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# A rapid and efficient CsF catalyzed tandem Knoevenagel–Michael reaction

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ABSTRACT

A simple, experimentally rapid and efficient CsF catalyzed tandem Knoevenagel–Michael reaction protocol is developed for the synthesis of a series of functionalized 9-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)-3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (**1**–**7**) by reacting dimedone with substituted salicylaldehydes. The use of CsF as a catalyst allowed reactions under moderate conditions and resulted in better yields.

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## 1. Introduction

Heterocyclic compounds are very important materials due to their biological and pharmacological activities [1]. Facile and robust synthesis of these materials is a major topic of organic chemistry, both in academia and industry. The exploration of new, facile, high yield and eco-friendly methods are very crucial even for classical compounds. The Knoevenagel condensation followed by the Michael addition reaction is one of the simplest methods for carbon–carbon double bond formation [2]. In tandem Knoevenagel–Michael reaction on different substrates with variety of catalysts opened a horizon of new and facile synthesis methods with improved yields.

One of the important classes of oxygen containing tricyclic organic compounds is xanthenes. The biological and pharmacological activities of xanthenes are well documented in literature, such as antiviral [3], antibacterial [4], antioxidants, antineoplastic, vasodilators and anti-inflammatory [5–15]. Blennolide C and diversonol (Fig. 1) are xanthene carrying natural compounds that showed anti-cell growth activity measured by National Cancer Institute [16].

There are myriad of research articles reporting synthesis of functionalized xanthenes. A wide range of starting materials and reaction protocols has been reported for synthesis of this fascinating class of compounds [17]. The synthesis of 1-oxohexahydroxanthene analogs have been reported by reacting substituted salicylaldehyde with dimedone using variety of catalysts such as TEBA in aqueous medium [18], 2,4,6-trichloro-1,3,5-triazine [19], $CeCl_3{\cdot}7H_2O$ [20], *p*-TSA/$H_2O$ [16].

The sole use of ionic salts for tandem Knoevenagel–Michael reaction is a relatively new idea. The use of ionic salts as catalyst in organic synthetic chemistry is very important because it leads to mild reaction conditions and simpler work-up.

The use of cesium fluoride as a catalyst has been reported by Jeanne et al. in which reported the enhancement of the reactivity of carboxylic ester toward trifluoromethylation under room temperature that afford silyl ether intermediate that on hydrolysis gives ketone [21]. Another group of scientist Dong et al. reported the use of cesium fluoride as a nucleophile in polar solvents (tert-alcohol) that significantly enhanced reactivity of the fluoride as a nucleophile [22]. Baldwin and co-workers targeted the Stille coupling reaction in the presence of cesium fluoride and copper salt [23]. Do et al. reported a facile method for deboronation of o-carboranes using cesium fluoride [24]. Murashima et al. reported synthesis of crown ether-annulated porphyrin in the presence of cesium fluoride [25]. Some other uses of cesium fluoride as a catalyst has been reported for the polymerizations [26] and cyclization reactions [27]. Fluoride ion increases the nucleophilic character of compounds that have acidic protons [28]. Some other reported examples of ionic salts as a catalyst are aromatic

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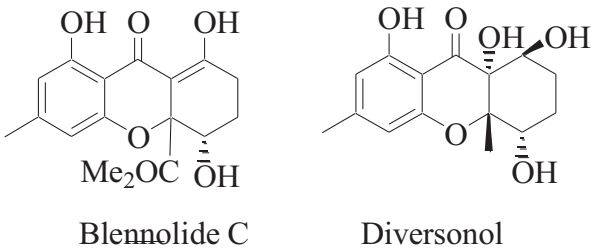



**Fig. 1.** Xanthene carrying natural compounds.

polysulfide synthesis [29], conversion of organic acids to organic esters [30] and promotion of chemo- and regio-selective ring opening reaction through $S_N2$ mechanism [31].

However, the major disadvantages of most of the methods are harsh reaction conditions, long reaction time and tedious work-up procedures.

The literature survey on cesium fluoride unfold a special effect like "cesium effect". Cesium effect describes the advantages regarding yield, short time, smaller amount of reagent, milder reaction conditions and easier work up procedure as compared to conventional non cesium protocol. While studying the literature on multidimensional role of cesium fluoride really inspire us to perform and optimized the tandem Knoevenagel–Micheal reaction. In this study we report an experimentally simple, efficient and rapid CsF catalyzed tandem Knoevenagel–Michael reaction for the synthesis of functionalized 9-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)-3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (**1**–**7**) by reacting dimedone with substituted salicylaldehyd.

## 2. Results and discussion

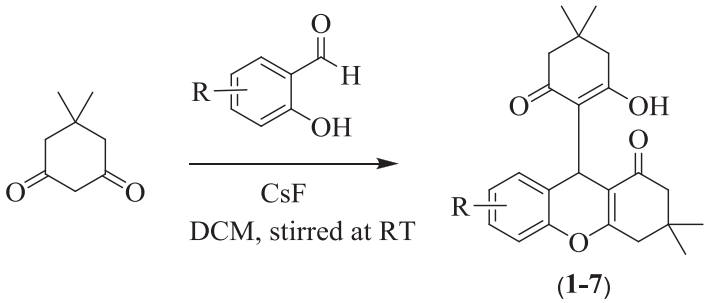
According to our previous research involving CsF as a solid base, fluoride ion has a strong affinity for active hydrogen [32–38]. This inspired us to explore the multidimensional studies which may lead us to new possibilities regarding the utility of utility of CsF for tandem Knoevenagel–Michael reaction. In current study, dimedone was reacted with functionalized salicylaldehydes in dichloromethane under mild conditions as compared to all of the previous reports for tandem Knoevenagel–Michael reaction.

The function of cesium fluoride in this reaction is very important due to several reasons. Scheme 2 shows the reaction mechanism on the basis of previous work reported by Ishikawa et al. [39]. It is well known that among alkaline metal salts, cesium salts have the lowest degree of solvation and ion pairing ability that makes cesium ion naked to coordinate more effectively with carbonyl oxygen making carbonyl carbon more electrophilic.

First the coordination of cationic part of the CsF with carbonyl oxygen of salicylaldehyde. The cationic part of the cesium fluoride, cesium coordinates with carbonyl carbon of salicylaldehyde. In the process, π–electrons from carbonyl carbon are withdrawn that induces electrophilicity. Secondly, the counter fluoride consumes the acidic protons of dimedone and generates an enolized dimedone. This enolized dimedone might attack the electrophilic center of salicylaldehyde and consequently a carbon–carbon double bond is formed. This condensation leads to an intermediate. In the next step hydroxyl group on salicylaldehyde might be attacked on the carbonyl carbon of the dimedone that results in cyclic 1,4-Michael-type substrate. This cyclic substrate serves for 1,4-attack by the second enolate of the dimedone produced by fluoride base. The general chemical reaction is shown in Scheme 1 and their plausible mechanism is given in Scheme 2.

Various substituted salicylaldehydes with electron donating and withdrawing groups have been used. The electron withdrawing group on salicyaldehydes resulted in excellent yields. However, good yields are obtained for salicylaldehyde with electron donating groups (Table 1).

The $^1$H NMR spectrum of 5-bromo-7-chloro-9-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)-3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (**1**) were recorded in deuterated dimethyl sulphoxide at 300 MHz. The spectrum showed two singlets for a aromatic protons at $\delta$ 7.40 and $\delta$ 6.93 respectively, benzylic protons resonated at $\delta$ 5.06, and 8 methelene protons as a multiplet appeared at $\delta$ 1.98–2.54. Two signals for six methyl protons appeared at $\delta$ 1.01 and 0.92. However, six protons for other two methyl groups resonated at $\delta$ 0.87 as a singlet. The compounds are stable enough and allowed performing E.I. mass spectrometry. The results confirm that the newly developed method provides a facile and robust reaction protocol for the synthesis of 9-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)-3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one derivatives. The reactions times were comparatively short under mild conditions with excellent yields and simple work-up. All synthesized compounds were characterized by using spectroscopic techniques like $^1$H NMR and EI-MS. The compounds were also subjected to elemental analyses and the results are in good agreement with the expected values. Since all the compounds are known. The physical data of our compounds have been compared with the earlier literature [40].




**Scheme 1.** Synthetic route for tandem Knoevenagel–Michael reaction by CsF. Structure **1**–**7** with R group, where R group are H, OH OMe, Cl, F and Br on the functionalized salicylaldehyde given in Table 1.

**Table 1**
Highly functionalized 9-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)-3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one (**1–7**).

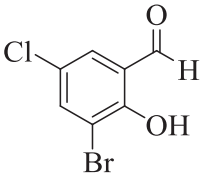
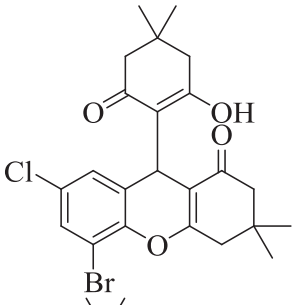
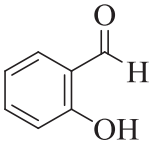
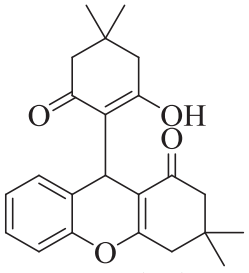
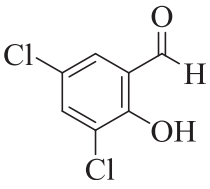
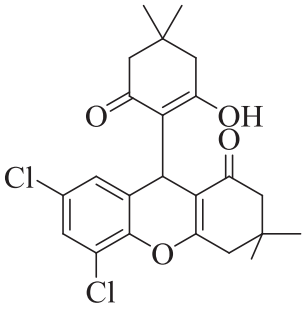
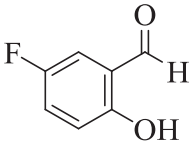
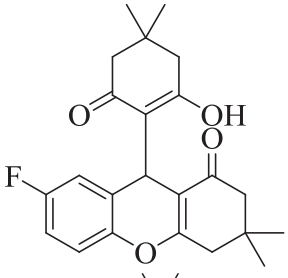
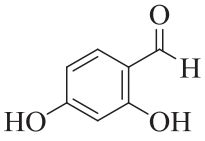
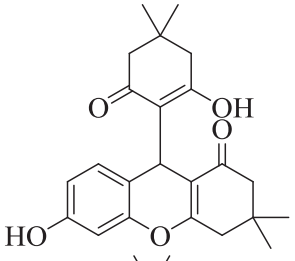
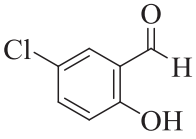
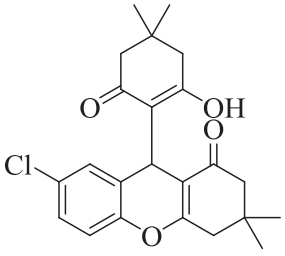
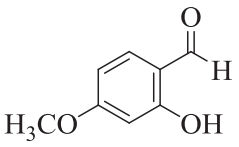
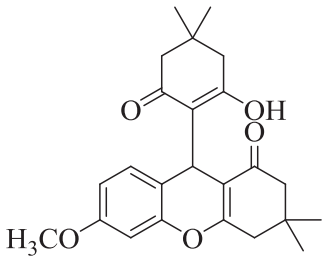
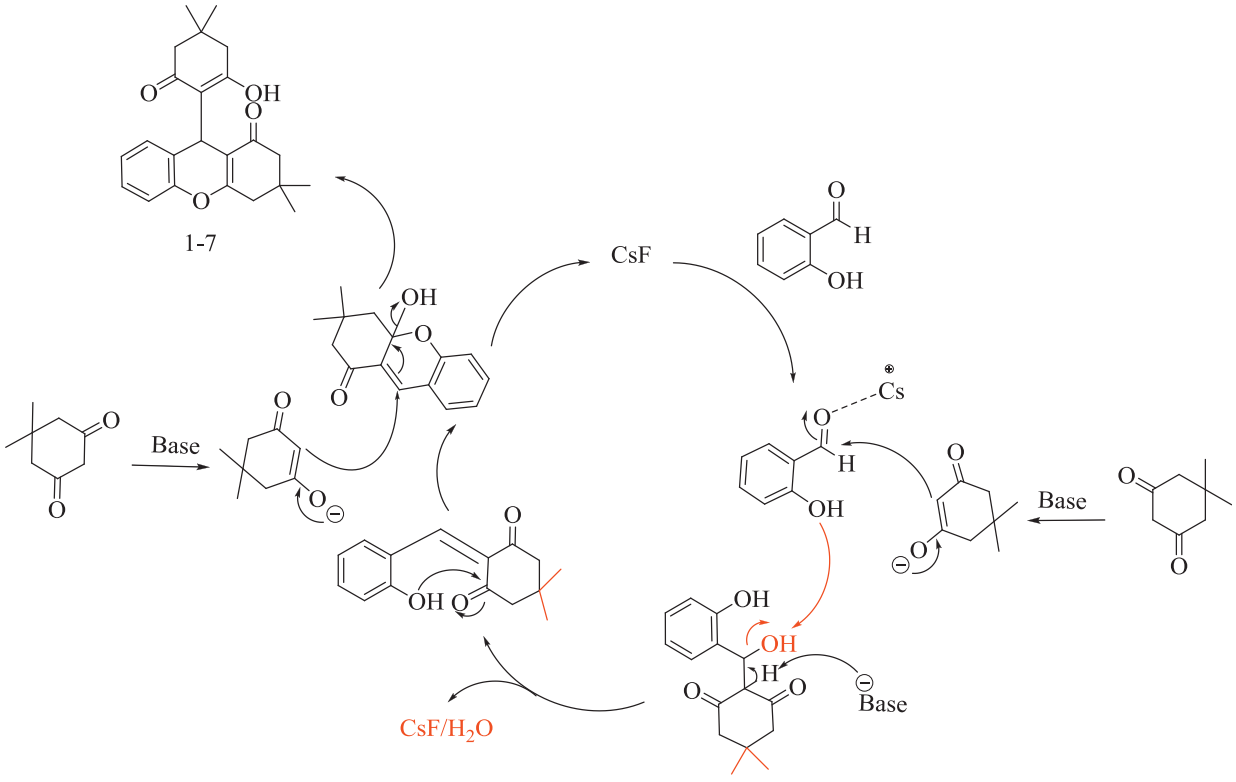
| S. No. | Functionalized salicylaldehydes | Products | Yield (%) |
|---|---|---|---|
| 1 |  |  | 80 |
| 2 |  |  | 70 |
| 3 |  |  | 75 |
| 4 |  |  | 70 |
| 5 |  |  | 78 |
| 6 |  |  | 86 |

**Table 1** (*Continued*)

| S. No. | Functionalized salicylaldehydes | Products | Yield (%) |
|---|---|---|---|
| 7 |  |  | 80 |




**Scheme 2.** Plausible mechanism of CsF catalyzed tandem Knoevenagel–Michael reaction for synthesis of highly functionalized 9-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)-3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one derivatives (**1**–**7**).

## 3. Conclusions

An expeditious and robust method has been devised for the synthesis of highly functionalized 9-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)-3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one **1**–**7**. The newly developed method expanded the scope of the tandem Knoevenagel–Michael reaction. The ionic salts such as CsF are an excellent base for promoting the tandem Knoevenagel–Michael reaction. Extensive studies are required to fully explore the potential of inorganic ionic compounds as catalysts in synthetic organic chemistry. This will be topic of our forthcoming publications of this series.

## 4. Experimental

All the salicylaldehyde analogs and other starting material were reacted together without purification as received from the supplier Sigma/Aldrich, USA. $^1$H NMR spectra were recorded on Bruker 300 MHz and 500 MHz spectrometers. Mass spectra were recorded at JEOL JMS-HX110 mass spectrometer using FABMS-H. CHN analysis was performed on a Carlo Erba Strumentazion-Mod-1106, Italy.

### *4.1. General procedure for the synthesis of functionalized 9-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)-3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one*

In a typical reaction, catalytic amount of CsF (5 Mol%) was added to the solution of appropriate substituted salicylaldehyde (**1**–**7**) (1.0 equiv) in dichloromethane (10 mL) at room temperature. Dimedone (2.0 equiv) was added slowly and reaction mixture was stirred for 30–40 min. The product was precipitated that was monitored by TLC. The resultant Precipitate was washed with distilled water to obtain the pure product. The structure of these compounds was confirmed by different spectroscopic techniques like $^1$H NMR, and MS.

### 4.2. Spectroscopic data

*4.2.1. 5-Bromo-7-chloro-9-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)-3,3-dimethyl-2,3,4,9-tetrahydro-1H-xanthen-1-one*

Yield: 80%; $^1$H NMR; (DMSO-$d_6$) $\delta$ ppm: 7.40 (s, 1H), 6.93 (s, 1H), 5.06 (s, 1H), 1.98–2.54 (m, 8H), 1.01 (s, 3H), 0.92 (s, 3H), 0.87 (s, 6H). EI-MS: m/z 480.1 (45.0), 396.0 (100), 341.0 (68.3), 325 (83.3), 78 (55.7), 63.0 (64.9).

*4.2.2. 9-(2-Hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)-3,3-dimethyl-2,3,4,9-tetrahydro-1H-xanthen-1-one*

Yield: 70%; $^1$H NMR; (DMSO-$d_6$) $\delta$ ppm: 10.43 (s, 1H, OH) 6.97–7.24 (m, 4H), 4.64 (s, 1H), 1.88–2.61 (m, 8H), 1.11 (s, 3H), 1.00 (s, 3H), 0.96 (s, 6H). EI-MS: m/z 366.1 (32.9), 282.1 (70.2), 227.1 (79.9), 211.0 (100), 83.1 (47.2).

*4.2.3. 5,7-dichloro-9-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)-3,3-dimethyl-2,3,4,9-tetrahydro-1H-xanthen-1-one*

Yield: 75%; $^1$H NMR; (DMSO-$d_6$) $\delta$ ppm: 7.34 (s, 1H), 6.87 (s, 1H), 5.05 (s, 1H), 2.05–2.49 (m, 8H), 1.02 (s, 3H), 0.92 (s, 3H), 0.87 (s, 6H). EI-MS: m/z 434.0 (45.1), 350.0 (100), 295.0 (71.2), 278.9 (49.5), 238.9 (23.8), 83.0 (26.1).

*4.2.4. 7-Fluoro-9-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)-3,3-dimethyl-2,3,4,9-tetrahydro-1H-xanthen-1-one*

Yield: 70%; $^1$H NMR; (DMSO-$d_6$) $\delta$ ppm: 6.64–6.98 (m, 3H), 5.03 (s, 1H), 1.98–2.54 (m, 8H), 1.02 (s, 3H), 0.95 (s, 3H), 0.87 (s, 6H). EI-MS: m/z 384.0 (39.1), 299.9 (100), 244.9 (59.0), 188.9 (30.0) 132.9 (29.1), 83.0 (5.7).

*4.2.5. 6-Hydroxy-9-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)-3,3-dimethyl-2,3,4,9-tetrahydro-1H-xanthen-1-one*

Yield: 78%; $^1$H NMR; (DMSO-$d_6$) $\delta$ ppm: 9.33 (s, 1H, ArOH) 6.29–6.73 (m, 3H), 4.90 (s, 1H), 1.97–2.49 (m, 8H), 1.02 (s, 3H), 0.95 (s, 3H), 0.87 (s, 6H). EI-MS: m/z 382.0 (1.1), 242.0 (20.6), 227.0 (100), 83.0 (36.1).

*4.2.6. 7-Chloro-9-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)-3,3-dimethyl-2,3,4,9-tetrahydro-1H-xanthen-1-one*

Yield: 86%; $^1$H NMR; (DMSO-$d_6$) $\delta$ ppm: 10.54 (s, 1H, OH), 6.89–7.16 (m, 3H), 5.02 (s, 1H), 1.99–2.56 (m, 8H), 1.03 (s, 3H), 0.96 (s, 3H), 0.88 (s, 6H). EI-MS: m/z 400.3 (36.2), 316.2 (100), 261.1 (81.1), 245.1 (80.1), 205.1 (33.0), 83.0 (27.9).

*4.2.7. 9-(2-Hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)-6-methoxy-3,3-dimethyl-2,3,4,9-tetrahydro-1H-xanthen-1-one*

Yield: 80%; $^1$H NMR; (DMSO-$d_6$) $\delta$ ppm: 6.43–6.86 (m, 3H), 4.96 (s, 1H), 3.67 (s, 1H), 1.95–2.49 (m, 8H), 1.01 (s, 3H), 0.96 (s, 3H), 0.88 (s, 6H). EI-MS: m/z 395.0 (46.5), 256.0 (52.7), 240.9 (100), 198.0 (19.2), 142.1 (97.0), 83.0 (32.2).

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