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ARTICLE

Magnetically Retrievable Cobalt Ferrite Nanoparticles as Heterogeneous Catalyst for Synthesis of 1-Oxo-hexahydroxanthenes

M.G. Kukade^{1,✉}, N.L. Gavade², A.N. Kadam³,
W.B. Chandane⁴, K.M. Garadkar² and A.J. Bodake¹

ABSTRACT

In present study, magnetically separable cobalt ferrite nanoparticles (CoFe₂O₄-NPs) have been prepared by low cost chemical precipitation method and reported as reusable, proficient heterogeneous catalyst for the synthesis of 1-oxo-hexahydroxanthenes among other ferrites. The structural and morphological studies by X-ray diffraction and scanning electron microscopy confirmed the formation of CoFe₂O₄ nanoparticles. The current protocol evaluated a proficient catalyst for reaction between various salicylaldehydes and 1,3-diketones. The ambient reaction conditions, shorter reaction time, good to excellent yields of the products, ease of purification of the products and reusability of catalyst up to five catalytic cycles without significant loss of catalytic activity making the current protocol promising for its practical application.

KEYWORDS

Ferrite nanoparticles, 1-Oxohexahydroxanthenes, Green solvents.

INTRODUCTION

Modern organic synthesis is intended to enhancement of reaction yield which is designed with readily available starting materials and mainly with nature friendly approach. For this matter green chemistry has been proved more serviceable tool. Green chemistry deals with the reduction of waste, toxic solvents and reagents [1]. Oxygen containing heterocycles is a diverse class of compounds; many of such heterocyclic compounds chiefly reoccur as basic functional units in numerous bio-active molecules and pharmaceutical products that mostly mimic naturally occurring biomolecules [2].

Xanthenes and their derivatives have wide applicability in the field of natural products, medicinal and material chemistry [3]. Xanthenes exhibit their involvement in the field of laser technology as leuco dyes [4], for visualization of biomolecules it serves as pH sensitive fluorescent material [5]. Owing to their spectroscopic properties 1,8-octahydroxanthenes derivatives with benzopyran moiety have been used as antispam [6], antiviral [7], antibacterial [8], antioxidant, antineoplastic, vasodilators, anti-inflammatory agents [9-17] and as a fluorescent fuels [18]. These myriads of applications of xanthenes encourage the researchers to develop more eco-benign methods for their synthesis.

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Author affiliations:

¹Department of Chemistry, Rajaram College, Kolhapur-416004, India

²Department of Chemistry, Shivaji University, Kolhapur-416004, India

³Department of Chemical and Biological Engineering, Gachon University, Seongnamdaero 1342, Seongnam-si, Republic of Korea

⁴Department of Chemistry, Jaysingpur College, Jaysingpur-416101, India

✉To whom correspondence to be addressed:

E-mail: mahesh.kukade@gmail.com

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In spite of remarkable applications in variety of fields as a versatile synthon as well as a bioactive moiety, 1-oxo-hexahydroxanthenes are much less attended by researchers. As per the literature survey, condensation of salicylaldehyde with two equivalents of dimedone or cyclohexane-1,3-dione is general synthetic route for 1-oxo-hexahydroxanthenes, which involves one-pot pseudo three-component condensation reaction. This pathway has been reported with different solvents as in, water in absence of catalyst at reflux condition [19], glycerol at 90 °C [20], and dimethylformamide at 80 °C [21]. But these synthetic routes are suffered by harsh reaction conditions such as longer reaction time (3-12 h) and use of high temperature. Many homogeneous catalysts have been employed to bring about same pathway such as $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ in water at reflux condition [22], acetic acid in comparatively large quantity with reflux at 100 °C [23], triethyl benzylammonium chloride (TEBA) as a cationic surfactant at 90 °C for 3-5 h [17], 2,4,6-trichloro-1,3,5-triazine at 120 °C [24], CsF at room temperature in dichloromethane [25], L-proline in ethanol at 60 °C [26], *p*-TSA in water by stirring at 90 °C [27], $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ a Lewis acid catalyst for model reaction [28] and using diethylamine in ethanol at room temperature [29]. Some reports also revealed the use of heterogeneous catalysts such as cellulose sulfuric acid [30], nano- ZnAl_2O_4 at reflux condition [31], NaY/Fe zeolite in water at reflux condition [32]. But these catalysts are associated with undesired difficulties like presence of halogen [17,22,25], requirement of tedious work up with decreased efficiency or more temperature requirement for each repetitive use of catalyst, use of acid, moisture sensitive expensive reagents for catalyst preparation [30] and use of flammable-volatile liquid catalyst [32].

Use and development of variety of heterogeneous catalysts to enhance the cleanliness of synthetic routes has been considered a promising research area. Reason for this is heterogeneous catalysts perform more superiorly for higher efficiency, mild reaction conditions, simplicity in reaction procedure, less waste generation and possible reusability of catalyst [33,34].

In the field of heterogeneous catalysis, nano-catalysts have gained remarkable attention due to their physical and chemical properties in particular high surface to volume ratio; selectivity and yield of reaction. But difficulties in recovery of catalysts restricted its reuse as well as its applicability to real research area. This difficulty cling to these catalysts shifted the focus of researchers toward the magnetically separable nano-catalysts [35-37]. Particularly spinel ferrites owing to their properties like existence of acidic as well as basic sites in them and hydroxyl groups on their surface are explored as an efficient catalyst in

various organic transformations [38-40]. Due to ferromagnetism in smaller nanoparticles, ferrites are easily separated from reaction mixture by using simple bar magnet.

In present report, we have synthesized 1-oxo-hexahydroxanthene derivatives using spinel CoFe_2O_4 nanoparticles as reusable efficient catalyst. XRD and SEM were used to characterize the nanoparticles. Further, the comparative results related to synthesis of 1-oxo-hexahydroxanthenes by different ferrite nanoparticles were evaluated.

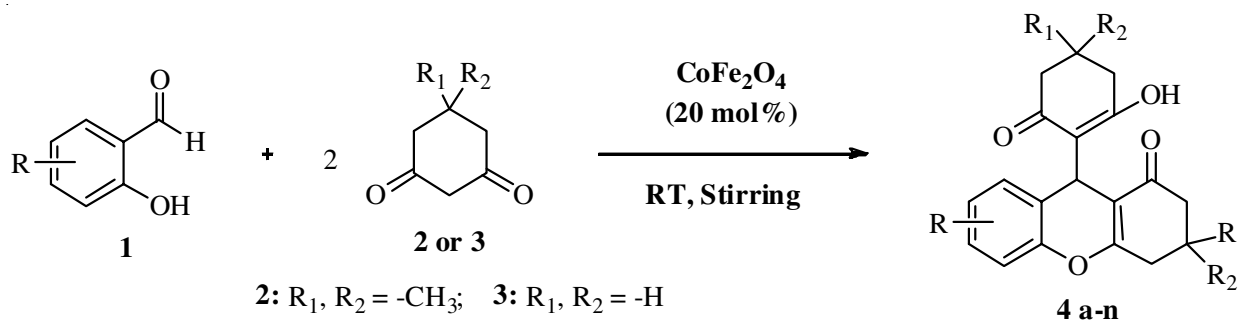
EXPERIMENTAL

All chemicals used were of analytical grade. The cobalt (II) nitrate hexahydrate [$\text{Co}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$], iron(III) nitrate nonahydrate [$\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$], nickel(II) nitrate hexahydrate [$\text{Ni}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$] and copper(II) nitrate hexahydrate [$\text{Cu}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$] were purchased from SD Fine Chemicals India Ltd. As well as various salicylaldehyde derivatives, dimedone and cyclohexane-1,3-dione were purchased from SD Fine Chemicals India Ltd. and used as received. The melting points were recorded using Kumar melting point apparatus. ^1H and ^{13}C NMR spectra were recorded using Bruker Advance-II spectrometer.

General procedure for synthesis of 1-oxohexahydroxanthenes: To a well stirred solution of salicylaldehyde (**1**) (1 mmol), and 1,3-dione (**2** or **3**) (2 mmol) in ethanol:water (1:2, 5 mL), CoFe_2O_4 nanoparticles (20 mol %) was added. The resultant reaction mixture was stirred at ambient temperature until the completion of the reaction as indicated by thin layer chromatography (TLC). The reaction mixture was diluted with water (5 mL) and stirring was continued until free flowing solid resulted in the reaction mixture. The product obtained by filtration was washed with water, dried and recrystallized using a mixture of cyclohexane: CHCl_3 (70:30, v/v) (**Scheme-I**). The catalyst was separated by using external magnet. The recovered catalyst was washed with acetone, dried and reused for next catalytic cycle.

Spectral data

3,4-Dihydro-9-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)-3,3-dimethyl-2H-xanthen-1(9H)-one (3a): solid; m.p.: 206-209 °C; ^1H NMR (300 MHz, $\text{DMSO}-d_6$), δ ppm: 1.01-1.13 (m, 12H), 1.98 (s, 2H), 2.34-2.46 (m, 4H), 2.52-2.64 (m, 2H), 4.68 (s, 1H), 7.02 - 7.27 (m, 4H); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$), δ ppm: 26.49, 27.19, 27.75, 29.17, 29.84, 30.96, 41.54, 43.17, 49.93, 50.59, 111.05, 115.73, 118.31, 124.33, 124.56, 127.51, 127.99, 151.02, 169.10, 170.73, 196.61, 200.85.



Scheme-I: Cobalt ferrite nanoparticles catalyzed synthesis of 1-oxo-hexahydroxanthene derivatives

6,8-Dichloro-3,4-dihydro-9-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)-3,3-dimethyl-2H-xanthen-1(9H)-one (3j): solid; m.p.: 202-205 °C; ^1H NMR (300 MHz, DMSO- d_6), δ ppm: 0.87 (s, 6H), 1.03 (m, 4H), 1.13 (m, 2H), 2.03-2.06 (m, 3H), 2.14-2.41 (m, 3H), 2.81 (brs, 1H), 4.97 (s, 1H), 6.83 (s, 1H), 6.96-7.01 (m, 1H); ^{13}C NMR (75 MHz, CDCl_3), δ ppm: 23.31, 26.63, 28.37, 29.32, 31.37, 31.98, 48.31, 48.71, 30.94, 31.23, 111.47, 114.41, 124.29, 131.31, 134.04, 143.10, 132.39, 197.13, 198.20.

3,4-Dihydro-5-hydroxy-9-(2-hydroxy-6-oxocyclohex-1-enyl)-2H-xanthen-1(9H)-one (4b): solid; m.p. 244-246 °C; ^1H NMR (300 MHz, DMSO- d_6), δ ppm: 1.71-1.73 (t, 2H, $J = 6.5$ Hz), 1.92-1.96 (t, 2H, $J = 3.5$ Hz), 2.02 (s, 4H), 2.29-2.31 (m, 2H), 2.30-2.61 (m, 1H), 4.83 (s, 1H), 6.41 (d, 1H, $J = 7.4$ Hz), 6.61 (d, 1H, $J = 8$ Hz), 6.67 (t, 1H, $J = 7.8$ Hz); ^{13}C NMR (75 MHz, CDCl_3), δ ppm: 20.23, 20.40, 26.76, 27.88, 36.89, 112.31, 114.18, 116.39, 118.79, 119.77, 124.00, 126.26, 129.89, 139.06, 144.37, 148.32, 168.43, 198.67.

3,4-Dihydro-9-(2-hydroxy-6-oxocyclohex-1-enyl)-6-methoxy-2H-xanthen-1(9H)-one (4d): Solid; m.p.: 238-240 °C; ^1H NMR (300 MHz, DMSO- d_6), δ ppm: 1.84-1.96 (m, 2H), 2.03-2.14 (m, 4H), 2.41-2.63 (m, 3H), 2.72-2.78 (m, 1H), 3.78 (s, 3H), 4.39 (s, 1H), 6.38-6.92 (m, 2H), 6.91 (d, 1H, $J = 9.1$ Hz), 10.80 (brs, 1H); ^{13}C NMR (75 MHz, CDCl_3), δ ppm: 19.63, 19.94, 27.47, 27.96, 36.02, 33.32, 110.92, 111.03, 112.63, 116.49, 119.79, 128.43, 131.42, 138.92, 170.94, 201.31.

RESULTS AND DISCUSSION

As an initial part of our work four representative spinel ferrites viz., Fe_3O_4 , CoFe_2O_4 , NiFe_2O_4 and CuFe_2O_4 were prepared and screened for their catalytic performance in the synthesis of 1-oxo-hexahydroxanthene derivatives. The spinel ferrites were prepared by adopting the literature procedure [41]. In general, 0.1 M solution of metal(II) nitrate ($M = \text{Co}, \text{Ni}$ and Cu) was added to 0.2 M Fe(III) nitrate solution with proper stirring. Then the solution formed was slowly added with NH_4OH solution, till pH of solution reached to 9. The brownish black precipitate formed was digested to 60 °C for 2 h. The resultant product was filtered, dried and calcined at 500 °C for 3 h to get magnetic crystals, which were ground to get fine powdered ferrite.

Owing to the better performance for reaction XRD and SEM analysis of CoFe_2O_4 nanoparticles were done. Fig. 1 shows XRD pattern of CoFe_2O_4 nanoparticles. The peaks observed at 30.04°, 35.47°, 43.62°, 57.20° and 62.64° corresponds to (220), (311), (400), (511) and (440), respectively. All peaks observed in the XRD patterns are very well matches with the JCPDS card No.00-003-0864. This confirms the formation of spinel cubic crystal structure. Fig. 2 shows the FE-SEM image of CoFe_2O_4 , which revealed that the agglomerated ferrite nanoparticles are well distributed. The grain size obtained was in approximate 20-30 nm.

Screening of various spinel ferrites catalysts for the formation of the 1-oxohexahydroxanthenes under different reaction conditions was carried (Table-1). To commence with this, the exemplar reaction of salicylaldehyde (**1**), (1.0 mmol) with 5,5-dimethyl-1,3-cyclohexanedione (**2**) (2.0 mmol) in ethanol (5 mL) in the presence of 20 mol % of Fe_3O_4 was carried out.

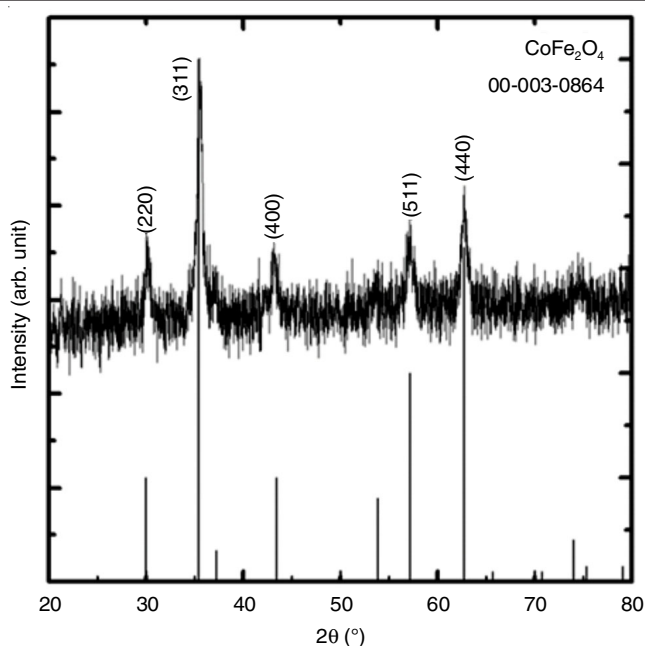


Fig. 1. XRD pattern of CoFe_2O_4 nanoparticles

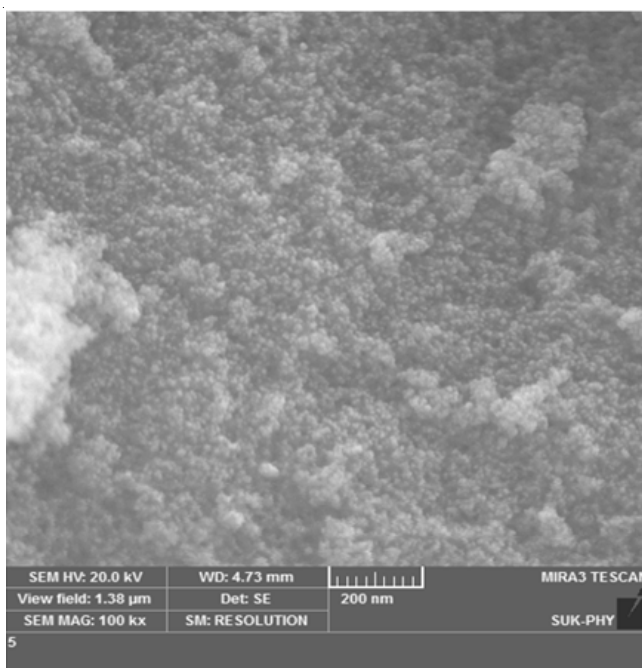


Fig. 2. FE-SEM image of CoFe_2O_4 nanoparticles

The furnished product **3a** obtained after 4 h of stirring at ambient temperature as monitored by TLC.

To find out best suitable condition for model reaction, same reaction was performed in catalyst and solvent free conditions. The reaction was found to be completed with only 15 % of product in 10 h (entry-1, Table-1). To check effect of water as a solvent, we repeated this reaction in water in absence of catalyst and we found noticeable yield here, but this protocol was associated with longer reaction time. To find the optimum conditions of catalyst for targeted reaction, we carried out same reaction using other metal ferrites prepared. However with the choice of any of these ferrites, yields of the product were surprisingly obtained in the range of 80-90 %.

TABLE-1
OPTIMIZATION FOR THE REACTION CONDITIONS FOR THE FORMATIONS OF THE 1-OXOHEXAHYDROXANTHENES^a

Entry	Catalyst (mol %)	Solvent	Time (h)	Yield (%)
1	–	–	10.0	15
2	Fe ₃ O ₄ (20)	H ₂ O	6.0	76
3	Fe ₃ O ₄ (20)	EtOH	4.0	83
4	CoFe ₂ O ₄ (20)	EtOH	3.0	87
5	NiFe ₂ O ₄ (20)	EtOH	3.0	82
6	CuFe ₂ O ₄ (20)	EtOH	3.0	83
7	Fe ₃ O ₄ (20)	EtOH:H ₂ O (1:1)	3.0	89
8	CoFe ₂ O ₄ (20)	EtOH:H ₂ O (1:1)	3.0	91
9	NiFe ₂ O ₄ (20)	EtOH:H ₂ O (1:1)	3.0	91
10	Fe ₃ O ₄ (20)	EtOH:H ₂ O (1:2)	3.0	88
11	CoFe ₂ O ₄ (20)	EtOH:H ₂ O (1:2)	2.5	95
12	NiFe ₂ O ₄ (20)	EtOH:H ₂ O (1:2)	3.0	85
13	Fe ₃ O ₄ (15)	EtOH:H ₂ O (1:2)	3.0	80
14	CoFe ₂ O ₄ (15)	EtOH:H ₂ O (1:2)	2.5	88
15	NiFe ₂ O ₄ (15)	EtOH:H ₂ O (1:2)	2.5	87
16	Fe ₃ O ₄ (10)	EtOH:H ₂ O (1:2)	3.0	78
17	CoFe ₂ O ₄ (10)	EtOH:H ₂ O (1:2)	2.5	85
18	NiFe ₂ O ₄ (10)	EtOH:H ₂ O (1:2)	2.5	82
19	CoFe ₂ O ₄ (20)	H ₂ O	5.0	76

^aReaction conditions: Salicylaldehyde (1 mmol), 5,5-dimethyl-1,3-cyclohexanedione (2 mmol), spinel ferrite (mol %) in solvent (5 mL) at given condition, room temperature.

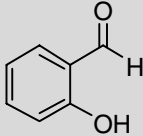
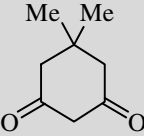
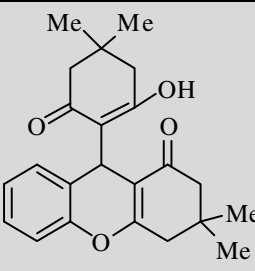
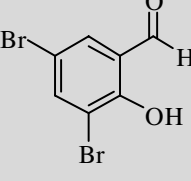
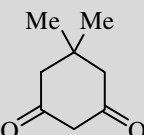
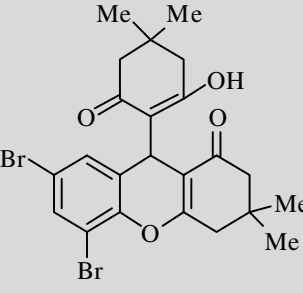
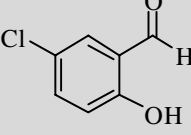
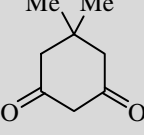
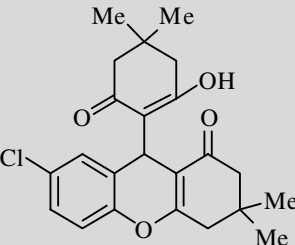
For subsequent optimization of reaction condition, the catalytic potential of various ferrites were explored by varying solvent systems. For this purpose, using same catalyst loading

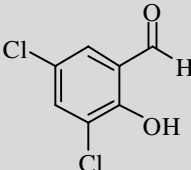
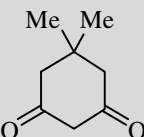
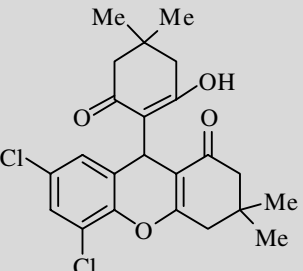
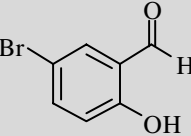
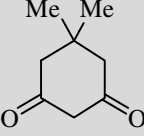
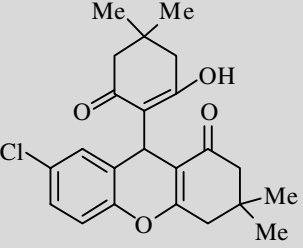
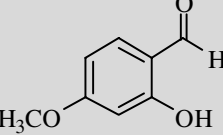
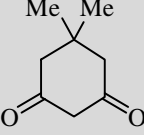
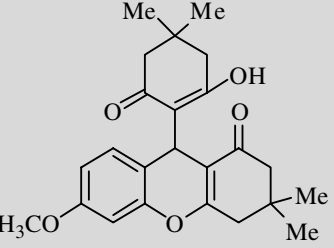
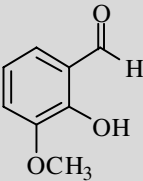
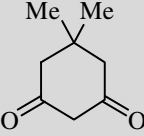
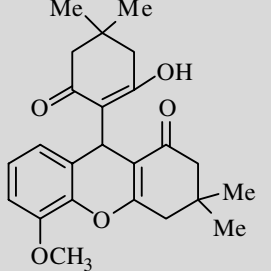
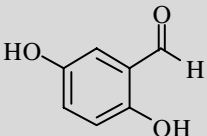
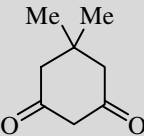
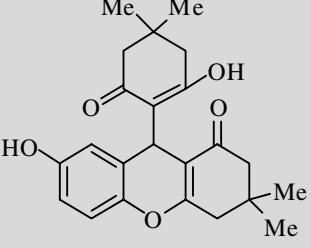
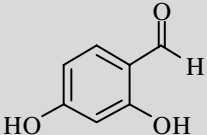
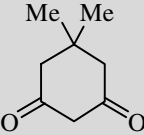
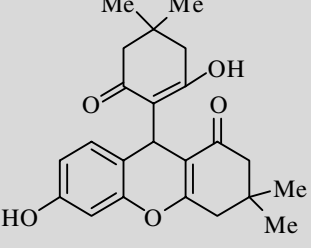
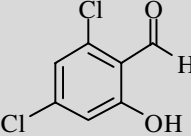
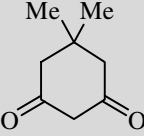
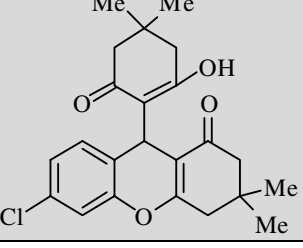
the effect of ethanol and water in different proportions have been studied, mainly to maintain the benign nature of our protocol.

The difference found in between yields of product **3a** in presence of Fe₃O₄, CoFe₂O₄ and NiFe₂O₄ made the selection of ferrite quit difficult for us. However, by considering important aspects like easy separation of spinel ferrites over simple ferrites and comparatively easy formation of pure CoFe₂O₄ than NiFe₂O₄ using simple method, we decided to choose CoFe₂O₄ as a catalyst for further studies. In optimization of reaction condition regarding the catalyst loading, repetitions of model reaction were done even with 15 and 10 mol % of ferrites. But 20 mol % of catalyst was found to give much better yield of compound **3a**. The effect of water in presence of catalyst also has been studied with 20 mol % CoFe₂O₄, but improper dispersion of catalyst in water doesn't show any profound effect on yield (entry-19, Table-1). In contrary, this set of condition took more time to furnish the product. As the next part of this work full characterization of CoFe₂O₄ were done to support most vital structural properties of catalysts.

The efficiency of newly established set of optimized parameters was extended to appraise the effect of electron withdrawing groups as well as electron releasing on product 1-oxohexahydroxanthenes by using various aldehydes. The results are tabulated in Table-2. The good to excellent yield of the products has been obtained as an outcome of the presented protocol. The reactions were clean and completion of reaction was identified by precipitation of product along with TLC. The catalyst was separated out from reaction product without

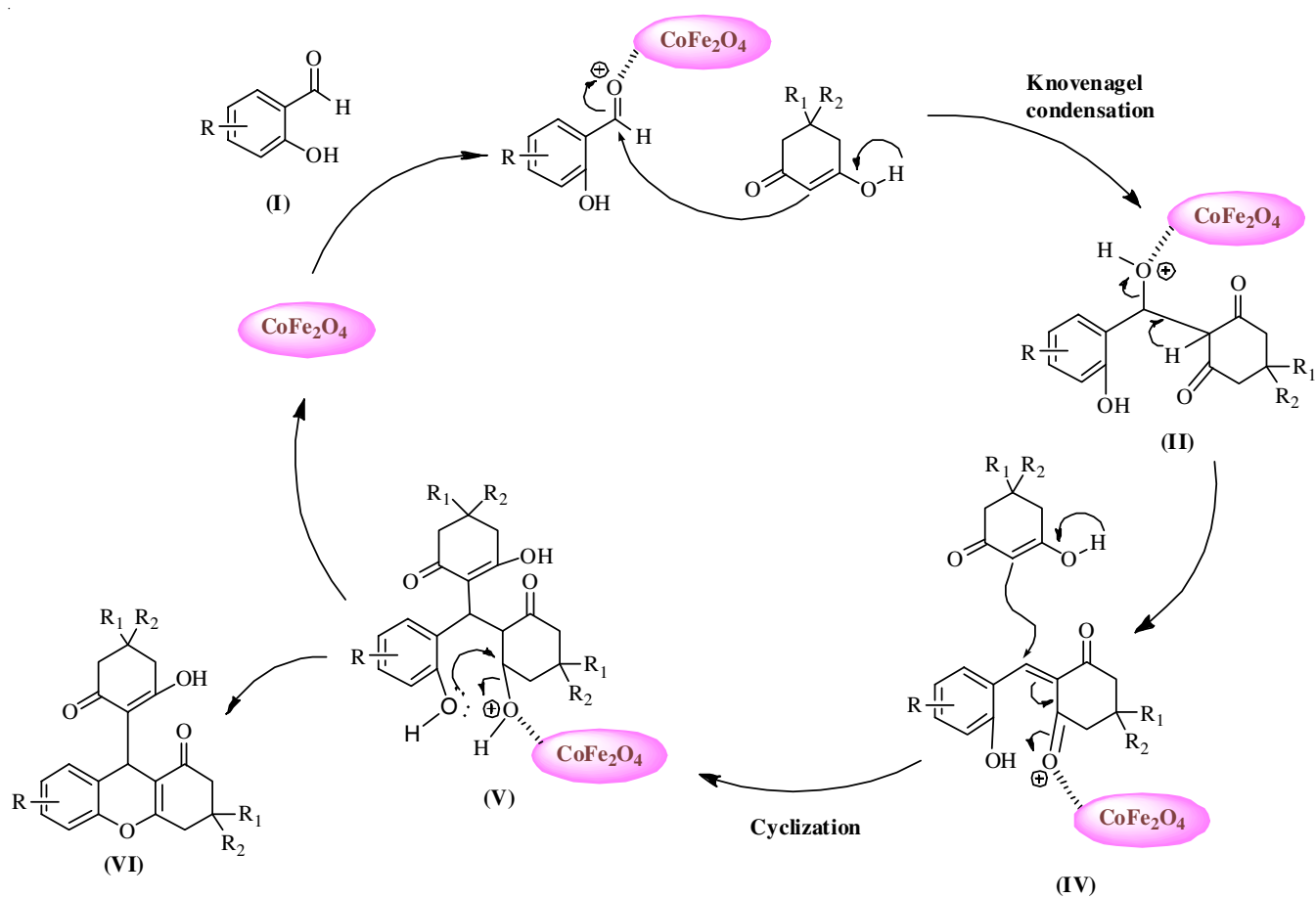
TABLE-2
TANDEM TRANSFORMATION OF SALICYLALDEHYDES AND 1,3-DIKETONES INTO 1OXOHEXAHYDROXANTHENES **4a-n**^a

Entry	Aldehyde (1)	1,3-Diketone (2 or 3)	Product (4a-n)	Time (h)	Yield (%)	m.p. (°C)	Ref.
1				2.5	95	206-209	[19]
2				3.0	90	224-227	[29]
3				3.0	92	232-235	[19]

4				3.0	90	230-233	[25]
5				3.0	92	249-251	[19]
6				3.5	89	212-215	[25]
7				3.5	91	184-186	[26]
8				3.0	88	242-244	[25]
9				3.0	85	222-225	[26]
10				4.0	82	202-205	[29]

11				3.5	91	240-243	[19]
12				4.0	86	244-246	[29]
13				4.0	85	236-240	[19]
14				3.5	89	238-240	[29]

^aReaction conditions: Salicylaldehyde, **1** (1 mmol) and 1,3-dione (**2/3**, 2 mmol), solvent (EtOH:H₂O 1:2) CoFe₂O₄ (20 mol %), room temperature.



any tedious work-up by just attaching the external magnet to the walls of reaction flask. The separated catalyst was washed repeatedly with acetone (3-5 mL), dried in oven for 3 h at 100 °C and then reused observed that the catalyst could be recycled efficiently for five cycles without appreciable loss in its activity (Fig. 3). The mechanism is believed to proceed by Knoevenagel-carba-Michael-cyclization pathway. The plausible reaction mechanism for the formation of 1-oxohexahydroxanthenes is given in **Scheme-II**.

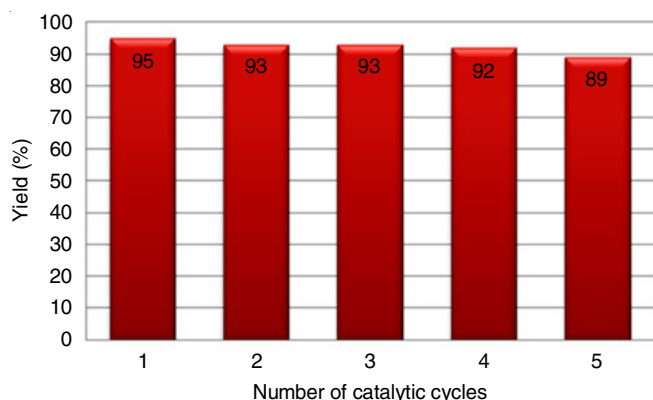


Fig. 3. Recyclability of the cobalt ferrite for the formation of the 1-oxohexahydroxanthenes

Conclusion

The magnetically separable cobalt ferrite (CoFe_2O_4) nanoparticles were prepared by chemical precipitation method, which shows cubic structure by structural and morphological studies. The CoFe_2O_4 nanoparticles have a proficient catalytic activity for synthesis of 1-oxo-hexahydroxanthenes with maximum yield of 95 %. The operationally simple and environmentally benign protocol with excellent yields, easy preparation of the catalyst with simple procedure at an extremely low cost, ambient reaction conditions, easy work-up and separation as well as purification enhances prevalence of this protocol.

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