

Choline Hydroxide-Catalyzed One-Pot Synthesis of Xanthenedione Derivatives in Aqueous Ethanol

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Abstract:

We present a convenient one-pot method for the preparation of 1,8-dioxooctahydroxanthene derivatives from dimedone and a series of aromatic aldehydes. The reaction was carried out in 50% aqueous ethanol using 10 mol% choline hydroxide at room temperature. The target xanthenedione derivatives were obtained in 80–95% yields within 120–180 min. The purified products were characterized by melting-point determination, FT-IR, ¹H NMR, and mass spectrometric analyses. The results show that choline hydroxide can serve as an effective catalyst for this transformation in an aqueous ethanol medium. The combination of convenient product isolation, good to excellent yields, and reasonably short reaction times makes this protocol a useful approach for the synthesis of 1,8-dioxooctahydroxanthene derivatives.

How to cite this article: Sindhu A. Bhosale¹ Akshaykumar B. Harepatil¹ Vivekanand B. Jadhav^{2*}. Choline Hydroxide-Catalyzed One-Pot Synthesis of Xanthenedione Derivatives in Aqueous Ethanol. *Int J Drug Deliv Technol.* 2026;16(82s):1528-1532. DOI: 10.25258/ijddt.16.82s.176.

Introduction:

1,8-Dioxooctahydroxanthenes (xanthenediones) are an important class of oxygen-containing heterocyclic compounds. Due to their versatile synthetic efficacy as well as various biological activities have engrossed significant consideration [1]. Various catalytic systems have been developed for xanthenedione synthesis. Reported methodologies employ strong acidic or basic catalysts, specialized heterogeneous materials, relatively expensive or less accessible catalytic systems, organic solvents, and elevated temperatures can be observed in some cases. Phase-transfer catalysis can facilitate reactions involving reagents or reactive species which exist in different phases, often improving reaction efficiency and simplifying product isolation [2]. This transformation proceeds through a succession which involves Knoevenagel condensation, Michael addition, and intramolecular cyclization by allowing assembly of the xanthene framework from simple as well as readily available starting materials. The reaction has developed a model conversion for evaluating greener catalytic systems in heterocyclic synthesis [3]. A wide range of catalysts and conditions have been introduced for this conversion over the past numerous years. Which includes zirconium tetrachloride (ZrCl₄) [4], ionic liquids [5], ZnO nanorod-decorated graphene oxide (GO/ZnO) [6], PPA–SiO₂ [7], Sulfate grafted iron stabilized zirconia nanoparticles (SO₄²⁻/xFe–Zr–O) [8], HPWA/MCM-41 [9], Pd/MWCNT [10], cyanuric chloride (TCT) [11], CuCeO₂ NPs [12], trifluoroacetic acid (TFA) [13], PVPP-p-TSA [14] and other heterogeneous or reusable catalytic platforms.

In the context of sustainable synthesis, solvent-free processing, catalyst recyclability, and reduced reaction times are especially desirable [15]. Greener approaches can deliver xanthenediones in excellent yields under mild or environmentally benign conditions [16]. One-pot methods are particularly attractive because they reduce intermediate handling, simplify purification, and align well with the principles of step economy [17, 18]. Several xanthenediones were reported to exhibit biological activities, such as antibacterial [19], anticancer [20], antifungal [21], antioxidant [22], anti-inflammatory [23], antihypertensive [24], anticonvulsant [25].

Despite the substantial advancement achieved with these catalytic systems, there remains a need for simple protocols that combine mild reaction conditions, readily accessible catalytic components, efficient product formation, and uncomplicated isolation. The use of choline hydroxide for the direct synthesis of xanthenediones from dimedone and aromatic aldehydes has received comparatively limited attention. These considerations prompted us to investigate choline hydroxide as a catalyst for this transformation under aqueous ethanol conditions.

In this context, choline hydroxide represents an attractive candidate because previous studies have demonstrated that it is an effective and readily accessible catalyst for a variety of organic transformations with mild reaction conditions, good product yields and simplified work-up procedures [26].

In the present study, we report an efficient one-pot synthesis of 1,8-dioxooctahydroxanthenes through the

condensation of dimedone with different aromatic aldehydes using choline hydroxide as a catalyst, followed by product characterization using melting point, FT-IR, ^1H NMR, LC-MS. The present work is intended to provide a practical synthetic route to xanthenedione derivatives and to contribute to the continuing development of greener and more sustainable methods with high yields for heterocyclic synthesis.

EXPERIMENTAL:

Methods and Materials:

All the reagents and aromatic aldehydes were purchased from commercial suppliers such as Sigma-Aldrich chemicals and BLD Pharmaceuticals and used without further purification. The completion of reactions was monitored by thin layer chromatography (TLC) on Merck pre-coated silica gel 60 F254 aluminum sheets, visualized by UV light. IR spectra were recorded on Shimadzu FT-IR 8300 Spectrophotometer. ^1H -NMR spectra were recorded in CDCl_3 using TMS as internal standard at ambient temperature on a BRUKER AVANCE DRX-500 MHz NMR spectrometer. Mass spectra [ES-MS] were recorded on a Waters SYNAPT XS Q-TOF Mass Spectrometer.

General Procedure: A mixture of dimedone (2.0 mmol), aromatic aldehyde (1.0 mmol), and choline hydroxide (10 mol %) were added in a round-bottom flask containing 10 mL of ethanol: water (1:1, v/v) as a solvent. The flask was equipped with a magnetic stir bar. The reaction mixture was stirred at room temperature for the required time as mentioned in the table 1. The progress of the reaction was monitored by thin-layer chromatography (TLC) using ethyl acetate/n-hexane (3:7 v/v) as the developing solvent and visualized under UV light.

After completion of the reaction, the resulting solid was separated by filtration and washed with small portions of cold water to remove water-soluble impurities. The product was purified by recrystallization from hot ethanol to afford the desired product. The purified compounds were characterized by melting point determination and spectroscopic techniques which includes FT-IR, ^1H NMR and mass spectrometry.

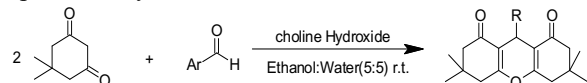


Fig.1. One pot synthesis of Xanthenediones.

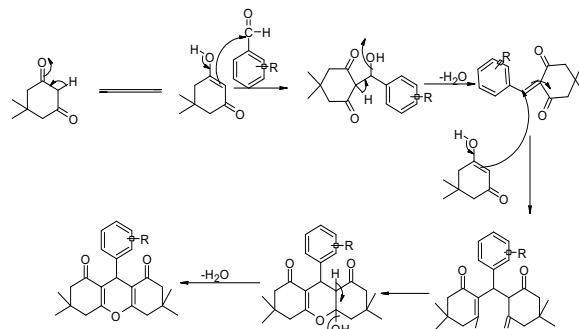


Fig.2. Proposed mechanism and possible intermediates of Xanthenedione synthesis.

Table.1. Choline hydroxide catalyzed one-pot two-component synthesis of Xanthenedione in aqueous ethanol medium.

Sr. No.	Ar-CHO	Products	Time (min)	Yield (%)	Melting Point (°C)	Sample Code
1			120	92	203-205	S3A
2			150	85	226-228	S3B
3			150	90	200-202	S3C
4			150	90	231-233	S3D
5			120	85	238-240	S3E
6			150	80	214-216	S3F

Spectral Data of Synthesized Compounds:

3,3,6,6-tetramethyl-9-phenyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (S3A):

FT-IR (KBr, ν_{max} , cm^{-1}): 3052 (Ar-H), 2958, 2926, 2863 (C-H), 1654 (C=O), 1601 (Ar-C=C), 1372 (CH_3), 1232, 1096 (C-O-C), 1164 (C-O), 755 and 698 cm^{-1} (Ar-H); ^1H NMR (CDCl_3 , 500 MHz) δ : 7.27(m, 2H, Ar-H), 7.17(s, 1H, Ar-H), 7.08 (m, 2H, Ar-H), 5.54 (s, 1H, H-9), 2.45–2.38 (m, 8H, CH_2), 1.23 (s, 6H, CH_3), 1.09 (s, 6H, CH_3); LC-MS ESI (m/z): 351.18. $[\text{M}+\text{H}]^+$

9-(4-hydroxy-3-methoxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (S3B):

FT-IR (KBr, ν_{max} , cm^{-1}): 3418 (O-H), 2956, 2924,

2865 (C–H), 1653 (C=O), 1604, 1512 (Ar C=C), 1454, 1371 (CH₃), 1263 (Ar–OCH₃), 1228 (C–O–C), 1168 (C–O), 1112, 1036 (C–O–C), 854 cm^{−1} (Ar–C–H) : ¹H NMR((CDCl₃, 500 MHz) δ: 11.96 (s, 1H, OH), 6.81(s, 1H, Ar-H), 6.61-6.56 (m, 2H, Ar-H), 5.49 (s, 1H, H-9), 3.77 (s, 3H, OCH₃), 2.42–2.33 (m, 8H, CH₂), 1.23 (s, 6H, CH₃), 1.10 (s, 6H, CH₃); LC-MS ESI (m/z): 397.21 [M+H]⁺

9-(2-hydroxy-3-methoxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (S3C):

FT-IR (KBr, v_{max}, cm^{−1}): 3408 (O–H), 2958, 2927, 2864 (C–H), 1652 (C=O), 1602, 1510 (Ar C=C), 1455, 1372 (CH₃), 1261 (Ar–OCH₃), 1226 (C–O–C), 1165 (Ar–OH), 1110, 1034 (C–O–C), 772 cm^{−1} (Ar–H): ¹H NMR (CDCl₃, 500 MHz) δ: 10.41 (s, 1H, OH), 6.95–6.58 (m, 3H, Ar-H), 4.66 (s, 1H, bridge methine H-9), 3.89 (s, 3H, OCH₃), 2.69–2.33 (m, 8H, CH₂), 1.11 (s, 6H, CH₃), 0.99 (s, 6H, CH₃); LCMS ESI (m/z): 397.20. [M+H]⁺

9-(2-hydroxy-4-methoxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (S3D):

FT-IR (KBr, v_{max}, cm^{−1}): 3415 (O–H), 2957, 2925, 2863 (C–H), 1653 (C=O), 1603, 1512 (Ar C=C), 1454, 1371 (CH₃), 1264 (Ar–OCH₃), 1227 (C–O–C), 1166 (Ar–OH), 1111, 1035 (C–O–C), 848 cm^{−1} (Ar–H): ¹H NMR (CDCl₃, 500 MHz) δ: 11.94 (s, 1H, OH), 6.76–6.55 (m, 3H, Ar-H), 5.46 (s, 1H, H-9), 3.85 (s, 3H, OCH₃), 2.46–2.28 (m, 8H, CH₂), 1.22(s, 6H, CH₃), 1.09 (s, 6H, CH₃) ; LC-MS; 397.483 [M+H]⁺

4-(3,3,6,6-tetramethyl-1,8-dioxo-2,3,4,5,6,7,8,9-octahydro-1H-xanthen-9-yl)benzonitrile (S3E):

FT-IR (KBr, v_{max}, cm^{−1}): 3054 (Ar–H), 2958, 2926, 2864 (C–H), 2226 (C≡N), 1654 (C=O), 1602, 1570 (Ar C=C), 1455, 1372 (CH₃), 1229 (C–O–C), 1163, 1108 (C–O), 833 cm^{−1} (Ar–H): ¹H NMR (CDCl₃, 500 MHz) δ: 7.56–7.55 (m, 2H, Ar-H), 7.20–7.10 (m, 2H, Ar-H), 5.51 (s, 1H, H-9), 2.49–2.30 (m, 8H, CH₂), 1.22(s, 6H, CH₃), 1.10 (s, 6H, CH₃); LC-MS ESI (m/z): 376.19.

9-(2,4-dimethoxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (S3F):

FT-IR (KBr, v_{max}, cm^{−1}): 3053 (Ar–H), 2957, 2925, 2863 (C–H), 1653 (C=O), 1602, 1511 (Ar C=C), 1455, 1372 (CH₃), 1266 (Ar–OCH₃), 1228 (C–O–C), 1167, 1113, 1034 (C–O), 827 cm^{−1} (Ar–H): ¹H NMR (CDCl₃, 500 MHz) δ: 7.78–7.76 (s, 1H, Ar-H), 6.63 (m, 2H, Ar-H), 5.50 (s, 1H, H-9), 3.84(s, 3H, OCH₃), 3.76(s, 3H, OCH₃), 2.42–2.34 (m, 8H, CH₂), 1.23(s, 6H, CH₃), 1.11 (s, 6H, CH₃); LC-MS ESI (m/z): 411.21. [M+H]⁺

9-(1H-indol-3-yl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (S3G):

FT-IR (KBr, v_{max}, cm^{−1}): 3382 (N–H), 3054 (Ar–H),

2958, 2925, 2863 (C–H), 1652 (C=O), 1604, 1513 (Ar C=C), 1455, 1372 (CH₃), 1318 (C–N), 1229 (C–O–C), 1164, 1109 (C–O), 744 cm^{−1} (indole Ar–H): ¹H NMR (CDCl₃, 500 MHz) δ: 9.60(s, 1H, NH), 8.73(s, 1H, Ar–H), 8.00 (s, 1H, Ar-H), 7.48 (s, 1H, Ar-H), 7.46(m, 2H, Ar-H), 3.94 (s, 1H, H-9), 2.61 (m, 8H, CH₂), 1.12 (s, 6H, CH₃), 1.10 (s, 6H, CH₃); LC-MS ESI (m/z): 390.18. [M+H]⁺

9-(4-fluorophenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (S3H):

FT-IR (KBr, v_{max}, cm^{−1}): 3055 (Ar–H), 2958, 2926, 2864 (C–H), 1654 (C=O), 1603, 1511 (Ar C=C), 1455, 1372 (CH₃), 1222 (C–F), 1206 (C–O–C), 1164, 1109 (C–O), 835 cm^{−1} (Ar–H): ¹H NMR (CDCl₃, 500 MHz) δ: 7.05–7.03 (m, 2H, Ar-H), 7.02–6.93 (m, 2H, Ar-H), 5.48 (s, 1H, H-9), 2.47–2.29 (m, 8H, CH₂), 1.21(s, 6H, CH₃), 1.09 (s, 6H, CH₃); LC-MS ESI (m/z): 370.20. [M+H]⁺

9-(3,5-dibromo-4-hydroxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione(S3J):

FT-IR (KBr, v_{max}, cm^{−1}): 3405(O–H), 2957, 2925, 2863 (C–H), 1653 (C=O), 1601, 1508 (Ar C=C), 1454, 1371 (CH₃), 1248 (Ar–OH), 1218 (C–O–C), 1163, 1110 (C–O), 612 (C–Br) cm^{−1} : ¹H NMR (CDCl₃, 500 MHz) δ: 11.91 (s, 1H, OH), 7.13(m, 2H, Ar-H), 5.41 (s, 1H, H-9), 2.48–2.29 (m, 8H, CH₂), 1.22(s, 6H, CH₃), 1.09 (s, 6H, CH₃); LC-MS ESI (m/z): 523.18. [M+H]⁺

9-(2,6-dichlorophenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (S3K):

FT-IR (KBr, v_{max}, cm^{−1}): 3054 (Ar–H), 2958, 2926, 2864 (C–H), 1653 (C=O), 1602, 1509 (Ar C=C), 1455, 1372 (CH₃), 1228 (C–O–C), 1164, 1110 (C–O), 758, 728 (C–Cl) cm^{−1}: ¹H NMR (CDCl₃, 500 MHz) δ: 7.08–6.98(m, 3H, Ar-H), 4.97 (s, 1H, H-9), 2.42–2.09 (m, 8H, CH₂), 1.15 (s, 6H, CH₃) 1.21 (s, 6H, CH₃); LC-MS ESI (m/z): 419.11. [M+H]⁺

Conclusion:

The present study demonstrates that choline hydroxide can be effectively employed as a phase transfer catalyst for the one-pot synthesis of xanthenedione derivatives from dimedone and substituted aromatic aldehydes. In summary, an operationally simple and potentially greener alternative has been developed for the one-pot synthesis of 1,8-dioxooctahydroxanthenes. The reaction proceeded efficiently to yield the target heterocycles in 80–95% yields within 120 to 180 minutes. All synthesized structures were confirmed using FT-IR, ¹H NMR, LC-MS analyses. With a phase transfer catalyst in aqueous media, this study highlights the efficacy of choline hydroxide as a sustainable catalytic platform for constructing complex functionalized polycyclic heterocycles.

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