



Green Protocol Synthesis of (*E*)-2-Arylmethylene) Hydrazinecarbothioamides Using Reusable Heterogeneous Ceria Promoted Lanthanum Catalyst

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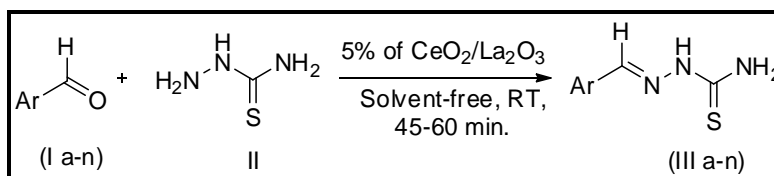
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ABSTRACT

A series of (*E*)-2-(Arylmethylene)hydrazinecarbothioamide compounds were synthesized by condensation of thiosemicarbazide with substituted aromatic aldehydes by using 5% of CeO₂/La₂O₃ as heterogeneous reusable catalyst under solvent-free condition. The synthesized compounds were characterized by spectral data such as IR and NMR spectra and the catalyst was characterized by using X-ray powder diffraction (XRD), Fourier transform infrared spectroscopy (FT-IR), Scanning electron microscopy (SEM), Brunauer-Emmett-Teller (BET) Surface Area, Energy Dispersive X-ray Spectrometry (EDS) and UV-Visible DRS.

Graphical Abstract



Synthesis of (*E*)-2-(Arylmethylene)hydrazinecarbothioamide (IIIa-n)

Keywords: Schiff's bases, Thiosemicarbazide, Ceria promoted Lanthanum catalyst, Solvent-free reactions.

INTRODUCTION

Schiff bases and their derivatives are extensively studied due to their wide range of applications includes activities as pharmacological [1, 2], catalytic [3, 4], crystal engineering [5], anti-corrosion agent [6]. The hydrazone derivative show many physiological activities such as antimicrobial [7], antibacterial [8], antifungal [9], antitubercular [10], anti-HIV [11] and anticancer activities [12]. Hydrazones constitute an important class of biologically active drug molecules for example of Iproniazide [13] and Nifuroxazide. The literature review of hydrazones lone pair on trigonally hybridized nitrogen atom of the azomethine group responsible for pharmacological activities [14].

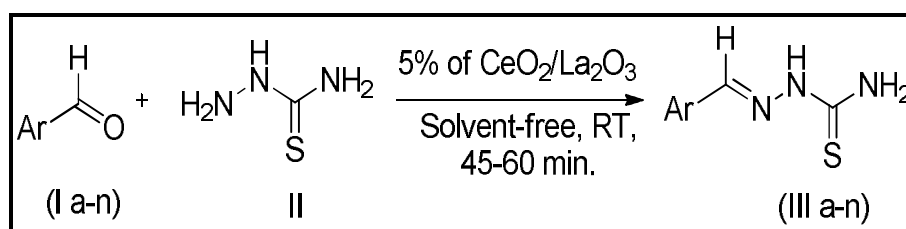
The previous methodologies for synthesis of hydrazones have various drawbacks such as long reaction times, tedious reaction conditions, with low yields and specially non-ecofriendly. Nowadays, multidisciplinary nature of Green Chemistry is recognized worldwide as a route to the development of chemical products and processes with lower environmental impact. In the recent year, use of recyclable metal catalyst in organic synthesis have been developed to reduce the reaction times, less by product formation, easy workup procedure and more eco-friendly. Hence researchers focus on selection and preparation of recyclable and reusable metal catalysts with low toxicity and more selectivity. In the view of green chemistry protocol and metal catalyst properties, we have developed a new solvent-free approach (*E*)-2-(Arylmethylene) hydrazinecarbothioamide by using 5% of CeO₂/La₂O₃ reusable heterogeneous catalyst.

MATERIALS AND METHODS

FTIR (KBr) spectra were recorded on a Shimadzu FT-IR-8400s spectrophotometer. The powder X-ray diffraction pattern has been recorded on a Siemens D-5000 diffract meter by using Cu K radiation source and a Scintillation counter detector. The XRD phases present in the samples were identified with the help of JCPDS data files. The BET surface area was determined by Nitrogen physisorption at liquid Nitrogen temperature on a Micromeritics Gemini 2360 instrument. Prior to measurements, samples were oven-dried at 393°K for 10 h and flushed with Argon gas for 1 h. Melting points were determined in open capillary tubes and are uncorrected. The purity of the compounds was checked by TLC using precoated silica gel plates 60₂₅₄(Merck). ¹H NMR spectra were recorded on Bruker Avance II 400 MHz spectrometer using tetramethylsilane as an internal standard.

General procedure for the synthesis of (*E*)-2-(Arylmethylene)hydrazinecarbothioamide (IIIa-n):

A mixture of aldehydes (**Ia-n**) (1 mmol), Thiosemicarbazide (**II**) (1mmol) and 5% of CeO₂/La₂O₃ (30 mg) as a catalyst was taken into round bottom flask then stirred at room temperature (**Table-1**). The progress of the reaction monitored by TLC, after completion of the reaction the mixture poured into ice cold water and the catalyst was separated out by using ethyl acetate. The organic layer concentrated under reduced pressure and the compound purified with column chromatography using silica gel, ethyl acetate and petroleum ether used as eluent to afford pure Schiff's bases (**IIIa-n**). The reaction carried out by using various solvent to optimize the reaction condition it is found that the maximum yield was obtained under solvent free condition (**Table 2**).



Scheme 1. Synthesis of (*E*)-2-(Arylmethylene)hydrazinecarbothioamide (**IIIa-n**)

Preparative method for 5% of CeO₂/La₂O₃: Dissolved Lanthanum nitrate hexahydrate (50 gm) in dist. water and 0.1 M ammonium hydroxide was added still white precipitate formation. The precipitate compound filtered using Buchner funnel and washed with ammonium hydroxide then the compound dried under oven at 150°C for 12 h. The pulverised Lanthanum (III) hydroxide (25 gm) of dissolved in dist. water and added Ceric ammonium nitrate [(NH₄)₂Ce(NO₃)₆], then heated on water bath up to dry precipitate is formed. The compound dried under oven 150°C for overnight and further calcinations at 650°C for 4 h to obtain pure pulverised 5% of CeO₂/La₂O₃.

Table 1. Physical data of (*E*)-2-(Arylmethylene)hydrazinecarbothioamide (IIIa-n)

| Compound (AR) | M.P (°C) | Reaction time (h) | Yield (%) | Compound (AR) | M.P (°C) | Reaction time (h) | Yield (%) |
|------------------------|----------|-------------------|-----------|----------------------------------|----------|-------------------|-----------|
| IIIa) phenyl | 157-158 | 50 | 96 | IIIh) 3-hydroxy-4-methoxy phenyl | 132-134 | 60 | 93 |
| IIIb) 4-meyhoxy phenyl | 182-183 | 55 | 93 | IIIi) 3,4-dimethoxy phenyl | 155-157 | 55 | 94 |
| IIIc) 2-chloro phenyl | 207-210 | 60 | 92 | IIIj) 3,4,5-trimethoxy phenyl | 161-163 | 60 | 92 |
| III d) 4-chloro phenyl | 210-211 | 55 | 95 | IIIk) 3,4-dichloro phenyl | 182-184 | 60 | 90 |
| IIIe) 4-methyl phenyl | 169-170 | 50 | 92 | III l) 2-furfuryl | 145-147 | 55 | 94 |
| III f) 3-nitro phenyl | 215-216 | 50 | 90 | III m) 2-thionyl | 161-163 | 55 | 94 |
| III g) 4-nitro phenyl | 223-224 | 45 | 97 | III n) naphthyl | 158-160 | 50 | 96 |

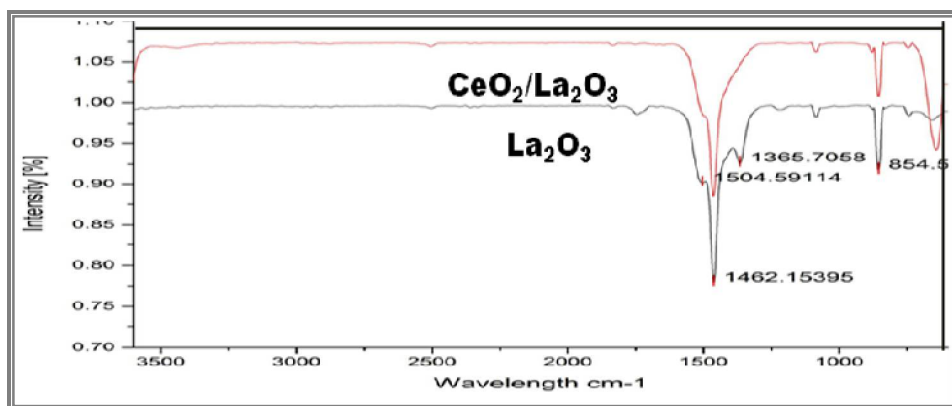
Table 2. Optimization of catalyst with different organic solvents.

| Entry | Reagent | solvent | Reaction time (min.) | Yield ^a (%) |
|-------|--|--------------|----------------------|------------------------|
| 1 | CeO ₂ /La ₂ O ₃ | Acetonitrile | 90 | <80% |
| 2 | CeO ₂ /La ₂ O ₃ | Chloroform | 120 | 80% |
| 3 | CeO ₂ /La ₂ O ₃ | DMF | 90 | 85% |
| 4 | CeO ₂ /La ₂ O ₃ | Ethanol | 150 | 80% |
| 5 | CeO ₂ /La ₂ O ₃ | t-butanol | 150 | 80% |
| 6 | CeO ₂ /La ₂ O ₃ | Neat | 45 | 97% |
| 7 | CeO ₂ /La ₂ O ₃ | water | 60 | 90% |

^a isolated yield

RESULTS AND DISCUSSION

Catalyst characterization: The FT-IR spectrum of La₂O₃ and CeO₂/La₂O₃ shows two characteristic stretching frequencies around 1462 and 854 cm⁻¹ (Figure 1). The peak around 1462 cm⁻¹ is representing presence oxide and the peak found at 854 cm⁻¹ is characteristics of crystalline La₂O₃. Basis on FT-IR data it concludes that the crystalline La₂O₃ do not changes with Ceria.

Figure 1 IR Spectra of La₂O₃ and CeO₂/La₂O₃

Spectral data

IIIa. (*E*)-2-benzylidenehydrazinecarbothioamide: IR spectrum, ν , cm⁻¹: 1098, 1602, 1736 and 3444; ¹H NMR (CDCl₃, ppm): δ 6.77 (bs, 1H, NH), 7.28-7.40 (m, 4H, ArH & NH), 7.64-7.66 (m, 2H, ArH), 7.58-7.60 (d, 2H, ArH), 8.20 (s, 1H, CH=N), 10.57 (bs, 1H, -NH).

IIIb. (E)-2-(4-Methoxybenzylidene)hydrazinecarbothioamide: IR spectrum, ν , cm^{-1} :1089, 1604, 1666, 1724, 3229, 3346 and 3470; ^1H NMR spectrum, δ , ppm: 3.85 (s, 3H, $-\text{OCH}_3$), 6.45 (bs, 1H, NH), 6.91-6.93 (d, 2H, ArH & NH), 7.21 (bs, 1H, NH), 7.58-7.60 (d, 2H, ArH), 7.88 (s, 1H.CH=N), 9.93 (bs, 1H.-NH).

IIIc. (E)-2-(2-chlorobenzylidene)hydrazinecarbothioamide: IR spectrum, ν , cm^{-1} :1093, 1597, 1674, 3252, 3340, and 3435; ^1H NMR spectrum, δ , ppm: 6.83 (bs, 1H, NH), 7.28-7.41 (m, 4H, ArH & NH), 7.91-7.93 (m, 1H, ArH), 8.36 (s, 1H.CH=N), 10.36 (bs, 1H.-NH).

III d. (E)-2-(4-chlorobenzylidene)hydrazinecarbothioamide: IR spectrum, ν , cm^{-1} :1086, 1601, 1645, 1697, 3244, 3342 and 3435; ^1H NMR spectrum, δ , ppm: 6.44 (bs, 1H, NH), 7.22 (bs, 1H, NH), 7.38-7.40 (d, 2H, ArH), 7.58-7.60 (d, 2H, ArH), 7.82 (s, 1H.CH=N), 9.89 (bs, 1H.-NH).

IIIe. (E)-2-(4-Methylbenzylidene)hydrazinecarbothioamide: IR spectrum, ν , cm^{-1} :1093, 1595, 1658, 1720, 3252, 3340 and 3435; ^1H NMR spectrum, δ , ppm: 2.38 (s, 3H, $-\text{CH}_3$), 6.61 (bs, 1H, NH), 7.19-7.27 (m, 3H, ArH & NH), 7.53-7.55 (d, 2H, ArH), 7.95 (s, 1H.CH=N), 10.28 (bs, 1H.-NH).

III f. (E)-2-(3-Nitrobenzylidene)hydrazinecarbothioamide: IR spectrum, ν , cm^{-1} :1053, 1597, 1685, 1724, 3310 and 3458; ^1H NMR spectrum, δ , ppm: 6.42 (bs, 1H, NH), 7.09 (bs, 1H.-NH), 7.60-7.64 (m, 1H, ArH), 7.84-7.96 (m, 2H, ArH), 8.26-8.28 (m, 1H, ArH), 8.53 (s, 1H.CH=N), 9.47 (bs, 1H.-NH).

IIIg. (E)-2-(4-Nitrobenzylidene)hydrazinecarbothioamide: IR spectrum, ν , cm^{-1} :1095, 1599, 1649, 1737, 3232, 3353 and 3465; ^1H NMR spectrum, δ , ppm: 6.77 (bs, 1H, NH), 7.43 (bs, 1H, NH), 7.80-7.82 (d, 2H, ArH), 8.00-8.02 (d, 2H, ArH), 8.23 (s, 1H.CH=N), 10.17 (bs, 1H.-NH).

IIIh. (E)-2-(3-hydroxy-4-methoxybenzylidene)hydrazinecarbothioamide: IR spectrum, ν , cm^{-1} : 1099, 1586, 1651, 1729, 3222 and 3439. ^1H NMR (CDCl_3 , ppm): 3.85 (s, 3H), 6.44 (bs, 1H, NH), 6.80-6.82 (d, 2H, ArH), 6.89 (s, 1H), 7.25 (m, 2H, ArH & NH), 7.79 (s, 1H.CH=N), 10.22 (bs, 1H.-NH).

IIIi. (E)-2-(3,4-dimethoxybenzylidene)hydrazinecarbothioamide: IR spectrum, ν , cm^{-1} :1086, 1610, 1645, 1703, 3238 and 3440; ^1H NMR spectrum, δ , ppm: 6.49-6.51 (dd, 1H, ArH), 6.78 (bs, 1H, NH), 6.75-6.76 (dd, 1H, ArH), 7.30 (bs, 1H, NH), 7.52-7.53 (dd, 1H, NH) 7.88 (s, 1H.CH=N), 10.60 (bs, 1H.-NH).

IIIj. (E)-2-(3,4,5-trimethoxybenzylidene)hydrazinecarbothioamide: IR spectrum, ν , cm^{-1} : 1092, 1605, 1644, 1717, 3241 and 3400; ^1H NMR spectrum, δ , ppm: 3.85 (s, 9H, OCH_3), 6.48 (bs, 1H, NH), 6.84 (s, 2H, ArH), 7.22 (bs, 1H, NH), 7.80 (s, 1H.CH=N), 10.36 (bs, 1H.-NH).

IIIk. (E)-2-(3,4-dichlorobenzylidene)hydrazinecarbothioamide: IR spectrum, ν , cm^{-1} :1100, 1599, 1642, 1722, 3243 and 3448; ^1H NMR spectrum, δ , ppm: 6.55 (bs, 1H, NH), 6.92-6.94 (d, 1H, ArH), 7.25 (bs, 1H, NH), 7.32-7.34 (m, 2H, ArH), 8.12 (s, 1H.CH=N), 10.42 (bs, 1H.-NH).

III l. (E)-2-(furan-2-ylmethylene)hydrazinecarbothioamide: IR spectrum, ν , cm^{-1} :1086, 1610, 1645, 1703, 3238 and 3440; ^1H NMR spectrum, δ , ppm: 6.49-6.51 (dd, 1H, ArH), 6.78 (bs, 1H, NH), 6.75-6.76 (dd, 1H, ArH), 7.30 (bs, 1H, NH), 7.52-7.53 (dd, 1H, NH) 7.88 (s, 1H.CH=N), 10.60 (bs, 1H.-NH).

III m. (E)-2-(thiophen-2-ylmethylene)hydrazinecarbothioamide: IR spectrum, ν , cm^{-1} :1039, 1589, 1668, 1737, 3182, 3333 and 3447; ^1H NMR spectrum, δ , ppm: 6.45 (bs, 1H, NH), 7.05-7.08 (dd, 1H, ArH), 7.17 (bs, 1H, NH), 7.30-7.31 (dd, 1H, ArH), 7.40-7.41 (dd, 1H, ArH), 8.12 (s, 1H.CH=N), 10.17 (bs, 1H.-NH).

III. (E)-2-(naphthalen-1-ylmethylene)hydrazinocarbothioamide: IR spectrum, ν , cm^{-1} : 1080, 1582, 1647, 1735, 3238 and 3436; ^1H NMR spectrum, δ , ppm: 6.46 (bs, 1H, NH), 6.89-6.92 (m, 2H, ArH), 7.20-7.24 (m, 4H, ArH), 7.34-7.40 (m, 3H, ArH), 8.02 (s, 1H), 10.35 (bs, 1H, -NH).

X-ray diffraction the compounds La_2O_3 and $\text{CeO}_2/\text{La}_2\text{O}_3$ calcined at 650°C shown in figure 2. The strongest three intense peaks appeared at 2θ values 25.34, 30.08 and 44.14 are associated with (111) (200) (201) h, k, l planes respectively, which indicates CeO_2 doped La_2O_3 is in hexagonal phase. The average particle size was calculated using the Scherer equation $D=0.9 \lambda/\beta \cos\theta$ (where D is the average crystalline size, λ is x-ray wavelength, β is FWHM diffraction line and θ is the diffraction angle). The average crystalline size is below 50 nm.

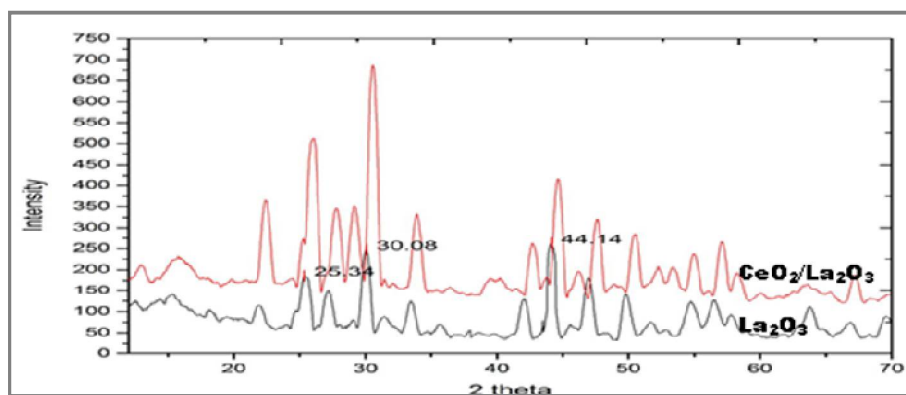


Figure 2.XRD Spectra of La_2O_3 and $\text{CeO}_2/\text{La}_2\text{O}_3$

In SEM images of La_2O_3 and $\text{CeO}_2/\text{La}_2\text{O}_3$ (Figure 3) similar to each other, the average crystalline size of the particles was also found to be same in both images. It indicates that the particles were uniformly distributed all over the surface and spherical in shape and this result was in agreement with XRD results.

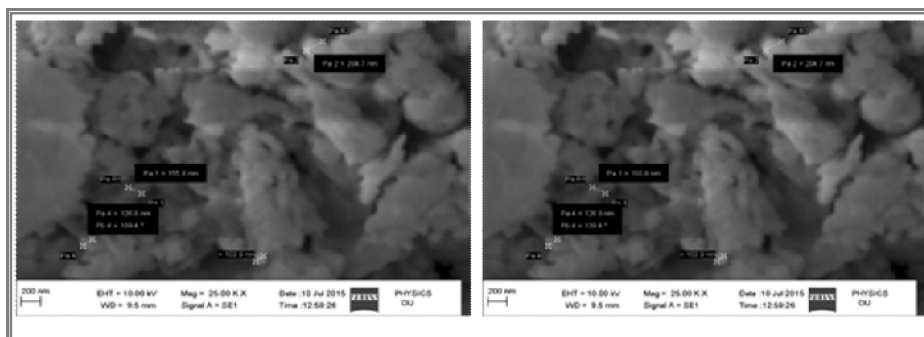


Figure 3. SEM Images of La_2O_3 (Image-1) and $\text{CeO}_2/\text{La}_2\text{O}_3$ (Image -2)

The EDX image-1(Figure 4) shows two characteristic signals which corresponds to La and O (Oxygen), confirms the presence of the compound La_2O_3 without any impurity and in the image-2 of shows La, Ce and O (Oxygen) characteristic signals which confirms Cerium incorporation of on La_2O_3 .

The UV-Visible DRS spectrums of La_2O_3 and $\text{CeO}_2/\text{La}_2\text{O}_3$ were presented in figure 5. The absorption edges obtained from the plots of absorbance vs. wavelength (The interception of the tangent on the descending part of the absorption peak of the wavelength axis gives the value of diffuse

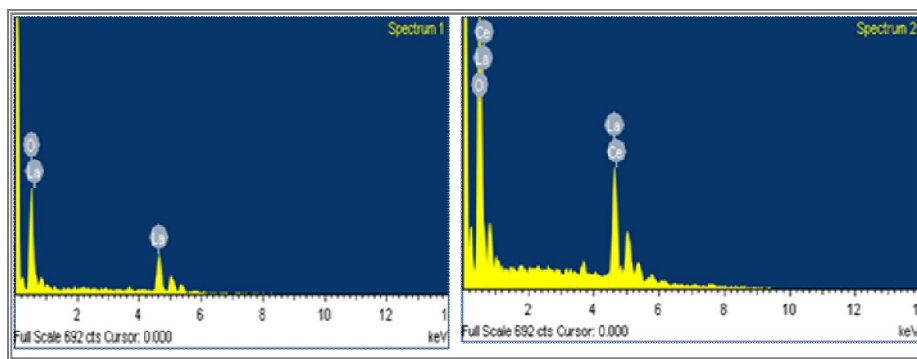


Figure 4. EXD images of La_2O_3 (Spectrum-1) and $\text{CeO}_2/\text{La}_2\text{O}_3$ (Spectrum -2)

absorption edge in nm). The UV-visible DRS spectrum of La_2O_3 shows absorption peak at 380 nm with band gap 3.26 eV (The band gap measured using $E_g = 1240/\lambda$ formula, where E_g is the band gap energy and λ is the wavelength of the absorption edge). The UV-visible DRS spectrum of $\text{CeO}_2/\text{La}_2\text{O}_3$ shows a red shift, when compared with La_2O_3 and observed at 410 nm with band gap of 3.02 eV. The red shift in UV-visible DRS spectrum clearly indicates incorporation of Ceria on La_2O_3 .

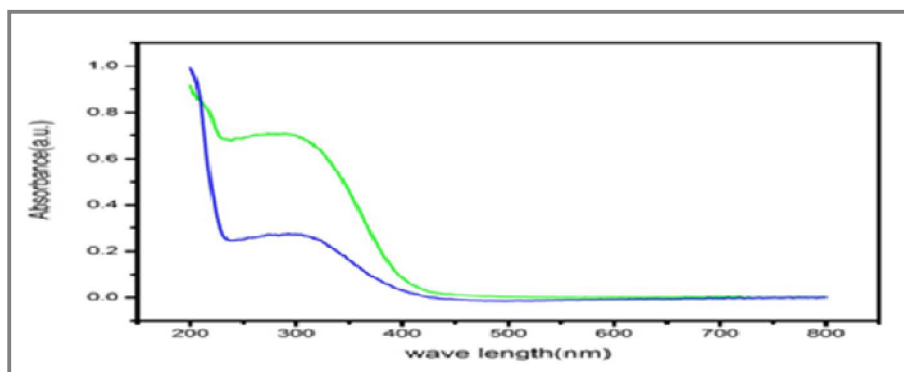


Figure 5. UV-Visible DRS spectra of La_2O_3 and $\text{CeO}_2/\text{La}_2\text{O}_3$

The BET surface area calculation shows that the specific surface area of Lanthanum was found to be $7.0157 \text{ m}^2 \text{ g}^{-1}$ and the Ceria promoted Lanthanum was found $12.95 \text{ m}^2 \text{ g}^{-1}$ (Figure 6). The specific surface area of $\text{CeO}_2/\text{La}_2\text{O}_3$ is heavier than that of pure La_2O_3 surface, the higher surface area may due to impression of Ceria on surface of the Lanthanum. It clearly represent the Ceria strongly influences the surface area of pure La_2O_3 .

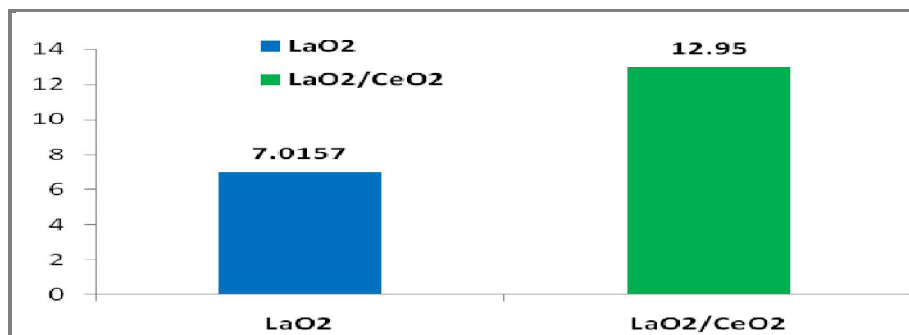


Figure 6. Images of BET surface area comparison with La_2O_3 and $\text{CeO}_2/\text{La}_2\text{O}_3$

APPLICATION

The (*E*)-2-(Arylmethylene)hydrazinecarbothioamide is useful in preparation with lesser reaction time using heterogeneous CeO₂/La₂O₃ catalyst.

CONCLUSIONS

The heterogeneous metal catalyst was successfully prepared by using Lanthanum nitrate hexahydrate and Ceric ammonium nitrate with good yield and the catalyst characterized on the basis of FTIR, XRD, SEM, and UV-DRS spectrums, its proved that the catalyst show similar properties with the pure La₂O₃, and the EDX spectrum confirms presence of La and Ce which confirms the Cerium doped on Lanthanum. The (*E*)-2-(Arylmethylene)hydrazinecarbothioamide have been synthesized with excellent yields in lesser reaction time using heterogeneous CeO₂/La₂O₃ catalyst and the structures of title compound confirmed by using spectral data.

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