

## [Fe(III)(Salen)Cl] Complex as a Catalyst for the Synthesis of 1, 8-Dioxo-Octahydroxanthene Derivatives

H. Khabazzadeh,\* I. Sheikhshoaei, and N. Sotudeh

*Department of Chemistry, Faculty of Sciences, Shahid Bahonar University of Kerman, 76169, Kerman, Islamic Republic of Iran*

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### Abstract

1, 8-Dioxo-octahydroxanthene derivatives have efficiently been synthesized from dimedone and aromatic aldehydes using [Fe(III)(salen)Cl] complex as an efficient and homogeneous catalyst in molten tetrabutyl ammonium bromide. This methodology offers several advantages, such as good yields, short reaction times, simple procedure, and mild conditions.

**Keywords:** 1, 8-Dioxo-octahydroxanthene; [Fe(III)(salen)Cl]; Dimedone; Aldehyde

### Introduction

Xanthene derivatives are parent compounds of a large number of naturally occurring products, as well as synthetic derivatives of many compounds, and occupy a prominent position in medicinal chemistry [1, 2]. In particular, xanthenediones constitute a structural unit in a number of natural products [3], and have been used as versatile synthons due to the inherent reactivity of the inbuilt pyran ring [4].

The synthesis of xanthenediones usually condenses appropriate active methylene carbonyl compounds with aldehydes catalyzed mainly by organic and mineral acids, which often suffer from the drawbacks of long reaction times, harsh reaction conditions, toxicity, and difficulty in product separation.

Some procedures have been reported for the synthesis of 1, 8-dioxo-octahydroxanthene derivatives employing dimedone and aromatic aldehydes in the presence of acidic catalysts such as Silica-bonded *N*-Propyl Sulfamic Acid [5] hypervalent iodine [6], FeCl<sub>3</sub>·6H<sub>2</sub>O in ionic liquid [7]. Each of these methods have their own advantages but also suffer from one or

more disadvantages such as prolonged reaction time, tedious work-up processes and low yields.

Therefore, to avoid these limitations, the discovery of a new and efficient catalyst with high catalytic activity, short reaction time and simple work-up under neutral, mild and practical conditions is of prime interest for the preparation of xanthenes. In continuation of our interest in using of transition metal complexes as catalyst in organic reactions [8, 9], herein we wish to report a condensation reaction of cyclohexanedione derivatives in the presence of such a catalyst with aromatic aldehydes (Scheme 1).

The aim of this study is to utilize an iron (III) complex as a catalyst for the synthesis of 1, 8-dioxo-octahydroxanthene derivatives.

### Materials and Methods

All chemicals used in the syntheses were purchased from Merck chemical company and were used without further purification. [M(salen)] complexes were synthesized according to the procedures reported in the literature [10-13].

\* Corresponding author, Tel.: +98(341)3202148, Fax: +98(341)3222033, E-mail: hkhazzadeh@uk.ac.ir

All products are known and were identified by comparing their spectral data and physical properties with those of the authentic samples. NMR spectra were recorded on a BRUKER DRX-500 AVANCE NMR spectrometer using CDCl<sub>3</sub> as a solvent.

### General Procedure for the Preparation of Hexahydroxanthene-1, 8-Diones

A mixture of dimedone (2 mmol), aldehyde (1 mmol) and [Fe(III)(salen)Cl] (0.1 mmol) in tetrabutylammonium bromide (1mmol) was stirred at 110 °C for the appropriate time (Table 3). The progress of the reaction was monitored by TLC. After completion of the reaction, as indicated by TLC, the reaction mixture was dissolved in ethanol and poured into water. The resulting precipitate was filtered and purified by silica gel column chromatography using chloroform as an eluent, to afford the desired compound in pure form.

**3, 3, 6, 6-Tetramethyl-9-phenyl-1, 8-dioxo-octahydroxanthene (Table 3, Entry 1):** <sup>1</sup>HNMR: δ (ppm) 1.38 (s, 6H, 2CH<sub>3</sub>), 1.27 (s, 6H, 2CH<sub>3</sub>), 2.18-2.62 (m, 8H), 5.58 (s, 1H), 7.03-7.38 (m, 5H, arom). <sup>13</sup>CNMR: δ (ppm) 27.8, 30.1, 31.8, 33.2, 46.8, 47.5, 116.0, 126.2, 127.2, 128.6, 138.5, 169.8, 190.8.

**3, 3, 6, 6-Tetramethyl-9-(4-chloro phenyl)-1, 8-dioxo-octahydroxanthene (Table 3, Entry 2):** <sup>1</sup>HNMR: δ (ppm) 1.13 (s, 6H, 2CH<sub>3</sub>), 1.25 (s, 6H, 2CH<sub>3</sub>), 2.32-2.51 (m, 8H, 4CH<sub>2</sub>), 5.50 (s, 1H), 7.46 (d, J=8.2 Hz, 2H, arom), 7.26 (d, J=8.5 Hz, 2H, arom). <sup>13</sup>CNMR: δ (ppm) 27.8, 30.0, 31.8, 32.8, 46.8, 47.5, 115.7, 128.6, 128.7, 132.0, 137.1, 169.8, 191.0.

**3, 3, 6, 6-Tetramethyl-9-(2, 4-dichlorophenyl)-1, 8-dioxo-octahydroxanthene (Table 3, Entry 3)** <sup>1</sup>HNMR: δ (ppm) δ 1.03 (s, 6H, 2CH<sub>3</sub>), 1.11 (s, 6H, 2CH<sub>3</sub>), 2.10-2.22 (m, 4H), 2.40 (s, 4H), 4.85 (s, 1H), 7.13-7.43 (m, 3H, arom). <sup>13</sup>CNMR: δ (ppm) 27.6, 29.8, 32.0, 32.2, 41.2, 51.1, 114.1, 126.7, 128.8, 131.5, 133.2, 133.8, 140.5, 164.5, 194.8.

**3, 3, 6, 6-Tetramethyl-9-(2-chlorophenyl)-1, 8-dioxo-octahydroxanthene (Table 3, Entry 4)** <sup>1</sup>HNMR: δ (ppm) 1.05 (s, 6H, 2CH<sub>3</sub>), 1.13 (s, 6H, 2CH<sub>3</sub>), 2.19 (d, J = 16.2 Hz, 2H), 2.26 (d, J = 16.2 Hz, 2H), 2.48 (s, 4H), 5.03 (s, 1H), 7.09-7.46 (m, 4H, arom). <sup>13</sup>CNMR: δ (ppm) 27.7, 29.6, 32.2, 32.4, 41.2, 51.1, 114.1, 126.7, 128.2, 130.5, 132.3, 132.8, 140.3, 165.3, 196.8.

**3, 3, 6, 6-Tetramethyl-9-(4-methoxyphenyl)-1, 8-dioxo-octahydroxanthene (Table 3, Entry 5)** <sup>1</sup>HNMR: δ (ppm) 1.01 (s, 6H, 2CH<sub>3</sub>), 1.12 (s, 6H, 2CH<sub>3</sub>), 2.18 (d, J = 16.4 Hz, 2H), 2.25 (d, J = 16.4 Hz, 2H), 2.48 (s, 4H), 3.75 (s, 3H), 4.72 (s, 1H), 6.77 (d, J = 8.8 Hz, 2H, arom), 7.22 (d, J = 8.8 Hz, 2H, arom). <sup>13</sup>CNMR: δ

(ppm) 27.3, 29.3, 30.9, 32.2, 40.9, 50.8, 55.1, 113.5, 115.8, 129.3, 136.5, 157.9, 162.1, 195.5.

**3, 3, 6, 6-Tetramethyl-9-(4-nitrophenyl)-1, 8-dioxo-octahydroxanthene (Table 3, Entry 6)** <sup>1</sup>HNMR: δ (ppm) 0.99 (s, 6H, 2CH<sub>3</sub>), 1.12 (s, 6H, 2CH<sub>3</sub>), 2.16 (d, J = 16.3 Hz, 2H), 2.26 (d, J = 16.3 Hz, 2H), 2.51 (t, J = 18.7 Hz, 4H), 4.83 (s, 1H), 7.48 (d, J = 8.2 Hz, 2H, arom), 8.08 (2H, J = 8.2 Hz, 2H, arom). <sup>13</sup>CNMR: δ (ppm) 27.7, 29.6, 32.6, 32.8, 41.2, 51.0, 114.9, 123.8, 129.8, 146.8, 152.0, 166.5, 196.7.

**3, 3, 6, 6-Tetramethyl-9-(4-methylphenyl)-1, 8-dioxo-octahydroxanthene (Table 3, Entry 7)** <sup>1</sup>HNMR: δ (ppm) 1.02 (s, 6H, 2CH<sub>3</sub>), 1.25 (s, 6H, 2CH<sub>3</sub>), 2.17-2.27 (m, 4H), 2.34 (s, 3H, CH<sub>3</sub>), 2.49 (m, 4H), 4.74 (s, 1H), 7.04 (d, J = 7.5 Hz, 2H, arom), 7.20 (d, J = 6.9 Hz, 2H, arom). <sup>13</sup>CNMR: δ (ppm) 21.5, 27.8, 29.7, 31.9, 32.6, 41.3, 51.2, 116.2, 128.7, 129.2, 136.1, 141.6, 164.5, 195.8.

**3, 3, 6, 6-Tetramethyl-9-(4-N, N-dimethylphenyl)-1, 8-dioxo-octahydroxanthene (Table 3, Entry 8)** <sup>1</sup>HNMR: δ (ppm) 1.01 (s, 6H, 2CH<sub>3</sub>), 1.13 (s, 6H, 2CH<sub>3</sub>), 2.22 (m, 2H), 2.25 (m, 2H), 2.46 (s, 4H), 2.83 (s, 6H), 4.71 (s, 1H), 6.68 (d, J = 8.8 Hz, 2H, arom), 7.20 (d, J = 8.8 Hz, 2H, arom). <sup>13</sup>CNMR: δ (ppm) 27.3, 29.2, 30.8, 32.2, 40.9, 42.2, 50.8, 113.5, 115.8, 129.3, 136.5, 150.1, 166.1, 196.5.

**3, 3, 6, 6-Tetramethyl-9-(3-nitro-Phenyl)-1, 8-dioxo-octahydroxanthene (Table 3, Entry 9)** <sup>1</sup>HNMR: δ (ppm) 0.91 (s, 6H, 2CH<sub>3</sub>), 1.04 (s, 6H, 2CH<sub>3</sub>), 2.11 (d, J = 16.1 Hz, 2H), 2.29 (d, J = 16.1 Hz, 2H), 2.57 (d, J = 17.9 Hz, 2H), 2.60 (d, J = 17.9 Hz, 2H), 4.65 (s, 1H), 7.56 (t, J = 7.7 Hz, 1H, arom), 7.66 (d, J = 7.6 Hz, 1H, arom), 8.00 (d, J = 7.6 Hz, 2H, arom). <sup>13</sup>CNMR: δ (ppm) 27.2, 29.6, 32.0, 32.7, 50.9, 56.6, 106.3, 115.1, 136.8, 140.7, 153.2, 163.9, 194.0.

**3, 3, 6, 6-Tetramethyl-9-(4-hydroxyphenyl)-1, 8-dioxo-octahydroxanthene (Table 3, Entry 10)** <sup>1</sup>HNMR: δ (ppm) 1.01 (s, 6H, 2CH<sub>3</sub>), 1.12 (s, 6H, 2CH<sub>3</sub>), 2.13-2.23 (m, 4H), 2.46 (s, 4H), 4.70 (s, 1H), 5.48 (br, 1H, OH), 6.85 (d, 2H, J = 8.0 Hz, arom), 7.24 (d, 2H, J = 8.0 Hz, arom). <sup>13</sup>CNMR: δ (ppm) 27.7, 29.1, 30.9, 32.2, 40.7, 50.9, 111.2, 115.4, 129.1, 133.1, 154.5, 168.2, 196.9.

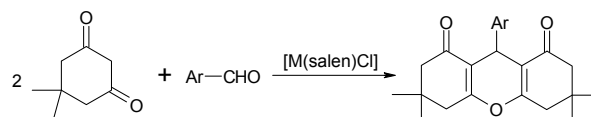


Figure 1. Synthesis of xanthenedione derivatives catalyzed by metal complex.

## Results and Discussion

Initially, the condensation reaction between benzaldehyde and dimedone was chosen as a model reaction, and 1 mol% of various metal-salen complexes have been used to promote this process at 110 °C, and the results were listed in Table 1. As it is revealed from Table 1, [Fe(III)salenCl] gives good yield in shorter reaction time, however Co(salen) gives slightly higher yield but its reaction time is longer than when [Fe(III)(salen)Cl] was used. Therefore [Fe(III)(salen)Cl] was selected as a proper catalyst for this reaction. It seems the higher catalytic activity of [Fe(III)(salen)Cl] is related to its electron configuration and its higher solubility in tetrabutyl ammonium bromide.

In the next step, we studied the influence of the amount of [Fe(III)(salen)Cl] on the reaction time and yield of the reaction. As shown in Table 2, there is no considerable difference between 10 and 15 mol% of the catalyst. So it was concluded that 10 mol% of [Fe(III)(salen)Cl] was sufficient for this reaction.

Such an interesting result prompted us to investigate other aromatic aldehydes, therefore other aromatic aldehydes have been subjected to the above-mentioned optimized conditions, and the results were listed in Table 3. Several aromatic aldehydes could be converted to the corresponding products in good to high yields in the presence of [Fe(III)(salen)Cl] as a catalyst. Benzaldehyde and other aromatic aldehydes containing electron-withdrawing groups (such as nitro group, halide) or electron-donating groups (such as hydroxyl group, alkoxy group) were employed and reacted to give the corresponding xanthenediones. As Table 3 shows aldehydes with electron-donating groups give lower yields.

In this catalytic system, all of the acid-labile substrates such as 4-methoxybenzaldehyde and *p*-N, N-dimethyl amino benzaldehyde went into completion with acceptable yields and without any side products, which makes the purification simple.

Table 4 compares the efficiency of the [Fe(III)(salen)Cl] catalyst against the efficiency of other catalysts in the synthesis of hexahydroxanthene-1, 8-diones which have been reported by the other research groups. It is clear that the current method is simpler, more efficient and less time-consuming for the synthesis of hexahydroxanthene-1, 8-diones derivatives.

It seems that [Fe(III)(salen)Cl] as a homogeneous catalyst might activate the carbonyl group of aldehyde to promote the reaction. A plausible mechanism is shown in Figure 2.

In summary, the electrophilic substitution reaction of 1, 3-dicarbonyl compounds with aldehydes was

successfully carried out in the presence of catalytic amount of [Fe(III)(salen)Cl] in molten TBAB as an ionic liquid. This method offers several significant advantages, such as high conversions, easy handling, cleaner reaction profile and shorter reaction times, which makes it a useful and attractive process for the rapid synthesis of hexahydroxanthene-1, 8-diones over the other reported procedures.

**Table 1.** Catalytic effect of different salen complex catalysts on the reaction of dimedone with benzaldehyde

Salen complex	Time(min)	Yield(%)
Zn(salen)	70	80
Cu(salen)	70	52
Ni(salen)	50	83
Co(salen)	70	87
[Fe(salen)Cl]	20	81
[Mn(salen)Cl]	40	61
VO(salen)	40	84

**Table 2.** The effects of different amounts of [Fe(III)(salen)Cl] on the reaction of dimedone with benzaldehyde

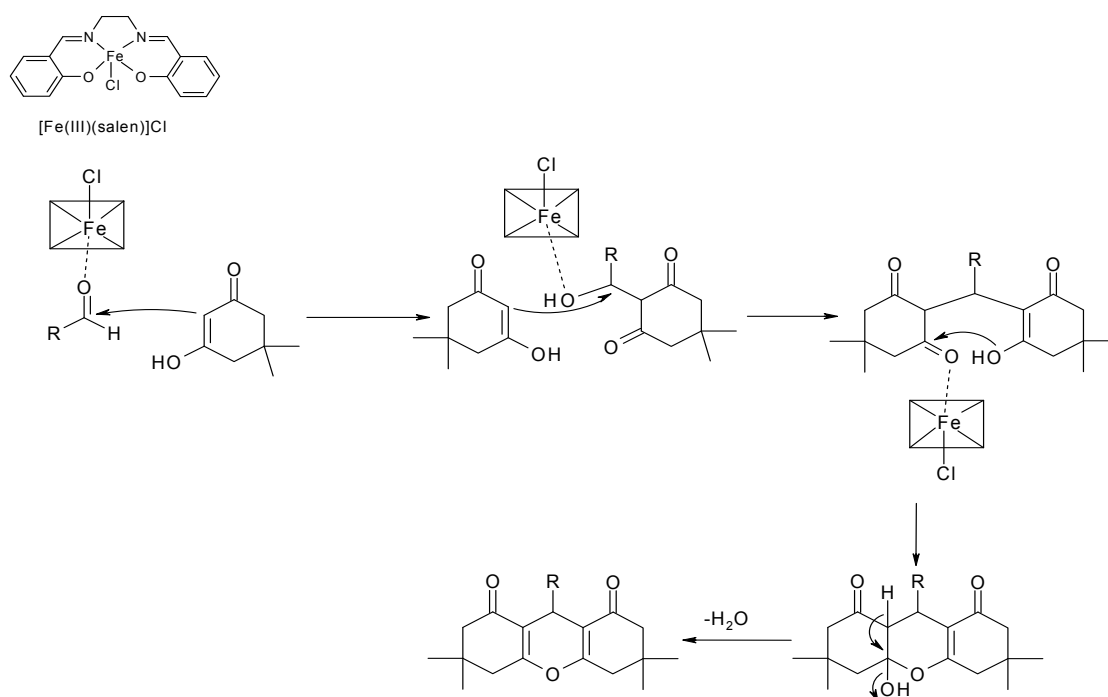
Entry	[Fe(III)(salen)Cl] mol%	Time (min)	Yield (%)
1	1	20	81
2	5	30	97
3	10	20	97
4	15	20	98

**Table 3.** Synthesis of hexahydroxanthene-1, 8-diones using [Fe(III)(salen)Cl] as a catalyst

Entry	Ar	Time (min)	Yield(%)
1	C <sub>6</sub> H <sub>5</sub>	20	98
2	4-Cl-C <sub>6</sub> H <sub>4</sub>	10	92
3	2, 4-di Cl-C <sub>6</sub> H <sub>3</sub>	20	86
4	2-Cl-C <sub>6</sub> H <sub>5</sub>	50	71
5	4-CH <sub>3</sub> O-C <sub>6</sub> H <sub>5</sub>	20	65
6	4-NO <sub>2</sub> -C <sub>6</sub> H <sub>5</sub>	30	70
7	4-CH <sub>3</sub> -C <sub>6</sub> H <sub>5</sub>	20	80
8	4-(CH <sub>3</sub> ) <sub>2</sub> N-C <sub>6</sub> H <sub>5</sub>	40	52
9	3-NO <sub>2</sub> -C <sub>6</sub> H <sub>5</sub>	60	89
10	4-OH-C <sub>6</sub> H <sub>5</sub>	10	58

**Table 4.** Comparison the results of [Fe(III)(salen)Cl] complex as catalyst in the synthesis of hexahydroxanthene-1, 8-diones with the literature

Entry	Carbonyl	Catalyst	Catalyst ratio	condition	Time (min)	Yield(%)	Reference
1	C <sub>6</sub> H <sub>5</sub> CHO	[Fe(III)(salen)Cl]	10 mol%	110°C	20	98	-
		[TMPSA] . HSO <sub>4</sub>	10 mol%	100°C	60	94	14
		Fe <sup>3+</sup> -montmorillonite	15 wt%	100°C	6h	94	15
		SbCl <sub>3</sub> /SiO <sub>2</sub>	10 mol%	120°C	50	93	16
2	4-Cl-C <sub>6</sub> H <sub>4</sub>	[Fe(III)(salen)Cl]	10 mol%	110°C	10	92	-
		[TMPSA] . HSO <sub>4</sub>	10 mol%	100°C	60	92	14
		Fe <sup>3+</sup> -montmorillonite	15 wt%	100°C	6h	88	15
		SbCl <sub>3</sub> /SiO <sub>2</sub>	10 mol%	120°C	40	95	16

**Figure 2.** Mechanism of synthesis of hexahydroxanthene-1, 8-diones using [Fe(III)(salen)Cl] as a catalyst.

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