ZINC OXIDE NANOPARTICLES: AN ENVIRONMENTALLY BENIGN AND REUSABLE CATALYST FOR THE SYNTHESIS OF 1,8-DIOXO-OCTAHYDROXANTHENE DERIVATIVES UNDER SOLVENT-FREE CONDITIONS

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ABSTRACT
Zinc oxide nanoparticles (ZnO-NPs) as an environmentally benign and reusable heterogeneous catalysts for the synthesis of series of biologically significant 1,8-dioxo-octahydroxanthene derivatives. This has been accomplished by the condensation of various aldehydes with 5,5-Dimethyl-1,3-cyclohexanedione using ZnO-NPs as an environmentally benign heterogeneous catalyst. ZnO-NPs catalyst exhibited remarkable catalytic activity to achieve the synthetic targets in the range of 80-93% yield under solvent-free condition. ZnO-NPs could be used up to four cycles with similar catalytic response. The protocol provided greater selectivity, cost-efficiency, clean reaction profiles, simple work-up procedure and high yields.

Keywords: 1,8-dioxo-octahydroxanthene, 5,5-Dimethyl-1,3-cyclohexanedione, Aldehyde, Zinc oxide nanoparticles, Heterogeneous catalyst.

1. INTRODUCTION

Xanthene, especially benzoxanthenes have emerged as a special class of heterocyclic compounds having active oxygen atom. Benzoxanthene possess wide range of pharmaceutical properties, such as antiviral,[I] antibacterial[II] and anti-inflammatory[III] activities. These compounds have been utilized as antagonists for paralysis action of zoxazolamine[IV] as well as in photodynamic therapy.[V] Xanthene also exhibit spectroscopic properties, so they are widely used as a leuco-dye,[VI] in laser technologies[VII] and in fluorescent materials for visualization of bio-molecule[VIII] cascades. Thus a great deal of attention has been paid by organic chemists for the synthesis of xanthenes and benzoxanthene derivatives. Several methods have been reported for the synthesis of 1,8-dioxo-octahydroxanthene employed by the union of aldehyde and 5,5-Dimethyl-1,3-cyclohexanedione including, solid-state condensation by grinding at room temperature,[IX] NH_2SO_3H in aqueous media,[X] microwave-included synthesis in solid or liquid phase,[XI] *p*-dodecylbenzenesulfonic acid in water,[XII] and tetrabutylammonium hydrogen sulfate.[XIII] In recent years, several attempts have been made for the synthesis of xanthenes derivatives to increase the yield and to develop environmental benign procedure. Each of these reagent/catalyst

have their own advantages, however suffers from some drawbacks, such as un-satisfactory yields, drastic reaction conditions, tedious work-up procedure and use of excess of reagents and catalysts. Therefore it's desirable to develop a new catalyst for the synthesis of 1,8-dioxo-octahydroxanthene derivatives which can result in excellent yields and that too under environmental benign conditions.

Nano-chemistry is an up growing research area due to their unique properties. [XIV, XV] ZnO-NPs were found to be the promising adsorbent for the degradation of environmental pollutants, UV blocking materials, and are widely used in cosmetics, paints and fibers. ZnO was also used as a catalyst in various organic transformations. [XVI, XVII]

In continuation of our research on development of new synthetic methodologies on the synthesis of various bioactive compounds,[XVIII] directed towards the development of practical, safe and environmentally benign methodologies. Herein, we report the efficient application of ZnO-NPs as reusable and eco-friendly catalyst for the synthesis of 1,8-dioxo-octahydroxanthene derivatives under solvent-free conditions (Scheme 1).

(Scheme 1)
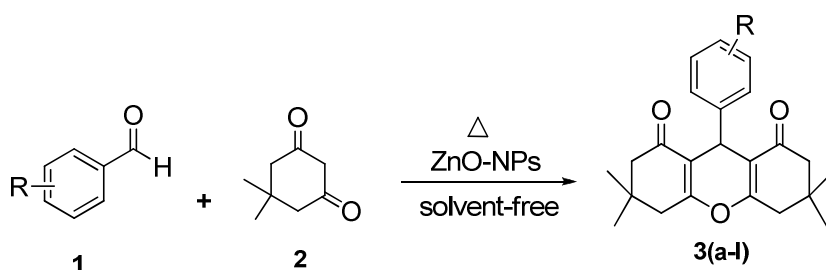
Scheme 1. Synthesis of 1,8-dioxo-octahydroxanthene (**3a-l**) using ZnO-NPs as a catalyst under solvent-free conditions

2. EXPERIMENTAL

2.1. Materials

Zinc acetate dihydrate, oxalic acid dihydrate, were obtained from M/s. S.D fine chemical India Ltd. Heterocyclic or arylaldehydes, 5,5-Dimethyl-1,3-cyclohexanedione were purchased from Sigma-Aldrich, India.

2.2. Synthesis of zinc oxide nanomaterials

Zinc oxide nanomaterials were synthesized by sol–gel method.[XIX] For this purpose, oxalic acid in methanolic solution was added to hot methanolic zinc acetate solution in a conventional reaction flask with a constant heating and stirring. The reaction temperature was maintained at 60°C throughout addition of above reactants. Thereafter, obtained materials were filtered, dried at 80°C and calcined at 500 °C. To obtain materials of other crystallite sizes, xero-gel was calcined at 900°C, 1000°C and 1100°C temperatures respectively.

2.3. Characterization of zinc oxide nanomaterials

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XRD patterns were obtained in an XPert Pro Diffractometer, Panalytical, Netherlands, using Cu Kα radiation. N_2 BET measurements were done on ASAP 2020 of Micromeritics, USA. Transmission electron microscopy (TEM) measurements were done on Tecnai transmission electron microscope of FEI make. Samples were suspended in 30 mL acetone, and then suspension was sonicated for 30 min. After that, suspension was placed on carbon coated copper grids of 3 mm dia and dried at room temperature prior to the analysis.

2.4. Catalyst activity: Synthesis of 1,8-dioxo-octahydroxanthene

The procedure for the synthesis of 1,8-dioxo-octahydroxanthene was employed by making use of a mixture of aldehyde (1.0 mmol) and 5,5-Dimethyl-1,3-cyclohexanedione (2.0 mmol) was charged in a round bottomed flask. A catalytic amount of ZnO-NPs (0.3 mmol) was added and the reaction was heated at 120°C (oil bath) with constant stirring under solvent free condition for certain period of time as required. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was cooled to room temperature and dissolved in ethylacetate. The catalyst was separated out by filtration from reaction mixture. Excess of solvent was removed under reduced pressure and the crude product recrystallized with ethanol which afford the pure 1,8-dioxo-octahydroxanthene product and no further purification was required.

All the products are known compounds and were confirmed by IR and NMR spectroscopic techniques and their melting points were compared with reported values. Spectroscopic data for some compounds are given below.

3,3,6,6-Tetramethyl-9-(3-methoxy-5-bromophenyl)-1,8-dioxo-octahydroxanthene (3j). Mp 204-206ºC; IR (KBr, cm−1) vmax 2947, 2875, 1663, 1483, 1359, 1248, 1198, 883; 1H NMR (400 MHz, DMSO-d_6) δ 0.85 (s, 6H), 1.02 (s, 6H), 1.997-2.037 and 2.268-2.228 (d, 4H), 2.54 (s, 4H), 3.67 (s, 3H), 4.49 (s, 1H), 6.83-7.31 (m, 3H); 13C NMR (100 MHz, DMSO-$d6$): δ 25.67, 29.03, 29.84, 31.90, 38.87, 50.03, 55.52, 111.27, 111.52, 113.39, 130.25,132.29, 134.10, 156.94, 163.91, 196.24; ESI-MS *m/z*: 459.

3,3,6,6-Tetramethyl-9-(pyridin-2-yl)-1,8-dioxo-octahydroxanthene (3l). Mp 188-190ºC; IR (KBr, cm−1) vmax 3053, 3007, 2957, 1656, 1467, 1364, 1199, 1156, 820; 1H NMR (400 MHz, $CDCl_3$) δ 1.00 (s, 6H), 1.10 (s, 6H), 2.13-2.17 and 2.22-2.26 (d, 4H), 2.435-2.479 and 2.508-2.552 (d), 4.86 (s, 1H), 6.99 (t, 1H), 7.54 (t, 1H), 7.60 (d, 1H), 8.38 (d, 1H); 13C NMR (100 MHz, CDCl3): δ 27.26, 29.47, 32.42, 34.57, 41.00, 50.90, 114.47, 121.49, 125.04, 135.78, 149.03, 161.88, 163.47, 197.05; ESI-MS *m/z*: 352.

3. RESULTS AND DISCUSSION

3.1. Characterization of zinc oxide nanoparticles

Crystallite sizes of ZnO particles prepared by calcination of the xerogel at 500˚ C, 900˚C, 1000˚C, and 1100˚C were determined by TEM. TEM image of ZnO particles obtained by calcinations at 500˚ C illustrated the crystallites with ~ 30 nm size (Figure.1(a)). Whereas, image of ZnO particles obtained by calcinations of the gel at 900˚C (Figure.1(b)), 1000˚C (Figure.1(c)) showed the crystallites with sizes at around 300-500 nm, ~ 1000 nm respectively. The crystallite size of the ZnO particles obtained by calcinations at 1100˚C was found to be ~ 2000 nm. Morphology of the ZnO-nanoparticles influences the chemical reactivity to a noticeable extent. TEM data also shows the formation of ZnO particles of various sizes with spherical shape. It also

shows the randomly oriented aggregates of spherical sized nanoparticles and these aggregates were found to be having sizes ranging from 30 nm to 2000 nm. Growth of the crystallite size with increased calcinations temperature can be ascribed to sintering of particles at high temperatures. In addition to this, nanoparticles were found to be self assembled in peculiar and random manner to form chain like aggregates with porous structure. Perhaps, the surface charges and structural similarity observed to have facilitated formation of these self assembled chain like nanostructures.
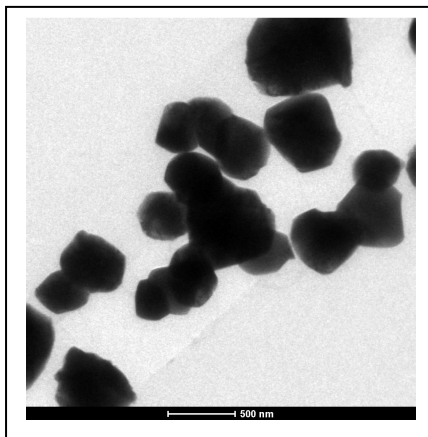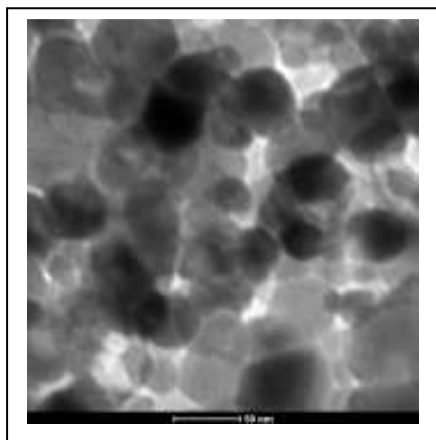

(a)
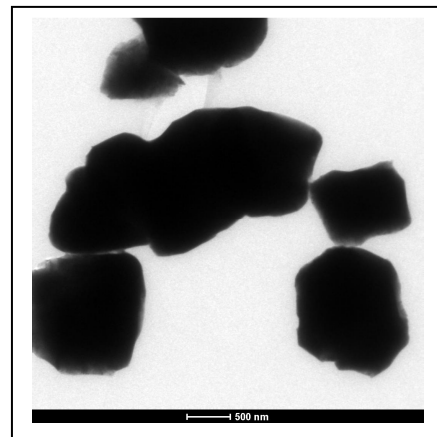
(b)

(c)

Figure 1. TEM Images of the ZnO particles calcined at 500˚C (a), 900˚C (b), 1000˚C (c)

Obtained ZnO materials were calcined at various temperatures such as 500˚ C, 900˚C, 1000˚C, and 1100˚C depicted peaks at 2θ values 31.775˚, 34.425˚, 36.275˚ and 47.625˚ as per XRD data. These peaks can be attributed to the presence of (1 0 0), (0 0 2), (1 0 1) and (0 0 2) indices. This XRD pattern illustrates 2θ values and relative intensities of peaks that match with JCPDS data of zincite and these results were shown in Figure 2.
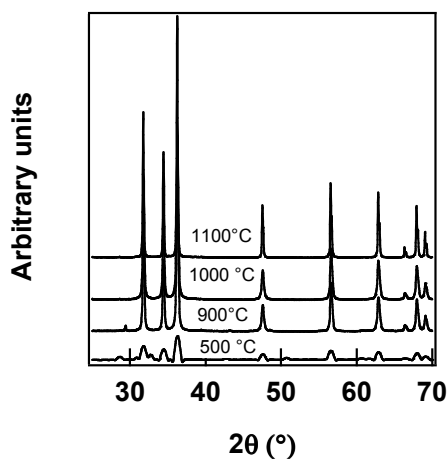
Figure 2. XRD data of ZnO particles obtained by calcination at various temperatures.

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Surface area of adsorbent materials influences their chemical reactivity to a greater extent, as adsorption capacity directly depends on surface area values. For this purpose, obtained ZnO-nanoparticles were subjected to N_2 BET analysis. The values of surface area and pore volume are incorporated in Table 1. As the crystallite size was reduced from 2000 nm to 30 nm, the value of surface area increased and the results are incorporated in Table 1.

Table 1. BET Surface area and pore volume values of ZnO particles synthesized by calcinations.

Calcination temperature of the xerogel (˚C)	BET Surface area (m^2/g)	Total pore volume (mL/g)
500	42.6	0.15
900	33.4	0.12
1000	18.1	0.04
1100	6.78	0.02

In order to investigate the catalytic activity of ZnO-NPs for the synthesis of 1,8-dioxo-octahydroxanthene derivatives, 2-pyridinaldehyde, and 5,5-dimethyl-1,3-cyclohexanedione was taken as model reactants under solvent-free, reflux conditions (Table 2, entry 12). The utility of ZnO bulk in synthesis of 1,8-dioxo-octahydroxanthene derivatives shows that its efficiency is lower than ZnO-NPs. It was observed that when 2-pyridinaldehydes, 5,5-dimethyl-1,3-cyclohexanedione and Zno-NPs were used in the ratio of 0.5 : 1.0 : 0.3 gave the best result under solvent-free condition. Further we extended the optimized reaction conditions to various arylaldehydes. From these experiments we found that, arylaldehydes bearing electron-releasing or electron-withdrawing substituent underwent reaction smoothly with 5,5-dimethyl-1,3-cyclohexanedione to give the corresponding 1,8-dioxo-octahydroxanthene derivative in good yields and all the results are appended in Table 2.

Table 2
ZnO-NPs catalyzed the synthesis of 1,8-dioxo-octahydroxanthene derivatives under solvent-free conditions.[a]

Entry	Aldehyde	Product	Time (min)	Yield (%)[b]	M.P (° C) Found	M.P (° C) Reported[ref]
1	4-Cl-C_6H_5	3a	60	93	230-232	229-230[13]
2	3-OH – C_6H_5	3b	65	86	224-226	225-227[20]
3	2-Cl – C_6H_5	3c	45	89	226-228	225-227[13]
4	3-OCH_3 - C_6H_5	3d	60	88	163-165	162-164[20]
5	4-NO_2- C_6H_5	3e	50	85	222-224	221-223[13]
6	4-CH_3 – C_6H_5	3f	55	88	216-218	217-218[13]
7	4-OCH_3 – C_6H_5	3g	65	83	241-243	240-242[13]
8	3-NO_2- C_6H_5	3h	45	89	170-172	170-172[13]
9	3-OC_2H_5 -4-OH- C_6H_5	3i	80	91	195-197	194-196[13]
10	5-Br-3-OCH_3- C_6H_5	3j	75	84	203-205	204-206[13]
11	1,3-bis- C_6H_5	3k	120	80	237-239	236-238[13]

| 12 | 2-C$_5$H$_4$N- | 3l | 70 | 83 | 187-189 | 188-190[13] |

3.2. Reusability of the Catalyst

From green chemistry point of view, efficient recovery and reuse of the catalyst is highly desirable. Thus the recovery and reusability of ZnO-NPs was investigated. After the reaction was completed, ethylacetate was added until the solid crude product was dissolved. Then, ZnO-NPs as the catalyst was isolated from the mixture of reaction by simple filtration and reused again after washing with ethylacetate. The reusability of ZnO-NPs was examined efficiently (without any activation) by using 2-pyridinaldehyde as a model substrate. The recovered ZnO-NPs was reused directly for four consecutive condensation reaction of 2-pyridinaldehyde with 5,5-dimethyl-1,3-cyclohexanedione and all the results are tabulated in Table 3.

Table 3
Recyclability of the catalyst for the synthesis of **3l**[a]

Entry	Cycle	Time (min)	Yield (%) [b]
1	Cycle 1	70	83
2	Cycle 2	90	78
3	Cycle 3	105	72
4	Cycle 4	120	65

On the basis of the above observations and literature reports, a plausible mechanism for the synthesis of 1,8-dioxo-octahydroxanthene with ZnO-NPs as catalyst is depicted (Scheme 2). The interaction of arylaldehyde with the catalyst surface generates the more electrophilic carbon centre followed by the nucleophilic attack of the enolic form of 5,5-Dimethyl-1,3-cyclohexanedione. Aryl-methylene biscyclohexanone was formed by the attack of 5,5-dimethyl-1,3-cyclohexanedione in second step. Final desired product 1,8-dioxo-octahydroxanthene was observed followed by dehydration (Scheme 2).
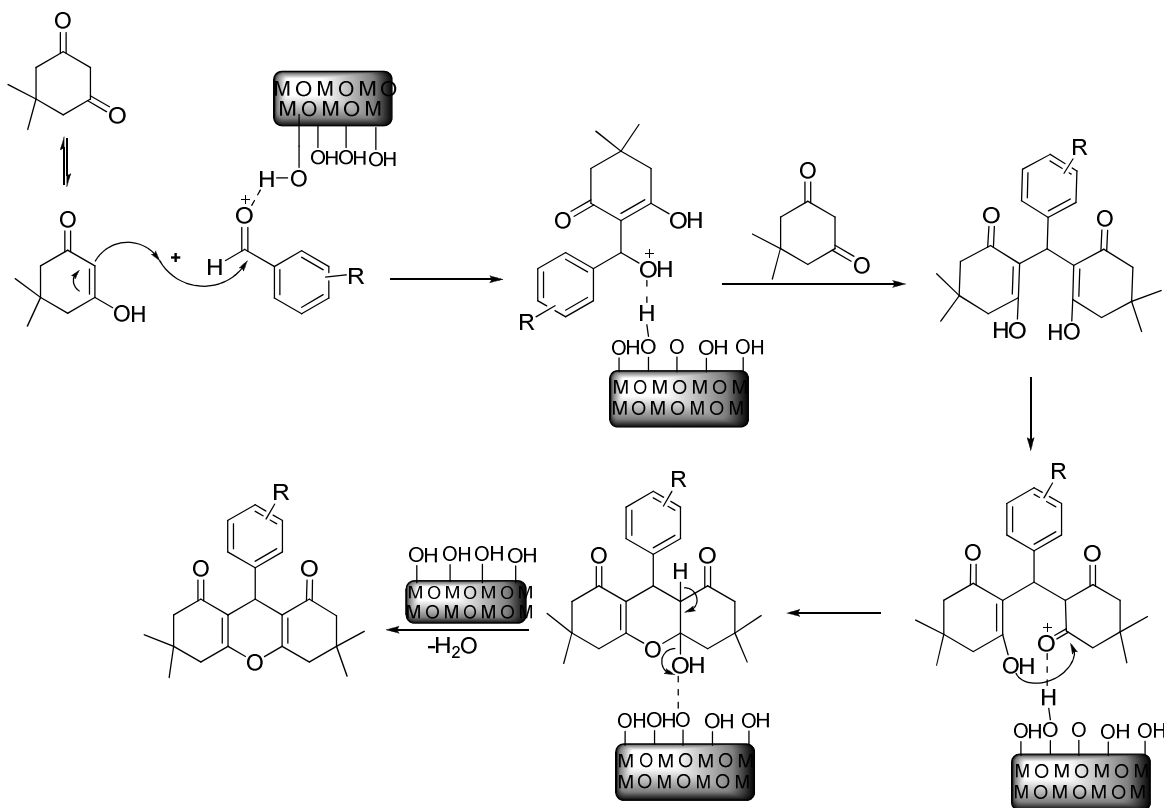
Scheme 2. Proposed path way for the synthesis of 1,8-dioxo-octahydroxanthenes

CONCLUSION

In summary, we have described a simple, efficient and environmentally benign one-pot procedure for the synthesis of 1,8-dioxo-octahyrdoxanthene derivatives by using catalytic amount of ZnO-NPs under solvent-free condition. Salient features of this method are mild reaction conditions, environmental compatibility, ease of isolation of product and excellent reusability of the catalyst. ZnO-NPs make the reaction inexpensive and the procedure is an attractive alternative to the existing methods for the synthesis 1,8-dioxo-octahyrdoxanthene derivatives.

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