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One-Pot synthesis of 5-(4-Substituted Phenyl)-1,3,4-Thiadiazole-2-Amines derivatives Catalysed by $CeZrO_4$ Nanocatalyst

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Abstract: *By using co-precipitation method to synthesize $CeZrO_4$ nanoparticles as nanocatalysts, an environmentally friendly solution was developed to obtain 5-(substituted phenol)- [1,3,4] thiadiazol-2-amine derivatives. It is possible to impart optical properties to the obtained products to create nanostructures with active sites. X-ray diffraction and scanning electron microscope characterization methods were used to determine the effect of organic additives on the properties of nanopowders. Current research includes cyclic condensation reaction of substituted aromatic carboxylic acids and thiosemicarbazide under microwave irradiation using EtOH as solvent. The process was found to be simple, inexpensive and painless. This work adopted for present study because of safety, environmental protection, low cost and the use of non-toxic and non volatile, This work includes the direct condensation of aromatic carboxylic acids with thiosemicarbazide and $CeZrO_4$ nanoparticle, due to use of $CeZrO_4$ nanoparticle reaction completed in less time and the excellent results of thiadiazol-2-amine appeared. The current study reported the synthesis of substituted thiadiazole in a one-step reaction using nanocatalyst EtOH solvent shown good purity with excellent yield.*

Keywords: $CeZrO_4$ nanocatalyst, Co-Precipitation method, aromatic acids, Thiadiazole, Thiosemicarbazide, Pharmacological activity etc

I. INTRODUCTION

Multicomponent reactions using one pot method have attracted considerable attention because of their ability to produce products in high yields[1,2]. Many biologically active compounds have been shown to contain substituted thiadiazole structures.

In the research of azoles, the synthesis of thiadiazole has been clarified in recent years. This may be due to many chemical activities of some of it's new derivatives. Like antibacterial[3], antimicrobial[4] antidepressant[5], antituberculosis[6], anti-inflammatory[7], anticonvulsant[8], antihypertensive[9] antifungal[10], antidiabetic[11], and anticancer[12]. thiadiazole containing medications, such as diuretics in clinics, acetazolamide and methazolamide as well as the medicines cefazedone and cefazoline sodium are already in use.

Thiadiazoles belong to the classes of nitrogen–sulfur containing heterocycles with extensive application as structural units of biologically active molecules and as useful intermediates in medicinal chemistry.It's also shows main applications in electronic and material science in conducting polymers and materials,organic light-emitting diodes and solar cells and photovoltaic devices etc.the biological activity of thiadiazoles is because of strong aromaticity of the ring system that offers higher in vivo stability.thiadiazole is a bioisosteric replacement of thiazole moiety also it is a bioisotere of oxadiazole,Oxazole and Benzene. To summarize it can be said that antimicrobial agents are used to manage accessible illness and they can be used prophylaxis for definite medical conditions and other surgical procedures[13,14]

1,3,4-thiadiazole is amongst the highly convenient isomeric form because of its having several biological actions in body. In particular compounds containing the 1,2,3 thiadiazole nucleus are thought to have specific antibacterial and

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antiviral properties. Based on these facts the purpose of present research work was to synthesize some thidiazole derivatives that have broad spectrum of antimicrobial activity and to project these synthesized derivatives vary antibiotics according to their effects.

In recent years, microwave radiation has emerged as a useful and well controlled method for treating a variety of chemical reactions for short periods of time and boosts product yields. Aqueous phase one pot multicomponent reactions have become as a important tools in organic synthesis[15].This study is an attempt to collect the 1,3,4-thiadiazole and its derivatives, which can be It has been shown to have antiviral properties reported in the literature between 2009 and 2020.

In the past few years, nanotechnology studies have become one of the most important activities in medical science, with wide application in various clinical applications, mainly due to
the fact that nanomaterials behave directly depending on the size[16,17]

Ceric Zirconium oxide nanoparticles reveal that amplify thermal stability,high surface area,good catalytic activity these characteristics makes cerium Zirconium Oxide nanoparticles ideal for catalytic converters in automotive industries,solid oxide fule cells,biomedical applications and optical and electronic devices etc. Main advantages of these synthesis is simple and cost effective ,contains high purity materials and uniform particle size.Ceric zirconium oxide nanoparticles gives a main applications in water treatment,energy storage,biomedical implants and drug delivery etc.

Ceria–zirconia mixed oxide nanoparticles was successfully obtained via the coprecipitation method at ambient temperature, followed by calcination at 500, 700 and 900 ◦C. Amongst the preparation methods,sol-gel[18],microemulsion[19]and some other techniques have been suggested for obtaining CeZrO4,Yet, the most straightforward method is coprecipitation.

II. EXPERIMENITAL

Materials and Method

Main chemicals such as Ce(NO3)3.6H2O,ZrO(NO3)2.6H2O,NH4OH,dist.H2O,EtOH, aromatic acids, Thiosemicarbazide and solvents used were of sigma alderich and AR grade and were utilized without additional purification. Melting points were determined in open capillary tubes and are uncorrected. For the 300-watt irradiation, a microwave synthesizer (Sineo microwave chemistry technology Model MAS-II) was employed. Xrd graph of nanoparticle obtained and SEM images also obtained.TLC was used to check the formation of the compounds on aluminum sheets , IR spectra were obtained using the KBr pellet method on a Shimadzu FT- IR- 8400 device. 1H NMR measurements were taken on a Bruker AC – 400 F, 400 MHz spectrometer for solutions in deuterochloroform (CDCl3) and deuterated dimethyl sulfoxide (DMSO-d6) and are presented in parts per million (PPM) down field from tetramethyl silane (Me4Si) as an internal reference standard.

III. GENERAL PROCEDURE

1] Synthesis of CeZrO4 nanoparticle by coprecipitation method

Cerium Zirconium Oxide succesfully obtained by coprecipitation method, mixture of Ce(NO3)3 .6H2O and ZrO(NO3)2 .6H2O in dist H2O basically a solution of NH4OH was quickly added to a container with an aqueous solution of ammonium cerium nitrate and zirconium nitrate solution with continuosus stirring the desired Ce:Zr ratio, A yellow Cerium Zirconium hydroxides ppt was formed instantly. Subsequently it was filtered ,washed with dist. Water until no pH change could be detected. hydrated precipitets were filtered. All other reagents and solvents were aldrich products 99% purity,the synthesized materials were dried at 600c for 50 min in air and at 1200c overnight in a drying oven under an air flow after that gave grinding that obtained material into very nano range size particle.the dried powders were finally calcined in air at 9000 c for 4h

2] By Using CeZrO4 Nanoparticle synthesis of Thiadiazole Derivatives

Substituted benzoic acid (1mmol) and thiosemicarbazide (1mmol), CeZrO4 nanocatalyst and ethanol Solvent was added, The reaction mixture was heated at 120oC for 50 min.The progress of the reaction was monitored by TLC (n-

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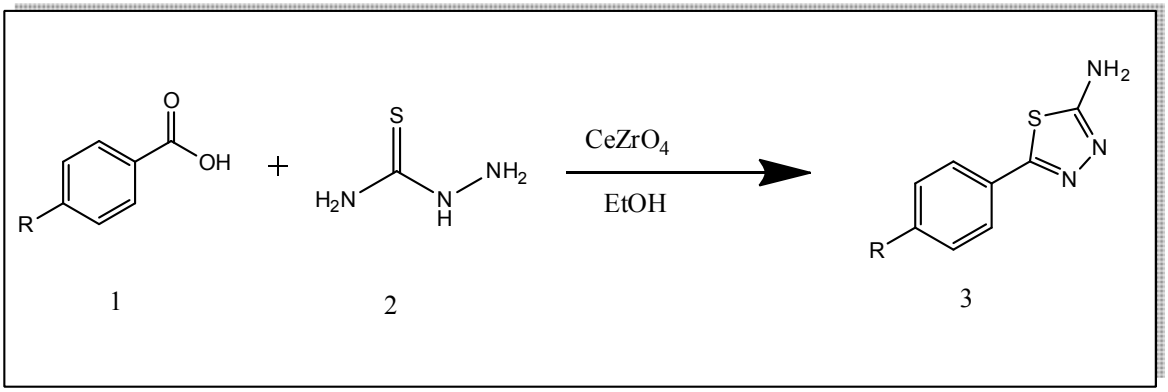
Hexane: ethyl acetate). The reaction was quenched by the addition of crushed ice and solid separated was filtered, basic solution. The crude thiadiazole was purified by recrystallization in ethanol to afford 90% yield.



Scheme: One-Pot synthesis of 5-(4-Substituted Phenyl)-1,3,4-Thiadiazole-2-Amines by using CeZrO4 Catalyst

Characterization of synthesized nanocatalyst

XRD Analysis

The XRD Pattern of the synthesized nanoparticles calcined at 8000c ,it is clear from the XRD pattern that ,the particles are crystalline in nature. It shows highly intense peak at 2θ0 at 22.55, 29.23, 33.82, 44.53, 48.58 corresponding for the planes (111),(200).(311) and (222) from FWHM of the high incensed peak the particle size is calculated using Debye-Scherer equation $D=K\lambda/\beta\cos\theta$,where shape factor, K=0.94, λ= 1.5418 Å represents the wave length of Cu K α radiation, β is the half width of each diffraction peak and represents the half angle of the diffraction peak. The average particle size is found to be 50 nm.

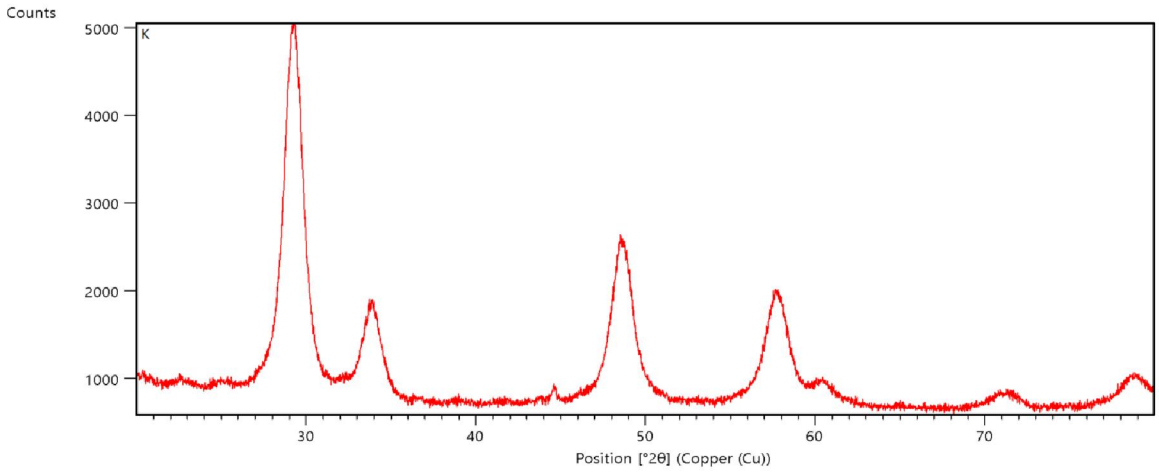


Figure 1. XRD of the CeZrO4 nanoparticles prepared by coprecipitation method

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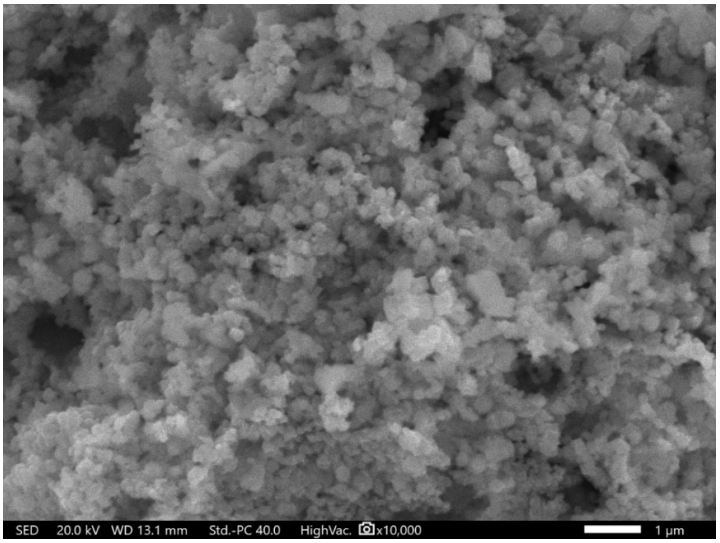
SEM (Scanning electron Microscopy)

The morphology and surface structure of the nanocomposite material were examined using SEM at different magnifications. CeZrO4 nanoparticles were also analyzed by SEM to assess the dispersion of the active species on the support. The results clearly indicate an increase in porosity and an improvement in the material's morphology with the synthesized nanoparticles showing a size a size of 39 nm



Fig; SEM Image of CeZrO4 nanoparticle

Characterization of thiadiazole Compound 3a-f

5-(4-Fluoro-phenyl)-[1,3,4]thiadiazole-2-amine (3a)

IR (, cm–1): 3361 (N-H stretching), 1635 (C¼ N stretch), 857 (C-S-C str, thiadiazole); 1 H NMR (DMSO-d6, d, ppm); 7.2–7.8 (m, 4H), 5.3 (s, 2H); 13C NMR 400MHz, (DMSO-d6, d, ppm): 174.3, 169.2, 154.3, 135.9, 125.6, 124.2; LCMS (m/z): 193 (Mþ), 197 (Mþ þ1); Elemental Analysis (C8H6FN3S), Found % (Calculated %): C, 48.042 (48.27); H, 3.068 (3.15); N, 22.45 (21.53); S, 17.38 (15.47).

All the characterization data was consistent with literature data. 10

5-(4-Chloro-phenyl)-[1,3,4]thiadiazole-2-amine (3b)

IR (, cm–1): 3357 (N-H stretching), 1640 (C ¼ N str,), 883 (C-S-C str, thiadiazole; 1 H NMR (DMSO-d6, d, ppm); 7.4–7.7 (m, 4H), 5.4 (s, 2H); 13C NMR 400 MHz, (DMSO-d6, d, ppm): 175.4, 161.9, 136.9, 135.1, 129.19, 127.9; LCMS (m/z): 217(Mþ), 225 (Mþ þ2); Elemental Analysis (C8H6ClN3S), Found % (Calculated %): C, 44.24 (44.40); H, 2.82 (2.85); N, 20.79 (20.85); S, 15.24 (15.26).

All the characterization data was consistent with literature data.10

5-(4-Bromo-phenyl)-[1,3,4]thiadiazole-2-amine (3c)

IR (cm–1): 3376 (N-H stretching), 1655 (C ¼ N stretching), 889 (C-S-C str, thiadiazole); 1 H NMR (DMSO-d6, d, ppm); 7.6–7.12 (m, 4H), 5.7 (s, 2H); 13C NMR 400 MHz, (DMSO-d6, d, ppm): 177.6, 165.2, 134.9, 133.1, 130.2, 118.9; LCMS (m/z): 256 (Mþ), 263 (Mþ þ2); Elemental Analysis (C8H6BrN3S), Found % (Calculated %): C, 38.37 (38.52); H, 2.48 (2.46); N, 16.48 (16.51); S, 13.49 (12.57).

All the characterization data consistent with literature data.10

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5-(4-Methyl-phenyl)-[1,3,4]thiadiazole-2-amine (3d)

IR (, cm–1): 3381 (N-H stretching), 1642 (C ¼ N str, ring), 1367 (C-H bend, aliphatic), 894 (CS-C str, thiadiazole); 1 H NMR (DMSO-d6, d, ppm); 7.3–7.9 (m, 4H), 5.6 (s, 2H); 1.8 (s, 3H); 13C NMR 400 MHz, (DMSO-d6, d, ppm): 168.7, 161.6, 136.6, 131.5, 127.5, 127.5, 20.9; LCMS (m/z): 197 (Mþ), 195 (Mþ þ1); Elemental Analysis (C9H9N3S), Found % (Calculated %): C, 58.40 (58.50); H, 4.81 (4.84); N, 22.08 (22.19); S, 16.86 (16.87).
All the characterization data consistent with literature data.10

5-(4-Hydroxy-phenyl)-[1,3,4]thiadiazole-2-amine (3e)

IR (, cm–1): 3450 (O-H, stretching), 3343 (N-H str),1633 (C ¼ N str, ring), 889 (C-S-C str, thiadiazole); 1 H NMR (DMSO-d6, d, ppm); 7.1–7.8 (m, 4H), 5.3 (s, 2H), 2.2 (s, 1H); 13C NMR 400 MHz,(DMSO-d6, d, ppm): 172.9, 162.5, 157.3, 124.5, 126.8, 118.2; LCMS (m/z): 192 (Mþ), 192 (Mþ þ1); Elemental Analysis (C8H7N3OS), Found % (Calculated %): C, 49.60 (47.63); H, 3.40 (3.45); N, 21.60 (22.75); S, 16.60 (16.69).
All the characterization data was consistent with literature data.10

5-(4-Methoxy-phenyl)-[1,3,4]thiadiazole-2-amine (3f)

1 H NMR (DMSO-d6, d, ppm); 7.5–7. 8(m, 4H), 5.3 (s, 2H); 3.5 (s, 3H); 13C NMR 400 MHz, (DMSO-d6, d, ppm): 173.9, 163.7, 157.4, 123.1, 126.7, 112.5, 56.9; LCMS (m/z): 205 (Mþ), 210 (Mþ þ1); Elemental Analysis (C9H9N3OS), Found % (Calculated %): C, 51.20 (53.17); H, 2.53 (4.30); N, 22.71 (22.65); S, 15.45 (16.52).
All the characterization data was consistent with literature data.

IV. RESULTS AND DISCUSSION

Most of the reported reaction for the synthesis of CeZrO4 Nanoparticles involves ceric nitrate and zirconium nitrates as a reactants, and thiadiazoles involves aldehyde and thiosemicarbazide as reactants that led to different thiadiazoles. We have reported synthesis of thiadiazoles carboxylic acid and thiosemicarbazide using CeZrO4 as a catalyst. Reaction completed in 50 min. To generalize scope of method a variety of aromatic acids have been treated with thiosemicarbazide in presence of CeZrO4 Catalyst to obtain thiadiazoles.It is observed that, in microwave, the yield of products significantly increases with high yield and purity. It has been also observed that electron withdrawing ring increases rate of reaction. Synthesized Catalyst analysed by Xrd Graph and the synthesized derivatives of thiadiazole were characterized by IR, NMR and Mass spectral analysis

	Catalyst	Reaction time (h/min)	Yield (%)
1	Net reaction	24 h	Trace
2	Cyclodextrin	8 h	52
3	Glycine	5 h	56
4	SiO2Cl	4 h	63
5	CeZrO4	1h	90

Table 1- selection of the catalyst

3a-k	3 (R)	% Yield		
		Reflux (t, hr)	Ultrasonic (t, hr)	Microwave (t, min)
3a	4-F	75(4:05)	82(2:50)	92(50min)
3b	4-Cl	65(4:07)	78(2:08)	89(47min)
3c	4-Br	62(3:55)	84(2:15)	93(49min)
3d	4-CH3	76(3:42)	81(2:10)	91(45min)
3e	4-OH	72(3:25)	84(2:12)	91(47min)
3f	4-OCH3	78(3:58)	82(2:00)	88(48min)

Table 2-Optimization of the CeZrO4 catalyzed synthesis of thiadiazole

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V. CONCLUSION

CeZrO4 Catalyst has been succesfully synthesized and characterized. The XRD Pattern of the synthesized nanoparticles calcined at 9000c, it is clear from the XRD pattern that ,the particles are fine crystalline in nature.Catalytic application of the obtained Catalyst in substituted Thiadiazoles gave a good yields to excellent products, multicomponent, environmentally being appoarch for the synthesis of substituted thiadiazole from the direct coupling of otherwise substituted aromatic carboxylic acids and thiosemicarbazide in the presence of CeZrO4 catalyst has been developed.This method several advantages including high yeild, short reaction time,inexpensive etc, The use of Nanocatalyst and the purity of the products (90% -93%) are key advantages of the current approach.

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