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### Nickel oxide nanoparticle: A green and recyclable catalytic system for the synthesis of diindolyloxindole derivatives in aqueous medium

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Abstract

This study focuses on nano-NiO particles as a green and inexpensive nanocatalyst for the synthesis of diindolyl oxindoles, an important class of potentially bioactive compounds. The oxindole derivatives were prepared by the condensation of indole and isatin compounds in water, an excellent solvent in terms of environmental impact and reduction waste production.

Keywords: Nano particle; Nano-NiO; Green chemistry; Diindolyloxindole

#### 1. Introduction

Recently, great attention has been focused from both environmental and economical points on the use of heterogeneous solid acid catalysts for various organic transformations.<sup>1,2</sup> Heterogeneous catalysts are always superior to their homogeneous counterparts in terms of many aspects such as operational simplicity, reusability, environmental compatibility and high selectivity. With the advancement of nanoscience and nanotechnology, nanoparticulate heterogeneous catalysts have received notable attention in organic transformations on the ground of their ability to enhance faster rates of organic reactions, high catalytic activity and higher yield of products which is due to their ability to afford high particle size-tovolume ratio along with greater surface area.<sup>3</sup> During recent years, nickel oxide nanoparticle has attracted much attention as an inexpensive and nonhazardous catalyst or an effective promoter that can enhance the reactivity and selectivity of various organic reactions.4

In many cases, organic solvents which are used in huge amounts for many different applications have a negative impact on the health and the environment. One of the key areas of green chemistry is the elimination of solvents in chemical processes or the replacement of hazardous solvents with environmentally benign solvents. Water emerged as a useful alternative solvent for several organic reactions owing to many of its potential advantages such as safety, economy and environmental concern. Sometimes it shows higher reactivity and selectivity compared to other conventional organic solvents due to its strong hydrogen bonding ability.  $^{6,7}$ 

On a different note, oxindole derivatives often appear as important structural components in biologically active and natural compounds. Among oxindole systems, spirooxindoles have received considerable attention due to their wide range of useful biological properties, which include antibacterial, antiprotozoal, anti-inflammatory activities and progesterone receptors (PR) agonists. <sup>8-13</sup> Due to the pharmacological properties of oxindoles, development of synthetic methods enabling easy access to these compounds are desirable. In continuation of our work on the synthesis of biologically important compounds using simple, efficient and nontoxic catalysts, <sup>14-17</sup> in this paper we report synthesis of diindolyloxindole derivatives by the coupling of indole and isatin derivatives in the presence of nano-NiO as an inexpensive and green catalyst in aqueous medium.

#### 2. Results and discussion

Initially, nickel oxide nanoparticles was synthesized by the reaction of nickel nitrate hexahydrate with urea in deionized water and was heated at 115 °C for 1.5 h in an oil bath. Resulting compound was dried and was calcined in at 400 °C for 1 h. Then Nano NiO were characterized by XRD, DLS, BET and TEM. XRD patterns of the products obtained after the precursors were calcined at 400 °C. All of these diffraction peaks in Figure 1, not only the peak positions

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appearing at  $2\theta = 37.37$ , 43.43, 62.97, 75.52, and 79.48 but also their lattice parameters, were quite consistent with those of the standard JCPDS Card No. 04-0835 for the standard spectrum of the pure NiO. The average size of the NiO particles was estimated to be about 9 nm by the Debye–Scherrer equation.



Fig. 1 XRD pattern of NiO nanoparticle

TEM analysis of NiO nanoparticle (Fig. 2) provided information on the size of NiO nanoparticles. the mean particle size determined by TEM is very close to the average particle size calculated by Debye– Scherer formula from the XRD pattern. The particle size distribution of NiO showed that the average diameter of the particles was 11 nm (Fig 3).



Fig. 2 TEM pattern of NiO nanoparticle



Fig. 3 particle size distribution of NiO nanoparticle

The average hydrodynamic size of NiO NPs in water determined by dynamic light scattering (DLS). Size dispersion by number patterns obtained befor and after the precursors were calcined at 400  $^{\circ}$ C (Fig 4 and 5). When NiO NPs were calcined number of nanoparticle with higher size decreased.





Fig. 5 Size dispersion by number NiO after calcinition

In order to show the merit of synthesized heterogeneous catalyst in organic reactions, Nano NiO was used as an efficient and inexpensive catalyst for synthesis of a series of analogues of oxindole using various isatins and indoles. Indole and isatin were selected as the model substrates and reacted under different experimental variants (Scheme 1).



#### Scheme 1. Synthesis of 3,3-diindolyloxindole

To obtain the optimized reaction conditions, we changed the amount of catalyst. The results are summarized in Table 1. Consequently, among the tested temperature and the amount of catalyst, the condensation of indole and isatin was best catalyzed by 0.004 gr of Nano NiO at 70  $^{\circ}$ C as the reaction was completed within a high yield. In the presence of 0.0004 gr of catalyst, the model reaction was not completed for 30 min and only 50% of the product was obtained. Further increases in the amount of Nano NiO (0.008 gr) in mentioned reaction did not show any significant effect on the product yield.

**Table 1** Effect of the amount of catalyst on the synthesis of<br/>oxindole catalyzed by nano-Ni $O^a$ 

Entry	Cat.(gr)	Time(min)	Yield(%)
1	0.008	15	92
2	0.004	15	87
3	0.0008	120	88
4	0.0004	120	83

 $^aReaction \ conditions: isatin (1 mmol), indole (2 mmol) and water (2 mL) at 70 <math display="inline">^oC$ 

<sup>b</sup> The yield refers to pure isolated product

To evaluate catalytic activity of nano-NiO, the model reaction was carried out in water (2 mL) at 70  $^{\circ}\mathrm{C}$  for 30 min in the presence of

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different catalytic systems (0.004 gr), separately. The results are shown in Table 2. As it is evident from the results, nano-NiO was the most effective catalyst in terms of yield of the oxindole (98%) while other catalysts formed the product with the yields of 33-68% (Table 2, Entries 2-6). To establish the catalytic role of Nano NiO, indole was treated with isatin in the absence of catalyst. In this case, the reaction proceeded in low yield over model reaction times (30 min) (Table 2, Entry 9).

 Table 2
 Synthesis of 3,3-diindolyloxindole in the presence of various catalytic systems

Entry	Catalyst	Yield(%)
1	NanoNiO	98
2	NiO	45
3	CdO	52
4	PbO	65
5	$As_2O_3$	67
6	CuO	68
7	CaO	38
8	$Al_2O_3$	33
9	None	10

<sup>a</sup>Reaction conditions: isatin (1 mmol), indole (2 mmol), catalyst (0.004 gr) and water (2 mL) at 70 °C for 30 min

<sup>b</sup> The yield refers to pure isolated product

Further explore the scope and limitation of this protocol under the optimized conditions (0.004 gr catalyst in  $H_2O$  at 70 °C), particularly in regard to library construction, was evaluated using various isatin and indole compounds (Table 3). In all cases, the reaction proceeded readily to afford the corresponding oxindoles in good to excellent yields (60- 98%) in very short reaction times (0.5- 1.5 h).

 Table 3 Preparation of 3,3-diindolyloxindole derivatives<sup>a</sup>



	Reacta	ant				
Entry	Indole		Isatin		Time(h)	Yield
	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>		(%) <sup>b</sup>
1	Н	Н	Н	Н	0.5	98
2	Н	Н	Н	$NO_2$	0.5	95
3	Н	Н	Н	Br	0.5	92
4	Н	Н	Me	$NO_2$	0.5	95
5	Н	Н	Me	Н	1.5	90
6	Н	Н	Me	Br	1.5	80
7	Н	Н	PhCH <sub>2</sub>	Br	1.5	93
8	Н	Н	PhCH <sub>2</sub>	Н	1.5	60
9	Н	Н	PhCH <sub>2</sub>	$NO_2$	1.5	75
10	Me	Н	Н	Н	1	90
11	Me	Н	PhCH <sub>2</sub>	Н	1.5	85
12	Me	Н	Н	Br	1	95
13	Me	Н	Н	OMe	1.5	80
14	Me	Н	Et	Br	1.5	90

<sup>a</sup>Reaction conditions: isatin compounds (1 mmol), indole compounds (2 mmol), Nano NiO (0.004 gr) and water (2 mL) at 70 °C <sup>b</sup> The yield refers to pure isolated product

These reactions also proceeded with 3-methyl indole (Table 4). In these cases, the reaction times are longer than 2-methyl indole/

#### Table 4 Synthesis of 2,2-diindolyloxindole derivatives<sup>a</sup>



Entry	R <sub>1</sub>	R <sub>2</sub>	Time(h)	Yield(%)
1	Н	Н	1	80
2	PhCH <sub>2</sub>	Br	0.5	85
3	Н	Br	0.5	90
4	PhCH <sub>2</sub>	Н	1	98
5	Me	Н	1.5	80
6	PhCH <sub>2</sub>	$NO_2$	1.5	82

<sup>a</sup>Reaction conditions: isatin compounds (1 mmol), 3- methyl indole (2 mmol), Nano NiO (0.004 gr) and water (2 mL) at 70 °C <sup>b</sup> The yield refers to pure isolated product

In Table 5, the efficiency of our method for the synthesis of diindolyloxindole is compared with some other compared with some other published works in literature. Each of these methods have their own advantages, but they often suffer from some troubles including the use of organic solvent (entries 2-4), long reaction time (entries 2, 4 and 5) and employ of non-recyclable catalyst (entry 5).

 Table 5 Comparison of results using Nano NiO with results

 obtained by other works for the synthesis of diindolyloxindole

Entry	Catalyst	Yield (%)	Time (h)	Condition	Solvent	Ref
1	Currnt	98	0.5	70	H <sub>2</sub> O	-
2	Bi(OTf) <sub>3</sub>	92	3.0	r.t.	CH <sub>3</sub> CN	18
3	Ru-Y	93	0.5	reflux	$C_2H_4Cl_2$	19
4	PEG- OSO₃H	93	2.5	r.t.	CH <sub>3</sub> CN	20
5	CAN	95	3.0	U.S.	EtOH	21

At the end of the reaction, the catalyst could be recovered by centrifuge. The recycled catalyst was washed with dichloromethane and subjected to another reaction process. The results show that the yield of product after five runs was only slightly reduced (Fig. 6).



Fig 6.Recyclability of nano-NiO as a catalyst in the synthesis of

#### oxindoles

A reasonable pathway for the reaction of indole with isatin compounds conducted in the presence of Nano NiO is presented by Scheme 2. The first step involves the formation of activated isatin (1) followed by its reaction with indole to generate compound 2 that subsequently undergoes elimination reaction to produce the compound 4. Intermediate 4 undergoes further addition with the second indole molecule to afford oxindole derivatives.

indole.



**Scheme 2.** The proposed mechanism for the synthesis of diindolyl oxindole in the

presence of Nano NiO.

#### 3. Experimental

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#### 2.1. General Methods

Indole and isatin derivatives were purchased from Merck Chemical Company. Purity determination of the products were accomplished by TLC on silica-gel polygram SILG/UV 254 plates. Melting points were measured on an Electro thermal 9100 apparatus. IR spectra were taken on a Perkin Elmer 781 spectrometer in KBr pellets and reported in cm<sup>-1</sup>. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were measured on a Bruker DPX-250 Avance instrument at 250 MHz and 62.9 MHz in CDCl<sub>3</sub> or DMSO-d<sub>6</sub> with chemical shift given in ppm relative to TMS as internal standard. The morphology of the products was determined by using CMPhilips10 model Transmission Electron Microscopy (TEM) at accelerating voltage of 100 KV. Power X-ray diffraction (XRD) was performed on a Bruker D<sub>8</sub>-advance X-ray diffractometer with Cu K<sub>a</sub> ( $\lambda = 0.154$  nm) radiation.

#### 2.2. Preparation of nano NiO

Nickel oxide nanoparticles were prepared through the following process. The molar ratio of nickel nitrate hexahydrate to urea at 1:4, a stoichiometric amount of Ni(NO<sub>3</sub>)<sub>2</sub>. 6H<sub>2</sub>O (0.08 mol) and  $CO(NH_2)_2$  (0.32 mol) was accurately weighed and dissolved into 60 mL of deionized water, respectively. The two solutions were mixed in a beaker and stirred with a magnetic stirrer at room temperature until a homogeneous solution obtained. Thereafter, the mixture was transferred into a round bottom flask, sealed and maintained heating at 115 °C for 1.5 h in an oil bath. In this process, a kind of light green sediment (i.e., the precursor) was formed. After the reaction was completed, the precipitated powders were filtered and washed with demonized water to neutral and colorless. This was to remove the possibly adsorbed ions and chemicals to reduce the potential of agglomeration. After being dried in an oven at 90 °C for 6 h, the precursors were calcined in a muffle furnace at 400 °C for 1 h to obtain the products in dark color (i.e., NiO nanoparticles). The calcined products were then collected for further analyses.

2.3. General procedure for the preparation of oxindol derivatives

A mixture of indole (2 mmol), isatin (1 mmol), nano-NiO (0.004 gr) and water (2 mL) was stirred for the appropriate time at 70 °C, as shown in Tables 3 and 4. Completion of the reaction was indicated by TLC monitoring. After completion of the reaction, the reaction mixture was dissolved in acetone and catalyst was isolated by centrifuged. The product was afforded by evaporation of solvent and was recrystallized from EtOH to afforded the pure products in high purity and yield. Structural assignments of the products are based on their <sup>1</sup>H NMR, <sup>13</sup>C NMR and IR spectra.

2.4. Spectral data for selected products:

3,3- $\overline{Diindolyloxindole}$  (compound 1, Table 3). White Solid, m.p> 250°C; <sup>1</sup>H NMR (250 MHz, DMSO-d<sub>6</sub>) 6.79 (2H, m, ArH), 6.84 (2H, m, ArH), 6.92 (1H, m, ArH), 6.97–7.02 (3H, m, ArH), 7.22 (4H, m, ArH), 7.35 (2H, m, ArH), 10.58 (1H, s, N–H), 10.94 (2H, br s, N–H); <sup>13</sup>C NMR (62.9 MHz, DMSO) 53.4, 110.4, 112.4, 115.2, 119.1, 121.6, 121.8, 122.3, 125.1, 125.8, 126.6, 128.7, 135.5, 137.8, 142.2, 179.6; IR (KBr, cm<sup>-1</sup>) 3420, 3300, 1704, 1610, 1105, 737 cm<sup>-1</sup>; Anal. Calcd for C<sub>24</sub>H<sub>17</sub>N<sub>3</sub>O: C, 79.32; H, 4.72; N, 11.56. Found: C, 79.39; H, 4.68; N, 11.63.

3,3-Diindolyl-5-bromooxindole (compound 3, Table 3). White Solid, mp> 250 °C; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) 6.81 (2H, t, ArH), 6.88 (2H, s, ArH), 6.96 (1H, m, ArH), 7.03 (2H, m, ArH), 7.21 (2H, m, ArH), 7.30 (1H, s, ArH), 7.38 (2H, m, ArH), 7.43 (1H, m, ArH), 10.77 (1H, s, NH), 11.03 (2H, s, NH) ppm; <sup>13</sup>C NMR (DMSO-d6) 53.64, 112.65, 114.00, 114.35, 119.23, 119.35, 121.35, 121.94, 125.21, 125.35, 126.34, 128.22, 137.79, 137.84, 141.53, 179.11 ppm; IR (KBr, cm<sup>-1</sup>): 3340, 3120, 1699 cm<sup>-1</sup>; Anal. Calcd for C<sub>24</sub> H<sub>16</sub>BrN<sub>3</sub>O: C, 65.17; H, 3.65; N, 9.50. Found: C, 65.11; H, 3.49; N, 9.62.

3,3-Bis(2-methylindolyl)oxindole (compound 9, Table 3). White Solid, m.p> 250 °C; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) 1.95 (3H, s, Me), 2.09 (3H, s, Me), 6.47 (1H, m, ArH), 6.61–6.66 (2H, m, ArH), 6.71 (1H, m, ArH), 6.85–6.92 (3H, m, ArH), 6.96 (1H, m, ArH), 7.16 (1H, m, ArH), 7.21–7.24 (3H, m, ArH), 10.57 (1H, s, NH), 10.87 (1H, s, NH), 10.90 (1H, s, NH) ppm; <sup>13</sup>C NMR (DMSO-d<sub>6</sub>) 13.87, 14.05, 53.28, 110.21, 110.29, 111.21, 111.27, 118.78, 118.84, 120.15, 120.21, 120.46, 120.63, 122.13, 126.32, 127.90, 128.54, 128.68, 132.84, 134.81, 135.76, 135.83, 136.44, 142.06, 180.21 ppm; IR (KBr, cm<sup>-1</sup>) 3400, 3250, 1700 cm<sup>-1</sup>; Anal. Calcd for  $C_{26}H_{21}N_{30}$ : C, 79.77; H, 5.41; N, 10.73. Found: C, 79.85; H, 5.32; N, 10.64.

#### Conclusions

In summary, an efficient protocol for the preparation of diindolyloxindole derivatives was described. The procedure offers several advantages including the cheapness and the availability of the catalyst, mild reaction conditions and high yields of the products as well as simple experimental and isolation procedures. All these, make this protocol a useful and an attractive procedure for the synthesis of oxindole derivatives.

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#### References

(1) Das, B.; Venkateswarlu, K.; Holla, H.; Krishnaiah, M. J Mol Catal.A. 2006, 253, 107

- (2) Shaabani, A.; Rahmati, A.; Badri, Z. Catal Commun. 2008, 9, 13
- (3) Carnes, C. L.; Klabunde, K. J. J Mol Catal A. 2003, 194, 227
- (4) Biju, V.; Abdul Khadar, M. Sci Eng A. 2001, 304, 814
- (5) Wang, Y.; Zhu, J.; Yang, X.; Lu, L.; Wang, X. *Thermochim Acta*. **2005**, 437,106
- (6) Li, C. J. Chem Rev. 2005, 105, 3095

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- (7) Bazi, F.; Badaoui, H. El.; Tamani, S.; Sokori, S.; Solhy, A.; Macquarrie, D. J.; Sebti, S. *Appl Catal A*. **2006**, 211, 301
- (8) Pajouhesh, H.; Parsons, R.; Popp, F. D.; Pharm, J. Sci **1983**, 72, 318

(9) Garrido, F.; Ibanez, J.; Gonalons, E.; Giraldez, A. *Eur J Med Chem.* **1975**, 10, 143

- (10) Kamano, Y.; Zhang, H. P.; Ichihara, Y.; Kizu, H.; Komiyama,
- K.; Itokawa, H.; Pettit, G. R. *Tetrahedron Lett.* **1995**, 36, 2783
- (11) Fischer, C.; Meyers, C.; Carreira, E. M. *Helv Chim Acta*. **2000**, 83, 1175
- (12) Jnaneshwarand, G. K.; Deshpande, V. H. J Chem Res. 1999, 632
- (13) Joshi, K. C.; Chand, P. Pharmazie. 1982, 37, 864
- (14) Nasseri, M. A.; Alavi, S. A.; Zakerinasab, B. J Chem Sci. 2013, 125, 109
- (15) Nasseri, M. A.; Alavi, S. A.; Zakerinasab, B. *J Iran Chem Soc.* **2013**, 10,109
- (16) Nasseri, M. A.; Salimi, M. Lett Org Chem. 2013, 10, 164
- (17) Nasseri, M. A.; Sadeghzadeh, S. M. J Iran Chem Soc. 2014, 11, 27
- (18) Yadav Jhillu, S.; Subbareddy Basireddy, V.; Gayathri
- Kamakolanu, U.; Meraj, S.; Parsad Attaluri, R. *Div Org Chem*. 2006
- (19) Khorshidi, A. R.; Tabatabaeian, K. Ori J Chem. **2010**, 26, 3
- (20) Nasseri, M. A.; Zakerinasab, B. *Iranian JOC*. 2013, 5, 109
  (21) Wang, Sh. Y.; Ji, Sh. J. *Tetrahedron*. 2006, 62