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Nano-cerium Oxide/Aluminum Oxide: An Efficient and Useful Catalyst for the Synthesis of Tetrahydro[a]xanthenes-11-one Derivatives

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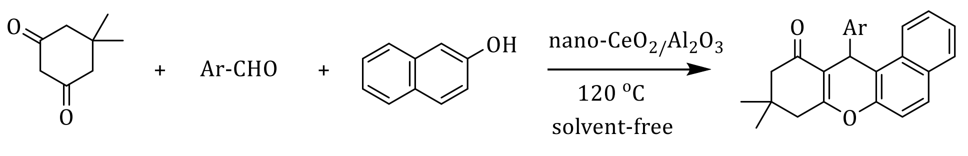
ABSTRACT

Tetrahydro[a]xanthenes-11-one derivatives have been widely used industrially as agrochemicals, cosmetics and pigments are reported to exert broad spectrum biological and pharmacological activities. Herein, we reported an efficient and environmentally benign one-pot multi–component reaction for the synthesis of tetrahydro[a]xanthenes-11-one derivatives from the reaction of dimedone, aromatic aldehydes, and 2-naphthols in the presence of a catalytic amount of nano-nano-CeO_2/Al_2O_3. The advantages of the effective method included good yields (91-98%), short reaction times, simple work-up and reusable catalyst. The catalyst could be recycled and reused for five times without much loss in its activity.

GRAPHICAL ABSTRACT



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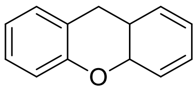
Introduction

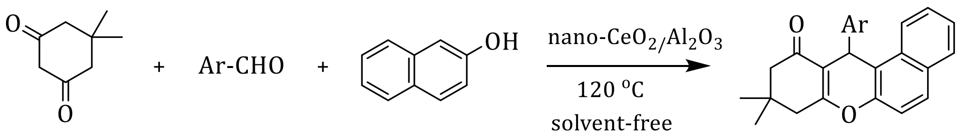
Xanthene and their derivatives have attracted much attention due to their wide range of biological and pharmaceutical properties and are used in various industries [1]. Xanthene derivatives are important heterocyclic compounds. They have been widely used as dye fluorescent materials for visualization of bio-molecules and laser technologies due to their useful spectroscopic properties [2]. Xanthene is a poly aromatic annular ether that has a tetrahedron ring attached to aromatic rings [3].



Scheme 1. Structure of xanthene

They have also been reported for their agricultural bactericide activity [4], photodynamic therapy [5], antiflammatory effect [6] and antiviral activity [7]. Xanthenes are used as dyes due to conjugated double bonding and spectrophotometric properties. Xanthene's luminescence colours include fluorones, pyronines, rhizomes, suxanines, saccharins, rhodamines, and rhododians [8]. Todays, different applications have been made for xanthene's dyes. For example, to study the absorption properties of lysosome protein, lattice crystals could use four colours of anionic eosin, fluorine, rose bengal, erythrosine and cadmium rhodamine 5 G6 and dipolar iodine of rhodamine 6B [9]. Xanthene and compounds are not widely found in nature [10]. On the other hand, the high demand for these compounds need more requirements for their synthesis in laboratories. The simplest and most commonly used xanthene synthesis method is the reaction of the aldehyde group with dimedone in the presence of an acid catalyst or other catalysts [11-15]. The synthesis of xanthene compounds and their derivatives, including the tetrahydroxanthene, has come into a great deal of attention. A wide variety of methods for the preparation of the xanthenes have been classified according to starting compounds, e.g. syntheses by cyclization of polycyclic aryltiflate esters [16], intramolecular trapping of benzynes by phenols [17] and the reaction of aryloxymagnesium halides with triethylorthoformate [18]. However, many of these methods are associated with several short comings such as long reaction times (16 h to 5 days), expensive reagents, harsh conditions, low product yields, use of toxic organic solvents and difficulty in recovery and reusability of the catalysts. Recently, synthesis of xanthene derivatives using *p*-dodecylbenzensulfonic acid under reflux condition [19] and ultrasound irradiation [20] and polyaniline-*p*-toluenesulfonate salt in aqueous media and using *p*-toluenesulfonic acid as catalyst in organic solvent have been reported [21,22]. Heterogeneous catalyzed synthesis of these compounds has also been documented [23].

In our continued interest in the development of highly effective methods for the synthesis of heterocyclic compounds [24], we wish to report a facile condensation of dimedone, 2-naphthol and aromatic aldehydes in the presence of a catalytic amount of nano-CeO_2/Al_2O_3 to produce the xanthene derivatives in 91-98% yields (Scheme 2).



1 **2(a-g)** **3** **4(a-g)**

Scheme 2: Synthesis of Tetrahydro[a]xanthenes-11-one Derivatives

Material and methods

All the chemicals were purchased from Merck Company. All products were identified by comparison of their spectra and physical data with the literature description.

General procedure

A mixture of an aromatic aldehyde (1 mmol), dimedone (1 mmol), 2-naphthol (1 mmol) and nano- CeO_2/Al_2O_3 (0.05g or 0.3mmol) was refluxed under solvent free condition. The mixture was stirred at 120 °C for 50 minutes. The progress of the reaction was monitored by thin-layer chromatography (TLC) in ethyl acetate: *n*-hexane, 1:4. After completion of the reaction (monitored by TLC), boiling ethanol was added to the reaction mixture. The catalyst was filtered off, and the reaction mixture was cooled to room temperature. The precipitated crude product was then collected by filtration and recrystallized from absolute ethanol to give a pure product.

*9,9-Dimethyl-12-(4-chlorophenyl)-8,9,10,12-tetrahydro-11H-benzo[a]xanthen-11-one (**4b**).* IR (KBr): 3056, 2959-2888, 1659, 1102 cm^{-1}.; ^1H-NMR (400 MHz,$CDCl_3$): δ 1.02 (s, 3H), 1.18 (s, 3H), 2.28 (d, 2H, J = 4.2 Hz), 2.57(d, 2H, J = 4.2 Hz), 5.72 (s, 1H), 7.19–7.48 (m, 7H, Ar-H), 7.76–7.88 (m, 3H, Ar-H); Mass spectra: 389 (M^+).

*9,9-Dimethyl-12-(2-nitrophenyl)-8,9,10,12-tetrahydro-11H-benzo[a]xanthen-11-one (**4d**).* IR (KBr): 3066, 2962-2881, 1661, 1568, 1328 cm^{-1}.; 1H-NMR (400 MHz,CDCl3): δ 0.89 (s, 3H), 1.13 (s, 3H), 2.21 (d, 2H, J = 4.3Hz), 2.59 (d, 2H, J= 4.3 Hz), 6.59 (s, 1H), 7.05 (d, 1H, J = 8 Hz), 7.13–7.46 (m, 5H, Ar-H), 7.76–7.89 (m, 3H, Ar-H), 8.55 (d, 1 H, J = 8 Hz); Mass spectra: 400 (M+),

Preparation of cerium oxide/aluminum oxide nano-catalyst

Al_2O_3-CeO_2 nanoparticles were prepared at room temperature by wet chemical method. 50 ml of 0.1 M solution of cerium nitrate and 50 ml of 0.1 M solution of aluminum sulfate were mixed. 100 ml of 2 M sodium hydroxide solution was added to the mixture. The resulting solution was maintained at 80 °C for 3 hours. The resulting white precipitate was washed several times with deionized water to remove impurities. The precipitate was dried at room temperature and calcinated at 700 °C [25].

Result and Dissection

The size of synthesized nanoparticles was further confirmed by TEM. The Transmission Electron Microscopy (TEM) image of Al_2O_3-CeO_2 mixed oxides are shown in Figure 1. The size of Al_2O_3-CeO_2 mixed oxide is found to be in the range of 20–50 nm (Figure 1).

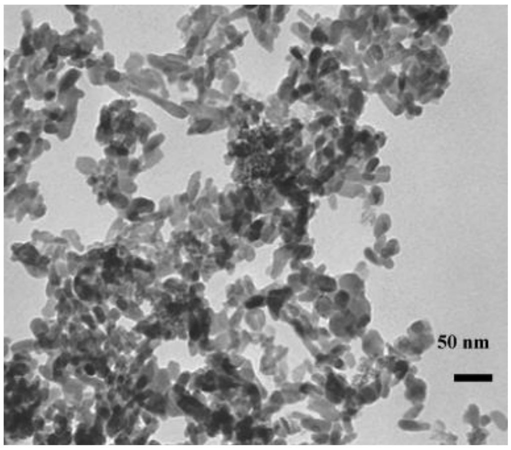


Figure 1: TEM spectra of nano-CeO_2/Al_2O_3

We began to examine the catalytic activity of nano- CeO_2/Al_2O_3 to optimize the reaction condition of dimedone with benzaldehyde in the presence of different catalytic amounts of nano-CeO_2/Al_2O_3 at different temperatures. When reaction was carried out at room temperature, the yield was not satisfactory (30%). After raising the temperature, it was shown that the yield increased (91-98%) at 120 °C. In order to show the general applicability of the method, the reaction of structurally diverse aldehydes with dimedone and 2-naphthol under similar conditions was investigated. By this method, the reactions were carried out easily and very cleanly in the presence of nano-CeO_2/Al_2O_3 to produce xanthene derivatives in good to excellent yields and no undesirable by-products were observed. The experimental procedure is very simple, convenient, and has the ability to tolerate a variety of other functional groups such as methyl, methoxy, nitro, hydroxyl, halide under these reaction conditions, which indicated that both electrons rich and electrons deficient aldehydes worked well, mostly leading to high yields of products.. The results are summarized in Table 1.

Table 1: Synthesis of substituted tetrahydro[a]xanthenes-11-one by nano-CeO_2/Al_2O_3 in solvent-free conditions at 120 ºC

Entry	X	Product	Yield(%)[a]	m.p. (ºC)	
				Found	Reported[26]
1	H	4a	97	151-153	150-151
2	4-Cl	4b	98	180-182	182-184
3	4-NO_2	4c	98	181-182	180-181
4	2-NO_2	4d	98	224-225	222-224
5	4-CH_3	4e	92	175-177	174-176
6	4-OCH_3	4f	92	206-207	205-206
7	4-OH	4g	91	222-224	221-223
8	2-Cl	4h	95	178-179	177-178

[a]Yields were analyzed by GC

It is known that the specific surface area and surface-to-volume ratio increase dramatically as the size of a material decreases. The high surface area brought about by nanoparticle size is beneficial to CeO_2/Al_2O_3 catalysis, as it facilitates reaction/interaction between the materials and the interacting media. Due to its excellent physical and chemical properties, CeO_2/Al_2O_3 has attracted much attention in recent years [25].

To optimize the amount of catalyst, 1 mmol of dimedone, 1 mmol of aldehyde, 1 mmol of 2-naphthol, and various amounts (0.01, 0.02, 0.03, 0.05, 0.08 g and 0.1 g) of cerium oxide/aluminium oxide nano-catalyst were used. Table 2 represents the test results performed to optimize the amount of catalyst in the presence of different amounts of cerium oxide/aluminium oxide nano-catalyst. The results presented in the Table 2 show that the amount of 0.05 g of CeO_2/Al_2O_3 nano-catalyst had the best efficiency.

Table 2: Comparison of amount of catalysts for the synthesis of **4a**

Entry	Amount of catalysts(g)	Yield (%)[a]
1	0.02g	80
2	0.03g	89
3	0.05g	97
4	0.08g	97
5	0.1g	97

[a] Yields were analyzed by GC

Preparing tetrahydro[a]xanthenes-11-one using 1 mmol of dimedone, 1 mmol of aldehyde, 1 mmol of 2-naphthol was performed in the presence of cerium oxide/aluminium oxide nano catalyst with different solvents and the results are listed in Table 3. These experiments yielded better results under solvent-free condition.

Table 3: Synthesis of 4a in the presence of different solvents using nano-CeO_2/Al_2O_3 as a catalyst

Entry	Solvent	Yield (%)[a]
1	THF	68
2	C_2H_5OH	91
3	CH_3CN	85
4	$CHCl_3$	71
5	water	93
6	Solvent-free	97

[a]Yields were analyzed by GC

Reusability of nano CeO_2/Al_2O_3

Next, the reusability of nano CeO_2/Al_2O_3 investigated. At the end of the reaction, the catalyst was recovered by simple filtration, washed with methanol, dried and subjected to a second run of the reaction process. To assure that the catalysts were not dissolved in methanol, they were weighed after filtration and before use and reuse for the next reaction. In Table 4, the comparison of the efficiency of nano CeO_2/Al_2O_3 in the synthesis of **4a** after five times is reported. As shown in Table 4, the first reaction using recovered CeO_2/Al_2O_3 afforded a similar yield to that obtained in the first run. In the second, third, fourth and fifth runs, the yields gradually decreased.

Table 4: Reuse of the nano CeO_2/Al_2O_3 for the synthesis of **4a**

Entry	run	Yield(%)[a]
1	first	97
2	second	92
3	third	90
4	fourth	88
5	fifth	85

[a] Yields were analyzed by GC

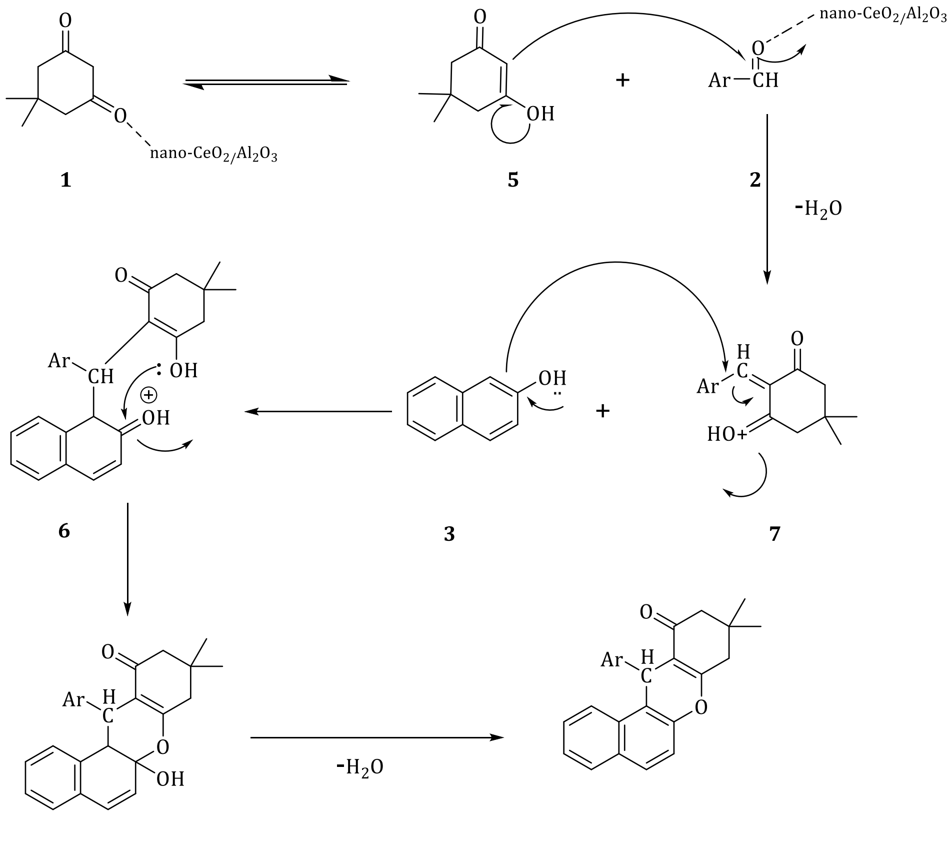
After comparing the results for the synthesis of **4a** with other methods, it was revealed that the nano- CeO_2/Al_2O_3 catalyst performed the reaction faster and with higher efficiency (Table 5).

Table 5: Comparison of various catalysts for the synthesis of substituted tetrahydro[a]xanthenes-11-one

Entry	Catalyst	Yield (%)	Time (min)	Ref
1	PEG-400	79-90	330-450	[27]
2	CAN	82-87	120-144	[28]
3	I_2	70-89	150-180	[29]
4	p-TSA	83-95	120-210	[30]
5	$Sr(OTF)_2$	70-88	390	[31]
6	Sulfamic acid	79-84	115-136	[32]
7	$NaHSO_4$-SiO_2	69-89	280-429	[33]
8	nano CeO_2/Al_2O_3	91-98	50	Present study

The proposed mechanism for the synthesis of 1,4-dihydropyridine derivatives in the presence of cerium oxide/aluminium oxide nanocatalyst is as follows:

Initially, the dimedone was activated by the catalyst to produce the enolate of dimedone. Then the enolate of dimedone made a nucleophilic attack to the catalyst-activated aldehyde. After that, it was dehydrated by the loss of a water molecule. 2-naphthol makes a nucleophilic attack to intermediate and turned into the desired product by dehydrated (Scheme 3).



Scheme 3: Mechanism for the Synthesis of Tetrahydro[a]xanthenes-11-one Derivatives

Conclusion

In summary, we found a simple, convenient, straightforward and practical procedure for the synthesis of xanthene derivatives. All starting materials are readily available from commercial sources. Some advantages of this procedure are:

1) the experimental simplicity and the easy work-up procedure, 2) the compatibility with various functional groups, 3) use of the green, easy to handle and reusable catalyst, and 4) high yields of the products. The procedure is very simple and can be used as an alternative to the existing procedures.

Conflict of Interest

We have no conflicts of interest to disclose.

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