

Eco-friendly and one-pot synthesis of 1,8-dioxooctahydroxanthene derivatives catalyzed by task-specific Brønsted acidic ionic liquid

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ABSTRACT

Efficient and one-pot synthesis of 1,8-dioxo-octahydroxanthenes was described by Knoevenagel condensation, Michael addition and cyclodehydration of dimedone. This reaction was carried out through condensation of dimedone and various aromatic aldehydes in the presence of task-specific Brønsted acidic ionic liquid under solvent free conditions. The catalyst could be recycled five times without significant loss of its catalytic activity.

Keywords: Dimedone, Aromatic aldehydes, 1,8-Dioxooctahydroxanthenes, Ionic liquid, Catalyst.

1. Introduction

A large amount of information is available on ionic liquids (ILs) attracting the attention of researcher in scientific community in the last decade. Their applications in organic synthesis [1], reaction media and catalysis [2], biocatalysis [3], liquid-liquid separations [4], extraction [5], synthesis of nanomaterials [6], polymerization reactions [7] and their role in electrochemistry [8] have been reported. In the recent years, ILs was initially introduced as excellent alternative green reaction media. Because of they have very low vapor pressures, activity as a catalyst, thermal stability, non-flammability and non-corrosives properties [9].

Xanthene core and its derivatives are the important biologically active heterocycles. [10] These compounds were shown a wide range of activities such as; antibacterial [11], anti-inflammatory [12], antiviral properties [13] and photodynamic therapy for destroying the tumor cells [14]. Some other compounds have found applications in industries such as dying [15], laser technology [16], and pH sensitive fluorescent materials for visualization of biomolecules [17]. 1,8-dioxo-octahydroxanthenes have been synthesized by many procedures in the presence of a number of Brønsted and Lewis acidic catalysts such as; Fe(HSO₄)₃ [18], [BMIM][BF₄] [19], [ZrO(OTf)₂] [20], [Hbim][BF₄] [21], 1,1,3,3-N,N,N',N'-tetramethyl-

guanidinium-trifluoroacetate (TMGT) [22], [cmmim][BF₄] [23], SmCl₃ [24], [H-NMP] [HSO₄]/US [25] were reported. To the best of our knowledge, using the [H-NMP] [HSO₄] as Brønsted acidic ionic liquid catalyst for the synthesis of 1,8-dioxo-octahydroxanthenes under solvent free condition has not been previously reported.

Recently, the synthesis of heterocycles under solvent free conditions has attracted much attention in synthetic organic chemistry [26]. Though each of the above mentioned methods has demonstrated its own merits, several of these methods suffer from one or more drawbacks such as; long reaction times, use of hazardous solvents and excess of catalysts, harsh reaction conditions or low yields of the desired products. Hence, there is a scope for the development of an efficient, simple, economical and eco-friendly synthetic strategy for the preparation of 1,8-dioxo-octahydroxanthenes.

2. Experimental

2.1. Material

All commercially available reagents were used without further purification and purchased from the Merck Chemical Company in high purity.

2.2. Apparatus

IR spectra were obtained as KBr pellets on a Perkin-Elmer 781 spectrophotometer and on an Impact 400 Nicolet FTIR spectrophotometer. ¹H NMR and

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¹³CNMR were recorded in CDCl₃ solvents on a Bruker DRX-400 spectrometer with tetramethylsilane as internal reference. Melting points obtained with a Yanagimoto micro melting point apparatus are uncorrected.

2.3. General procedure for the synthesis of [H-NMP] [HSO₄]

1-Methyl-2-pyrrolidone (0.2 mol) was charged into a 250 mL three necked flask with a magnetic stirrer. Then equimolar concentrated sulfuric acid (98 wt %) was added drop wise slowly into the flask for 12 h. The mixture was washed by CH₂Cl₂ three times to remove non-ionic residues and dried by a rotary evaporator in vacuum to obtain the viscous clear [H-NMP] [HSO₄]. [H-NMP][HSO₄]: ¹HNMR (D₂O, 400 MHz): δ = 3.11-3.08 (t, 2H, CH₂), 2.41 (s, 3 H, CH₃), 2.06-2.04 (t, 2H, CH₂), 1.63-1.60 (quint, 2H, CH₂) ppm.

2.4. General procedure for the synthesis of 1,8-dioxooctahydroxanthenes

A mixture of aldehyde (1 mmol), dimedone (2 mmol, 0.28 g) and 2-pyrrolidonium hydrogen sulfate (20 mol %) were reacted in an oil bath at 110 °C for the appropriate times indicated in Table 2. Progress of the reaction was monitored by TLC (ethyl acetate/petroleum ether: 3/7). After completion of the reaction, the reaction mixture was cooled, and ice crush was added into the mixture. The ionic liquid was dissolved in water, and filtered for separation of the crude product. The solid product was purified by recrystallization from ethanol. Products were characterized by comparison of their physical and spectral data with those of authentic samples [27-31].

Selected spectral data

9-Phenyl-3,3,6,6-tetramethyl-1,2,3,4,5,6,7,8-octahydroxanthene-1,8-dione (3a):

White solid, m.p.= 202-203 °C, (m.p.= 203-204 °C, [27]), IR (KBr): $\bar{\nu}$ = 2956, 1666, 1460, 1363, 1198, 698 cm⁻¹. ¹HNMR (CDCl₃, 400 MHz): δ = 7.27-7.30 (t, 3H, J=7.6 Hz, ArH), 7.20-7.23 (t, 3H, J=7.2 Hz, ArH), 7.10-7.12 (t, 1H, J=7.2 Hz, ArH), 4.75 (s, 1H, CH); 2.47 (s, 4H, 2CH₂), 2.15-2.26 (dd, 4H, 2CH₂), 1.10 (s, 6H, 2CH₃), 0.99 (s, 6H, CH₃) ppm.

9-(4-Chlorophenyl)-3,3,6,6-tetramethyl-1,2,3,4,5,6,7,8-octahydroxanthene-1,8-dione (3c):

White solid, m.p.= 231-233 °C, (m.p.= 230-232 °C, [27]), IR (KBr): $\bar{\nu}$ = 2956, 1663, 1469, 1362, 1197, 1139, 846 cm⁻¹. ¹HNMR (CDCl₃, 400 MHz): δ = 7.27-7.52 (d, 2H, ArH), 4.84 (s, 1H, CH), 2.51 (s, 4H, 2CH₂), 2.15- 2.28 (dd, 4H, J=16.4 Hz, 2CH₂), 1.12 (s, 6H, 2CH₃), 0.99 (s, 6H, CH₃) ppm.

9-(2,4-Dichlorophenyl)-3,3,6,6-tetramethyl-1,2,3,4,5,6,7,8-octahydroxanthene-1,8-dione (3d):

White solid, m.p.= 250-252 °C, (m.p.= 248-250 °C, [27]), IR (KBr): $\bar{\nu}$ = 2943, 2930, 1717, 1657, 1587, 1383, 1169 cm⁻¹. ¹HNMR (CDCl₃, 400 MHz): δ = 7.37 (s, 1H, ArH), 7.25-7.27 (d, 1H, J=8.0 Hz, ArH), 7.14-7.16 (d, 1H, J=8.4, ArH), 4.95 (s, 1H, CH), 2.45 (s, 4H, 2CH₂), 2.14-2.25 (dd, 4H, J=16.0 Hz, 2CH₂), 1.11 (s, 6H, 2CH₃), 1.02 (s, 6H, CH₃) ppm.

9-(3-Nitrophenyl)-3,3,6,6-tetramethyl-1,2,3,4,5,6,7,8-octahydroxanthene-1,8-dione (3f):

White solid, m.p.= 171-172 °C, (m.p.= 168-170 °C, [27]), IR (KBr): $\bar{\nu}$ = 2960, 1664, 1527, 1357, 1198, 1138, 814 cm⁻¹. ¹HNMR (CDCl₃, 400 MHz): δ = 7.39-8.01 (m, 4H, ArH), 4.84 (s, 1H, CH), 2.51 (s, 4H, 2CH₂), 2.15-2.28 (dd, 4H, J=16.4 Hz, 2CH₂), 1.12 (s, 6H, 2CH₃), 0.99 (s, 6H, CH₃) ppm. ¹³CNMR (CDCl₃, 100 MHz): δ = 196.36, 169.03, 148.33, 146.31, 135.37, 128.80, 122.55, 121.66, 114.55, 50.64, 40.82, 32.25, 32.10, 29.21, 27.31 ppm.

9-(4-Nitrophenyl)-3,3,6,6-tetramethyl-1,2,3,4,5,6,7,8-octahydroxanthene-1,8-dione (3g):

Pale yellow solid, m.p.= 224-226 °C, (m.p.= 226-227 °C, [27]), IR (KBr): $\bar{\nu}$ = 2959, 1664, 1517, 1359, 1199, 865 cm⁻¹. ¹HNMR (CDCl₃, 400 MHz): δ = 8.08-8.10 (d, 2H, J=8.0 Hz, ArH), 7.46-7.48 (d, 2H, J=8.0 Hz, ArH), 4.48 (s, 1H, CH), 2.50 (s, 4H, 2CH₂), 2.14-2.28 (dd, 4H, J= 16.4 Hz, 2CH₂), 1.12 (s, 6H, 2CH₃), 0.99 (s, 6H, CH₃) ppm. ¹³CNMR (CDCl₃, 100 MHz): δ = 196.32, 169.32, 163.02, 151.58, 146.45, 129.38, 123.42, 114.49, 50.60, 40.82, 32.38, 32.24, 29.24, 27.27 ppm.

9-(4-Chloro-3-nitrophenyl)-3,3,6,6-tetramethyl-1,2,3,4,5,6,7,8-octahydroxanthene-1,8-dione (3h):

White solid, m.p.= 251-253 °C, IR (KBr): $\bar{\nu}$ = 2961, 1665, 1534, 1361, 1198, 828 cm⁻¹. ¹HNMR (CDCl₃, 400 MHz): δ = 7.67 (s, 1H, ArH), 7.63-7.66 (d, 1H, J=8.4 Hz, ArH); 7.40-7.42 (d, 1H, J= 8.4 Hz, ArH), 4.77 (s, 1H, CH); 2.50 (s, 4H, 2CH₂), 2.17- 2.28 (dd, 4H, J= 16.4 Hz, 2CH₂), 1.12 (s, 6H, 2CH₃), 1.02 (s, 6H, CH₃) ppm.

9-(3-Methoxy)-3,3,6,6-tetramethyl-1,2,3,4,5,6,7,8-octahydroxanthene-1,8-dione (3l):

White solid, m.p.= 181-182 °C, (m.p.= 179-181 °C, [29]), IR (KBr): $\bar{\nu}$ = 2959, 1662, 1485, 1363, 1274, 1201, 1048, 763 cm⁻¹. ¹HNMR (CDCl₃, 400 MHz): δ = 7.15-7.18 (t, 1H, J=8.0 Hz, ArH), 6.86-6.89 (d, 1H, ArH), 6.64-6.67 (d, 1H, ArH), 4.74 (s, 1H, CH), 2.46 (s, 4H, 2CH₂), 2.16-2.26 (dd, 4H, J= 16.4 Hz, 2CH₂), 1.10 (s, 6H, 2CH₃), 1.01 (s, 6H, CH₃) ppm.

9-(4-Methoxy)-3,3,6,6-tetramethyl-1,2,3,4,5,6,7,8-octahydroxanthene-1,8-dione (**3m**)

White solid, m.p.= 245-247 °C, (m.p.= 243-245 °C, [29]), IR (KBr): $\bar{\nu}$ = 2957, 1667, 1510, 1461, 1359, 1260, 1194, 1137, 1032, 568 cm^{-1} . $^1\text{H NMR}$ (CDCl_3 , 400 MHz): δ = 7.19-7.21 (d, 2H, J = 8.4 Hz, ArH), 6.74-6.79 (d, 2H, ArH), 6.64-6.67 (d, 1H, ArH), 4.70 (s, 1H, CH), 3.73 (s, 3H, OCH_3), 2.46 (s, 4H, 2CH_2), 2.14-2.25 (dd, 4H, J =16.4 Hz, 2CH_2), 1.10 (s, 6H, 2CH_3), 0.99 (s, 6H, CH_3) ppm. $^{13}\text{CNMR}$ (CDCl_3 , 100 MHz): δ = 196.47, 162.08, 157.96, 136.51, 131.99, 129.31, 110.579, 114.33, 113.46, 55.10, 50.78, 40.86, 32.19, 30.97, 29.28, 27.34, 23.43 ppm.

3. Results and Discussion

In this study, we report the synthesis of 1,8-dioxo-octahydroxanthene derivatives from corresponding aldehydes and dimedone using [H-NMP][HSO_4] as an efficient catalyst. The corresponding products were obtained in excellent yields and short reaction times under green and solvent free conditions.

Initially, in order to optimize the reaction conditions, it was considered to represent the reaction of dimedone and 4-nitrobenzaldehyde. The trial was performed using various amount of catalytic [H-NMP][HSO_4] and 2:1 ratio of the substrates at 110 °C (Scheme 1).

The corresponding results are indicated in Table 1. The best result was obtained using 20 mol % (0.037 g) of catalyst (Table 1, entry 5), while the higher amount of catalyst did not have significant effect on the reaction time and yield (Table 1, entry 6). Also any product wasn't found in the absence of catalyst (Table 1, entry 1).

To generalize the optimum conditions, different derivatives of 1,8-dioxo-octahydroxanthene were

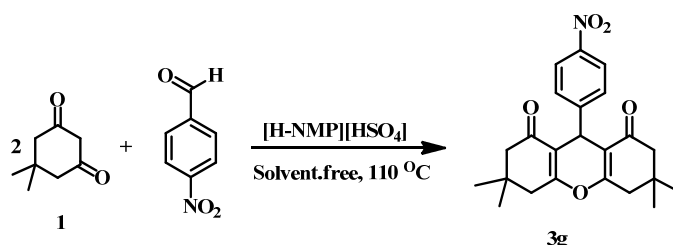
prepared from the reaction mixture of dimedone and appropriate aldehyde in the presence of [H-NMP][HSO_4] under solvent-free conditions. In all cases, the corresponding xanthenediones were obtained in high to excellent yields. The final results are summarized in Table 2. The structures of products were confirmed by spectroscopic and physical data such as; IR, $^1\text{H NMR}$, $^{13}\text{CNMR}$.

From the Table 2, the best activities of aromatic aldehydes were indicated with electron-withdrawing groups (such as $-\text{NO}_2$) at para or meta positions gave good results. There is more steric hindrance for the ortho substituted aldehydes ($-\text{OH}$, $-\text{Cl}$, $-\text{NO}_2$) decreasing both the reaction rate and the yield of the product.

To examine reusability of the catalyst, after the complete separation of solid products (**3g**) with water, the water containing Brønsted acidic ionic liquids (BAILs is soluble in water) was evaporated under vacuum and catalyst was recycled and reused for five times without any remarkable decrease in catalytic activity; the yields ranged from 94% to 86%.

3.1. Basic characterizations of Brønsted-acidic ILs

The prepared Brønsted-acidic ILs, [H-NMP][HSO_4] are colorless, light yellow liquid at room temperature and was characterized by $^1\text{H NMR}$ spectroscopy. In the $^1\text{H NMR}$ spectra, the signal around δ =3.11-3.08 ppm is assigned to the protons of the CH_2 group near the nitrogen, the signal around δ =2.06-2.04 ppm is assigned to the protons of the CH_2 group near the carbonyl group and the signal around δ =2.41 ppm is assigned to the protons of the methyl group, this signal confirm that the ionic liquid was obtained. Also, the acidity level of the ionic liquid was calculated by Hammett method in accordance to the literature [2] that the obtained amount was equal to 1.66.



Scheme 1. Synthesis of 1,8-dioxo-octahydroxanthenes under solvent free conditions.

Table 1. The synthesis of **3g** under different amount of [H-NMP][HSO_4].

Entry	Catalyst (mol%)	Time (min)	Yield (%) ^a
1	0	50	-
2	5	15	40
3	10	7	70
4	15	7	83
5	20	5	94
6	30	5	94

^aThe yields refer to the isolated pure products.

Table 2. Synthesis of 1,8-dioxo-octahydroxanthenes catalyzed by [H-NMP][HSO₄].^a

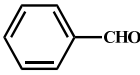
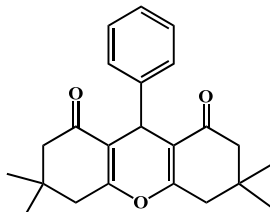
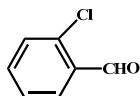
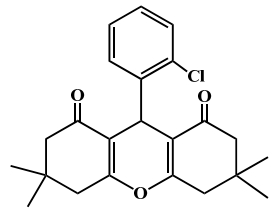
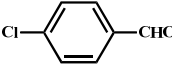
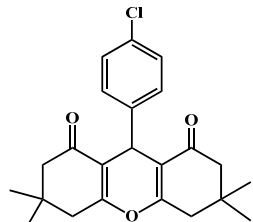
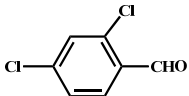
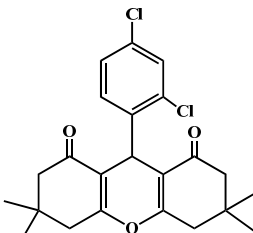
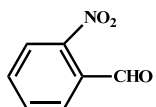
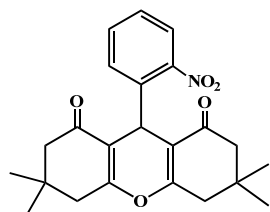
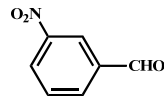
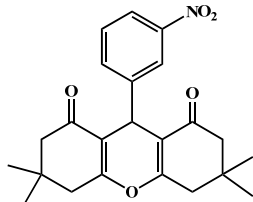
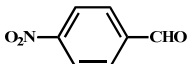
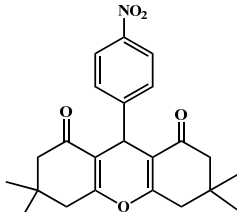
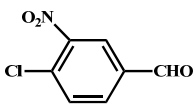
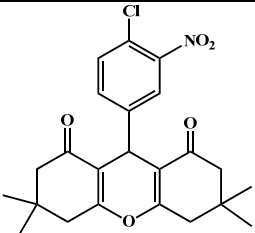
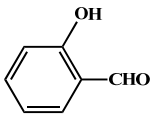
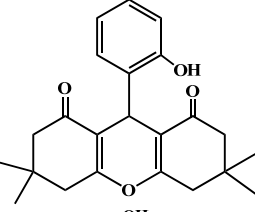
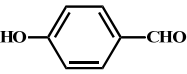
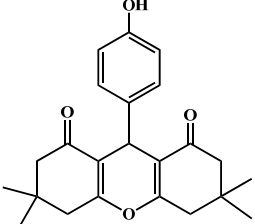
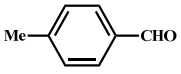
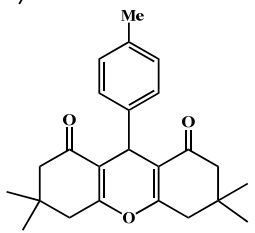
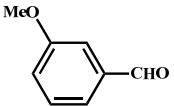
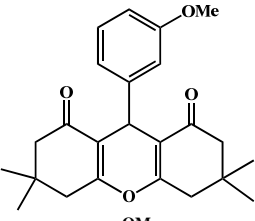
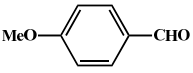
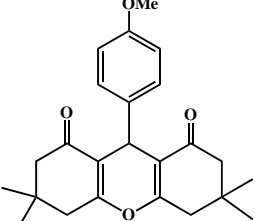
Entry	R	Product	Time (min)	Yield (%) ^a
1			10	93
2			15	82
3			7	94
4			10	85
5			11	87
6			6	92
7			5	94

Table 2. (Continued)

8			5	95
9			17	75
10			13	79
11			15	85
12			10	80
13			8	77

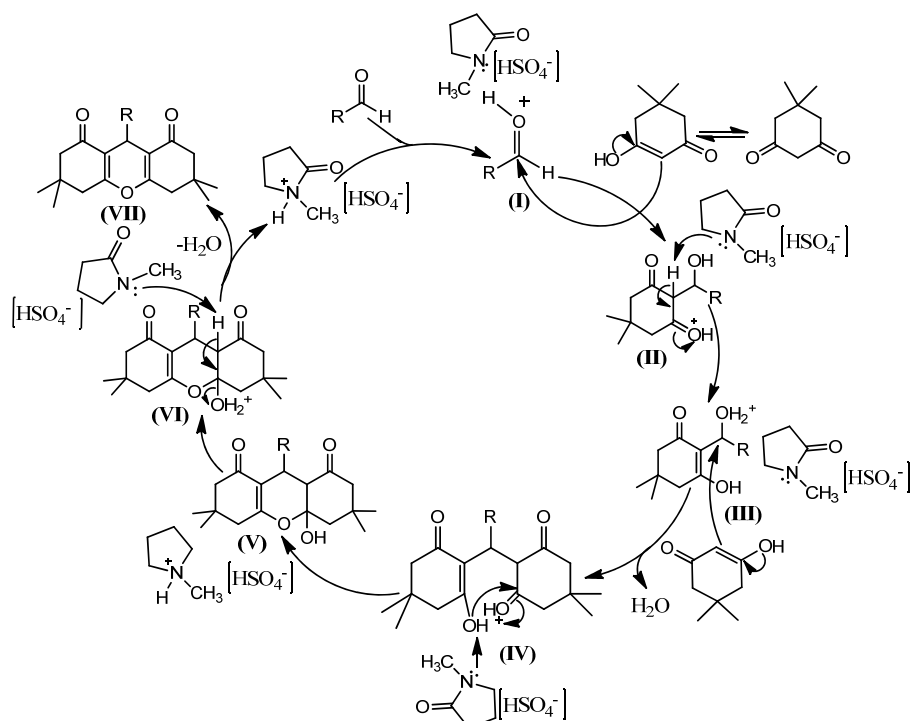
^aReaction condition: aldehyde (1 mmol), dimedone (2 mmol), [H-NMP][HSO₄] (20 mol%).

^bYields based on isolated pure product.

3.2. The proposed reaction mechanism

The proposed reaction mechanism for the [H-NMP][HSO₄] catalyzed synthesis of 1,8-dioxo-octahydroxanthenes using dimedone and aldehyde is shown in Scheme 2. The aldehyde is first activated by protonation with [H-NMP][HSO₄] to give (I). Nucleophilic attack of dimedone on (I) affords (II),

which in turn was activated by [H-NMP][HSO₄] to afford (III). Nucleophilic attack of second molecule of dimedone to (III), gives the species (IV) and (V), respectively which is subsequently converted to the (VI). The (VI) can easily liberate H₂O molecule to form the 1,8-dioxo-octahydroxanthenes (VII) and release [H-NMP][HSO₄] for the next catalytic cycle.



Scheme 2. Proposed reaction mechanism.

4. Conclusions

In conclusions, an efficient procedure was reported for the synthesis of 1,8-dioxo-octahydroxanthenes using of dimedone and aldehyde in the presence of $[H-NMP][HSO_4]$ under solvent-free conditions. The $[H-NMP][HSO_4]$ was reused five runs without efficient loss of its activity for the preparation of 1,8-dioxo-octahydroxanthenes. In addition, high yields of the products non toxicity of the catalyst and short reaction time are other worthwhile advantages of the present work.

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