



GREEN AND HIGHLY EFFICIENT ONE-POT SYNTHESIS OF 1, 8-DIOXOOCTAHYDROXANTHENE DERIVATIVES USING TRIETHYLAMINE AS AN EFFICIENT CATALYST

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Abstract : A highly efficient one-pot synthesis of 1,8-dioxo-octahydroxanthenes from 1, 3-cyclohexanedione and various aromatic aldehydes under reflux conditions in AcOH, catalyzed by triethylamine (TEA) is reported. Short reaction time, facile procedure, excellent yields and avoiding of cumbersome apparatus are the main advantages of this procedure which makes it more efficient than the other conventional methods.

Keywords : One-pot synthesis; 1, 8-Dioxo-octahydroxanthene; Triethylamine (TEA); 1,3-Cyclo- hexanedione; Knoevenagel condensation; Michael addition.

Introduction : Xanthene and their derivatives are an important sort of oxygen-heterocycles compounds in medicinal chemistry, because they have wide range of biological and pharmaceutical properties such as antibacterial [1], anti-inflammatory [2], antiviral [3], antimalarial agents and anti-depressants [4]. Also, they are important class of compounds that are found in numerous biologically active molecules, and the xanthenedione structure is present in a number of natural products [5] and has been a component of dyes [6], laser technologies [7], and pH-sensitive fluorescent materials for visualization of biomolecules [8].

Because of their large range of applications, these compounds have attracted much attention in the context of their synthesis. A wide variety of methods for the preparation of xanthenes have

been reported. The frequent method for the synthesis of 1, 8-dioxooctahydroxanthenes involves the condensation of two equivalent of 1, 3-diketones, such as dimedone or 1, 3-cyclohexanedione with various aldehydes [9]. This reaction can be carried out in the presence of p-TSA [10], ceric ammonium nitrate (CAN) [11], Na⁺montmorillonite sulfonic acid [12], B(HSO₄)₃[13], CsF [14], and nano ZnAl₂O₄[15], Nano Fe/NaY zeolite [16], Polyvinylpolypyrrolidone-supported boron trifluoride (PVPP-BF₃) [17], sulfated zirconia [18], SmCl₃[19], thiamine hydrochloride [20], uccinimidinium hydrogensulfate ([H-Suc]HSO₄) [21], amberlyst-15 [22], and SiO₂-R-SO₃H [23], FeCl₃ 6H₂O/ [Hmim]BF₄[24], diammonium hydrogen phosphate [25].

However, many of these methods are associated with several shortcomings such as long reaction times, harsh conditions, expensive reagents, difficult process of purification and low product yields. We report here on the synthesis of 1, 8-dioxooctahydroxanthene derivatives in short periods of time and easy work in acetic acid in presence of triethylamine as catalyst.

Results and Discussion

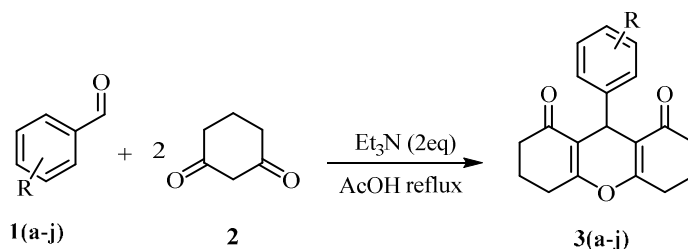
One-pot synthesis of 1, 8-dioxo-octahydroxanthenes :

To find out the optimum reaction condition, for the synthesis of 1, 8-dioxo-octahydroxanthenes (3a-j), the condensation reaction between benzaldehyde (1a) and 1,3- cyclohexanedione (2) was chosen as a model reaction under different reaction conditions (Scheme 01). The obtained results are recorded in Table 1.

Table 1 Optimization of reaction condition for the synthesis of 1,8-dioxo-octahydroxanthene.

| Entry | Catalyst (2eq) | Solvent | Time | Yield ^a % |
|-------|------------------------|------------------|------------|----------------------|
| 1 | Piperidine | Ethanol | 5 | 72 |
| 2 | Piperidine | Methanol | 5 | 67 |
| 3 | Piperidine | H ₂ O | 5 | 45 |
| 4 | Piperidine | AcOH | 3.5 | 82 |
| 5 | Et ₃ N | Ethanol | 5 | 68 |
| 6 | Et ₃ N | Methanol | 5 | 78 |
| 7 | Et ₃ N | H ₂ O | 5 | 62 |
| 8 | Et₃N | AcOH | 1.5 | 96 |

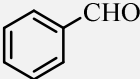
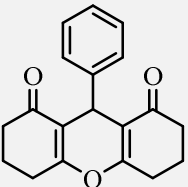
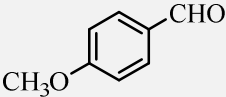
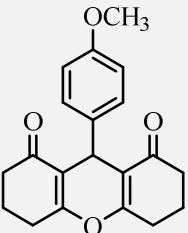
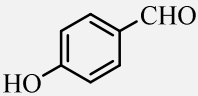
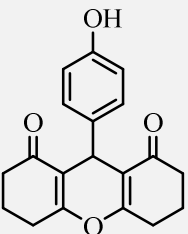
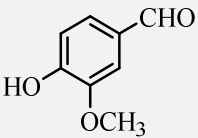
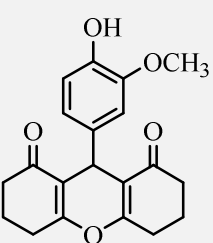
It is clear from the results that 1,8-dioxo-octahydroxanthene can be synthesized with high yield and purity using 2eq of TEA in acetic acid as a solvent within short time (1.5 h).

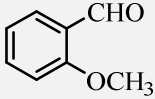
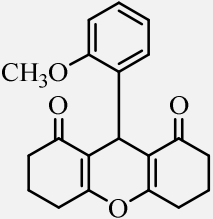
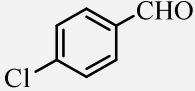
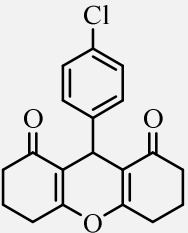
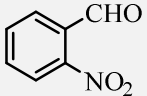
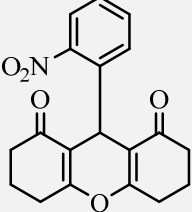
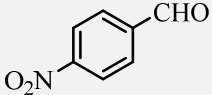
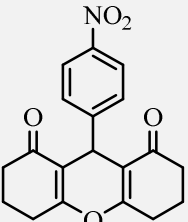
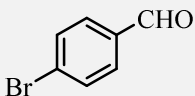
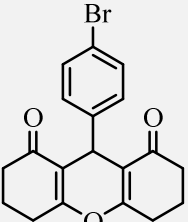
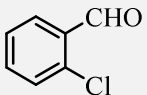
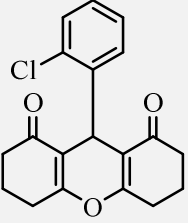


Scheme 1: One-pot reaction for the preparation of 1,8-dioxo-octahydroxanthenes derivatives

To examine the scope and general applicability of the methodology, a broad range of structurally diverse aromatic aldehydes (aromatic aldehydes having electron withdrawing and electron donating groups) was condensed with 1,3-cyclohexanedione under the found optimum reaction condition. All the reactions were monitored by thin layer chromatography (TLC) for completion and for establishing purity. The time taken for the completion of each conversion, aldehyde and the isolated yields are summarized in **Table 2**. In all the cases corresponding xanthenes derivatives were obtained in good to excellent yields.

Table 2: TEA-Catalyzed one-pot synthesis of 1, 8-dioxo-octahydroxanthenes^a.

| Entry | Aldehyde | Product | Time (h) | Yield ^b (%) | M.p (C°) | |
|-------|---|--|----------|------------------------|----------|----------------|
| | | | | | Found | Reported [Ref] |
| 1 |  |  3a | 1.5 | 96 | 203-204 | 203-205 [26] |
| 2 |  |  3b | 2 | 86 | 200-201 | 200-202 [27] |
| 3 |  |  3c | 1.5 | 95 | 244-246 | 245-247 [28] |
| 4 |  |  3d | 1.5 | 91 | 225-228 | 225-227 [29] |

| | | | | | | |
|----|---|---|-----|----|---------|--------------|
| 5 |  |  | 2 | 92 | 162-163 | 160-162 [30] |
| 6 |  |  | 1.5 | 96 | 229-231 | 228-232 [26] |
| 7 |  |  | 1.5 | 94 | 238-240 | 238-240 [28] |
| 8 |  |  | 1.5 | 95 | 263-266 | 263-265 [26] |
| 9 |  |  | 1 | 96 | 226-229 | 227-231 [26] |
| 10 |  |  | 1.5 | 97 | 247-248 | 248-251 [26] |

^a **Reaction condition:** 1,3-Cyclohexanedione (**2 mmol**), aldehyde (**1 mmol**), Triethylamine (**2 mmol**), Acetic acid (10 ml), Reflux.

^b Yields of isolated pure product.

Purity checks with melting points, TLC, and the ¹H NMR spectroscopic data reveal that only one product is formed in all cases and no undesirable side-products are observed. The structures of all known products **3a-j** were deduced from their ¹H NMR and FT-IR spectral data and a comparison of their melting points with those of authentic samples. For example, the IR spectrum of **3a** showed characteristic absorptions at 1671 cm⁻¹ for the carbonyl groups. ¹H NMR spectrum of **3a** (**Fig.1**) remarked a singlet at 4.81 ppm for aliphatic CH while aromatic signals were observed at 7.40-7.11 ppm. Signals between 2.77 and 1.82 ppm were assigned for CH₂ protons. ¹³C NMR of this compound showed two characteristic peaks at 196.54 ppm for carbonyl groups.

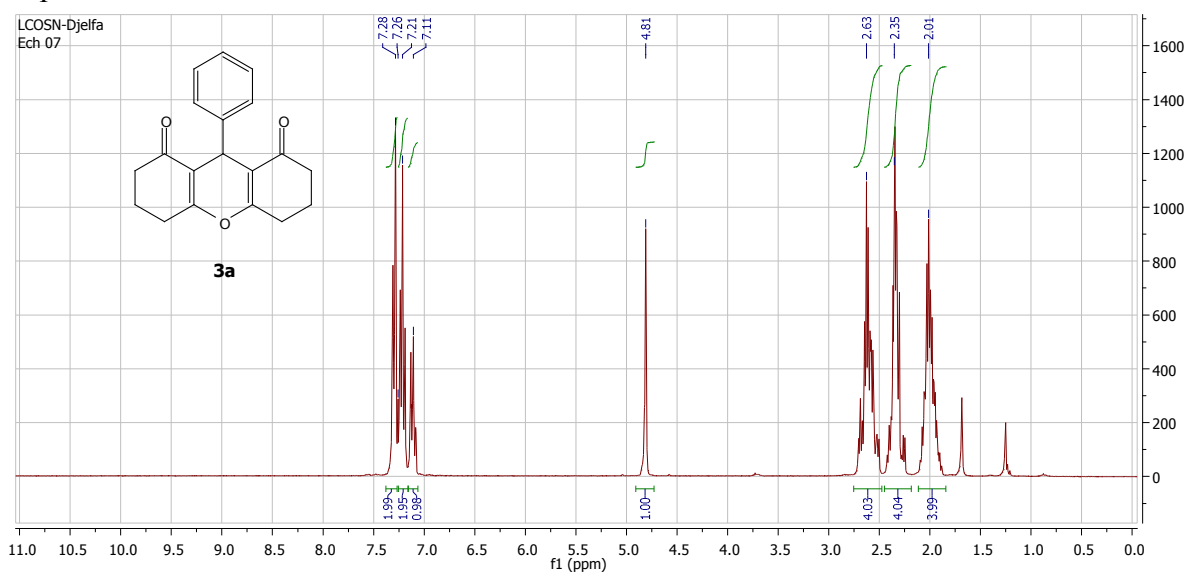
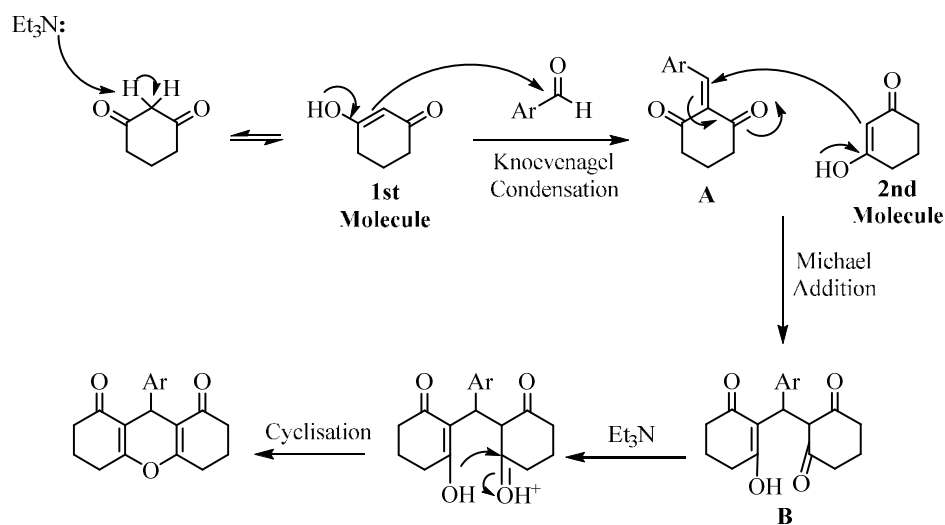


Fig. 1. The ¹H NMR spectrum of compound **3a** in CDCl₃ solvent.

The mechanism of the reaction was proposed in **Scheme 2**. As can be seen, reaction proceeds via one-pot Knoevenagel condensation-Michael addition and cyclodehydration. The formation of the products **3(a-j)** was assumed to proceed via formation of a Knoevenagel product **A**, which on addition of 2nd molecule of 1, 3-cyclohexanedione to give the Michael adduct intermediate **B** was followed by cyclization reaction.



Scheme 02: Proposed mechanism for TEA catalyzed 1,8-dioxo-octahydroxanthenes synthesis

To demonstrate the merit of the proposed method, **Table 3** compares the efficiency of Et_3N in acetic acid, with other catalysts in the synthesis of compound (**3f**) 9-(4-chlorophenyl)-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (**Table 1**, entry **6**).

Table 3: Compared performance of various catalysts in the synthesis of compound (**3f**) 9-(4-chlorophenyl)-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (**Table 1**, entry **6**).

| Entry | Catalyst | Conditions | Time (h) | Yield (%) | Reference |
|-------|--------------------------------------|----------------------------|------------|-----------|------------------|
| 1 | [Hmim]TFA | Neat 80 °C | 2.5 | 93 | [31] |
| 2 | Dowex-50W | Solvent-free, 100°C | 2.5 | 78 | [32] |
| 3 | PVPP-BF ₃ | CH ₃ CN / RT | 3.5 | 98 | [33] |
| 4 | SBNPSA | EtOH / RT | 3 | 91 | [34] |
| 5 | PSA | Solvent-free, 80 °C | 1.5 | 90 | [35] |
| 6 | ZnO-NPs | Solvent-free, 80 °C | 0.37 | 91 | [36] |
| 7 | NaHSO ₄ .SiO ₂ | CH ₃ CN, reflux | 6.5 | 90 | [37] |
| 8 | DBSA | reflux, H ₂ O | 3 | 84 | [38] |
| 9 | Sulfamic acid: | Solvent free, 125°C | 8 | 93 | [39] |
| 10 | Fe(HSO ₄) ₃ | DCM | 4 | 85 | [40] |
| 11 | Et₃N | AcOH | 1.5 | 96 | This Work |

These results show that this method provided the simplest conditions for the synthesis of xanthene derivatives than other catalysts and methods that were reported.

Conclusion : In summary, an efficient, simple, convenient, and straightforward practical one-pot procedure for the synthesis of 1, 8-dioxooctahydroxanthenes by condensation reaction of aldehydes with 1,3-cyclohexanediones by the use of triethylamine as an inexpensive and readily available catalyst has been described. This method is simple as no extraordinary apparatus, reagents or chemicals, for work up are required. The procedure is fairly general, high-yielding, and cost-effective. All these factors justify that it is superior over the existing methods.

Experimental

General Melting points were measured using Kofler bench method. All reactions were followed by TLC (E. Merck Kieselgel 60 F-254), using ethyl acetate: hexane (5:5) as eluent with detection by UV light at 254 nm. IR spectra were recorded on ALPHA's Platinum ATR single reflection diamond ATR spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC 300 MHz FTNMR spectrometer, in CDCl_3 and DMSO- d_6 Chemical shifts (δ) were reported in parts per million (ppm) relative to tetramethylsilane (0 ppm) as an internal reference and the following multiplicity abbreviations were used: s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet. All chemicals were obtained from Merck and were used without further purification.

General procedure for the octahydroxanthens synthesis of 1, 8-dioxo-octahydroxanthenes 3(a-j): A mixture of aldehyde **1** (1 mmol) and 1, 3-cyclohexanediones **2** (2 mmol) and triethylamine (2mmole) in 10 ml of acetic acid was allowed to stir at reflux for the total recorded time. After completion of the reaction (the reaction was monitored by TLC using nhexan : ethylacetate (5:5/v:v) as eluent), the solvent was evaporated in vacuum, and the solid product obtained was washed with cold ethanol and then cold water to remove excess of the triethylamine and the aldehyde. Then the products were purified by recrystallization (95% ethanol). All the products are known compounds and the spectral properties and melting points of them matched well with those reported earlier [26-30]. Spectroscopic and physical data of some representative compounds are given below:

9-phenyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (3a): White solid; yield 96% M. P: 203-204°C; IR (Cm^{-1}) ν max: 3020, 1671, 1528, 1362, 1328, 1222, 1163, 1131, 1089, 845, 740. ^1H NMR (300 MHz, CDCl_3) δ 7.40 – 7.26 (m, 2H), 7.25 – 7.16 (m, 2H), 7.11 (ddd, J = 7.4, 3.8, 1.3 Hz, 1H), 4.81 (s, 1H), 2.77 – 2.46 (m, 4H), 2.45 – 2.16 (m, 4H), 2.15 – 1.82 (m, 4H). ^{13}C NMR (75 MHz, CDCl_3) δ : 196.54, 163.77, 142.01, 137.15, 136.22, 129.88, 128.89, 128.31, 117.11, 113.70, 36.88, 32.34, 27.17, 21.21, 20.40.

9-(4-methoxyphenyl)-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (3b): White solid; yield 86% M. P.: 200-201 °C; IR (Cm^{-1}) ν max: 34482, 2961, 1657, 1501, 1461, 1361, 1230, 1201, 858. ^1H NMR (300 MHz, CDCl_3) δ : 7.34 – 7.09 (m, 2H), 6.75 (dd, J = 9.2, 2.5 Hz, 2H), 4.75 (s, 1H), 3.73 (s, 3H), 2.75 – 2.47 (m, 4H), 2.44 – 2.18 (m, 4H), 2.13 – 1.82 (m, 4H). ^{13}C NMR (75 MHz, CDCl_3) δ : 196.6, 163.7, 158.0, 129.3, 117.0, 113.5, 55.1, 37.0, 30.8, 27.1, 20.3.

9-(4-hydroxyphenyl)-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (3c): White solid; yield 95% M. P: 244-246 °C; ; IR (Cm^{-1}) ν max: 3382, 3019, 2949, 2920, 2889, 1665, 1611, 1519, 1363, 1210, 1181, 1130, 845, 761. ^1H NMR (300 MHz, CDCl_3) δ : 9.18 (d, J = 1.1 Hz, 1H), 7.24 – 6.77 (m, 2H), 6.73 – 6.32 (m, 2H), 4.48 (s, 1H), 2.61 (d, J = 5.6 Hz, 4H), 2.25 (t, J = 5.4 Hz, 4H), 1.91 (s, 4H). ^{13}C NMR (75 MHz, CDCl_3) δ : 196.27, 196.24, 164.42, 164.39, 155.61, 155.59, 135.05, 135.02, 128.83, 128.79, 115.94, 115.92, 114.66, 114.63, 36.47, 36.42, 29.78, 29.74, 26.45, 26.40, 19.92, 19.86.

9-(4-bromophenyl)-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (3i): White solid; yield 96% M. P: 226-229 °C; IR (Cm^{-1}) ν max: 2986, 1665, 1522, 1374, 1329, 1220, 1152, 1141, 1081, 825, 750.; ^1H NMR (300 MHz, CDCl_3) δ : 7.72 – 7.25 (m, 2H, Ar), 7.25 – 6.83 (m, 2H, Ar), 4.52 (s, 1H, CH), 2.74 – 2.51 (m, 4H, 2CH₂), 2.26 (d, J = 2.0 Hz, 4H, 2CH₂), 2.02 – 1.52 (m,

4H,2CH₂). ¹³C NMR (75 MHz, CDCl₃) δ: 207.93, 198.50, 196.24, 170.57, 164.93, 143.89, 134.16, 130.75, 130.28, 119.18, 114.97, 36.31, 30.66, 26.40, 19.78.

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