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ZrO_2 nanoparticles: a highly efficient catalyst for solvent-free and mild synthesis of indeno[1,2-*b*]quinoline derivatives

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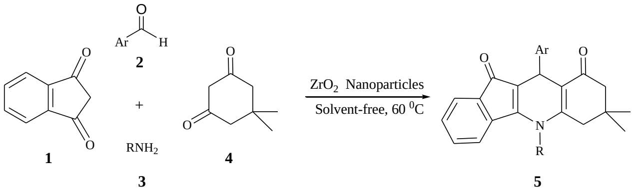
Abstract: A novel and practically useful protocol has been designed herein, by a one-pot four-component coupling reaction of 1,3-indanedione, aromatic aldehydes, primary amines, and dimedone catalyzed by commercially available ZrO_2 nanoparticles (ZrO_2 Nps) to afford the corresponding indeno[1,2-*b*]quinolinediones in high yields under solvent-free conditions.

Keywords: Indeno[1,2-*b*]quinoline, One-pot four-component, Solvent-free, ZrO_2 nanoparticles.

Introduction

In the last few years, nanoscale inorganic solid oxides as catalysts have gained tremendous importance due to their good activation of adsorbed compounds which cannot be achieved by their bulk counterparts [1-3]. Nanoscale heterogeneous catalysts offer higher surface area and low coordination sites, which are responsible for the higher catalytic activity [4-9]. The most preferred surface of solids would be those which possess easy preparation, potent catalytic activity, possible processability, high stability and ease of recyclability.

Thus, according to our previous works aimed at development of new facile routes in heterocyclic synthesis, we considered ZrO_2 nanoparticles (ZrO_2 NPs) to be an efficient catalyst for the synthesis of indeno[1,2-*b*]quinolinedione derivatives as a class of important biologically active compounds *via* a four-component coupling reaction of 1,3-indanedione, aromatic aldehydes, primary amines, and dimedone catalyzed by commercially available ZrO_2 nanoparticles (ZrO_2 Nps) with an average size of 15 nm (Scheme **1**).



Scheme 1: Synthesis of indeno[1,2-*b*] quinolinediones.

The indenoquinoline derivatives constitute an important group of bioactive compounds displaying a broad range of biological activities, such as antitumor [10, 11], acetylcholinesterase inhibitors [12], antimalarials [13], steroid reductase inhibitors [14], and new potential topo I/II inhibitors activities [15,16]. Therefore, the preparation of this heterocyclic nucleus is of particular importance to the organic chemists [17-20].

Various methods have been reported for the synthesis of compounds belonging to this class [21–25] which have their own advantages. Meanwhile, some of them are not fully satisfactory with regard to operational simplicity, cost of the reagent and isolated yield. Thus, there is always the need for better and improved methodology. In this paper, we have demonstrated a very efficient and environmental

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friendly process for the synthesis of indeno[1,2-*b*] quinolinediones.

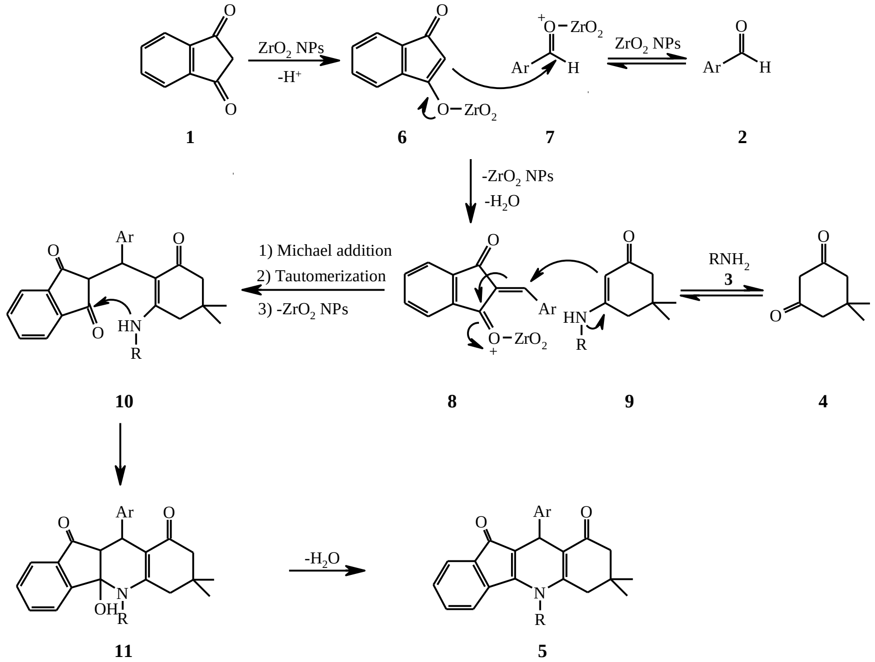
Results and discussion

Firstly, 4-bromobenzaldehyde was chosen as a model for the reaction with 1,3-indanedione, methylamine, and dimedone with various amounts of ZrO_2 NPs and under different conditions (Table **1**). The best result was obtained when 10 mol% of ZrO_2 has been used in solvent-free conditions (Table **1**, entry 2).

Table 1: The synthesis of 10-(4-bromophenyl)-5,7,7-trimethyl-6,7,8,10-tetrahydro-5*H*-indeno[1,2-*b*]quinoline-9,11-dione (**5a**) under different conditions.

Entry	Solvent	Catalyst (mol%)	Temp. (˚C)	Time (h)	Yield (%)[a]
1	neat	ZrO_2 NPs (5%)	80	3	53
2	neat	ZrO_2 NPs (10%)	80	1	98
3	neat	ZrO_2 NPs (20%)	80	1	97
4	CH_3CN	ZrO_2 NPs (10%)	80	6	37
5	CH_2Cl_2	ZrO_2 NPs (10%)	80	6	45
6	DMF	ZrO_2 NPs (10%)	80	6	49

[a] Isolated yield.



Scheme 2: Propsed mechanism for the synthesis of indeno[1,2-*b*]quinolinediones catalyzed by ZrO_2 NPs under solvent-free conditions.

To prove the generality of the protocol, benzaldehydes with various functionalities and primary amines with different substitutents were employed. The results are summarized in Table **2**.

According to both Lewis acid and Lewis base character of metal oxides [26], a suggested mechanism for the formation of indeno[1,2-b]quinolinediones **5** is presented in Scheme **2**. It is reasonable that ZrO_2 NPs catalyzes the formation of carbocation **7** which then undergoes a Knoevenagel condensation with enolized 1,3-indanedione **6**, which produces alkene **8**. The enamine **9**, which is obtained from the reaction of of dimedone **4** and primary amine **3**, adds to alkene **8** to produce the Michael adduct **10**. Intramolecular cyclization of **10** gives product **5**, after dehydration of intermediate **11.**

Table 2: Synthesis of indeno[1,2-*b*]quinolinediones 5(a-j) using ZrO_2 NPs as catalyst.

Product	Ar	R	Yield (%)^{a,b}	MP (˚C)	
				Obs.	Lit.
5a	4-BrC_6H_4	CH_3	98	230-231	228-230[22]
5b	4-BrC_6H_4	4-$CH_3C_6H_4$	96	254-256	255-256[21]
5c	4-BrC_6H_4	C_6H_5	94	279-281	280-283[23]
5d	4-BrC_6H_4	4-BrC_6H_4	98	272-274	271-273[23]
5e	2-ClC_6H_4	4-$CH_3C_6H_4$	96	264-266	263-265[23]
5f	4-ClC_6H_4	Cyclopropyl	98	296-298	295-297[22]
5g	4-$CH_3OC_6H_4$	Cyclopropyl	95	220-221	220-222[22]
5h	4-$CH_3OC_6H_4$	CH_3	96	231-233	230-233[22]
5i	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	95	281-283	283-285[21]
5j	4-$NO_2C_6H_4$	Cyclopropyl	97	269-271	268-270[22]

[a] Yields refer to those of pure isolated products characterized by IR, ^{1}H NMR spectroscopy and elemental analysis.
[b] In all cases, reaction time was 1 h stirring at 60 ˚C.

The structures of known compounds **5a-j** were established by their satisfactory elemental analyses, IR and ^{1}H NMR spectroscopy, which were found to be identical with those described in the literature. Selected spectroscopic data are reported.

The catalyst could be recovered from the reaction mixture after adding DMF, and dried in vacuum. It could then be reused for further catalytic reactions. In each cycle >85% of the catalyst was easily recovered. As shown in Table **3**, the yields of the model reaction after second and third uses of the catalyst were almost same without loss of catalytic activity.

Table 3: Using of recovered ZrO_2 NPs for the synthesis of 5a.

No. of uses	Yield(%)^a	Recovery of ZrO_2 NPs (%)
1	98	94
2	95	81
3	94	78

[a] Isolated yield.

Conclusion

We have developed a practically efficient and novel protocol for the synthesis of indeno[1,2-*b*]quinolinedione derivatives using ZrO_2 NPs as the catalyst under solvent-free conditions. The yields and the reaction time completely highlight the practical synthetic efficiency of this novel protocol.

Experimental

All chemicals used in this work purchased from *Fluka* and used without further purification. Melting points were determined with *Electrothermal 9100* melting point apparatus and were uncorrected. IR spectra were obtained on an *ABB FT-IR* (FTLA 2000) spectrometer. ^{1}H NMR spectra were run on a *Bruker DRX-500 AVANCE* at 500 MHz using TMS as internal standard and DMSO-d_6 as solvent. Elemental analyses were carried out using a *Heraues CHN* rapid analyzer.

General Procedure for Preparation of Compounds 5a-j:

A mixture of 1,3-indanedione (**1**, 1 mmol), aromatic aldehydes **2** (1 mmol), primary amines **3** (1 mmol), dimedone (**4**, 1 mmol) and ZrO_2 NPs (12.3 mg, 10 mol%) was stirred at 60 ˚C for 1 h. The progress of the reaction was monitored with TLC. Upon completion of the reaction, DMF (3 mL) was added to the reaction mixture, and ZrO_2 NPs was removed by filtration. The organic solution was then poured into cold water (15 mL), filtered and washed with aqueous ethanol to afford the pure products **5** after drying at 80 ˚C for several hours in vaccum.

Selected spectral data:

10-(4-Bromophenyl)-5,7,7-trimethyl-6,7,8,10-tetra hydro-5H-indeno[1,2-b]quinoline-9,11-dione (5a):

Orange powder, yield: 0.439 g (98%), m.p. 230-231˚C. IR (KBr): 3004, 2947, 2859, 1671, 1636, 1624, 1544 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ: 1.00 (s, 3 H, CH_3), 1.07 (s, 3 H, CH_3), 2.17 (m, 2 H, CH_2), 2.54 (d, ^2J = 17.0 Hz, 1 H, CH_2), 2.91 (d, ^2J = 17.0 Hz, 1 H, CH_2), 3.73 (s, 3 H, NCH_3), 4.78 (s, 1 H, H-10), 7.17 (d, ^3J = 8.5 Hz, 2 H, H_{Ar}), 7.34 (m, 2 H, H_{Ar}),7.40 (d, ^3J = 8.5 Hz, 2 H, H_{Ar}), 7.45 (m, 1 H, H_{Ar}), 7.66 (d, ^3J = 7.5 Hz, 1 H, H_{Ar}) ppm. Anal. Calc. for $C_{25}H_{22}BrNO_2$ (448.36): C 66.97, H 4.95, N 3.12; Found: C 66.84, H 5.07, N 3.06.

10-(4-Bromophenyl)-7,7-dimethyl-5-phenyl-6,7,8,10-tetrahydro-5H-indeno[1,2-b]quinoline-9,11-dione (5c):

Brick red powder, yield: 0.480 g (94%), m.p. 279-281˚C. IR (KBr): 3035, 2957, 2864, 1682, 1641, 1577, 1542 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ: 0.81 (s, 3 H, CH_3), 0.93 (s, 3 H, CH_3), 2.01 (d, ^2J = 17.1 Hz, 1 H, CH_2), 2.06 (d, ^2J = 16.4 Hz, 1 H, CH_2), 2.25 (d, ^2J = 16.4 Hz, 1 H, CH_2), 2.42 (d, ^2J = 17.1 Hz, 1 H, CH_2), 4.85 (s, 1 H, H-10), 5.08 (d, ^3J = 7.5 Hz, 1 H, H_{Ar}), 6.98 (t, ^3J = 7.5 Hz, 1 H, H_{Ar}), 7.20 (m, 2 H, H_{Ar}), 7.35 (d, ^3J = 8.1 Hz, 2 H, H_{Ar}), 7.45 (d, ^3J = 8.1 Hz, 2 H, H_{Ar}), 7.70 (br s, 5 H, H_{Ar}) ppm. Anal. Calc. for $C_{30}H_{24}BrNO_2$ (510.43): C 70.59, H 4.74, N 2.74; Found: C, 70.67; H, 4.86; N, 2.88.

5,10-Bis(4-bromophenyl)-7,7-dimethyl-6,7,8,10-tetrahydro-5H-indeno[1,2-b]quinoline-9,11-dione (5d):

Brick red powder, yield: 0.578 g (98%), m.p. 272-274˚C. IR (KBr): 3076, 2963, 2879, 1688, 1644, 1611, 1592, 1549 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ: 0.81 (s, 3 H, CH_3), 0.94 (s, 3 H, CH_3), 1.99 (d, ^2J = 17.4 Hz, 1 H, CH_2), 2.04 (d, ^2J = 16.2 Hz, 1 H, CH_2), 2.26 (d, ^2J = 16.2 Hz, 1 H, CH_2), 2.40 (d, ^2J = 17.4 Hz, 1 H, CH_2), 4.82 (s, 1 H, H-10), 5.25 (d, ^3J = 7.5 Hz, 1 H, H_{Ar}), 7.10 (m, 1 H, H_{Ar}), 7.22 (m, 2 H, H_{Ar}), 7.34 (d, ^3J = 8.0 Hz, 2 H, H_{Ar}), 7.44 (d, ^3J = 8.0 Hz, 2 H, H_{Ar}), 7.71 (br s, 2 H, H_{Ar}), 7.89 (d, ^3J = 8.0 Hz, 2 H, H_{Ar}) ppm. Anal. Calc. for $C_{30}H_{23}Br_2NO_2$ (589.32): C 61.14, H 3.93, N 2.38; Found: C 61.05, H 3.84, N 2.47.

10-(2-Chlorophenyl)-7,7-dimethyl-5-(4-methylphenyl)-6,7,8,10-tetrahydro-5H-indeno[1,2-b]quinoline-9,11-dione (5e):

Brick red powder, yield: 0.460 g (96%), m.p. 264-266˚C. IR (KBr): 3047, 2961, 2929, 1665, 1641, 1586, 1557 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ: 0.82 (s, 3 H, CH_3), 0.93 (s, 3 H, CH_3), 2.00 (d, ^2J = 16.5 Hz, 2 H, 2 CH_2), 2.22 (d, ^2J = 16.2 Hz, 1 H, CH_2), 2.37 (d, ^2J = 16.8 Hz, 1 H, CH_2), 2.49 (s, 3 H, NCH_3), 5.19 (d, ^3J = 7.8 Hz, 1 H, H_{Ar}), 5.24 (s, 1 H, CH_2), 7.01 (m, 1 H, H_{Ar}), 7.17 (m, 3 H, H_{Ar}), 7.28 (m, 2 H, H_{Ar}), 7.53 (m, 5 H, H_{Ar}) ppm. Anal. Calc. for $C_{31}H_{26}ClNO_2$ (480.00): C 77.57, H 5.46, N 2.92; Found: C 77.49, H 5.33, N 2.80.

5-(Cyclopropyl)-7,7-dimethyl-10-(4-nitrophenyl)-6,7,8,10-tetrahydro-5H-indeno[1,2-b]quinoline-9,11-dione (5j):

Orange powder, yield: 0.427 g (97%), m.p. 269–271˚C. IR (KBr): 3007, 2962, 2870, 1681, 1642, 1566, 1524 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ: 0.96 (m, 2 H, CH_2), 1.04 (s, 6 H, CH_3), 1.30 (m, 2 H, CH_2), 2.19 (d, ^2J = 16.2 Hz, 1 H, CH_2), 2.27 (d, ^2J = 16.2 Hz, 1 H, CH_2), 2.75 (d, ^2J = 17.2 Hz, 1 H, CH_2), 3.13 (d, ^2J = 17.2 Hz, 1 H, CH_2), 3.61 (t, ^3J = 3.5 Hz, 1 H, CH), 4.63 (s, 1 H, H-10), 7.32 (d, ^3J = 7.5 Hz, 1 H, H_{Ar}), 7.36 (d, ^3J = 8.5 Hz, 2 H, H_{Ar}), 7.47 (m, 2 H, H_{Ar}), 7.83 (d, ^3J = 7.5 Hz, 1 H, H_{Ar}), 8.11 (d, ^3J = 8.5 Hz, 2 H, H_{Ar}) ppm. Anal. Calc. for $C_{27}H_{24}N_2O_4$ (440.50): C 73.62, H 5.49, N 6.36; Found: C 73.54, H 5.57, N 6.41.

Acknowledgments

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