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Research Article

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ZrO_2 nanopowder catalyzed one-pot green synthesis of Hantzsch 1,4-dihydropyridine derivatives under dry media

Muthuvel Ramanathan Ezhilarasi[1*] and Mannathusamy Gopalakrishnan[2]

[1]Department of Chemistry, Karpagam University, Coimbatore, Tamilnadu, India
[2]Department of Chemistry, Annamalai University, Annamalainagar, Tamilnadu, India

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ABSTRACT

A mild, general, convenient, and efficient one-pot synthesis of 1,4-dihydropyirdines(1-5) is described using conventional heating, and microwave irradiation(1-5) have been synthesized from ethyl-3-oxo-3-phenylpropanoate, ammonium acetate and respective substituted benzaldehydes catalysed by ZrO_2 nanopowder in dry media under microwave irradiation . The structure of the synthesized compounds was characterized by FT-IR, MS, elemental analysis, ^1H NMR and ^{13}C NMR spectral studies.

Keywords: 1,4-dyhydropyridine, ZrO_2 nanopowder, drymedia, ethyl-3-oxo-3-phenylpropanoate, microwave irradiation

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INTRODUCTION

Multicomponent condensation strategies offer significant advantages over conventional linear-type synthesis in providing products with the diversity needed for the discovery of new lead compounds or lead optimization employing combinatorial chemistry [1-7]. The pyridine moiety has been found in a wide variety of both naturally occurring and synthetic bioactive compounds. 1, 4-dihydropyridines (1, 4 DHPs) are important class of compounds in the field of drugs and pharmaceuticals. Hantzsch 1, 4-dihydropyridines (dialkyl 1, 4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylates) are widely used clinically as calcium channel blockers for the treatment of cardiovascular diseases, including hypertention [8,9]. 1, 4-dihydropyridine posses a wide range of biological activities, being vasodilators, bronchodilators, geroprotectives, hepatoprotectives, antitumor, antiatherosclerotic and antidiabetic agents [10a-e]. In 1882Authur Rudolf Hantzsch, a German chemist, reported a cyclocondensation between ethylacetoacetate, aldehyde and aqueous ammonium hydroxide to afford a hererocyclic system of 1, 4-dihydropyridine; since then, it became familiar as the Hantzsch reaction [11, 12].

In recent years, there are several modifications of the Hantzsch synthesis of 1,4-Dihydropyridine derivatives, including the use of microwaves [13], ionic liquids [14], TMSCl-NaI [15], metal triflates [16], molecular iodine [17],SiO_2-$NaHSiO_2$ [18], SiO_2-$HCiO_4$ [19], CAN [20], Phenyl boronic acid [21], TsOH-sodium dodecyl sulphate [22],Organocatalysts [23],triphenyl phosphine[24], Hetero polyacids [25], Zn complex [26], magnesium perchlorate [27], cyanuric chloride [28], L-proline [29], tetrabutylammonium hydrogen sulfate [30] ,$CdCl_3$ [31],Sodium perchlorate [32] and glycerine-$CeClO_2.7H_2O$[33, 34]. But in many of the methods are suffering from some drawbacks such as long reaction time, low yields, tedious workup procedures and the use of expensive catalysts. Therefore the development of efficient protocol is still in demand. As part of our research program in developing

new methodologies [35-39], we report herein a simple and efficient procedure for the synthesis of 1, 4-Dihydropyridine derivatives using ZrO_2 nanopowder as a catalyst.

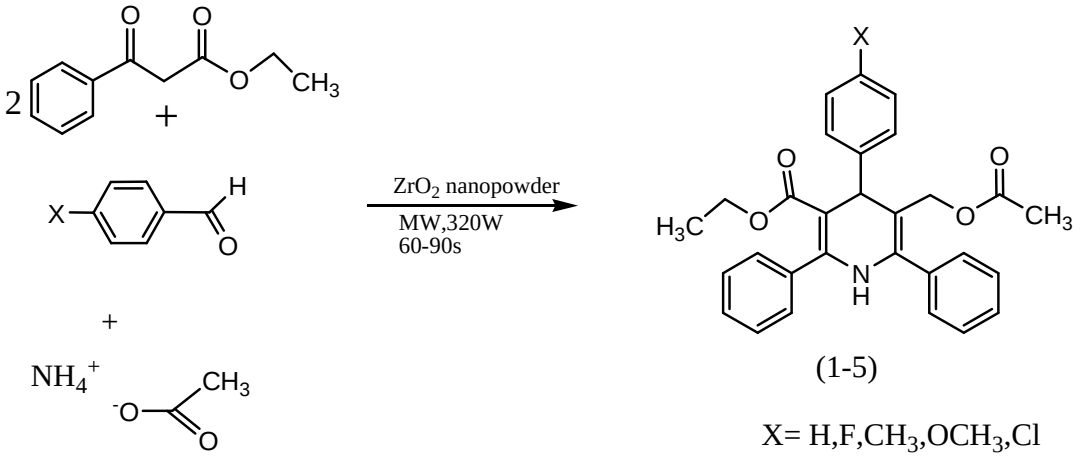
EXPERIMENTAL SECTION

General

All Experiments were performed in oven dried glass apparatus. Melting points were measured in open capillaries and were uncorrected. The progress of the reaction was monitored by TLC using silica gel. Visualization of spots was effected by exposure to iodine vapours using iodine chamber. The morphological characteristic of the ZrO_2 nanopowder was recorded on JOEL-JSM- 5610 LV with INCA EDS Scanning Electron Microscope, with an accelerating voltage of 20kV .IR spectra were recorded in KBr (pellet forms) on a Thermo Nicolet-Avata-330 FT-IR spectrophotometer and note worthy absorption values (cm^{-1}) alone were listed. ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz respectively on Bruker AMX 400 NMR spectrometer using CDCl3 as solvent. The ESI +ve MS spectra were recorded on a Varian Saturn 2200 MS spectrometer. Satisfactory microanalyses were obtained on Carlo Erba 1106 CHN analyzer. A conventional (unmodified) household microwave oven equipped with a turntable (LG, MG-395 WA, 230V~50Hz, 760 W), operating at 2450 Hz was used for the reaction. By adopting the literature precedent, ZrO_2 nanopowder [40, 41] catalyst was prepared.

Synthesis of novel diethyl-1, 4-dihydro-2, 6-diphenyl-4-arylpyridine-3, 5-dicarboxylates (1-5) catalyzed by ZrO_2 nanopowder in dry media.

A mixture containing ethyl-3-oxo-3-phenylpropanoate (0.02 mol), ammonium acetate (0.01 mol) and respective substituted benzaldehydes (0.01 mol) and zirconia nanopowder (25 mg) was mixed properly using a morter and pestle and then irradiated in a microwave oven for 60-90 s at a power of 320W. The completion of the reaction was monitered by TLC. After completion of the reaction, the reaction mixture was extracted with methanol (3x10 ml). The catalyst was removed by filtration. The filtrate was concentrated in *vacuo* to furnish the title compound and recrystallized from methanol. (Scheme-1)



Sheme-1: Synthetic route for Diethyl 1,4-dihydro-2,6-diphenyl-4-arylpyridine-3,5-dicarboxylates

RESULTS AND DISCUSSION

CHARECTERIZATION OF ZrO_2 NANOPOWDER

Scanning Electron Microscope with INCA EDS

The SEM has been employed for studying the shape, size and morphological features of t- ZrO_2 nanopowder Fig-1. EDS confirms the presence of only zirconium and oxygen of ZrO_2 nanopowder and its surface morphology is depicted as micrograph in Fig -2.

Spectrum processing
No peaks omitted
Processing option: All elements analyzed

(Normalised)
Number of iterations = 3
Standard:
O SiO2 1-Jun-1999 12:00 AM
Zr Zr 1-Jun-1999 12:00 AM

Element	Weight %	Atomic %
O K	27.70	68.60
Zr L	73.30	31.40
Total	100.00	

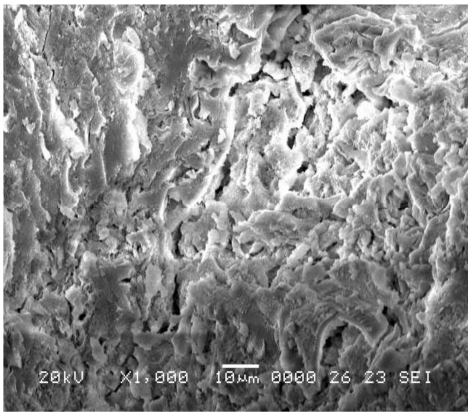


Fig-1: SEM Micrograph of ZrO_2 Nanopowder annealed at 500°C for 5 hrs(x 1000)

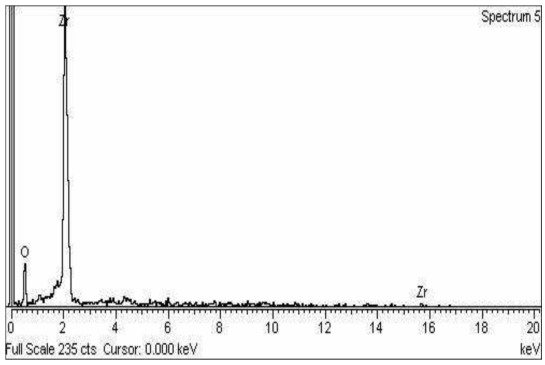


Fig-2. EDS of ZrO_2 Nanopowder

Analysis of IR Spectra of ZrO_2 Nanopowder:
A medium strong absorption was observed at 746.57 cm^{-1} was due to the stretching of ZrO_4 group vibrations. Both SEM and IR spectral analysis confirm the structure of ZrO_2 Nanopowder.

Analysis of IR spectrum of compound (1-5)
FT-IR spectrum of compound **1** shows characteristic absorptions at 1734 and 1600 cm^{-1} due to ester carbonyl functional group and C=C stretching frequencies respectively. Absorption frequencies observed at 3269 cm^{-1} suggesting the presence of-NH group. The absorption frequencies at 3056 and 3024 cm^{-1}- is assigned to aromatic C-H stretching vibration and the absorption frequencies at 2975, 2921 and 2851 cm^{-1} is assigned to aliphatic C-H stretching vibration. Moreover, aromatic ring stretching frequencies are observed at 789,757 and 691cm^{-1}.Physical and analytical data of the compounds **1-5** are given in Table-1.

Table-1 Physical and analytical data of compounds (1-5)

Compound	Molecular Formula	Melting point(°C)	Yeild(%)	IR Frequencies cm^{-1}
1	$C_{29}H_{27}NO_4$	60	90	3269, 3056, 3024, 2975,2921, 2851,1734,1600,789,757,691
2	$C_{29}H_{26}FNO_4$	74	93	3265, 3063, 2975, 2921, 2851, 1732, 1610, 756,692, 559
3	$C_{30}H_{29}NO_4$	78	85	3276, 3030,3063,2986,2936,2904,1734, 1594,753, 692, 647
4	$C_{30}H_{29}NO_5$	82	88	3329,3068,2980, 2930, 2843, 1737, 1609, 772, 691, 563
5	$C_{29}H_{26}ClNO_4$	165	93	3372, 3064, 2977, 1730, 1596, 778, 756 692

Mass Spectrum and Elemental analysis of compound (1)
Mass spectrum of compound shows molecular ion peak at m/z 454 (M+●+1) which is consistent with the proposed molecular formula of compound **1**.Elemental analysis of compound **1** (Ccal 76.80, Cobs 76.42; Hcal 6.00, Hobs 5.89; Ncal 3.09, Nobs 3.01) are consistent with the proposed molecular formula ($C_{29}H_{27}NO_4$) of compound **1**.

Analysis of ^{1}H NMR spectrum of compound (1)
^{1}HNMR spectrum of compound **1**, a triplet observed at 1.09 ppm (J=6.8 Hz) corresponding to six protons and this signal is due to ester methyl protons. A multiplet observed in the range of 3.84-3.78 ppm corresponding to four protons and this signal is due to ester methylene protons. The singlet observed at 5.91 ppm can be assigned to H-1 proton and the benzylic proton H-4 of pyridine moiety appears at 5.15 ppm. The aromatic protons appear as a multiplet in the range 7.88-7.15 ppm. The ^{1}H NMR chemical shifts values of compound **1-5** are given in **Table-2.**

Table-2 ^{1}H NMR chemical shift values (ppm) of compound (1-5)

Compound	H-1 Proton	H-4 Proton	Ester methylene Proton	Ester methyl Proton	Aromatic Protons	Others
1	5.91	5.15	3.84-3.78	1.09, J=6.8Hz	7.88-7.15	
2	5.97	5.21	3,91-3.88	0.92, J=7.0Hz	7.55-7.00	
3	5.86	5.11	3.82-3.80	0.82,J=7.0Hz	7.38-7.05	2.26-CH3 at Phenyl ring
4	6.67	6.65	4.12,J=7.0Hz	1.07,J=7.0Hz	7.87-7.22	3.60-OCH3 atPhenyl ring
5	5.89	5.01	3.79-3.67	0.72,J=7.2Hz	7.33-7.02	

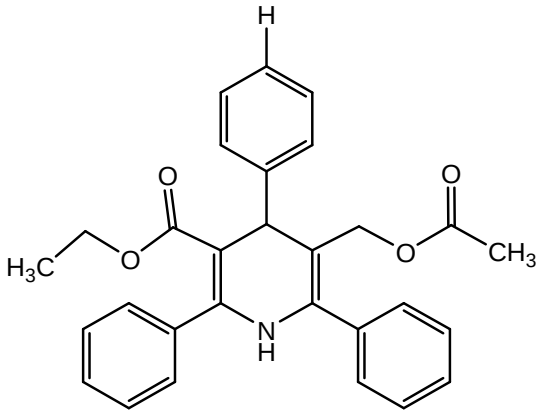
Analysis of ^{13}C NMR spectrum of Compound (1)

^{13}CNMR spectrum, resonance in the aliphatic range 59.76, 40.14 and 14.01ppm has been observed. The ^{13}C resonance at 40.14 ppm is assigned to C-4 benzylic carbon of pyridine moiety. Two ^{13}C resonances at 59.76 and 14.01 ppm are due to ester methylene and methyl carbons respectively. The ^{13}C resonance observed at 104.42 is assigned to C-3 and C-5carbons whereas the signal at 142.57 ppm is assigned to C-2 and C-6carbons of pyridine moiety respectively. The signal observed at 164.99ppm is assigned to ester carbonyl carbon. The aromatic carbons are observed in the range of 131.38-126.04 ppm. The remaining ^{13}C signals at 133.84, 133.71 and 132.86 ppm are due to *ipso* carbons. The ^{13}C NMR chemical shifts of compound **1-5** are given in **Table-3**

Table-3 ^{13}C NMR chemical shift values (ppm) of compound (1-5)

Compound	C-2& C-6	C-3 &C-5	C-4	Ester Carbonyl Carbon	Ester methylene Carbon	Ester methyl Carbon	Aromatic Carbons	Ipso Carbons	Others
1	142.57	104.42	40.14	164.99	59.76	14.01	131.38-126.04	133.84, 133, 71, 132.86	
2	145.56	104.37	39.55	164.81	61.46	13.66	129.36-114.80	161.29, 162.40, 136, 75, 133.68, 131.50	
3	145.41	104.58	39.71	166.84	61.31	13.68	129.48-127.74	136.84, 135.93, 144.61	21.14-CH3 at Phenyl ring
4	142.3	104.63	41.04	165.29	61.31	14.04	129.14-114.28	161.35, 136.35, 133.79, 132.24	55.27-OCH3at Phenyl ring
5	146.01, 145.76	104.04	39.73	166.69	61.48	13.67	131.32-128.13	136.53, 135.98, 133.73, 132,15	

The above spectral values and elemental analysis give the proposed structure of the title compound. The synthesized compound is shown in **Fig-1**



Diethyl 1,4-dihydro-2,6-diphenyl-4-phenylpyridine-3,5-dicarboxylates

Fig: 1- Structure of Diethyl 1,4-dihydro-2,6-diphenyl-4-phenylpyridine-3,5-dicarboxylates

Reusability of the Catalyst:

The reuse of ZrO_2 nanopowder was studied and the results are shown in **Fig-2.** The catalyst was reused up to five times without significant loss of activity.

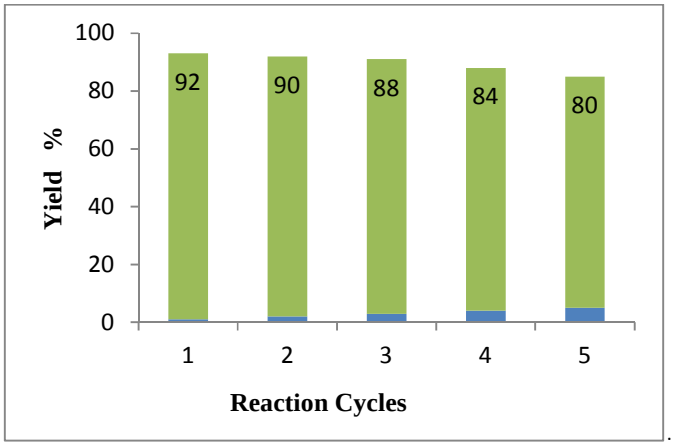


Fig-2: Reusability of the Catalyst

3D optimization Structure of the synthesized Diethyl 1, 4-dihydro-2, 6-diphenyl-4 phenylpyridine-3, 5-dicarboxylates:

The 3d optimization of the synthesized compound (1) is shown in **Fig-3**

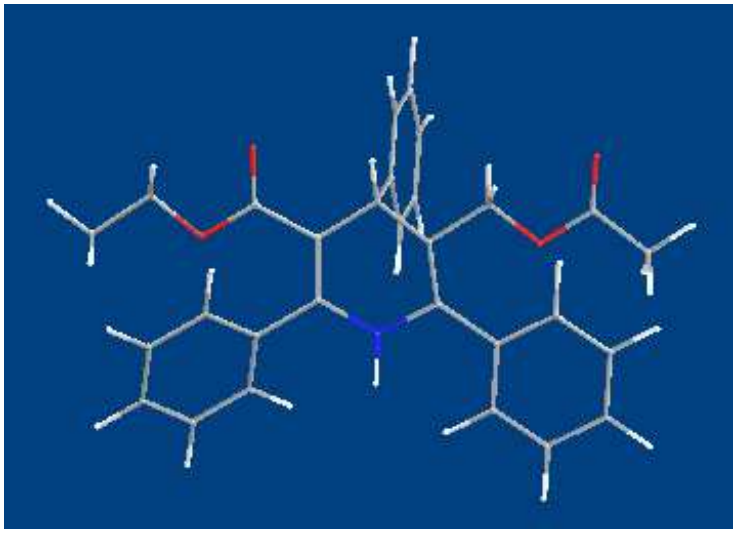


Fig-3: Diethyl 1, 4-dihydro-2, 6-diphenyl-4-phenylpyridine-3, 5-dicarboxylates

CONCLUSION

In conclusion, we have reported a simple new catalytic method for the synthesis of Diethyl 1, 4-dihydro-2, 6-diphenyl-4-phenylpyridine-3, 5-dicarboxylates by one pot three component reaction of ethyl-3-oxo-3-phenylpropanoate, ammonium acetate and respective substituted benzaldehydes catalysed by an efficient reusable ZrO_2 nanopowder in dry media under microwave irradiation. The catalyst can be recycled after simple work-up, and used at least five times without sustainable in catalytic activity. The work-up of these reactions are clean and fast and these reactions provide elimination or reduction of the solvent. The use of microwave afforded compounds (1-5) with excellent yield and the reaction is in minute in states of hour.

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