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Aqueous citric acid as "green" reaction media for the synthesis of octahydroxanthenes

Ácido cítrico acuoso como medio de reacción "verde" en la síntesis de octahidroxantenos

Ácido cítrico aquoso como meio de reação "verde" para a síntese de octaidroxantenos

Abstract

A simple, convenient and environmentally friendly one-pot procedure for the synthesis of 1,8-dioxo-octahydroxanthenes by the reaction of dimedone and aromatic aldehydes in aqueous citric acid is described. In this green synthetic protocol promoted by the reaction media, the use of any other catalysts and hazardous organic solvents are avoided, making the work up procedure greener and easier. The isolation of the products, obtained in good yields, is readily performed by filtration and crystallization from ethanol when required and the aqueous acidic media can be easily recycled and reused several times without significant loss of catalytic activity.

Resumen

En esta contribución se describe un procedimiento one-pot simple, conveniente y medioambientalmente amigable para la síntesis de 1,8-dioxo-octahidroxantenos mediante la reacción de dimedona y aldehídos aromáticos en ácido cítrico acuoso. En este protocolo de síntesis "verde", promovido por el medio de reacción, se elimina el uso de otros catalizadores y solventes orgánicos peligrosos, haciendo el tratamiento final de la reacción más fácil y "verde". El aislamiento de los productos, obtenidos con buenos rendimientos, se lleva a cabo mediante filtración y recristalización en etanol cuando es necesario y el medio acuoso ácido puede ser reciclado y reutilizado varias veces sin pérdida significativa de la actividad catalítica.

Resumo

É descrito um procedimento simples, conveniente, e ambientalmente amigável para a síntese de 1,8-dioxo-octaidroxantenos pela reação de dimedona e aldeídos aromáticos em ácido cítrico aquoso em uma só etapa. Em este protocolo de síntese verde, promovido pelo meio de reação, a utilização de algum outro catalisador e solvente orgânico perigoso é evitada, fazendo o procedimento mais fácil e mais "verde". O isolamento dos produtos, obtidos em grande rendimento, é feito por meio de filtração e cristalização a partir de etanol quando é requerido e o meio aquoso ácido pode ser facilmente recuperado e reutilizado várias vezes sem perder significativamente sua atividade catalítica.

Keywords: Citric acid, dimedone, green synthesis, octahydroxanthenes.

Palabras clave: ácido cítrico, dimedona, síntesis verde, octahidroxantenos.

Palavras-chave: ácido cítrico, dimedona, síntese verde, octaidroxantenos.

Introduction

Xanthenes are a very interesting class of oxygen-containing heterocycles with a large number of naturally occurring and synthetic derivatives (1-6). A variety of xanthenes and derivatives based on this nucleus exhibit potential applications in the field of medicinal chemistry and materials science as anti-viral (7), anti-bacterial (8), and anti-inflammatory agents (9), as fluorescent materials (10), in photodynamic therapy (11, 12), dyes (13), luminescent sensors (14), and laser technologies (15).

Recently enormous efforts has been made in expanding the scope of the synthesis of 1,8-dioxo-octahydroxanthenes, being the condensation of the appropriate aldehyde and dimedone or 1,3-ciclohexanedione

the commonly performed method for obtaining these heterocyclic compounds. Several synthetic procedures using alternative solvents (16), solvent-free conditions with different catalysts (17-23), ionic liquids (24-27), homogeneous (28-30), and heterogeneous (31-38) catalysts, as well as microwave (39) and ultrasound-assisted (40-44) synthesis have been reported. Although many of the reported methods are effective, some of them require a previous preparation of the catalyst or involve the use of expensive reagents, toxic solvents, tedious work-up, low yields, long reaction times and harsh reaction conditions.

Citric acid is a low-cost, non-volatile, stable, readily available weak organic acid produced by several microbial fermentation processes, substrates and microorganisms (45). It is a natural preservative and anti-oxidant available in vegetables and fruits, most notably in citrus fruits

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where it constitutes around 8% of the dry weight. In food chemistry, this acid has been used in the production of candies, fruit juice, ice cream, marmalade, jelly, also to supress the browning process in fruits and as a synergetic compound for antioxidants (46). Citric acid forms a wide range of salts and complexes with metals like copper, iron, manganese, magnesium and calcium, being this the reason for its use as a sequestering agent in industrial processes and as an anticoagulant blood preservative. In fats and oils citric acid acts as antioxidant reducing the metal-catalysed oxidation by chelating traces of metals such as iron. Other pharmaceutical and industrial applications include antioxidant (vitamins and cosmetics), salt formation (iron preparations), sequestering (cleaning metals, polimerizations) and buffering (detergents and photography) (47). In the field of organic synthesis, this acid has been used as efficient promoter of the Beckmann rearrangement (48, 49) and for the synthesis of dihydropyrimidin-(2H)-ones (50), 2,3-dihydroquinazolin-4(1H)-ones (51) and quinolones (52).

Recently, we described the simultaneous synthesis and photophysical characterization of decahydroacridine-1,8-diones and 1,8-dioxo-octahydroxanthenes, where a competitive one-pot reaction yielding both products was achieved under refluxing acetic acid (53). In connection with our ongoing studies on the photophysical properties of chromophoric compounds (54) and motivated for the aforementioned results, we decide to develop a green synthetic methodology, in which a selected group of xanthene derivatives could be obtained avoiding harsh conditions.

In the present work, we report an efficient, convenient and environmentally friendly one pot procedure for the synthesis of 1,8-dioxo-octahydroxanthenes by the use of aqueous citric acid as a green reaction media which promoted the reaction.

Materials and methods

General

All chemicals were purchased from Merck, Aldrich and Fluka Chemical companies and used without further purification. Absolute ethanol and glacial acetic acid were used as solvent for some reactions. Solutions of organic acids were prepared in distilled water. Melting points were determined using open glass capillaries on a Stuart SMP10 melting point apparatus and are uncorrected. The infrared spectra (IR) were recorded using a Shimadzu IR prestige 21 FT-IR™ instrument with potassium bromide pellets. The ^{1}H-NMR (400 MHz) and ^{13}C-NMR (100 MHz) spectra were measured in CDCl$_3$ using a Bruker Avance 400™ spectrometer and chemical shifts are expressed in δ ppm using TMS as internal standard. HPLC-MS analyses was performed in a Shimadzu LCMS-IT-TOF™ equipment (Shimadzu, Kyoto, Japan) equipped with an electrospray ionisation (ESI) probe. The electrospray ionization (ESI) probe was operated simultaneously in the positive and negative mode: CDL, 250 °C; block at 200 °C; flow gas (N$_2$) at 1,5 L/min; CDL voltage, 1,8 kV; ion accumulation, 20 ms; and scan range m/z, 100–2000 u. The energy of the collision gas (Argon) was fixed at 50%. LCMS Solution software was used for data collection and analysis. All reactions were conducted in a 5 mL capped flask equipped with a magnetic stirring.

General synthetic methodology

A mixture of the selected aldehyde (0.5 mmol) and 5,5-dimethylcyclohexane-1,3-dione (1,0 mmol) in 0.3 M citric acid (2.0 mL) was stirred at 90 °C for the appropriate time. After reaction completion (TLC), the formed solid was filtered, washed with water and recrystallized from ethanol when required.

Selected spectral data

3,3,6,6-Tetramethyl-9-phenyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8-(2H)-dione 3a
White solid. Yield 85% (148 mg, 0.42 mmol), mp 204–206 °C. FT-IR (KBr pellet, cm^{-1}): 2956, 2854, 1662, 1491. ^{1}H NMR (400MHz, CDCl$_3$) δ (ppm): 7.30 (dd, 2H, ^3J= 7.0 Hz, ^4J= 1.5 Hz), 7.23 (t, 2H, ^3J= 7.2 Hz), 7.12 (t, 1H, ^3J= 7.3 Hz), 4.77 (s, 1H), 2.48 (s, 4H), 2.25 (d, 2H, ^2J= 16.3 Hz), 2.18 (d, 2H, ^2J= 16.3 Hz), 1.12 (s, 6H), 1.01 (s, 6H). ^{13}C NMR (100 MHz, CDCl$_3$) δ (ppm): 196.3, 162.2, 144.1, 128.3, 128.0, 126.3, 115.6, 50.7, 40.8, 32.2, 31.8, 29.2, 27.3. HRMS (ESI-TOF) calcd. for C$_{23}$H$_{27}$O$_3$: [M+H]$^+$: 351.1882; found: 351.1882.

9-(4-(Dimethylamino)phenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione 3c
White solid. Yield 80% (157.4 mg, 0.40 mmol), mp 219-221 °C. FT-IR (KBr pellet, cm^{-1}): 2952, 2875, 1659, 1572. ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm): 7.14 (d, 2H, ^3J= 8.8 Hz), 6.60 (d, 2H, ^3J= 8.7 Hz), 4.66 (s, 1H), 2.87 (s, 6H), 2.45 (s, 4H), 2.23 (d, 2H, ^2J= 16.3 Hz), 2.17 (d, 2H ^2J= 16.3 Hz), 1.09 (s, 6H), 1.00 (s, 6H). ^{13}C NMR (100 MHz, CDCl$_3$) δ (ppm): 196.6, 161.8, 128.9, 116.0, 112.4, 50.7, 40.8, 40.7, 32.2, 30.6, 29.2, 27.4. HRMS (ESI-TOF) calcd. for C$_{25}$H$_{32}$NO$_3$: [M+H]$^+$: 394.2304; found: 394.2333.

9-(4-Chlorophenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione 3g
White solid. Yield 83% (159.5 mg, 0.41 mmol), mp 230-232 °C. FT-IR (KBr pellet, cm^{-1}): 2954, 2875, 1661, 1573. ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm): 7.13-7.24 (m, 4H), 4.71 (s, 1H), 2.46 (s, 4H), 2.21 (m, 4H), 1.10 (s, 6H), 0.99 (s, 6H). ^{13}C NMR (100 MHz, CDCl$_3$) δ (ppm): 196.3, 162.4, 142.7, 132.0, 129.8, 128.2, 115.83, 50.7, 40.9, 32.2, 31.5, 29.3, 27.3. HRMS (ESI-TOF) calcd. for C$_{23}$H$_{26}$ClO$_3$: [M+H]$^+$: 385.1492; found: 385.1501.
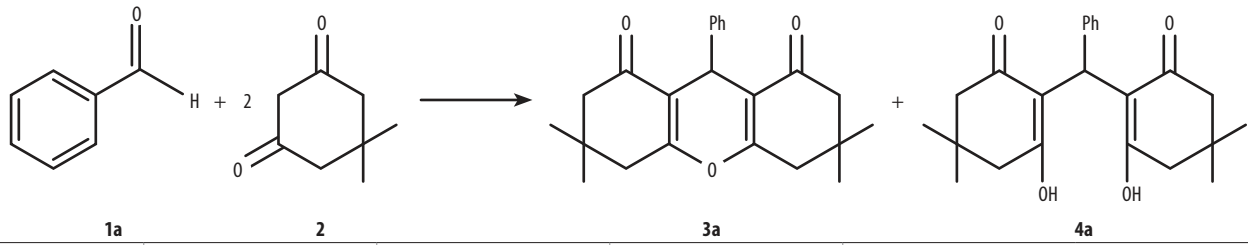
3,3,6,6-Tetramethyl-9-(2-nitrophenyl)-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione 3i
Yellow solid. Yield 78% (154.2 mg, 0.39 mmol), mp 258-261°C. FT-IR (KBr pellet, cm^{-1}): 2954, 2935, 1662, 1515, 1463. ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm): 7.76 (d, 1H, ^3J= 7.3 Hz), 7.43 (m, 1H), 7.37 (d, 1H, ^3J= 7.4 Hz), 7.24 (m, 1H), 5.51 (s, 1H), 2.46 (s, 4H), 2.23 (d, 2H, ^2J= 16.3 Hz), 2.16 (d, 2H, ^2J= 16.3 Hz), 1.10 (s, 6H), 1.01 (s, 6H). ^{13}C NMR (100 MHz, CDCl$_3$) δ (ppm): 196.4, 196.4, 192.2, 163.0, 149.8, 131.9, 127.2, 124.6, 114.1, 50.6, 40.8, 32.1, 28.9, 27.6. HRMS (ESI-TOF) calcd. for C$_{23}$H$_{26}$NO$_5$: [M+H]$^+$: 396.1733; found: 396.1763.

Results and discussion

Since our interest was focused on the development of a green synthetic methodology for the synthesis of a selected group of 1,8-dioxo-octahydroxanthenes, the reaction of dimedone with benzaldehyde was used as a model reaction in order to find the best reaction conditions (Table 1).

The use of solvents like acetonitrile and dimethyl sulfoxide gave the tetraketone **4a** in very poor yields (Table 1, entries 2 and 4). On the other hand, ethanol, THF and water afforded the tetraketone **4a** in good yields; however formation of **3a** was not detected (TLC) (Table 1, entries 1, 3, and 5). As reported by Yu and co-workers (55), the formation of **4a** can be explained by the fact that these solvents may help in the enolization of dimedone by making hydrogen bonds with the OH of the enol form of **2** and, thus, it increases the nucleophilic character of the methylene carbon (C-2). In addition, water and ethanol can also increase the electrophilic character of the carbonyl carbon of benzaldehyde by forming hydrogen bonds with the carbonyl oxygen.

Table 1. Optimization of reaction conditions for the synthesis of **3a**[a].

Entry	Time (h)	T (ºC)	Solvent	Yield (%)[b]	
				3a	**4a**
1	6	70	EtOH	---	78
2	6	70	CH_3CN	---	10
3	6	60	THF	---	80
4	6	100	DMSO	---	15
5	6	80	H_2O	---	75
6	6	100	Acetic acid	65	---
7	8	100	Acetic acid 50%	58	---
8	6	90	0.3 M Oxalic acid	77	---
9	6	90	0.3 M Succinic acid	80	---
10	6	90	0.3 M Tartaric acid	78	---
11	6	90	0.3 M Citric acid	85	---
12	8	90	0.15 M Citric acid	50	20
13	6	90	Lemon juice	86	---

[a] **1a:** 0.5 mmol; **2:** 1.0 mmol; solvent: 2.0 mL. [b] Isolated yield.

It is known that the 1,8-dioxo-octahydroxanthenes can be obtained by intramolecular cyclization of **4a** promoted by acid catalysts (29, 31, 35). Therefore, acetic acid and other naturally occurring organic acids were examined for the obtention of **3a** (Table 1, entries 6 to 13). Acetic acid afforded **3a** with 65% yield, but a dilution of 50% decrease the yield to 58%. When 0.3 M solutions of oxalic, succinic, tartaric and citric acid were used as reaction media, yields above 77% were obtained for compound **3a** and no tetraketone **4a** was detected (Table 1, entries 8 to 11). However, similarly to entry 7, when the concentration of citric acid decreased the compound is formed in a low yield together with **4a**. Interestingly, lemon juice also provided compound **3a** in good yield. As shown in Figure 1, at the beginning of the
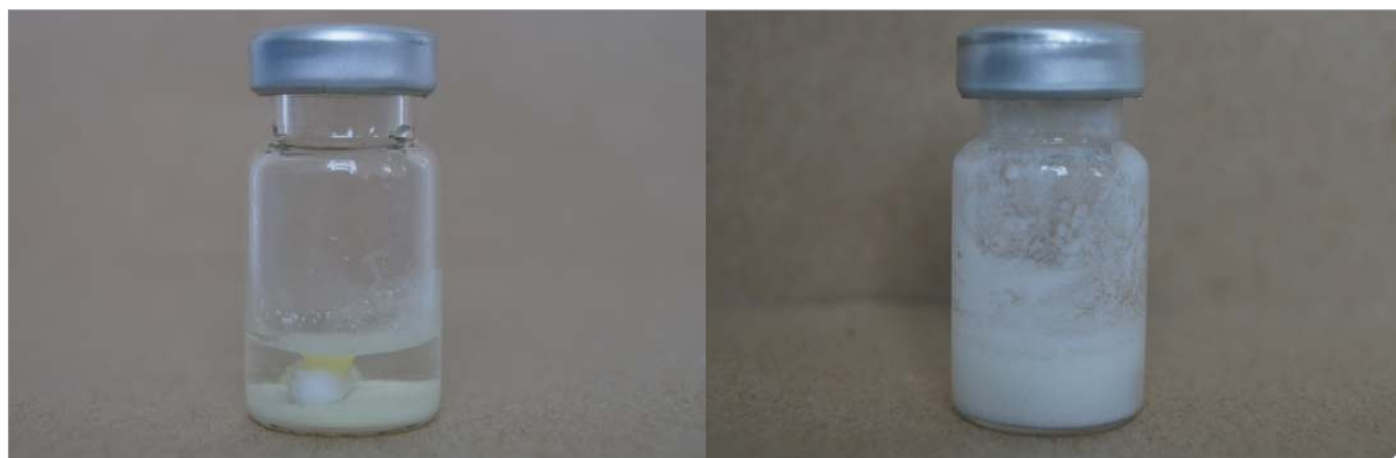
Figure 1. Reaction progress for the reaction of benzaldehyde and 5,5-dimethyl-1,3-cyclohexanedione in 0.3 M citric acid (left: beginning of the reaction; right: the end of the reaction).
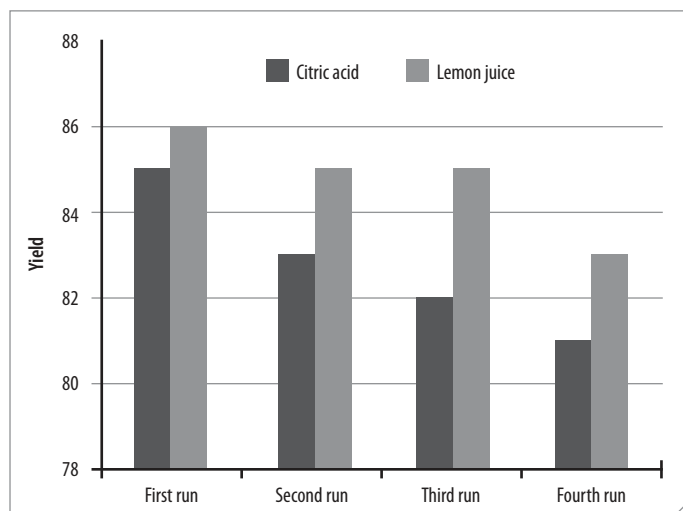
Figure 2. Reusability of the reaction media for the obtention of **3a**.

reaction after benzaldehyde and 5,5-dimethyl-1,3-cyclohexanedione were added to aqueous citric acid (2 mL, 0.3M), a two-phase heterogeneous system was formed (Figure 1 left). After this, within the reaction progress, the formation of a white solid was observed. This precipitate product (Figure 1 right) could be easily filtrated and washed with water and aqueous ethanol. The same phenomenon was observed when the other aqueous naturally occurring organic acids and lemon juice were used.

To study the reusability of the acidic media, we performed the same experiment described above by using lemon juice and 0.3 M citric acid (highest yields found, Table 1). After the reaction was completed the mixture was cooled to room temperature and the product was isolated by filtration. The recovered citric acid aqueous solution and lemon juice were reused as acidic media for three additional reactions to obtain the compound **3a**. These experiments showed small decreases in the yield of **3a**, which evidence the high reusability of this reaction media (Figure 2).

Additionally, using the best experimental conditions to perform the xanthene synthesis, indicated in entries 11 and 13 of Table 1, we examine the scope and generality of the citric acid and lemon juice-mediated synthesis by employing various aromatic aldehydes (Table 2). First, the reaction was carried out by using a series of different aldehydes, 5,5-dimethylcyclohexane-1,3-dione and lemon juice as solvent (Table 2, entries 2, 6, and 8). Although lemon juice was proved to be capable of promoting the reaction with benzaldehyde, it was found that when both electron-rich and electron-deficient aromatic aldehydes were used, the reaction was not completed and a mixture of the desired xanthene and tetraketone was obtained in low yields, together with starting materials (Table 2, entries 2, 6, and 8). Increasing the reaction time and temperature did not improve the yield of xanthenes and the lemon juice turned brown probably due to the decompositions of some components present in it. However, when the reaction was conducted in 0.3 M citric acid the xanthene derivatives **3b**, **3f** and **3h** were obtained in good yields (Table 2, entries 2, 6, and 8). Following the same procedure, both electron-rich (Table 2, entries 3-5) and electron-deficient aromatic aldehydes (Table 2, entries 7 and 9) as well as heteroaromatic aldehydes (Table 2, entries 10 and 11) were converted into desired products in moderate to good

Table 2. One-pot reaction of dimedone **2** and different aromatic aldehydes **1a-k**[a].
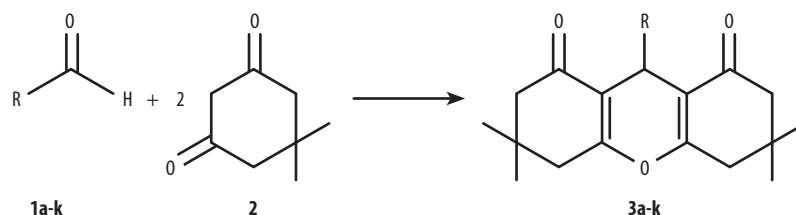
| Entry | Aldehyde | Product | Yield[b] | | Mp [ref.] ºC |
			Lemon juice	0.3 M citric acid	
1	Benzaldehyde (1a)	3a	86	85	204-206 [17]
2	4-Methoxybenzaldehyde (1b)	3b	20, 5[c]	78	245-248 [17]
3	4-Dimethylaminobenzaldehyde (1c)	3c	---	80	219-221 [17]
4	3,4,5-Trimethoxybenzaldehyde (1d)	3d	---	83	204-207 [18]
5	Piperonal (1e)	3e	---	82	218-220 [18]
6	4-Bromobenzaldehyde (1f)	3f	22, 12[c]	84	228-230 [25]
7	4-Chlorobenzaldehyde (1g)	3g	---	83	230-232 [17]
8	4-Nitrobenzaldehyde (1h)	3h	25, 10[c]	85	225-227 [17]
9	2-Nitrobenzaldehyde (1i)	3i	---	78	258-261 [17]
10	2-Pyridinecarbaldehyde (1j)	3j	---	79	190-192 [18]
11	2-Thiophenecarbaldehyde (1k)	3k	---	73	163-165 [18]

[a] **1a-k:** 0.5 mmol, **2:** 1.0 mmol, 2.0 mL of reaction media, 6h, 90 ºC. [b] Isolated yield. [c] Yield of the corresponding tetaketone obtained.
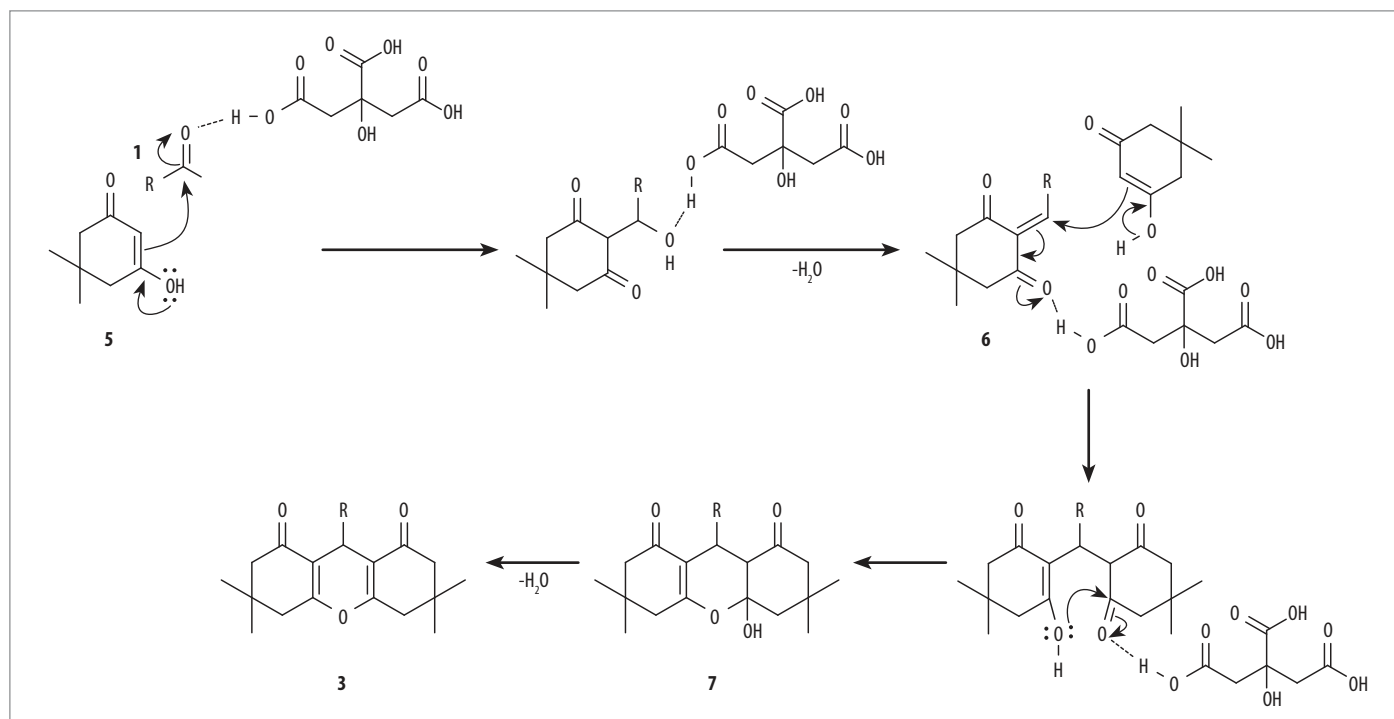
Figure 3. Mechanism proposed to obtain 1,8-dioxo-octahydroxanthenes **3a-k**.

yields. It is important to note here that just compounds **3i**-**3k** were purified by recrystallization from ethanol and the other derivatives were obtained as pure compounds after washing with water and aqueous ethanol.

A plausible mechanism for the formation of compounds **3a**-**k** is given in Figure 3. First, the formation of the Knoevenagel adduct **6** promoted by citric acid takes place by the reaction of the enolic form of dimedone **5** with the aromatic aldehyde. Then **6** may further undergo Michael addition with another molecule of dimedone, in its enol form, to yield intermediate **7**, which after a dehydration reaction gives compounds **3.**

Conclusions

We described a simple, practical, economically viable and environmentally benign one-pot method for the synthesis of 9-aryl-1,8-dioxo-octahydroxanthenes. All reactions were performed in aqueous citric acid under mild conditions and using aromatic aldehydes containing both electro-donating and electron-withdrawing groups yielding the desired compounds in good yields.

Compared with the previously reported methods, our green protocol has the following advantages: mild reaction conditions, all products could be easily isolated by filtration avoiding the use of toxic organic solvents for the workup and thus minimizing waste, easy purification by recrystallization in ethanol when required (bypassing the need for costly column chromatography), reusability of the reaction media and the use of low-cost and readily available citric acid to promote the reaction.

Acknowledgements

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