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Nanocrystalline CeO_2 As A Highly Active And Selective Catalyst For The Dehydration Of Aldoximes To Nitriles And One-Pot Synthesis Of Amides And Esters

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Abstract

The dehydration of aldoximes into nitriles has been performed in the presence of various metal oxides with different acid-base properties (Al_2O_3, TiO_2, CeO_2, MgO). The results showed that a nanocrystalline CeO_2 was the most active catalyst. An *in situ* IR spectroscopy study supports a polar elimination mechanism in the dehydration of aldoxime on metal oxide catalysts, in which Lewis acid sites and basic sites are involved. The Lewis acid sites intervene in the adsorption of the oxime on the catalyst surface while surface base sites are responsible for the C1-H bond cleavage. Thus, the acid-base properties of nanocrystalline CeO_2 are responsible for the high catalytic activity and selectivity. A variety of aldoximes including alkyl and cycloalkyl aldoximes have been dehydrated into the corresponding nitriles in good yields (80-97%) using nanosized ceria which moreover resulted a stable and reusable catalyst. Additionally, it has been showed that a variety of pharmacologically important products such as picolinamide and picolinic acid alkyl ester derivatives can be obtained in good yields from 2-pyridinaldoxime in a one pot process using the nanoceria as catalyst.

Keywords: nanocrystalline CeO_2, acid-base catalyst, aldoxime dehydration, nitriles, one-pot synthesis, amides, esters.

Introduction

Nitriles are important compounds not only due to its presence in a variety of natural products, pharmaceuticals and bioactive molecules[1-3], but also because they are useful precursors for a wide variety of organic compounds such as amides, carboxylic acids, amines and ketones.[4]

The most efficient and green alternative route for the preparation of aromatic and aliphatic nitriles, and which has received much recent attention, involves the dehydration of aldoximes that can be easily obtained from the corresponding aldehydes. A wide variety of homogeneous catalytic systems have been reported for the dehydration of aldoximes into nitriles including different metal organic compounds such as oxorhenium (VII) complexes,[5] $Pd(OAc)_2/PPh_3$ and Cs_2CO_3 in CH_3CN[6], $Cu(OAc)_2$,[7] $[RuCl_2(p\text{-cymene})]_2$,[8] $Ga(OTf)_3$,[9] $TiCl_3(OTf)$ in [bmim]Br[10], pyridinium chlorochromate, [11] diaryl diselenides in the presence of H_2O_2,[12] $Pd(en)X_2$ complexes ($X=NO_3$, BF_4, OTf, ClO_4),[13] Pd(II) complexes with phosphino-oxime ligands,[14] cobalt/nitrophenolate complex,[15] guanidinate-osmium (II) complexes,[16] inorganic salts such as $InCl_3$,[17] $SnCl_4$,[18] $NiCl_2$ $2H_2O$,[19], $Co(II)Cl_2$,[20] $Fe(ClO_4)_3$,[21] phosphonium salts,[22] Cu, Ni, Co, Zn, Fe and Mn salts with cupric acetate,[23] and organocatalysts such as cyclopropenone[24] and acetic anhydride and K_2CO_3 in DMSO.[25] Although these methods can be effective for dehydrating aldoximes, most of them encounter some limitations such as expensive or not readily available reagents, hazardous organic solvents, long reaction times and tedious work-up procedure. Therefore, alternative procedures with more general applicability and environmental friendly conditions are still required.

The use of heterogeneous catalysts presents important advantages from an industrial and environmental point of view since they are easily recovered by simple filtration with the possibility of catalyst regeneration and reuse. However, and in clear contrast with the extensive variety of homogeneous catalysts used for this transformation, the use of heterogeneous catalysts for dehydration of aldoximes to nitriles is really scarce. For example, Montmorillonite K-10 clay, gamma-alumina, acid zeolites (H-Y, H-MOR, H-Beta, H-ZSM-5),[26] and basic zeolites (XCs)[27] have been reported for gas phase dehydration of aldoximes in a fixed bed reactor, giving moderate to good yields of the corresponding nitriles.

In liquid phase, different heterogeneous catalysts such as Montmorillonite KSF,[28] Envirocat-EPZG,[29] KF/alumina,[30] $[RuCl_2(p\text{-cymene})]_2$ complex supported on Carbon,[31] H_2SO_4 supported on SiO_2 ,[32] and on resin,[33] heteropolyacids,[34] Cu(II) modified molecular sieves,[35] and more recently, tungsten-tin mixed hydroxide (W-Sn-hydroxide)[36] and Cu (II) immobilized on aminated ferrite nanoparticles,[37] have been used in dehydration of aldoximes with different success. However, most of these catalytic systems suffer from leaching problems of the active phase while a high catalysts/aldoxime weight ratio ($\geq$ 1) is necessary to achieve high performances. Very recently, we have presented that Fe containing MOFs, particularly a post-synthesis treated MIL-100(Fe), is an efficient catalyst to convert aldoximes into nitriles, showing increased catalytic activity when compared with a wide variety of Brönsted and Lewis acid and base catalysts.[38]

CeO_2 is a robust metal oxide with acid-base and redox properties that has been used as an active catalyst for a variety of organic reactions[39,40] such as alkylation of aromatic compounds,[41] dimerization of alcohols[42] and carboxylic acids into ketones,[39] dehydration of alcohols,[44-46] reduction of carboxylic acids,[47] oxyhalogenation of activated arenes [48] and CO_2 conversion into valuable chemicals.[49] Recently, Tamura et al. have showed that CeO_2 is an efficient and recyclable catalyst for the selective one pot synthesis of esters[50] and amides [51] from nitriles in liquid phase (30-160 ^oC). Thus, if one could prepare an active and selective CeO_2 catalyst for the dehydration of aldoximes, it could be possible to achieve the direct synthesis of amides and esters starting from aldoximes. In the present work we presented for the first time that nanosized CeO_2 is a selective, stable and recyclable heterogeneous_catalyst for the dehydration of aldoximes into nitriles in liquid phase at moderate temperature, and that dehydration of aldoximes can be coupled with hydration and esterification of nitriles to obtain, amides and esters respectively in one-pot process.

Experimental Section

Catalysts and reagents

Nanocrystalline ceria ($nCeO_2$, 115 m^2/g) was supplied by Rhodia Electronic Catalysis. Regular CeO_2 (surface area, 56 m^2/g) was supplied by Aldrich and γ-Al_2O_3 (150 m^2/g) was purchased from Merck. TiO_2 (anatase-rutile mixture (3:1)) (56 m^2/g) and MgO sample with a surface area of 670 m^2 were supplied by GmbH and NanoScale

Materials respectively. All reagents were purchased from Sigma Aldrich.

Synthesis of aldoximes

2-Chlorobenzaldehyde oxime, 4-nitrobenzaldehyde oxime and syn-2-pyridinealdoxime were supplied by Aldrich and used as received. The rest of oximes were synthesized by the following method: hydroxylamine hydrochloride ($NH_2OH·HCl$, 0.065 mol), sodium hydroxide (0.133 mol) and ethanol (45 mL) were successively placed into a round bottom flask of 100 mL. The reaction mixture was stirred (800 rpm) with a magnetic stir bar under ambient temperature during 15 minutes. After that the aldehyde (0.043 mol) was introduced into the reaction mixture and the reaction was continued until the total conversion of aldehyde. The reaction was monitored by GC analysis. When the reaction was finished, distilled water was added to the mixture in order to remove the inorganic residues and then the product was extracted with ethyl acetate. Finally, the solvent was removed by distillation at vacuum and the oximes with purity of 98-99 % were obtained. All synthesized oximes were identified by Mass Spectroscopy analysis using HP Agilent 5973 Mass Spectrometer with a 6980 mass selective detector.

Reaction procedure for dehydration of aldoximes

Aldoxime (1 mmol), o-xylene (3 mL) and catalyst were added to the two-neck bottom flask (10 mL) which was connected to a Dean Stark instrument to remove the water formed during the reaction. The suspension was stirred and heated at 160 °C in a silicon oil bath with an automatic temperature control system and magnetic stirrer (1000 rpm) under N_2 atmosphere. The reaction was followed by taking samples at regular time periods and analyzing them by gas chromatography using a FID detector and a capillary column (HP5, 30 m - 0.25 mm - 0.25 μm). Undecane was used as the external standard. All products were identified by Mass Spectroscopy analysis.

When the reaction was finished the catalyst was filtered, thoroughly washed with ethyl acetate and acetone and dried at 100 ^{o}C overnight. Before recycling the catalyst was calcined at 450 ^{o}C under air flow during 5 h.

Reaction procedure for one-pot synthesis of 2-picolinamide from 2-pyridinealdoxime

A mixture of 2-pyridinealdoxime (1 mmol), o-xylene (3mL) and $nCeO_2$ (50 mg) was placed to the two-neck bottom flask (10 mL) connected to the reflux condenser. Then, the suspension was heated at 160 °C in a silicon oil bath with an automatic temperature control system and magnetic stirrer (1000 rpm) under N_2 atmosphere. After 2-pyridinealdoxime was consumed, the temperature of the bath was decreased from 160 to 110 °C and then, water was added to the reaction mixture. The reaction was followed by taking samples at regular time periods and analyzing them by gas chromatography using a FID detector and a capillary column (HP5, 30 m -0.25 mm - 0.25 μm). Undecane was used as the external standard. All products were identified by Mass Spectroscopy analysis.

Reaction procedure for one-pot synthesis of picolinic acid esters from 2-pyridinealdoxime

A mixture of 2-pyridinealdoxime (1 mmol), o-xylene (3mL), octanol (10 mmol), water (2 mmol) and CeO_2 (50 mg) were placed to the two-neck bottom flask (10 mL) connected to the reflux condenser. Then, the suspension was heated at 160 °C in a silicon oil bath with an automatic temperature control system and magnetic stirrer (1000 rpm) under N_2 atmosphere. The reaction was followed by taking samples at regular time periods and analyzing them by gas chromatography using a FID detector and a capillary column (HP5, 30 m -0.25 mm - 0.25 μm). Undecane was used as the external standard. All products were identified by Mass Spectroscopy analysis.

Characterization methods

FTIR spectra have been collected with a Nexus spectrometer from Thermo equipped with a DTGS detector (4cm^{-1} resolution, 32 scans). For the CO adsorption experiments, an IR cell allowing *in situ* treatments under controlled atmospheres and temperatures from -176 ^{o}C to 500 ^{o}C has been connected to a vacuum system with gas dosing facility. Self-supporting pellets (ca. 10 mg cm^{-2}) were prepared from the sample powders and treated at 250 ^{o}C under dynamic vacuum (10^{-4} mbar). After activation, the samples were cooled down to -176 ^{o}C followed by CO dosing at increasing pressures (0.1-4 mbar) and the IR spectrum recorded after each dosage. For the $CHCl_3$ adsorption experiments and the *in situ* IR studies of oxime dehydration a quartz IR cell allowing *in situ* treatments under controlled atmospheres and temperatures from 25 ^{o}C to 600 ^{o}C has been connected to a vacuum system with gas dosing facility. Self-supporting pellets (ca. 10 mg cm^{-2}) were prepared from the sample powders and treated at 250 ^{o}C under dynamic vacuum (10^{-4} mbar). After activation, the samples were cooled down to 25^{o}C. In the $CHCl_3$ IR studies chloroform was adsorbed at increasing pressures (1- 30mbar) and the IR spectrum recorded after each dosage. In the *in situ* oxime dehydration IR studies, propionaldehyde oxime was adsorbed on the pre-activated samples at 25 ^{o}C and increasing pressure (0.5-7mbar) until spectra saturation, followed by evacuation at 10^{-4} mbar. At that moment, the temperature was increased to 70, 90, 120 and 160 ^{o}C and the sample kept at each temperature 45 min. IR band areas have been normalized to sample weight and catalyst surface area, for specific discussion along the text.

Surface area measurements were obtained with a Micrometrics ASAP 2000 apparatus following the BET procedure by means of nitrogen adsorption at 77 K. Thermogravimetric analyses (TGA) were performed with a Netzsch STA 409 EP thermal analyzer with about 20 mg of sample and a heating rate of 10 ^{o}C min^{-1} in air flow.

Results and discussion

Synthesis of nitriles

The dehydration of 4-methoxybenzaldehyde oxime was taken as a model substrate. The reaction was performed in liquid phase using *o*-xylene as a solvent at reflux temperature (149 ^{o}C) and removing the water formed in a Dean-Stark apparatus. Metal oxides with different acid-base properties such as nanocrystalline high surface area (115 m^2/g) ceria (nCeO_2), regular ceria (56 m^{2}g^{-1}) (CeO_2), γ-alumina (Al_2O_3), titania (TiO_2) and magnesia (MgO), were used as catalysts, and the results obtained are presented in Table 1 and Figure 1. As can be observed there (Table 1, entries 1-4) the order of activity (initial reaction rate) was nCeO_2 > MgO > Al_2O_3 >CeO_2 >TiO_2, when the order of activity per unit surface area was calculated the nCeO_2 is still the most active one, while MgO was clearly lower owing to its very high specific surface area. Total conversion of aldoxime with 93 % selectivity to nitrile (**2**) has been achieved with nCeO_2 with only 1.5 h reaction time. In all cases, little amounts of 4-methoxybenzaldehyde (**3**) (Scheme 1), coming from the hydrolysis of the aldoxime was detected. This result indicates that, in spite of using a Dean-Stark apparatus for removing the water produced during the oxime dehydration, some amount of water remains adsorbed on the catalyst promoting the hydrolysis of the aldoxime. Moreover, the formation of benzamide which is formed by further hydration of the nitrile was only observed in the case of the alumina catalyst at the level of traces (Table 1, entry 4). For comparison purposes the reaction was also performed using a conventional homogeneous catalysts such as $Ce(NO_3)_3·6H_2O$ and Ce(III)triflate (Table 1, entry 6 and 7). Total conversion of oxime was achieved in both cases after 6 hours of reaction but both homogeneous catalysts promote in a large extent the hydrolysis of the oxime, being Ce(III)triflate more selective to the nitrile than $Ce(NO_3)_3·6H_2O$. Since the Ce salts showed considerable activity, in order to clarify that the dehydration takes place on the surface of $nCeO_2$, a leaching test was performed. To do that, in an additional experiment, the catalyst was removed by filtration in hot when a 40 % conversion was achieved, and the reaction was then continued in the absence of catalyst. No conversion was observed after filtration, confirming that Ce species were not leached from the solid into the reaction medium (see Figure S1 in SI)

Additionally, when the results obtained with nanosized ceria were compared with previously reported results using a variety of solid catalysts (see Table 2) it is possible to see that the $nCeO_2$ catalyst is among the best in terms of nitrile yield, reaction time and catalyst/oxime ratio.

Nature of the catalytic active sites for dehydration of aldoxime to nitrile

It has been reported that the presence of basic (O^{2-}) and Lewis acid sites (Ce^{4+}) on CeO_2 were responsible for the dehydration of 1,4-butanediol in vapor phase,[52] as well as for the direct conversion of CO_2 into dimethyl carbonate,[53] cyclic carbonates, cyclic carbamates and cyclic ureas .[49] Then, in order to establish if the different activity found for the different metal oxides is related with their acid and/or base properties, their acid and basic properties were measured by adsorption of CO and $CHCl_3$ probe molecules, respectively, using IR spectroscopy for monitoring.

When CO is adsorbed on Lewis acid sites, the νC≡O frequency is shifted to higher frequencies relative to the gas phase value of 2145 cm^{-1}, being the shift directly related to the acid strength of the adsorption site.[54] In our case, two band maxima at 2180 and 2153 cm^{-1} are observed on Al_2O_3, and at 2177 and 2150 cm^{-1} on TiO_2, after CO adsorption (Figure 2). On both samples, the high frequency IR bands (2180 and 2177cm^{-1}) corresponds to CO interacting with surface Lewis acid sites, while the low frequency IR bands (2153 and 2150 cm^{-1}) are due to CO interacting with surface hydroxyl groups, according to the simultaneous shift in the OH IR band. On the MgO sample, two band maxima at 2171 and 2148 cm^{-1} are evidenced after CO adsorption. Both bands are associated to Lewis acid sites, since no shift in the hydroxyl groups is observed. Finally on the CeO_2 samples, one peak with maxima at 2153 cm^{-1} is observed, associated to Lewis acid sites. From the ν(C≡O) frequency shift, the acid strength of the samples can be ranged in the order: $Al_2O_3 > TiO_2 > MgO > nCeO_2 > CeO_2$, in good agreement with previous studies.[55] However normalizing the CO IR band area to catalyst surface area, it doesn't follow the same order, being $CeO_2 > TiO_2 > nCeO_2 > Al_2O_3 > MgO$ (Table 3).

For studying surface basicity on solid catalysts, several probe molecules have been recommended,[56-58] while there is not a clear consensus about which one is the most adequate probe molecule. Therefore, and on the bases of our previous study in where

$CHCl_3$ was successfully used to probe surface basicity, [59] we have selected this probe molecule in the present study. Interaction of chloroform with surface basic sites through its hydrogen atom shifts the νC-H stretching frequency (3030 cm^{--1} in the liquid phase) to lower frequencies, and the band shift can be used as an indicator of basic strength.[60,61]

Thus, chloroform adsorbed on TiO_2 and Al_2O_3 give rise to a well symmetric IR band located at ~3010cm^{-1}, while in the case of CeO_2 samples an asymmetric IR band with a main component at ~3010 cm^{-1} and a shoulder at lower frequencies (~2965 cm^{-1}) is observed (see Figure 3). Chloroform adsorbed on MgO shifts the IR band maxima to even lower frequencies showing two band maxima at 2980 and 2890 cm^{-1} (Figure 3) The IR band at around 3010 cm^{-1} is related to chloroform interacting with surface hydroxyl groups, according to the simultaneous shift in the OH stretching vibration, while the IR bands at lower frequencies (2980-2880 cm^{-1}) are due to chloroform adsorbed on surface base sites of different strength. Based on the frequency shift of the νC-H stretching frequencies, the basicity of the samples can be ranked in the order: $Al_2O_3 < TiO_2 < CeO_2 < nCeO_2 <$ MgO. On the other hand, normalizing the νC-H IR band area of adsorbed chloroform to catalyst surface area, (Table 4) a higher value is obtained on the MgO and $nCeO_2$ sample compared to the other samples, in agreement with previous studies.[62]

Therefore, from the IR study of adsorbed probe molecules we can conclude that the most active and selective catalysts ($nCeO_2$ and MgO) possess strong basic sites while the Lewis acidity on both samples is rather weak.

As previously indicated in the introduction, catalysts with either acid or base properties have been reported in the literature for aldoxime dehydration,[26-28,36] however no clear understanding about the role of each site in the reaction mechanism has been given. Recently, Limtrakul et al.[63] based on a DFT study performed on FeZSM5 zeolite, proposed two reaction mechanisms for the dehydration of benzaldoxime: a) an oxidative dehydration mechanism and b) a polar elimination mechanism. While, in both cases the reaction proceeds through a transition state structure where surface acid and base sites are involved, they mainly differ in the initial step of interaction of the aldoxime with the metal surface sites. In the oxidative dehydration mechanism the reaction starts with the interaction of the oxygen of the oxime with Lewis surface sites, while in the polar elimination mechanism a coordination complex with the N is initially formed. Taking this into account, an *in situ* IR study of propionaldehyde oxime dehydration has been performed on different solid catalysts to explain the catalytic data reported in Table 1 and contribute to the understanding the reaction mechanism.

***In situ* IR spectroscopy study**

Propionaldehyde oxime adsorption on the different metal oxides followed by IR spectroscopy, shows a shift in the N-OH and C=N vibration to higher frequency versus the gas phase frequency. While a blue shift would be expected if one assumes coordination through the oxygen atom of the aldoxime with surface Lewis sites of the metal oxide support,[59,63] a red shift has been reported in the case of an N–bound interaction of the aldoxime with surface Lewis acid sites.[63] More specifically, in the C=N stretching vibration region (1640 cm^{-1} in gas phase), an IR band at 1646 cm^{-1} is observed when propionaldehyde oxime was adsorbed on $nCeO_2$, while the band is shifted to higher frequencies on the more acid supports (1659 cm^{-1} in MgO, 1662 cm^{-1} in TiO_2 and 1667 cm^{-1} in Al_2O_3) (Figure 4a). In a similar way, in the N-OH frequency region (1028 cm^{-1} in gas phase) a symmetric IR band at ~1037 cm^{-1} is observed with the less acid CeO_2 samples, while a high frequency component at ~1051 cm^{-1} appears on the more acid supports (Al_2O_3, TiO_2 and MgO) (Figure 4b). It should be considered that MgO, normally considered as basic support, shows few relatively stronger acid sites (see Table 3), that can be associated to uncoordinated surface sites like steps or corners. In conclusion, in both N-OH and C=N vibration modes, a correlation between Lewis acid strength and IR frequency shift is clearly detected. Moreover, the IR peak area associated to the N-OH vibration normalized to catalyst surface area (included in Table S1) is higher on CeO_2 and TiO_2 samples than on Al_2O_3 and MgO as it occurs with the surface area normalized CO IR peak area, associated to Lewis acid sites.

If one now compares the above spectroscopic results with the catalytic results (Table 1) it should be possible to conclude that, although Lewis acid sites are involved in the first step of oxime interaction with the catalysts surface, no correlation between Lewis acid strength and initial reaction rates could be observed. On the contrary, both $nCeO_2$ and MgO samples, with the highest basic strength, appear as the most active samples at least per gram of catalyst. Thus, surface basicity should play a determinant role in the reaction mechanism. However, if basicity would be the only parameter that determines catalytic activity, MgO being more basic than $nCeO_2$, should exhibit a higher initial reaction rate, which obviously is not the case (Table 1). The difference in activity would be explained by also taking into account the less presence of Lewis acid sites on MgO which corresponds to a lower IR band area of adsorbed oxime molecule (see Table S1). Thus, we can conclude that both Lewis acid sites (number) and basic sites (strength) play a role in the reaction mechanism, being the Lewis acid sites involved in the adsorption of the oxime through the N atom activating the molecule in such a way that the hydrogen at the C1-H of the oxime becomes slightly more positive and more reactive toward the attack by the basic site to perform the C1-H cleavage.

Surface reaction steps

The reaction mechanism of aldoxime dehydration at increasing temperature followed by *in situ* IR spectroscopy can be clearly evidenced in the MgO sample (Figure 5). As indicated above, oxime adsorption at 25 ^{o}C on MgO shifts the N-OH and the C=N stretching frequency to higher frequencies. Specifically, a broad asymmetric IR band with two components at 1050 and 1037 cm^{-1} ascribed to the N-OH IR frequency and an IR band at 1660 cm^{-1} due to the C=N vibration are observed. No change in the IR spectra is observed at 70 ^{o}C. Increasing the temperature to 90 ^{o}C the intensity of the 1050-1037 cm^{-1} IR band and the 1660 cm^{-1} IR band decrease and a new band at 1184 cm^{-1} start to appear (Figure 5a). This last band has been associated to the nitrile, being this the desired reaction product. The C≡ N stretching vibration is not yet detected, because of its lower extinction coefficient compared to the 1184 cm^{-1} IR band vibration. Moreover an IR band at 3430 cm^{-1}, due to hydroxyl groups, is clearly detected at 90 ^{o}C (Fig.5b). Hydroxyl groups are formed due to C1-H cleavage catalyzed by oxygen atoms of the support, and N-OH elimination, leading sequentially to C≡N bond formation. Increasing the temperature to 120 and 160 ^{o}C the C≡N IR band at 2244 cm^{-1} (Fig. 5c) and H_2O at 1628 cm^{-1} (Fig. 5a) and 3475 cm^{-1} (Fig. 5b) are clearly detected on the catalyst surface as well as the IR band at 1184 cm^{-1} which grows in intensity due to nitrile. In parallel a strong decrease of the 1050 and 1037 cm^{-1} IR bands associated to oxime is observed (Figure 5a). Accordingly the following reaction steps can be established from all the above *in situ* IR results: a) oxime activation through an N-bond complex to Lewis acid sites, b) N-*OH* bond elimination and C1-*H* cleavage with subsequent OH formation and finally water and nitrile formation. Similar reaction mechanism has been observed on the TiO_2 and $nCeO_2$ samples (see Figure S2 for the $nCeO_2$ sample) with the only difference being their different reactivity. Nitrile formation has been observed at 90 ^{o}C on the $nCeO_2$ (C≡N IR band at 2247 cm^{-1}, very weak) and at 160 ^{o}C in the TiO_2 (C≡N IR band at 2283 cm^{-1}), which match perfectly their reactivity performance in the macrokinetic studies. In the case of $nCeO_2$, nitrile adsorption (being this the reaction product) is much weaker than on the other catalyst sample, being only detected at 90 ^{o}C on the surface as adsorbed specie (weak IR band). At increasing temperatures it is desorbed to the gas phase. Owing to the base character and further reactivity of the nitrile their fast desorption from the catalyst surface is highly desired for maximizing catalyst activity, selectivity and catalyst life. Therefore the desorption is favored in less acid catalysts.

In conclusion the *in situ* IR adsorption and reactivity results suggest a reaction mechanism for the dehydration of aldoxime on metal oxides that would be consistent with a polar elimination mechanism. [63] Both Lewis acid and basic sites are involved, being the controlling step in the reaction rate, the C1-H bond cleavage in which the basic sites would be involved. Accordingly, we can assess that the basicity of the $nCeO_2$, coupled to an appropriate number of Lewis acid sites responsible for the adsorption of the oxime through the N atom and the activation of the C1-H of the oxime, are responsible for the high catalytic performance observed on this sample compared to the other metal oxide samples.

Reusability and scope of the reaction on $nCeO_2$

To study the catalyst reusability after dehydration of 4-methoxybenzaldoxime, the $nCeO_2$ sample was washed, calcined at 450 °C and reused during four consecutive cycles. As can be seen in Figure 6 the $nCeO_2$ maintains its activity during four consecutive cycles.

The scope of $nCeO_2$ for the synthesis of nitriles was studied starting from a variety of aromatic, heterocyclic, cyclic and aliphatic aldoximes, which were converted predominantly in the corresponding nitriles (Table 5). In the case of aromatic aldoximes the presence of electron withdrawing groups in the aromatic ring (entries 2-4) increases the reactivity with respect to non-substituted aldoximes and aldoximes with electron donating groups (entries 1 and 6). In the case of heterocyclic aldoximes, such as thiophen-2-carbaldehyde oxime, pyridine-2-carbaldehyde oxime and furan-2-carbaldehyde oxime (entries 5, 7 and 8), the corresponding heterocyclic nitriles were obtained in lower yields due to the formation of the corresponding amides by subsequent hydration of the nitrile. Similar behavior has been reported for dehydration of heterocyclic aldoximes in the presence of cupric acetate in acetonitrile.[23]These results agree with those reported by Tamura et al.[61] who observed that CeO_2 promotes efficiently the hydration of nitriles to amides provided that the nitrile possess a heteroatom adjacent to the α-carbon of the C≡N group. Finally, good yields of nitriles (80-95%) were also obtained from cycloalkyl and alkyl aldoximes (entries 9-12) using n-CeO_2 as catalyst.

Taking into account the good results showed by the nanoceria for the dehydration of aldoximes and considering the previous results reported by Tamura et al.[50,51] on the conversion of nitriles into amides and esters using CeO_2 as catalyst, we have envisioned a one pot synthesis of amides and esters starting from the corresponding aldoximes.

One-pot synthesis of 2-picolinamide from 2-pyridinealdoxime

It has been demonstrated that CeO_2 is able to promote efficiently the hydration of nitriles to amides using water as a solvent, [51] particularly when a heteroatom (N or O) is adjacent to the α-carbon of the nitrile group, as it is the case of the 2-cyanopyridine. Mechanistic studies suggested that the catalytic activity of the CeO_2 for this transformation arises from the cooperation of Lewis acid sites (Ce^{+4}) and acid-base (Ce-O) pair sites which activate an electrophile and a nucleophile, respectively. Thus, considering the ionic nature of CeO_2, a mechanism has been proposed in where the catalytic cycle starts with the dissociation of H_2O on CeO_2 to give H^+ and OH^-. In a second step the nitrile is adsorbed onto the CeO_2 forming a nitrile-CeO_2 complex which in a third step (the rate determining step) will undergo an addition of the OH^- to the carbon atom of the nitrile group to give the amide, followed by desorption of the amide from CeO_2 surface. [64]

Owing to the fact that 2-picolinamide derivatives have important pharmacological activities, for instance in the treating of neurological and psychiatric disorders associated with glutamate dysfunction,[65] we selected 2-pyridine aldoxime as substrate for the one pot synthesis of 2-picolinamide starting from the aldoxime. Since, water cannot be used in our case as a solvent since it could promote the aldoxime hydrolysis, we have designed a one-pot process which involves two consecutive steps catalyzed by the nanocrystalline CeO_2. Firstly the dehydration of 2-pyridinealdoxime to nitrile (2-cyanopyridine), which takes place at reflux of o-xylene and then the addition of a controlled amount of water which promotes the hydration of nitrile to give the corresponding amide (2-picolinamide) (Scheme 2).

In this one pot process the presence of water plays an important role, since it was observed that in the first step the water formed during the dehydration of aldoxime was already able to promote the hydration of the nitrile to amide yielding picolinamide (40%), and 2-cyanopyridine (60%). Thus, to complete the hydration of 2-cyanopyridine, while avoiding the over-hydrolysis into the undesired carboxylic acid, the temperature was decreased at 110 ^{o}C in the second step, while different amounts of water were added. Results from Table 6 indicate that when working with a molar ratio water/substrate ≥ 14, a yield of 99% of picolinamide (99% selectivity) was obtained.

In Figure 7 the evolution of products versus the reaction time is depicted for the one pot synthesis of picolinamide from 2-pyridinealdoxime when water (14mmol) was added. As can be seen from the results presented in Figure 7, the nitrile formed in the first step was immediately hydrated to picolinamide reaching 99 % of yield after 8h reaction time. The reaction was extended to other heteroaromatic aldoximes and good yields of the corresponding amides were obtained, although longer reaction times were required (Table 7).

One pot synthesis of picolinic acid alkyl esters from 2-pyridinealdoxime

It is known that picolinic acid alkyl esters are important pharmacological compounds as they possess high activity inducing apoptosis for human leukemia cells.[66] Then, the possibility to obtain esters from aldoximes through a one pot process was studied here by selecting the coupling of 2-pyridinealdoxime and n-octanol as reaction model (Scheme 3). The reaction was performed by reacting 2-pyridinealdoxime with an excess of octanol in the presence of water in o-xylene at reflux temperature and using the nanocrystalline $nCeO_2$ as catalyst. Results showed that excellent yield (89 %) and selectivity to picolinic acid octyl ester (90 %) can be obtained after 26h reaction time. These results are similar to those reported by Tamura et al.[46] starting from 2-cyanopyridine.

Figure 8 shows the kinetic curve for ester formation from the pyridinealdoxime. As can be seen there the picolinamide (2-pyridinecarboxamide) appears as a primary and unstable product with a maximum yield (62 %) at 2h reaction time, and then decreases. It is interesting to point out that the hydrolysis of aldoxime was not detected in the reaction media in spite of the presence of water as reactant. The corresponding nitrile was neither detected as intermediate compound, indicating that dehydration of aldoxime is not the controlling step of the reaction. Then, from the above results and those of the Tamura el al.[50] for the esterification of 2-cyanopyridine with octanol, who found that the rate of hydration of 2-cyanopyridine was calculated to be 86 times larger than that of esterification of amide, we have to conclude that in our one pot process, the 2-pyridinealdoxime is rapidly dehydrated to the corresponding nitrile (2-cyanopyridine) and hydrolyzed into 2-picolinamide which finally reacts with the alcohol to obtain the corresponding ester. The reaction was extended to the synthesis of other picolinic acid alkyl esters starting from 2-pyridinealdoxime and different alcohols (Table 8), achieving good results of the corresponding esters._It appears then that it is possible in a one pot system using

$nCeO_2$ as catalyst to carry out a process that involves three consecutive reaction steps and which yields the corresponding ester directly from 2-pyridinealdoxime.

Conclusions

The dehydration of aldoximes to nitriles has been studied in the presence of various metal oxides (Al_2O_3, TiO_2, CeO_2, MgO) being the nanocrystalline ceria the most active catalyst. A polar elimination mechanism has been proposed in the dehydration of aldoxime on metal oxide catalysts, in which Lewis acid sites and basic sites intervene. The Lewis acid sites are involved in the adsorption of the oxime on the catalyst surface and surface base sites are responsible for the C1-H bond cleavage. Thus, the basicity showed by $nCeO_2$ coupled with the Lewis acid sites is responsible for the high catalytic activity and selectivity. Good yields of nitriles (80-97%) from aromatic aldoximes involving electron withdrawing and electron donating groups as well as from alkyl and cycloalkyl aldoximes were obtained. Nanosized ceria is a stable and reusable catalyst; it was reused four consecutive cycles without loss of activity. Based on the above reactions, it is possible to obtain pharmacologically important products such as picolinamide and picolinic acid alkyl esters from 2-pyridinaldoxime in a one pot process using the nanoceria as catalyst.

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Supporting Information Available: Table of Surface density of adsorbed propionaldehyde oxime on the different oxides; IR spectra of $nCeO_2$ sample after oxime adsorption at increasing temperatures; Figure corresponding to the leaching test of $nCeO_2$. This material is available free of charge via the Internet at http://pubs.acs.org.

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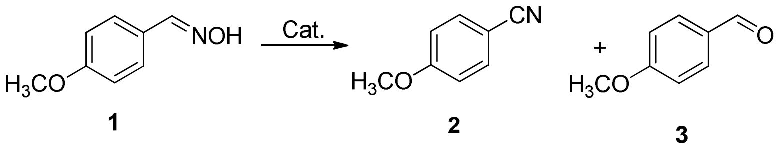
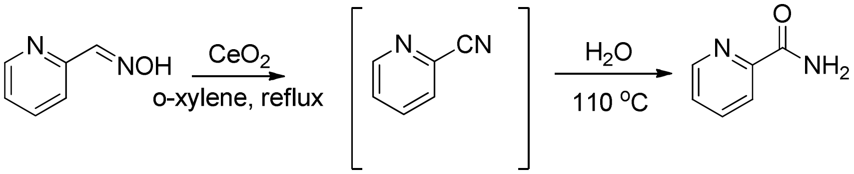
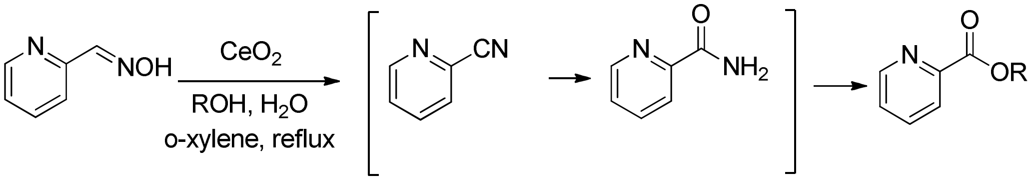


Scheme 1. Dehydration of 4-methoxybenzaldehyde oxime in presence of metal oxides as catalyst



Scheme 2. Reaction pathway of the one pot synthesis of 2-picolinamide from 2-pyridinealdoxime in the presence of $nCeO_2$ as a catalyst.



Scheme 3. Reaction pathway of the one pot synthesis of esters of 2-picolinic acid from 2-pyridinealdoxime in the presence of $nCeO_2$ as a catalyst.

Table 1. Results of dehydration of 4-methoxybenzaldehyde oxime in the presence of different heterogeneous and homogeneous catalysts

Entry	**Catalyst**	**Time**	**Conv.(%)**	**Yield (%)**			**r^0**	**r^0**
		(h)	**1**	**2**	**3**	**4**	**(mmol/h g)[a]**	**(mmol/h m^2)[b]**
1	CeO_2	7	63	56	5	0	80	1.40
2	$nCeO_2$	1.5	100	93	7	0	480	4.17
3	TiO_2	8	41	38	2	0	16	0.28
4	Al_2O_3	7	23	20	2	1	176	1.17
5	MgO	6	>99	>99	0	0	220	0.32
6	$Ce(NO_3)_3.6H_2O$	6	100	43	56	0	14	-
7	Ce(III)triflate	6	100	82	18	0	100	-

Reaction conditions: 4-methoxybenzaldehyde oxime (1 mmol, 151 mg), catalyst 50 mg at reflux of o-xylene (3 mL) under N_2 using a Dean Stark apparatus. [a] Initial rate of formation of nitrile per gram of catalyst. [b] Initial rate of formation of nitrile per unit surface area .

Table 2. Comparative results of dehydration of 4-methoxybenzaldehyde oxime obtained with different heterogeneous catalyst

Entry	Catalyst	Time	Solvent	*T* [^{o}C]	Yield Nitrile[a]	C/S [wt/wt]	Ref.
1	$nCeO_2$	1.5h	o-xylene	149	93	0.33	This work
2	MIL-100(Fe)-NH_4F	1h	o-xylene	149	91	0.40	38
3	W-Sn hydroxide	1h	o-xylene	149	95	1.52	36
4	Fe_3O_4@$AEPH_2$-Cu(II)[b]	1h	CH_3CN	82	95	0.58	37
5	Montmorillonite KSF	18h	Toluene	115	78	3.95	28
6	Envirocat EPZG	24h	-	100	92	0.13	29
7	$[N_aP_5W_{30}O_{110}]^{14-}$	5h	AcH	119	80 [c]	0.50	34
8	KF/alumina	8h	DMF	85	90	47.7	30
9	H_2SO_4/SiO_2	MW, 3min	-		89	3.30	32
10	Cu(II)-MS (4A)[d]	8h	CH_3CN	80	96	0.65	35
11	H_2SO_4/MF resin[e]	MW 5 min	-		80b	4.13	33
12	$[RuCl_2(p\text{-cymene})]_2/C$	20min	CH_3CN	80	93	3.30	31

[a] 4-methoxybenzonitrile; [b]Cu(II) immobilized on aminated ferrite nanoparticles; [c]benzonitrile; [d] 4A Molecular sieve modified with Cu(II);[e]H_2SO_4 supported on Melamine-Formaldehyde resin; C/S: Catalyst/oxime (wt/wt) .

Table 3. Distribution of Lewis acid sites on the different samples monitored by FTIR of CO adsorption.

Catalyst	IR Lewis Acid sites (cm^{-1})					OH[a]	Phy[b]
Al_2O_3	2180(1.68)	2177(1.65)				2153(20.86)	2140
TiO_2	2180(26.9)	2175(8.4)				2154(21.5)	2138
MgO		2171(0.6)	2163(0.6)		2148 (0.9)		2136
$nCeO_2$				2154(4.4)	2145(3.5)		
					2130[c] (1.2)		
CeO_2				2153(98.5)	2142(13.9)		
					2128[c] (5)		

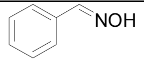
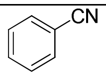
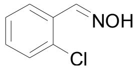
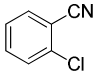
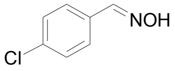
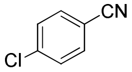
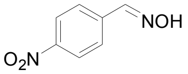
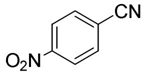
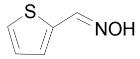
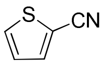
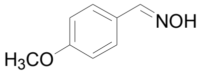
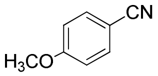
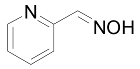
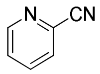
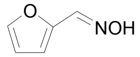
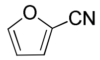
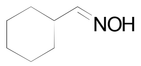
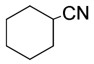
Values in brackets corresponds to the respective CO IR band area normalized to catalyst surface area (see details in experimental section).[a] CO interacting with hydroxyl groups, [b] physisorbed CO, [c]CO interacting with Ce^{3+} (55).

Table 4. Distribution of Lewis base sites on the different samples monitored by FTIR of $CHCl_3$ adsorption

Catalyst	**OH**[a]	**IR Lewis Basic sites (cm^{-1})**				
MgO	3020(0.8)		2988(10.7)		2951(10)	2890-2835(12.2)
$nCeO_2$	3026(5.6)	2995(12.9)			2960(4.87)	
CeO_2	3006(16.1)			2970(5.6)		
TiO_2	3008(60.6)				2967(3.5)	
Al_2O_3	3001(0.3)					

Values in brackets correspond to the respective νC-H IR band area normalized to catalyst surface area (see details in experimental section). [a] $CHCl_3$ interacting with hydroxyl groups.

Table 5. Dehydration of aliphatic and aromatic oximes in the presence of $nCeO_2$ as a catalyst

Entry	Aldoxime	Product	t (h)	Conv. (%)	Yield Nitrile (%)	Yield Aldehyde (%)	Yield Amide (%)
1			3	100	90	7	0
2			0.5	100	97	2	0
3			1	100	93	4	0
4			1	100	91	6	0
5			1	100	80	0	18
6			1.5	100	93	7	0
7			6	100	61	0	39
8			0.5	100	65	0	30
9			6	100	80	9	0
10	$CH_3(CH_2)_5C=NOH$	$CH_3(CH_2)_5C\equiv N$	2	100	95	5	0
11	$CH_3(CH_2)_6C=NOH$	$CH_3(CH_2)_6C\equiv N$	2	100	89	10	0
12	$CH_3(CH_2)_8C=NOH$	$CH_3(CH_2)_8C\equiv N$	4	100	93	7	0

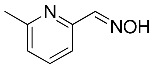
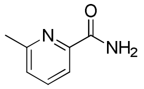
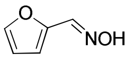
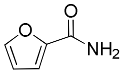
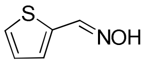
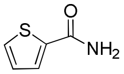
Reaction conditions: Oxime (1 mmol), catalyst 50 mg, at reflux of o-xylene (3 mL) under N_2 using a Dean Stark apparatus.

Table 6. One pot synthesis of 2-picolinamide from 2-pyridinealdoxime in the presence of $nCeO_2$ and different amount of water added

Entry	**H_2O/Substrate Molar ratio (II step)**	**Time (h)**	**Conv. (%)**	**Yield amide (%)**	**Yield Nitrile (%)**
1	2	21	100	78	22
2	14	8	100	99	1
3	56	8	100	99	1

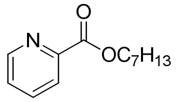
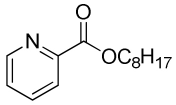
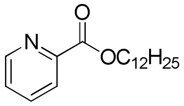
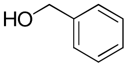
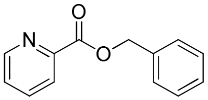
Reaction conditions: 2-pyridinealdoxime (1 mmol, 122 mg), $nCeO_2$ (50 mg) in o-xylene (3 mL) under atmosphere of N_2; I step at reflux of o-xylene. After 6 hours of reaction water was added and the temperature was lowered at 110 °C (II step).

Table 7. One pot synthesis of amides from aldoximes in the presence of $nCeO_2$

Aldoxime	**Product**	**t (h)**	**Conv. (%)**	**Yield Amide (%)**	**Yield Nitrile (%)**
		20	100	73	27
		32		88	11
		20	100	81	19
		34		94	6
		22	100	75	25
		36		85	15

Reaction conditions: aldoxime (1 mmol), $nCeO_2$ (50 mg), o-xylene (3 mL)under atmosphere of N_2; I step at reflux of o-xylene. In the second step 56 mmol of water was added and the temperature was lowered at 110 °C.

Table 8. One pot synthesis of 2-picolinic acid alkyl esters from 2-pyridinealdoxime in the presence of $nCeO_2$ as a catalyst

Alcohol	Product	t (h)	Conv. (%)	Yield Ester (%)	Yield Amide (%)
$CH_3(CH_2)_5CH_2OH$		26	100	84	16
$CH_3(CH_2)_6CH_2OH$		26	98	89	11
$CH_3(CH_2)_{10}CH_2OH$		36	98[a]	84	14
		48	98[a]	64	34

Reaction conditions: 2-pyridinealdoxime (1 mmol, 122 mg), alcohol (10 mmol), H_2O (2 mmol, 36 mg), catalyst $nCeO_2$ (50 mg) at reflux of o-xylene (3 mL) under atmosphere of N_2. [a] Reaction was carried out using n-butylbenzene as a solvent at 180 °C.

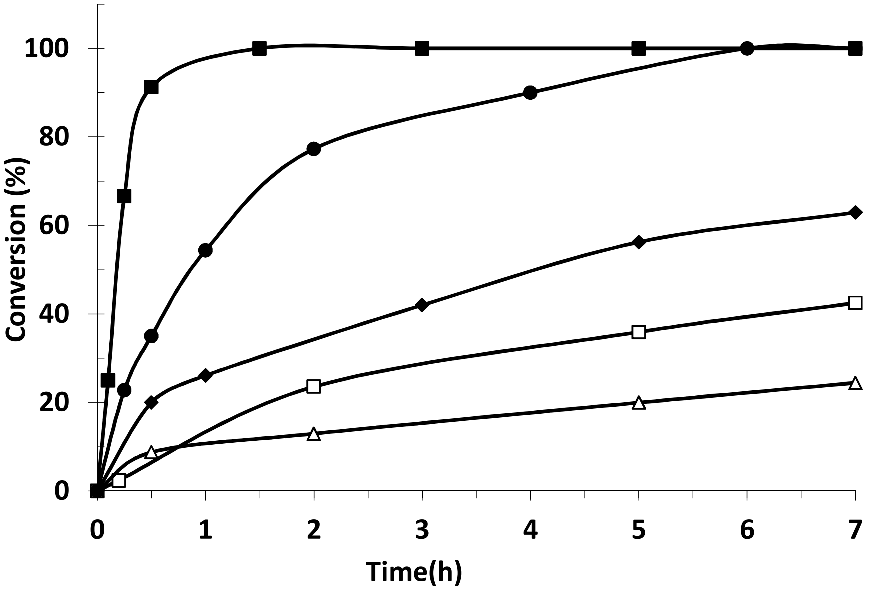


Figure 1. Conversion kinetic plots of dehydration of 4-methoxybenzaldehyde oxime by various metal oxides. $nCeO_2$ (■), CeO_2 (♦), TiO_2 (□), Al_2O_3 (Δ), MgO (●). Reaction conditions: 4-methoxybenzaldehyde oxime (1 mmol, 151 mg), catalyst (48 mg) at reflux of o-xylene (3 mL) under N_2 using a Dean Stark apparatus.

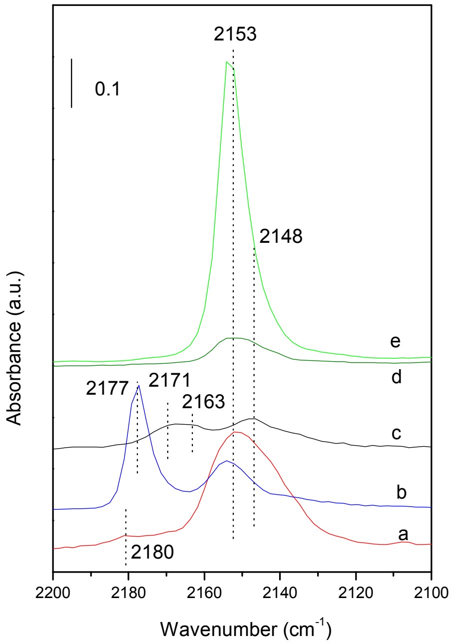


Figure 2. IR spectra of CO adsorption at saturation coverage on a) Al_2O_3, b) TiO_2, c) MgO, d) $nCeO_2$ and e) CeO_2 (Spectra normalized to sample weight).

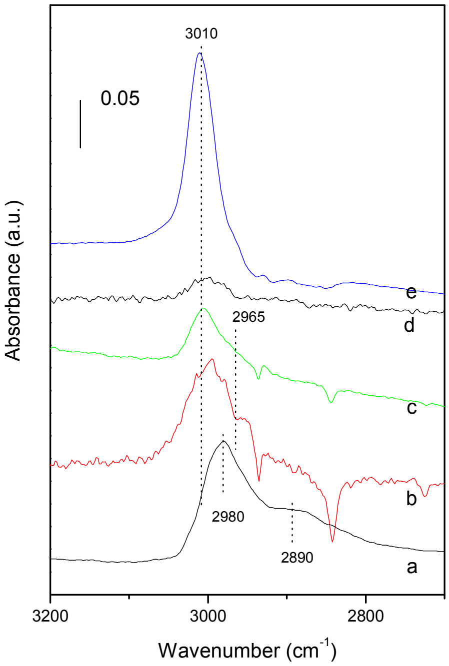


Figure 3. IR spectra of $CHCl_3$ adsorption at saturation coverage on a) MgO, b) $nCeO_2$, c) CeO_2, d) Al_2O_3 and e) TiO_2. (Spectra normalized to sample weight).

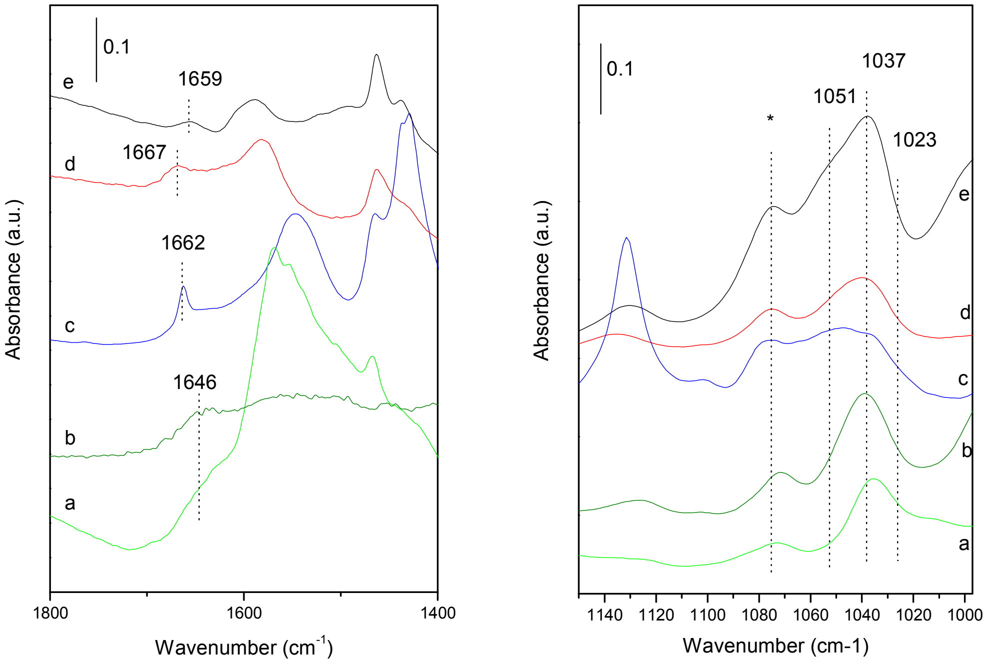


Figure 4 IR spectra of 7mbar Propionaldehyde oxime adsorbed at 25 °C on a) CeO_2 b) $nCeO_2$ c) TiO_2 d) Al_2O_3 e) MgO, in the 1800-1400 cm^{-1} IR region (νC=N) **(a),** and in the 1150-990 cm^{-1} IR region (νN-OH) **(b).** Spectra normalized to sample weight. *Stretching vibration not directly related to the N-OH group

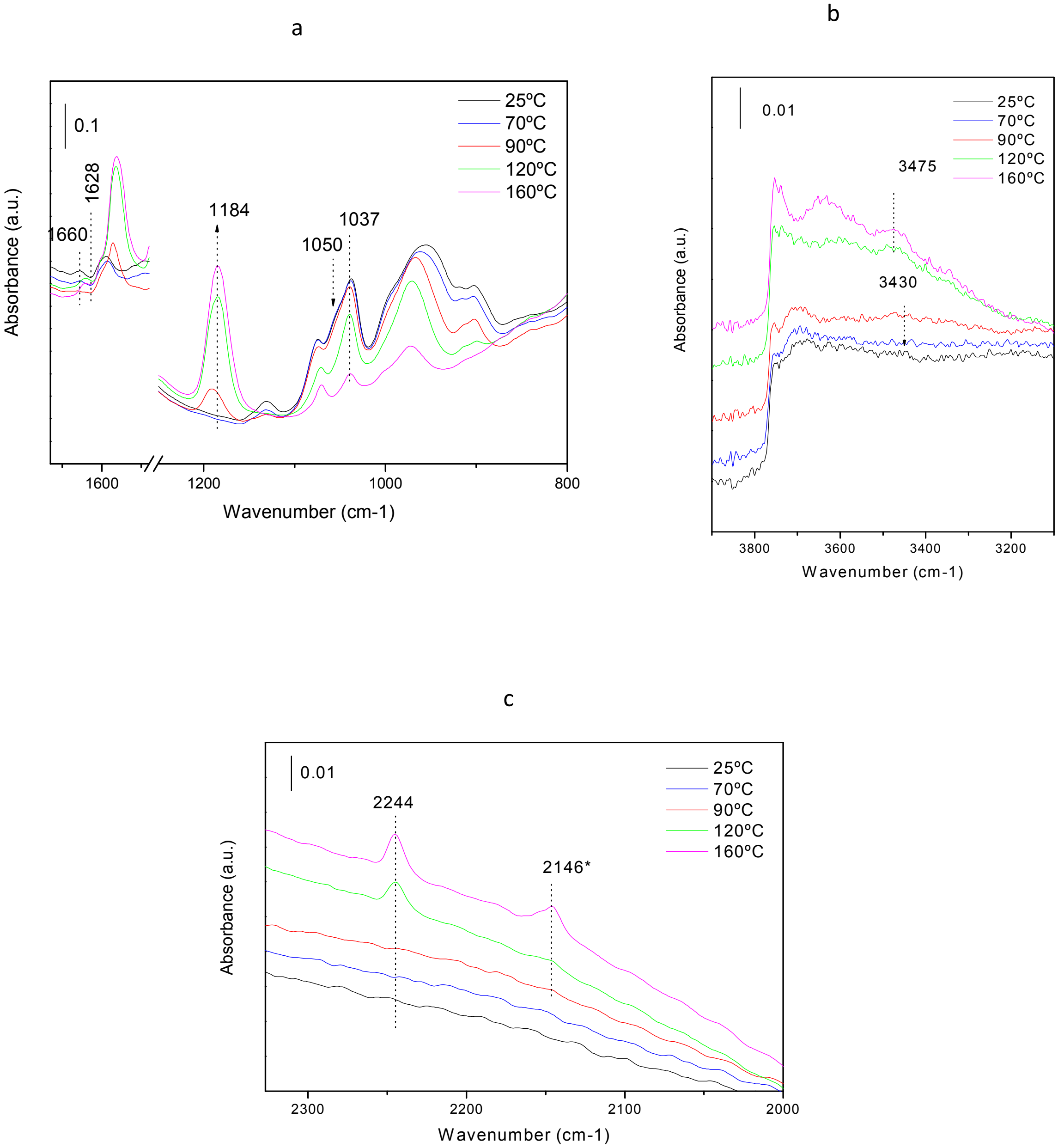


Figure 5 a-c. IR spectra in the 1730-800 cm^{-1} (a), 3800-3000 cm^{-1} (b) and 2300-2000 cm^{-1} (c) IR region of MgO sample after oxime adsorption at increasing temperatures, 25 ^{o}C, 70 ^{o}C, 90 ^{o}C, 120 ^{o}C and 160 ^{o}C. *2145 cm^{-1} IR band in Fig. 5c is due to carbon monoxide. CO is formed due to oxime decomposition on the catalysts surface.

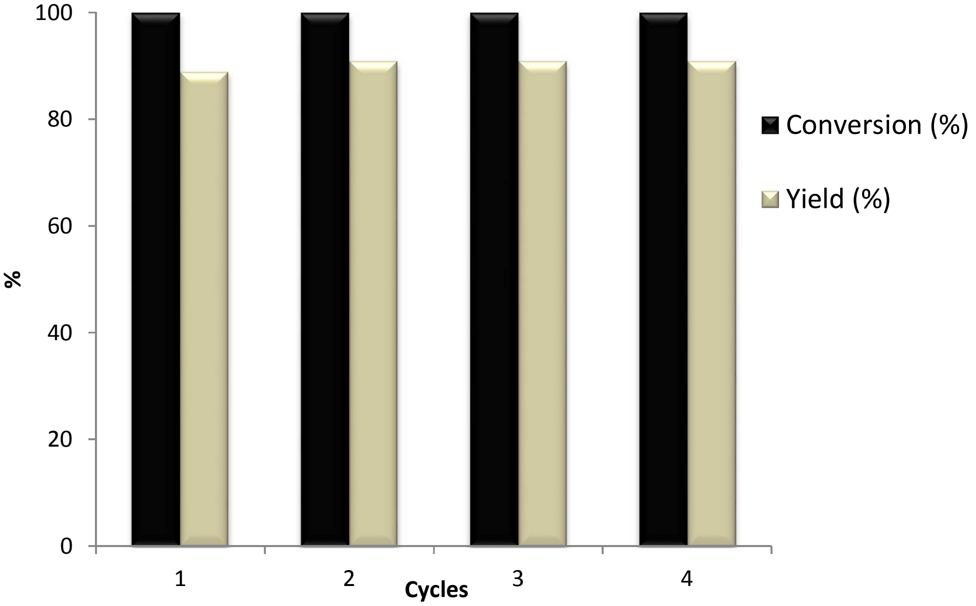


Figure 6. Yield of nitrile and 4-methoxybenzaldoxime conversion for the each catalytic cycle.

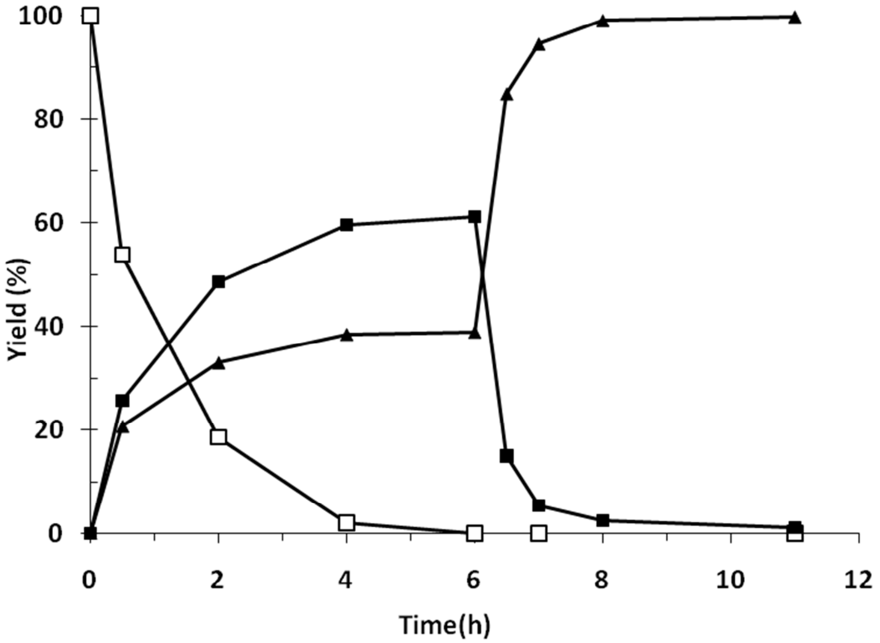


Figure 7. Yield versus time plot for one pot synthesis of 2-pyridinecarboxamide from 2-pyridinealdoxime using $nCeO_2$ as a catalyst. 2-Pyridinecarboxamide (▲), 2-cyanopyridine (■),2-pyridinealdoxime (□). Reaction conditions: 2-pyridinealdoxime (1 mmol, 122 mg), catalyst $nCeO_2$ (50 mg), o-xylene (3 mL) under atmosphere of N_2; I step at reflux of o-xylene. After 6 hours of reaction water (14mmol) was added and the temperature was lowered at 110 °C (II step).

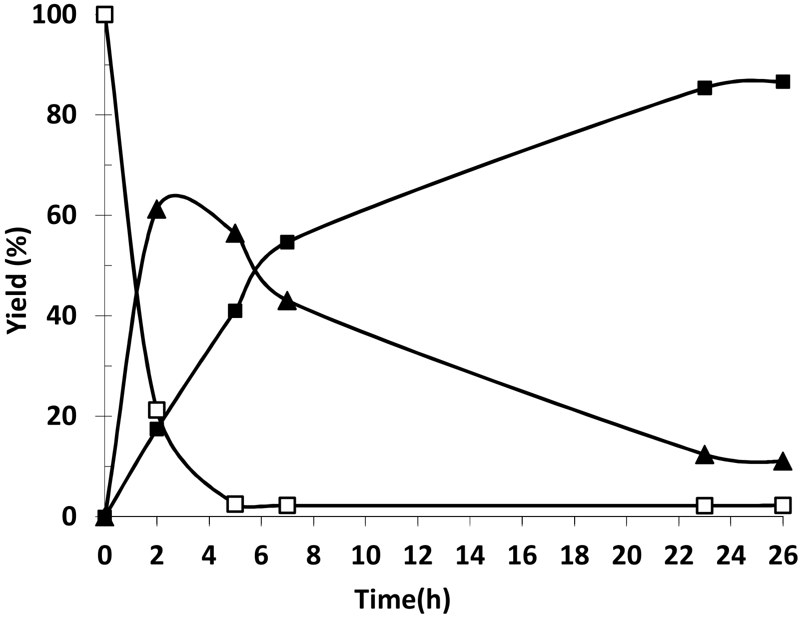
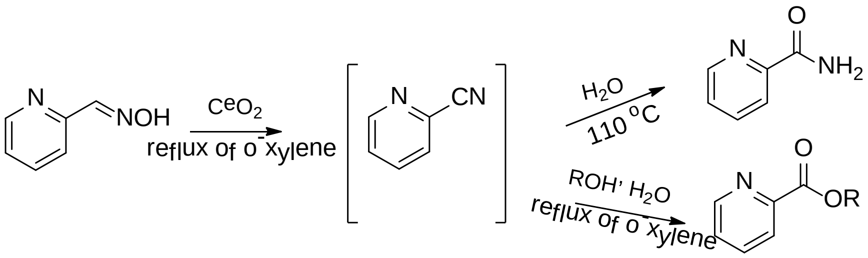


Figure 8. Yield versus time plot for one pot synthesis of 2-picolinic acid octyl ester from 2-pyridinealdoxime using $nCeO_2$ as a catalyst. 2-picolinic acid octyl ester (■), 2-pyridinecarboxamide (▲), 2-pyridinealdoxime (□). Reaction conditions: 2-pyridinealdoxime (1 mmol, 122 mg), H_2O (2 mmol, 36 mg), catalyst $nCeO_2$ (50 mg) at reflux of o-xylene (3 mL) under atmosphere of N_2.

Graphic for manuscript



Nitriles can be obtained selectively by dehydration of aldoximes using nanosized CeO_2 as acid-base catalyst. The reaction can be coupled with hydration and esterification of nitriles to obtain amides and esters respectively in one-pot process.