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Short Note

9-(4-Hydroxybutyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione

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Abstract: The title compound 9-(4-hydroxybutyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione was synthesized in 72% yield through a simple, convenient and environmentally friendly one-pot reaction between dimedone and 3,4-dihydro-2*H*-pyran in aqueous citric acid. Additionally, a plausible reaction mechanism for the formation of the target xanthene is proposed.

Keywords: dimedone; Knoevenagel condensation; Michael addition; citric acid

1. Introduction

Xanthenes are a very interesting class of oxygen-containing heterocycles with a large number of synthetic and naturally occurring derivatives [1–3] that exhibit diverse applications in the field of medicinal chemistry [4,5] and materials science [6,7]. In particular, the hexahydro-1*H*-xanthene-1,8(2*H*)-diones have shown potential as antioxidant, [8] anticancer [9,10] and leishmanicidal agents [11].

The synthesis of hexahydro-1*H*-xanthene-1,8(2*H*)-diones is commonly performed by the condensation of the appropriate aldehyde and dimedone or 1,3-cyclohexanedione under verious various conditions which include the use of alternative solvents [12–15], homogeneous [16,17], and heterogeneous [18–20] catalysts, and ultrasound- [21,22] or microwave-assisted [23] synthesis.

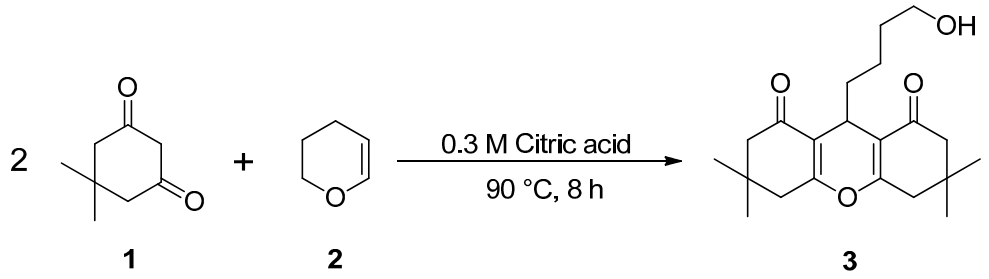
In this paper we describe the synthesis of 9-(4-hydroxybutyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione, a novel hexahydroxanthene, using an environ-mentally friendly one-pot reaction.

2. Results and Discussion

For the preparation of the target xanthene **3**, one equivalent of 3,4-dihydro-2*H*-pyran **2** was reacted with two equivalents of dimedone **1** in 0.3 M citric acid in a closed vessel at 90 °C during 8 h (Scheme 1). After reaction completion (monitoring by thin layer chromatography) and purification by recrystallization, the desired title compound **3** was isolated in 72% yield.

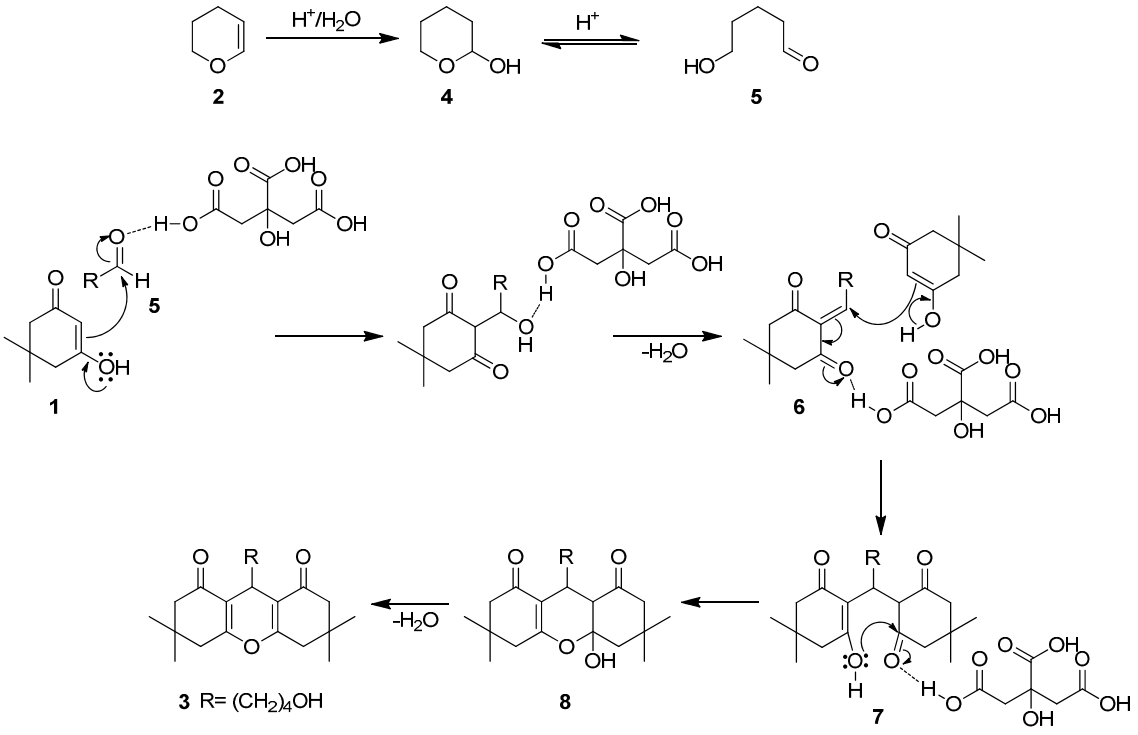
The title compound was characterized by IR, ^{1}H-NMR, ^{13}C-NMR and elemental analysis. As expected, the IR spectrum shows the OH band at 3390 cm^{-1} and a strong absorption band at 1664 and 1643 cm^{-1} for the C=O stretching vibration. The proton NMR spectrum showed the following signals: singlet at 1.10 ppm assigned to the CH_3 groups, three multiplets centered at 1.15, 1.48 and 1.55 ppm assigned to three CH_2 groups of the alkyl chain, a broad singlet at 1.60 ppm assigned to the OH proton, two doublets at 2.24 and 2.30 ppm assigned to two CH_2 groups of the xanthene core,

a singlet at 2.37 ppm assigned to two CH_2 groups of the xanthene core and two triplets at 3.55 and 3.78 ppm corresponding to CH_2OH and CH groups respectively.



Scheme 1. Synthesis of 9-(4-hydroxybutyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione **3**.

A plausible mechanism for the formation of compound **3** is given in Scheme 2. First, the hydrolysis in situ of the cyclic enol ether takes place yielding the cyclic hemiacetal **4** [24] which is in equilibrium with its ring-opened form 5-hydroxypentanal **5** [25]. This aldehyde **5** forms the Knoevenagel adduct **6** by the reaction of the enolic form of dimedone promoted by citric acid. Then **6** may further undergo Michael addition with another molecule of dimedone, in its enol form, to yield intermediate **7**, which after an intramolecular cyclization and dehydration gives compound **3**.



Scheme 2. Plausible mechanism for the formation of the new hexahydro-1*H*-xanthene-1,8(2*H*)-dione **3**.

3. Experimental Section

3.1. General Information

Melting points, reported without correction, were measured using a Stuart SMP10 apparatus (Stuart, Staffordshire, UK). The FT-IR spectra were obtained with a Shimadzu IR prestige 21 spectrophotometer (Columbia, MD, USA). ^{1}H and ^{13}C-NMR spectra were recorded with a Bruker

AVANCE III system (Billerica, MA, USA) operating at 400 MHz, using residual (δ_H 7.26) and deuterated solvent (δ_C 77.0) peaks of $CDCl_3$ as reference standards. The elemental analysis was performed on a Thermo Scientific Flash 2000 CHNS/O analyzer (Waltham, MA, USA). Reagents and solvents were obtained from commercial sources and used without further purification. 0.3 M citric acid was prepared using distilled and deionized water.

3.2. Synthesis of 9-(4-Hydroxybutyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione

A mixture of dimedone **1** (80.9 mg, 0.58 mmol) and dihydro-2*H*-pyran **2** (26.3 µL, 0.29 mmol) in 2 mL of 0.3 M citric acid was placed in a 10 mL glass vial. The vial was sealed and stirred at 90 °C for 8 h. After cooling the mixture the product was recovered by filtration. The solid was finally purified by recrystallization from a mixture ethanol/water (1/1). The target compound **3** (72.0 mg, 72%) was recovered as white crystals, m.p: 125–127 °C. FT-IR (ATR): 3514, 3390, 2958, 2933, 1664, 1643, 1616, 1348, 1192, 1136, 1064, 1001 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ(ppm): 1.10 (s, 12H, $4CH_3$), 1.12–1.18 (m, 2H, CH_2 alkyl), 1.46–1.51 (m, 2H, CH_2 alkyl), 1.51–1.57 (m, 2H, CH_2 alkyl), 1.60 (bs, 1H, OH), 2.24 (d, 2H, *J* = 16.2 Hz, CH_2 xanthene), 2.30 (d, 2H, *J* = 16.2 Hz, CH_2 xanthene), 2.37 (s, 4H, $2CH_2$ xanthene), 3.55 (t, 2H, *J* = 6.5 Hz, CH_2OH), 3.78 (t, 1H, *J* = 4.5 Hz, CH). ^{13}C-NMR (100 MHz, $CDCl_3$) δ(ppm): 21.5, 25.2, 27.3, 29.4, 32.0, 32.6, 33.6, 40.9, 50.9, 62.7, 114.9, 164.0, 197.2. Anal. calcd for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.53; H, 8.68.

Supplementary Materials: Copies of the IR, ^{1}H, ^{13}C-NMR spectra for compound **3** are available in the supplementary information. They and the molfiles can be found at http://www.mdpi.com/1422-8599/2016/1/M884.

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Author Contributions: The authors C.A.N., C.S., C.O.-P. designed, accomplished research and wrote the paper together. Finally, all authors read and approved the final manuscript.

Conflicts of Interest: The authors declare no conflict of interest.

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