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Original Article

Simple route to indeno[1,2-*b*]quinoline derivatives *via* a coupling reaction catalyzed by TiO_2 nanoparticles

Shahrzad Abdolmohammadi

Department of Chemistry, Faculty of Science, East Tehran Branch, Islamic Azad University, PO Box 33955-163, Tehran, Iran

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ABSTRACT

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Keywords: Aqueous media Indeno[1,2-*b*]quinoline Reusability of catalyst TiO₂ nanoparticles A simple, efficient and high yielding approach for the synthesis of indeno[1,2-b]quinolinediones has been developed by a one-pot, four-component, coupling reaction utilizing TiO₂ nanoparticles (TiO₂-NPs) as a heterogeneous catalyst at 80 °C in aqueous media.

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1. Introduction

In the last few years, nanoscale inorganic solid oxides as catalysts have gained great importance in surface synthetic organic chemistry, due to the good activation of adsorbed compounds, enhancement of reaction rates, simplicity of operation, reusability of the catalyst, and readily available at low cost [1-3]. Nanoscale heterogeneous catalysts offer higher surface area and low coordination sites, which are responsible for the higher catalytic activity [4-9]. The catalysts with the most preferred surfaces would be those, which are easy to handle, inexpensive, non-toxic and easily removed during work-up. TiO₂ nanoparticles (TiO₂-NPs) as an inexpensive, non-toxic, moisture stable, reusable, commercially available white powder is of great interest to many scientists in the recent years. In general, several similar applications of this nanoscale method, as an effective catalyst in green synthetic organic chemistry, have already been highlighted in the literature [10–17]. It has been my interest to develop a novel, simple method for the synthesis of indeno[1,2*b*]quinolinediones $5(\mathbf{a}-\mathbf{i})$ by a one-pot, four-component coupling reaction of 1,3-indanedione (1), aromatic aldehydes (2), primary amines (3) and dimedone (4). This method should be successfully accomplished by using commercially available TiO₂-NPs with an average size of 20 nm, as catalyst in aqueous media (Scheme 1). The indenoquinoline derivatives play a prominent role in medicinal chemistry by possessing a diverse spectrum of biological properties, such as antitumor [18,19], acetylcholinesterase inhibitors [20], antimalarials [21], steroid reductase inhibitors [22] in addition to potential new topo I/II inhibitor activities [23,24]. Therefore, the preparation of this heterocyclic nucleus is of particular importance to both organic and medicinal chemists [25–28]. Previous methods for the synthesis of indeno[1,2-*b*]quinolinediones have been reported [29–33]. However, despite the potential utility of these existing methods, many have displayed drawbacks. Our new approach provides noticeable benefits as TiO₂ is non-toxic inexpensive, work-up is simple, and uses a four-component reaction for the synthesis of these compounds, which could improve the bond forming efficiency and atom economy.

2. Experimental

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 TiO₂ NPs (7.9 mg, 10 mol%) was stirred at 80 °C in water (10 mL) for 2 h. After completion of the reaction (monitored by TLC), the reaction mixture filtered and the solid mass was then diluted with DMF (5 mL), and the mixture was centrifuged at 2000–3000 rpm for 5 min to remove the TiO₂-NPs catalyst. The organic solution was then poured into cold water (15 mL), filtered and washed with

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E-mail addresses: abdolmohamadi_sh@yahoo.com, s.abdolmohamadi@iauet.ac.ir.



Scheme 1. Synthesis of indeno[1,2-b]quinolinedione derivatives.

Table 1

The synthesis of **5a** from 1,3-indanedione, 4-bromobenzaldehyde, methylamine and dimedone under different conditions.

Entry	Solvent	Catalyst (mol%)	Temp. (°C)	Time (h)	Yield (%) ^a
1	Neat	No catalyst	80	9	trace
2	H_2O	No catalyst	80	8	54
3	H_2O	TiO ₂ -NPs (5%)	80	4	82
4	H_2O	TiO ₂ -NPs (10%)	80	2	97
5	H_2O	TiO ₂ -NPs (20%)	80	2	97
6	Neat	TiO ₂ -NPs (10%)	80	2	83
7	CH ₃ CN	TiO ₂ -NPs (10%)	90	4	71
8	CH_2Cl_2	TiO ₂ -NPs (10%)	80	4	68
9	DMF	TiO ₂ -NPs (10%)	100	7	88
10	H_2O	TiO ₂ -NPs (10%)	70	3	91
11	H_2O	TiO ₂ -NPs (10%)	90	2	98

^a Isolated yield.

aqueous ethanol and then dried at 80 °C for several hours in vacuo to afford the pure products **5** (Scheme 1).

Selected spectral data: 10-(4-Bromophenyl)-5,7,7-trimethyl-6,7,8,10-tetrahydro-5H-indeno[1,2-b]quinoline-9,11-dione (5a): Yield 435 mg (97%). Orange powder. Mp 230–231 °C. IR (KBr, cm⁻¹): ν_{max} 3004, 2947, 2859, 1671, 1636, 1624, 1544. ¹H NMR (500 MHz, DMSO- d_6): δ 1.00 (s, 3H, CH₃), 1.07 (s, 3H, CH₃), 2.17 (m, 2H, CH₂), 2.54 (d, 1H, ²J = 17.0 Hz, CH₂), 2.91 (d, 1H, ²J = 17.0 Hz, CH₂), 3.73 (s, 3H, NCH₃), 4.78 (s, 1H, H-10), 7.17 (d, 2H, ³J = 8.5 Hz,

Table 2

TiO₂-NPs catalyzed synthesis of indeno[1,2-*b*]quinolinediones 5(a-j) in water at 80 °C.

Product	Ar	R	Yield (%) ^a	MP (°C)	
				Obs.	Lit.
5a	4-BrC ₆ H ₄	CH ₃	97	230-231	228-230 ³⁰
5b	4-BrC ₆ H ₄	4-CH ₃ C ₆ H ₄	96	254-256	255-256 ²⁹
5c	4-BrC ₆ H ₄	C ₆ H ₅	96	279-281	280-283 ³¹
5d	4-BrC ₆ H ₄	4-BrC ₆ H ₄	98	272-274	271–273 ³¹
5e	2-ClC ₆ H ₄	4-CH ₃ C ₆ H ₄	97	264-266	263-265 ³¹
5f	4-ClC ₆ H ₄	Cyclopropyl	98	296-298	295–297 ³⁰
5g	$4-CH_3OC_6H_4$	Cyclopropyl	95	222-224	220-222 ³⁰
5h	$4-CH_3OC_6H_4$	CH ₃	96	231-233	230–233 ³⁰
5i	$4-CH_3C_6H_4$	$4-CH_3C_6H_4$	95	281-283	283–285 ²⁹
5j	$4-NO_2C_6H_4$	Cyclopropyl	98	269-271	268–270 ³⁰

^a Yields refer to those of pure isolated products.

H_{Ar}), 7.34 (m, 2H, H_{Ar}),7.40 (d, 2H, ${}^{3}J$ = 8.5 Hz, H_{Ar}), 7.45 (m, 1H, H_{Ar}), 7.66 (d, 1H, ${}^{3}J$ = 7.5 Hz, H_{Ar}). ${}^{13}C$ NMR (125 MHz, DMSO-*d*₆): δ 30.8, 33.6, 36.4, 40.1, 42.4, 48.5, 102.3, 115.4, 122.3, 123.2, 123.8, 126.1, 126.7, 128.1, 130.9, 131.4, 134.9, 141.3, 143.2, 144.9, 181.7, 194.6. Anal. Calcd. for C₂₅H₂₂BrNO₂ (448.36): C 66.97, H 4.95, N 3.12; found: C 66.84, H 5.07, N 3.06.

3. Results and discussion

Initially, 4-bromobenzaldehyde was chosen as a model for the reaction with 1,3-indanedione, methylamine and dimedone to afford 10-(4-bromophenyl)-5,7,7-trimethyl-6,7,8,10-tetrahydro-5*H*-indeno[1,2-*b*]quinoline-9,11-dione **5a** under several conditions (Table 1). The optional result was obtained when 10 mol% of TiO₂-NPs had been used in aqueous media (entry 4).

To demonstrate the utility of this method, some benzaldehydes with various functionalities and primary amines with different substitutents were employed successfully to produce corresponding products in high yields (Table 2). The structures of the synthesized compounds 5(a-j) were confirmed by their



Scheme 2. Proposed mechanism for the synthesis of indeno[1,2-b]quinolinediones catalyzed by TiO₂-NPs in aqueous media.

satisfactory elemental analyses, IR and ¹H NMR spectroscopy, and were found to be identical with data described in the literature [29–31].

According to both Lewis acid and Lewis base characteristics of metal oxides, a plausible mechanism for the formation of indeno[1,2-*b*]quinolinediones **5** is presented in Scheme 2. It is not unreasonable to assume that TiO₂-NPs catalyzes the formation of carbocation **7** which then undergoes a Knoevenagel condensation with enolized 1,3-indanedione **6**, producing the alkene **8**. The enamine **9**, obtained by the reaction of of dimedone **4** with primary amine **3**, then adds to alkene **8** to produce the Michael adduct **10**. Intramolecular cyclization of **10** gives product **5**, after dehydration of intermediate **11**.

To check the viability of the catalyst, after the completion of the model reaction, the resulting product **5a** was treated with DMF and the catalyst removed by filtration. It was repeatedly washed with water, dried in vacuo and reused for successive reaction. It was determined that the catalyst can be recycled for at least four cycles without any change in activity.

4. Conclusion

In summary, a highly efficient and environmentally green methodology for the synthesis of indeno[1,2-b]quinolinedione derivatives *via* the one-pot four-component coupling reaction of 1,3-indanedione, aromatic aldehydes, primary amines, and dimedone has been developed. The attractive features of this protocol are the simple reaction procedure, short reaction time, easy work-up, reusability of TiO₂-NPs catalyst, and high product yields. To the best of our knowledge, this is the first report on the synthesis of indeno[1,2-b]quinolinedione derivatives by a four-component reaction using TiO₂-NPs as a catalyst.

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