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Article

Nano-sized $NiLa_2O_4$ spinel–$NaBH_4$-mediated reduction of imines to secondary amines

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ABSTRACT

Nano-sized $NiLa_2O_4$ spinel was produced by thermal decomposition of Ni–La compounds via a sol-gel method. The well-crystallized spinel structure was formed after calcination at 750 °C. The physicochemical properties of the spinel were investigated using differential thermal analysis, X-ray diffraction, transmission electron microscopy, scanning electron microscopy, and particle size distribution analysis. The results show that the nanoparticles have regular shapes with well-defined crystal faces and consist of uniform quasi-spherical crystallites of average size 40 nm. The refined unit cell parameters are a = 3.861205 Å and c = 12.6793 Å. This new nano-sized $NiLa_2O_4$ spinel is an efficient heterogeneous catalyst for the selective conversion of imines to the corresponding secondary amines in the presence of $NaBH_4$ as a reducing agent, in good to excellent yields. All the reactions were completely chemoselective at room temperature and had relatively short reaction times. Secondary amines with different aryl groups, including those bearing electron-withdrawing or electron-donating groups, were obtained under the optimum reaction conditions. The catalyst was readily recovered and was recycled four times with no significant loss of catalytic activity.

1. Introduction

Imine reduction to the corresponding amine is a widely used and important functional group transformation reaction in synthetic organic chemistry. Many amines are used in the pharmaceutical and agricultural industries [1–7]. Two approaches are commonly used to convert imines to amines. One is catalytic hydrogenation, which requires high pressure. The other is hydride reduction, which uses metal hydrides such as $LiAlH_4$ or $NaBH_4$ [8]. $LiAlH_4$ is normally used in a dry organic solvent in a protective inert atmosphere [9,10]; in contrast, $NaBH_4$ is an inexpensive, safe, and environmentally friendly reducing agent. Various Lewis acids such as LiCl [11], $TiCl_4$ [12], $TiCl_3$ [13], Ni_2B [14], I_2 [15], $ZrCl_4$ [16], and $CoCl_2$ [17] have been used to reduce C=N bonds in the presence of $NaBH_4$, but they are not always effective.

Spinel oxides play important roles in various catalytic applications, e.g., gaseous pollutant decomposition [18] and the water-gas-shift reaction [19]. In normal spinels, AB_2O_4, A is generally a divalent cation occupying tetrahedral sites, and B is a trivalent cation occupying octahedral sites. In inverse spinels, half of the B cations occupy tetrahedral sites, and the formula is $B(AB)O_4$.

Spinels are prepared using various methods, including hydrothermal synthesis [20], modified oxidation processes [21], forced hydrolysis [22], and ball-milling [23], solid-state [24], and microemulsion methods [25]. Sol-gel methods are preferred because they are effective and convenient techniques and use less energy and materials [26].

In this study, as part of our research on organic transfor-

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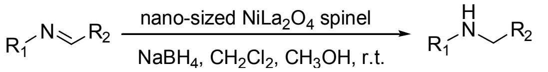


Scheme 1. Imines to the corresponding secondary amines by $NaBH_4$ and $NiLa_2O_4$.

mations using simple reagents, catalysts, and reaction media [27], we investigated the direct reduction of imines to the corresponding secondary amines by $NaBH_4$ in the presence of a catalytic amount of nano-sized $NiLa_2O_4$ spinel (Scheme 1).

2. Experimental

2.1. Preparation of $NiLa_2O_4$ powders

Citric acid (18 mmol, 3.50 g) was gradually added to a solution of $LaCl_3$ (4 mmol, 1.48 g) and $Ni(NO_3)_2\cdot4H_2O$ (2 mmol, 0.58 g) in deionized water (10 mL), with constant magnetic stirring. The gel was heated at 80 °C for 3 h and dried at 120 °C for 24 h. It was then ground to a powder in an agate mortar and fired at 750 °C in air for 4 h.

2.2. Characterization

Decomposition of the dried polymeric gel precursor was investigated using differential thermal analysis (DTA; NETZSCH, Germany) at a heating rate of 10 °C/min in the range 25–1000 °C. Crystal structures were examined by X-ray diffraction (XRD; Xpert 200, Philips, Cu K_α radiation) at a scanning rate of 0.02°/s in the 2θ range 0° to 70°. The morphologies and dimensions of the nanoparticles were examined using transmission electron microscopy (TEM; LEO 912AB, accelerating voltage 120 kV). The morphologies of the calcined powders were examined using scanning electron microscopy (SEM; LEO 1450VP, accelerating voltage 120 kV).

2.3. General procedure for imine reduction to amines

$NaBH_4$ (0.37 mmol, 0.014 g) was added at room temperature to a stirred mixture of the appropriate imine (0.5 mmol) and nano-sized spinel $NiLa_2O_4$ (0.3 mol%, 6.0 mg) in CH_2Cl_2 (1 mL). Methanol (1 mL) was added slowly under constant magnetic stirring. On completion of the reaction, which was monitored using thin-layer chromatography (TLC; *n*-hexane:ethyl acetate = 8:2), the catalyst was removed by centrifugation and the solvent was evaporated under reduced pressure. Addition of water (10 mL) gave an oily liquid; the mixture was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure to afford the product. The sample purity was confirmed using TLC and ^1H nuclear magnetic resonance (NMR) spectroscopy.

3. Results and discussion

3.1. Thermal analysis

Figure 1 shows the DTA curve of the $NiLa_2O_4$ gel precursor obtained using the sol-gel method. The DTA curve has a large endothermic peak at around 100 °C, which is related to the evaporation of water. The combustion of organic compounds such as citric acid causes the exothermic peak at around 200 °C. The small exothermic peak at 350 °C is attributed to the decomposition of nitrate, which decomposes completely at around 420 °C, giving a large exothermic peak [28]. The exothermic peak at 750 °C corresponds to crystallization of the $NiLa_2O_4$ phase. No obvious change is observed above 800 °C. It is therefore concluded that the optimum calcination temperature is 750 °C.

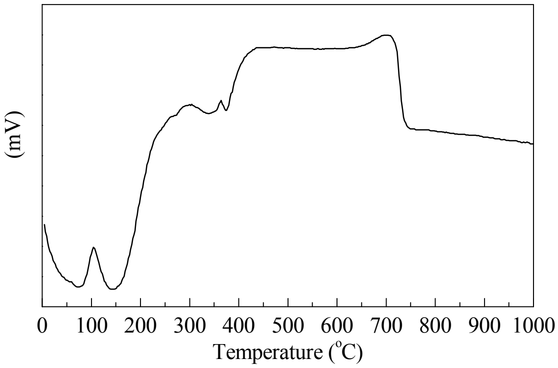


Fig. 1. DTA curve of $NiLa_2O_4$ gel precursor obtained using the sol-gel method.

3.2. XRD analysis

Figure 2 shows the XRD pattern of spinel-type $NiLa_2O_4$, which was formed when the gel was calcined at 750 °C for 4 h. No secondary phase is observed. The good agreement between the experimental and calculated data confirms that the sample consists of a single phase. Rietveld refinement showed that the material had a tetragonal unit cell with the I_4/mmm space group. The refined unit cell parameters were a = 3.861205 Å and c = 12.6793 Å. The unit cell volume was 189.035 $Å^3$, which is in close agreement with the results reported in the literature [29].

3.3. Powder morphology

Figure 3 shows a TEM image of the $NiLa_2O_4$ nanoparticles prepared at 750 °C. It shows that nanoparticles were homogeneous and consisted of uniform quasi-spherical crystallites of

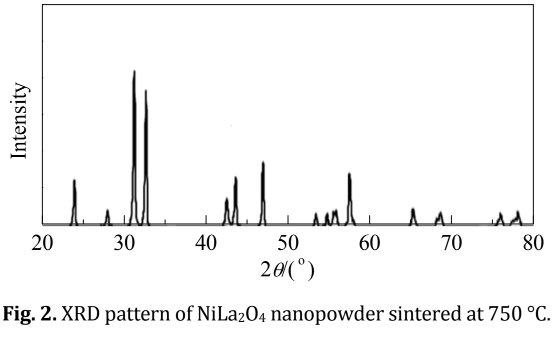


Fig. 2. XRD pattern of $NiLa_2O_4$ nanopowder sintered at 750 °C.

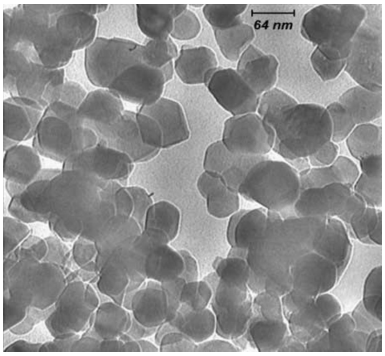


Fig. 3. TEM image of nano-sized $NiLa_2O_4$ spinel calcined at 750 °C.

average size 40 nm. This is in agreement with the results obtained using XRD [30].

The nanoparticle size affects many properties of nanomaterials and is a major indicator of quality and performance. Figure 4 shows the nano-$NiLa_2O_4$ spinel particle size distribution; this was determined from the TEM image based on more than 100 particles.

The SEM image in Fig. 5 of the $NiLa_2O_4$ nanoparticles prepared using the sol-gel method shows the typical morphology of the obtained powder. It shows that the nanoparticles had regular shapes with well-defined crystal faces [31].

3.4. *Catalysis of reduction of imines to amines by $NiLa_2O_4$ spinel nanoparticles*

The imines were synthesized by treatment of the corresponding carbonyl compounds with the appropriate amines, using a previously reported method [32,33]. *N*-(4-chlorobenzylidene)aniline was used as a model compound for optimization of the catalytic conditions for reductive hydrogenation.

Various solvents were screened for the reduction of *N*-(4-chlorobenzylidene)aniline with $NaBH_4$ using $NiLa_2O_4$ spinel nanoparticles as a catalyst (Table 1). The results show that CH_2Cl_2 was the best solvent in terms of activity. The polarity of CH_2Cl_2 is appropriate for dissolving the reactant, and appropriate interactions between the hydrogenated surface of the nanocatalyst and the substrate are triggered. Furthermore, CH_2Cl_2 is a solvent with a low moisture content, toxicity, and boiling point, and is used in many organic transformations.

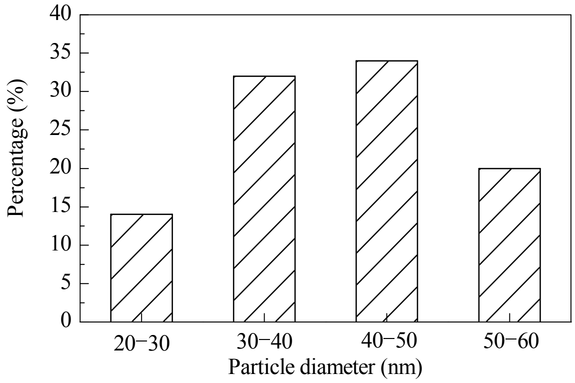


Fig. 4. Particle size distribution for calcined nano-sized $NiLa_2O_4$ spinel catalyst.

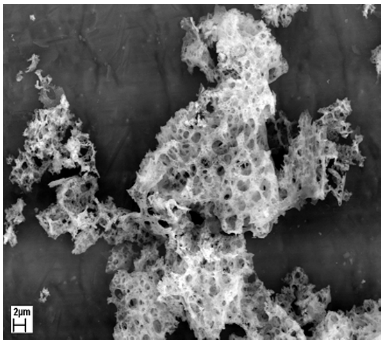


Fig. 5. SEM image of nano-sized $NiLa_2O_4$ prepared by a sol-gel method.

The catalytic role of the nano-sized $NiLa_2O_4$ spinel was clarified by performing the model reaction in the absence of a nanocatalyst and in the presence of the micro-$NiLa_2O_4$ spinel catalyst (Table 2, entries 1 and 2). Neither reaction was complete after 60 min. The reduction of *N*-(4-chlorobenzylidene)aniline was then performed using different molar ratios of the nanocatalyst to identify the optimum reaction conditions. The results show that the minimum amount of nanocatalyst needed to significantly affect the reduction process was 0.3 mol%, with 0.75 equiv. of $NaBH_4$ (Table 2, entry 9). The results also show that the use of 0.15 mol% of nanocatalyst gave a low conversion because of the lack of appropriate surface active sites at low nanocatalyst concentrations (Table 2, entry 10).

Table 1

Solvent optimization for chemoselective reduction of *N*-(4-chlorobenzylidene)aniline to *N*-(4-chlorobenzyl)aniline.

Solvent	Time (min)	Conversion [a] (%)
DMF	30	90
THF	30	88
CH_2Cl_2	5	97
$CHCl_3$	5	96
n-Hexane	5	85

Reaction conditions: *N*-(4-chlorobenzylidene)aniline 1 mmol, nano-sized $NiLa_2O_4$ spinel 1 mg, solvent 2 mL, $NaBH_4$ 4 eq., room temperature.

[a] Based on ^1H NMR spectroscopic integrations.

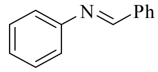
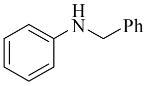
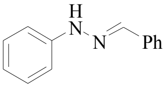
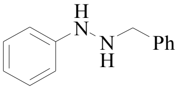
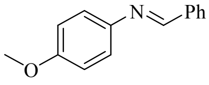
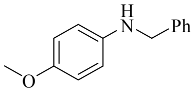
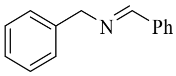
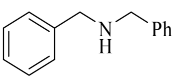
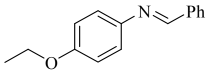
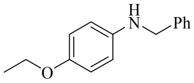
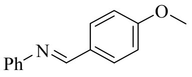
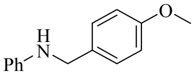
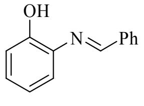
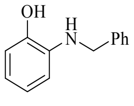
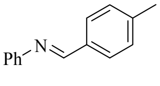
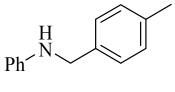
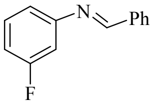
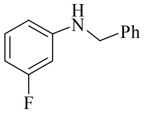
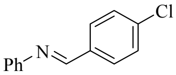
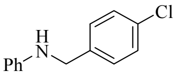
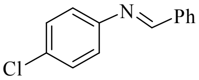
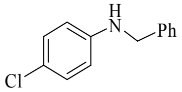
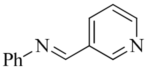
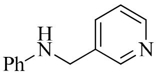
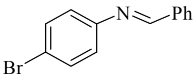
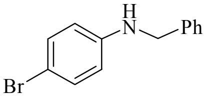
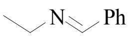
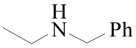
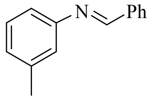
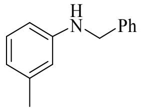
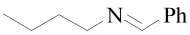
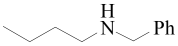
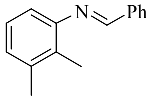
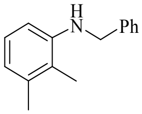
Table 2

Data for reduction of *N*-(4-chlorobenzylidene)aniline to *N*-(4-chlorobenzyl)aniline.

Entry	Nano-sized $NiLa_2O_4$ (mol%)	$NaBH_4$ (eq.)	Time (min)	*t* (°C)	Conversion [a] (%)
1	None	4	60	25	40
2	Micro-$NiLa_2O_4$ (1 mol %)	4	60	25	63
3	1	4	10	25	95
4	1	2	10	25	96
5	1	1	10	25	98
6	1	0.75	10	25	97
7	1	0.50	10	25	50
8	0.6	0.75	10	25	97
9	0.3	0.75	10	25	95
10	0.15	0.75	60	25	50
11	0.3	0.75	35	0	73
12	0.3	0.75	6	40	96

[a] According to TLC monitoring and ^1H NMR spectroscopic integration.

Table 3
Substrates tested in reduction of imines to amines with $NaBH_4$ in the presence of nano-sized $NiLa_2O_4$.

Entry	Imine	Time (min)	*Sec*-amine	Yield [a] (%)	TOF [b] (h^{-1})	Entry	Imine	Time (min)	*Sec*-amine	Yield [a] (%)	TOF [b] (h^{-1})
1		10		98	1963	10		15		92	1228
2		15		90	1202	11		2		92	9212
3		15		97	1295	12		2		88	8812
4		20		97	971	13		5		85	3405
5		5		90	3605	14		15		95	1268
6		2		95	9513	15		5		97	3885
7		2		98	9813	16		15		91	1215
8		5		92	3685	17		15		86	1155
9		10		86	1722						

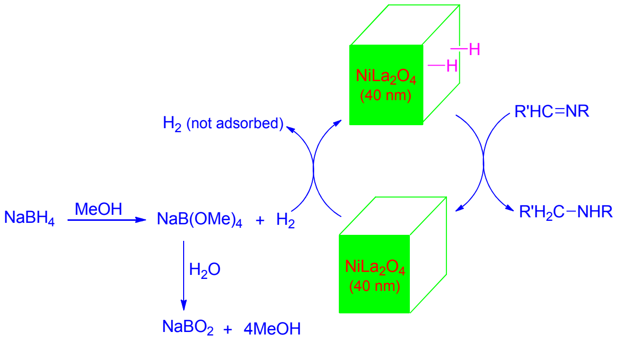
Reaction conditions: Substrate 0.5 mmol, $NiLa_2O_4$ spinel nanoparticles 6 mg, CH_2Cl_2 1 mL, MeOH 1 mL, $NaBH_4$ 0.75 eq., room temperature.
[a] Determined by ^1H NMR spectroscopy.
[b] Turnover frequency defined as mmoles of products obtained per mmoles of catalyst per hour.

Table 3 shows the general applicability of the current method in the synthesis of a wide variety of secondary amines. The reactions were performed by mixing the synthesized imines with $NaBH_4$ in methanol in an ambient atmosphere until TLC showed the complete disappearance of the imine and formation of the corresponding secondary amine. In all cases, excellent yields of secondary amines with different aryl groups, including those bearing electron-withdrawing or electron-donating groups, were obtained in short reaction times under the optimum reaction conditions.

The mechanism of heterogeneous hydrogenation is unclear, partly because the reactive sites on the metal surface cannot be as precisely described as can small molecule reagents in solution. However, it is probable that hydrogen is adsorbed onto the surface of the catalyst, forming metal–hydrogen bonds; this type of intermediate has been implicated in the hydrogenation of unsaturated double bonds, particularly on the nanoscale [34–36]. A suggested mechanism for the reduction of imines to their corresponding secondary amines over the nano-sized $NiLa_2O_4$ spinel catalyst in the presence of $NaBH_4$ is shown schematically in Scheme 2.

The nano-sized $NiLa_2O_4$ spinel catalyst is insoluble in organic solvents, therefore it can easily be recovered. The catalyst reusability was examined under the optimum reaction conditions, using *N*-(4-chlorobenzylidene)aniline reduction as a model reaction. In each cycle, the catalyst was recovered, washed with ethyl acetate, and dried before use in the next reaction. It is important to note that the catalyst was reused four times without significant loss of activity and selectivity, as shown in Fig. 6.

The SEM and TEM images of the nano-sized $NiLa_2O_4$ spinel after the fourth cycle are shown in Fig. 7. The surface rough-



Scheme 2. Proposed mechanism for the reduction of imines to secondary amines.

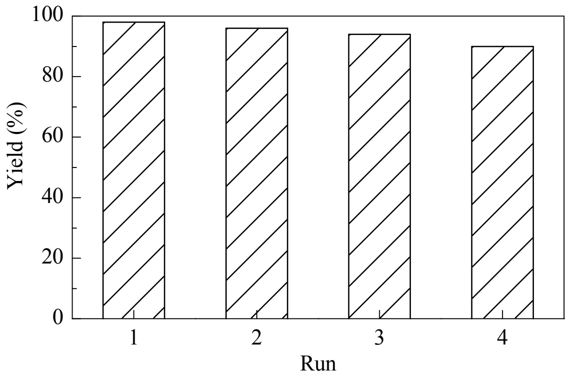


Fig. 6. Recycling of $NiLa_2O_4$ spinel nanopowder in selective reductive hydrogenation of imines to corresponding secondary amines.

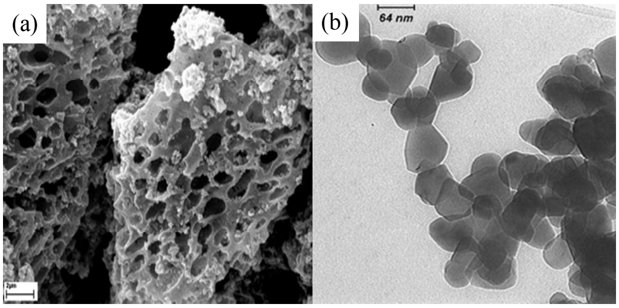


Fig. 7. SEM (a) and TEM (b) images of nano-sized $NiLa_2O_4$ spinel after fourth cycle.

ness of the used catalyst increased, which could be attributed to carbon deposition on the catalyst surface, but its activity did not decrease significantly.

A literature survey was performed to compare this method with some previously reported methods, including $NaBH_4$ reductive hydrogenation of imines. As shown in Table 4, the nano-sized $NiLa_2O_4$ spinel is an efficient catalyst for this selective reduction.

4. Conclusions

We developed a novel, highly efficient, and easy protocol for the synthesis of secondary amines from the corresponding imines in the presence of $NaBH_4$. The procedure has several advantages over other methods, including improved yields, cleaner reactions, a simple experimental procedure, and the use of easily prepared and inexpensive starting materials. This approach is therefore a useful and attractive strategy in synthetic organic chemistry.

Acknowledgments

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Table 4
Comparison of some other catalysts with nano-sized $NiLa_2O_4$ spinel.

Catalyst	Amount of catalyst (eq.)	Temperature (°C)	Time (min)	Amount of $NaBH_4$ (eq.)	Yield (%)	Ref.
H_3BO_3	1	r.t.	40	1	80	[37]
Al_2O_3	1.4	r.t.	5–15	3	80–98	[38]
Rany Ni	27–55 mol%	40–60	10–30	3.2	75–93	[39]
Nano-sized $NiLa_2O_4$	0.75 mol%	r.t.	2–20	0.75	90–98	This work

Graphical Abstract

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Nano-sized $NiLa_2O_4$ spinel–$NaBH_4$-mediated reduction of imines to secondary amines

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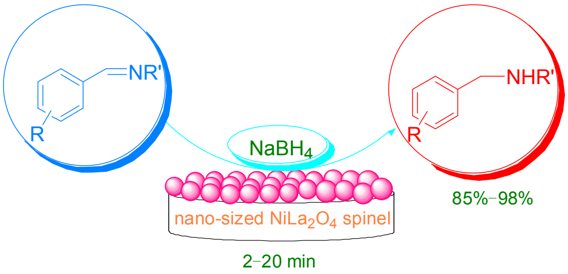

The well-crystallized nano-sized $NiLa_2O_4$ spinel structure is formed and applies as an efficient heterogeneous catalyst for selective conversion of imines to the corresponding secondary amines in the presence of $NaBH_4$ as reducing agent.

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