



## Short Communication

# Ultrasound assisted synthesis of tetrahydrobenzo[c]xanthene-11-ones using CAN as catalyst

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## ABSTRACT

Tetrahydrobenzo[c]xanthenes-11-ones was synthesized by a three component reaction of  $\alpha$ -naphthol, aromatic aldehyde and dimedone. Ceric ammonium nitrate acts as a suitable eco-friendly catalyst for this method. Shorter reaction duration, mild reaction condition and low cost make this protocol more effective.

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## 1. Introduction

Xanthenes and benzoxanthenes are important structures which have been investigated extensively in recent years. Xanthene skeleton is present in a number of natural products [1], and these motifs are found to bear diverse biological applications such as bactericidal [2], anti-inflammatory [3], antiviral [4] activities. They act as antagonists for paralyzing the action of zoxazolamine, [5] and are useful in the photodynamic therapy [6]. Their applications are also found in laser technology [7], are used as pH sensitive fluorescent materials for visualization of bimolecular assemblies [8] and as dyes [9]. In recent years there is a growing demand for the synthesis of such biologically and industrially significant molecules.

Literature survey indicates that, a few methods have been reported for the synthesis of tetrahydrobenzo[a]xanthene-11-ones from  $\beta$ -naphthol. Different catalysts such as sulfamic acid [10], *p*-TSA [11], selectfluor TM [12], iodine [13], silica sulfuric acid [14], Yb(OTf)<sub>3</sub> [15] and ionic liquids [16] find application in the synthesis of benzo[a]xanthenes. The existing methods have not been conceded for the synthesis of tetrahydrobenzo[c]xanthene-11-ones from  $\alpha$ -naphthol (Scheme 1), this is because, the electron density at the  $\beta$ -position of the  $\alpha$ -naphthol is not sufficient for the formation of the corresponding *ortho*-Quinone Methides (*o*-QMs, Scheme 2) under these conditions. As per our knowledge, there is only one article which involves use of proline triflate as a catalyst for the synthesis of tetrahydrobenzo[c]xanthenes-11-ones from

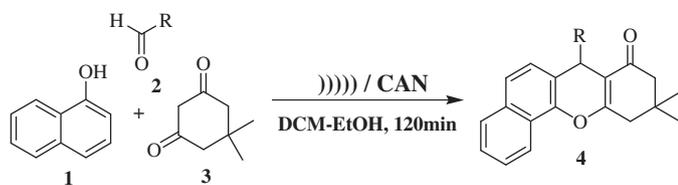
$\alpha$ -naphthol in the literature [17]. The search for new methods for the synthesis of tetrahydro[c]xanthene-11-ones from  $\alpha$ -naphthol is therefore, exceedingly demanding. We herein, propose to use ultrasound for their synthesis, which we feel can activate  $\alpha$ -naphthol and act as a very good energy source in the synthesis of tetrahydrobenzo[c]xanthenes-11-ones.

Use of ultrasound in the field of organic chemistry has received considerable attention in the last two decades. The technique reduces the reaction duration, improves the yields and involves easier work-up procedures than conventional methods [18a]. Ultrasound works by the phenomenon of cavitation; which involves the growth, oscillation, and collapse of bubbles under the action of an acoustic field. There are three different theories about cavitation: the hot-spot, the electrical and the plasma theory; and the most popular one is the hot spot theory. It has been experimentally shown that, the cavitation collapse creates drastic conditions inside the medium for an extremely short time and temperatures of 2000–5000 K, pressures up to 1800 atm inside the collapsing cavity have been produced under sonic condition [18a,b]. The collapse causes a couple of strong physical effects outside the bubble such as-shear forces, jets and shock waves. These cavitation-induced effects can cause physical, chemical, and biological transformations more effectively. Thus, ultrasound has found applications in chemistry, in materials, in life sciences as well as in medicine [18c].

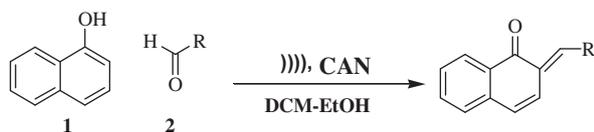
It is noted that, ceric ammonium nitrate (CAN) as a catalyst shows superior properties like eco-friendliness and is commercially available. It is inexpensive and can be easily handled. Its wider usability in the reactions like carbon–carbon and carbon–heteroatom bond formation, single-electron oxidation reactions has recently attracted much attention [19a–e]. The use of CAN

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**Scheme 1.** Synthesis of tetrahydrobenzo[*c*]xanthene-11-ones.



**Scheme 2.** Formation of *ortho*-Quinone Methides.

for the synthesis of tetrahydrobenzo[*c*]xanthene-11-ones (Scheme 1) will therefore be of greater advantage.

## 2. Methods

### 2.1. Materials and instruments

All chemicals were commercial and used without further purification; ultrasonication was performed using SIDILU, Indian make sonic bath working at a constant frequency of 35 kHz and an output power of 70 W at 26 °C (maintained by circulating water). The reactions were performed in open vessels without any mechanical stirring. Melting points were recorded on a RAAGA melting point apparatus (Indian make). <sup>1</sup>H NMR spectra were recorded in CDCl<sub>3</sub> using a Bruker 400 MHz instrument with TMS as an internal standard.

### 2.2. General procedure for the synthesis of tetrahydrobenzo[*c*]xanthene-11-ones

$\alpha$ -Naphthol (2 mmol), aromatic aldehydes (2 mmol) and dimedone (2 mmol) were taken in a test tube to which CAN (5 mol%) and a 1:1 mixture of DCM–ethanol (2 mL) was added. The test tube was placed in a sonic bath and sonicated at 26 °C until the reaction was complete (about 120 min, monitored on TLC; eluent: *n*-hexane:EtOAc:: 2:1). The mixture was filtered to remove the catalyst, the catalyst was washed with minimum quantity of ethyl acetate, the organic layer (filtrate) was then evaporated and the crude product was purified by silica gel column chromatography (EtOAc: light petrol:: 2:8). All the products were characterized by their

physical and spectral data (<sup>1</sup>H NMR) and are compared with those of authentic samples [17].

### 2.3. <sup>1</sup>H NMR spectral data

**4a:** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 6.8–7.3 (m, 11H, ArH); 5.6 (s, 1H); 2.2 (s, 2H); 1.9 (d, *J* = 17.2 Hz, 2H); 0.95 (s, 3H, CH<sub>3</sub>); 0.92 (s, 3H, CH<sub>3</sub>).

**4d:** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 7.5 (m, 4H, ArH); 7.3 (m, 3H, ArH); 7.1 (m, 3H, ArH); 5.1 (s, 1H); 3.74 (s, 3H, OCH<sub>3</sub>); 2.5–2.15 (m, 2H); 2.14–1.9 (m, 2H); 0.84 (s, 6H, 2 × CH<sub>3</sub>).

**4e:** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 7.5 (m, 4H, ArH); 7.3 (m, 3H, ArH); 7.1 (m, 3H, ArH); 5.1 (s, 1H); 2.25–2.23 (m, 2H); 2.20–2.19 (m, 2H); 0.87 (s, 6H, 2 × CH<sub>3</sub>).

**4i:** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 7.39–7.37 (m, 1H, ArH); 7.28–7.20 (m, 4H, ArH); 7.18–7.15 (m, 1H, ArH); 7.05–6.99 (m, 2H, ArH); 6.85–6.83 (m, 1H, ArH); 5.3 (s, 1H); 2.25–2.03 (m, 2H); 1.83–1.78 (m, 2H); 0.99 (s, 3H, CH<sub>3</sub>); 0.95 (s, 3H, CH<sub>3</sub>).

**5a:** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 7.7–7.3 (m, 2H, ArH); 6.9–6.6 (m, 3H, ArH); 5.9 (s, 1H); 2.5–2.4 (m, 4H, 2 × CH<sub>2</sub>); 0.94–0.89 (m, 12H, 4 × CH<sub>3</sub>).

## 3. Results and discussion

In search of simple energy efficient methods and eco-friendly catalysts for the synthesis of tetrahydrobenzo[*c*]xanthene-11-ones, we studied the model reaction of  $\alpha$ -naphthol, benzaldehyde and dimedone by a solvent-free ultrasonic reaction (Scheme 1). The reaction was initially carried out without catalyst, and it did not yield any product. It was found that, CAN showed better catalytic activity under sonic conditions among other catalysts that were tested (Table 1) under solvent-free condition. The above reaction was also carried out under silent condition to study the effect of ultrasound; the results of which are given in Table 1, under silent condition, in some cases (Table 1, entries 3 and 5) a minimum period of 10 h is required to form the *ortho*-Quinone Methides (*o*-QM, TLC), and in most of the cases the reaction did not proceed at all. Since dimedone is more reactive compared to  $\alpha$ -naphthol, 1,8-dioxo-dodecahydroxanthene (**5a**) was formed as major product under silent condition as shown in Scheme 3. This clearly indicates that, formation of the intermediate *o*-QM and cyclization to xanthenes are the two important steps governing the formation of tetrahydrobenzo[*c*]xanthene-11-ones. Under solvent-free sonic condition, 5 mol% of CAN was sufficient to give the product **4a** but only in moderate yield. This could be because of the non-reactive nature of  $\alpha$ -naphthol with the solid aromatic aldehydes or may be due to non-participation of dimedone with the thick reaction mass which was formed when liquid aromatic aldehydes were treated with  $\alpha$ -naphthol in the absence of any solvent.

The model reaction, with 5 mol% of CAN, was then reinvestigated in different solvent systems under sonic condition, the results of the

**Table 1**  
Optimization of catalysts for the one-pot condensation: a comparative study under ultrasonic and silent conditions.

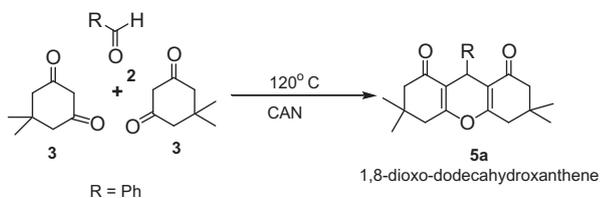
Sl. No.	Catalyst	Silent condition <sup>a</sup> (120 °C)	Ultrasonic condition <sup>b</sup> (26 °C)
1	MgCl <sub>2</sub>	No product	No product
2	CuCl	No product	No product
3	<i>p</i> -TSA	Trace	30% <sup>c</sup> with by-product <sup>d</sup>
4	Lithium perchlorate	No product	No product
5	CAN	By product <sup>d</sup>	65% <sup>c</sup>
6	Anhyd. AlCl <sub>3</sub>	No product	25% <sup>c</sup>

<sup>a</sup> Reaction condition:  $\alpha$ -naphthol (2 mmol), benzaldehyde (2 mmol), dimedone (2 mmol), catalyst (2 mmol) solvent-free condition, 14 h.

<sup>b</sup>  $\alpha$ -Naphthol (2 mmol), benzaldehyde (2 mmol), dimedone (2 mmol), catalyst (5 mol%), solvent-free, 2 h.

<sup>c</sup> Tetrahydrobenzo[*c*]xanthene-11-one; isolated yield by column chromatography.

<sup>d</sup> 1,8-Dioxo-dodecahydroxanthene.



**Scheme 3.** Formation of 1,8-dioxo-dodecahydroxanthene under solvent-free silent condition at 120 °C.

**Table 2**  
Effect of solvent on the rate of CAN catalyzed reaction.<sup>a</sup>

Sl. No.	Solvent	Silent condition <sup>b</sup>	Ultrasonic condition <sup>d</sup> (4a) (%)
1	Ether	No product	30
2	THF	No product	30
3	Acetonitrile	20% byproduct (5a) <sup>c</sup>	50
4	DCM	No product	60
5	DCM:ethanol (1:1)	85% byproduct (5a) <sup>c</sup>	85

<sup>a</sup>  $\alpha$ -Naphthol (2 mmol), benzaldehyde (2 mmol), dimedone (2 mmol), CAN (5 mol%).

<sup>b</sup> Reflux, 14 h.

<sup>c</sup> 1,8-Dioxododecahydroxanthene.

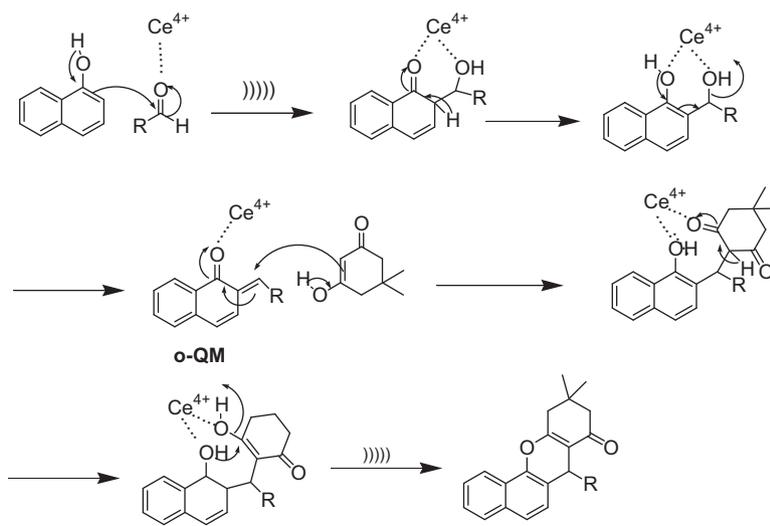
<sup>d</sup> 26 °C, 2 h; isolated yield of the product tetrahydrobenzo[c]xanthene-11-one.

effect of solvents on the rate of the reaction and yield of the products is given in Table 2, and it is clear from Table 2 that, ultrasound

mediated reaction is more faster and high yielding than the reaction carried out under reflux condition in DCM–ethanol (1:1) system.

It is clear from the above studies that, best results were achieved with the use of 5 mol% of the CAN, and a mixture of DCM/ethanol (1:1) as solvent under sonic condition (35 kHz). Various aromatic aldehydes containing electron-withdrawing and electron-donating substituents at *ortho*, *meta* and *para*-positions showed equal ease towards the product formation in good to high yields. The results of this outcome are given in Table 3. The by-product 1,8-dioxo-dodecahydroxanthene (5a) formed by the condensation of one aldehyde molecule and two dimedone molecules was either formed to a very little extent or did not form at all under the sonic condition.

The formation of tetrahydrobenzo[c]xanthene-11-one from  $\alpha$ -naphthol, benzaldehyde and dimedone in the presence of CAN can be explained by a tentative mechanism presented in Scheme 4. The ultrasonic cavitation induced shear forces and the jets produced near the surface of the vessel and the catalyst may activate the passive  $\alpha$ -naphthol through sonolysis of the O–H bond. The reaction between the activated  $\alpha$ -naphthol and the aromatic aldehyde (activated by CAN) may facilitate the formation of the corresponding *o*-QM under sonic condition, and this *o*-QM intermediate may then react with the active methylene of dimedone, followed by cyclization to give tetrahydrobenzo[c]xanthene-11-one with the removal of a molecule of water as shown in Scheme 4. As mentioned earlier, the formation of *o*-QM and the formation of tetrahydrobenzo[c]xanthene-11-one in the last step by a cyclization reaction are crucial and both the steps are accelerated by ultrasound.



**Scheme 4.** A probable mechanism of formation of tetrahydrobenzo[c]xanthene-11-ones.

**Table 3**  
Synthesis of tetrahydrobenzo[c]xanthene-11-ones by the condensation of  $\alpha$ -naphthol, aromatic aldehydes and dimedone using DCM:ethanol (1:1) as solvent and CAN as catalyst.<sup>a</sup>

Product	Aldehyde	Yield (%)	Time (min)	Melting point (°C)/Lit [17]
4a	Benzaldehyde	85	120	149–152/151–152
4b	4-Hydroxybenzaldehyde	85	120	222–224/223–225
4c	4-Methoxybenzaldehyde	83	135	207–209/206–207
4d	4-Hydroxy-3-methoxybenzaldehyde	86	120	235–237
4e	3-Nitrobenzaldehyde	82	144	167–170/170–180
4f	2-Chlorobenzaldehyde	87	135	179–181/180–181
4g	4-Chlorobenzaldehyde	85	144	185–187/185–186
4i	Furaldehyde	87	120	155–158

<sup>a</sup> Reaction condition:  $\alpha$ -naphthol (2 mmol), aromatic aldehyde (2 mmol), dimedone (2 mmol), CAN (5 mol%), solvent DCM:ethanol (1:1, 2 mL) was taken in test tube and subjected to sonication.

**Table 4**  
Study of the effect of ultrasound on the formation of tetrahydrobenzo [c]xanthene-11-one (**4a**).<sup>a</sup>

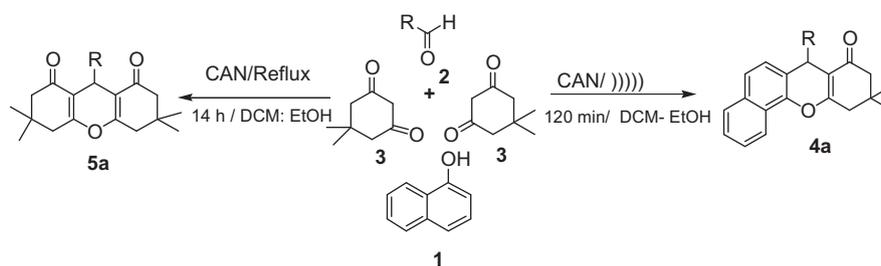
Quantity of starting materials	Silent (14 h)	Ultrasound <sup>c</sup> (2 h)
$\alpha$ -Naphthol (2 mmol) benzaldehyde (2 mmol) and dimedone (2 mmol)	No reaction <sup>b</sup>	Product
$\alpha$ -Naphthol (4 mmol) benzaldehyde (4 mmol) and dimedone (2 mmol)	No reaction <sup>b</sup>	Product
$\alpha$ -Naphthol (4 mmol) benzaldehyde (4 mmol) and dimedone (2 mmol)	1,8-Dioxo-dodecahydroxanthene ( <b>5a</b> , 85%) <sup>d</sup>	Product ( <b>4a</b> , 85%) with trace amount of 1,8-dioxo-dodecahydroxanthene

<sup>a</sup> All the reaction were carried out using, CAN (5 mol%), solvent: DCM:ethanol (1:1, 2 mL).

<sup>b</sup> Silent condition: 26 °C; stirring.

<sup>c</sup> Ultrasonic condition: 26 °C; 2 h.

<sup>d</sup> Silent condition: CAN (5 mol%), solvent: DCM:ethanol (1:1, 2 mL) reflux for 14 h.



**Scheme 5.** Sonochemical switching.

The energy and temperature parameters of the solvents influencing the sonochemical reactivity depend on the intensity- $I_{\max}$  (maximum cavitation intensity) and  $T_{I_{\max}}$  (the temperature at which  $I_{\max}$  is reached), and in the present reaction, the solvents DCM and ethanol have a better  $I_{\max}$  values at ambient conditions [18c]. The effect of ultrasound on the present reaction which uses DCM:ethanol as the solvent system can be viewed as follows: The transmission of the sound waves induces vibrational motion to the solvent; the solvent molecules then alternatively compress, stretch and oscillate around their mean position due to time-varying pressure, at a point when the intensity of ultrasound is higher enough to break the intermolecular forces existing between the solvent molecules it breaks down and a cavity is formed [18]. This cavity is called cavitation bubble, the process is called acoustic cavitation and the point where it starts is the cavitation threshold [18]. It is worthy to note that, ultrasound with frequencies less than 50 kHz and presence of solid CAN in the reaction mixture has resulted in increase in the reaction rate when compared with the silent reaction because of the local raise in the temperature and pressure due to the cavitation of some bubbles next to the surface of the catalyst/reactants [18c].

From the optimized set of conditions we have made a comparative study to highlight the effect of ultrasound on the present reaction. The amount of product and by product formed under silent and sonic condition are compared, these studies are presented in Table 4, surprisingly the reaction under silent condition predominantly gave 1,8-dioxo-dodecahydroxanthene (characterized by <sup>1</sup>H NMR spectral analysis), whereas under sonic condition tetrahydrobenzo [c]xanthene-11-one is formed exclusively. We feel that, sonication has modified the reactivity's of the substrates, hence we can consider this reaction to be an example of "sonochemical switching" [20] as shown in Scheme 5.

#### 4. Conclusion

In summary, ultrasound has accelerated the reaction of passive  $\alpha$ -naphthol with aromatic aldehydes and dimedone in the presence of catalytic amounts of CAN. The synthesis of tetrahydrobenzo

[c]xanthene-11-ones by this new and energy efficient method has proved to be useful both from economical and environmental point of view. This methodology also overcomes the formation of unwanted by-products, low yields and external high temperatures.

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#### Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ultsonch.2012.02.002.

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