Cl, 4-CN

(Scheme-I)

In this experiment, the catalyst plays the most significant role in the synthesis of the derivatives with the given names. Catalysts influence a variety of processes, including temperature optimization, short reaction times, productivity growth, and the pace at which all reactants are used.

The catalyst's range plays a critical role in the mode reaction's performance; it is readily available commercially, inexpensive, and simple to work.The reaction's outcomes are displayed below after various catalysts, temperatures, solvents, and loaded catalysts were optimized. Several transition metal catalysts were used in this reaction, which was conducted at a steady 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 "90".

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

Entry	Catalyst	Time (h)	Yield (%)
1	TiO_2	8	49
2	$CuBr_2$	6	64
3	$ZnCl_2$	10	55
4	CuI_2	3	90
5	$CuCl_2$	9	60

The catalyst's amount is crucial to the outcome of this reaction; 1 mmol of catalyst was used at first, followed by traces of product and a progressive increase to 10 mmol of catalyst as the reaction progressed. Consequently, the highest yield of 90 was obtained. Furthermore, as Table-II illustrates, the catalyst's amount rose up to entry "5" without producing any improvements.

Table II. Optimization amount of the catalyst (CuI_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	90
5	15	3	90

We used a range of solvents, such as H_2O, CH_3CN, EtOH, MeOH, and Toluene, to screen for solvent effects after the aforesaid catalyst was used during the reaction process. According to our observations, the best reaction conditions are those in which no solvents are used, and they also include the completion of the reaction and a higher yield of the intended product than any of the solvents examined (Table-III).

Table-III. 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	90
4	DMF	3	51
5	Toluene	3	62

The first step in one-pot three-component reaction involving dimedone, substituted aromatic aldehydes, and 5-(4-nitrophenyl)-1, 3, 4-thiadiazol-2-amine in the presence CuI_2in ethanol as a solvent, which produced an array of new thiadiazolo (2,3-b) quinazolin-6-one scaffolds with CuI_2 in order to examine the catalytic activity of transition metals. The reaction conditions were optimized to synthesis titled chemicals efficiently in a solvent-free environment with a

catalytic amount of CuI_2, even at higher temperatures. Still, the outcomes were insufficient. Consequently, we conducted reactions at different temperatures and added reaction catalyst to a variety of solvents (Table-IV).

Table IV. 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	70	3	90
4	90	3	85
5	110	3	80

Through trials, we were able to achieve 90% of the product yield in the ethanol system. 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. In order to scaffold, the corresponding derivatives of imidazole (6a–6f) in good to excellent yields. The catalytic ability of CuI_2 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.

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 CuI_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. High to excellent yields, high reaction rates, avoiding toxic organic solvents, ease of operation, straightforward catalyst separation and recycling, suitability for large-scale synthetic applications, production of water as green waste, superior atom economy, high reaction mass efficiency, and low E-factor are some of this protocol's standout features.

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