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# $Zn(OAc)_2·2H_2O$-Catalyzed Efficient Synthesis of 1,8 Dihydrooctahydroxanthenes

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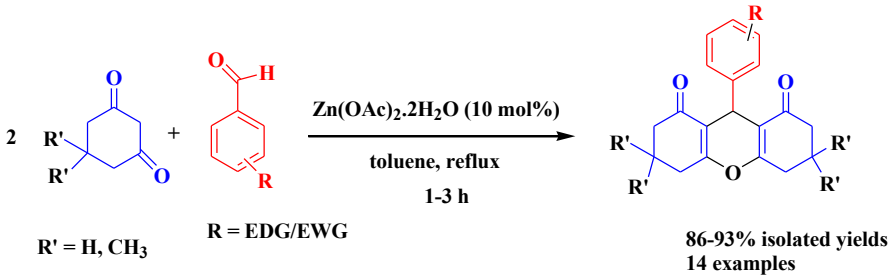
**Abstract**

This study used inexpensive and readily available Lewis acid catalyst $Zn(OAc)_2·2H_2O$ (ZA, 5 mol%) to synthesize 1,8-dihydrooctahydroxanthene derivatives efficiently, with yields of up to 93 %, using a one-pot condensation reaction involving substituted cyclic 1,3-diketones and aldehydes in toluene under reflux conditions.




*Keywords*: $Zn(OAc)_2·2H_2O$ (ZA); 1,8-Dihydrooctahydroxanthenes; Lewis acid; Catalysis; Multicomponent reactions (MCRs).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## 1. Introduction

In organic, combinatorial, and medicinal chemistry, the use of multicomponent reactions (MCRs) to form bonds has grown in popularity [1-4]. Compared to conventional multistep synthesis, the MCRs approach offers substantial benefits due to its atom-efficient, convergent, and customizable features. MCRs are excellent examples of eco-friendly practices as they involve fewer steps, consume less energy, and generate less waste. The

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characteristics of MCRs make it simple to assemble a variety of useful heterocyclic scaffolds [5-7]. Because of their pharmaceutical uses and agricultural bactericide properties, xanthene ring systems are significant heterocyclic compounds (Fig. 1) [8-12]. Specifically, they are employed as photosensitizers in laser therapy technology, pH-sensitive fluorescent materials for biomolecule imaging, and photosensitizers in photodynamic therapy for tumor eradication [13].

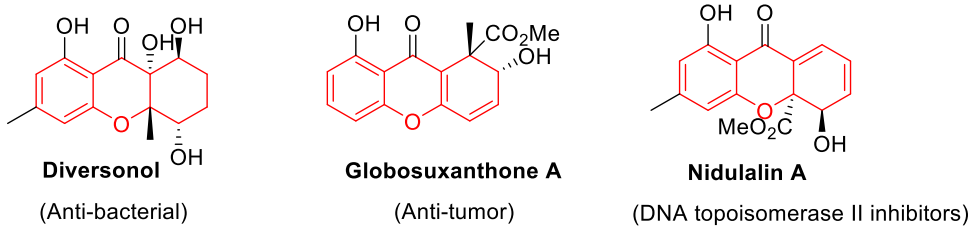



Fig. 1. Some xanthene derivatives in clinical use

A class of xanthene derivatives known as 1,8-dioxo-octahydroxanthenes (xanthenediones) has two fused cyclohexen-2-one rings on the left and right sides, as well as an aryl substituted pyran ring in the middle. The diverse biological properties of these oxygen-containing fused heterocycles, such as their potential as antivirals, antimicrobials, antioxidants, anticancer, leishmanicidal, anti-tubercular, and anti-inflammatory medicines, make them interesting (Fig. 2) [14-16]. Furthermore, these fused heterocyclic systems serve as a synthon for the synthesis of additional heterocycles and provide a structural core in a variety of naturally occurring compounds [17].

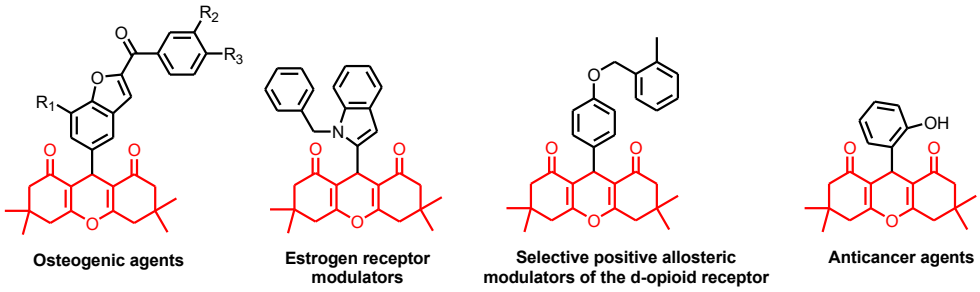



Fig. 2. Some biologically relevant1,8-dioxo-octahydroxanthenes derivatives.

Organic chemists and pharmacologists have been studying 9-aryl-1,8-xanthene-dione heterocycles extensively in recent years due to their intriguing biological characteristics. Even without a catalyst, the intermediate 2,2'-arylmethylenebis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) can be produced during the synthesis of 1,8-dioxo-octahydroxanthenes. A catalyst is always needed during the cyclization step in order to obtain the cyclized molecule. The pseudo-three-component cyclocondensation (3-CC) of 5,5-dimethyl-1,3-

cyclohexanedione (dimedone) and the appropriate aldehydes employing various liquid acidic catalysts, ionic liquids, homogeneous catalytic systems, heterogeneous catalysts, organocatalysts, heteropoly acids, organometallic complexes, and polymeric catalysts were typically used to synthesize 1,8-dioxo-octahydroxanthenes [18-22].

Other documented techniques for the synthesis of 9-aryl-1,8-xanthenediones include photoreaction using eosin Y under green light-emitting diode (LED), grinding utilizing solid super-acid catalyst, and microwave and ultrasound-assisted conditions employing various catalysts [23-28]. Some of these protocols, however, have drawbacks, including relatively low yields, laborious reaction processes, costly catalysts, comparatively long reaction durations, catalyst production, the use of hazardous organic solvents, and the use of unusual equipment like microwaves and ultrasonics. Therefore, it is beneficial to look for a catalyst that is safe, affordable, environmentally friendly, and convenient.

In terms of isolated yield and shorter reaction times, zinc acetate proved to be the best Lewis Acid (LA) among those evaluated, while being more affordable and easily accessible. $Zn(OAc)_2 \cdot 2H_2O$ (ZA) is referred to as a multifunctional catalyst due to its distinct physical and chemical properties, which demonstrate that it can be useful in facilitating a wide range of synthetic transformations in both organic synthesis and catalysis [29-35]. Here, we report our efforts in synthesizing title compounds utilizing zinc acetate as a catalyst, continuing our interest in investigating C-C and C-hetero atom bond formations [36,37]. The results are shown here.

## 2. Experimental

### 2.1. *General*

All products were identified by their spectra and physical data. NMR spectra were recorded on a Bruker AQS AVANCE-300 MHz spectrometer using TMS as an internal standard ($CDCl_3$ solution). FTIR spectra were recorded from KBr disk on the FT-IR Bruker Tensor 27 spectrometer.

### 2.2. *General procedure for the preparation of xanthene derivatives*

A mixture of dimedone (2 mmol) or 1,3-cyclohexanedione (2 mmol) and different aromatic aldehydes (1 mmol) was dissolved in toluene for the time specified as in Table 1. Under reflux conditions, this reaction was carried out with 10 mol% of ZA acting as the catalyst. Thin-layer chromatography (TLC) on silica gel plates employing a dichloromethane:acetone (9:1) eluent was used to track the reaction's development. ZA was precipitated and subsequently filtered out once the reaction was finished and the TLC showed the anticipated result. The reaction mixture was then concentrated using vacuum-assisted evaporation. The analytically pure product was obtained by using petroleum ether/ethyl acetate column chromatography to further attain the desired products of purity. Compounds were characterized using IR, $^1$H NMR, and $^{13}$C NMR.

### 2.3. *Spectral data of compounds*

3,3,6,6-Tetramethyl-9-phenyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (3a):[18] $^1$H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.28 (d, *J*=8.4 Hz, 2H), 7.21 (t, *J*=7.6 Hz, 2H), 7.09 (t, *J*=7.6 Hz, 1H), 4.75 (s, 1H, CH), 2.46 (s, 4H, 2x $CH_2$), 2.25-2.14 (m, 4H, 2x $CH_2$), 1.10 (s, 6H, 2x $CH_3$), 0.99 (s, 6H, 2x$CH_3$). $^{13}$C NMR (100 MHz, $CDCl_3$): δC (ppm) = 196.5, 162.4, 144.2, 128.5, 128.2, 126.5, 115.8, 50.9, 41.0, 32.3, 31.9, 29.4, 27.5.

9-(4-Chlorophenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (3b):[21] $^1$H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.22 (d, *J*=8.4 Hz, 2H), 7.17 (d, *J*=8.4 Hz, 2H), 4.70 (s, 1H, CH), 2.46 (s, 4H, 2x $CH_2$), 2.24-2.13 (m, 4H, 2x$CH_2$), 1.09 (s, 6H, 2x $CH_3$), 0.97 (s, 6H, 2x$CH_3$). $^{13}$C NMR (100 MHz, $CDCl_3$): δC (ppm) = 196.5, 162.6, 142.8, 132.1, 129.9, 128.3, 115.3, 50.8, 40.9, 32.3, 31.6, 294, 27.4.

3,3,6,6-Tetramethyl-9-(4-nitrophenyl)-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (3c):[18] $^1$H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 8.08 (d, *J*=8.8 Hz, 2H), 7.47 (d, *J*=8.4 Hz, 2H), 4.82 (s, 1H, CH), 2.49 (s, 4H, 2x $CH_2$), 2.27-2.14 (m, 4H, 2x$CH_2$), 1.11 (s, 6H, 2x$CH_3$), 0.98 (s, 6H, 2x$CH_3$). $^{13}$C NMR (100 MHz, $CDCl_3$): δC (ppm) = 196.4, 163.1, 151.6, 146.6, 129.5, 123.6, 114.7, 50.7, 40.9, 32.5, 32.4, 29.4, 27.4.

3,4,6,7-Tetrahydro-3,3,6,6-tetramethyl-9-(3-nitrophenyl)-2*H*-xanthene-1,8-(5*H*,9*H*)-dione (3d):[18] $^1$H NMR: ($CDCl_3$, 400 MHz): δ (ppm) = 1.00 (s, 6H), 1.11 (s, 6H), 2.19 (d, *J* =5.6 Hz, 4H), 4.84 (s, 4H), 5.25 (s, 1H), 7.40 (d, *J* =7.6 Hz, 1H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.97-8.01 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$): δC (ppm) = 196.4, 163.02, 148.33, 146.28, 128.8, 122.48, 121.69, 114.55, 50.62, 40.84, 32.26, 32.08, 29.20, 27.31.

3,3,6,6-Tetramethyl-9-(*p*-tolyl)-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (3e):[18] $^1$H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.17 (d, *J*=8.0 Hz, 2H), 7.01 (d, *J*=8.0 Hz, 2H), 4.70 (s, 1H, CH), 2.45 (s, 4H, 2x $CH_2$), 2.24-2.13 (m, 7H, 2x $CH_2$, $CH_3$), 1.09 (s, 6H, 2x $CH_3$), 0.98 (s, 6H, 2x $CH_3$). $^{13}$C NMR (100 MHz, $CDCl_3$): δC (ppm) = 196.55, 162.23, 141.3, 135.8, 129.1, 128.7, 128.1, 115.8, 87.2, 50.8, 40.9, 32.3, 31.6, 29.3, 27.5, 21.1.

9-(4-Methoxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (3f):[18] $^1$H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.19 (d, *J*=8.8 Hz, 2H), 6.74 (d, *J*=8.7 Hz, 2H), 4.68 (s, 1H, CH), 3.71 (s, 3H, $OCH_3$), 2.45 (s, 4H, 2x$CH_2$), 2.24-2.13 (m, 4H, 2x$CH_2$), 1.08 (s, 6H, 2x$CH_3$), 0.98 (s, 6H, 2x$CH_3$). $^{13}$C NMR (100 MHz, $CDCl_3$): δC (ppm) = 196.6, 162.2, 158.0, 136.6, 129.4, 115.8, 113.5, 55.2, 50.8, 40.9, 32.3, 31.0, 29.3, 27.4, 20.4.

9-(4-Hydroxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8 (2*H*)-dione (3g):[20] $^1$H NMR ($CDCl_3$, 400 MHz): δ (ppm) = 7.07 (d, *J*=8.8 Hz, 2H), 6.55 (d, *J*=8.4 Hz, 2H), 4.66 (s, 1H, CH), 2.45 (s, 4H, 2x $CH_2$), 2.26-2.16 (m, 4H, 2x$CH_2$), 1.09 (s, 6H, 2x$CH_3$), 0.99 (s, 6H, 2x $CH_3$). $^{13}$C NMR (100 MHz, $CDCl_3$): δC (ppm) = 197.3, 162.5, 154.7, 135.8, 129.5, 116.0, 115.3, 50.9, 41.0, 32.4, 31.1, 29.3, 27.52.

9-(4-(Dimethylamino)phenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (3h):[20] $^1$H NMR ($CDCl_3$, 400 MHz): δH (ppm) = 7.13-7.27 (m, 4H, Ar), 4.58 (s, 1H, CH), 3.08 (s, 6H, *N*($CH_3$)$_2$), 2.56-2.66 (q, 4H, 2x$CH_2$), 2.31-2.50 (q,

4H, $CH_2$), 2.11-2.15 (d, 4H, $CH_2$), 1.10 (s, 6H, $C(CH_3)_2$), 0.98 (s, 6H, $C(CH_3)_2$), $^{13}$C NMR (100 MHz, $CDCl_3$): δC (ppm) 196.7, 162.5, 129.8, 50.7, 40.8, 32.2, 29.3, 27.4.

9-Phenyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (3i):[18] $^1$H NMR ($CDCl_3$, 400 MHz): δH (ppm) = 7.30 (d, *J*=8.0 Hz, 2H), 7.21 (t, *J*=7.6 Hz, 2H), 7.11 (t, *J*=7.2 Hz, 1H), 4.81 (s, 1H), 2.69-2.52 (m, 4H, 2x$CH_2$), 2.40-2.26 (m, 4H, 2x$CH_2$), 2.08-1.91 (m, 4H, 2x$CH_2$). $^{13}$C NMR (100 MHz, $CDCl_3$): δC (ppm) = 196.6, 164.0, 144.5, 128.5, 128.2, 126.5, 117.0, 37.0, 31.7, 27.3, 20.4.

9-(4-Chlorophenyl)-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (3j):[19] $^1$H NMR ($CDCl_3$, 400 MHz): δH (ppm) = 7.25 (d, *J*=7.6 Hz, 1H), 7.19 (s, 1H), 7.14 (t, *J*=8.0 Hz, 1H), 7.09-7.06 (m, 1H), 4.77 (s, 1H, CH), 2.70-2.52 (m, 4H, 2x$CH_2$), 2.41-2.26 (m, 4H, 2x$CH_2$), 2.08-1.91 (m, 4H, 2x$CH_2$). $^{13}$C NMR (100 MHz, $CDCl_3$): δC (ppm) = 196.6, 164.3, 146.4, 133.9, 129.3, 128.3, 127.2, 126.7, 116.4, 36.9, 31.6, 27.2, 20.3.

9-(4-Nitrophenyl)-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (3k):[18] $^1$H NMR ($CDCl_3$, 400 MHz): δH (ppm) = 8.07 (d, *J*=8.8 Hz, 2H), 7.47 (d, *J*=8.6 Hz, 2H), 4.87 (s, 1H, CH), 2.72-2.55 (m, 4H, 2x$CH_2$), 2.41-2.28 (m, 4H, 2x$CH_2$), 2.11-1.91 (m, 4H, 2x$CH_2$). $^{13}$C NMR (100 MHz, $CDCl_3$): δC (ppm) = 196.57, 164.71, 151.84, 146.58, 129.53, 123.54, 115.86, 36.93, 32.30, 27.26, 20.34.

9-(*p*-Tolyl)-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (3l):[18] $^1$H NMR ($CDCl_3$, 400 MHz): δH (ppm) = 7.19 (d, *J*=8.0 Hz, 2H), 7.02 (d, *J*=8.0 Hz, 2H), 4.77 (s, 1H, CH), 2.68-2.51 (m, 4H, 2x$CH_2$), 2.40-2.25 (m, 7H, 2x $CH_2$, $CH_3$), 2.07-1.90 (m, 4H, 2x$CH_2$). $^{13}$C NMR (100 MHz, $CDCl_3$): δC (ppm) = 196.6, 163.9, 141.6, 135.9, 128.8, 128.3, 117.0, 37.0, 31.3, 27.2, 21.1, 20.3.

9-(4-Methoxyphenyl)-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (3m):[19] M.P. >220 °C; FT-IR (KBr, $cm^{-1}$): 3068, 2943, 2887, 1639, 1608, 1458, 1364, 1232, 1176. $^1$H NMR ($CDCl_3$, 400 MHz): δH (ppm) = 7.12-7.21 (2H, d, *J*= 7.6 Hz), 7.03-7.05 (2H, d, *J*= 8.0 Hz), 3.56 (3H, s), 3.26 (1H, s), 2.52-2.69 (4H, t, *J*= 6.2 Hz), 2.29-2.42 (4H, m), 1.96-2.07 (4H, m).

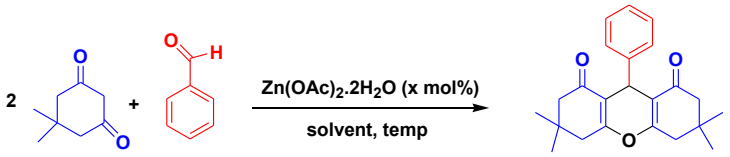
9-(4-Hydroxyphenyl)-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (3n):[22] $^1$H NMR ($CDCl_3$, 400 MHz): δH (ppm): 9.16 (1H, s), 6.95 (d, 2H, *J* = 8.0 Hz), 6.58 (d, 2H, *J* = 8.0 Hz), 4.48 (s, 1H), 2.33-2.26 (m, 4H), 2.25−2.20 (m, 4H), 2.09-1.92 (m, 4H). $^{13}$C NMR (100 MHz, $CDCl_3$): δC (ppm) = 196.81, 164.95, 156.10, 129.32, 116.41, 115.14, 36.92, 30.23, 26.90, 20.37.

## 3. Results and Discussion

We first looked into the catalytic activity of ZA at different temperatures in order to improve the reaction conditions of dimedone and benzaldehyde in the presence of different catalytic amounts of ZA (Scheme 1). We discovered that the ideal catalyst concentration is 10 mol%, and that increasing the catalyst had no effect on either the yield or the reaction time. Further investigation, however, showed that raising the temperature can modify the reaction to some extent. The reaction did not progress at room temperature, even after 48 h. It was shown that raising the temperature to reflux increased the yield to 90 %. Under these conditions

(neither anhydrous nor oxygen-free conditions are required), the reaction yields the proper xanthene-1,8-dione derivative after two hours of operation. In terms of reaction time and isolated yield, toluene outperformed the other solvents tested, including DCM, THF, $CH_3CN$, $CHCl_3$, EtOH, and others. The former turned out to be the catalyst of choice for the intended transformation among the zinc salts that were evaluated, including zinc acetate (90 %), $Zn(OTf)_2$ (68 %), ZnO (NR), $ZnCl_2$ (47 %), and $Zn(NO_3)_2$ (trace).

The method's general applicability was demonstrated by investigating the reactions of structurally different aromatic aldehydes with dimedone or 1,3-cyclohexanedione under comparable conditions (Table 1). In the presence of 10 mol% catalyst in toluene under reflux conditions, this method yielded xanthene-1,8-dione derivatives in good to exceptional yields with no undesirable byproducts found. The reactions were conducted very easily and cleanly. This method's simplicity, high yields, and ease of setup make it advantageous.




| entry | solvent/reflux (10 mol% STO) | time (h) | yield (%)[a] |
|---|---|---|---|
| 1 | $CH_2Cl_2$ | 4 | 18 |
| **2** | **toluene** | **2** | **90** |
| 3 | $CH_3CN$ | 2.5 | 41 |
| 4 | $CHCl_3$ | 2.5 | 27 |
| 5 | EtOH | 2 | 35 |
| 6 | THF | 3 | 28 |
| 7 | Neat/RT | 48 | NR |

[a] Isolated yield

Scheme 1. Optimization studies.

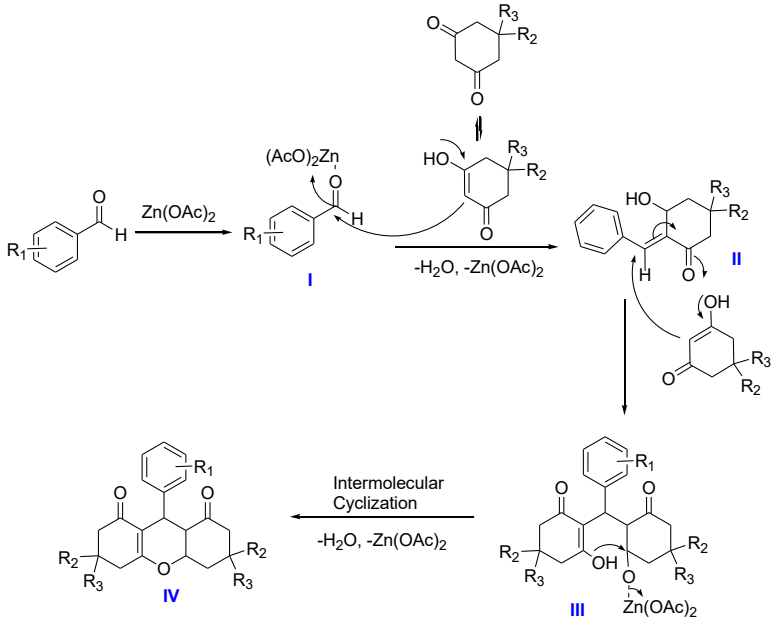
Table 1. ZA-Catalyzed synthesis of 9-aryl-1,8-xanthene-diones.

| Entry | Aldehyde | R | Product | Time (h) | Yield (%)[a] |
|---|---|---|---|---|---|
| 1 | $C_6H_5CHO$ | $CH_3$ | **3a** | 2.00 | 90 |
| 2 | 4-Cl-$C_6H_4CHO$ | $CH_3$ | **3b** | 1.50 | 92 |
| 3 | 4-$NO_2$-$C_6H_4CHO$ | $CH_3$ | **3c** | 1.50 | 90 |
| 4 | 3-$NO_2$-$C_6H_4CHO$ | $CH_3$ | **3d** | 2.50 | 93 |
| 5 | 4-Me-$C_6H_4CHO$ | $CH_3$ | **3e** | 2.00 | 92 |
| 6 | 4-OMe-$C_6H_4CHO$ | $CH_3$ | **3f** | 2.50 | 91 |
| 7 | 4-OH-$C_6H_4CHO$ | $CH_3$ | **3g** | 2.50 | 87 |
| 8 | 4-N(Me)$_2$-$C_6H_4CHO$ | $CH_3$ | **3h** | 1.00 | 86 |
| 9 | $C_6H_5CHO$ | H | **3i** | 2.00 | 92 |
| 10 | 4-Cl-$C_6H_4CHO$ | H | **3j** | 2.00 | 90 |
| 11 | 4-$NO_2$-$C_6H_4CHO$ | H | **3k** | 2.00 | 92 |
| 12 | 4-Me-$C_6H_4CHO$ | H | **3l** | 1.50 | 91 |

| | | | | | |
|---|---|---|---|---|---|
| 13 | 4-OMe-$C_6H_4CHO$ | H | **3m** | 2.00 | 92 |
| 14 | 4-OH-$C_6H_4CHO$ | H | **3n** | 2.00 | 93 |

[a]Isolated yields

A plausible mechanism for the synthesis of xanthene derivatives using $Zn(OAc)_2$ has been shown in Scheme 2. First, $Zn(OAc)_2$ is coordinated with aldehydes, producing the zinc oxide-aldehydes intermediate (I). After $Zn(OAc)_2$ is dehydrated and removed, it combines with dimedone/1,3-cyclohexanedione to generate intermediate (B). After that, intermediate (II) underwent a conjugate Michael addition reaction with the active methylene group of the second molecule of dimedone/1,3-cyclohexanedione, resulting in intermediate (III). The final product xanthenes (IV) were then formed by intermolecular cyclization of this intermediate with $H_2O$, $Zn(OAc)_2$ elimination.




Scheme 2. Proposed mechanism for the ZA-catalyzed synthesis of xanthene derivatives.

## 4. Conclusion

In conclusion, we have developed a safe and effective process for synthesizing xanthene derivatives by employing zinc acetate as a mild catalyst in toluene under reflux conditions. High yields (86-93 %) of the synthesized compounds were produced in a brief reaction time. All compounds in this series have structural confirmation, which was determined using standard spectroscopic techniques.

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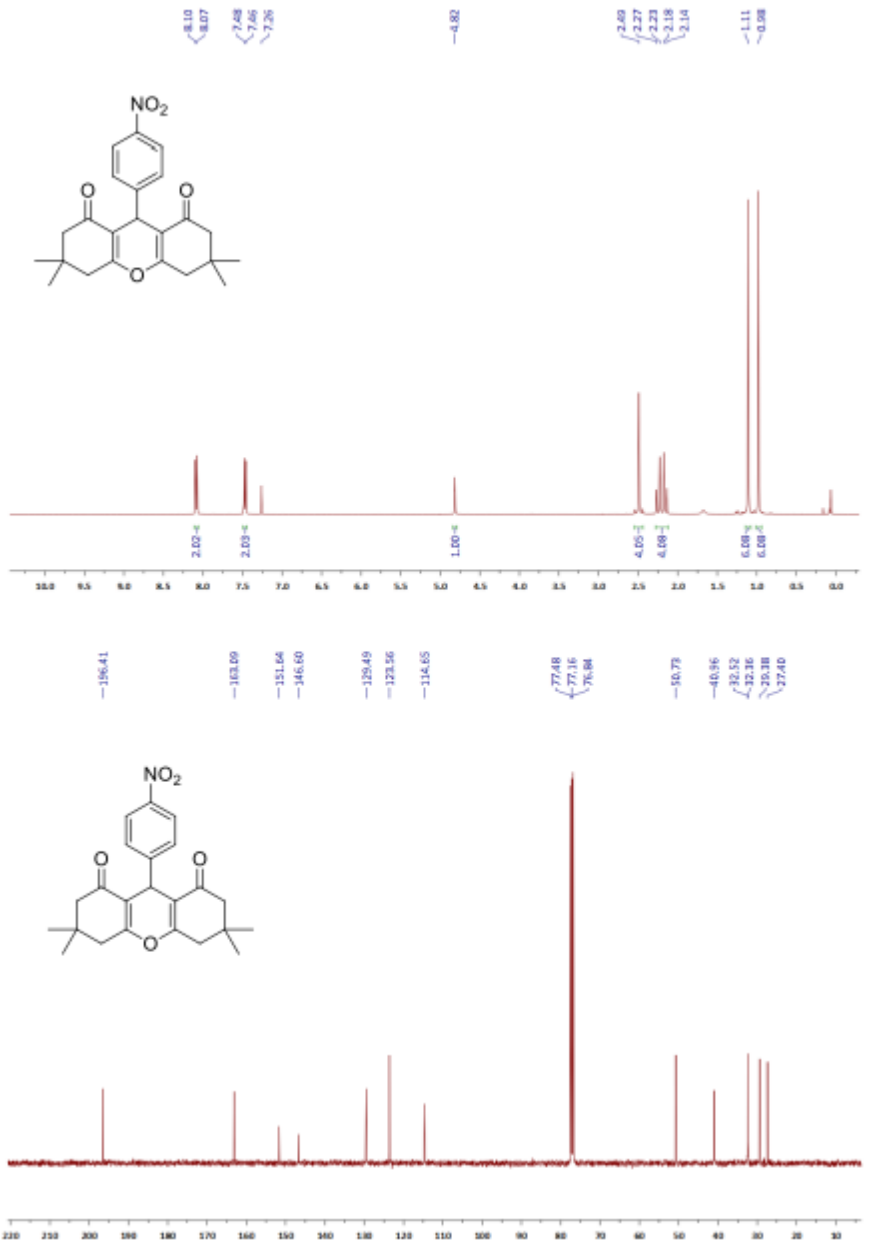
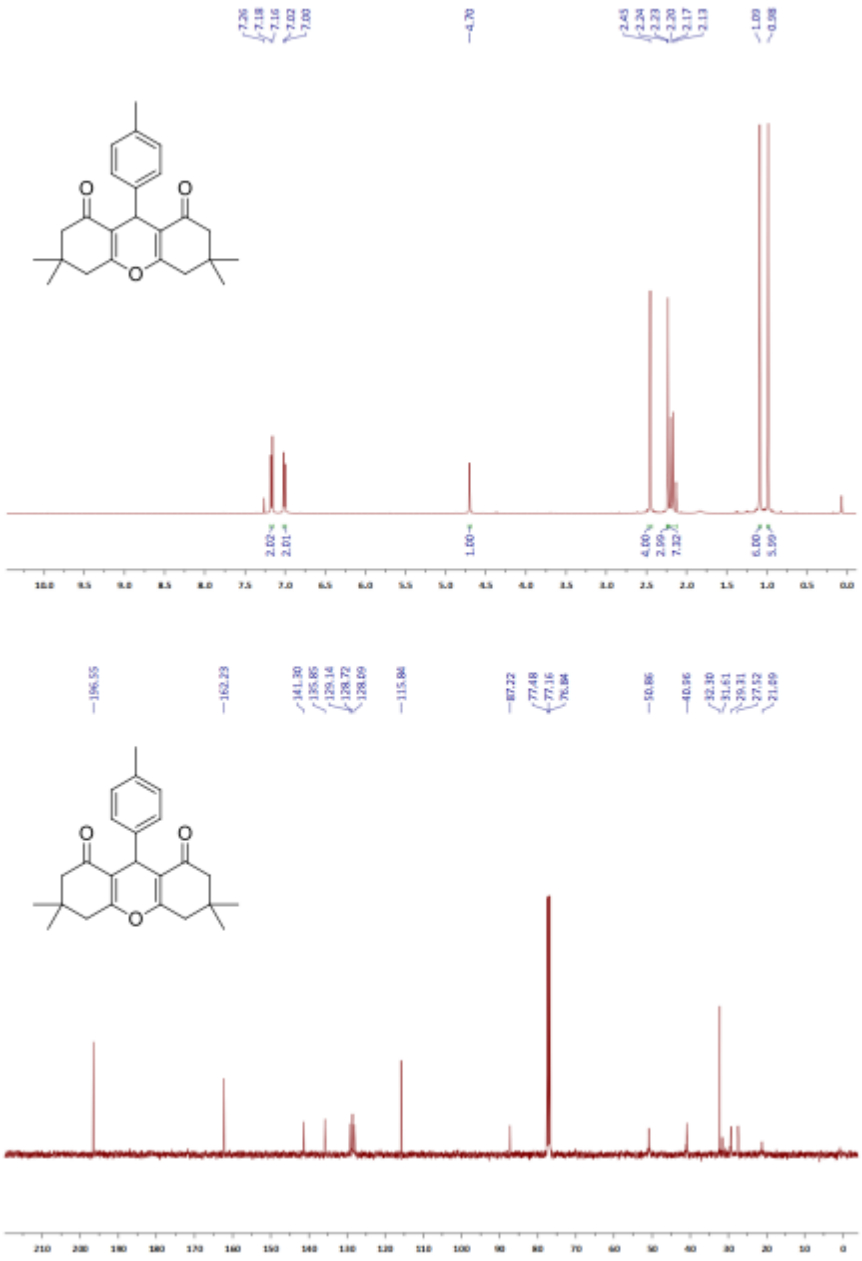



$^1$H and $^{13}$C NMR spectral data of **3c**



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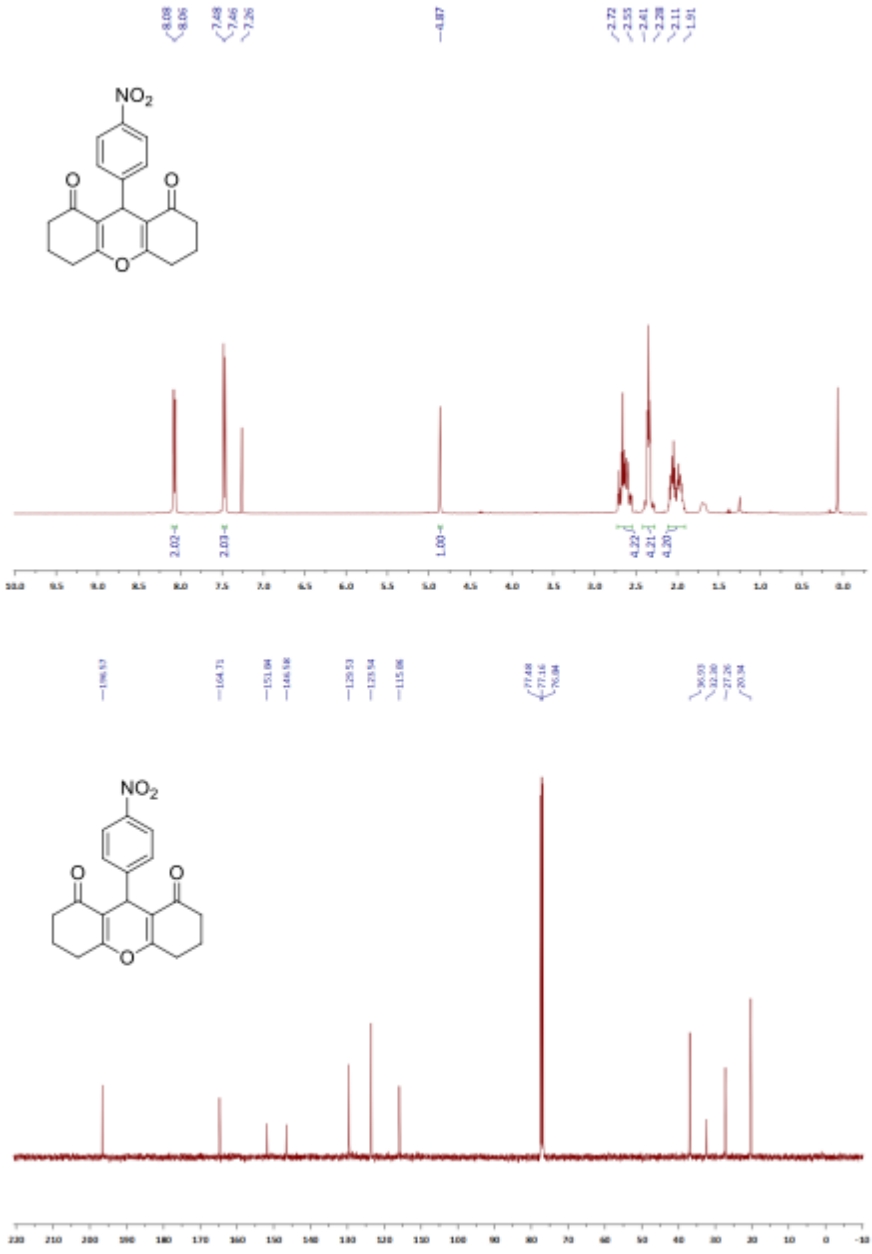

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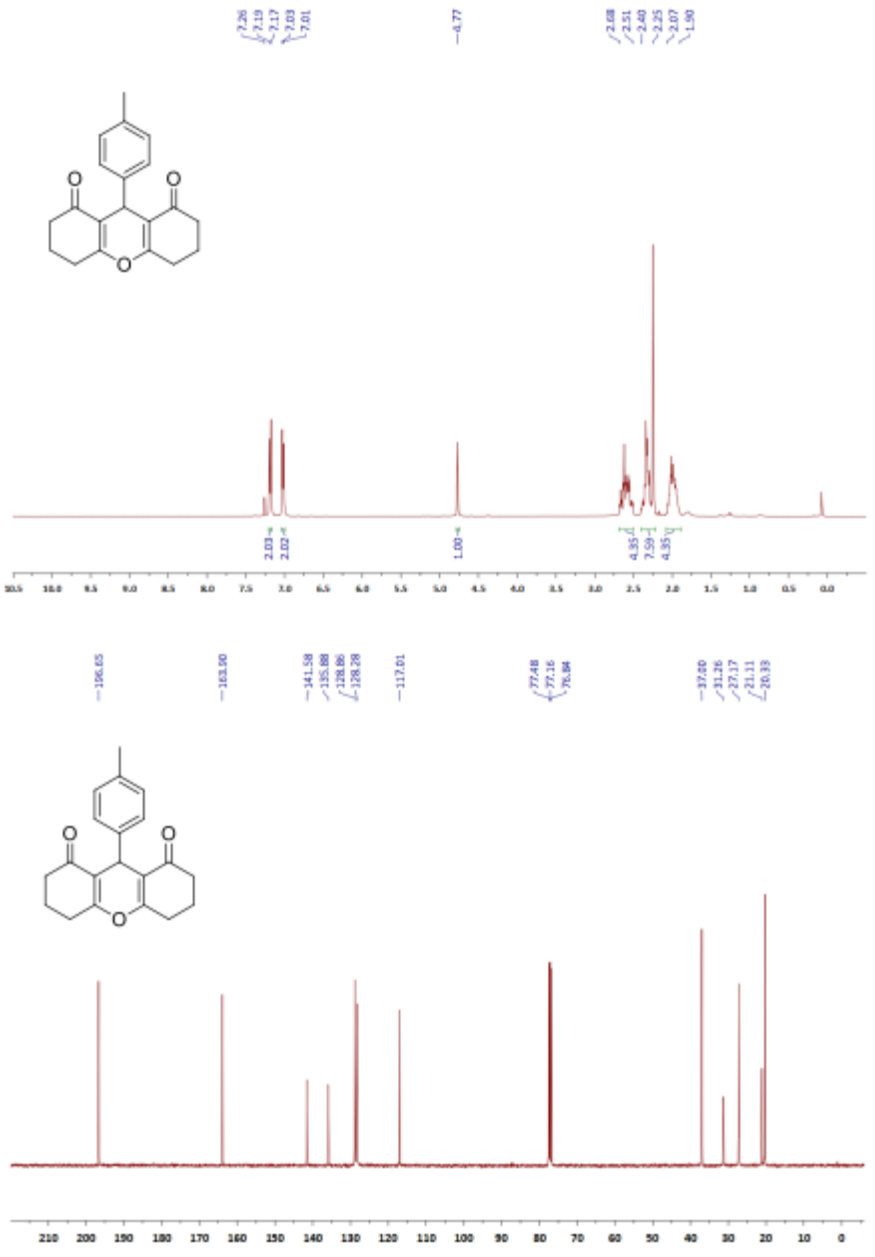

$^{1}$H and $^{13}$C NMR spectral data of **3l**