

Original Article: Nano-Cerium Oxide/Aluminum Oxide as an Efficient Catalyst for the Synthesis of Xanthene Derivatives as Potential Antiviral and Anti-Inflammatory Agents



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ABSTRACT

Xanthenes have been considered in medicine and biology. Their medicinal properties include antiviral, antibacterial, anti-inflammatory, and therapeutic photodynamic activities, as well as the antagonist for paralytic action. 1,8-Dioxo-octahydroxanthenes have synthesized good yields *via* a reaction of aldehydes and dimedone in the presence of cerium oxide/aluminum oxide nano-catalyst as a catalyst. High efficiency, short time and reuseability of catalyst are the advantages of this method.

Introduction

Among many heteroaromatic compounds, xanthenes, as one of the most important organic compounds, have attracted the attention of many pharmaceutical and organic compounds researchers due to their strong biological and medicinal activities such as antiviral, antibacterial, and anti-malarial actions [1].

In particular, xanthenes form a structural unit in a number of natural products and are used in a variety of compounds due to the strong reaction of the inner pyran ring. Therefore, artificial methods have been developed for the production of xanthenes. However, some of these methods have disadvantages such as low product yields, long reaction time, use of toxic solvents and reagents, and harsh reaction conditions. One of

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the available methods for the synthesis of xanthenes is the reaction of dimedone with aldehydes using various catalysts [2-12]. Practical applications of metal oxides as catalysts in organic synthesis have increased due to their large surface area and high catalytic activity. 1,8-Dioxo-octahydroxanthenes are an important group of oxygenated heterocycles in which a pyran is replaced with a phenyl ring attached to two cyclohexenone rings on either side. Xanthenes are useful medicinal compounds that are very important in the field of pharmaceutical and biological activities. They can be used as an antidepressant, antibacterial drug, for staining the cytoplasm, collagen, and muscle fibers, anti-cancer drug and as a ligand [13-17]. In most chemical reactions, a catalyst is used to increase the reaction rate. The goal of chemists is to produce catalysts with high activity and efficiency, complete selectivity, the ability to separate and recover from the reaction mixture, low energy consumption, and long life. Among the types of catalysts, nanocatalysts are one of the most widely used. High efficiency, economic efficiency, low waste of chemicals, low heat and energy consumption, as well as optimal use of raw chemicals, are the advantages of using them. Given the importance of this type of research compounds in the field of nanocatalysts, it is always one of the most interesting topics in nanochemistry. The nanoscale has provided excellent conditions for the use of nanoparticles as catalysts. Their high active surface and excellent selectivity increase the pace and efficiency of the reaction. Nanocatalysts have the advantages of both homogeneous (high level) and heterogeneous (separability) catalysts. Nanocatalysts can be classified into the following groups: 1) Metal nanoparticles, 2) Protected metal nanoparticles, 3) Nano metal oxides, 4) A mixture of two or more metal

nanoparticles, and 5) Nano-press systems [18-20].

Metal oxides play an important role in many fields of chemistry, physics, and materials science. Metallic elements are able to form a wide variety of oxides. They can adopt a large number of structures. Geometries with electronic structures can represent metal, semiconductor, or insulation characteristics. In technological applications, oxides are used in the manufacture of microelectronic circuits, sensors, piezoelectric devices, fuel cells, coatings against corrosion, and as catalysts. Cerium oxide/aluminum oxide nano-catalyst is an important rare oxide from the earth that attracts more attention due to its diversity. This oxide has been used in fuel cells, oxygen gas sensors, polishing materials, oxygen permeation membrane systems, and as a catalyst in various technological processes. Ceria is the main component of the three-way catalyst (TWC), which is also used for environmental cleaning purposes, various emerging fields of analysis such as hydrocarbon oxidation, removal of all organic carbons from waste, and conversion of car exhaust gas.

Experimental

General

Materials and equipment

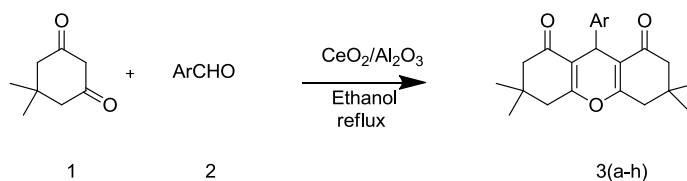
Chemicals were supplied from Merck (Darmstadt, Germany) and Sigma-Aldrich chemical Co. (USA). Melting points were taken as uncorrected using a digital Electrothermal melting point apparatus (model 9100, Electrothermal Engineering Ltd., Essex, UK). ¹H-NMR spectra were obtained using a Bruker 300 MHz (model AMX, Karlsruhe, Germany) spectrometer (Internal standard: TMS) and values were expressed in ppm. The IR spectra were recorded using a Thermo Nicolet FT-IR (model *Nexus-870*, Nicolet Instrument Corp, Madison, Wisconsin, U.S.A.) spectrometer. Mass spectra were obtained using an Agilent Technologies 5973, Mass Selective Detector (MSD) spectrometer (Wilmington, USA). The

purity of compounds was confirmed by TLC. Thin layer chromatography (TLC) on commercial aluminum-backed plates of silica gel, 60 F254 was used to monitor the progress of reactions.

General procedure for the synthesis of xanthene derivatives

Dimedone (2 mmol), desired aldehyde (1 mmol), CeO₂/Al₂O₃ nano-catalyst (0.05 g), and ethanol (5 mL) were mixed, as the solvent, in a

50 mL flask. The mixture was stirred by a magnetic stirrer under reflux conditions to evaluate the progress of the reaction with TLC papers in a mixture of hexene and ethyl acetate at a ratio of 3:1. After the reaction is complete, the temperature of the flask was allowed to reach ambient temperature, then the contents of the flask were filtered. Water was added drop-wise to the resultant filtrate to obtain a precipitate. It was then filtered, and the obtained solid was recrystallized from ethanol (96%). (Scheme 1, Table 1).



Scheme 1. Synthesis of xanthenes

(3a): M.p: 202-204 °C. IR (KBr) (ν_{max} , cm⁻¹): 1671, 1676 (C=O); ¹H NMR (CDCl₃, 300 MHz) δ H (ppm): 1.16 (6H, s), 1.21 (6H, s), 2.04 (4H, dd), 2.13 (4H, dd), 3.46 (1H, s), 7.25-7.67 (m, 5H, CH aromatic).

Preparation of cerium oxide/aluminum oxide nano-catalyst

Al₂O₃-CeO₂ 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 h. 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 [22]. The size of synthesized nanoparticles was further confirmed by SEM and TEM (Figures 1 and 2). The size of the catalyst is found to be in the range of 20–50 nm.

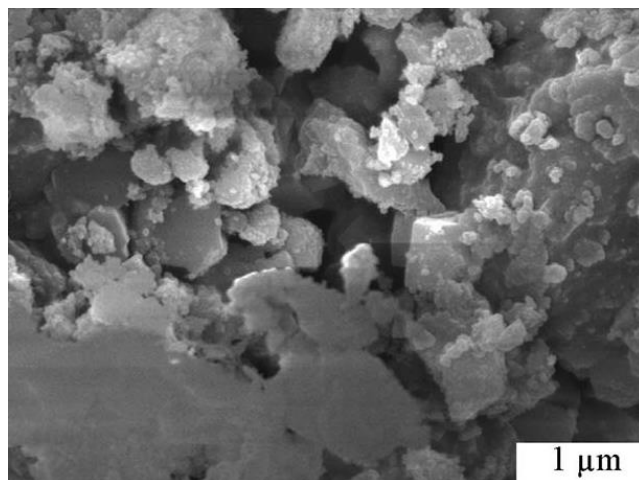


Figure 1. SEM of nano-CeO₂/Al₂O₃

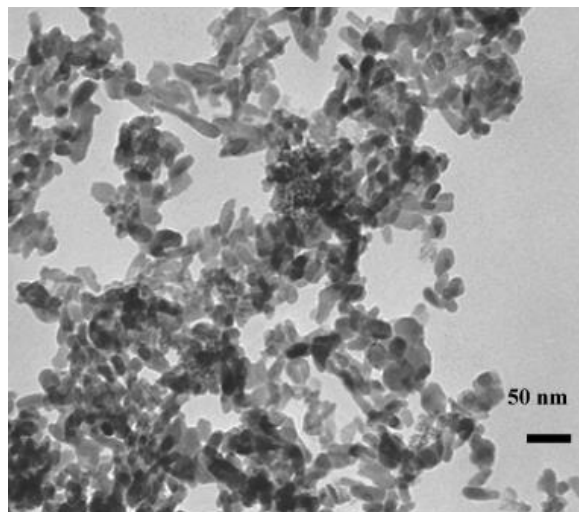


Figure 2. TEM of nano-CeO₂/Al₂O₃

Result and Discussion

In this reaction, optimization was performed by changing the solvent. The best solvent for the reaction was found to be the ethanol solvent (Table 2).

Reusability of nano CeO₂/Al₂O₃

After the reaction, 10 mL of ethyl acetate was added to the compounds on filter paper containing catalyst. The mixture was stirred at room temperature for 5 minutes using a magnetic stirrer. The reaction mixture was filtered, and the catalyst remained on filter paper due to its insolubility in ethyl acetate solvent. Then, in order to reuse the catalyst, the filter material was washed several times with acetone. After drying, the reaction was repeated to check the potency of the catalyst (Figure 3).

Comparison of the performance of cerium oxide/aluminum oxide nano-catalyst with a

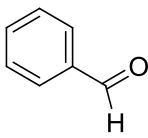
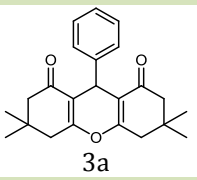
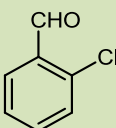
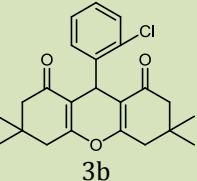
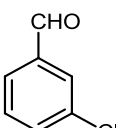
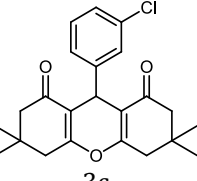
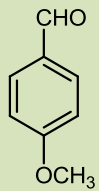
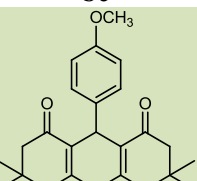
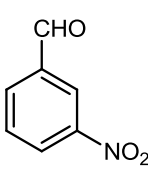
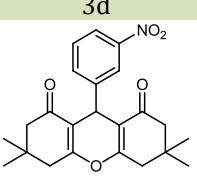
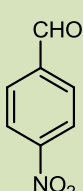
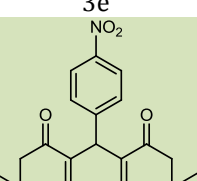
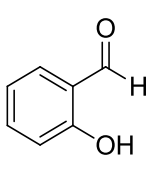
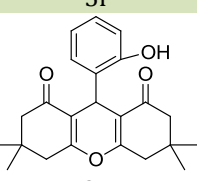
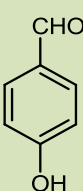
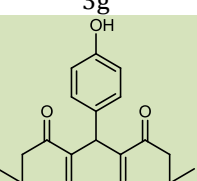
number of different catalysts in the synthesis of xanthene derivatives

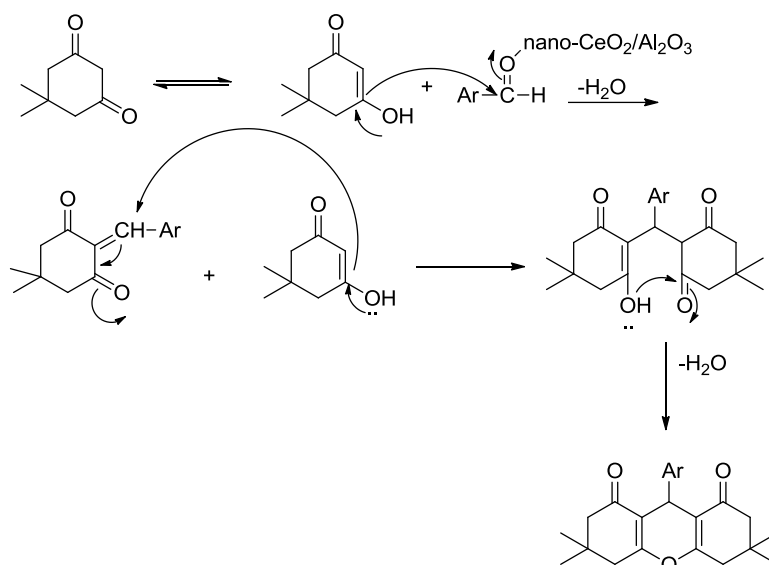
Comparing the reaction results with other methods, we found that the cerium oxide/aluminum oxide catalyst performed the reaction in a shorter time and with higher efficiency (Table 3).

To optimize the amount of catalyst, various amounts (0.01, 0.02, 0.03, 0.05, and 0.08 g) of cerium oxide nano-catalyst were used. Table 4 represents the test results performed to optimize the amount of catalyst in the presence of different amounts of cerium oxide/aluminum oxide nano-catalyst. The results presented in the table show that the amount of 0.05 g of cerium oxide/aluminum oxide nano-catalyst had the best efficiency.

The proposed mechanism for the preparation of 1,8-dioxo-octahydroxanthenes is as follows (Scheme 2):

Table 1. Synthesis of xanthene derivatives catalyzed by cerium oxide/aluminum oxide nano-catalyst

Entry	Aldehyde	Product	Time (h)	Melting Point Reported [21]	Melting Pint Observed	Yield (%)
1		 3a	1	205	202-204	95
2		 3b	1	228-230	227-229	94
3		 3c	1	230-231	230-232	97
4		 3d	1	241-243	245-246	93
5		 3e	1	246-248	23242-244	95
6		 3f	1	222-224	220-222	96
7		 3g	1	205-206	206-207	91
8		 3h	1	246	246-248	92



Scheme 2. Mechanism for the synthesis of xanthenes

Table 2. Synthesis of 3a in the presence of different solvents using nano-CeO₂/Al₂O₃ as a catalyst

Entry	Solvent	Yield (%) ^a
1	THF	68
2	C ₂ H ₅ OH	95
3	CH ₃ CN	85
4	CHCl ₃	71
5	water	90
6	Solvent-free	92

Isolated yields

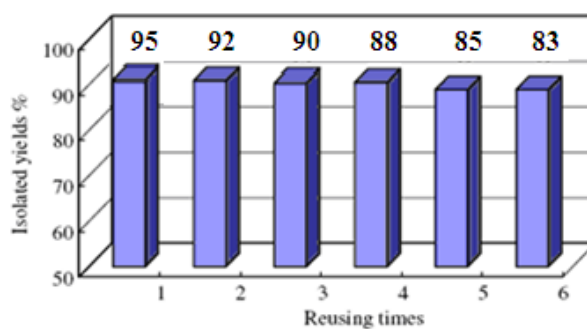


Figure 3. Reusing of Fe-MCM-41 for the synthesis of 3a

Table 3. Comparison of various catalysts for the synthesis of 3a

Entry	Catalyst	Yield (%)	Time(h)	Ref.
1	Selecfleur	93	1.5	[23]
2	SaSA	90	1	[24]
3	DABCO - bromine	80	2.5	[25]
4	TCCA	89	1	[26]
7	SiO ₂	95	3	[27]
8	nano CeO ₂ /Al ₂ O ₃	95	1	Present study

Table 4. Comparison of amount of catalysts for the synthesis of 3a

Entry	Amount of catalyst(g)	Yield (%) ^a
1	0.02 g	80
2	0.03 g	89
3	0.05 g	95
4	0.08 g	95

Conclusion

Xanthene derivatives are the main constituents of many synthetic and natural derivatives and have occupied an important place in the medical chemistry industry. Due to the great importance of compounds with xanthene core and their application in the pharmaceutical industry, various methods have been proposed to optimize these reactions. Many of these reactions are expensive, or their synthesis requires difficult conditions. In some cases, very high reaction temperatures and long reaction times have been reported. We report here a facile and improved protocol for preparation of xanthene derivatives using nano-cerium oxide/aluminum oxide as an efficient and recyclable catalyst from the reaction of dimedone and aldehydes. A simple experimental and work-up procedure, cleaner reaction, mild reaction conditions and also high yields of products are all advantages of this method which makes it useful and noteworthy for the synthesis of these compounds.

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References

- [1] A. Walter, *Am. Soc. Clinical. Oncolog.*, **2010**, *35*, 469-474. [[Google Scholar](#)], [[Publisher](#)]
- [2] B. Baghernejad, M. Alikhani, *Iran. Chem. Commun.*, **2020**, *8*, 240-248. [[Google Scholar](#)]
- [3] Z. Arzehgar, H. Ahmadi, *J. Chin. Chem. Soc.*, **2019**, *66*, 303-306. [[Crossref](#)], [[Google Scholar](#)], [[Publisher](#)]
- [4] S.C. Azimi, E. Abbaspour-Gilandeh, *Iran. Chem. Commun.*, **2016**, *4*, 236-258.
- [5] R. Khoeiniha, A. Ezabadi, A. Olyaei, *Iran. Chem. Commun.*, **2016**, *4*, 273-282. [[Google Scholar](#)], [[Publisher](#)]
- [6] B. Zakerinasab, M. Nasser, H. Hassani, *Iran. Chem. Commun.*, **2016**, *4*, 133-235. [[Google Scholar](#)], [[Publisher](#)]
- [7] A. Davoodnia, H. Nakhaei, *J. Chem. Rev.*, **2019**, *1*, 139-153. [[Crossref](#)], [[Google Scholar](#)], [[Publisher](#)]
- [8] A. Nakhaei, S. Yadegarian, *J. Appl. Chem. Research.*, **2017**, *11*, 72-83. [[Crossref](#)], [[Google Scholar](#)], [[Publisher](#)]
- [9] A. Davoodnia, *Russ. J. General. Chem.*, **2016**, *86*, 2849-2854. [[Crossref](#)], [[Google Scholar](#)], [[Publisher](#)]
- [10] A. Nakhaei, A. Davoodnia, A. Morsali, *Research. Chem. Intermediat.*, **2015**, *41*, 7815-7826. [[Crossref](#)], [[Google Scholar](#)], [[Publisher](#)]
- [11] A. Davoodnia, A. Nakhaei, S. Basafa, N. Tavakoli-Hoseini, *Adv. J. Chem-Sect. A.*, **2018**, *1*, 96-104. [[Crossref](#)], [[Google Scholar](#)], [[Publisher](#)]
- [12] E. Ezzatzadeha, S. Nazaraliana, F. Sheikholeslami, *Iran. J. Org. Chem.*, **2017**, *9*, 2057-2065.
- [13] M.P. Lande, T. Gadekar, G. Pawar, R. Magar, *Bull. Chem. React. Eng. Catal.*, **2018**, *3*, 436-437.
- [14] Sh. Babadoust, *Int. J. Chem. Biochem. Sci.*, **2014**, *6*, 72-73. [[Google Scholar](#)], [[PDF](#)]
- [15] F. Darviche, S. Balalaie, F. Chadegani, P. Salehi, *Synth. Commun.*, **2007**, *37*, 1059-1063. [[Crossref](#)], [[Google Scholar](#)], [[Publisher](#)]
- [16] S. Deshmukh, G.U. Kadam, K. Shisodia, M.V. *Int. J. Chem. Phys. Scienc.*, **2018**, *7*, 75-76.
- [17] F. Noori Sadeh, M. Fatahpour, N. Hazeri, M. Taher maghsoodlou, M. Lashkari, *Acta. Chemica. Iasi.*, **2017**, *25*, 24-37. [[Google Scholar](#)]
- [18] K.P. Nandre, V.S. Patil, S. Bhosale, *Chin. Chem. Lett.*, **2011**, *22*, 777-780. [[Crossref](#)], [[Google Scholar](#)], [[Publisher](#)]

- [19] G. Ertl, H. Knozinger, J. Weitkamp, *Handbook of Heterogeneous Catalysis*, VCH. Weinheim, **1997**, *1*, 16. [[Google Scholar](#)], [[PDF](#)]
- [20] V. Polshettiwar, S. Rajender, *Green. Chem.*, **2010**, *12*, 743-754. [[Google Scholar](#)]
- [21] A. Gosslau, S. Pabbaraja, S. Knapp, K.Y. Chen, *Eur. J. Pharmacol.*, **2008**, *587*, 25-34. [[Crossref](#)], [[Google Scholar](#)], [[Publisher](#)]
- [22] R.R. Muthuchudarkodi, S. Kalaiarasi, *Int. J. ChemTech Res.*, **2016**, *9*, 813-821. [[Google Scholar](#)]
- [23] T. Hideo, *Chemical Abstract.*, **1981**, 95, 80922b. [[Google Scholar](#)]
- [24] J.P. Poupelin, G. Saint-Ruf, O. Foussard-Blanpin, G. Narcisse, G. Uehida, R. Lacroix, *Europ. J. Med. Chem.*, **1978**, *13*, 67-71. [[Google Scholar](#)]
- [25] G. Saint-Ruf, H.T. Hieu, *Bull. Chem. Soc. Jap.*, **1972**, *7*, 83-86. [[Google Scholar](#)]
- [26] A. Cvetkovic, J. Adrie, J. Straathof, K. Rajamani, A.M. Luuk, *Derwielen. Langmuir.*, **2005**, *21*, 1475-1478. [[Crossref](#)], [[Google Scholar](#)], [[Publisher](#)]
- [27] J.F. Callan, P. De Silva, D. Magri, *Tetrahedron.*, **2005**, *61*, 8551-8588. [[Google Scholar](#)]

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