

Ferric Hydrogen Sulfate as an Efficient Heterogeneous Catalyst for Environmentally Friendly Greener Synthesis of 1,8-Dioxo-Octahydroxanthenes

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Ferric hydrogen sulfate was used as an environmentally friendly heterogeneous acidic catalyst for the greener, 1-pot, 3-component synthesis of 1,8-dioxo-octahydroxanthene via condensation reactions between aromatic aldehydes and dimedone under solvent-free thermal and microwave irradiation as well as in aqueous media conditions in short periods of times with excellent yields. The catalyst was easily separated in simple work-up and was recycled several times without loss of reactivity under the described reaction conditions.

Key Words: $\text{Fe}(\text{HSO}_4)_3$; dimedone; heterogeneous catalyst; 1,8-dioxo-octahydroxanthene.

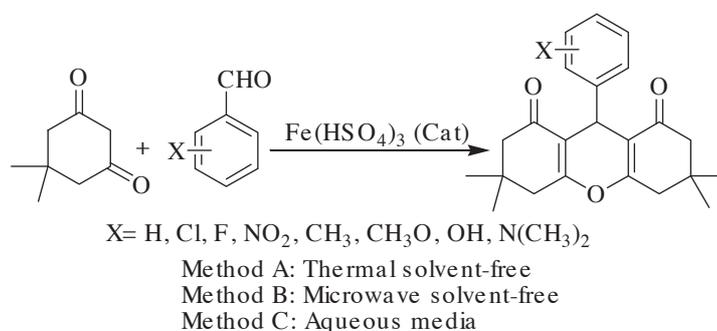
Introduction

Xanthene's derivatives are parent compounds of a large number of naturally occurring and synthetic derivatives, and occupy a prominent position in medicinal chemistry.¹

The synthesis of xanthenes has attracted the attention of organic chemists due to their wide ranging biological and therapeutic properties including antibacterial² and antiviral,³ and because they are good candidates for use in photodynamic therapy (PDT).^{4,5} In particular, xanthenediones constitute a structural unit in a number of natural products⁶ and have been used as versatile synthons because of the inherent reactivity of the inbuilt pyran ring.⁷ The synthesis of xanthenediones usually condenses appropriate active methylene carbonyl compounds with aldehydes catalyzed by sulfuric acid or hydrochloric acid.⁸ Recently, many procedures have been reported for the synthesis of 1,8-dioxo-octahydroxanthene derivatives by condensation of dimedone

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and aldehydes using silica sulfuric acid,⁹ Dowex-50W,¹⁰ HClO₄-SiO₂ and PPA-SiO₂,¹¹ silica chloride and NaHSO₄-SiO₂,¹² *p*-dodecylbenzenesulfonic acid,¹³ Fe³⁺-montmorillonite,¹⁴ amberlyst-15,¹⁵ diammonium hydrogen phosphate,¹⁶ TMSCl,¹⁷ tetrabutylammonium hydrogen sulphate,¹⁸ and hydrochloric acid¹⁹ as catalyst. In spite of the potential utility of the synthesis of xanthene derivatives, many of these methods involve strong acidic conditions,⁸ long reaction times,^{12,13,15,17} low yields,¹¹ the use of excess reagents/catalysts,¹⁷ harsh reaction conditions,¹⁶ and the use of special equipment.¹³ Therefore, to avoid these limitations, the discovery of a new and efficient catalyst with high catalytic activity, short reaction time, recyclability and simple work-up for the preparation of 1,8-dioxo-octahydroxanthene derivatives under mild and practical conditions is of prime interest. The aim of the present study was to utilize the ferric hydrogensulfate, Fe(HSO₄)₃, as an inexpensive catalyst for the synthesis of 1,8-dioxo-octahydroxanthene derivatives via the condensation reaction of various aromatic aldehydes with dimedone in solvent-free thermal, microwave irradiation, as well as in aqueous media conditions (Scheme 1).



Scheme 1. One-pot preparation of 1,8-dioxo-octahydroxanthenes using ferric hydrogen sulfate as the catalyst.

Experimental

All reagents were purchased from Merck and Aldrich and were used without further purification. All yields refer to isolated products after purification. Fe(HSO₄)₃ was prepared according to a reported procedure.²⁰ Products were characterized based on comparison with authentic samples and on spectroscopic (IR, ¹H NMR, ¹³C NMR spectra) and melting point data. NMR spectra were recorded on Bruker Avance DPX 500 and 300 MHz instruments. The spectra were measured in CDCl₃ relative to TMS (0.00 ppm). Mass spectra were recorded on an Agilent Technologies 5973 network mass selective detector (MSD) operating at an ionization potential of 70 eV. IR spectra were recorded on a JASCO FT-IR 460 Plus spectrophotometer. All of the compounds were solid and solid state IR spectra were recorded using the KBr disk technique. Melting points were determined in open capillaries with a BUCHI 510 melting point apparatus and are uncorrected. TLC was performed on polygram SIL G/UV 254 silica-gel plates.

General procedure for Preparation of 1,8-Dioxo-Octahydroxanthene Derivatives using $\text{Fe}(\text{HSO}_4)_3$ as a Catalyst

Method A

Dimedone (2 mmol) and ferric hydrogen sulfate (0.14 mmol, 0.05 g) were added to a mixture of aldehyde (1 mmol), and the mixture was inserted into an oil bath and heated to 120 °C for the appropriate time (Table 5). Completion of the reaction was indicated by TLC. After completion, the reaction mass was cooled to 25 °C, then warm pure EtOAc was added and the mixture was stirred until a solid crude product was dissolved. The ferric hydrogen sulfate was filtered, washed with ethyl acetate, and oven-dried to be used again; The filtrate ethanol solution was concentrated. The solid product was purified via a recrystallization procedure in aqueous EtOH (15%).

Method B

Dimedone (2 mmol) and ferric hydrogen sulfate (0.29 mmol, 0.1 g) were added to a mixture of aldehyde (1 mmol), and the mixture was placed in a microwave oven (Samsung, model KE300R) and heated at the 450-W setting for the appropriate time (Table 5). Completion of the reaction was indicated by TLC. After completion, the reaction mass was cooled to 25 °C, then warm pure EtOAc was added and the mixture was stirred until a solid crude product was dissolved. The ferric hydrogen sulfate was filtered, washed with ethyl acetate, and oven-dried to be reused again. The filtrate ethanol solution was concentrated. The solid product was purified via a recrystallization procedure in aqueous EtOH (15%).

Method C

Dimedone (2 mmol), ferric hydrogen sulfate (0.14 mmol, 0.05 g), and water (2 mL as solvent) was added to a mixture of aldehyde (1 mmol), and the mixture was refluxed for the appropriate time (Table 5). Completion of the reaction was indicated by TLC. After completion, the reaction was extracted by ethyl acetate (2 × 10mL) and then the organic phase was concentrated. The solid product was purified via a recrystallization procedure in aqueous EtOH (15%).

The desired pure product(s) was/were characterized by comparing their physical data with those of known 1,8-dioxo-octahydroxanthenes. The spectral data of unknown 1,8-dioxo-octahydroxanthenes are given below:

9-(3-fluorophenyl)-3,3,6,6-tetramethyl-3,4,6,7-tetrahydro-2H-xanthene-1,8(5H,9H)-dione (Table 5, Entry 16): ^1H NMR (CDCl_3 , 500 MHz): δ = 0.99 (s, 6H), 1.10 (s, 6H), 2.17 (d, J = 16.3 Hz, 2H), 2.23 (d, J = 16.3 Hz, 2H), 2.46 (s, 4H), 4.75 (s, 1H), 6.78 (t, J = 8.3 Hz, 1H), 6.96 (d, $^3J_{F-H}$ = 10.0 Hz 1H), 7.10 (d, J = 7.6 Hz, 1H), 7.15 (t, J = 7.8 Hz, 1H) ppm; ^{13}C NMR (CDCl_3 , 125 MHz): δ = 27.30, 29.14, 31.68, 40.83, 50.70, 113.35 (d, $^2J_{C-F}$ = 21.1 Hz), 115.18, 115.23 (d, $^2J_{C-F}$ = 21.5 Hz), 124.20 (d, $^4J_{C-F}$ = 2.6 Hz), 129.31 (d, $^3J_{C-F}$ = 8.1 Hz), 146.64 (d, $^3J_{C-F}$ = 6.5 Hz), 162.46, 163.73 (d, $^1J_{C-F}$ = 243.6 Hz), 196.14 ppm; IR (KBr, cm^{-1}): 2961, 2873, 1660, 1624, 1590, 1485, 1450, 1361, 1241, 1201, 1165, 1140, 1003, 930, 769, 696, 575; Mass(m/z): 368 (M^+ , 56%), 274 (20%), 273 (100%), 231 (23%), 217 (16%).

9-(2,5-dimethoxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7-tetrahydro-2H-xanthene-1,8(5H,9H)-dione (Table 5, Entry 17): ^1H NMR (CDCl_3 , 500 MHz): δ = 0.95 (s, 6H), 1.07 (s, 6H), 2.11 (d, J = 17.6 Hz, 2H), 2.19 (d, J

= 17.6 Hz, 2H), 2.36 (d, $J = 17.6$ Hz, 2H), 2.44 (d, $J = 17.6$ Hz, 2H), 3.73 (s, 3H), 3.74 (s, 3H), 4.82 (s, 1H), 6.62 (dd, $J = 8.8, 3.0$ Hz, 1H), 6.67 (d, $J = 8.8$ Hz, 1H), 6.95 (d, $J = 3.0$ Hz, 1H) ppm; ^{13}C NMR (CDCl_3 , 125 MHz): $\delta = 26.81, 29.33, 31.97, 40.90, 50.75, 55.50, 55.76, 111.59, 112.70, 113.72, 117.38, 131.79, 152.06, 153.21, 162.68, 196.30$ ppm; IR (KBr, cm^{-1}) 2962, 2872, 1675, 1655, 1617, 1502, 1463, 1350, 1247, 1226, 1165, 1136, 1045, 1004, 860, 813, 730, 686, 573; Mass(m/z): 410 (M^+ , 85%), 380 (18%), 379 (100%), 323 (10%), 295 (12%), 273 (38%), 217 (14%), 161 (14%), 83 (13%) .

3,3,6,6-tetramethyl-9-(naphthalen-1-yl)-3,4,6,7-tetrahydro-2H-xanthene-1,8(5H,9H)-dione (Table 5, Entry 18): ^1H NMR (CDCl_3 , 500 MHz): $\delta = 0.96$ (s, 6H), 1.10 (s, 6H), 2.11 (d, $J = 16.3$ Hz, 2H), 2.20 (d, $J = 16.3$ Hz, 2H), 2.53 (s, 4H), 5.57 (s, 1H), 7.23-7.33 (m, 1H), 7.34 (t, $J = 7.4$ Hz, 1H), 7.47 (t, $J = 7.1$ Hz, 1H), 7.60-7.71 (m, 2H), 7.77 (d, $J = 8.0$ Hz, 1H), 8.80-8.97 (m, 1H) ppm; ^{13}C NMR (CDCl_3 , 125 MHz): $\delta = 27.29, 29.23, 32.11, 40.91, 50.63, 116.59, 124.82, 125.20, 125.50, 125.75, 126.18, 127.32, 128.06, 131.70, 133.56, 142.38, 162.05, 196.40$ ppm; IR (KBr, cm^{-1}) 3049, 2954, 2869, 1667, 1628, 1508, 1466, 1356, 1195, 1165, 1142, 1006, 767, 567, 459; Mass(m/z): 400.4 (M^+ , 67%), 384 (18%), 383 (57%), 274 (20%), 273 (100%), 217 (21%), 189 (7%), 161 (13%).

Results and Discussions

We report for the first time a facile and efficient synthetic strategy for the preparation of 1,8-dioxo-octahydroxanthenes using $\text{Fe}(\text{HSO}_4)_3$ as a heterogeneous catalyst. First, to determine the optimum quantity of ferric hydrogen sulfate, the reaction of dimedone and 2,5-dimethoxybenzaldehyde was carried out under thermal solvent-free conditions (Method A), using different quantities of ferric hydrogen sulfate as a model for this study (Table 1). As can be seen from Table 1, 0.05 g of ferric hydrogen sulfate gave an excellent yield in 5 min. Blank experiments in the absence of the catalyst showed that the reaction did not give corresponding 9-(2,5-dimethoxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7-tetrahydro-2H-xanthene-1,8(5H,9H)-dione (Table 1, Entry 5). Thus, the catalyst had a catalytic effect on the mentioned reaction.

Table 1. Optimization of the quantity of catalyst (heat, 120 °C) in the reaction of dimedone and 2,5-dimethoxybenzaldehyde.

Entry	Catalyst (g)	Time (min)	Yield (%) ^a
1	0.2	4	90
2	0.1	4.4	93
3	0.05	5	94
4	0.025	7.4	86
5	none	120	-

^aYields refer to the isolated pure products.

Next, we attempted to optimize the temperature for thermal solvent-free conditions. The reaction of 2,5-dimethoxybenzaldehyde with dimedone was carried out in the presence of 0.05 g of catalyst in different temperature conditions. The temperature chosen was 120 °C (Table 2).

Table 2. Optimization of temperature in the reaction of dimedone and 2,5-dimethoxybenzaldehyde (solvent-free, 0.05 g catalyst).

Entry	T (°C)	Time (min)	Yield (%) ^a
1	120	5	94
2	100	12	93
3	80	45	64
4	50	100	40

^aYields refer to the isolated pure products.

We also optimized microwave irradiation power and the quantity of catalyst under solvent-free conditions (Tables 3 and 4). As shown in Tables 3-4; the best results were obtained when the reaction was carried out in the presence of a catalyst (0.1 g) and with 450-W microwave irradiation. In continuation of our research, we chose following 3 methods for the mentioned transformation: Method A: aldehyde (1 equiv.)/dimedone (2 equiv.)/catalyst (0.05 g, 14 mol %) under thermal conditions in an oil bath at 120 °C; Method B: aldehyde (1 equiv.)/dimedone (2 equiv.)/catalyst (0.1 g, 29 mol %) under microwave irradiation (450 W); Method C: aldehyde (1 equiv.)/dimedone (2 equiv.)/catalyst (0.05 g, 14 mol %) in water (2 mL), as a green solvent, under reflux conditions.

Table 3. Optimization of microwave power in the reaction of dimedone and 2,5-dimethoxybenzaldehyde using Fe(HSO₄)₃ (0.05 g).

Entry	Power (W)	Time (min)	Yield (%) ^a
1	600	2.25	-
2	450	4.1	84
3	300	10	77
4	180	20	50

^aYields refer to the isolated pure products.

Table 4. Optimization of the quantity of amount of catalyst in the reaction of dimedone and 2,5-dimethoxybenzaldehyde under microwave irradiation conditions (450 W).

Entry	Catalyst (g)	Time (min)	Yield (%) ^a
1	0.2	5	88
2	0.1	3.5	89
3	0.05	4.1	84
4	0.025	9	40
5	none	20	-

^aYields refer to the isolated pure products.

Thus, we prepared a range of 1,8-dioxo-octahydroxanthene derivatives under the optimized reaction conditions of the 3 methods (Table 5).

Table 5. Preparation of 1,8-dioxo-octahydroxanthene derivatives.

Entry	Aldehyde	Method A	Method B	Method C	mp (lit. mp) ^{ref}
		Time (min)/ Yield (%) ^a	Time (min)/ Yield (%) ^a	Time (h)/Yield (%) ^a	
1	Benzaldehyde	5/94	4/82	2/89	204-205 (204-205) ¹⁴
2	2-Chloro benzaldehyde	5/91	4/79	2.8/83	228-230 (229-230) ¹⁴
3	3-Chloro benzaldehyde	5/90	3/81	2.5/86	182-184 (182-184) ¹³
4	4-Chloro benzaldehyde	6/91	4/87 (85-87) ^b	2.5/78	241-244 (230-232) ¹⁷
5	2,4-Dichloro benzaldehyde	6/95	4/90	2.5/76	253-254 (254-255) ¹⁷
6	3-Nitro benzaldehyde	11/85	7/87	3/70	171-174 (170-173) ¹⁴
7	4-Nitro benzaldehyde	5/89	5/90	3/76	228-230 (225-227) ¹¹
8	4-Methyl benzaldehyde	7/97	5/88	2/94	210-213 (217-218) ¹³
9	4-Methoxy benzaldehyde	5/98	3/93	1.5/93	257-258 (244-246) ¹⁴
10	4-(N,N-Dimethylamino) benzaldehyde	5/87	4/81	15/76	224-226 (222-225) ¹¹
11	4-Hydroxy benzaldehyde	6/92	5/77	1.5/90	256-257 (249-251) ¹⁴
12	4-Hydroxy-3-methoxy benzaldehyde	7/90	5/81	1.5/83	225-227 (226-228) ¹³
13	2-Pyridine carbaldehyde	18/81	11/70	3/69	197-200 (188-190) ¹⁸
14	Cinnamaldehyde	10/84	7/75	3/80	176-177 (175-177) ¹³
15	4-Fluorobenzaldehyde	6/91	4/90	1.5/87	232-233 (-) ^{9,10}
16	3-Fluorobenzaldehyde	7/93	6/87	1.5/90	178-179 (-)
17	2,5-Dimethoxy benzaldehyde	5/94 (91-93) ^b	4/89	2/83	201-202 (-)
18	1-Naphthaldehyde	8/89	5/80	1.5/82	236-238 (-)

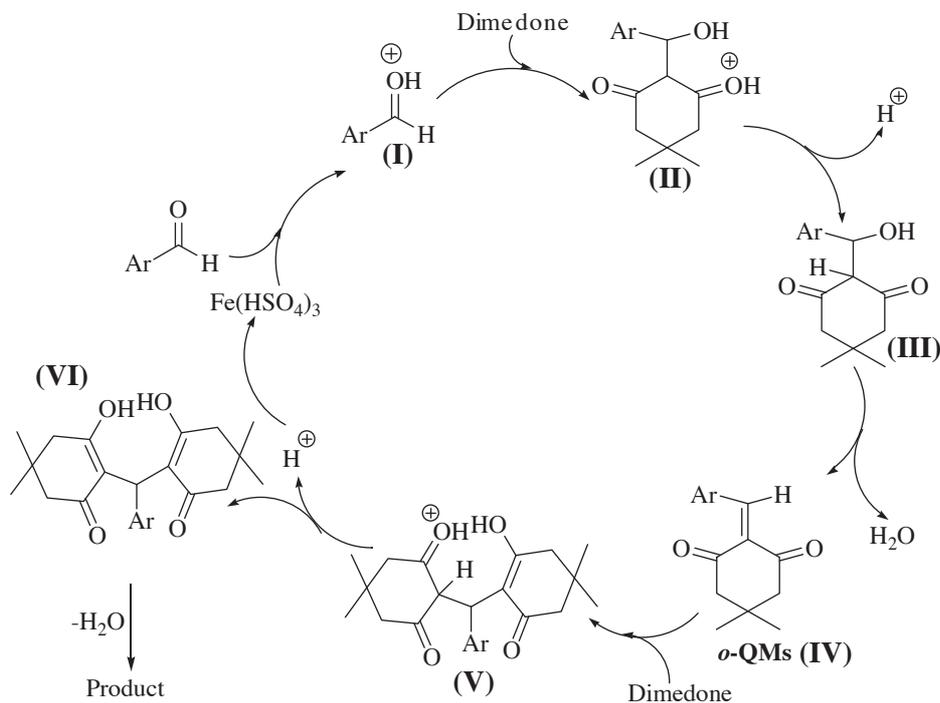
^aYields refer to the pure isolated products. All known products have been reported in the literature and were characterized by comparing their IR and NMR spectra with authentic samples.⁹⁻¹⁹. ^bYields after 5× recovery of the catalyst.

Various 1,8-dioxo-octahydroxanthene derivatives were prepared from different aromatic aldehydes and 5,5-dimethyl-1,3-cyclohexanedione via 3 methods (Table 5) in the presence of a catalyst. The aromatic aldehydes containing both electron-donating and electron-withdrawing groups afforded the corresponding products in high yields. Cinnamaldehyde also converted to the desired product facilely in the same experimental conditions (Table 5, Entry 14).

A mechanistic rationale portraying the probable sequence of events is given in Scheme 2.

As reported in the literature, the reaction of dimedone with aldehydes in the presence of an acid catalyst is known to give *ortho*-quinone methides (*o*-QMs). The same *o*-QMs, generated in-situ, have been reacted with another dimedone to form intermediate **V**. A reasonable explanation for this result can be that the 1,4-addition of dimedone CH acid to the *o*-QMs intermediate is favorable due to the conjugate addition of an

α, β -unsaturated carbonyl group. Cyclo-dehydration of intermediate **VI** affords 1,8-dioxo-octahydroxanthene.



Scheme 2. Suggested mechanism for the preparation of 1,8-dioxo-octahydroxanthenes.

To demonstrate the merit of the present work in comparison with previously reported results, we compared results of silica sulfuric acid,⁹ Dowex-50W,¹⁰ amberlyst-15,¹⁵ TMSCl,¹⁷ and TBAHS¹⁸ in the synthesis of 1,8-dioxooctahydroxanthene derivatives. As shown in Table 6, $\text{Fe}(\text{HSO}_4)_3$ can act as an effective catalyst with respect to reaction times, yield, and the obtained products (Table 6).

Table 6. Comparison of the results of $\text{Fe}(\text{HSO}_4)_3$ with those of other catalysts reported in the literature in the synthesis of 1,8-dioxo-octahydroxanthene derivatives.

Entry	Catalyst	Conditions (Catalyst)	Time/Yield (%)
1	$\text{Fe}(\text{HSO}_4)_3$	Solvent-free, 120 °C (0.14 mmol)	5-18 min/81-98
2	$\text{Fe}(\text{HSO}_4)_3$	Solvent-free, 450 W (0.29 mmol)	3-11 min/70-93
3	$\text{Fe}(\text{HSO}_4)_3$	H_2O , reflux (0.14 mmol)	1.5-3 h/70-94
4	$\text{SiO}_2\text{-SO}_3\text{H}$	Solvent-free, 80 °C (0.03 g)	1-2.5 h/88-97
5	Dowex-50W	Solvent-free, 100 °C (0.1 g)	2-5 h/78-91
6	Amberlyst-15	CH_3CN , reflux (0.2 g)	5 h/90-96
7	TMSCl	CH_3CN , reflux (2 mmol)	8-10 h/72-84
8	TBAHS	H_2O :1,4-dioxan(1:4), reflux (0.1 mmol)	3-3.5 h/88-94

In summary, an efficient protocol for the synthesis of 1,8-dioxo-octahydroxanthene derivatives via the reactions of aromatic aldehydes and dimedone under solvent-free thermal and microwave irradiation conditions,

as well as in aqueous media in the presence of $\text{Fe}(\text{HSO}_4)_3$, as an easily available catalyst, was described. The catalyst was easily separated in simple work-up and was recycled several times without loss of reactivity under the described reaction conditions. Moreover, the procedure offers several advantages, including high yields, operational simplicity, cleaner reactions, and minimal environmental impact, which makes it a useful and attractive process for the synthesis of these compounds.

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