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CERIC AMMONIUM SULFATE-CATALYZED SOLVENT-FREE SYNTHESIS OF XANTHENE DERIVATIVES

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ABSTRACT: We report an environmentally friendly and highly efficient synthesis of xanthene derivatives under solvent-free conditions, catalyzed by Ceric Ammonium Sulfate (CAS). This facile one-pot, multi-component reaction, carried out at 70-80°C for a remarkably short duration of 10-30 minutes, utilizes aromatic aldehydes and active methylene compounds are dimedone or β-naphthol. The developed methodology provides high to excellent product yields, an inexpensive and readily available catalyst. Its operational simplicity, rapid reaction times, and mild conditions offer a valuable and practical alternative in organic synthesis.

KEY WORDS: Ceric Ammonium Sulfate, xanthenes derivatives, dimedone, *β*-naphthol, Solvent free etc.

INTRODUCTION:

Antimicrobial resistance is a serious global challenge that requires a constant effort to discover and create new medicines. A specific class of heterocyclic compounds called xanthenes has shown great promise in this area. Xanthenes, characterized by their unique dibenzo[b,e]pyran structure, have a wide range of biological activities that make them a promising subject for therapeutic research. In addition to their notable antimicrobial properties, xanthene derivatives exhibit activity in areas such as anti-malarial[i], anti-inflammatory[ii], and photodynamic therapy[iii]. Xanthenes aren't just for medicine; they're versatile chemicals used as additives in the food industry[iv-v], as dyes[vi-vii], as fluorescent materials[viii], and in laser technologies[ix].

The synthesis of xanthene derivatives has seen the development of various catalytic methods recently. Catalysts such as succinic acid[x], γ-Fe_2O_3 hydroxyapatite-Fe^{2+} nanoparticles[xi], Santa Barbara Amorphous FeNP@SBA-15[xii], acetic acid[xiii], sulphamic acid[xiv-xv], succinamide-*N*-sulphonic acid[xvi], silica sulphuric acid[xvii], citric acid[xviii], lactic acid[xix], tartaric acid[xx], niobium pentachloride[xxi],
p-toluenesulphonic acid[xxii-xxiii], indium(III) chloride and metaphosphoric acid[xxiv], silica functionalized propyl sulphonic acid[xxv], montmorillonite K_{10}[xxvi], iodine[xxvii] have all been

explored. Despite these advancements, many existing synthetic routes suffer from drawbacks including harsh reaction conditions, prolonged reaction durations, elevated temperatures, reliance on expensive and hazardous catalysts, the need for excess solvent, and often result in modest yields. The methodology presented in this study seeks to overcome these disadvantages, offering a more efficient and higher-yielding alternative.

In organic synthesis, Ceric Ammonium Sulfate (CAS) stands out as a noteworthy cerium (IV) salt that is both readily available and comparatively non-toxic. Its appeal as a dual function reagent acting as a powerful oxidizing agent and an effective Lewis acid catalyst stems from its high redox potential and its capacity to activate a range of functional groups. Utilizing CAS in lieu of more traditional catalysts often translates into several benefits, including the use of milder reaction conditions, achieving higher product yields, and simplifying purification steps.

EXPERIMENTAL:

Reagents and solvents were sourced from Merck, S.D. Fine-Chem, and Sigma-Aldrich. Melting points, recorded on a Contemp Melting Point Apparatus (MEPOAP121) via the open-tube capillary method, are uncorrected. Reaction progress and compound purity were monitored by thin-layer chromatography (TLC) using Merck 60 F254 silica gel plates. Spectroscopic analysis included ^{1}H and ^{13}C NMR (Bruker Avance Spectrometer, 500 and 125 MHz respectively, in $CDCl_3$ with TMS; chemical shifts in ppm, coupling constants in Hz and mass spectrometry (Bruker IMPACT HD, ESI method). All synthesized products were identified by comparing their melting points to reported literature values. Furthermore, the structures of some products were corroborated by their ^{1}H, ^{13}C NMR, and mass spectral data.

General procedure for the synthesis of 14H-dibenzo [a,j]xanthene derivatives (Table 2, Entry 1-6)

A mixture containing an aromatic aldehyde **1a-i** (1.0 mmol), β-naphthol **(2)** (2.0 mmol), and Ceric Ammonium Sulfate (CAS) (10 mol%) was prepared. This reaction mixture was then heated at 80°C for the specified reaction time. Upon completion, the mixture was washed with cold water, and the resulting solid product was isolated by filtration. The crude product was subsequently purified by recrystallization from ethanol.

14-(4-Hydroxyphenyl)-14H-dibenzo [a,j]xanthene ***(3b)****.* ^{1}H NMR: δ 4.73 (1H, brs, OH), 6.42 (1H, s, CH), 6.56 (2H, d, J =8.8 Hz, Ar-H), 7.35-7.58 (8H, m, Ar-H), 7.76-7.82 (4H, m, Ar-H), 8.34 (2H, d, J=8.4 Hz, Ar-H), ^{13}C NMR: δ 37.0, 115.2, 117.4, 118.0, 122.6, 124.2, 126.7,128.7, 128.8, 129.3, 131.0, 131.3, 137.4, 148.6, 153.8 ppm. MS: m/z = 375 (M+H).

14-(4-Chlorophenyl)-14H-dibenzo [a,j]xanthene ***(3c)****.*^{1}H NMR: δ 6.45 (1H, s, CH), 7.07 (2H, d, J=9.3 Hz, ArH), 7.39-7.83 (12H, m, ArH), 8.29 (2H, d, J=9.5 Hz, ArH). ^{13}C NMR: δ 37.3, 116.7, 118.0, 122.4, 124.3, 126.9, 128.6, 128.9, 129.0, 129.4, 131.0, 131.2, 132.0, 143.4, 148.7. MS: m/z = 393 (M+H).

General procedure for the synthesis of 1,8-dioxo-octahydroxanthene derivatives (Table 2, Entry 7-12)

A mixture containing an aromatic aldehyde **1a-i** (1.0 mmol), dimedone **(4)** (2.0 mmol), and Ceric Ammonium Sulfate (CAS) (10 mol%) was prepared and heated at 80°C for the specified reaction time. Once the reaction was complete, the mixture was washed with cold water, and the resulting solid product was isolated by filtration. The crude product was subsequently purified by recrystallization from ethanol.

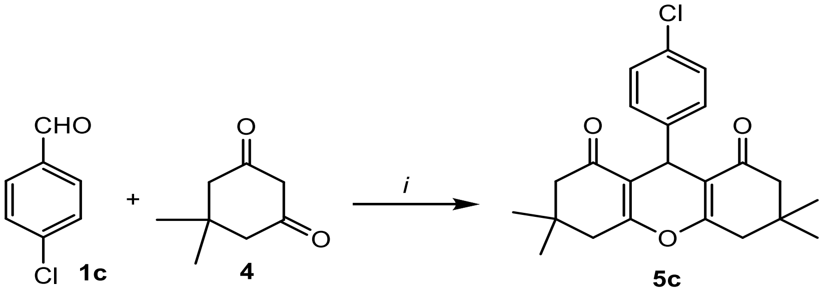
9-(4-methoxyphenyl)-1,8-dioxo-octahydroxanthene ***(5b)****.* ^{1}H NMR: δ 0.99 (6H, s, $2CH_3$), 1.09 (6H, s, $2CH_3$), 2.18(4H, d, J=18.2 Hz, $2CH_2$), 2.45 (4H, d, J=16.2 Hz, $2CH_2$), 3.73 (3H, s, OCH_3), 4.69 (1H, s, CH), 6.76 (2H, d, J=8.8Hz, Ar-H), 7.20 (2H, d, J=8.8Hz, Ar-H) ppm. ^{13}C NMR: δ 27.3, 29.2, 30.9, 32.2, 40.8, 50.7, 55.1, 113.4, 115.8, 129.3, 136.5, 157.9, 162.0, 196.5 ppm. MS: m/z = 381 (M+H).

9-(4-nitrophenyl)-1,8-dioxo-octahydroxanthene ***(5d)***. ^{1}H NMR: δ 0.99 (6H, s, $2CH_3$), 1.12 (6H, s, $2CH_3$), 2.15-2.27 (4H, d, *J*=18.2 Hz, $2CH_2$), 2.49 (4H, d, *J*=16.2 Hz, $2CH_2$), 4.82 (1H, s, CH), 7.48 2H, (d, *J*=8.6 Hz, ArH), 8.08 (2H, d, *J*=8.8 Hz, Ar-H), ppm. ^{13}C NMR δ 27.2, 29.2, 32.2, 32.3, 40.8, 50.6, 114.5, 123.4, 129.3, 146.4, 151.5, 162.9, 196.2 ppm. MS: m/z = 396 (M+H).

RESULT AND DISCUSSION:

We investigated ceric ammonium sulfate as an efficient catalyst for synthesizing 1,8-dioxo-octahydroxanthene and 14H-dibenzo[a,j]xanthene derivatives. These reactions involve the solvent-free condensation of various aromatic aldehydes (1a-i) with either dimedone (4) or β-naphthol (2) at 80°C. Our initial experiments focused on optimizing the catalyst loading and reaction conditions. We chose the reaction between dimedone (4) (2.0 mmol) and *p*-chlorobenzaldehyde (1c) (1.0 mmol) as a model system, conducted under solvent-free conditions at 70-80°C (Table 1). A preliminary test without ceric ammonium sulfate at 70°C yielded no significant product formation (Table 1, Entry 1), clearly indicating the catalyst's crucial role in initiating the reaction. We observed a gradual increase in product yield from 35% to 92% as the catalyst amount was incrementally raised from 2 mol% to 10 mol% (Table 1, Entries 2-6). The optimal results were achieved with 10 mol% catalysts, completing the reaction in just 10 minutes with a 92% yield at 80°C (Table 1, Entry 6). Further increasing the catalyst loading from 10 mol% to 20 mol% at 80°C showed no additional improvement in reaction time or yield (Table 1, Entries 7-9). Similarly, elevating the reaction temperature beyond 80°C did not lead to higher product yields (Table 1, Entries 5-7).

Based on these optimized conditions, we then explored the generality of this cyclization reaction. We conducted the reaction of β-naphthol (2) or dimedone (4) with a variety of aldehydes, including those with electron-withdrawing and electron-donating substituents, all in the presence of CAS under solvent-free conditions. Both types of aromatic aldehydes, bearing either electron-withdrawing or electron-donating groups, demonstrated good reactivity. A comprehensive summary of all results is presented in Table 2.



Reagent and conditions: i. CAS 10mol%, solvent free, 80ºC, 10 min, 92%.

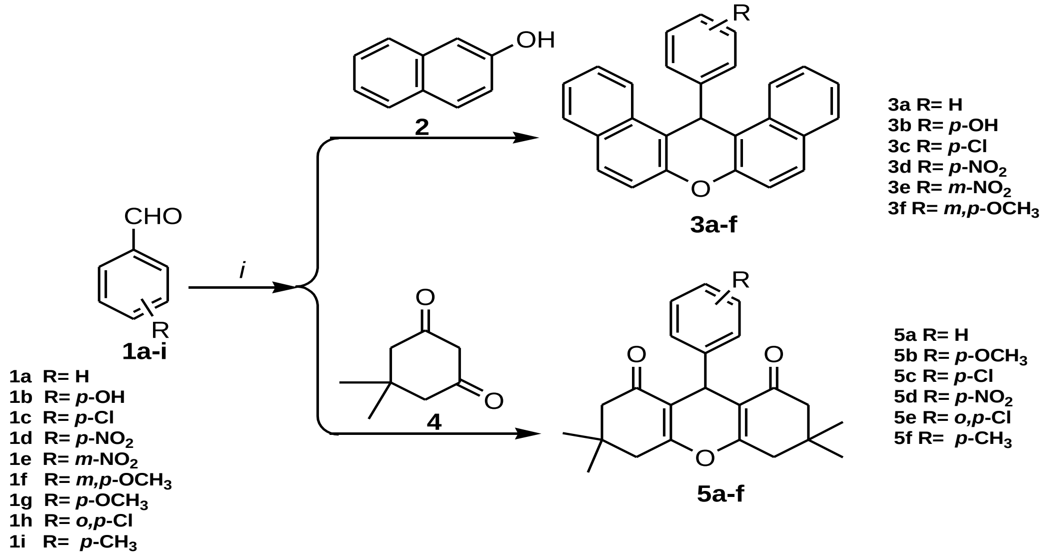
Scheme 1. Synthesis of 9-(4-chlorophenyl)-1,8-dioxo-octahydroxanthene (5c).

Table 1 The optimization of reaction conditions[a].

Entry	*Catalyst (mol%)*	*Temperature (ºC)*	*Time (min)*	*Yield[b] (%)*
1	-	70	60	No reaction
2	2	70	50	35
3	5	70	40	65
4	7	70	25	81
5	10	70	15	90
6	**10**	**80**	**10**	**92**
7	10	90	10	92

8	15	80	10	92
9	20	80	10	91

*[a]**Reaction conditions:** p-chlorobenzaldehyde (**1c**) (1 mmol), dimedone (**4**) (2 mmol), CAS (10 mol%) under solvent-free conditions. [b]Isolated yield.*



Reagent and conditions: i. CAS, solvent free, 70-80ºC, 10-30 min.

Scheme 2. General procedure for synthesis of xanthene derivatives.

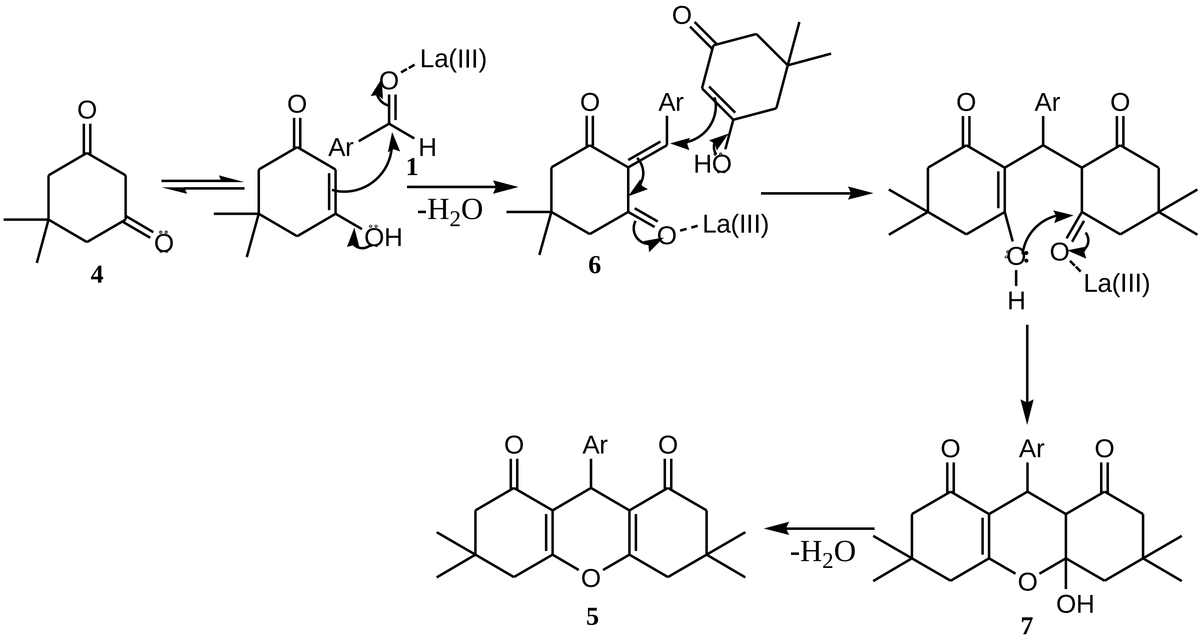
Table 2 Ceric Ammonium Sulfate catalysed synthesis of xanthene derivatives.

Entry	*Product*	*Time (min)*	*Yield[b] (%)*	*M.P. (ºC)*	
				Found	*Reported[Ref.]*
1	**3a**	25	90	181-182	180-183[xiv]
2	**3b**	30	85	138-140	136-139[xxi]
3	**3c**	15	92	287-290	286-289[xiv]
4	**3d**	15	92	307-309	306-308[xiii]
5	**3e**	20	90	212-213	211-213[xiii]
6	**3f**	25	88	170-172	-
7	**5a**	10	92	202-204	203-206[xiv]
8	**5b**	10	92	247-249	249-251[xiv]
9	**5c**	10	92	230-232	231-233[xiv]
10	**5d**	12	90	228-230	229-231[xiv]
11	**5e**	14	85	255-257	254-256[xiv]
12	**5f**	10	92	215-216	216-218[xv]

*[a]**Reaction conditions:** Aromatic aldehyde (1 mmol), β-naphthol (**2**) or dimedone (**4**) (2 mmol), CAS (10 mol%) under solvent free conditions.*

[b]Isolated yield.

The proposed synthesis mechanism for xanthenes derivatives is detailed in Scheme 3. The Lewis acidity of Ce(IV) can coordinate with the oxygen atom of the aldehyde's carbonyl group. This coordination enhances the electrophilicity of the carbonyl carbon, making it more susceptible to nucleophilic attack by the active methylene compound. The activated aldehyde can then readily undergo Knoevenagel condensation with the active methylene compound (e.g., dimedone) to form an α,β-unsaturated carbonyl intermediate. The Ce (IV) catalyst can further promote the subsequent Michael addition of another molecule of the active methylene compound to the newly formed α,β-unsaturated system, followed by an intramolecular cyclization to form the xanthene core.



Scheme 3. Proposed mechanism for the synthesis of 5.

CONCLUSION:

We have developed an efficient, environmentally friendly method for synthesizing xanthene derivatives. This one-pot, multi-component reaction is catalyzed by ceric ammonium sulfate ($Ce(NH_4)_4(SO_4)_4$) and condensation reaction between aromatic aldehydes and either dimedone or β-naphthol was performed. We used 10 mol% of ceric ammonium sulfate as a catalyst, and the reaction was carried out at temperature of 70-80°C without the use of any solvent. The synthesized compounds were characterized using mass and NMR spectroscopy. The strong affinity of cerium for oxygen, known as oxophilicity, is believed to contribute to the high catalytic efficiency of ceric ammonium sulfate in this reaction.

This synthesis protocol offers several benefits, including low-cost and non-toxic catalyst, eco-friendly conditions and high efficiency. These advantages make this method a compelling alternative to traditional, multi-step approaches for synthesizing xanthene derivatives.

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