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A facile one-pot ultrasound assisted synthesis of 1,8-dioxo-octahydroxanthene derivatives catalyzed by Brønsted acidic ionic liquid (BAIL) under green conditions

Hossein Naeimi *, Zahra Sadat Nazifi

Department of Organic Chemistry, Faculty of Chemistry, University of Kashan, Kashan 87317, Islamic Republic of Iran

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ABSTRACT

A simple and efficient one-pot procedure for the synthesis of 1,8-dioxo-octahydroxanthene derivatives in water under ultrasound irradiation is described. These heterocycles were prepared by condensation of dimedone with various aromatic aldehydes in the presence of Brønsted acidic ionic liquids as a convenient, cheap, readily synthesized and eco-friendly catalyst. This procedure has a lot of advantages such as: excellent yields, simplicity of the workup, low cost, short reaction times and green conditions. Ionic liquids could be recycled several times without significant loss of activity and high purity.

1. Introduction

Ultrasonic-assisted organic synthesis (UAOS) as an eco-friendly synthetic approach is a powerful technique used more and more to accelerate organic reactions [1–5]. Ultrasonic irradiation generates the cavitation phenomenon, nucleation, growth and implosive collapse [6]. UAOS can be extremely convenient, and it is applicable to a broad range of practical synthesis. Notable features of the ultrasound approach are: increased reaction rates, formation of purer products in high yields, facile manipulation. In addition, a processing aid in terms of energy conservation and waste minimization can be considered which compared to traditional methods. This method is more convenient because it takes green chemistry concepts into account [7,8]. However, the use of ultrasonic irradiation in the heterocyclic system is not fully explored [9]. The advantages of ultrasound procedures, such as: good yields, short reaction times and mild reaction conditions, are well documented [10].

Xanthenes and benzoxanthenes are active oxygen heterocycles which are important drug intermediates. They are known as, antibacterial activities [11], anti-inflammatory [12], and antiviral properties [13]. Furthermore, some of the xanthenes based heterocycles have been proved to show application as photodynamic therapy for destroying the tumor cells [14]. The other useful applications of these heterocycles are as dyes [15], laser technology [16], and in fluorescent materials for visualization of biomolecules [17].

However, several methods have been reported for the efficient and facile synthesis of 1,8-dioxo-octahydroxanthene scaffolds [18,19]. Any of these methods, however, suffer from one or more drawbacks such as prolonged reaction times, unsatisfactory yields, use of hazardous solvents and excessive use of reagents and catalysts. Hence, there is a scope for the development of an efficient, economical and green synthetic strategy for the preparation of these important heterocyclic molecules.

Considering the above issues, this study is an attempt to demonstrate the present report of the synthesis of 1,8-dioxo-octahydroxanthenes under ultrasonic irradiation in water. The reported route is an efficient, general and eco-friendly method for condensation of aromatic aldehydes and dimedone in the presence of $[H\text{-}NMP]^+[HSO_4]^-$ as a reusable catalyst to afford the 1,8-dioxo-octahydroxanthene derivatives as corresponding products with excellent yields and short reaction times. The products were identified and confirmed by physical and spectroscopic data such as: IR, ^1H NMR, and ^{13}C NMR.

2. Experimental

2.1. Materials

All commercially available reagents such as: dimedone and the aldehydes (benzaldehyde, 2-chloro-benzaldehyde, 4-chloro-benzaldehyde, 2,4-dichlorobenzaldehyde, 2-nitrobenzaldehyde,

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* Corresponding author. Tel.: +98 361 5912388; fax: +98 361 5912397.
E-mail address: naeimi@kashanu.ac.ir (H. Naeimi).

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4-nitrobenzaldehyde, 3-chloro-4-nitrobenzaldehyde, 2-hydroxybenzaldehyde, 4-hydroxybenzaldehyde, 3-methoxybenzaldehyde, 4-methoxybenzaldehyde and 4-methylbenzaldehyde) were purchased from the Merck Chemical Company in high purity. The aldehydes (purity $\geq$ 98%) and dimedone (purity = 99.5%) were used without any further purification. The used solvents were purified by standard procedure including: ethanol (99.5%) and dichloromethane (99.5%).

2.2. Apparatus

IR spectra were obtained as KBr pellets on a Perkin-Elmer 781 spectrophotometer and on an Impact 400 Nicolet FTIR spectrophotometer. ^{1}H NMR and ^{13}C NMR were recorded in $CDCl_3$ solvents on a Bruker DRX-400 spectrometer with tetramethylsilane as internal reference. Melting points were obtained with a Yanagimoto micro melting point apparatus and are uncorrected. The Bandelin ultrasonic HD 3200 with probe model KE 76, 6 mm diameter, was used to produce ultrasonic irradiation and homogenizing the reaction mixture. Piezoelectric crystal of this kind of probe normally works in the range of 700 kHz, but using through some proper clamps the output frequency of piezoelectric crystal have controlled and reduced to 20 kHz. Therefore, the induced frequency of probe into the reaction mixture is equal to 20 kHz. It means that the Tip frequency under all amount of power is constant. The purity determination of the substrates and reaction monitoring were accomplished by TLC on silica-gel polygram SILG/UV 254 plates (from Merck Company).

2.3. Power measurement by calorimetric method

Cavitational energy was assessed by applying ultrasonication calorimetrically with water. The piezoelectric transducer was connected to the frequency generator, HD-3200 (with frequency; 20 kHz). The probe (KE-76) was dipped in a jacketed cylindrical vessel. For calorimetric measurement, the jacket was emptied and connected to vacuum to minimize heat losses. In this method, the rate of temperature increasing due to the conversion of ultrasound energy into heat and the ultrasonic power dissipated into the solution was measured with a standard calorimetric by using the following relation. $P(W) = mc\triangle T/t$; where m is the mass of water (g), c is the specific heat capacity of water (4.18 Jg^{-1} k^{-1}), $\triangle T$ is the difference in temperature (K) and t is the sonication time (s) (Table 2).

2.4. General procedure for the synthesis of [H-NMP]$^{+}$[HSO$_4$]$^{-}$

[H-NMP]$^{+}$[HSO$_4$]$^{-}$ was achieved by mixing *N*-methyl-2-pyrrolidone (9.9 g, 0.1 mol) was charged into a 250 mL three necked flask with magnetic stirrer. Then sulfuric acid (9.6 g, 0.1 mol) was added drop wise slowly into the flask at 0–5 °C and stirring for 4 h at room temperature. The reaction mixture was washed with ethyl acetate (3 × 10 mL) and dried at 80 °C in vacuum. The ionic liquid was prepared in quantitative yield [20] and characterized by ^{1}H NMR data before using in the reaction and after the recovery as follow: ^{1}H NMR ([D_6] DMSO): δ = 3.28–3.31 (t, 2H, J = 7.2 Hz), 2.75 (s, 3H), 2.15–2.19 (t, 2H, J = 8.1 Hz), 1.88–1.96 ppm (q, 2H, J = 7.60 Hz).

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

2-Pyrolidonium hydrogen sulfate (20 mol%) was added to a mixture of an aromatic aldehydes (1 mmol), dimedone (2 mmol) and water (20 ml); then ultrasonic probe was directly immersed in the reactor. The progress of the reactions was monitored by TLC (ethyl acetate/petroleum ether 3/7). After completion of the reaction, the reaction mixture was cooled and the solid was collected by filtration. The product was purified by recrystallization from ethanol. The resulted products were characterized and identified by comparing their physical and spectral data with those of authentic samples [21–24]. The ionic liquid in water could be recovered easily by evaporation at 80 °C in the vacuum. The product yields (%) were calculated as: amount of experimental xanthene (g)/amount of theoretical xanthene (g) × 100.

*2.5.1. 9-Phenyl-3,3,6,6-tetramethyl-1,2,3,4,5,6,7,8-octahydroxanthene-1,8-dione (**4a**)*

White solid, m.p. = 202–203 °C, (m.p. = 203–204 °C [21]), IR (KBr)/υ(cm^{-1}): 2956, 1666, 1460, 1363, 1198, 698; ^{1}H NMR ($CDCl_3$, 400 MHz)/δ ppm: 7.27–7.30 (t, J = 7.60 Hz, 3H, ArH), 7.20–7.23 (t, J = 7.20 Hz, 3H, ArH), 7.10–7.12 (t, J = 7.20 Hz, 1H, ArH), 4.75 (s, 1H, CH); 2.47 (s, 4H, 2CH_2), 2.15–2.26 (q, 4H, 2CH_2), 1.10 (s, 6H, 2CH_3), 0.99 (s, 6H, CH_3).

*2.5.2. 9-(2-Chlorophenyl)-3,3,6,6-tetramethyl-1,2,3,4,5,6,7,8-octahydroxanthene-1,8-dione (**4b**)*

White solid, m.p. = 223–225 °C, (m.p. = 226–228 °C [19]), IR (KBr)/υ(cm^{-1}): 3390, 3064, 2962, 2929, 1720, 1665, 1595, 1380, 1165, 855, 690, 650; ^{1}H NMR ($CDCl_3$, 400 MHz)/δ ppm:1.05 (s, 6H, CH_3), 1.15 (s, 6H, CH_3), 2.22–2.51 (m, 8H, CH_2), 5.60 (s, 1H, CH), 7.11–7.39 (m, 4H, ArH).

*2.5.3. 9-(4-Chlorophenyl)-3,3,6,6-tetramethyl-1,2,3,4,5,6,7,8-octahydroxanthene-1,8-dione (**4c**)*

White solid, m.p. = 231–233 °C, (m.p. = 230–232 °C [19]), IR (KBr)/υ(cm^{-1}): 2956, 1663, 1469, 1362, 1197, 1139, 846; ^{1}H NMR ($CDCl_3$, 400 MHz)/δ ppm: 7.27–7.52 (d, 2H, ArH), 4.84 (s, 1H, CH), 2.51 (s, 4H, 2CH_2), 2.15–2.28 (q, J = 16.40 Hz, 4H, 2CH_2), 1.12 (s, 6H, 2CH_3), 0.99 (s, 6H, CH_3).

*2.5.4. 9-(2,4-Dichlorophenyl)-3,3,6,6-tetramethyl-1,2,3,4,5,6,7,8-octahydroxanthene-1,8-dione (**4d**)*

White solid, m.p. = 250–252 °C, (m.p. = 248–250 °C [22]), IR (KBr)/υ(cm^{-1}): 2943, 2930, 1717, 1657, 1587, 1383, 1169; ^{1}H NMR ($CDCl_3$, 400 MHz)/δ ppm: 7.37 (s, 1H, ArH), 7.25–7.27 (d, J = 8.00 Hz, 1H, ArH), 7.14–7.16 (d, J = 8.4, 1H, ArH), 4.95 (s, 1H, CH), 2.45 (s, 4H, 2CH_2), 2.14–2.25 (q, J = 16.00 Hz, 4H, 2CH_2), 1.11 (s, 6H, 2CH_3), 1.02 (s, 6H, CH_3).

*2.5.5. 9-(2-Nitrophenyl)-3,3,6,6-tetramethyl-1,2,3,4,5,6,7,8-octahydroxanthene-1,8-dione (**4e**)*

White solid, m.p. = 263–264 °C, (m.p. = 258–262 °C [25]), IR (KBr)/υ(cm^{-1}): 3091, 2932, 2922, 1705, 1645, 1556, 1365; ^{1}H NMR ($CDCl_3$, 400 MHz)/δ ppm: 5.50 (1H, s, CH); 7.27–7.82 (m, 4H, ArH), 2.52 (4H, s, 2 CH_2), 2.06–2.25 (q, 4H, J = 16.2 Hz, 2 CH_2), 1.15 (6H, s, 2 CH_3), 1.10 (6H, s, 2 CH_3).

*2.5.6. 9-(3-Nitrophenyl)-3,3,6,6-tetramethyl-1,2,3,4,5,6,7,8-octahydroxanthene-1,8-dione (**4f**)*

White solid, m.p. = 171–172 °C, (m.p. = 168–170 °C [21]), IR (KBr)/υ(cm^{-1}): 2960, 1664, 1527, 1357, 1198, 1138, 814; ^{1}H NMR ($CDCl_3$, 400 MHz)/δ ppm: 7.39–8.01 (m, 4H, ArH), 4.84 (s, 1H, CH), 2.51 (s, 4H, 2CH_2), 2.15–2.28 (q, J = 16.40 Hz, 4H, 2CH_2), 1.12 (s, 6H, 2CH_3), 0.99 (s, 6H, CH_3); ^{13}C NMR/($CDCl_3$, 100 MHz)/δ ppm: 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.

*2.5.7. 9-(4-Nitrophenyl)-3,3,6,6-tetramethyl-1,2,3,4,5,6,7,8-octahydroxanthene-1,8-dione (**4g**)*

Pale yellow solid, m.p. = 224–226 °C, (m.p. = 226–227 °C [22]), IR (KBr)/υ(cm^{-1}): 2959, 1664, 1517, 1359, 1199, 865; ^{1}H NMR