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$FeCl_3 \cdot 6H_2O$ as a green and readily available catalyst for the synthesis of 1-oxo-hexahydroxanthenes by the condensation of salicylaldehydes with 1,3-diketones in aqueous media

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Abstract:

A facile and efficient method for the synthesis of 1-oxo-hexahydroxanthenes catalyzed by $FeCl_3 \bullet 6H_2O$ is described. The iron-catalyzed condensation of salicylaldehydes with cyclic 1,3-diketones afforded 1-oxo-hexahydroxanthene derivatives in a good to excellent yields at room temperature. The use of water as a green solvent, purification of the products by non-chromatographic methods, catalyst reusability and high yields are some of the advantages of this protocol.

Keywords: Catalytic reactions, $FeCl_3 \bullet 6H_2O$, Green chemistry, 1-Oxo-hexahydroxanthenes, Organic synthesis

Introduction:

A prominent goal of modern organic chemistry is to maximize the efficiency of reactions using readily available starting materials and minimize the generation of waste, which are prime principles of green chemistry.[1] In recent years, green chemistry has attracted considerable attention from organic and medicinal chemists. One of the most important roles of green chemistry is the design and application of chemical reactions that reduce or eliminate the use of toxic solvents and reagents.[2] Water as a reaction medium has numerous advantages including ease of product isolation, nontoxicity, nonflamability, high specific heat capacity, low cost, large surface tension and high polarity which make it both economical and environmentally friendly, and thus suitable as a green solvent.[3, 4]

Heterocyclic compounds, especially oxygen-containing heterocycles, are ubiquitous in natural products and pharmaceuticals and represent the most important class of key structural units in a large number of bioactive molecules.[5] In particular, xanthenes and their derivatives play an important role in the fields of natural products, medicinal and materials chemistry.[6] Xanthenes are used as leuco-dyes in laser technology[7] and as pH-sensitive fluorescent materials for the visualization of biomolecules.[8] Octahydroxanthene derivatives containing the benzopyran moiety have been used as antispasm,[9] antiviral,[10] antibacterial,[11] antioxidant, antineoplastic, vasodilators and anti-inflammatory agents[12-20] as well as fluorescent fuels.[21] The many applications of xanthenediones have stimulated the development of environmentally benign methods for their synthesis. There are a myriad of research articles reporting the synthesis of functionalized xanthenes and a wide range of starting materials and reaction protocols have been applied for the synthesis of this fascinating class of compounds.[22, 23]

Although there have been many reports related to the synthesis of xanthene derivatives, there are few regarding the synthesis of 1-oxo-hexahydroxanthenes. Synthetic routes to these compounds generally involve the condensation of salicylaldehydes with 1,3-diketones under various conditions. Although the reaction has been accomplished under catalyst free conditions in solvents such as water, glycerol and dimethylformamide, high temperatures (80-90 °C) and long reaction times (3-12 h) were needed to furnish the corresponding 1-oxo-hexahydroxanthenes in reasonable yields.[24-26] Various homogeneous catalysts such as $CeCl_3 \bullet 7H_2O$,[27] acetic acid,[28] triethyl-benzylammonium chloride (TEBA) as a cationic surfactant,[20] 2,4,6-trichloro-1,3,5-triazine,[29] CsF,[30] L-proline,[31] and PTSA[32] have been used. However, some of these catalysts contain halogens[20, 30] and require high temperatures[28, 29, 32] or long reaction times.[27] Heterogeneous systems such as cellulose sulfuric acid and nano-$ZnAl_2O_4$ have also been developed for the synthesis of 1-oxo-hexahydroxanthenes. Despite showing efficient catalytic activity, these methods suffer from drawbacks such as the requirement of catalyst preparation and the use of expensive and/or moisture sensitive reagents.[33, 34]

Significant interest has been focused on the development of new protocols for environmentally benign processes that are both economically and technologically practical. In particular is the use of nonhazardous and inexpensive metals has attracted continued interest in organic synthesis. In this regard iron salts which efficiently catalyze organic reactions have attracted considerable attention since iron is inexpensive, sustainably produced,

easily accessible, non-toxic, air and moisture stable and easy to store for long periods under normal laboratory conditions. It is also an environmentally benign metal.[35, 36] These factors have led chemists to pay more attention to iron-based catalysis for mild and green reactions.[37-39]

$FeCl_3•6H_2O$ as a Lewis acid catalyst has been increasingly utilized in a wide variety of organic reactions such as the preparation of xanthenediones,[2] and Hantzsch 1,4-dihydropyridines,[40] Biginelli condensations[41] and Beckmann rearrangements.[42] The synthesis of 1-oxo-hexahydroxanthene derivatives is still highly desirable in terms of developing more practical procedures and mild reaction conditions. As a consequence of our interest in developing new and efficient synthetic methodologies for the synthesis of organic compounds,[43-47] we report herein a convenient, mild and environmentally benign method for the preparation of 1-oxo-hexahydroxanthenes by the condensation of salicylaldehydes with cyclic 1,3-diketones using catalytic $FeCl_3•6H_2O$ at room temperature in aqueous media. To the best of our knowledge, the synthesis of 1-oxo-hexahydroxanthenes catalyzed by $FeCl_3•6H_2O$ has not been reported.

Results and discussion

The reaction of salicylaldehyde (1.0 mmol) with dimedone (2.0 mmol) using $FeCl_3•6H_2O$ was chosen as a model reaction to determine the optimal reaction condition. When the model reaction was performed under solvent-free conditions in the absence of catalyst, only 10% yield of the desired product **3a** was obtained after 9 h (Table 1, entry 1). The use of water as solvent, significantly improved the yield from 10% to 80% however the reaction time was still long (Table 1, entries 1-2). The reaction conducted in the presence of $FeCl_3•6H_2O$ (10 mol %) in water for 30 minutes gave **3a** in 97% yield (Table 1, entry 3). In subsequent optimization, use of 15 mol% $FeCl_3•6H_2O$ did not improve the reaction rate and furnished **3a** in 97% yield (Table 1, entry 4). Lowering the catalyst loading to 5 mol% decreased the yield to 90% (Table 1, entry 5).We also examined different Lewis acids using the same model compounds and reaction conditions. It was found that $FeCl_3•6H_2O$ exhibited higher efficiency than other Lewis acids examined (entries 6-9) or reported (entry 10). The model reaction was also carried out under solvent free conditions and in different solvents such as EtOH, CH_2Cl_2, CH_3CN, THF and EtOH/H_2O (1:1), however this resulted in lower yields of **3a** (Table 1, entries 11-17). Therefore, the best results were obtained from the reaction of salicylaldehyde (1 mmol) with dimedone (2 mmol) in water (3 mL) in the presence of $FeCl_3•6H_2O$ (10 mol%) at room temperature (Table 1, entry 3).

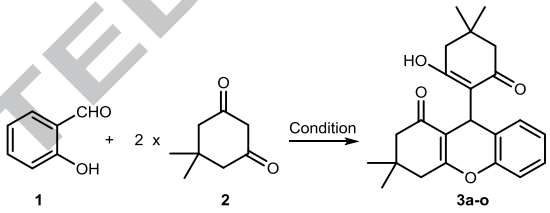


Table 1. Optimization for the reaction of **1** with **2**.

Entry	Catalyst (mol %)	Solvent	Time (min)	Yield (%)[a]
1	-	-	720	10
2	-	H_2O	360	80
3	**$FeCl_3$•6H_2O (10)**	**H_2O**	**30**	**97**
4	$FeCl_3$•6H_2O (15)	H_2O	30	97
5	$FeCl_3$•6H_2O (5)	H_2O	30	90
6	$CrCl_3$•6H_2O (10)	H_2O	30	50
7	$CoCl_2$•6H_2O (10)	H_2O	30	60
8	$Co(NO_3)_2$•6H_2O (10)	H_2O	30	85
9	$ZnCl_2$ (10)	H_2O	30	80
10	$CeCl_3$•7H_2O [b]	H_2O	180	92[27]
11	$FeCl_3$•6H_2O (10)	Solvent Free	30	30
12	$FeCl_3$•6H_2O (10)	Solvent Free (60 °C)	30	60
13	$FeCl_3$•6H_2O (10)	EtOH	30	50
14	$FeCl_3$•6H_2O (10)	CH_2Cl_2	30	30
15	$FeCl_3$•6H_2O (10)	THF	30	10
16	$FeCl_3$•6H_2O (10)	CH_3CN	30	40
17	$FeCl_3$•6H_2O (10)	EtOH/H_2O (1:1)	30	80

Reaction conditions: salicylaldehyde (1.0 mmol), dimedone (2.0 mmol), solvent (3mL), catalyst, room temperature. [a]Yields refer to isolated products. [b]Reflux, catalyst amount not given.

Encouraged by these results, and in order to show the generality and scope of this new protocol, the optimized reaction conditions were applied to a variety of salicylaldehydes and cyclic 1,3-diketones (Table 2). The 1-oxo-hexahydroxanthenes were generally obtained by filtration of the reaction mixture, avoiding solvent extraction or tedious chromatographic purification steps, and where necessary the crude products were further purified by crystallization. This simple workup procedure illustrates the attractiveness of this protocol and afforded the target 1-oxo-hexahydroxanthene derivatives in good to excellent yields.

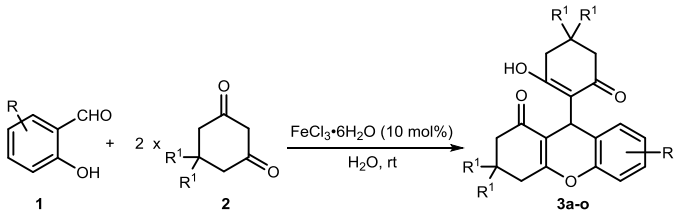
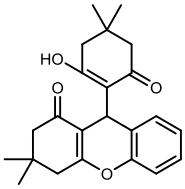
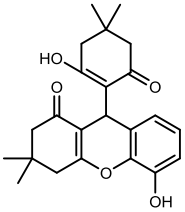
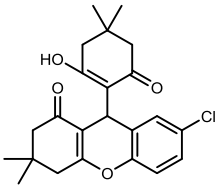
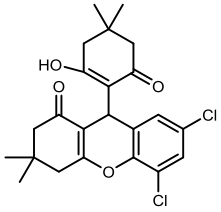
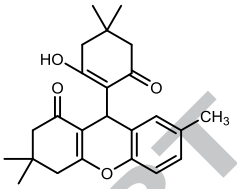
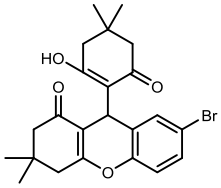
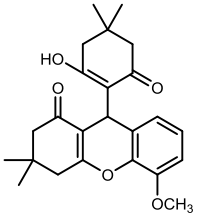
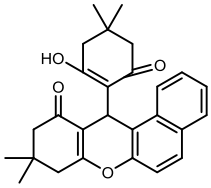
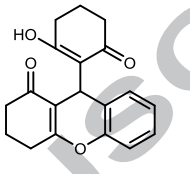
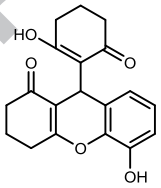
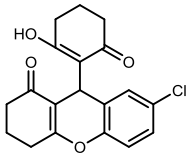
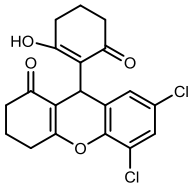
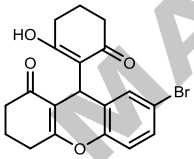
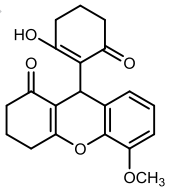
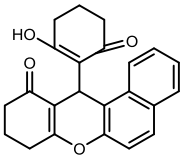


Table 2. Synthesis of 1-oxo-hexahydroxanthenes (**3a-o**) using $FeCl_3•6H_2O$ [a, b, c]

				
3a[48]	**3b**[31]	**3c**[48]	**3d**[48]	**3e**[20]
30 min, 97%[c]	60 min, 90%	60 min, 95%	120 min, 90%	90 min, 90%
				
3f[27, 32]	**3g**[27]	**3h**[29]	**3i**[32]	**3j**[31]
60 min, 95%	30 min, 95%	75 min, 95%	45 min, 95%	90 min, 90%
				
3k[32]	**3l**[20]	**3m**[20, 32]	**3n**[34]	**3o**[20, 49]
60 min, 97%	150 min, 95%	75 min, 95%	45 min, 98%	90 min, 97%

[a] Reaction conditions: dimedone or 1,3-cyclohexanedione (2 mmol), substituted salicylaldehyde (1 mmol), $FeCl_3•6H_2O$ (10 mol%), water (3 mL), room temperature. [b] All compounds are known and their structures were established from comparison of their spectral data and melting points with literature values. [c] Yields refer to isolated products.

$FeCl_3•6H_2O$ showed remarkable reactivity and considerably accelerated the reaction. On the basis of our experimental results and literature reports,[34, 49, 50] we propose a plausible mechanism for the formation of 1-oxo-hexahydroxanthene derivatives **3a-o** in the presence of $FeCl_3•6H_2O$ (Scheme 1). $FeCl_3•6H_2O$ facilitates a Knoevenagel type coupling through Lewis acid sites (Fe^{3+}) coordinated to the oxygen of the carbonyl group of 2-hydroxybenzaldehyde, thus generating intermediate (**I**). Subsequently, during the Michael addition step, nucleophilic attack of intermediate (**I**) by the carbon nucleophile afforded intermediate (**II**). The phenol oxygen first attacks the enone in an 'oxy-Michael' reaction to give intermediate (**III**) (possibly with iron acting as a Lewis acid on the enone oxygen), forming an enolate, which then undergoes elimination of water to afford product **3.** The structures of all synthesized compounds (**3a–o**) were ascertained on the basis of IR, ^{1}H NMR and ^{13}C NMR spectra (see ESI).

In order to show the advantage of the present method, we compared the model reaction with previously reported catalysts for the preparation of 1-oxo-hexahydroxanthene **3a** (Table 3).

Table 3. Comparison of the catalytic activity of $FeCl_3·6H_2O$ with selected reported catalysts for the synthesis of **3a** (Table 2, entry 1)

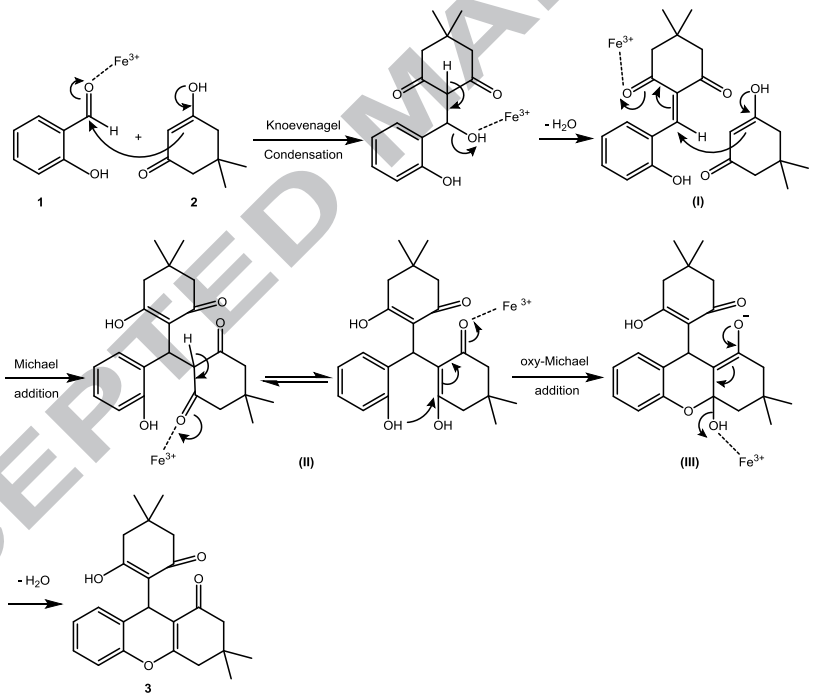
Entry	Catalyst/ Reference	Time (min)	Yield [b]

			(%)
1	*para*-Toluenesulfonic acid (H_2O, 90 °C, 10 mol%)[32]	30	83
2	2,4,6-Trichloro-1,3,5-triazine (Solvent free, 120 °C, 10 mol%)[29]	105	92
3	L-proline (EtOH, 60 °C, 35 mol%)[31]	30	95
4	$CeCl_3$•$7H_2O$ (H_2O, 90°C, small amount)[27]	180	92
5	Triethylbenzylammonium chloride (H_2O, 90 °C, 44 mol%)[20]	240	92
6	Cellulose sulfuric acid (ground, r.t, 0.08gr)[33]	20	90
7	Nano $ZnAl_2O_4$ (EtOH, 80 °C, 50 mol%)[34]	15	92
8	**$FeCl_3$•$6H_2O$** (H_2O, r.t, 10 mol%)[a]	30	97

[a] This work, [b] Yields refer to isolated products, [c] Amount not given.

It was clear from Table 3 that $FeCl_3 \cdot 6H_2O$ was good candidate for the synthesis of 1-oxo-hexahydroxanthenes.

Scheme 1. Plausible mechanism for the synthesis of 1-oxo-hexahydroxanthene derivatives.



To investigate the recovery and reusibility of $FeCl_3 \cdot 6H_2O$, after filtration of the reaction mixture, the filtrate was charged with the same substrates and reused for four cycles. This afforded the desired product in high yields that were similar to that obtained in the first run, although an increase was observed in the reaction time (Table 4).

Table 4. Reusability of the catalyst for the synthesis of compound **3a** (Table 2, entry 1)[a].

Run No	Isolated yield (%)	Reaction time (min)
1	97	30

2	95	40
3	94	45
4	93	50

[a] Reaction conditions: salicylaldehyde (1 mmol), dimedone (2 mmol), $FeCl_3$•$6H_2O$ (10 mol%), water, room temperature.

Conclusion

In conclusion, a convenient one-pot procedure for the synthesis of 1-oxo-hexahydroxanthenes derivatives by condensation of salicylaldehydes with cyclic 1,3-diketones in the presence of catalytic of $FeCl_3$•$6H_2O$ as a reusable homogenous catalyst has been developed. The main advantages of this methodology include; (i) a simple procedure, using a catalyst that does not require inert or anhydrous conditions; (ii) simple work-up without chromatographic purification; (iii) high atom economy by avoiding the use of organic solvents; (iv) catalyst reusability, and (vi) mild reaction conditions, giving the products in excellent yields using an environmentally benign procedure. These advantages render this protocol facile and suitable to create a diversified library of derivatives of 1-oxo-hexahydroxanthenes.

Acknowledgments

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