



## ORIGINAL ARTICLE

# Ionic liquid promoted facile and green synthesis of 1,8-dioxo-octahydroxanthene derivatives under microwave irradiation



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Received 16 August 2013; revised 20 November 2013; accepted 11 December 2013

Available online 3 January 2014

## KEYWORDS

Homogeneous catalysis;  
Microwave assisted synthesis;  
Green chemistry;  
Ionic liquid

**Abstract** An efficient and environmentally benign procedure for the synthesis of 1,8-dioxo-octahydroxanthene by condensation reaction between 5,5-dimethyl-1,3-cyclohexanedione (dimedone) and structurally diverse aldehydes using carboxy functionalized ionic liquid under microwave irradiation is described. The methodology provides synergy of ionic liquid and microwave irradiation which offers several advantages such as high yields in shorter reaction time, convenient operation, reusability of catalyst and easy work-up.

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## 1. Introduction

Xanthene core and its derivatives serve as an important class of compounds, as it is present in natural products with broad biological activities [4,29,34,35]. Most notably among them, xanthenedione constitutes structural unit in a number of natural products, and having a wide range of therapeutic and pharmacological properties [18,7,47]. Several functionalized 1,8-dioxo-octahydroxanthene derivatives possess the significant synthetic

interest as they exhibit anticancer [28], antiplasmodial [53], antiviral [45,40], antibacterial [24,40] and anti-inflammatory [37,40] activities. Besides, these heterocyclic molecules have been widely used as luminescent dyes [15,40], sensitizers in photodynamic therapy [43,21,41,30], in laser technology [3,1] as well as pH sensitive fluorescent materials [6,26]. There are several methods reported for the synthesis of xanthenedione derivatives over various catalysts such as sulfuric acid or hydrochloric acid [19], InCl<sub>3</sub>/ionic liquid [13], SmCl<sub>3</sub> [20], Fe<sup>+3</sup> montmorillonite [44], amberlyst-15 [11], FeCl<sub>3</sub>/[bmim][BF<sub>4</sub>] [14], p-dodecylbenzenesulfonic acid [38], sulfamic acid [39], HClO<sub>4</sub>·SiO<sub>2</sub> [50], trimethylsilyl chloride (TMSCl) [22]. However, most of the reported methods require expensive reagents, hazardous organic solvents, longer reaction time and tedious workup. Hence, the further innovation toward contemporary reaction with easy isolation of product, reusability of catalyst, perhaps with minimal or no waste is highly attractive.

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Peer review under responsibility of King Saud University.



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The development of sustainable, environmentally benign processes for the synthesis of heterocyclic compounds is one of the fundamental goals in current organic chemistry. Synthetic chemists in both academia and industry are constantly challenged to consider more green methods for generation of the target molecules. As a result, ionic liquid (ILs) catalyzed reactions have received considerable attention due to the unique properties such as negligible vapor pressure, broad liquid ranges, reusability and high thermal stability [49,48]. Apart from this, due to its inherent Lewis/Brønsted acidity, much attention has been focused on their use as a reaction media, which can promote and catalyze organic transformations of commercial importance in excellent yields [25]. The high efficacy of ionic liquids as reaction medium, conveniently solves the problem of solvent emission and recycling of catalyst [12,17,51].

The use of microwave irradiation in combination with ILs, which has very high heat capacity, high polarity and no vapor pressure, and their high potentiality to absorb microwaves and convert them into heat energy, may accelerate the reaction very quickly. The synergy of microwave and ionic liquid in catalyst-free methodologies for the synthesis of heterocyclic compounds has attracted much interest because of the shorter reaction time, milder conditions, reduced energy consumption and higher product selectivity and yields [42,16,27,52].

As a part of our continuing studies in developing efficient catalyst-free synthetic methodology, using ionic liquid and non-conventional energy source in organic preparations [10,9,8,2,32,33], herein we report a general method for the synthesis of 1,8-dioxo-octahydroxanthenes promoted by synergistic effect of ionic liquid and microwave irradiation without any added catalyst.

## 2. Experimental

### 2.1. General

All chemicals were of research grade and were used as obtained from Sigma–Aldrich, Alfa-Aesar and SDFCL. The IL was prepared according to the method reported earlier [10]. The melting points were determined in capillary tubes using heavy paraffin liquid in Thiele tube. Melting points are uncorrected and are compared with the reported literature values. The reaction progress and purity of products were determined by TLC silica gel plates (Merck 60 F<sub>254</sub>). IR Spectra were recorded on a Shimadzu FT-IR-S8401 and FT-IR-8400 spectrophotometer using KBr, mass spectra on AB APPLIED BIOSYSTEMS IMDS SCIEX. API-2000 LC/MS/MS spectrometer. The <sup>1</sup>H NMR (400 MHz), <sup>13</sup>C NMR (100 MHz) and DEPT-135 spectra were recorded on BRUKER AVANCE 400 MHz instrument using CDCl<sub>3</sub> as the solvent and TMS as the internal standard. All the reactions were carried out in scientific microwave system (Catalyst system ‘CATA-R’, 700 W). The reactions were carried out in a round-bottom flask of 25 mL capacity.

### 2.2. General procedure for the synthesis of 1,8-dioxo-octahydroxanthenes

A mixture of 5,5-dimethyl-1,3-cyclohexanedione (2 mmol), aldehyde (1 mmol) and [cmmim][BF<sub>4</sub>] (200 mg) was charged

into a 25 mL flask. The mixture was stirred gently with a spatula for a few seconds to ensure homogeneous mixing of reactants with ionic liquid. The reaction mixture was then subjected to microwave irradiation at 40% power level (280 W) for appropriate time shown in Table 1. After completion of reaction (as indicated by TLC), the reaction mixture was poured onto crushed ice (~20 g) and stirred well. The separated solid was washed with ice cold water (~4 × 5 mL) and then recrystallized from hot ethanol to afford pure 1,8-dioxo-octahydroxanthenes. The combined aqueous filtrate was subjected to vacuo at 80 °C under reduced pressure (10 mmHg) for 4 h to leave behind the IL pure enough for the next run in near complete recovery.

### 2.3. Spectral data of some selected compounds

#### 2.3.1. 3,4,6,7-Tetrahydro-3,3,6,6-tetramethyl-9-phenyl-2H-xanthene-1,8(5H,9H)-dione (3a)

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.29 (m, 2H), 7.23 (m, 2H), 7.11 (m, 1H), 4.77 (s, 1H), 2.48 (s, 4H), 2.21 (dd, 4H, *J* = 16.4 Hz), 1.12 (s, 6H), 1.01 (s, 6H). <sup>13</sup>C NMR: δ 27.34, 29.26, 31.84, 32.19, 40.90, 50.76, 115.70, 126.36, 128.04, 128.38, 144.10, 162.22, 196.32. DEPT-135: up peaks: δ 27.34, 29.26, 31.84, 126.36, 128.04, 128.38. Down peaks: δ 40.89, 50.75. IR (KBr): 3030, 2955, 1662, 1624, 1361, 1197, 1163 cm<sup>-1</sup>. *m/z* (ESI): 351.0 [M + H<sup>+</sup>].

#### 2.3.2. 3,4,6,7-Tetrahydro-3,3,6,6-tetramethyl-9-(4-methylphenyl)-2H-xanthene-1,8(5H,9H)-dione (3h)

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.02 (m, 2H), 6.82 (m, 2H), 4.92 (s, 1H), 2.51 (s, 4H), 2.29 (s, 3H), 2.19 (dd, 4H, *J* = 16.3 Hz), 1.09 (s, 6H), 1.00 (s, 6H). <sup>13</sup>C NMR: δ 21.20, 27.23, 29.24, 31.95, 32.18, 42.06, 50.09, 112.11, 125.23, 129.25, 135.26, 141.50, 162.54, 195.83. DEPT-135: up peaks: δ 21.20, 27.23, 29.24, 32.18, 125.23, 129.25. Down peaks: δ 42.06, 50.09. IR (KBr): 3135, 2954, 1720, 1592, 1378, 1191, 1081 cm<sup>-1</sup>.

#### 2.3.3. 3,4,6,7-Tetrahydro-3,3,6,6-tetramethyl-9-(4-hydroxy-3-methoxyphenyl)-2H-xanthene-1,8(5H,9H)-dione (3k)

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 6.93 (m, 1H), 6.71 (m, 1H), 6.64 (m, 1H), 5.81 (s, 1H), 4.66 (s, 1H), 3.88 (s, 3H), 2.44 (s, 4H), 2.19 (dd, 4H, *J* = 16.3 Hz), 1.10 (s, 6H), 1.01 (s, 6H). <sup>13</sup>C NMR: δ 27.31, 29.15, 31.98, 32.08, 42.36, 51.13, 55.92, 111.13, 113.16, 117.12, 120.54, 132.31, 145.56, 148.23, 162.21, 196.12. DEPT-135: up peaks: δ 27.31, 29.15, 32.08, 55.92, 111.13, 117.12, 120.54. Down peaks: δ 42.36, 51.13. IR (KBr): 3692, 3581, 3155, 2964, 2228, 1645, 1509, 1362, 1164 cm<sup>-1</sup>.

#### 2.3.4. 3,4,6,7-Tetrahydro-3,3,6,6-tetramethyl-9-(2-thienyl)-2H-xanthene-1,8(5H,9H)-dione (3t)

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.82-7.98 (m, 2H), 6.78 (m, 1H), 4.92 (s, 1H), 2.53 (s, 4H), 2.26 (dd, 4H, *J* = 16.0 Hz), 1.13 (s, 6H), 1.01 (s, 6H). <sup>13</sup>C NMR: δ 27.18, 29.33, 31.02, 31.89, 41.06, 49.63, 113.69, 119.39, 124.01, 132.26, 136.25, 161.84, 196.33. DEPT-135: up peaks: δ 27.18, 29.33, 31.89, 119.39, 124.01, 132.26. Down peaks: δ 41.06, 49.63. IR (KBr): 2955, 2896, 2871, 1659, 1624, 1371, 1360, 1201 cm<sup>-1</sup>.

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