Available online at **www.joac.info**

ISSN: 2278-1862

Journal of Applicable Chemistry

2019, 8 (1): 56-65

(International Peer Reviewed Journal)

Sustainable Cs_2O/ZrO_2 Oxide Catalyst for the Synthesis of 1, 4-Dihydropyridine Analogues

Santhosh Kumar Jureddi[1]*, G. Susheela Bai [1], G. Himabindu[1] and G. Ravi Kumar[2]

1. Department of Engineering Chemistry, A.U. College of Engineering(A), Andhra University, Visakhapatnam-530 003, Andhra Pradesh, **INDIA**
2. Department of Chemistry, Gitam Institute of Science Visakhapatnam, Andhra Pradesh, **INDIA**

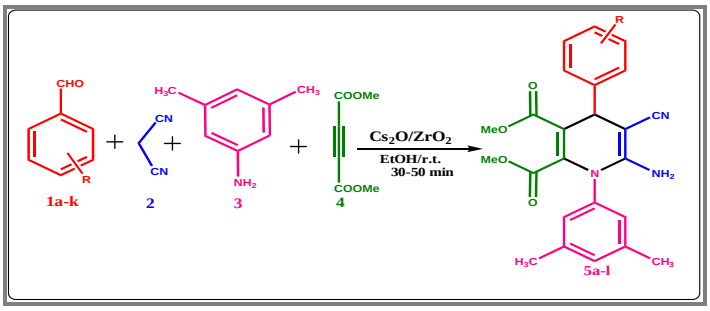
Email: santhoshkumr.jureddi@gmail.com

Accepted on 21st December, 2018

ABSTRACT

Cesia loaded on zirconia (Cs_2O/ZrO_2) was prepared as heterogeneous catalyst for the synthesis of 1,4-dihydropyridine analogues via a one-pot, multi-component reaction involving substituted aldehyde, malononitrile, dimethylaniline and dimethylacetylene dicarboxylate with good to excellent product yields (83 to 97%). The notable benefits of the facile approach with ethanol as solvent are excellent yields and short reaction times. Catalyst is fully reusable with minor loss of activity up to six cycles. While, P-XRD, TEM and SEM analysis performances were revealed for the structural interpretation of Cs_2O/ZrO_2, the identity of products were established and confirmed by various spectral (^1H NMR, ^{13}C NMR, FT-IR and HRMS) techniques.

Graphical Abstract



Model reaction

Keywords: Malononitrile, Cs_2O/ZrO_2 heterogeneous catalyst, Multi component reaction.

INTRODUCTION

Heterocyclic compounds are organic cyclic compounds containing more than one kind of atoms [1]. The hetero atom may be O, N, S and these compounds need not be unsaturated. The unsaturated

heterocyclic compounds are aromatic in nature [2].Heterocyclic compounds contain either five membered rings or six membered rings [2]. Pyridine is heterocyclic six membered ring containing N as one of the atoms [3]. The pyridine core is one of the best attractive heterocyclic structures that are present in several drugs and medicines [4]. The pyridine framework has established better consideration owing to its depth of pharmaceutical activities, ranging from anti-microbial [5], anti-oxidant [6], anti-cancer [7], anti-coagulant [8], anti-malarial [9], anti-tubercular agents [10]. Due to their commercial and systematic importance, several synthetic approaches were pronounced in literature for production of various pyridine derivatives [11-13]. Numerous those reactions either demand high energy and expensive reagents or punitive reaction conditions and long reaction times or give low yields [11-13].Jing Sun et al reported Synthesis of Polysubstituted Dihydropyridines by Four-Component Reactions of Aromatic Aldehydes, Malononitrile, Aryl amines, and Acetylene dicarboxylate [14].

However, reported methods suffered from drawbacks like long reaction times, low efficiency, expensive raw materials, toxic metals as catalysts, hazardous organic solvents, tedious workup, use of excess reagents. In order to overcome these problems, development of a simple and efficient method is desirable for the synthesis of 1,4-dihydropyridine analogues. Consequently, continued pursuit for improved and greener approaches for the synthesis of pyridine derivatives is a vital. To the best of our knowledge, there are no reports on the use of cesium oxide or cesia loaded on zirconia as a catalyst for the synthesis of 1,4-dihydropyridine analogues via multi-component reactions.

MATERIALS AND METHODS

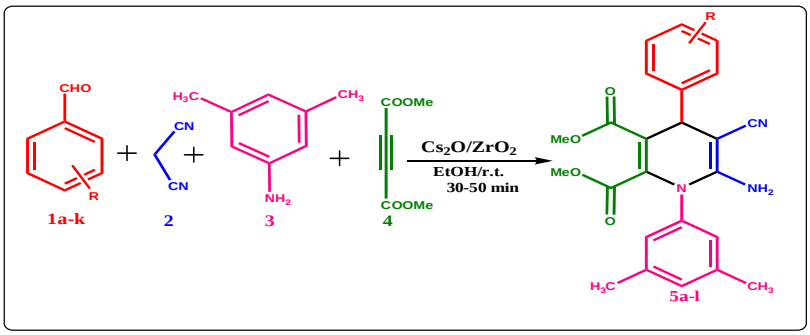
All chemical reactions were monitored by thin layer chromatography (TLC) performed on pre-coated silica gel plates. After elution, plate was visualized under UV illumination at 254nm for UV active materials. Further visualization was achieved by staining with $KMnO_4$ and charring on a hot plate. Column chromatography was performed on silica gel (100-200 mesh) by standard techniques. Commercial grade reagents and solvents were used without further purification.

Preparation of Catalyst and Characterization: A sequence of supported catalysts, weight percentage Cs_2O/ZrO_2 (1, 5 and 10 wt%), were synthesized using the wet-impregnation procedure. The heterogeneous catalyst was achieved from mixture of zirconia (ZrO_2, 2 g, Catalyst support, Alfa Aesar) and an appropriate wt% amount of cesium nitrate [$Cs(NO_3)_36H_2O$ (Alfa Aesar)] in (50 mL) dissolved in distillated water. The mixture was stirred at room temperature for 10 h after which the resulting slurry was filtered under vacuum. Further, it was dried in an oven at 110–120 °C for 6 h and calcined in the presence of air, at 450 °C for 5 h to acquire (1, 5 and 10 wt%) of Cs_2O/ZrO_2 catalysts.

Synthesis of 1,4-dihydropyridine analogues by using prepared Cs_2O/ZrO_2 oxide catalyst(5a-5l)

General procedure for synthesis of 1,4-dihydropyridine analogues: A concoction of substituted aldehyde (1 mmol), malononitrile (1.1 mmol), dimethylaniline (1 mmol), dimethyl acetylene dicarboxylate (1.0 mmol), and Cs_2O/ZrO_2 (50 mg) in 10 mL ethanol was taken a reaction flask and stirred at room temperature. The progress and completion of reaction was monitored by TLC (Scheme 1). After completion of reaction, the crude solid was collected by filtration and followed by two washings with ethanol, it was further purified by recrystallization to obtain pure products. The molecular structures of the resulting products were established on the basis of their physical properties and spectral data.

Optimization Procedure: In the first example typical conditions were trailed by a model reaction which was accomplished by involving different types of catalysts and also solvent-free conditions, with the expectation to decrease the reaction time and increase product yield. When the reaction of aromatic aldehyde (1 mmol), malononitrile (1.1 mmol), dimethylaniline (1 mmol) and dimethylacetylenedicarboxylate (1.0 mmol) were stirred together, no product formation took place in catalyst-free and solvent-free condition at room temperature, after 12 h of reaction (Table 1, entries 1



Scheme 1. Synthesis of functionalized 1,4-dihydro pyridine-2,3-dicarboxylate derivatives

and 2). To determine the scope of acid catalyst, the reaction was examined at room temperature. in presence of acetic acid (AcOH) catalyst in EtOH solvent for 12 h, and no product obtained (Table 1, entry 3). Next, to explore the homogeneous catalysts, the reaction was then repeated in the presence of basic catalysts like TEA, NaOH and piperidine in EtOH solvent for 5-7 h, and the yield was low to moderate (Table 1, entries 4-6). The reaction was performed in the presence of pure metal oxides SiO_2, ZrO_2, $MnO_2$and Cs_2O, and then yields were moderate to good at R.T in ethanol solvent after 1.5 to 3.5 h (Table 1, entry 7-10). Based on the positive results obtained with ZrO_2in order to further enhance the catalytic activity of ZrO_2, different metals such as $MnO_2$and Cs_2O were supported loaded as dopants and activity of the metal supported ZrO_2 catalysts were examined (Table 1, entry 11 and 12). Interestingly, Cs_2O/ZrO_2 gave excellent yield (**95%**) within 30 min reaction time due to optimum dispersion of Cs_2O on ZrO_2 when compared to the MnO_2/ZrO_2 loading resulting in lower activity.

Table 1. Optimal condition for the synthesis of **5a**by 5% Cs_2O/ZrO_2 catalyst[a]

Entry	Catalyst	Solvent	Condition	Time (h)	Yield (%)[b]
1	--	--	Room temp.	12	--
2	--	--	Reflux	12	--
3	AcOH	EtOH	Room temp.	12	--
4	TEA	EtOH	Room temp.	7.0	23
5	NaOH	EtOH	Room temp.	6.0	29
6	piperidine	EtOH	Room temp.	5.0	32
7	SiO_2	EtOH	Room temp.	3.5	51
8	ZrO_2	EtOH	Room temp.	2.5	67
9	MnO_2	EtOH	Room temp.	3.0	54
10	Cs_2O	EtOH	Room temp.	1.5	78
11	MnO_2/ZrO_2	EtOH	Room temp.	0.75	76
12	Cs_2O/ZrO_2	EtOH	Room temp.	0.50	95

[a] All products were characterized by ^{1}H NMR, ^{13}C NMR, FI-IR and HR-MS spectral analysis. [b] Isolated yields. -- No reaction

Table 2. Optimization of various solvents conditions for 5% Cs_2O/ZrO_2catalyst

Entry	Solvent	Time (minutes)	Yield* (%)
1	No solvent	120	--
2	n-hexane	120	--
3	toluene	120	--
4	DMF	90	34
5	THF	90	45
6	MeOH	60	84
7	EtOH	30	95
8	isopropanol	60	70

Table-2 represents the yield when different solvents are used. It shows that a solvent is required for carrying out a reaction in presence of catalyst of Cs_2O/ZrO_2. When the reaction was carried out in the

absence of solvent there is no yield (Table 2, entry 1). In non-polar solvents like n-hexane and toluene, no reaction proceeds (Table 2, entries 2 and 3). Next, with aprotic (polar) solvents such as dimethyl formamide (**DMF**) and tetrahydrofuran (**THF**), the reaction occurred and the yield was low (Table 2, entries 4 and 5). Further, protic (polar) solvents such as MeOH, EtOH and isopropyl alcohol (Table 2, entries 6-8), the yield of the desired product was good to excellent in short reaction time.

RESULTS AND DISCUSSION

SEM analysis: The SEM Image of cesium loaded zirconia shows that large number of particles agglomerated into big rock like structures and the surface is darken color in some parts. While in some areas it is white in color. It shows that cesium got impregnated on a part of the catalyst. In essence the cesium is not distributed homogeneously.

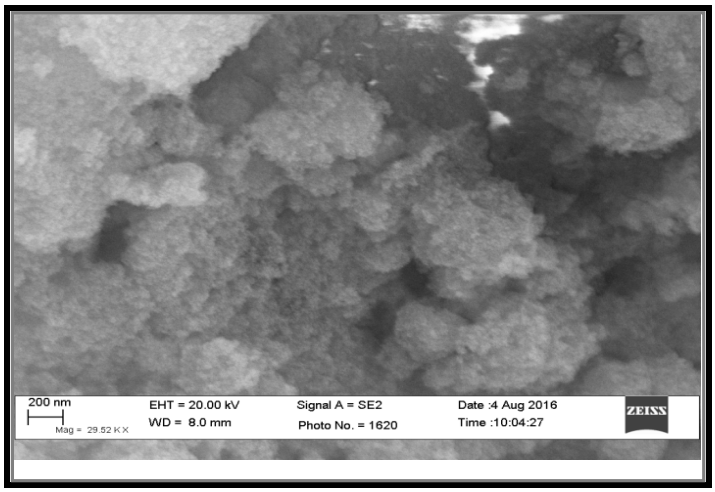


Figure 1. SEM micrograph of5% Cs_2O/ZrO_2 catalyst.

TEM analysis: The TEM micrograph of cesia loaded ZrO_2 particles appear as the capsules of lump under evenly dispersed. The particles are of 50nm size. The darken parts of the images show the presence of Cs dispersed evenly on the surface of ZrO_2. The TEM micrograph reveals that the catalyst substance modified into elongated rod like particles with particle size of 40-50nm.

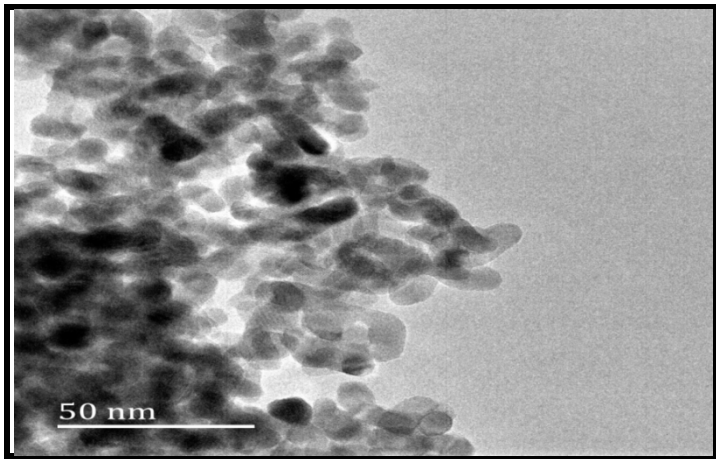


Figure 2. TEM micrograph of 5% Cs_2O/ZrO_2 catalyst.

XRD analysis: The powder XRD diffraction patterns (Fig.3) of the prepared catalyst show the presence of the CsO_2, Cs_3O and Cs_2O phases, with d-spacing values of 2.35, 1.87 and 3.42˚A for 2θ angles of 36, 47 and 27˚ respectively. The d-spacing phases are of the correlating with the ICDD File numbers are 03-065-2662, 01-085-0437 and 01-074-1918 for CsO_2, Cs_3O and Cs_2O phases respectively. Further, the PXRD patterns of catalytic sample show the major 2θ peak values at 24.2°, 28.2°, 31.3°, 35.4°, 40.5°, 45.0°, 50.3°, 55.4° and 60.1° correspond to different diffraction planes of zirconia (JCPDS no. 37-1484).

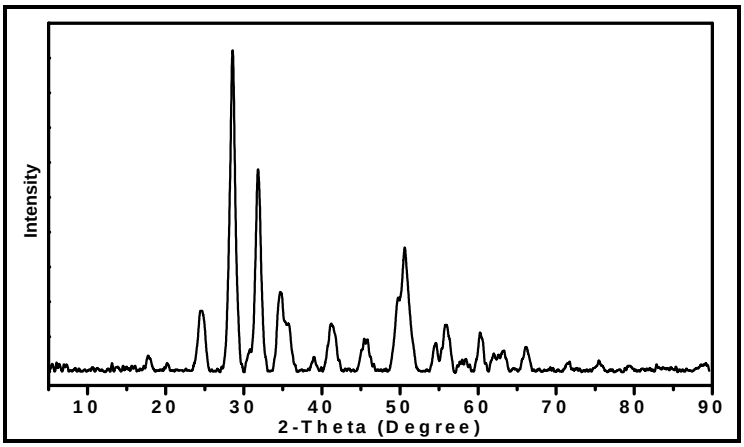


Figure 3. Powder XRD spectra of 5% Cs_2O/ZrO_2 catalyst.

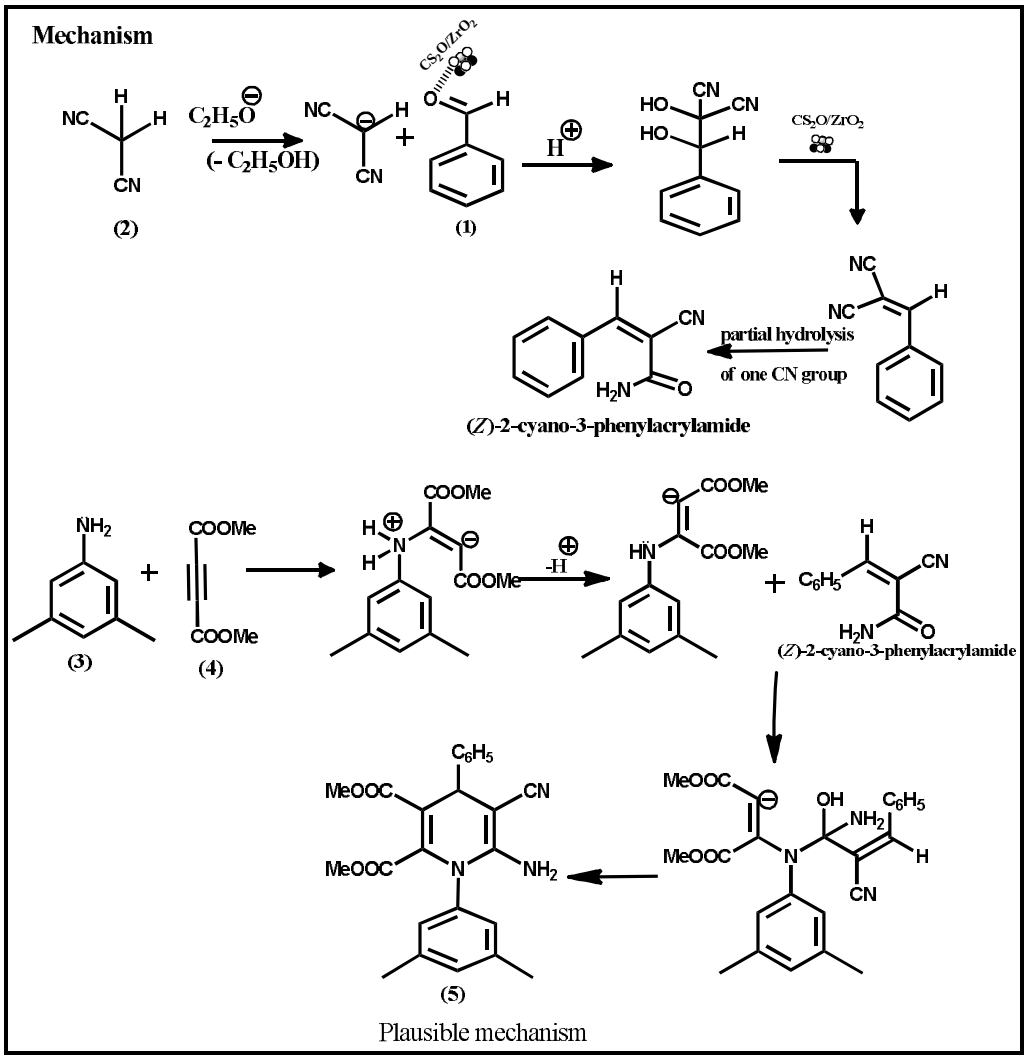
Continuing the success, different aldehydes were tested in our attempt to synthesize 1, 4-dihydropyridine analogues at the same reaction conditions (Scheme 1) and the results are summarized in table 3. From the results it is evident from table 3, we can conclude that the aldehydes with electron releasing groups as substituent formed lower yields than aldehydes having electron withdrawing substituent. Aromatic aldehydes having methoxy group (electron releasing group) results lower yields (83%-91%) (Table-3, entry 5a, 5g, 5h, 5i, 5k and 5l). Aromatic aldehydes having halogen substituent results higher yield (93%-97%) (Table 3, entry 5b, 5c, 5d, 5e, 5f and 5j). These compounds were confirmed by ^{1}H NMR, ^{13}C NMR and Mass spectra.

Table 3. Synthesis of functionalized pyridine-2,3dicarboxylate derivatives

Entry	R	Time (minutes)	Yield	product
1	2-OCH_3-C_6H_4	35	91	5a
2	2-F-C_6H_4	30	95	5b
3	2-Cl-C_6H_4	30-40	97	5c
4	2-Br-C_6H_4	30	95	5d
5	4-Cl-C_6H_4	30-40	94	5e
6	4-Br--C_6H_4	50	93	5f
7	2,3-$(OCH_3)_2$-C_6H_3	40	89	5g
8	3,4 -$(OCH_3)_2$-C_6H_3	45	88	5h
9	2,5 -$(OCH_3)_2$-C_6H_3	30	91	5i
10	4-F-C_6H_4	30-40	93	5j
11	2,4,6-$(OCH_3)_3$-C_6H_2	30	83	5k
12	2-OCH_3-C_6H_4	45	89	5l

The plausible mechanism for the formation of 1, 4-dihydropyridine from substituted aldehyde, malononitrile, dimethylaniline and dimethylacetylenedicarboxylate using Cs_2O/ZrO_2 is shown in figure 1. The reaction may proceed through the formation of highly reactive (Z)-2-cyano-3-phenylacrylamide. The efforts to isolate intermediates were not successful.

Plausible mechanism:



Reusability of catalyst: A viable application for any catalyst can be comprehended if reusability thereof becomes a validated benefit and we thus examined the recovery and reusability of the Cs_2O/ZrO_2 catalyst. The reusability of the catalyst was tested by separating the Cs_2O/ZrO_2 from the reaction mixture by simple filtration under vacuum, washed with acetone, and drying in a vacuum oven at 100°C for 3 h to reuse in consequent reactions. The recovered catalyst can be reused at least six runs in successive reactions without significant loss in product yield. The results are summarized in table-4.

Table 4. Reusability of the catalyst

S.NO	Cycle	yield
1	1st	95
2	2nd	94
3	3rd	94
4	4th	93
5	5th	91
6	6th	91
7	7th	46

Spectral data of synthesized 1,4-dihydropyridine analogs:

(5a).Dimethyl6-amino-5-cyano-1-(3,5-dimethylphenyl)-4-(2-methoxyphenyl)-1,4-dihydro pyridine-2,3-dicarboxylate[1]**:** H NMR (400 MHz, DMSO-d_6): δ 2.19 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 3.24 (s, 3H, OCH_3), 3.49 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 5.10 (s, 1H, CH), 5.32 (s, 2H, NH_2), 6.96-7.04 (m, 2H, ArH), 7.07 (s, 1H, ArH), 7.18-7.22 (m, 4H, ArH), 7.30 (t, J = 7.52 Hz, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 17.33, 17.81, 31.13, 51.67, 52.16, 55.75, 58.59, 103.04, 111.57, 120.77, 120.91, 127.92, 128.84, 130.09, 132.97, 134.35, 135.38, 138.86, 138.90, 142.01, 149.60, 155.79, 162.78, 165.32, 169.15; FT-IR: 3310, 2190, 1710, 1645, 1568, 1495, 1350, 1210 cm^{-1} ; HRMS of $[C_{25}H_{25}N_3O_5 + Na]^+$ (m/z):found 470.0338; Calcd: 470.0331.

(5b).Dimethyl 6-amino-5-cyano-1-(3,5-dimethylphenyl)-4-(2-fluorophenyl)-1,4-dihydro pyridine-2,3-dicarboxylate: ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.31 (s, 6H, $(CH_3)_2$), 3.37 (s, 3H, OCH_3), 3.49 (s, 3H, OCH_3), 4.78 (s, 1H, CH), 5.56 (s, 2H, NH_2), 6.91 (s, 2H, ArH), 7.15-7.26 (m, 1H, ArH), 7.28-7.36 (m, 4H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 20.60, 33.12, 51.87, 52.26, 58.07, 102.33, 115.56, 115.78, 120.72, 124.89, 127.34, 128.98, 129.06, 129.21, 129.25, 131.40, 131.88, 132.02, 134.87, 139.01, 142.74, 151.04, 158.47, 160.91, 162.82, 164.90; FT-IR: 3380, 2950, 2175, 1710, 1655, 1570, 1440, 1345, 1235; HRMS of $[C_{24}H_{22}FN_3O_4 + H]^+$ (m/z): 436.1474; Calcd: 436.1465.

(5c). Dimethyl 6-amino-5-cyano-1-(3,5-dimethylphenyl)-4-(2-chlorophenyl)-1,4-dihydro pyridine-2,3-dicarboxylate: ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.31 (s, 6H, $(CH_3)_2$), 3.37 (s, 3H, OCH_3), 3.46 (s, 3H, OCH_3), 5.10 (s, 1H, CH), 5.55 (s, 2H, NH_2), 6.95 (s, 2H, ArH), 7.15 (s, 1H, ArH), 7.25-7.30 (m, 1H, ArH), 7.42-7.45 (m, 3H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 20.59, 35.31, 51.84, 52.27, 58.59, 103.13, 120.47, 127.36, 128.16, 128.58, 129.43, 129.47, 131.22, 131.44, 134.77, 139.04, 142.80, 142.88, 150.82, 162.78, 164.87; FT-IR: 3380, 2960, 2185, 1710, 1655, 1570, 1520, 1435, 1380, 1240; HRMS of $[C_{24}H_{22}ClN_3O_4 + H]^+$ (m/z): 452.1087; Calcd: 452.1085.

(5d). Dimethyl 6-amino-5-cyano-1-(3,5-dimethylphenyl)-4-(2-bromophenyl)-1,4-dihydro pyridine-2,3-dicarboxylate: ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.30 (s, 6H, $(CH_3)_2$), 3.36 (s, 3H, OCH_3), 3.52 (s, 3H, OCH_3), 4.50 (s, 1H, CH), 5.59 (s, 2H, NH_2), 6.89 (s, 2H, ArH), 7.14 (s, 1H, ArH), 7.20-7.25 (m, 2H, ArH), 7.31-7.35 (m, 2H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 8.56, 20.55, 37.88, 51.88, 52.26, 59.28, 104.10, 115.40, 105.61, 117.65, 120.90, 127.26, 128.54, 128.62, 131.38, 134.88, 138.43, 139.04, 141.84, 150.75, 159.95, 162.36, 162.87, 165.04, 168.57; FT-IR: 3375, 2951, 2178, 1734, 1650, 1565, 1435, 1340, 1232.

(5e). Dimethyl 6-amino-5-cyano-1-(3,5-dimethylphenyl)-4-(4-chlorophenyl)-1,4-dihydro pyridine-2,3-dicarboxylate: ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.29 (s, 6H, $(CH_3)_2$), 3.37 (s, 3H, OCH_3), 3.52 (s, 3H, OCH_3), 4.50 (s, 1H, CH), 5.63 (s, 2H, NH_2), 6.90 (s, 2H, ArH), 7.14 (s, 1H, ArH), 7.32 (d, J = 8.44 Hz, 2H, ArH), 7.48 (d, J = 8.44 Hz, 2H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 20.56, 38.07, 5.91, 52.28, 58.96, 103.78, 120.82, 127.27, 128.57, 128.77, 131.40, 131.57, 134.83, 139.04, 142.02, 144.38, 150.82, 162.81, 164.97; FT-IR: 3458, 3375, 2950, 2174, 1745, 1652, 1568, 1441, 1375, 1232; HRMS of $[C_{24}H_{22}ClN_3O_4 + H]^+$ (m/z): 452.1432; Calcd: 452.1437.

(5f). Dimethyl 6-amino-5-cyano-1-(3,5-dimethylphenyl)-4-(4-bromophenyl)-1,4-dihydro pyridine-2,3-dicarboxylate: ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.29 (s, 6H, $(CH_3)_2$), 3.36 (s, 3H, OCH_3), 3.51 (s, 3H, OCH_3), 4.47 (s, 1H, CH), 5.63 (s, 2H, NH_2), 6.89 (s, 2H, ArH), 7.13 (s, 1H, ArH), 7.25 (d, J = 8.40 Hz, 2H, ArH), 7.60 (d, J = 8.36 Hz, 2H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 20.54, 20.75, 38.15, 51.89, 52.26, 58.89, 103.70, 117.64, 119.32, 120.07, 120.80, 125.49, 126.12, 127.26, 128.94, 131.68, 134.81, 138.41, 139.04, 142.03, 144.79, 147.50, 150.81, 162.79, 164.50, 164.95, 168.56; FT-IR: 3381, 2951, 2181, 1736, 1707, 1655, 1565, 1443, 1342, 1230; HRMS of $[C_{24}H_{22}BrN_3O_4 + 2H]^+$ (m/z): 497.2487; Calcd: 497.2485.

(5g). Dimethyl 6-amino-5-cyano-1-(3,5-dimethylphenyl)-4-(2,3-dimethoxyphenyl)-1,4 dihydro pyridine-2,3-dicarboxylate: ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.30 (s, 6H, $(CH_3)_2$), 3.46 (s, 6H, $(OCH_3)_2$) , 3.80 (s, 6H, $(OCH_3)_2$), 4.84 (s, 1H, CH), 5.41 (s, 2H, NH_2), 6.85 (dd, J = 7.76 Hz, 1H, ArH), 6.85 (dd, J = 1.16 Hz, 1H, ArH), 6.89 (s, 1H, ArH), 6.81 (s, 2H, ArH), 6.94 (dd, J = 8.24 Hz, 1H, ArH), 6.94 (dd, J = 1.32 Hz, 1H, ArH), 7.09 (d, J = 7.92 Hz, 1H, ArH), 7.13 (d, J = 4.44 Hz, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 20.59, 20.76, 32.55, 51.72, 52, 17, 55.52, 56.02, 59.53, 103.87, 111.39, 117.66, 119.80, 120.98, 124.16, 127.25, 131.25, 135.16, 138.33, 138.95, 142.40, 145.56, 150.82, 152.23, 163.03, 165.15; FT-IR: 3378, 2951, 2181, 1736, 1653, 1566, 1443, 1376, 1230.

(5h). Dimethyl 6-amino-5-cyano-1-(3,5-dimethylphenyl)-4-(3,4-dimethoxyphenyl)-1,4-dihydro-pyridine-2,3-dicarboxylate: ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.18 (s, 6H, $(CH_3)_2$), 3.47 (s, 6H, $(OCH_3)_2$), 3.81 (s, 6H, $(OCH_3)_2$), 4.85 (s, 1H, CH), 5.42 (s, 2H, NH_2), 6.86(dd, J = 7.76 Hz, 1H, ArH), 6.86 (dd, J = 1.16 Hz, 1H, ArH), 6.90 (s, 1H, ArH), 6.82 (s, 2H, ArH), 6.95 (dd, J = 8.24 Hz, 1H, ArH), 6.95 (dd, J = 1.32 Hz, 1H, ArH), 7.10 (d, J = 7.92 Hz, 1H, ArH), 7.14 (d, J = 4.44 Hz, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 20.76, 20.85, 34.37, 51.04, 52.90, 55.37, 55.33, 59.71, 111.53, 111.94, 114.10, 115.59, 118.93, 121.08, 125.49, 129.74, 138.40, 139.77, 147.50, 147.92, 148.42, 149.70, 153.44, 164.50, 168.56; FT-IR: 3375, 2951, 2182, 1734, 1650, 1564, 1435, 1232.

(5i). Dimethyl 6-amino-5-cyano-1-(3,5-dimethylphenyl)-4-(2,5-dimethoxyphenyl)-1,4-dihydro pyridine-2,3-dicarboxylate: ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.28 (s, 6H, $(CH_3)_2$), 3.50 (s, 6H, $(OCH_3)_2$), 3.71 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 4.83 (s, 1H, CH), 5.44 (s, 2H, NH_2), 6.72 (d, J = 3.04 Hz, 1H, ArH), 6.82 (s, 3H, ArH), 6.98 (d, J = 8.8 Hz, 1H, ArH), 7.13 (s, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 18.43, 20.60, 30.63, 31.89, 51.87, 52.30, 56.03, 56.35, 59.49, 103.55, 111.84, 112.92, 113.54, 120.80, 127.13, 131.16, 134.14, 135.38, 138.94, 142.83, 150.35, 151.25, 153.32, 163.11, 164.06; FT-IR: 3378, 2960, 2185, 1710, 1655, 1564, 1435, 1374, 1230; HRMS of $[C_{26}H_{27}N_3O_6 + Na]^+$ (m/z): 500.2573; Calcd: 500.2559.

(5j). Dimethyl 6-amino-5-cyano-1-(3,5-dimethylphenyl)-4-(4-fluorophenyl)-1,4-dihydro pyridine-2,3-dicarboxylate: ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.31 (s, 6H, $(CH_3)_2$), 3.36 (s, 3H, OCH_3), 3.44 (s, 3H, OCH_3), 5.09 (s, 1H, CH), 5.53 (s, 2H, NH_2), 6.96 (s, 2H, ArH), 7.15-7.21 (m, 2H, ArH), 7.45 (dd, J = 7.76 Hz, 1H, ArH), 7.45 (dd, J = 1.72 Hz, 1H, ArH), 7.48-7.52 (m, 1H, ArH), 7.60 (dd, J = 7.96 Hz, 1H, ArH) 7.60 (dd, J = 1.00 Hz, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 20.58, 37.61, 51.81, 52.27, 58.85, 103.47, 120.33, 121.75, 127.35, 128.86, 129.60, 131.46, 132.62, 134.73, 139.05, 142.66, 144.79, 150.67, 162.77, 164.90; FT-IR: 3472, 3315, 3218, 2960, 2195, 1711, 1655, 1570, 1416, 1315, 1265; HRMS of $[C_{24}H_{22}FN_3O_4 + H]^+$ (m/z): 436.1461; Calcd: 436.1465.

(5k). Dimethyl 6-amino-5-cyano-1-(3,5-dimethylphenyl)-4-(2,4,6-trimethoxyphenyl)-1,4-dihydro pyridine-2,3-dicarboxylate: ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.20 (s, 6H, $(CH_3)_2$), 3.47 (s, 6H, $(OCH_3)_2$), 3.81 (s, 6H, $(OCH_3)_2$), 4.85 (s, 1H, CH), 5.42 (s, 2H, NH_2), 6.86(dd, J = 7.76 Hz, 1H, ArH), 6.86(dd, J = 1.16 Hz, 1H, ArH), 6.90 (s, 1H, ArH), 6.82 (s, 2H, ArH), 6.95 (dd, J = 8.24 Hz, 1H, ArH), 6.95 (dd, J = 1.32 Hz, 1H, ArH), 7.10 (d, J = 7.92 Hz, 1H, ArH), 7.15 (d, J = 4.44 Hz, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 20.75, 30.61, 51.05, 52.91, 55.64, 55.96, 56.10, 91.03, 92.54, 103.67, 113.86, 116.40, 117.63, 125.50, 138.42, 139.77, 147.50, 150.79, 161.40, 164.51, 167.42, 168.56; FT-IR: 3379, 2965, 2172, 1708, 1656, 1570, 1435, 1345, 1235; HRMS of $[C_{27}H_{29}N_3O_7 + Na]^+$ (m/z): 530.2393; Calcd: 530.2409.

(5l). Dimethyl 6-amino-5-cyano-1-(3,5-dimethylphenyl)-4-(4-methoxyphenyl)-1,4-dihydro pyridine-2,3-dicarboxylate: ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.20 (s, 6H, $(CH_3)_2$), 3.65 (s, 6H, $(OCH_3)_2$), 3.88 (s, 3H, OCH_3), 5.22 (s, 1H, CH), 6.51 (s, 2H, NH_2), 6.71 (s, 1H, ArH), 7.13 (d, J = 8.56 Hz, 2H, ArH), 7.44 (dd, J = 8.52 Hz, 2H, ArH), 7.44 (dd, J = 2.16 Hz, 2H, ArH), 7.52 (s, 2H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): 20.74, 30.57, 51.03, 52.88, 55.91, 112.08, 113.86, 114.90,

115.22, 117.64, 124.25, 125.48, 126.40, 138.40, 139.76, 146.86, 147.51, 153.82, 160.60, 164.48, 168.57; FT-IR: 3465, 3370, 3315, 2185, 2235, 1744, 1651, 1565, 1410, 1345.

APPLICATION

Cesium supported zirconium is efficient heterogeneous catalyst for the synthesis of 1,4-Dihydropyridine analogues. It is non-toxic, easily separable and enhances the rate of reaction.

CONCLUSION

In this study, We report on a green and efficient one-pot protocol for the synthesis of functionalized pyridine-2,3-dicarboxylate derivatives through a four-component reaction between malononitrile, dimethylacetylenedicarboxylate, dimethylaniline and substituted aldehydes using 5% Cs_2O/ZrO_2 as a catalyst in EtOH and at room temperature. This methodology has several advantages such as short reaction times (< 30 min), high product yields (85-95%), ease of handling, facile and green work-up. The easy recoverable and reusable catalyst meets the industrial and environmental requirements and it is versatile and cost effective.

ACKNOWLEDGEMENTS

I wish to express my sincere thanks to Prof Susheela Bai G, Research Ditector, Dr G Hima Bindu, Co-Research Director and Department of Engineering Chemistry, Andhra Univeristy to provide laboratory facilities.

REFERENCES

[1]. P. Ramakanth, M. Suresh,Sreekantha B. Jonnalagadda, Eco-efficient ultrasonic responsive synthesis of pyrimidines/pyridine,*Ultrasonics Sonochemistry*, **2014**, 21, 472–477.
[2]. D. Alexander, F. Stephen Martin, Synthesis of oxygen- and nitrogen-containing heterocycles by ring-closing metathesis, *Chem. Rev*, **2004,** 104(5), 2199–2238.
[3]. Adrien Albert, J. N. Phillips, Ionization constants of heterocyclic substances, Part II. Hydroxy-derivatives of nitrogenous six-membered ring-compounds, *J. Chem. Soc*, **1956**, 1294-1304.
[4]. Jesús A.Varela, Carlos Saa, Construction of pyridine rings by metal-mediated [2 + 2 + 2] cycloaddition, *Chem. Rev*, **2003**, 103(9), 3787–3802.
[5]. Fatma E.Goda, Alaa A.-M.Abdel-Aziz, Omer A.Attef, Synthesis, antimicrobial activity and conformational analysis of novel substituted pyridines: BF_3-promoted reaction of hydrazine with 2-alkoxy pyridines, *Bioorganic and Medicinal Chemistry*, **2004,** 12, 1845-1852.
[6]. M. A. Al-Omar, Khairia. M. Youssef, Magda.A.El-Sherbeny, Albanat.A.Awadalla, H. I. El-Subbagh, Synthesis and *In Vitro* antioxidant activity of some new fused pyridine analogs, *Archive Der Pharmazie*, **2005**, 338,175–180.
[7]. Abouzid KAM, Al-Ansary GH, El-Naggar AM, Eco-friendly synthesis of novel cyanopyridine derivatives and their anticancer and PIM-1 kinase inhibitory activities, *Eur. J. Med. Chem.*, **2017**, 134, 357-365.
[8]. C. Mahan, A. C. Spyropoulos, Improving prevention and treatment of venous thrombo embolism clinical trial results, *J.Med. Econ.*, **2012**, 15(4), 611-22.
[9]. T. B. Silva., A. M. R. Bernardino, M. L. G. Ferreira, K. R. Rogerio, L. J. M Carvalho, N. Boechat, L. C. S. Pinheiro., Design, synthesis and anti-*P.falciparum* activity of pyrazolo pyridine-sulfonamide derivatives, *Bioorg Med Chem*, **2016**, 24(18), 4492-4498.
[10]. G. Jose, T. H. Suresha.Kumara, G. Nagendrappa, H. B. Sowmya, D. Sriram, P. Yogeeswari, J. P. Sridevi, T. N. Guru.Row, A. A. Hosamani, P. S. SujanGanapathy, N. Chandrika, L. V. Narendra, Synthesis, molecular docking and anti-mycobacterial evaluation of new imidazo[1,2-a]pyridine-2-carboxamide derivatives, *Eur.J.Med. Chem.*, **2015**, 89, 616-27.

[11]. P. Suman, H. C. Lokman, P. Tasneem, One-pot multicomponent reactions for the efficient synthesis of highly functionalized dihydropyridines, *Synth.Commun.*, **2013**, 43, 986–992.
[12]. P. Suman, S. Vandana, D. Prolay, H. C. Lokman, PEG-functionalized dihydropyridines and their functional group dependent DNA cleavage activity, *Bio.org. Chem*., **2013**, 48, 8–15.
[13]. C. Hong-Shuo, D. Rui-Yun, Meglumine, an efficient, biodegradable, and recyclable green catalyst for one-pot synthesis of functionalized dihydropyridines, *Monatsh Chem*., **2015**, 146, 1355–1362.
[14]. Jing.Sun, Er-Yan.Xia, Qun.Wu, Chao-Guo.Yan, Synthesis of Polysubstituted Dihydropyridines by Four-Component Reactions of Aromatic Aldehydes, Malononitrile, Arylamines and Acetylenedicarbo–xylate,*Org. Lett.*, **2010**, 12(16), 3678-3681.