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FULL PAPER

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A green, efficient and recoverable CeO_2/MWCNT nanocomposite catalyzed click synthesis of pyridine-3-carboxamides

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A facile, green and environmentally-friendly protocol for the preparation of ceria doped multi-walled carbon nanotubes (2.5%CeO_2/MWCNTs) composite catalysts are developed. The synthesized catalyst materials have been characterized by using P-XRD, SEM, TEM and BET analysis. Further, the composite was utilized as a highly efficient and reusable heterogeneous nano-catalyst for the synthesis of pyridine-3-carboxamide derivatives by multicomponent condensation of acetoacetanilide, ammonium acetate, substituted aromatic aldehyde and ethyl cyanoacetate via one-pot reaction under ethanol solvent conditions at R.T. The remarkable advantages of this green protocol exhibits operational simplicity, easy workup procedure, inexpensive, evading of toxic solvents, shorter reaction times ($\leq$ 15 mins), excellent yields and also avoidance of column chromatography. Furthermore, the catalyst was recyclable and reusability endured for a minimum of six consecutive cycles without significant loss in the catalytic activity.

KEYWORDS

green synthesis, multicomponent reactions, one-pot reaction, Pyridine-3-carboxamides, synthesized catalyst

1 | INTRODUCTION

Multi-component reactions (MCRs) are a synthetic methodology involving the preparation of a large moiety in superior yields through the combination of two or more reactants at a time in a single-step reaction.[1–3] Primarily, MCRs are an ultimate conversion method to rapidly-produce functionally varied frameworks for agricultural, chemical, combinatorial and pharmaceutical chemistry fields owing to high atom efficiency, saves time and energy as well, thus serving as a diversified approach for the synthesis of new organic complex molecules.[3,4] Further, MCRs show many benefits like operational simplicity, short reaction times, mild reaction conditions, using inexpensive reagents and catalysts, synthetic efficiency, diminished by-products, and higher yields.[4–6] Consequently, the scheming of innovative MCRs is a vital and gorgeous task.

Nowadays, heterogeneous solid catalysts are extensively used for chemical reactions and industrial processes.[7] They offer various advantages over the homogeneous catalysts like simple handling, extended stability, simple recyclability and reusability without loss in activity, and low-cost of the catalyst which can make synthetic procedures very safer, cleaner, non-toxic, and greener.[8–11] Particularly, nano-catalysts owing to their vast surface area and more catalytic active sites, are mostly accountable for their admirable catalytic activity.

Multi-walled carbon nanotubes (MWCNTs) are nested forms of single-walled carbon nanotubes.[12] The doping of multi-walled carbon nanotubes with some competent materials has prominent applications in various fields due to their unique properties which include large surface area, porous structure, morphologies, and improved mechanical, thermal and electrical properties.[13] Mainly MWCNTs as supports provide a large surface area for high dispersal of catalysts, excellent crystallinity, distinctive porosity, assisting electron conveyance for the length of reactions and worthy interaction between the carbon support and nanoparticles.[13,14] On the other hand, metal oxides are significant nanomaterials used in various fields of chemistry particularly in heterogeneous catalysis areas. In recent times, more attention has been focused on an eco-friendly transition metal oxide ceria (CeO_2) due to its non-hazardous, inexpensive, easy accessibility, non-volatility, high chemical and thermal stability. Mostly, the usage of heterogenized version of ceria is a desirable choice for green organic transformations.[15–17] Therefore, CNTs with metal oxides have been broadly examined to obtain loaded catalysts, which effectively cartels the benefits of metal oxide with CNTs and offers an extensive potential application.

Heterocyclic frameworks are utilized as a significant class of bioactive drug targets in the potent biological and medicinal agents.[18,19] Particularly, pyridines and their derivatives are a vital class of heterocyclic molecules due to their application in several fields like drug discovery, natural products, and functional materials. Pyridines exhibit a broad range of various biological properties, like anti-psychotic,[20] anti-inflammatory,[21] antitumor,[22] antimicrobial,[23] antioxidant,[24] anti-tubercular,[25] anti-proliferative,[26] anti-leishmanial,[27] anticonvulsant,[28] anti-diabetic[29] and anti-malarial[30] activities. Moreover, these are useful as pesticides, herbicides, insecticidal and dye-stuff agents.[31–33] Literature study shows that several synthetic procedures have been published for the synthesis of different pyridine scaffolds using catalysts such as *p*-toluenesulfonic acid,[34] Indium triflate,[35] TEA[36] and NaOH.[37] Even though several reported techniques are effective, nevertheless suffer from weaknesses like prolong reaction times, low product yields, harsh reaction conditions, expensive catalysts, toxic solvents, and reagents, difficult handling and hard work-up process. Additionally, the main drawback is that the catalysts are not recyclable. For that reason, the instigation of a simple, efficient and enhanced environmentally-benign protocol to the synthesis of novel pyridine-3-carboxamide derivatives is still indispensable.

Reinforced with the encouraging biological activities displayed by the diverse heterocycle privileged scaffolds and our sustained research focus on the synthesis of medicinally fascinating heterocyclic molecules,[38–42] recently we have developed various heterocyclic molecules using efficient green protocols.[8,43–46] Herein the synthesis of new ceria doped MWCNT catalysts and its efficacy in the C–C bond evolving reactions is portrayed. We report 2.5% CeO_2/MWCNTs to catalyze the multicomponent reaction of acetoacetanilide, ammonium acetate, aromatic aldehyde and ethyl cyanoacetate under mild reaction conditions. This protocol is found to be an efficient and excellent catalyst for the synthesis of pyridine-3-carboxamides in aqueous ethanol medium for the first time.

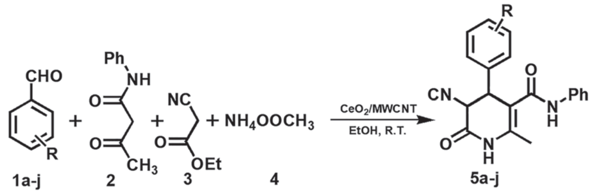
2 | EXPERIMENTAL SECTION

2.1 | Synthesis of ceria doped multi-walled carbon nanotubes (CeO_2/MWCNTs) nano-catalysts

Initially, MWCNTs were preserved with a mixture of concentrated sulfuric acid and concentrated nitric acid (0.5 M H_2SO_4: 2.5 M HNO_3) and sonicated for 5 hr at 60 °C. Next, the MWCNTs material was afforded by washing with deionized water. Then, it was vacuum dried at 120 °C. Further, the supported catalyst was prepared by adding synthesized MWCNTs to a solution comprising weight percentage (1, 2.5 & 5 wt%) of cerium nitrate (Ce $(NO_3)_3$, Aldrich). The mixture was sonicated for 1 hr and stirred at R.T. for 12 hr after which the resultant slurry was filtered under air vacuum. Furthermore, it was dried in an oven at 110 °C for 4 hr and calcined at 400 °C for 6 hr to afford (1, 2.5 & 5 wt%) of CeO_2/MWCNTs catalysts.

2.2 | General procedure for the synthesis of pyridine-3-carboxamides (5a–j)

In a round bottom flask, a mixture of acetoacetanilide (1 mmol), ammonium acetate (1.1 mmol), substituted aromatic aldehyde (1 mmol), ethyl cyanoacetate (1 mmol) and 2.5%CeO_2/MWCNTs (30 mg) was stirred in the presence of EtOH solvent (99.9%, 10 ml) at room temperature (R.T) for 15 min (Scheme 1). The completion of the



SCHEME 1 Synthesis of novel pyridine-3-carboxamide derivatives

reaction was monitored by TLC (7:3 ratio n-Hexane: EtOAc). Then the catalyst was separated by simple filtration. Further, the EtOH solvent of the filtrate was concentrated and dried under reduced pressure to obtain pure products with excellent yields (**5a-j**). Instrumental details and target molecules characterization data (^{1}H-NMR, ^{15}N NMR and ^{13}C-NMR) are included in the supporting information (S1).

3 | RESULTS AND DISCUSSIONS

3.1 | Catalyst characterization

3.1.1 | SEM analysis

The surface morphology of the synthesized CeO_2/MWCNT nanoparticles was examined by using SEM analysis. The SEM micrograph exhibits a comparatively uniform and equivalent particle dispersal. Ceria nanoparticles nurtured homogeneously on MWCNTs. Figure 1a displays that the aggregated fluffy particles of ceria along with tube-like MWCNTs perceived in the surface morphology. Additionally, the SEM-EDS investigation was used to study the CeO_2 doped MWCNTs nano-catalyst. The EDS analysis reveals that the nano-catalyst mostly consisted of Ce, C and O elements, which evidences that the CeO_2/MWCNTs were efficiently prepared (Figure 1b).

3.1.2 | TEM analysis

The TEM image of the CeO_2/MWCNT is shown in Figure 2. The micrograph reveals that the average crystallite size of the catalyst is 15–25 nm and also in good concord with the P-XRD analysis. The TEM micrograph endorses that ceria particles are equally settled on MWCNT. Further, the selected area electron diffraction (SAED) image displays the fastening of the crystalline structure of ceria particles on the MWCNTs.

3.1.3 | BET surface analysis

Figure 3 displays N_2 adsorption–desorption isotherm of 2.5% CeO_2/MWCNT catalyst sample. The isotherm of CeO_2/MWCNT is a type-IV with an H2 hysteresis loop, which concurs with the presence of mesoporous structured material and the P/Po range is 0.69–0.98. The isotherm of CeO_2/MWCNT nanocomposite revealed a BET specific surface area of 111.67 m^2g^{-1}, a pore volume of 0.65 cm^3/g and pore size of 23.8 nm owing to the mesoporous and high surface area of the material.

3.1.4 | P-XRD analysis

The diffraction peaks of CeO_2 are observed at 2θ of 28.7°, 33.2°, 47.5°, 56.3°, 59.3°, 69.8°, 76.6° and 79.4°, which correspond to the (111), (200), (220), (311), (222), (400), (331) and (420), respectively, which conform with the JCPDS data file No. 43–100254-0964 (Fig. The representative peaks at 2θ of 26.1°and 43.1° are ascribed to the (002) and (010) planes of the MWCNTs, which are approved with the JCPDS data file No. 75–1621. Further, the peaks observed in the diagram match the polycrystalline nature of the catalyst (Figure 4). The average crystallite size of the material was 7.8 nm based on the maximum intensity diffraction peaks of ceria doped MWCNT using the Scherrer formula.

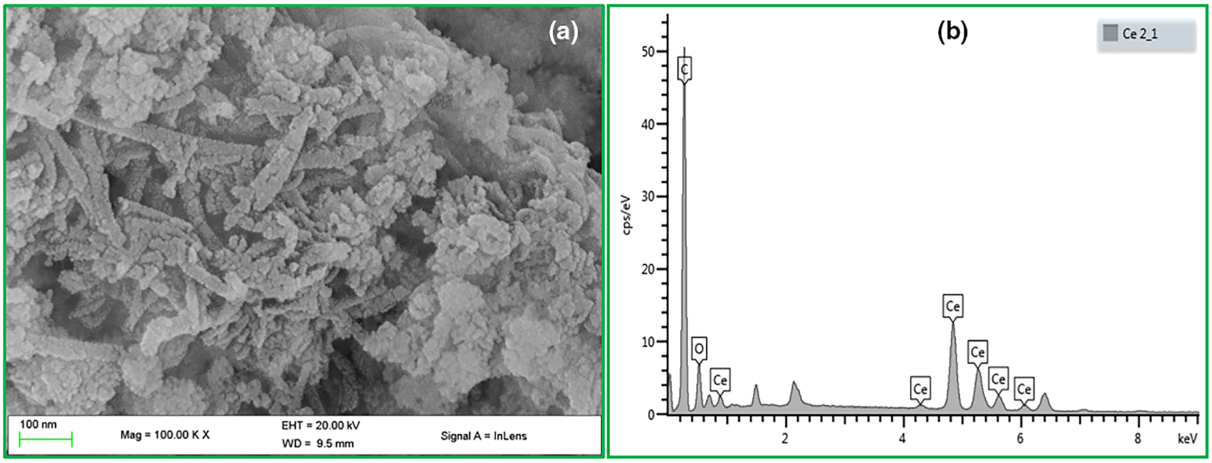


FIGURE 1 SEM micrograph of (a) 2.5% CeO_2-MWCNT and (b) SEM–EDX catalyst

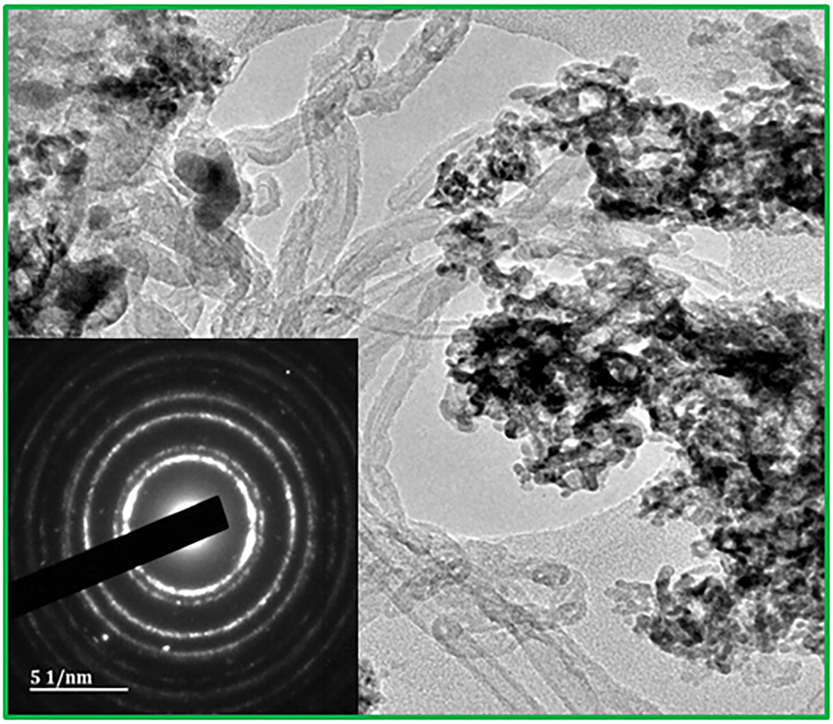


FIGURE 2 A TEM micrograph of 2.5% CeO_2/MWCNT catalyst

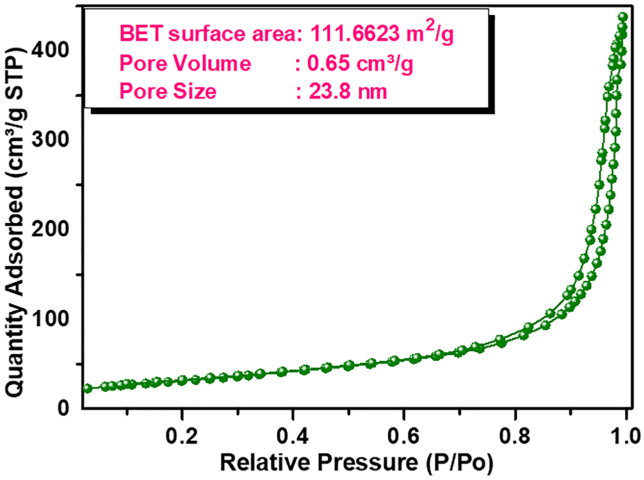


FIGURE 3 N_2 absorption and desorption isotherms of 2.5% CeO_2MWCNT catalyst

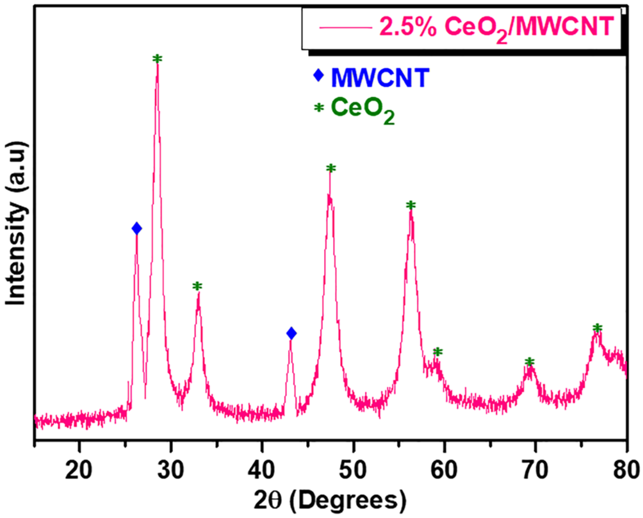


FIGURE 4 P-XRD spectra of 2.5% CeO_2/MWCNT catalyst

3.1.5 | Optimization of reaction conditions

The pilot reaction containing equal molar of acetoacetanilide, ammonium acetate, 4-methoxybenzaldehyde, and ethyl cyanoacetate as reactants were experimented under different reaction conditions like presence/absence of several catalysts, using various solvents and temperature conditions to improve the reaction conditions. Initially, the reaction was conducted under the absence of catalyst in EtOH solvent, but the reaction did not progress and no product yielded even after 12 hr at R. T and reflux conditions (Table 1, entry 1 & 2). Then the reaction was ventured with several varieties of inorganic and organic acidic catalysts like CH_3COOH, $FeCl_3$, H_3PO_4, and BF_3 in EtOH as a solvent, no product was formed at R. T after 6 hr (Table 1, entries 3–6). Next, the same reaction was carried out with various basic catalysts such as TEA, pyridine, Na_2S, and urea in ethanol systems, which generated low product yields (Table 1, entries 7–10). The same reaction was then tested by pure metal oxide/non-metal oxide catalysts like ceria, titania, silica, and MWCNT in EtOH at R.T. The desired product was obtained in moderate yields only after 2 hr. Further to enhance the efficacy of the model reaction, a

TABLE 1 Optimum conditions for the preparation of trial reaction by 2.5%CeO_2/MWCNT catalyst[a]

Entry	Catalyst	Solvent	Temperature	Time (hr)	Yield (%)[b]
1	--	EtOH	RT	12	--
2	--	EtOH	Reflux	12	--
3	CH_3COOH	EtOH	RT	6	--
4	$FeCl_3$	EtOH	RT	6	--
5	H_3PO_4	EtOH	RT	6	--
6	BF_3	EtOH	RT	6	--
7	TEA	EtOH	RT	6.0	13
8	Pyridine	EtOH	RT	5.0	19
9	Na_2S	EtOH	RT	6.0	10
10	Urea	EtOH	RT	5.5	21
11	CeO_2	EtOH	RT	2.1	78
12	SiO_2	EtOH	RT	3.5	51
13	TiO_2	EtOH	RT	4.5	48
14	MWCNT	EtOH	RT	2.5	69
15	2.5% CeO_2/MWCNT	EtOH	RT	0.25	97
16	1% CeO_2/MWCNT	EtOH	RT	0.50	89
17	5% CeO_2/MWCNT	EtOH	RT	0.25	96

[a] 4-Methoxybenzaldehyde (1 mmol), acetoacetanilide (1 mmol), ammonium acetate (1.1 mmol), ethyl cyanoacetate (1 mmol) and 2.5%CeO_2/MWCNTs (30 mg).

[b] Isolated yields. -- No reaction.

combination of the two solid materials, 2.5% CeO_2 loaded on MWCNTs was utilized as a catalyst, an MCR reaction progressed with a remarkable product yield (97%) of target pyridine-3-carboxamide at R. T in 15 min.

Solvents play a crucial role in the selectivity and yields of the MCRs. Therefore, we examined the influence of different solvents (non-polar, aprotic and protic) on the trial reaction. No anticipated product obtained, when solvent-free and non-polar solvents like toluene, n-hexane, and 1,4-dioxane were used. Next, low yields were observed with polar aprotic solvents like acetonitrile, and THF. Fascinatingly, when the reaction was studied with polar solvents like EtOH, MeOH, $(Me)_2CHOH$, H_2O and miscible mixture of aqueous EtOH (1:1) respectively, the target molecule yields were moderate to excellent (Table 2). Interestingly, the highly polar solvent (EtOH), which can generate some heat, hence quickly supplies optimal surroundings for the production of intermediates on the solid surface and its subsequent conversion to final molecules. In the perception of the green principle, eco-friendliness, remarkable yields and short reaction time, EtOH proved to be the best solvent for the current protocol.

TABLE 2 Optimum solvent conditions for the synthesis of model reaction by 2.5% CeO_2/MWCNT catalyst[a]

Entry	Solvent	Time (hr)	Yield (%)
1	--	4.0	--
2	Toluene	4.0	--
3	n-hexane	4.0	--
4	Dioxane	4.0	--
5	MeCN	3.0	45
6	THF	2.5	51
7	EtOH	0.25	97
8	isopropyl alcohol	1.0	89
9	MeOH	0.50	93
10	H_2O	2.0	15

[a] 4-Methoxybenzaldehyde (1 mmol), acetoacetanilide (1 mmol), ammonium acetate (1.1 mmol), ethyl cyanoacetate (1 mmol) and 2.5%CeO_2/MWCNTs (30 mg).

-- No solvent/No reaction

After obtaining the above results, we studied the effect of a catalytic amount of ceria doped MWCNTs on the synthesis of pyridine-3-carboxamide (Table 3). The reaction evidenced that when the quantity of catalyst material was reduced from 30 mg to 10 mg, the product yield decreased from 97% to 83% and reaction time also increased. Next, when the amount of catalyst material was augmented from 30 mg to 60 mg, the product yield slightly reduced from 97% to 94%. Therefore, 30 mg of

TABLE 3 Optimization of the quantity of by 2.5% CeO_2/ MWCNT catalyst in the reaction

Entry	Catalyst (mg)	Time (min)	Yield (%)
1	10	90	83
2	20	45	89
3	30	15	97
4	40	15	97
5	50	15	95
6	60	20	94

CeO_2/MWCNTs catalyst, which afforded product yield (97%), was adequate to endorse the reaction.

To ensure the reproducibility of this protocol and to simplify the optimal circumstances, various substituted aldehydes bearing both electron-withdrawing and/or electron-donating groups were selected for the generation of different types of pyridine-3-carboxamide derivatives (Table 4). Both electron-withdrawing/electron-donating groups on the aromatic ring (o/p/m) of the aldehydes reacted well to afford the resulting target molecules in excellent yields. However, it reveals that electronic effects do not play much role in the desired product yields. Target molecules characterization data (^{1}H-NMR, ^{15}N NMR, ^{13}C-NMR and HR-MS) are included in the supporting information (S2).

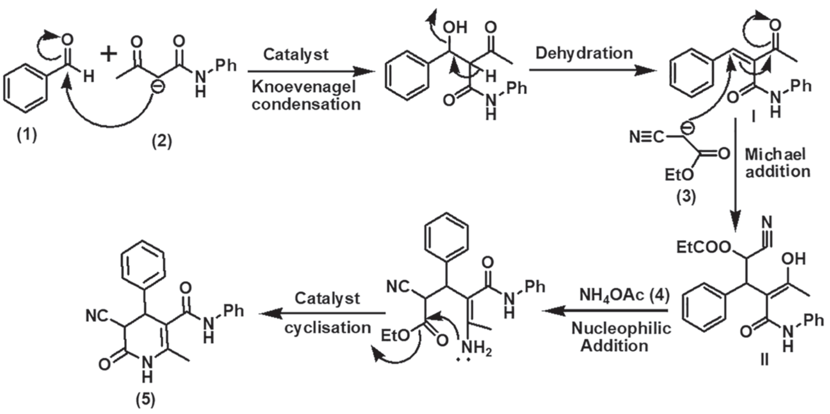
TABLE 4 Synthesis of pyridine-3-carboxamide catalyzed by 2.5% CeO_2/MWCNT catalyst

Entry	R	Product	Yield (%)	m.p °C
1	4-OMe-C_6H_4	**5a**	97	228–230
2	3-OMe-C_6H_4	**5b**	95	236–235
3	4-Cl-C_6H_4	**5c**	93	211–212
4	2-F-C_6H_4	**5d**	94	251–252
5	2-NO_2-C_6H_4	**5e**	90	209–210
6	2-OMe-C_6H_4	**5f**	97	259–261
7	H	**5 g**	93	242–243
8	Pyridyl	**5 h**	90	271–272
9	2-Cl-C_6H_4	**5i**	92	205–206
10	2,6-OH-C_6H_4	**5j**	93	218–219

The plausible reaction mechanism for the synthesis of pyridine-3-carboxamide, based the investigational consequences is showed in Scheme 2. First reaction includes the Knoevenagel condensation between an aryl aldehyde (1) and acetoacetanilide (2) to obtain intermediate **I**. Subsequently, up on dehydration, Michael addition follows with active ethylcyanacetate (3), ensuing in the generation of intermediate **II**. Further, its reactive ketone functional group being reacted with NH_4OAc (4), amino substitution occurs, via nucleophilic addition. The amidation reaction takes place between the amino group and ester, prior to the cyclization to afford target molecule (5). The reaction intermediates were confirmed by the HRMS analysis and included in the supporting information (S3).

3.1.6 | CeO_2/MWCNT catalyst recyclability

In view of environmental friendliness and cost-effectivity, the test of recyclability and reusability of the solid catalyst was carried out for the reaction between acetoacetanilide, ammonium acetate, 4-methoxybenzaldehyde and ethyl cyanoacetate under optimum reaction conditions. After completion of the first run, the catalyst was separated, systematically washed with EtOH solvent, and dried at 120 °C under vacuum oven. Then it was reused in the next run. It was found that, the catalyst exhibited superb catalytic activity up to six consecutive cycles without any significant reduction in desired target yields (Figure 5). Based on the above result, it displays that the catalyst leaching is very small. Moreover, the catalyst after the reaction was investigated by SEM-EDS incorporated (Figure 6). This



SCHEME 2 Proposed mechanism of pyridine-3-carboxamide derivatives

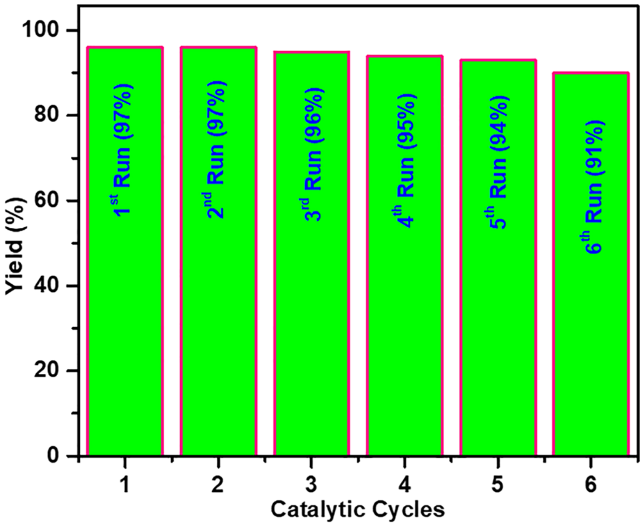


FIGURE 5 Recyclability of the CeO_2/MWCNT nanocomposite catalyst

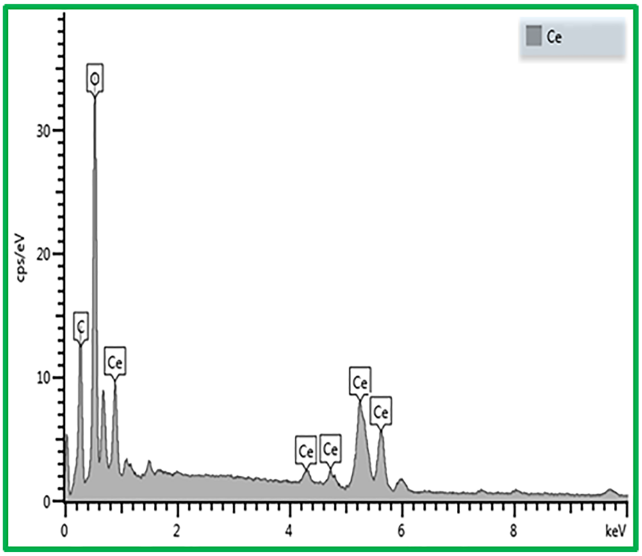


FIGURE 6 SEM-EDS micrograph of Reused 2.5% CeO_2-MWCNT catalyst

elemental pattern of the recycled catalyst is much equal to that of the fresh one, which shows that there is no such attrition of the active material from the support.

4 | CONCLUSION

In conclusion, we have exhibited an efficient and green protocol to synthesize pyridine-3-carboxamide derivatives with opportune heterocyclic scaffolds, through the multicomponent reaction of acetoacetanilide, ammonium acetate, substituted aldehydes and ethyl cyanoacetate in the presence of ceria loaded MWCNTs nanocomposite as heterogeneous catalyst. The present method suggests various benefits including low catalyst support, effortless operation, clean reaction profiles, mild reaction conditions, environmentally friendly, cost-effectiveness, short reaction times, excellent yields, demanding no chromatographic purification and catalyst recyclability for several times without loss of activity.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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