



ORIGINAL ARTICLE

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



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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], InCl₃/ionic liquid [13], SmCl₃ [20], Fe⁺³ montmorillonite [44], amberlyst-15 [11], FeCl₃/[bmim][BF₄] [14], p-dodecylbenzenesulfonic acid [38], sulfamic acid [39], HClO₄·SiO₂ [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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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 F₂₅₄). 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 ¹H NMR (400 MHz), ¹³C NMR (100 MHz) and DEPT-135 spectra were recorded on BRUKER AVANCE 400 MHz instrument using CDCl₃ 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][BF₄] (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)

¹H NMR (400 MHz, CDCl₃): 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). ¹³C 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⁻¹. *m/z* (ESI): 351.0 [M + H⁺].

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

¹H NMR (400 MHz, CDCl₃): 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). ¹³C 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⁻¹.

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)

¹H NMR (400 MHz, CDCl₃): 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). ¹³C 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⁻¹.

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

¹H NMR (400 MHz, CDCl₃): 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). ¹³C 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⁻¹.

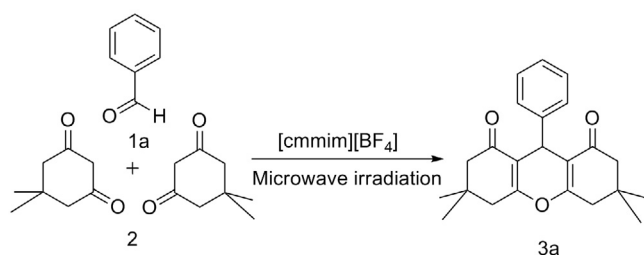
Table 1 Catalyst-free synthesis of 1,8-dioxo-octahydroxanthenes under microwave and thermal conditions in [cmmim][BF₄] using variously substituted aromatic aldehydes.

Compound	R	Time (min) ^a		Yield (%) ^b		M.P. (°C)	
		MW	Δ	MW	Δ	Found	Reported
3a	C ₆ H ₅	2	150	92	87	198–200	199–201 [13]
3b	4-O ₂ NC ₆ H ₄	2	120	95	83	222–224	222–224 [13]
3c	2-ClC ₆ H ₄	3	180	91	84	226–228	225–227 [13]
3d	3-ClC ₆ H ₄	2	150	88	78	184–186	183–185 [54]
3e	4-ClC ₆ H ₄	2	150	94	82	230–232	226–228 [54]
3f	2-O ₂ NC ₆ H ₄	3	150	84	76	258–260	258–262 [23]
3g	3-O ₂ NC ₆ H ₄	3	180	89	83	166–168	165–166 [54]
3h	4-H ₃ CC ₆ H ₄	3	120	85	78	216–218	215–216 [54]
3i	4-MeOC ₆ H ₄	4	180	87	81	240–242	242–243 [54]
3j	4-HOC ₆ H ₄	4	120	83	76	246–248	247–248 [54]
3k	4-HO,3-MeOC ₆ H ₃	4	180	91	85	226–228	225–227 [54]
3l	2-BrC ₆ H ₄	3	150	87	80	226–228	226–229 [54]
3m	3-BrC ₆ H ₄	3	180	93	84	192–194	190–192 [46]
3n	4-FC ₆ H ₄	2	120	94	88	224–226	226–227 [54]
3o	2,5-(MeO) ₂ C ₆ H ₃	4	210	96	89	172–174	174–175 [54]
3p	3,4-(MeO) ₂ C ₆ H ₃	4	180	86	84	174–176	175–176 [54]
3q	3,4,5-(MeO) ₃ C ₆ H ₂	4	180	83	78	186–188	187–189 [46]
3r	2-HOC ₆ H ₄	3	120	84	82	202–204	202–205 [5]
3s	2-Furyl	2	150	78	85	60–62	62–64 [46]
3t	2-Thienyl	2	150	89	81	164–166	164–165 [54]
3u	2-Pyridyl	3	180	91	86	204–206	203–205 [54]

MW = microwave irradiation (280 W), Δ = conventional heating (80 °C).

^a Reactions were run till the completion as indicated by TLC.

^b Yield after crystallization.

**Scheme 1** General reaction scheme for the synthesis of 1,8-dioxo-octahydroxanthene.

3. Results and discussion

Benzaldehyde (**1a**) and dimesone (**2**) were allowed to react in the presence of 200 mg [cmmim][BF₄] under microwave

irradiation (Scheme 1). To investigate the influence of microwave irradiation on a reaction mixture, we carried out a series of experiments with respect to power levels of the microwave. The obtained results at different power levels are recorded in Table 2. From the results, it became evident that the titled compounds (**3a–u**) can be synthesized with high purity and yield at power level 4 (280 W) and 5 (350 W) (Entry 4 and 5, Table 2). Scope and general applicability of the present methodology were demonstrated by subjecting a broad range of structurally diverse aromatic aldehydes, having electron withdrawing and electron donating groups as well as hetero aromatic aldehydes, with dimesone under the found optimum power level in the presence of 200 mg IL. The amount of ionic liquid does not appear to be critical as we successfully carried out a model reaction with 100 and 150 mg of ionic liquid. However, 200 mg IL helped to maintain the homogeneity of the medium when the solid aldehydes were used with dime-

Table 2 Optimization of reaction condition for the synthesis of 1,8-dioxo-octahydroxanthene under microwave set up.

Entry	Power levels in Watt	Reaction time (min) ^a	% Yield	Purity of product
1	140	5.5	48	Contained intermediate along with final product
2	210	4.0	61	
3	240	3.0	81	Contained intermediate in minor amount
4	280	2.0	92	Purity was fine
5	350	2.0	91	
6	420	2.0	79	Loss of yield
7	450	2.0	67	
8	490	2.0	53	Contained some degraded product
9	560	2.0	42	
10	700	2.0	40	

^a Reactions were run till the completion as indicated by TLC.

done. All the reactions were monitored by TLC and taken to completion. The time taken for the completion of each conversion, aldehyde employed, isolated yields and melting points of products are summarized in Table 1. It can be observed that all the aldehydes have reacted in short reaction times (2–4 min) under these conditions to afford xanthenes in very good to excellent isolated yields. The process was tolerated well by all the aldehydes irrespective of the nature of substituent present in them. It was found that at power level 1 (140 W), 2 (210 W) and 3 (240 W) the desired product 3a was formed in 48%, 61% and 81% yields, respectively (Entry 1, 2 and 3, Table 2). TLC of reaction mixture also indicated the presence of uncyclised intermediate. ^1H NMR spectrum of the intermediate is shown in Fig. 1 for the perusal. At high power level the reaction became sluggish and gradually shrinkage was observed in yield (Entry 6–10, Table 2). All the synthesized xanthenes were homogeneous on TLC and pure enough for the further practical purpose. However, all the compounds were crystallized from hot ethanol. All the synthesized compounds were characterized by melting point, ^1H NMR, ^{13}C NMR and DEPT-135 spectral techniques. Additional confirmation for the structures is also obtained by IR and mass spectrometric studies for some representative samples. All the data were in agreement with the literature cited earlier.

We also tried thermal reaction in an oil bath maintained at 80 °C by taking the same amount of the [cmmim][BF₄]. The results are summarized in Table 1. It is clear that the reactions under microwave irradiation led to relatively high yields in shorter reaction time.

The increase in rate and yield of the reaction under microwave irradiation appears to be due to efficient heating of reaction mass by “microwave dielectric heating”. This depends on the ability of a reaction mass to absorb microwave energy and convert it into heat by two main mechanisms: dipolar polarization effect and ionic conduction [31]. When the reaction mass is irradiated at microwave frequencies, the molecules which possess a dipole moment as has the ionic liquid, try to align in the applied field. As the oscillation occurs in applied field the dipoles try to realign themselves with alternating electric field. Consequently, the energy lost in the form of heat occurs through molecular friction and dielectric loss [36]. A considerable amount of energy is also generated through the ionic conduction. The reaction mass containing ions, as has the ionic liquid, the ions will move through the reaction mass under the influence of applied electric field. The faction of moving ions results in to outflow of energy due to collision. It can be concluded that due to their ionic nature, ionic liquids appear to be good reaction media in microwave assisted reactions. It therefore appeared synergy of ionic liquid-MW couple in speeding up the reported organic transformation with high yield.

IL also promotes the reactions due to its inherent Brønsted acidity. In our previous study [8], we demonstrated that hydrogen bonding is formed between carboxylic proton of IL and carbonyl oxygen of aldehyde during the reaction. In the same way hydrogen bonding may also be formed between carboxylic proton of IL and carbonyl oxygen of dimedone. The formation of hydrogen bond between IL and substrate may be responsi-

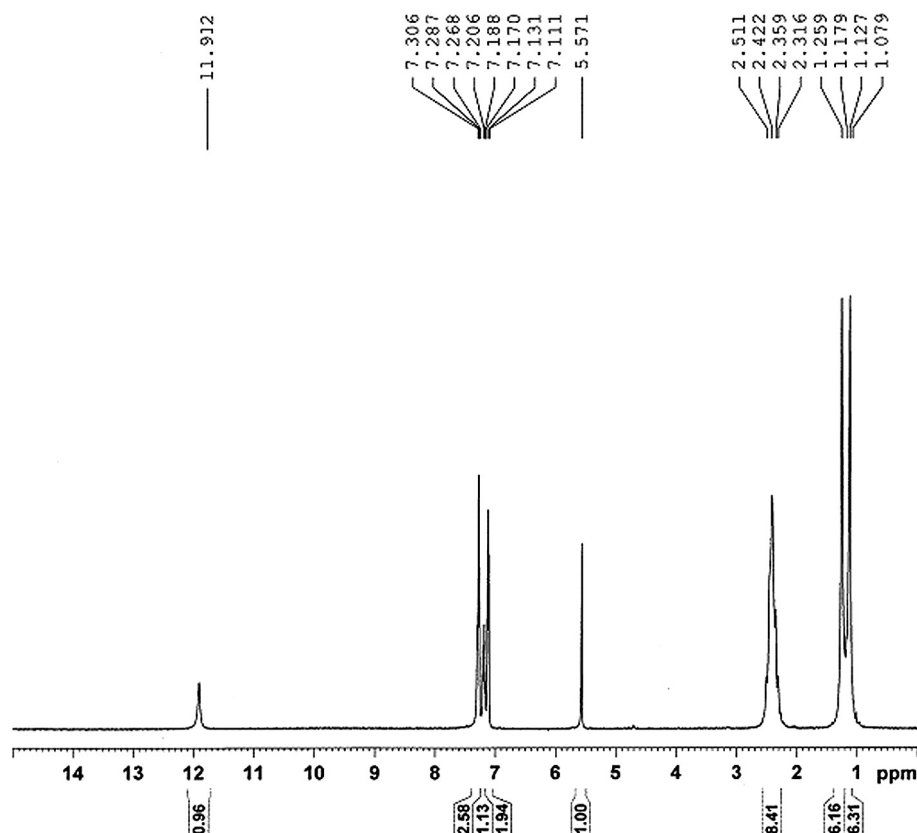
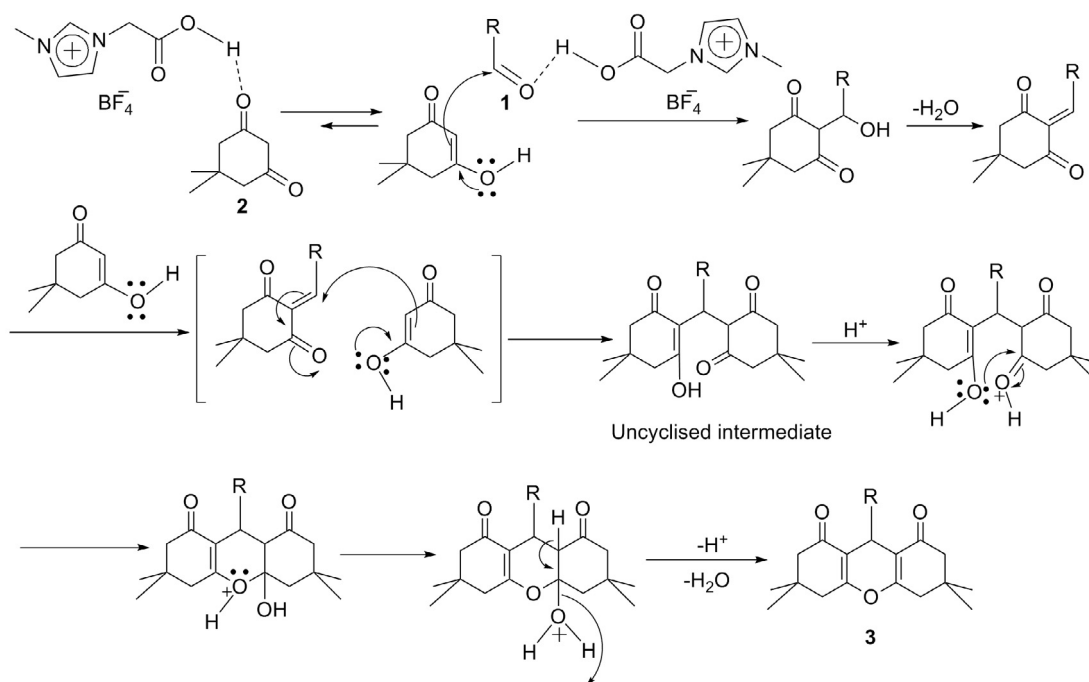


Figure 1 ^1H NMR spectrum of uncyclized intermediate.



Scheme 2 Plausible mechanistic pathway.

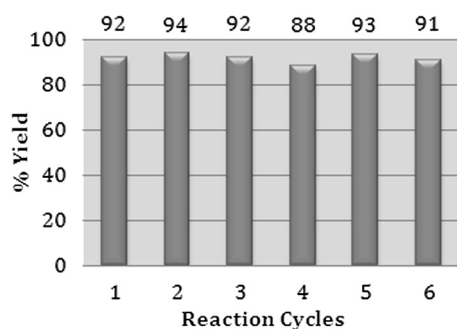


Figure 2 Recyclability of ionic liquid in the model reaction between benzaldehyde and dimedone.

ble for the activation. Based on this fact, we suggest the plausible mechanistic pathway for this reaction (Scheme 2).

To investigate recycling efficiency of ionic liquid, six successive cycles of the model reaction were run under the optimum reaction conditions using recycled IL from the previous run. To our privilege, the ionic liquid was found to be effective for at least six reaction cycles with prominent retention in its activity. The obtained results are plotted in Fig. 2.

4. Conclusion

In conclusion, the described protocol provided an improved practical alternative to access functionalized xanthenes in excellent yields. The beneficial features of the reaction, such as microwave activation, absence of added catalyst and reusability of ionic liquid; put it on advantage over conventional acid/base catalyzed reaction. Significant rate and yield enhancement are observed in microwave assisted transforma-

tions as compared to conventional protocols. The ionic liquid-MW synergistic couple gave a new methodology apt for the further development.

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