

Nickel Ferrite Nanoparticles: A Magnetically Separable and Reusable Catalyst for Enviro-Economic Synthesis of 1-Oxo-Hexahydroxanthenes and Bis-Coumarins.

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Abstract:

A Simple, economical and environmentally benign protocol has been described for one-pot synthesis of 1-oxo-hexahydroxanthenes by pseudo three component condensation between salicylaldehydes and dimedone or 1,3-cyclohexanedione using Nickel ferrite nanoparticles a magnetically separable and reusable catalyst. Based upon the philosophy of the reaction, the protocol has been extended towards the synthesis of by pseudo three component condensation using Nickel ferrite nanoparticle as catalyst as a magnetically separable and reusable catalyst for synthesis of bis-coumarins. Ambient reaction conditions, shorter reaction times, good to excellent yields of the products, ease of purification of the products and reusability of the catalyst for five consecutive runs without significant loss in its activity are the major features of the established protocol.

Keywords: Domino reactions, 1-oxo-hexahydroxanthenes, Nickel ferrites nanopartilces, magnetically seprable and reusable, bis-coumarins.

Introduction

The main issue in the synthesis of biologically important organic molecules is currently aimed at improvement of efficiency, avoidance of toxic agents and reduction in waste with responsible utilization of natural sources. Aiming towards this goal of green chemistry, use of alternate energy sources, reaction media, use of *reusable catalysts*, development of solvent-free / catalyst-free synthesis, etc. have been playing their own role in organic synthesis.^[1] On the other hand, multicomponent as well as domino reactions are also contributing significantly for the enviro-economic synthesis of complex organic molecules.^[2] Among domino reactions, Knoevenagel-Michael domino reactions have emerged as a very powerful strategy in the synthesis of heterocycles as well as structurally diverse organic compounds having promising synthetic as well as biological potential.^[3] 1-oxo-hexahydroxanthenes, tetraketones, bis-coumarins, bis-N-methyl-quinolones, bis-pyrazoles, bis-indolyl alkanes, bis-Meldrum's acid and, bis-uracils are a few such heterocycles with important biological properties

Construction of xanthene scaffold has attracted much attention of organic chemists in recent years due to their importance in the field of medicine as well as material science.^[4] Two important class of compounds containing xanthene structural motif are 1,8-octahydroxanthenes and 1-oxo-hexahydroxanthenes. Amongst these 1-oxo-hexahydroxanthenes are of particular interest to synthetic organic chemists due to their important pharmacological properties such as, anti-estrogenic, anti-bacterial, anti-microbial as well as hypoglycemic activities.^[5] They also exhibit thrombin-inhibitory activity and are known to serve as neuropeptide Y5 receptor antagonist.^[6] In spite of having remarkable applications in variety of fields as a versatile synthones and derivative intact, 1-oxohexahydroxanthenes are much less attended by researchers.

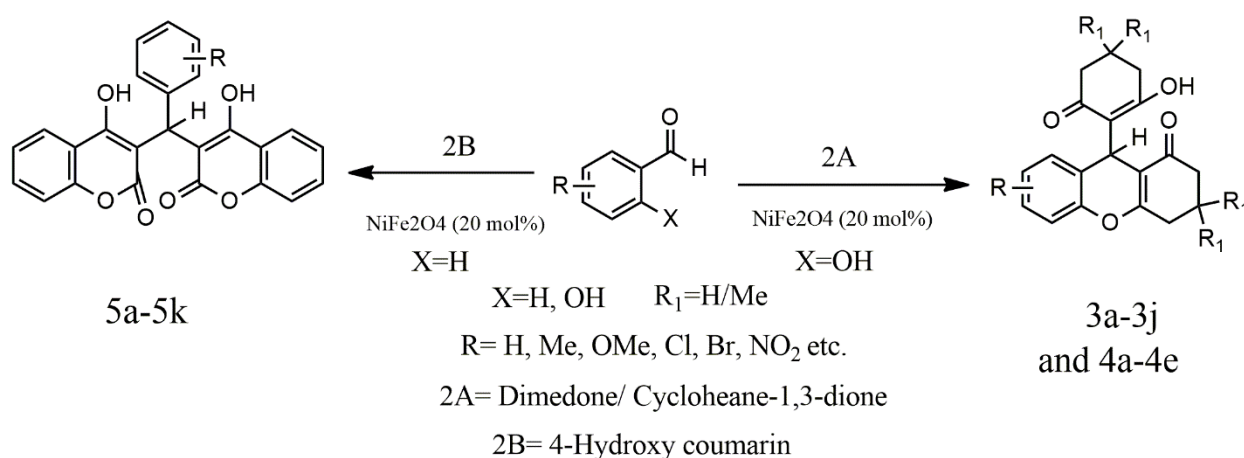
Their synthesis involving one-pot, *pseudo* three component condensation between salicylaldehyde and two equivalents of dimedone or 1,3-cyclohexanedione has been reported earlier using a range of Bronsted,^[7] heteropoly^[8] as well as Lewis acid catalysts.^[9] On the other hand a few catalyst-free protocols have also been reported using glycerol as well as water as solvent^[10] and there exists only one protocol that reports the synthesis of hexahydroxanthenes using basic catalyst.^[10d] triethyl benzyl ammonium chloride (TEBA) as a cationic surfactant at 90 °C for 3–5 h,^[11] 2,4,6-trichloro-1,3,5-triazine at 120 °C,^[16] CsF at room temperature in dichloromethane,^[17] L-proline in ethanol at 60 °C,^[18] p-TSA in water by stirring at 90 °C,^[19] and FeCl₃.6H₂O a Lewis acid catalyst for model reaction.^[20] Recently the new article evident synthesis of using diethylamine in ethanol at room temperature.^[20] Some reports are also reveal the use of heterogeneous catalysts such as cellulose sulfuric acid,^[21] nanoZnAl₂O₄ at reflux condition,^[22] NaY/Fe Zeolite in water at reflux condition.^[23] But these catalysts are associated with undesired difficulties like contain of halogen,^[11-16, 17] requirement of tedious work up with decreased efficiency or more temperature requirement for each repetitive use of catalyst as well as use of acid, moisture sensitive expensive reagents for catalyst preparation^[21] and use of flammable-volatile liquid catalyst.^[23]

Apart from various merits associated with these protocols, it is worthy to note that, most of the reported protocols are operable at reflux temperature. Thus, it is desirable to develop a cost as well as energy efficient protocol for the synthesis of 1-oxo-hexahydro-xanthenes. With our continued attempts to make chemistry simple and easily adaptable for the synthesis of biologically active compounds,^[11] we planned to develop an enviro-economic protocol for the synthesis of 1-oxo-hexahydroxanthenes use of magnetically separable and reusable catalysts. In this context, use and development of variety of heterogeneous and magnetically separable catalysts to enrich the cleanliness of synthetic methods has been considered as a greatest research area. To achieve this goal, heterogeneous catalysts perform more superiorly for higher proficiency, mild reaction conditions, ease in reaction procedure less waste generation and possible reusability of catalyst.^[25-26]

In the field of heterogeneous catalysis, Nano catalysts got remarkable attention due to their intrinsic properties significant for improvement of reactivity, selectivity and yield of reaction. But difficulties in recovery of catalysts restrict its reuse as well as its applicability throughout research area. This difficulty cling to these catalysts shifted the focus of researcher toward the magnetically separable Nano catalysts.^[27-29] 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.^[30-32] Recently Heterogenous catalyst played an important role in the synthesis of various type of organic transformations and its reusability is noteworthy.^{[33-40].}

In this communication we report nickel ferrite nanoparticles as a magnetically separable and reusable heterogeneous catalyst for synthesis of a 1-oxo-hexahydroxanthenes and based upon mechanism extension of the protocol towards the synthesis of bis-coumarins (**Scheme 1**)

To best of our knowledge there is no report on employment of Spinel ferrites for the synthesis of 1-oxo hexahydroxanthenes. So in present report we endeavored to synthesize 1-oxo hexahydroxanthenes using spinel ferrites and extended toward the synthesis of the bis-coumarins.



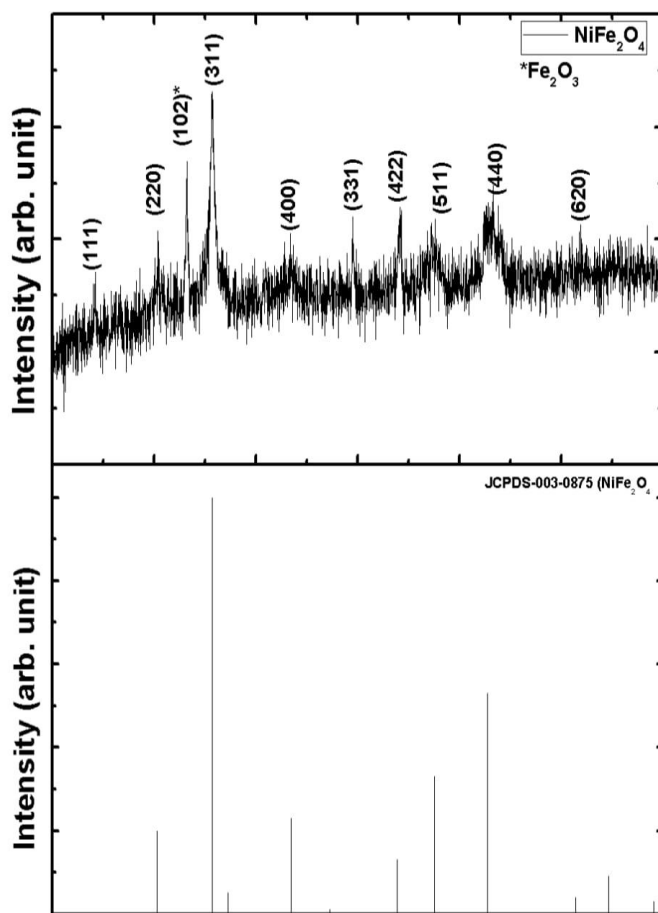
Scheme 1. Nickel ferrite nanoparticles catalyzed synthesis of 1-oxo-hexahydroxanthenes and bis-coumarins.

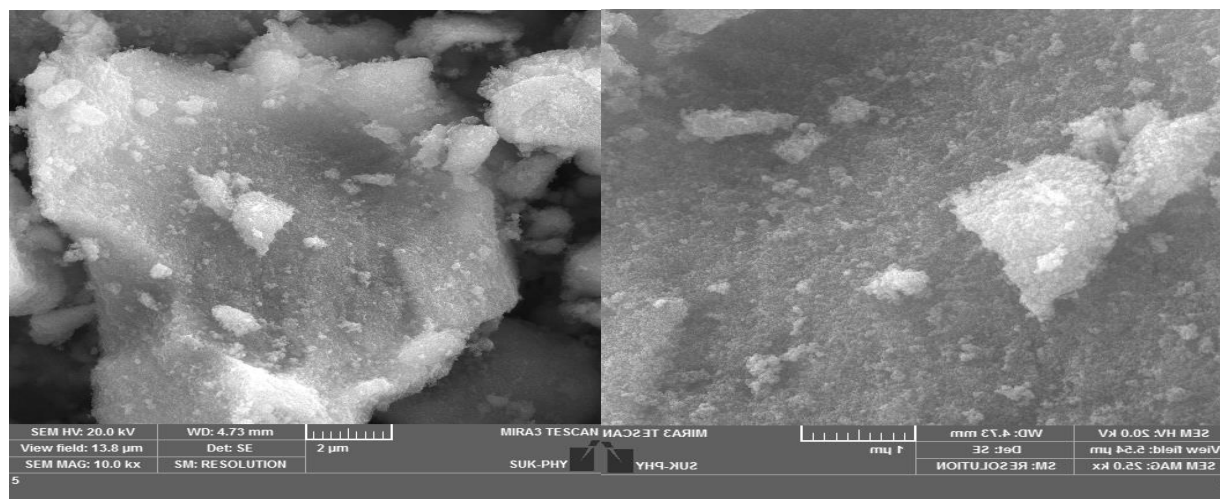
Results and Discussion

The Spinel ferrites used were prepared by using simple method. 0.1 M solution of metal (II) nitrate ($M = \text{Fe, Co, Ni and Cu}$) was added to 0.2 M Fe (III) nitrate solution with proper stirring. Then the solution formed was slowly added with NH_4OH solution at this stage, till pH of solution reached to 9, and then the brownish black precipitate formed was digested to 60°C for 2 hours. The resultant product was filtered, dried and calcined at 500°C for 3 hours to get magnetic crystals, which were ground to get fine powdered ferrite.^[33] As an initial part of our work four representative ferrites *viz.*, Fe_3O_4 , CoFe_2O_4 , NiFe_2O_4 and CuFe_2O_4 were prepared and screening of their catalytic properties for desired reaction were done.

The **Fig. No.1** revealed XRD of NiFe_2O_4 which had been synthesized by a co-precipitation method wherein calcination temperature plays key role in tailoring its properties. The XRD was recorded using Bruker D2 phaser table top model. NiFe_2O_4 found as the inverse spinel structure with Five major characteristic peaks of reflections plane *viz.* (2 2 0), (3 1 1), (4 0 0), (5 1 1), and (4 4 0) indexed as the spinel structure according to the standard JCPDS (Card No. 003-0875).

NiFe_2O_4 nanoparticles were studied morphologically to elucidate the structural aspects, high temperature causes merging of fine particles to agglomerated one as a result of magnetic dipole interaction among the particles, which was supported by the reported FESEM in **Fig. No-2**.



Fig. No. 1. XRD Pattern of NiFe₂O₄Fig. No. 2. FESEM images of NiFe₂O₄

In Initial exploratory reaction, to a well stirred solution of salicylaldehyde (2mmol) and dimedone, **2A**, (4 mmol) in ethanol (6 mL) was added Fe₃O₄ (20 mol %). Stirring was continued at ambient temperature and progress of the reaction was monitored by TLC (**Scheme 1**). Upon completion of the reaction, water (10 mL) was added and the resultant solid was filtered, washed with water and dried. Dried product was washed with hexane (3 x 7 mL) and dried again. On the basis of comparison of physical as well as spectroscopic data of the resultant solid with that reported earlier,^[7] it was identified to be the desired 1-oxo-hexahydroxanthene, **3a**.

To find out best suitable condition for exploratory reaction, same reaction was carried out in no catalyst –no solvent condition. The reaction was found to be completed with only 17% of product in 12 hours (Table-1, entry-1). We perform this reaction in water to check its effect as a solvent, in absence of catalyst. Although we found noticeable increase in yield, this protocol was associated with longer reaction time (Table-1, entry-2). To establish most appropriate ferrite amongst prepared ones for targeted reaction, we carried out this reaction using other metal ferrites. However, with the choice of any of these ferrites, yields of product **3a** was surprisingly obtained in the range of 80-90 % (Table-1, entries-3-6).

For subsequent optimization of reaction condition, the catalytic potential of various ferrites was explored by varying solvent systems. For this purpose, effect of ethanol and water in different proportions have been studied, mainly to maintain the benign nature of our protocol using same catalyst loading (Table-1, entries-7-13).

The minor difference found in between yields of product **3a** in presence of Fe₃O₄, CoFe₂O₄ and NiFe₂O₄ made the selection of ferrite quite 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 NiFe₂O₄ as a catalyst for further studies. In optimization of reaction condition regarding the catalyst loading, repetitions of model reaction were done with 15 mole% and 10 mole% of ferrites (Table-1, entries-14-19). But 20 mole % of catalyst was found to give much better yield of **3a** (Table-1, entries-13).

The effect of water in presence of catalyst also has been studied with 20 m% NiFe₂O₄, but improper dispersion of catalyst in water doesn't show any effective result on yield. In contrary this set of condition took more time to furnish the product. (Table-1, entry-19). As the next part of this work full characterization of NiFe₂O₄ were done to support most vital structural properties of catalysts.

Table 1: Optimization for the reaction for the synthesis of the 1-oxo-hexahydroxanthene, **3a^a**

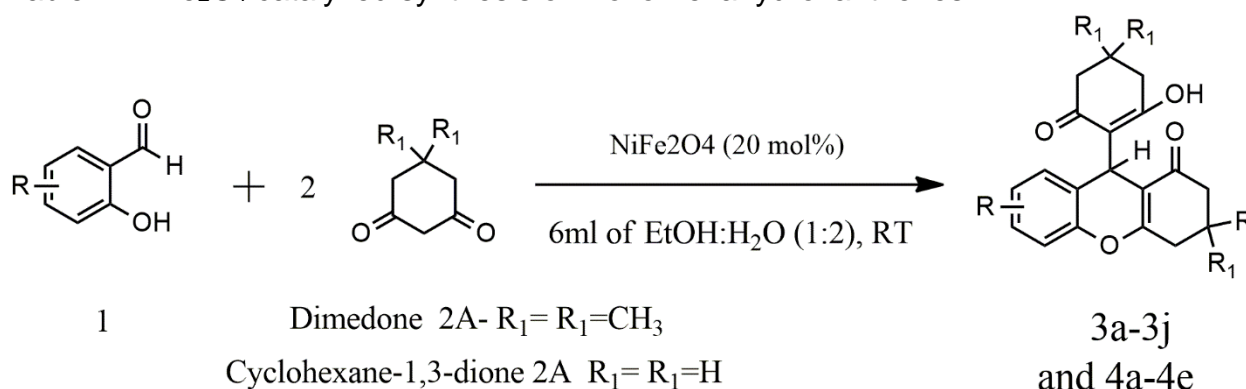
Entry	Catalyst (Mol %)	Solvent	time(hrs)	Yield (%)
1	--	--	12	17 ^b
2	--	H ₂ O	10	45
3	Fe ₃ O ₄ (20)	H ₂ O	6	76
4	Fe ₃ O ₄ (20)	EtOH	4	80
5	CoFe ₂ O ₄ (20)	EtOH	3	87
6	NiFe ₂ O ₄ (20)	EtOH	3	90
7	CuFe ₂ O ₄ (20)	EtOH	3	83
8	Fe ₃ O ₄ (20)	EtOH : H ₂ O (1:1)	3	83
9	CoFe ₂ O ₄ (20)	EtOH : H ₂ O (1:1)	3	90
10	NiFe ₂ O ₄ (20)	EtOH : H ₂ O (1:1)	3	93
11	Fe ₃ O ₄ (20)	EtOH : H ₂ O (1:2)	4	85
12	CoFe ₂ O ₄ (20)	EtOH : H ₂ O (1:2)	3	92
13	NiFe₂O₄ (20)	EtOH : H₂O (1:2)	2	95
14	Fe ₃ O ₄ (15)	EtOH : H ₂ O (1:2)	4	82
15	CoFe ₂ O ₄ (15)	EtOH : H ₂ O (1:2)	2.5	87
16	NiFe ₂ O ₄ (15)	EtOH : H ₂ O (1:2)	2.5	91
17	Fe ₃ O ₄ (10)	EtOH : H ₂ O (1:2)	3	78
18	CoFe ₂ O ₄ (10)	EtOH : H ₂ O (1:2)	2.5	84
19	NiFe ₂ O ₄ (10)	EtOH : H ₂ O (1:2)	2.5	86

^aReaction conditions: salicylaldehyde, **1** (2 mmol) and 1, 3-dione (**2** / **3,4** mmol), ethanol-water (6 mL 1: 1, v/v), NiFe₂O₄ (20 mol %), RT.

During the studies on this model reaction, as targeted product, **3a**, was obtained in good yields as well as purity by using NiFe_2O_4 as an inexpensive catalyst and by avoidance of conventional isolation as well as purification procedures. We next planned to examine the scope of the developed protocol. Thus, dimedone component from the aforementioned model reaction was replaced with 1,3-cyclohexanedione, **2A**. The reaction required slightly longer reaction time however; upon completion of the reaction followed by work-up as described earlier, corresponding 1-oxo-hexahydroxanthene, **3a** was obtained in excellent yield. Encouraged with this initial success, we then planned to investigate generality of the reaction conditions. Accordingly, under the established reaction conditions salicylaldehydes bearing electron-withdrawing as well as electron-donating groups were allowed to react with dimedone as well as 1,3 - cyclohexanedione. In all the cases corresponding 1-oxo-hexahydroxanthene **3a-3j** and **4a-4e** resulted in excellent yield as well as purity (**Table 2**).

From the philosophic view point, synthesis of 1-oxo-hexahydroxanthenes is delineated to proceed by two different paths *viz.* Knoevenagel-cyclization-carba-Michael pathway or Knoevenagel-carba-Michael-cyclization pathway. In the presence of a NiFe_2O_4 catalyst, former pathway is less probable. Thus, if the reaction follows, reaction between an aromatic aldehyde devoid of *ortho* hydroxyl group e.g. 4-methoxybenzaldehyde, with two equivalents of dimedone, should furnish 2,2'-(4-phenylmethylene)-bis-(3-hydroxy-3,3-dimethyl-2-cyclohexene-1-one), tetraketone, while the similar reaction with the choice of another 1,3-diketone, 4-hydroxycoumarin, should furnish 3,3'-(4-phenylmethylene)-bis-(4-hydroxycoumarin), **5a**, respectively, as Knoevenagel-carba-Michael domino reaction products.

Table 2. NiFe_2O_4 catalyzed synthesis of 1-oxo-hexahydroxanthenes



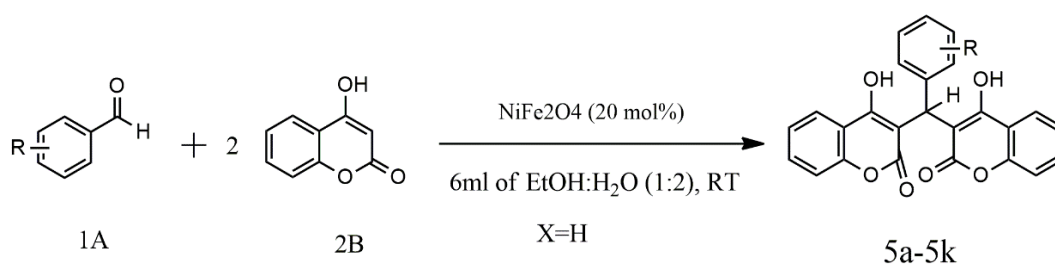
Product	Aldehyde (1) R =	R ¹	Time (h)	Yield (%)	M.P. (°C) Obs.	M.P. (°C) Lit. ^{Ref}
3a	H	CH ₃	2.00	95	204 – 206	206 – 208 ^{7b}
3b	5-Br	CH ₃	1.45	92	251 – 253	253 – 255 ^{10b}
3c	5-Cl	CH ₃	1.45	90	234 – 236	236 – 238 ⁹
3d	3,5-Cl ₂	CH ₃	2.45	86	227 – 228	231 ^{7b}
3e	4-OCH ₃	CH ₃	2.15	92	215 – 218	217 – 221 ^{10d}
3f	3-OH	CH ₃	2.30	88	247 – 249	251 ^{7d}
3g	4-OH	CH ₃	3.00	84	225 – 228	232 ^{10d}
3h	3-Br-5-NO ₂	CH ₃	3.15	80	232 – 235	228 – 232 ²⁰
3i	5-OCH ₃	CH ₃	2.45	85	181 – 184	177 – 181 ^{7a}
3j	4,6-Cl ₂	CH ₃	3.30	75	203 – 206	208 – 210 ²⁰
4a	H	H	3.00	93	240 – 242	242 – 244 ^{7b}
4b	4-OCH ₃	H	2.30	88	238 – 242	236 – 240 ²⁰
4c	3-OH	H	4.00	89	245 – 249	247 – 248 ²⁰
4d	4-OH	H	3.30	82	238 – 241	242 ^{7d}
4e	4,6-Cl ₂	H	4.30	72	215 – 218	220 – 223 ²⁰

^a Reaction conditions: salicylaldehyde, **1** (2 mmol) and 1, 3-dione (**2A**, 4 mmol), ethanol-water (6 mL 1: 2, v/v), NiFe₂O₄ (20 mol %), RT.

So as to confirm these speculations, two model reactions were performed between 4-methoxybenzaldehyde, **1A**, (1 mmol) and 4-hydroxycoumarin, **2B** (2 mmol) employing the reaction conditions established for the synthesis of **5a**. Upon completion of the reactions (TLC), it was truly gratifying to notice the formation of anticipated bis-coumarin, **5a**, in excellent yield. In each case, resultant solid was simply filtered, washed with water, dried and washed again with hexane (3 x 10 mL) to obtain pure **5a**. As regards earlier protocols reported for the synthesis of bis-coumarins is concerned, few interesting reports are noteworthy. On the other hand, synthesis of bis-coumarins has been reported earlier using varieties of catalysts under the range of experimental conditions.^[40-43] However, most of the reported protocols required elevated temperature^[40] or MW irradiation,^[41] while a few of them require the use of an expensive catalyst.^[42] Furthermore, to the best of our knowledge there exists only one method involving the synthesis of bis-coumarins at ambient temperature, using piperidine as the catalyst.^[43] A number of protocols developed for synthesis of the bis-coumarins synthesis.^[56-61] In light of these observations, we surmised that, the development of a protocol that would circumvent the drawbacks associated with most of the earlier reported protocols is desirable. The other reason to

undertake the synthesis of bis-coumarins is concerned with their well-established biological activities. For instance, bis-coumarins are known to exhibit urease inhibitor, anticoagulant as well as snake venom NPP1 inhibitory activity^[44a-c] while a few naturally occurring bis-coumarins do serve as DNS polymerase beta lyase inhibitor.^[44d] In light of all these observations, we planned to extend the scope of the established reaction conditions towards the synthesis of various bis-coumarins. Accordingly, aromatic aldehydes tethered with electron-withdrawing as well as electron-donating groups and a few heterocyclic aldehydes were allowed to react with 4-hydroxy coumarin. In all the cases, desired bis-coumarin, **5a-k**, was obtained in excellent yield following a very simple work-up as well as purification method. Results are summarized in **Table 3**.

Table 3. NiFe₂O₄ catalyzed synthesis of the bis - coumarins, 5.



Product	Aldehyde (1A)	Time (h)	Yield (%)	Melting point (°C)	
				Obs.	Lit. ^{Ref}
5a	4 –Methoxybenzaldehyde	3.0	83	138 – 140	140 - 141 ^{16g}
5b	2,5 –Dimethylbenzaldehyde	4.0	84	197 – 200	198 – 200 ²⁰
5c	4 –Bromobenzaldehyde	3.5	87	261 – 264	265 - 267 ^{16b}
5d	6 –Nitropiperonal	3.0	83	150 – 153	153 – 156 ²⁰
5e	4 –Hydroxybenzaldehyde	4.0	86	205 – 207	202 - 204 ^{20a}
5f	4 – Nitrobenzaldehyde	5.0	81	228 – 231	232 - 234 ^{16g}
5g	Thiophene-2-carbaldehyde	4.0	78	150 – 152	156 - 158 ¹⁸
5h	5 –Methylfurfural	5.0	80	186– 189	185 – 187 ²⁰
5i	3 - Methyl thiophen-2-carbadehyde	4.0	81	130 – 134	134 – 136 ²⁰
5j	4-Allyloxybenzaldehyde	4.0	79	220 – 224	222 – 225 ²⁰
5k	4-cyanobenzaldehyde			238 – 241	240 - 242 ^{16b}

Reaction conditions: aldehyde (2 mmol), 4- hydroxy coumarin (4 mmol), NiFe₂O₄ (20 mol %), ethanol-water (6 mL, v / v), RT; Yields refer to isolated products

Conclusion

In summary, we have developed an extremely simple and environmentally benign protocol for the synthesis of 1-oxo-hexahydroxanthenes and bis-coumarins NiFe₂O₄ as the catalyst. Commercial availability of the catalyst at extremely low cost, ambient reaction conditions and avoidance of conventional work-up as well as purification procedures offer added advantages of the energy efficient protocols developed. If a comparison is made between the various protocols available for the synthesis of 1-oxo-hexahydroxanthene, **3a** and **4a**, and bis-coumarins, **5a**, as model compounds, it would be evident that, the protocol developed by us is superior to most of the protocols reported earlier for their synthesis.

Experimental

General experimental procedure for synthesis of 3 and 4: To a well stirred solution of salicylaldehyde, **1** (2 mmol) and appropriate dimedone or cyclohexane-1,3-dione (**2A**, 4 mmol) in aqueous-ethanol (6 mL, 1:2, v/v) was added NiFe₂O₄ (20 mol %) and stirring continued. Upon completion of the reaction (TLC), water (10 mL) was added and the resultant solid was filtered, washed with ethanol, dried, washed again with hexane mixture (7ml *3 times) and dried. The resultant product, **3/4**, was found to be pure and did not require any further purification.

General experimental procedure for 5: To a well stirred solution of aldehyde, **1A**, (2 mmol) and 4-hydroxycoumarin, **2B**, in aqueous-ethanol (6 mL, 1:2, v/v) was added NiFe₂O₄ (20 mol %) and stirring continued. Upon completion of the reaction (TLC), resultant solid was filtered, washed with ethanol, dried, washed again with hexane (7ml *3 times) and dried. The resultant bis-coumarin, **5**, was found to be pure and did not require any further purification.

Spectral data

Many of the synthesized compounds are known compounds and they were characterized by comparison of their physical constants while all unknown compounds were characterized by spectral methods. The spectral data of unknown compounds is summarized below.

5-bromo-3,4-dihydro-9-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)-3,3-dimethyl-7-nitro-2H-xanthen-1(9H)-one, **3h**: Pale yellow solid; **M. P.:** 232 – 235 °C; **¹H-NMR : (300 MHz, CDCl₃)** : δ 1.08 (s, 4H), 1.16 (s, 8H), 2.27 – 2.33 (m, 3H), 2.41 (s, 2H), 2.32 – 2.39 (m, 3H), 4.83 (s, 1H), 7.78 (s, 1H), 8.29 (s, 1H), 10.38 (brs, 1H); **¹³C-NMR : (75 MHz, CDCl₃)** : δ 26.19, 27.27, 29.29, 30.00, 32.04, 32.26, 40.91, 46.33, 30.19, 113.23, 114.13, 113.10, 122.86, 124.00, 124.43, 126.13, 127.78, 141.23, 133.13, 137.47, 163.33, 189.90, 198.23 ppm.

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**: White solid; **M. P.:** 203 – 206 °C; **¹H-NMR: (300 MHz, CDCl₃)** : δ 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); **¹³C-NMR: (75 MHz, CDCl₃)** δ 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 ppm.

3,4-dihydro-9-(2-hydroxy-6-oxocyclohex-1-enyl)-6-methoxy-2H-xanthen-1(9H)-one, **4b**: White solid; M. P.: 238 – 242 °C; ¹H-NMR: (300 MHz, CDCl₃) : δ 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); ¹³C-NMR: (75 MHz CDCl₃) : δ 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 ppm.

3,4-dihydro-5-hydroxy-9-(2-hydroxy-6-oxocyclohex-1-enyl)-2H-xanthen-1(9H)-one, **4c**: White solid; M. P.: 245 – 249 °C; ¹H-NMR: (300 MHz, DMSO-*d*₆) : δ 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); ¹³C-NMR : (75 MHz, DMSO-*d*₆) : δ 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 ppm.

6,8-dichloro-3,4-dihydro-9-(2-hydroxy-6-oxocyclohex-1-enyl)-2H-xanthen-1(9H)-one, **4e**: Colorless solid; M. P.: 215 – 218 °C; ¹H-NMR: (300 MHz, DMSO-*d*₆) : δ 1.92 – 1.98 (m, 3H), 2.00 – 2.09 (m, 1H), 2.23 – 2.48 (m, 6H), 2.80 (m, 2H), 4.33 (s, 1H), 7.11 (d, 1H, *J* = 2.4 Hz), 7.34 (d, 1H, *J* = 2.4 Hz); ¹³C-NMR : (75 MHz, DMSO-*d*₆) : δ 20.07, 20.31, 24.36, 27.46, 34.33, 36.33, 40.17, 49.13, 110.91, 113.98, 121.06, 126.74, 127.13, 127.61, 127.72, 144.94, 168.34, 193.28, 202.67 ppm.

2-hydroxy-3-((2-hydroxy-4-oxo-4H-chromen-3-yl)(2,5-dimethylphenyl)methyl)-4H-chromen-4-one, **5c**, solid; M. P.: 197 - 200 °C; IR (KBr): 3434, 2972, 1645, 1614, 1565, 1510, 1321, 1132, 876 cm⁻¹; ¹H-NMR: (300 MHz, DMSO-*d*₆): δ 2.03 (s, 3H), 2.18 (s, 3H), 5.60 (s, 1H), 6.09 (s, 1H), 6.88 (d, 1H, *J* = 7.5 Hz), 6.96 (d, 1H, *J* = 7.3 Hz), 7.03 (s, 1H), 7.30 (d, 1H, *J* = 7.3 Hz), 7.34 (s, 1H), 7.37 (s, 1H), 7.58 (t, 2H, *J* = 7.7 Hz), 7.62 (d, 1H, *J* = 8.0 Hz), 7.82 (d, 1H, *J* = 7.7 Hz), 7.91 (d, 2H, *J* = 7.8 Hz), 12.56 (brs, 1H); ¹³C-NMR:, (75 MHz, DMSO-*d*₆): δ 19.56, 21.44, 36.19, 91.48, 104.84, 116.26, 116.47, 116.81, 117.88, 123.66, 124.19, 124.23, 124.36, 127.12, 128.72, 130.82, 132.29, 133.13, 133.36, 134.49, 152.56, 153.98, 162.35, 164.39, 164.62, 166.10 ppm.

2-hydroxy-3-((2-hydroxy-4-oxo-4H-chromen-3-yl)(6-nitrobenzo[d][1,3]dioxol-6-yl)methyl)-4H-chromen-4-one, **5d**, solid; M. P.: 150-153 °C; IR (KBr): 3465, 2948, 1651, 1610, 1555, 1532, 1505, 1367, 1155, 865 cm⁻¹; ¹H-NMR: (300 MHz, DMSO-*d*₆): δ 5.59 (s, 1H), 6.10 (s, 2H), 6.71 (d, 1H, *J* = 4.0 Hz), 6.88 (d, 1H, *J* = 2.1 Hz), 7.20 (d, 1H, *J* = 2.5 Hz), 7.23 (s, 2H), 7.25 (d, 2H, *J* = 3.4 Hz), 7.28 (d, 1H, *J* = 2.6 Hz), 7.32 (d, 1H, *J* = 2.2 Hz), 7.52 (t, 2H, *J* = 8.3 Hz), 7.92 (d, 2H, *J* = 8.0 Hz); ¹³C-NMR: (300 MHz, DMSO-*d*₆) (75 MHz, DMSO-*d*₆): δ 39.78, 96.27, 107.99, 109.51, 110.51, 114.30, 121.09, 121.15, 121.68, 128.28, 128.57, 137.05, 137.24, 147.99, 151.20, 156.01, 157.27, 158.70, 168.59, 169.11, 170.82 ppm.

2-hydroxy-3-((2-hydroxy-4-oxo-4H-chromen-3-yl)(5-methylfuran-2-yl)methyl)-4H-chromen-4-one, **5h**, solid, M. P.: 186 - 189 °C; IR (KBr): 3445, 2943, 1654, 1621, 1532, 1499, 1353, 823 cm⁻¹; ¹H-NMR: (300 MHz, DMSO-*d*₆): δ 2.13 (s, 3H), 5.85 (s, 1H), 5.96 (s, 1H), 6.10 (d, 1H, *J* = 3.1 Hz), 7.27 (s, 1H), 7.29 (s, 2H), 7.31 (s, 1H), 7.54 (t, 2H, *J* = 7.6 Hz), 7.93 (d, 2H, *J* = 7.6 Hz), 11.50 (brs, 2H); ¹³C-NMR:, (75 MHz, DMSO-*d*₆): δ 13.63, 32.00, 103.51, 106.32, 107.98, 116.46, 116.62, 124.17, 124.62, 132.71, 151.28, 152.31, 164.31, 166.54 ppm.

2-hydroxy-3-((2-hydroxy-4-oxo-4H-chromen-3-yl)(3-methylthiophene-2-yl)methyl)-4H-chromen-4-one, **5i**, solid, M. P.:130 - 134°C; **IR (KBr)**: 3455, 2988, 1674, 1612, 1514, 1491, 1377, 888 cm⁻¹; **¹H-NMR: (300 MHz, DMSO-d₆)**: δ 2.13 (s, 3H), 5.85 (s, 1H), 5.96 (s, 1H), 6.10 (d, 1H, *J* = 3.1 Hz), 7.27 (s, 1H), 7.29 (s, 2H), 7.31 (s, 1H), 7.54 (t, 2H, *J* = 7.6 Hz), 7.93 (d, 2H, *J* = 7.6 Hz), 11.50 (brs, 2H); **¹³C-NMR:, (75 MHz, DMSO-d₆)**: δ 13.58, 32.95, 104.46, 107.27, 108.93, 117.41, 117.57, 125.12, 125.57, 133.66, 148.78, 152.53, 153.26, 165.26, 167.49 ppm.

3-((4-(allyloxy)phenyl)(4-hydroxy-2-oxo-2H-chromen-3-yl)methyl)-4-hydroxy-2H-chromen-2-one, **5j**: Solid; M. P.:220 - 224 °C; **IR (KBr)**: 3435, 2917, 1640, 1612, 1545, 1490, 1342, 808 cm⁻¹; **¹H-NMR: (300 MHz, DMSO-d₆)**: δ 4.53 (d, 2H, *J* = 5.4 Hz), 5.28 (dd, 1H, *J* = 9.2 & 10.5 Hz), 5.41 (dd, 1H, *J* = 17.1 & 15.4 Hz), 5.99 – 6.12 (m, 1H), 6.87 (d, 2H, *J* = 8.8 Hz), 7.12 (d, 2H, *J* = 8.2 Hz), 7.41 (s, 2H), 7.44 (s, 2H), 7.61 – 7.67 (m, 2H), 8.02 (d, 1H, *J* = 8.0 Hz), 8.09 (d, 1H, *J* = 7.7 Hz), 11.31 (s, 1H), 11.50 (s, 1H); **¹³C-NMR:, (75 MHz, DMSO-d₆)**: δ 35.53, 68.74, 104.20, 105.81, 114.80, 116.57, 117.59, 124.41, 124.74, 127.04, 127.57, 132.65, 133.31, 152.28, 157.46, 164.39, 165.51, 166.63 ppm.

Acknowledgement:

Author KSP are thankful to my Professor U. V. Desai sir, Shivaji University Kolhapur for assistance in every way and we are honored and fortunate have such wonderful person as guide.

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