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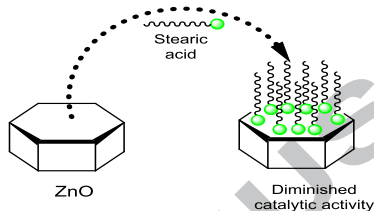
Graphical Abstract

Zinc oxide surface: A versatile nanoplatform for solvent-free synthesis of diverse isatin derivatives

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Jagatheeswaran Kothandapani, Asaithampi Ganesan, Ganesh Kumar Mani, Arockia Jayalatha Kulandaisamy, John Bosco Balaguru Rayappan and Subramaniapillai Selva Ganesan*

- Advantages**
1. Presence of Lewis acidic and basic sites
 2. Solvent-free reaction
 3. Reusable catalyst
 4. High product yield



ACCEPTED MANUSCRIPT



Zinc oxide surface: A versatile nanoplatform for solvent-free synthesis of diverse isatin derivatives

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ABSTRACT

Multicomponent reactions performed on the surface of nanostructured zinc oxide gave 3,3-bis(indolyl)indolin-2-one and xanthene derivatives with excellent yields. Both Lewis acidic (Zn^{2+}) and basic (O^{2-}) sites on the surface of zinc oxide were utilized to perform the aforementioned transformations. The significance of surface catalysis was further proved by performing the experiment with surface masked zinc oxide. The developed zinc oxide nanocatalyst was reusable up to five times without significant loss in its activity.

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Introduction

Identification of novel green methods to synthesize structurally diverse and biologically relevant molecules has received paramount importance. Among the available methods, reactions performed on solid surfaces have gained significant attention since surface catalytic properties which cannot be imitated in a solution state or gaseous state reactions.¹ Moreover, reactions run on solid surfaces enormously reduce the solvent dependency in the reaction and thereby reduce the waste formation. Hence, extensive research is devoted in developing solvent-free reactions performed with heterogeneous catalysts such as amberlyst,² clay,³ zeolite,⁴ hydrotalcite,⁵ etc. Among the heterogeneous catalysts, zinc oxide secured unique place due to the presence of both Lewis acidic (Zn^{2+}) and Lewis basic (O^{2-}) sites on surface, with high stability towards air and moisture, ready availability, inexpensive and non-toxic nature, easily tunable physical and chemical properties.^{1a,6}

The major limitation associated with bulk zinc oxide mediated surface catalysis is the requirement of stoichiometric quantities of reagent. The advent of nanotechnology substantially has solved this limitation because of the reduced size of the particles and thereby increased surface area in many folds. Hence, catalytic quantities of nanostructured zinc oxide provide sufficient surface area equal to stoichiometric quantities of bulk zinc oxide for organic transformations. Besides size, catalytic properties of zinc oxide can be further tuned by designing highly reactive structural morphologies.⁷ It is of interest to explore the surface catalytic potential of zinc oxide nanodiscs to develop a convenient green

method for the synthesis of diverse isatin derivatives. Isatin is a valuable bioactive molecule widely present in several natural systems.⁸ Isatin is the precursor of indigo dyes.⁹ Carbohydrate tethered indigo dyes are potential candidates for cancer therapy.¹⁰ Isatin derivatives displayed good anti-HIV,¹¹ anticancer,^{12a} spermicidal,^{12b} antimalarial,¹³ antiviral,¹⁴ antimicrobial,¹⁵ anticonvulsant¹⁶ and cytotoxic activities.¹⁷ Furthermore, they also exhibit human rhinovirus 3C protease,¹⁸ β -Lactamase¹⁹ and protein kinase²⁰ inhibitory activities. Representative examples of bioactive isatin derivatives are shown in Fig. 1.

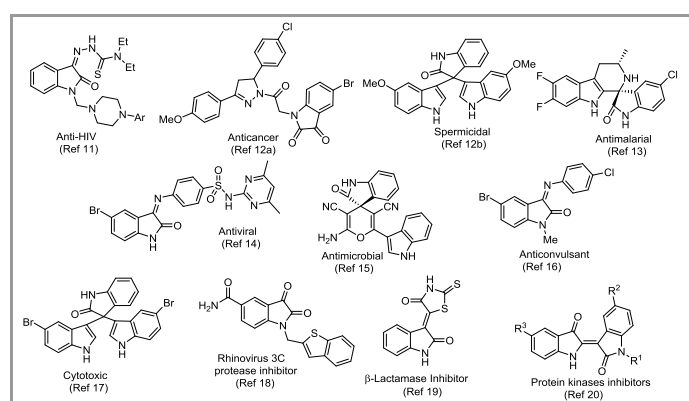


Figure 1. Representative bioactive isatin derivatives.

Results and Discussion

Simple and elegant precipitation method for the preparation of zinc oxide nanodiscs was followed instead of temperature intensive thermal evaporation²¹ or solvothermal approaches.²² The zinc oxide formed by precipitation method²³ was characterized as given below.

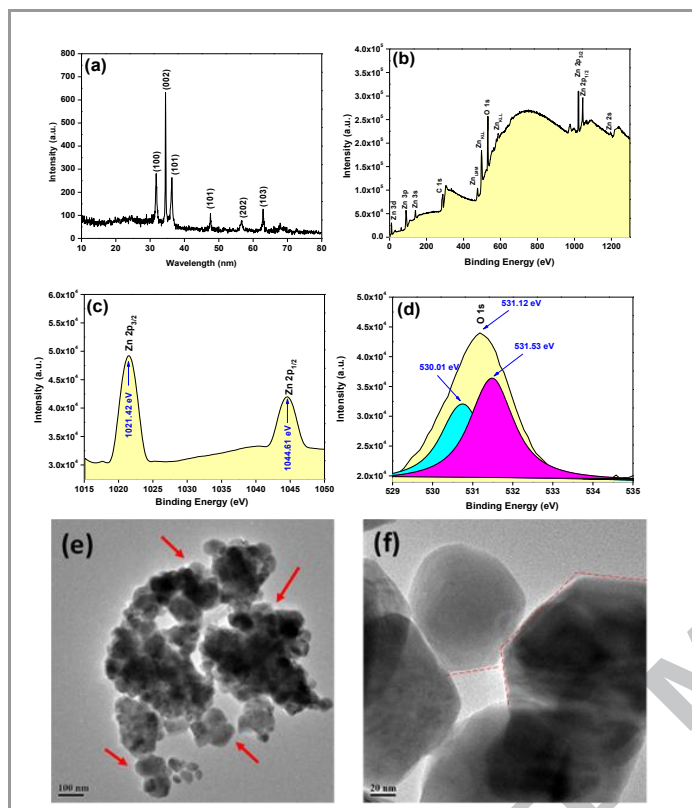
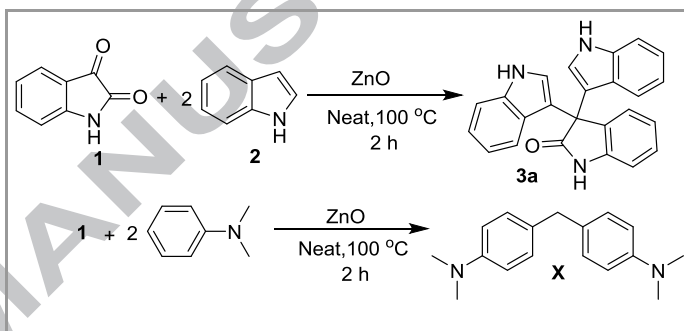


Figure 2. a) XRD pattern of ZnO nanodiscs, b) XPS survey spectra, c) narrow scan spectra of Zn-2p, d) O 1s spectra of ZnO nanodiscs, e) low and f) high magnification FE-TEM images of ZnO nanodiscs.

Fig. 2(a) shows the XRD pattern of zinc oxide nanodiscs prepared by simple precipitation technique. The sharp and intense diffraction peaks revealed the high crystalline quality of the sample. Moreover, the observed peaks confirmed the formation of zinc oxide nanodiscs with hexagonal wurtzite crystal structure and it is in agreement with JCPDS card number 36-1451.²⁴ The average crystallite size was estimated using Scherrer's formula²⁵ and found to be 44 nm. Further, zinc oxide nanodiscs were analyzed through XPS to gain information about surface composition and chemical states. Fig. 2(b) shows the survey scan spectra of the zinc oxide nanodiscs and it clearly indicated the presence of Zn, O and C elements. The presence of weak C peak in the sample might be due to the adsorption of carbon during their exposure in ambient atmosphere.²⁶ Apart from C, no other contaminants from the sample were detected. XPS spectra of Zn-2p core levels are shown in Fig. 2(c). It displayed the doublet around 1021.42 and 1044.61 correspond to Zn-2p_{3/2} and Zn-2p_{1/2}. The sharp peak at 1021.42 associated with Zn elements was in completely oxidized state.²⁷ The O 1s (Fig. 2(d)) peak can be deconvoluted into two peaks using Gaussian fitting curve. The peak about 530.01 eV corresponds to the lattice oxygen (O²⁻) of zinc oxide (Zn-O bonding). Whereas, another peak at 531.53 eV corresponds to the chemisorbed oxygen, which caused by surface hydroxyl ions (O-H bonding).²⁸ In order to examine the morphology, FE-TEM observations were carried out and are shown in Fig. 2(e) & (f). Particles were found to have smooth surface with hexagonal disc like appearance. A large amount of

nanodiscs were observed on the micrographs (highlighted in arrowhead). The size of the nanodiscs estimated from XRD is closely matched with the FE-TEM micrographs.

The Lewis acidic nature of the zinc oxide is due to the presence of Zn²⁺ ions present at the outermost layer of the zinc oxide surface. To identify the catalytic potential of Lewis acidic Zn²⁺ ions on the surface of the zinc oxide, a representative pseudo three-component reaction was carried out with isatin (1 mmol), indole (2 mmol) and zinc oxide (0.25 mmol) under neat condition at 100 °C (Scheme 1). The product **3a** was obtained in 87% yield. Decrease in the reaction temperature from 100 °C to 80 °C and 60 °C reduced the product yield to 62% and 48% respectively. Similar reactions carried out with isatin (1 mmol) and *N,N*-dimethylaniline (2 mmol) and zinc oxide (0.25 mmol) yielded 4,4'-methylenebis(*N,N*-dimethylaniline) product **X**. The formation of **X** was further confirmed by performing the reaction in the absence of isatin. A plausible mechanism for the zinc oxide catalyzed formation of **X** was given in the supporting information.



Scheme 1. Surface catalysis by ZnO.

In **3a** synthesis, after the completion of reaction, chloroform:methanol (3:3 v/v) mixture was added to the reaction medium and the zinc oxide catalyst was easily recovered by simple filtration. Evaporation of the filtrate followed by single recrystallization in ethanol solvent yielded the product **3a**. The isolated catalyst was washed with chloroform:methanol (3:3 v/v) mixture and dried in oven. The catalyst recyclability studies revealed that catalyst retained its activity till five cycles (SI). The reaction carried out with bulk zinc oxide yielded the product **3a** with 47% yield.

Interestingly, zinc oxide nanodisc catalyzed reaction performed in ethanol did not yield the product **3a**. The poor interaction of the substrates and catalyst in ethanol medium may be the reason for the diminished yield of the product. The observed high reactivity under solvent-free condition could be attributed to the proximity of the substrates on the surface of the zinc oxide. Zn²⁺ sites on the surface of zinc oxide activated the isatin carbonyl group for nucleophilic attack. To further understand the significance of surface catalysis, zinc oxide surface was masked with stearic acid by closely following a reported procedure.²⁹

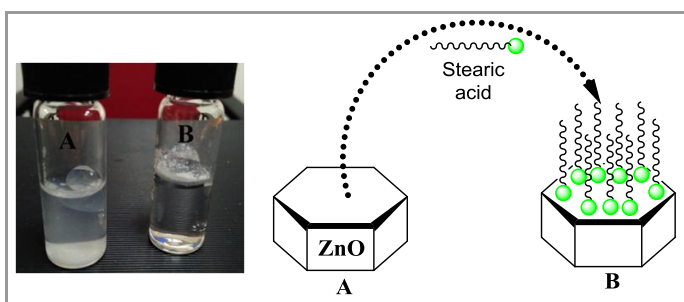
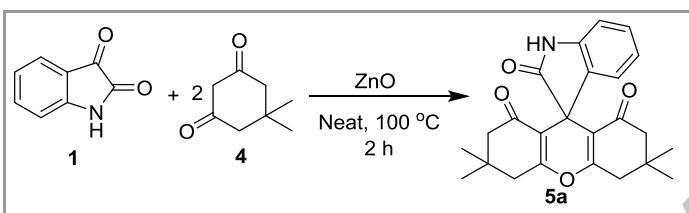


Figure 3. (A) ZnO in water. (B) Stearic acid coated ZnO on water.

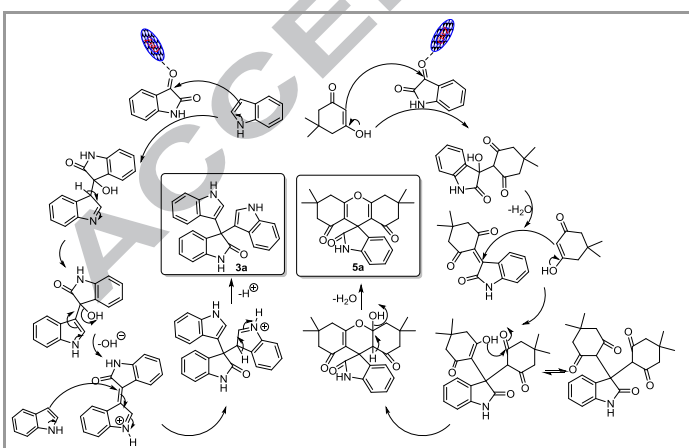
The presence of stearic acid on zinc oxide was confirmed by dispersing zinc oxide in water (Fig. 3). Due to the presence of hydrophobic fatty acid coating, stearic acid covered zinc oxide floated on the surface of water. It is reported in the literature that in the stearic acid coated zinc oxide, the hydrophobic tail would be pointing perpendicular to the surface.³⁰ The reaction carried out with stearic acid coated zinc oxide failed to yield the desired product **3a** uttering the significance of surface catalysis by unmasked zinc oxide.

Similar to Lewis acidic nature, zinc oxide also displays Lewis basic nature due to the presence of oxyanions at the zinc oxide surface. The oxyanion is capable of sequestering acidic protons from active methylene group of dimedone molecule and thereby facilitates one-pot multicomponent reactions. The initial screening of reaction of isatin (1 mmol), dimedone (2 mmol) and zinc oxide (0.25 mmol) in water under reflux condition for 2 h yielded only trace amounts of product **5a**. The same reaction under solvent-free reaction condition, gave the product **5a** with 85% yield (Scheme 2).³¹ The formation of **5a** was not observed when the reaction temperature was lowered from 100 °C to 80 °C.



Scheme 2. ZnO nanodisc assisted synthesis of xanthenes derivatives.

Plausible mechanism for the formation of **3a** and **5a** are depicted in Scheme 3. Lewis acidic Zn^{2+} ions may activate the isatin carbonyl group for the nucleophilic addition of indole to the isatin leading to the formation of **3a**. Similarly, Lewis basic sites (O^{2-}) on zinc oxide sequester the acidic protons in dimedone and thereby enabled the formation of the corresponding enolate. Addition of dimedone enolate to indole followed by intramolecular dehydration of the intermediate resulted in the formation of xanthenes product **5a**.



Scheme 3. Plausible mechanism for the ZnO catalysed isatin derivatives synthesis.

To find the substrate scope of zinc oxide catalysed synthesis of 3,3-bis(indolyl)indolin-2-one and xanthenes derivatives, the reaction was performed with various substituted indole and isatin derivatives. All the products were obtained with good to

excellent yields. The substrate scope of this reaction is shown in Fig. 4.

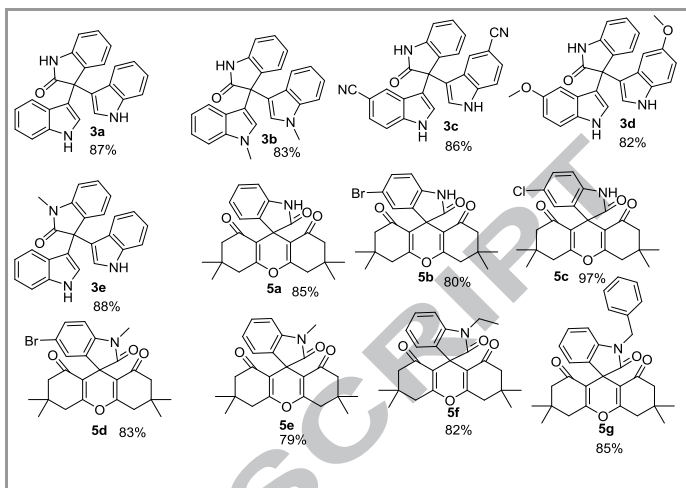


Figure 4. Substrate scope for ZnO catalyzed synthesis of **3** and **5**.

The efficiency of zinc oxide nanodiscs in **5a** synthesis was compared with other zinc oxide morphologies such as nanoflakes and nanoplatelets (Fig. 5). Both zinc oxide nanoflakes and nanoplatelets gave the product **5a** in 53% and 55% yield respectively. We presume, the number of catalytically active sites are higher in zinc oxide nanodiscs compared to other morphologies.

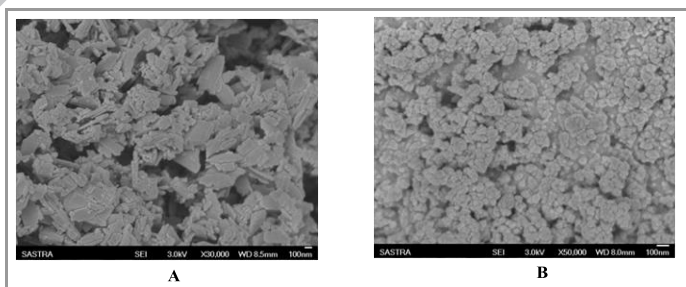


Figure 5. SEM images of (A) ZnO nanoflakes (B) ZnO nanoplatelets.

In summary, zinc oxide nanodisc mediated diverse isatin derivative synthesis was devoid of tedious work-up and chromatographic purification steps. The products were obtained with excellent yields and a single recrystallization of the products in ethanol solvent yielded analytically pure samples. Moreover, the catalyst was easily isolated from the reaction mixture by simple filtration.

Acknowledgment

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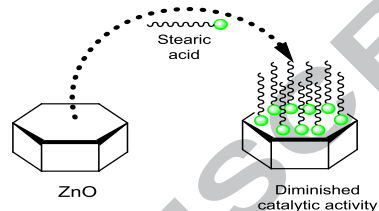
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Advantages
1. Presence of Lewis acidic and basic sites
2. Solvent-free reaction
3. Reusable catalyst
4. High product yield



Highlights

- Surface catalysis by ZnO nanodiscs is superior to other morphologies.
- Diverse isatin derivatives were synthesized under solvent-free reactions.
- The ZnO catalyst is reusable up to 5 cycles.

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