Reusable Ce-V Loaded Alumina Catalyst for Multicomponent Synthesis of Substituted Pyridines in Green Media

Suresh Maddila,[a] Surya N. Maddila,[a] Sreekantha B. Jonnalagadda,[a] and Palakondu Lavanya[b]*

[a]School of Chemistry, University of KwaZulu-Natal, West Ville Campus, Chilten Hills, Durban 4000, South Africa
[b]Department of Chemistry, Annamacharya Institute of Technology & Sciences, J.N.T. University, Tirupati 517 502, Andhra Pradesh, India
*E-mail: gajulapallilavanya@gmail.com

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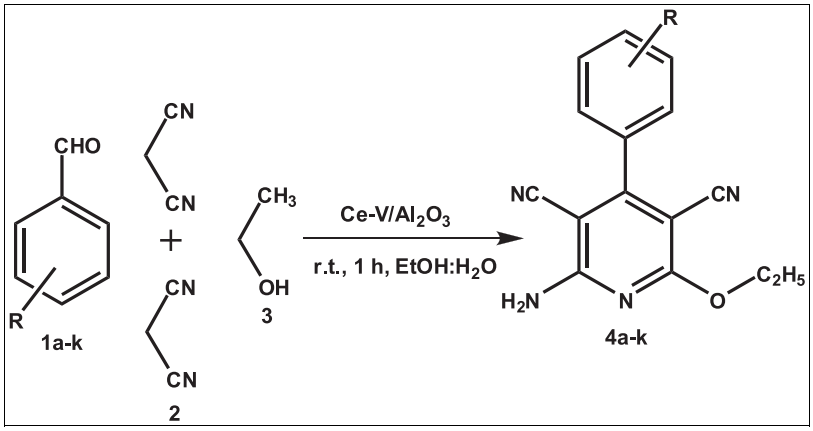

Ce-V/Al2O3 as an effective heterogeneous catalyst is synthesized by a simple technique. The catalyst was identified by powder X-ray diffraction, SEM, TEM, and BET surface area analysis. The catalyst is fully recyclable and reusable for several runs preserving its high activity. The catalytic activity of Ce-V/Al2O3 is described by synthesis of a series of multisubstituted pyridines in good to excellent yields via a facile one-pot multicomponent reaction within shorter reaction time.

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INTRODUCTION

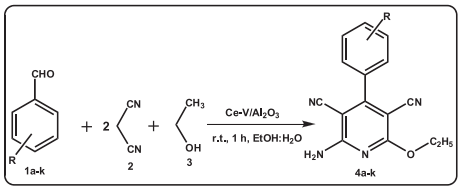
Multicomponent reactions (MCRs) have been developed as an efficient and powerful implements in modern synthetic organic [1], bioactive medicinal [2], pharmaceutical [3], agro [4], and combinatorial chemistry [5], because of the synthesis of these complex molecules from simple and readily available substrates that can be accomplished in a very fast and efficient manner without use of chromatograms for any intermediates. Advantages of MCRs are wide, including simple protocols, low-cost reactants, and green principles. Therefore, developing new MCRs and improving known MCRs are widespread areas of research in current heterocyclic synthesis. Thus, such environmentally benign protocols are suitable and well desired.

Heterogeneous catalysts have attracted much consideration in heterocyclic synthesis because of several benefits which include reusability, cost effectiveness, non-environmental compatibility, non-harsh, and ease of separation [6–8]. Among the various solid catalysts, metal doped with silica has attracted widespread attention because of its unique properties, including high surface area, excellent thermal stability, large pore volume, and tunable pore diameter [9,10]. For these reasons, development of metal-functionalized alumina as recoverable heterogeneous catalysts for the synthesis of heterocyclic compound is a topic of present interest.

Synthesis of polysubstituted pyridines and its derivatives have recently fascinated much interest because of their biological and pharmacological activities [11]. They are constituents of many pharmaceuticals and natural products, which reveal wide range of biological activity [12]. Within a long-term research program aimed at developing pharmaceutically active materials, synthesis of substituted pyridines are of special implication because of varied biological activities [13] such as anticancer [14], antimicrobial [15], antibacterial [16], antifungal [17], anti-inflammatory [18], antioxidant activity [19], cytotoxicity [20], and anti-HIV [21]. Thus, the synthesis of polysubstituted pyridine derivatives have fascinated many researchers, and several approaches have been pursued using catalysts, such as K_2CO_3 [22], NaH [23], Et_3N [24], [bmIm]OH [25], $ZnCl_2$ [26], DBU [27], MgO [28], KF/Al_2O_3 [29], H_3BO_3 [30], and NaOH [31].

In continuation of our research work in the domains of MCRs [32–35] herein, we report a novel, environmentally benign, a facile and efficient method for the first time of the use of $Ce\text{-}V/Al_2O_3$ as heterogeneous catalyst to promote a fast MCR protocol for the synthesis of polysubstituted pyridines at room temperature (R.T.) in eco-friendly in aqueous ethanol media (Scheme 1).

Scheme 1. Synthesis of multisubstituted pyridines (**4a-k**).



RESULTS AND DISCUSSION

To determine the optimum conditions, reaction of benzaldehyde, malononitrile, and ethanol for the synthesis of polysubstituted pyridines, in the presence of Ce-V/Al_2O_3 as catalyst, was preferred as ideal reaction (Table 1). In the first example, benzaldehyde (1 mmol), malononitrile (2.2 mmol), aqueous ethanol (1:1 ratio), and catalyst (30 mg) were stirred at R.T. The condensation reaction of **4a** in various solvents was examined. It was found that only a trace of the target molecule was obtained in H_2O or Dichloromethane (DCM) for 10 h (Table 1, entries 1 and 2) and in MeOH, EtOH, or MeCN, the cyclization reaction was slow, and the yield of product was minor after 6 h (25–38%, Table 1, entries 3–5), while the addition of equal ratio of water to them could efficiently accelerate the reaction and increase its yield (65–90%, Table 1, entries 6–8), the reason is that the addition of water is favorable to excited state intramolecular proton transfer. From the economic and environmental point of view, EtOH : H_2O (1:1) was finally chosen as the reaction medium for all further reactions. Further, the reaction was investigated under various catalysts. Low amount of the anticipated product was achieved, when K_2CO_3 and NaOH were used as catalysts (Table 1, entries 9 and 10). With Ce/Al_2O_3, V/Al_2O_3, and simple alumina as catalyst, a 61%, 58%, and 48% yield was obtained (Table 1, entries 11–13), respectively. Then, we tried to synthesize the heterocyclic framework using Ce-V/Al_2O_3 as catalyst with aqueous ethanol as solvent. To our delight, MCR was accomplished successfully, just in 1 h at R.T. and obtained the expected substituted pyridines selectively and in good yield. The heterogeneous catalyzed reaction was found to proceed almost instantaneously, although it took about 1 h for completion of reaction. In the proposed MCR, Ce-V/Al_2O_3 displayed greater efficiency compared with the other catalysts investigated because of its synergetic effect of the metals. The surface properties of this catalyst can be modified by loading cations of varied properties. Inclusion of Ce^{3+}, V^{3+} into the place of Al^{3+} provides acidity and acidic sites on the catalyst surface. An optimal distribution of the acidic and basic sites due to loading of Ce-V/Al_2O_3 mixed oxides possibly contributed to its enhanced catalytic efficiency, which is evident from the high yield, selectivity, and speed of the reaction achieved in the title reaction.

Table 1

Optimization condition for the synthesis of multisubstituted pyridines by Ce-V/Al_2O_3 catalyst[a].

Entry	Catalyst	Solvent	Condition	Time (h)	Yield (%)[b]
1	Ce-V/Al_2O_3 (30 mg)	H_2O	R.T.	10	21
2	Ce-V/Al_2O_3 (30 mg)	DCM	R.T.	10	18
3	Ce-V/Al_2O_3 (30 mg)	MeOH	R.T.	6	30
4	Ce-V/Al_2O_3 (30 mg)	EtOH	R.T.	6	38
5	Ce-V/Al_2O_3 (30 mg)	MeCN	R.T.	6	25
6	Ce-V/Al_2O_3 (30 mg)	MeOH : H_2O	R.T.	3	76
7	Ce-V/Al_2O_3 (30 mg)	EtOH : H_2O	R.T.	1	94
8	Ce-V/Al_2O_3 (30 mg)	MeCN : H_2O	R.T.	4	61
9	K_2CO_3	EtOH : H_2O	R.T.	3	48
10	NaOH	EtOH : H_2O	R.T.	5	40
11	Ce/Al_2O_3	EtOH : H_2O	R.T.	3.5	61
12	V/Al_2O_3	EtOH : H_2O	R.T.	4	58
13	Al_2O_3	EtOH : H_2O	R.T.	4.5	39
14	Ce-V/Al_2O_3 (40 mg)	EtOH : H_2O	R.T.	1	94
15	Ce-V/Al_2O_3 (50 mg)	EtOH : H_2O	R.T.	1	95
16	Ce-V/Al_2O_3 (20 mg)	EtOH : H_2O	R.T.	2	70
17	Ce-V/Al_2O_3 (10 mg)	EtOH : H_2O	R.T.	2.5	66

[a]All product were characterized by ^{1}H NMR, ^{13}C NMR, and ^{15}N NMR (GHSQC) spectral analysis.
[b]Isolated yields.
No reaction.

Consequently, to find the optimal quantity of catalyst needed, the reaction was carried out using various amounts of catalyst at R.T. It was found that 30 mg of catalyst gave maximum yield of 94% in 1 h. Using more than 30 mg of catalyst for the reaction had no significant improvement on the yield or the reaction time. However, the decrease in amount of the catalyst from 20 to 10 mg, affected the product yield by reducing to 70% and 66%, respectively (Table 1, entries 14–17).

The scope of the Ce-V/Al_2O_3 catalyzed MCR was further explored. Choosing the conditions optimal for the synthesis of **4a**, that is, 30 mg of Ce-V/Al_2O_3 at R.T. and EtOH : H_2O as solvent (Scheme 1), we employed varied structurally different aldehydes (**1a–k**) for the MCR. To our delight, most of the reactions afforded desired pyridine derivatives (**4a–k**) in good yields (86–94%) with good selectivity and with no byproducts. The results are depicted in Table 2. The MCRs with substrates bearing electron-

Table 2

Synthesis of multisubstituted pyridines catalyzed by Ce-V/Al_2O_3 catalyst.

Entry	R	Product	Yield (%)	Mp °C	Lit mp °C
1	H	**4a**	94	179–180	—
2	2-MeO	**4b**	92	185–187	185–186 [31]
3	3-MeO	**4c**	89	255–256	—
4	2-Cl	**4d**	91	208–210	—
5	2-NO_2	**4e**	88	169–171	—
6	2-Br	**4f**	86	223–224	—
7	4-$N(CH_3)_2$	**4g**	92	205–206	—
8	2-Br	**4h**	90	190–192	—
9	Furyl	**4i**	87	214–215	—
10	4-F	**4j**	94	162–163	163—164 [31]
11	4-CF_3	**4k**	93	214–215	—

[a]Reaction conditions: aromatic aldehyde (1.0 mmol), malononitrile (2.2 mmol), and EtOH (1 mmol), EtOH : water (1:1 v/v, 10 mL), R.T.
[b]All synthesized compounds are identified, and their structures were conformed with ^{1}H NMR, ^{13}C NMR spectral data, and melting points as compared with literature values.
New compounds/no literature available.

donating or electron-withdrawing groups on the aromatic ring proceeded smoothly and formed the corresponding multisubstituted pyridines in good yields under the chosen conditions. Structures of the multisubstituted pyridines (**4a–k**) were established and confirmed on the basis of ^{1}H NMR, ^{13}C NMR, ^{15}N NMR (GHSQC), and HR-MS spectral analysis.

Powder X-ray diffractogram. The powder diffraction patterns (Fig. 1) of 1%, 2.5%, and 5 wt% Ce-V/Al_2O_3 catalyst reveals that different phases of metal oxides are present with alumina support (Joint Committee on Powder Diffraction Standards [JCPDS] file 10–425). The presence of V_2O_5 phase and CeO_2 phase are evident and in agreement with the JCPDS 41–1426 and JCPDS 34–0394, respectively. Sharp diffraction peaks of V_2O_5 were observed at 2θ value of 17.4°, 26°, 42.2°, 49°, and 62.4° as well as CeO_2 peaks were also observed at 29.8°, 32.5°, 37.2°, 46.2°, 49.1°, 67.1°, and 72.4° 2θ value. Diffractogram shows the intense and sharp characteristic peaks of both the metal oxides with support, it means that there may be less agglomeration of metals on the support, and this is a very important factor to improve in catalytic activity under reaction.

SEM and TEM analysis. Figure 2a is the SEM images of the 2.5 wt% Ce-V/Al_2O_3 catalyst, and it shows that CeO_2 and V_2O_5 particles are dispersed on the alumina support, and they are in nanodimension but varying in size. During microscopy,

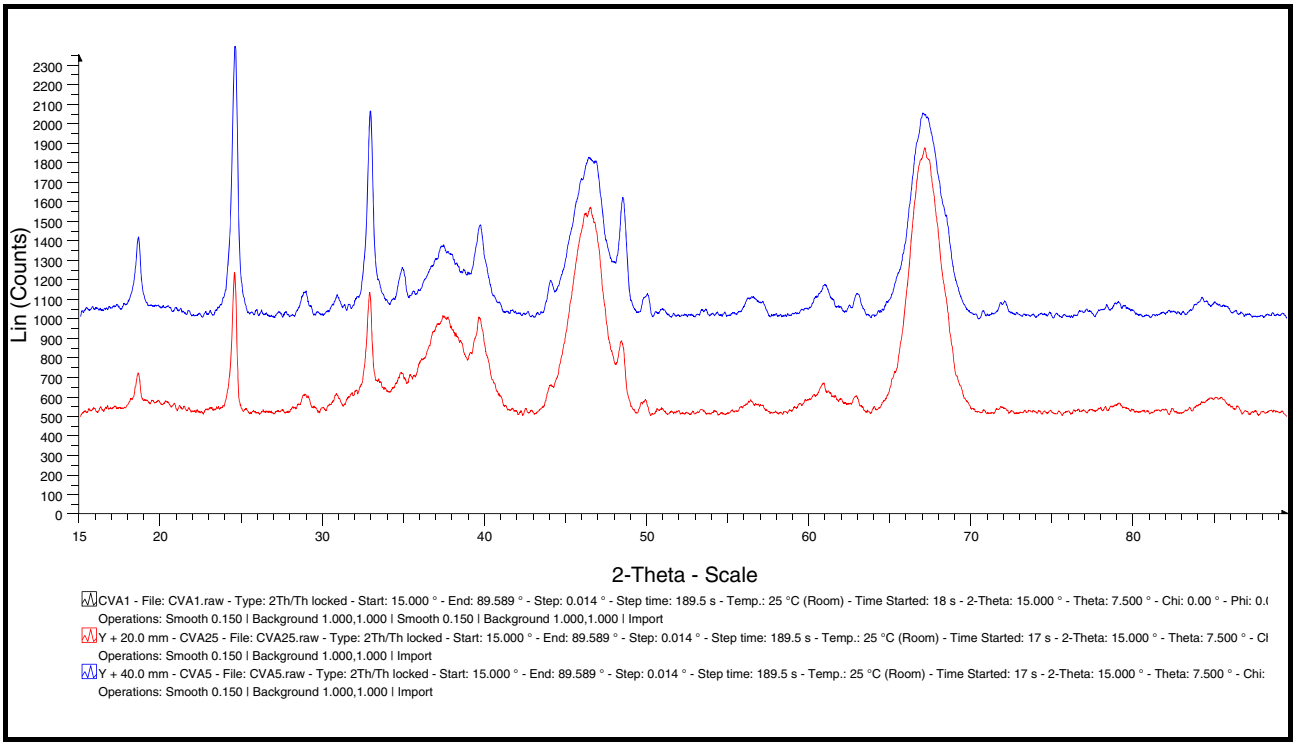


Figure 1. Powder X-ray diffraction spectra of Ce-V/Al_2O_3 catalyst. [Color figure can be viewed in the online issue, which is available at www.wileyonlinelibrary.com.]

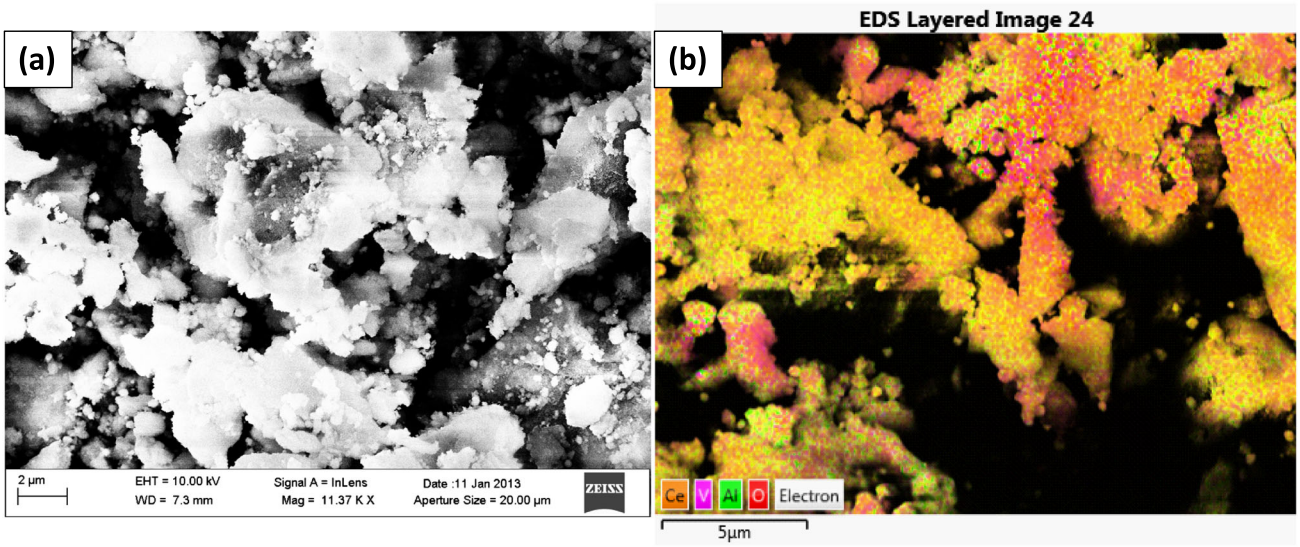


Figure 2. (a) SEM images and (b) SEM–EDX mapping of 2.5 wt% Ce-V/Al_2O_3 catalyst. [Color figure can be viewed in the online issue, which is available at www.wileyonlinelibrary.com.]

samples were found with similar morphology throughout the surface. We can clearly see from images that micron size alumina support agglomerates are present with different morphologies and shapes. SEM–EDX image (Fig. 2b) reveals the distribution and dispersion of both CeO_2 and V_2O_5 on alumina surface. Total 2.5 wt% loading of both the metal oxides cover the maximum surface of alumina. No agglomeration of oxide particles on support was observed during SEM–EDX mapping. Less agglomeration plays a very important role in catalysis, and it also helps to provide good metal–support interaction. TEM images of catalyst show the metal oxides present on the alumina support with different shapes and sizes. Elongated rod shape particles are mostly of alumina support, and the other irregular shape particles are of metal oxides. The size of all particles was found less than 20 nm during random scanning under TEM (Fig. 3).

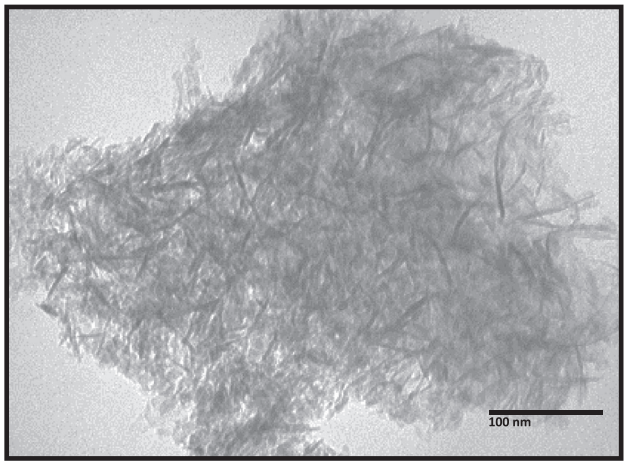


Figure 3. TEM image of 2.5 wt% Ce-V/Al_2O_3 catalyst.

BET surface area analysis. The surface characteristics of the catalyst depend on the metal loadings of the catalyst and type of metal particles present with the support. It can be seen from the results, with the addition of total 2.5 wt% Ce and V on alumina is responsible to decrease the total surface area, pore volume, and pore size gradually of the sample. Major change was found in the surface properties of catalyst after impregnation of metals on alumina, it means metals are well dispersed on the support, and there might be possibility of blocking the pores of the support. The isotherm (Fig. 4) shows IUPAC type IV patterns with sharp inflections of nitrogen adsorbed at P/P_0 of about 0.60, and indicating the presence of mesopores. BET analysis study also shows the sharp decrease in pore volume from 0.98 to 0.49 cm^3/g

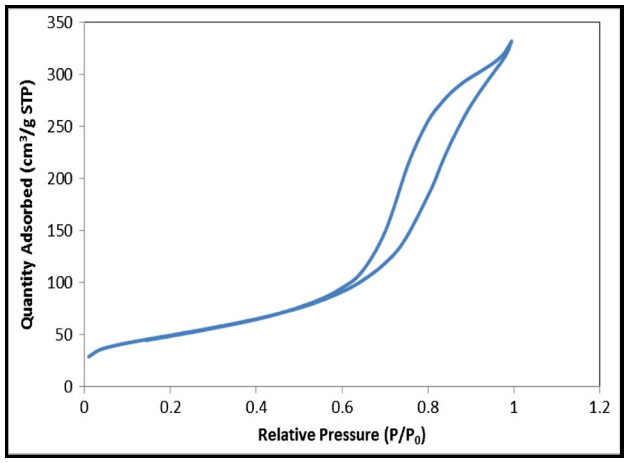


Figure 4. Nitrogen adsorption–desorption isotherm of 2.5 wt% Ce-V/Al_2O_3 catalyst. [Color figure can be viewed in the online issue, which is available at www.wileyonlinelibrary.com.]

and pore size from 12.5 to 9.3 nm in the case of bimetallic catalyst of Ce and V with 2.5 wt% total metal loadings on alumina in comparison with alumina only.

Reusability of Ce-V/Al_2O_3. The facile heterogeneous character of the catalyst, recycling experiment was employed using model reaction. After completion of reaction, the catalyst was recovered by filtration, washed with ethanol, and dried under vacuum. The recovered catalyst was reused five times with a slight loss in catalytic activity. The minor loss observed in the catalytic activity after fifth run could be due to temporary poisoning by organic impurities or due to minor changes in the structure and morphology of the catalyst under the operating conditions.

CONCLUSION

In conclusion, we report an efficient and environmentally benign one-pot multicomponent protocol for synthesis of multisubstituted pyridines with good atom efficiency. We have developed simple, highly efficient, and recyclable heterogeneous catalyst Ce-V/Al_2O_3 for MCR protocol at R.T., which be put into practice for the selective synthesis of multisubstituted pyridines using eco-friendly water and ethanol solvent. Main objectives of mild reaction conditions, use of recyclable catalyst, cost-effectiveness, and eco-friendly simple method are achieved.

EXPERIMENTAL

All chemicals and reagents required for the reaction were of analytical grade and were used without any further purification. Bruker AMX 400 MHz NMR spectrometer was used to record the ^{1}H NMR, ^{13}C NMR, and ^{15}N NMR Gradient Heteronuclear Single Quantum Coherence (GHSQC) spectral values. HRMS data were obtained using a Bruker microTOF-Q II ESI instrument operating at ambient temperature. The DMSO-d_6 solution was utilized for this, while TMS served as the internal standard. TMS was further used as an internal standard for reporting all the chemical shifts in δ (parts per million). Purity of all the reaction products was confirmed by TLC using aluminum plates coated with silica gel (Merck Kieselgel 60 F254).

Preparation of catalyst. The wet impregnation method was used in the preparation of metal oxide supported catalysts [36,37]. The catalysts were prepared by wet impregnation method by dissolving appropriate amount of Ce (cerium nitrate, Aldrich-99%) and V (vanadyl sulfate, Aldrich-99%) with a ratio of 1:1 in distilled water (50.0 mL) and adding it to 5 g of Alumina (Al_2O_3, Aldrich). The mixture is stirred for 3 h using a magnetic stirrer at room temperature and left at R.T. overnight. All the catalysts are dried in an oven at 110–120°C for 12 h and calcined in the presence of air, at 450°C for 3 h to obtain the 2.5% w/w of Ce-V supported catalysts.

CHARACTERIZATION OF CATALYSTS

Micromeritics Tristar-II porosity and surface area analyzer was used for estimation of pore size, pore volume, and surface area of the catalysts. Barret–Joyner–Halenda adsorption–desorption curves were obtained at −196°C, to assess the particulate properties of the catalyst. All the catalyst materials were degassed by passing nitrogen overnight at 200°C. Bruker D8 advance instrument with a Cu K radiation source by λ = 1.5406 was used for the X-ray diffraction data for the catalyst. JEOL JEM-1010 electron microscope and JEOL JSM-6100 microscope (JEOL Solutions for Innovation, Peabody, MA) were used for TEM and SEM analyses, respectively. In TEM analysis for particles distribution, size of 40–60 particles were averaged and with standard deviation. An emission current (100 μA) by a Tungsten (W) filament with 12 kV accelerator voltage was employed for EDX analysis of the SEM images. Elemental composition of the catalyst materials was established by using Inductively Coupled Plasma Optical Emission Spectrometer (Optima 5300 DV Perkin-Elmer, San Diego, CA).

General procedure for the synthesis of pyridines. A mixture of benzaldehyde (1 mmol), malononitrile (2.2 mmol), and ethanol (1 mmol) were dissolved in water (5 mL) and added Ce-V/Al_2O_3 (30 mg) catalyst at R.T. and stirred continuously for 1 h. TLC was performed to notice the complete consumption of starting material in the reaction mixture. A crude product was afforded upon filtering the reaction mass and subsequent evaporation under reduced pressure. Further, this crude was recrystallized by EtOH solvent to obtain pure product (**4a–k**). The filtered catalyst is washed with ethanol and dried, reused for successive five runs.

2-Amino-6-ethoxy-4-phenylpyridine-3,5-dicarbinitrile (4a). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ = 1.46 (t, 3H, *J* = 7.06 MHz, CH_3), 4.58 (q, 2H, *J* = 7.08 MHz, CH_2), 7.29 (d, 2H, *J* = 7.81 MHz, Ar-H), 7.43 (t, 3H, *J* = 7.86 MHz, Ar-H), 7.86 (s, 2H, NH_2) ppm. ^{15}N NMR-GHSQC (400 MHz, $CDCl_3$, 25°C): δ = 7.86 (s, 2H, NH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ = 14.9, 64.5, 82.8, 83.9, 114.2, 115.6, 127.8, 128.3, 130.4, 134.2, 159.5, 162.0, 164.9. HRMS of $[C_{15}H_{12}N_4O + H]^+$ (*m*/*z*): Calcd for: 265.0125 Found: 265.0120.

2-Amino-4-(2-methoxyphenyl)-6-ethoxypyridine-3,5-dicarbinitrile (4b). MP: 189–190°C; ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ = 1.30 (t, 3H, *J* = 7.08 MHz, CH_3), 3.85 (s, 3H, OCH_3), 4.56 (q, 2H, *J* = 7.04 MHz, CH_2), 7.03–7.09 (m, 3H, Ar-H), 7.36 (d, 1H, *J* = 7.84 MHz, Ar-H), 7.84 (s, 2H, NH_2) ppm. ^{15}N NMR-GHSQC (400 MHz, $CDCl_3$, 25°C): δ = 7.84 (s, 2H, NH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ = 15.2, 56.2, 64.2, 83.1, 83.8, 114.4, 115.5, 120.2, 121.9, 128.1, 129.7, 130.8, 155.0, 160.8, 162.3, 165.4. HRMS of $[C_{16}H_{14}N_4O_2 + H]^+$ (*m*/*z*): Calcd for: 295.1105 Found: 295.1101.

2-Amino-4-(3-methoxyphenyl)-6-ethoxypyridine-3,5-dicarbinitrile (4c). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ = 1.38 (t, 3H, *J* = 7.06 MHz), 3.76 (s, 3H, OCH_3), 4.56 (q, 2H, *J* = 7.06 MHz, CH_2), 7.05 (d, 2H, *J* = 7.71 MHz, Ar-H), 7.52 (d, 2H, *J* = 7.66 MHz, Ar-H), 7.79 (s, 2H, NH_2) ppm. ^{15}N NMR-GHSQC (400 MHz, $CDCl_3$, 25°C): δ = 7.79 (s, 2H, NH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ = 15.1, 56.4, 63.8, 82.7, 83.9, 113.7, 114.6, 115.8, 128.5, 130.8, 159.8, 160.4, 163.2, 165.1 ppm. HRMS of $[C_{16}H_{14}N_4O_2 + H]^+$ (*m/z*): Calcd for: 295.0560 Found: 295.0562.

2-Amino-4-(2-chlorophenyl)-6-ethoxypyridine-3,5-dicarbinitrile (4d). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ = 1.47 (t, 3H, *J* = 7.06 MHz, CH_3), 4.58 (q, 2H, *J* = 7.10 MHz, CH_2), 7.22 (d, 2H, *J* = 7.78 MHz, Ar-H), 7.65 (d, 2H, *J* = 7.70 MHz, Ar-H), 7.81 (s, 2H, NH_2) ppm. ^{15}N NMR-GHSQC (400 MHz, $CDCl_3$, 25°C): δ = 7.81 (s, 2H, NH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ = 15.3, 64.7, 83.3, 83.9, 113.8, 114.6, 126.6, 128.3, 129.5, 130.1, 132.8, 137.1, 160.7, 163.4, 165.3. HRMS of $[C_{15}H_{11}ClN_4O + H]^+$ (*m/z*): Calcd for: 298.1015 Found: 298.1018.

2-Amino-4-(2-nirtophenyl)-6-ethoxypyridine-3,5-dicarbinitrile (4e). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ = 1.55 (t, 3H, *J* = 7.02 MHz, CH_3), 4.54 (q, 2H, *J* = 7.12 MHz, CH_2), 7.54 (d, 1H, *J* = 7.56 MHz, Ar-H), 7.80 (d, 2H, *J* = 7.94 MHz, Ar-H), 7.88 (s, 2H, NH_2), 8.10 (d, 1H, *J* = 8.22 MHz, Ar-H) ppm. ^{15}N NMR-GHSQC (400 MHz, $CDCl_3$, 25°C): δ = 7.88 (s, 2H, NH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ = 15.5, 64.9, 83.5, 83.9, 114.3, 115.3, 123.6, 128.2, 128.8, 129.8, 132.8, 143.8, 160.7, 163.6, 165.4. HRMS of $[C_{15}H_{11}N_5O_3 + H]^+$ (*m/z*): Calcd for: 310.1141 Found: 310.1141.

2-Amino-4-(4-bromophenyl)-6-ethoxypyridine-3,5-dicarbinitrile (4f). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ = 1.45 (t, 3H, *J* = 7.08 MHz, CH_3), 4.57 (q, 2H, *J* = 7.04 MHz, CH_2), 7.53 (d, 2H, *J* = 7.64 MHz, Ar-H), 7.59 (d, 2H, *J* = 7.64 MHz, Ar-H), 7.86 (s, 2H, NH_2) ppm. ^{15}N NMR-GHSQC (400 MHz, $CDCl_3$, 25°C): δ = 7.86 (s, 2H, NH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ = 14.8, 63.9, 83.4, 83.9, 114.2, 115.2, 121.0, 122.6, 128.6, 139.1, 159.8, 163.2, 165.8 ppm. HRMS of $[C_{15}H_{11}BrN_4O + 2H]^+$ (*m/z*): Calcd for: 344.0893 Found: 344.0889.

2-Amino-4-(4-dimethylaminophenyl)-6-ethoxypyridine-3,5-dicarbinitrile (4g). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ = 1.46 (t, 3H, *J* = 7.06 MHz, CH_3), 3.08 (s, 6H, $N(CH_3)_2$), 4.54 (q, 2H, *J* = 7.05 MHz, CH_2), 7.20 (d, 2H, *J* = 7.24 MHz, Ar-H), 7.74 (d, 2H, *J* = 7.80 MHz, Ar-H), 7.86 (s, 2H, NH_2) ppm. ^{15}N NMR-GHSQC (400 MHz, $CDCl_3$, 25°C): δ = 7.86 (s, 2H, NH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ = 14.8, 39.6, 63.7, 111.8, 113.9, 115.6, 126.4, 127.8, 154.6, 160.1, 163.2, 165.7 ppm. HRMS of $[C_{17}H_{17}N_5O + H]^+$ (*m/z*): Calcd for 308.0988 Found: 308.0984.

2-Amino-4-(2-bromophenyl)-6-ethoxypyridine-3,5-dicarbinitrile (4h). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ = 1.46 (t, 3H, *J* = 7.08 MHz, CH_3), 4.57 (q, 2H, *J* = 7.08 MHz, CH_2), 7.35 (d, 2H, *J* = 7.64 MHz, Ar-H), 7.65 (d, 2H, *J* = 7.80 MHz, Ar-H), 7.80 (s, 2H, NH_2) ppm. ^{15}N NMR-GHSQC (400 MHz, $CDCl_3$, 25°C): δ = 7.80 (s, 2H, NH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ = 15.3, 64.4, 83.0, 83.7, 113.8, 114.9, 121.6, 127.5, 129.7, 130.2, 132.6, 135.5, 159.8, 162.8, 165.2. HRMS of $[C_{15}H_{11}BrN_4O + 2H]^+$ (m/z): Calcd for: 344.0838 Found: 344.0844.

2-Amino-4-(furan-2-yl)pyridine-6-ethoxy-3,5-dicarbinitrile (4i). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ = 1.46 (t, 3H, *J* = 7.08 MHz, CH_3), 4.55 (q, 2H, *J* = 7.08 MHz, CH_2), 6.54 (t, 1H, Ar-H), 7.12 (d, 1H, *J* = 7.66 MHz, Ar-H), 7.78 (d, 1H, Ar-H), 7.85 (s, 2H, NH_2) ppm. ^{15}N NMR-GHSQC (400 MHz, $CDCl_3$, 25°C): δ = 7.85 (s, 2H, NH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ = 14.6, 63.6, 83.0, 83.8, 108.5, 111.2, 114.1, 115.2, 141.5, 150.2, 159.3, 163.4, 165.7 ppm. HRMS of $[C_{13}H_{10}N_4O_2 + H]^+$ (*m/z*): Calcd for: 255.0093 Found: 255.0103.

2-Amino-4-(4-fluorophenyl)-6-ethoxypyridine-3,5-dicarbinitrile (4j). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ = 1.47 (t, 3H, *J* = 7.06 MHz, CH_3), 4.57 (q, 2H, *J* = 7.07 MHz, CH_2), 7.17 (d, 2H, *J* = 6.98 MHz, Ar-H), 7.51 (d, 2H, *J* = 7.48 MHz, Ar-H), 7.88 (s, 2H, NH_2) ppm. ^{15}N NMR-GHSQC (400 MHz, $CDCl_3$, 25°C): δ = 7.88 (s, 2H, NH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ = 15.4, 64.5, 83.5, 84.5, 114.1, 115.8, 117.6, 130.7, 132.2, 142.9, 161.5, 163.6, 165.7 ppm. HRMS of $[C_{15}H_{11}FN_4O + H]^+$ (*m/z*): Calcd for: 283.1083 Found: 283.1079.

2-Amino-4-(4-(trifluoromethyl)phenyl)-6-ethoxypyridine-3,5-dicarbinitrile (4k). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ = 1.47 (t, 3H, *J* = 7.06 MHz, CH_3), 4.59 (q, 2H, *J* = 7.08 MHz, CH_2), 7.54 (d, 2H, *J* = 7.7 MHz, Ar-H), 7.62 (d, 2H, *J* = 8.1 MHz, Ar-H), 7.85 (s, 2H, NH_2) ppm. ^{15}N NMR-GHSQC (400 MHz, $CDCl_3$, 25°C): δ = 7.85 (s, 2H, NH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ = 15.5, 63.8, 83.4, 84.2, 114.5, 115.3, 123.7, 124.8, 126.7, 130.3, 139.6, 159.8, 163.5, 165.6 ppm. HRMS of $[C_{16}H_{11}F_3N_4O + H]^+$ (*m/z*): Calcd for: 333.1162 Found: 333.1166.

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REFERENCES AND NOTES

[1] Orru, R. V. A.; Ruijter, E. Synthesis of Heterocycles via Multicomponent Reactions I & II (Topics in Heterocyclic Chemistry); Springer: Heidelberg, 2010.

[2] Fredholm, B. B.; Ijzerman, A. P.; Jacobson, K. A.; Klotz, K. N.; Linden, J. Pharmacol Rev 2001, 53, 527.

[3] Schwoerer, M.; Volf, V. C. Organic Molecular Solids; Wiley-VCH: Weinheim, 2005.

[4] Ruijter, E.; Scheffelaar, R.; Orru, R. V. A. Angew Chem Int Ed 2011, 50, 6234.

[5] Burke, M. D.; Schreiber, S. L. Angew Chem Int Ed 2004, 43, 46.

[6] Reinhardt, D.; Ilgen, F.; Kralisch, D.; Konig, B.; Kreisel, G. Green Chem 2008, 10, 1170.
[7] Gu, Y Green Chem 2012, 14, 2091.
[8] Zhu, J.; Bienayme, B. Multicomponent Reactions; Wiley-VCH: Weinheim, 2005.
[9] Maddila, S.; Dasireddy, V. D. B. C.; Jonnalagadda, S. B. Appl Catal B: Environ 2014, 150, 305.
[10] Maddila, S.; Dasireddy, V. D. B. C.; Jonnalagadda, S. B. Appl Catal B: Environ 2013, 138, 149.
[11] Satavisha, S.; Das, D. K.; Khan, A. T. RSC Adv 2014, 4, 53752.
[12] Chen, M. Z.; Micalizio, G. C. J Am Chem Soc 2012, 134, 1352.
[13] Sangshetti, J. N.; Zambare, A. S.; Khan, F. A.; Gonjari, I.; Zaheer, Z. Mini Rev Med Chem 2014, 14, 988.
[14] Davari, A. S.; Abnous, K.; Mehri, S.; Ghandadi, M.; Hadizadeh, F. Bioorg Chem 2014, 57, 83.
[15] Janardhan, B.; Vijayalaxmi, S.; Rajitha, B. J. Heterocyc Chem 2013, 50, 1230.
[16] Salem, M. S.; Sakr, S. I.; El-Senousy, W. I.; Madkour, H. M. F. Archiv Der Pharmazie 2013, 346, 766.
[17] Luo, Y.; Hu, Y. Archiv Der Pharmazie 2006, 339, 262.
[18] Girgis, A. S.; Mishriky, N.; Ellithey, M.; Hosni, H. M.; Farag, H. Bioorg Med Chem 2007, 15, 2403.
[19] Shi, F.; Li, C.; Xia, M.; Miao, K; Zhao, Y.; Tu, S.; Zheng, W.; Zhang, G.; Ma, N. Bioorg Med Chem Lett 2009, 19, 5565.
[20] Basnet, A.; Thapa, P.; Karki, R.; Na, Y.; Jahng, Y.; Byeong-Seon, J.; Jeong, T. C.; Lee, C.-S.; Lee, E.-S. Bioorg Med Chem 2007, 15, 4351.
[21] Puerstinger, G.; Paeshuyse, J.; Heinrich, S.; Mohr, J.; Schraffl, N.; Clercq, E. D.; Neyts, J. Bioorg Med Chem Lett 2007, 17, 5111.
[22] Karimi, A. R.; Khodadadi, A. Lett Org Chem 2012, 9, 422.
[23] Fuentes, L.; Lorenzo, M. .; Galakhov, M.; Marquez, C.; Martin, A.; Gomez-Sal, P. Chem Commun 2000, 18, 1775.
[24] Evdokimov, N. M.; Magedov, I. V.; Kireev, A. S. Org Lett 2006, 8, 899.
[25] Ranu, B. C.; Jana, J.; Sowmiah, S. J. Org Chem 2007, 72, 3152.
[26] Sridhar, M.; Ramanaiah, B. C.; Narsaiah, C.; Mahesh, B.; Kumaraswamy, M.; Mallu, K. K. R.; Ankathi, V. M.; Rao, P. S. Tetrahedron Lett 2009, 50, 3897.
[27] Mamgain, R.; Singh, R.; Rawat, D. S. J. Heterocycl Chem 2009, 46, 69.
[28] Kantam, M. L.; Mahendar, K.; Bhargava, S. J. Chem Sci 2010, 122, 63.
[29] Singh, K. N.; Singh, S. K. Arkivoc 2009, xiii, 153.
[30] Shinde, P. V.; Sonar, S. S.; Shingate, B. B.; Shingare, M. S. Tetrahedron Lett 2010, 51, 1309.
[31] Xin, X.; Wang, Y.; Kumar, S.; Liu, X.; Lin, Y.; Dong, D. Org Biomol Chem 2010, 8, 3078.
[32] Maddila, S.; Rana, S.; Pagadala, R.; Maddila, S.; Jonnalagadda, S. B. Catal Commun 2015, 61, 26.
[33] Maddila, S.; Jonnalagadda, S. B. Bull Chem Soc Ethiop 2012, 26, 121.
[34] Maddila, S.; Jonnalagadda, S. B. Bull Chem Soc Ethiop 2012, 26, 1.
[35] Maddila, S.; Jonnalagadda, S. B. J. Chile Chem Soc 2012, 57, 1099.
[36] Maddila, S.; Dasireddy, V. D. B. C.; Oseghe, E. O.; Jonnalagadda, S.B. Appl Catal B: Environ 2013, 142, 129.
[37] Chetty, E. C.; Maddila, S.; Southway, C.; Jonnalagadda, S. B. ACS-Indu & Eng Chem Res 2012, 51, 2864.