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Eco-Friendly one Pot Synthesis of Aryl Xanthenes in Water

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Abstract: Aryl xanthenes were synthesized by reaction of aldehyde on cyclodienone in presence of potash alum as a catalyst at 80 °C in water. This methodology offers synthesis of xanthenes with simplicity in operation, inexpensive reagents and green approach.

Keywords: Alum, Water, Cyclodienone, Benzoxanthene

Introduction:

Recent research on xanthenes more particularly benzoxanthenes have up raised in organic synthesis due to its broad range of biological and therapeutic properties like antiviral¹, antibacterial² and anti-inflammatory activities³. It is also used in photodynamic therapy⁴ and as antagonists for paralyzing action of zoxazolamine⁵. The photodynamic theory is the method which is used to kill the tumour cells. Here, photosensitizers are introduced into the tumour effected tissue known as malignant tissue by passing particular wavelength of light. The photosensitizer drug gets excited and tumour cells are killed. Natural xanthenes are also available, which are known as santalin pigments and it has been acquired from a number of plant species⁶. Because of its spectroscopic properties, they are used as dyes⁷ commonly called as leuco dyes in laser technology⁸ and as fluorescent materials for visualization of biomolecules⁹. Several methods have been described for the synthesis of benzoxanthenes, including (a) dehydration of *bis*-(2-hydroxy-1-naphthyl)methane using POCl₃¹⁰ or by boiling acetic acid diester of *bis*(2-hydroxy-1-naphthyl) methane¹¹ (b) condensation of naphthol with aliphatic and arylaldehydes in presence of hydrochloric acid or phosphoric acid¹² or sulfuric acid¹³ in acetic acid as solvent. The above mentioned methods disclose that the synthesis of xanthenes involves expensive reagents, strong acidic conditions, toxic reagents, toxic catalysts and long time (more than 12 hrs). Homogeneous acidic catalysts such as H₂SO₄, HCl, AlCl₃ and BF₃ are commonly employed in the synthesis of organic compounds in laboratories and industries¹⁴. Hitherto, the above-mentioned catalysts have several disadvantages because of their corrosive nature, toxicity or volatile nature and brought forth large quantities of waste. As we know, the classical reaction process is switching to eco-friendly technology due to the evolution of green chemistry. In this context, apart from other issues the main subject to look at is the selection of appropriate solvent which can be easily utilized in organic reaction. Water is the essential element for the existence of life. Water being a natural solvent, has unique chemical and physical properties. Water has powerful hydrogen bonding, large dielectric constant (80.4) when compared with acetic acid (6.2), ethanol (24.3), methanol (33.1), toluene (2.0-2.4), chloroform (4.8), ether (4.3). It has high heat capacity. Water can enhance and accelerate the reaction rate and increases the selectivity of organic reactions. In spite of having these properties it is not being frequently used as an exclusive solvent in organic reaction. In recent years, certain heterocyclic molecules are synthesized using water a solvent. Water being utilized as a solvent for the synthesis of heterocyclic reactions has become a

topic of pursuit. The current pioneer is to analyze the effect of water as a solvent in the synthesis of benzoxanthenes.

Experimental:

Material:

All the chemicals were sourced from Sigma Aldrich and used without further refining. Preparative plates were made use silica gel (S.D. fine) was utilized to perform the TLC. Visualization was made with iodine chamber. The purity of the products was also confirmed by TLC.

Instrumentation:

The IR spectra using KBr pellets were recorded on a Perkin Elmer 781 Spectrophotometer, and only noteworthy absorption levels have been listed. The NMR spectra were recorded on a Bruker Avance III 400 MHz spectrometer using CDCl_3 as solvent and TMS as internal standard (chemical shifts δ in ppm). The obtained products were identified from their spectral (^1H NMR, ^{13}C NMR and IR) analyses.

General Procedure for the Synthesis:

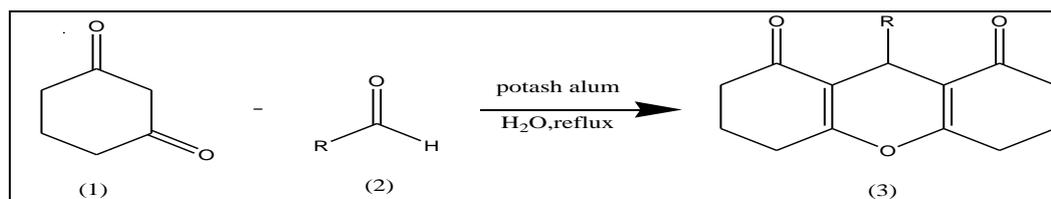
Synthesis of alkyl or aryl xanthene: A mixture of cyclodione (2 mmol), aldehydes (1 mmol), potash alum (0.5 mmol) and 15 mL of millipore water was taken in round bottom flask. The suspension was stirred in an oil bath at 80°C for a specified period of time required to complete the reaction. The progress of the reaction was monitored by TLC. The reaction mixture was cooled to the room temperature on completion of the reaction. The obtained product was extracted using the chloroform. The obtained product was dried using water bath at 90°C and further recrystallized using ethanol. The purity of the products was checked using the TLC and its melting point was observed with open capillaries using melting point apparatus.

Characterization of the Compounds is carried out on the Basis of Spectral Data:

Decahydro-9-(3,4-dimethoxyphenyl)-8aH-xanthene-1,8-dione (**3a**): IR ($\text{KBr}\cdot\text{cm}^{-1}$) ν_{max} : 1661, 1620, 1589, 1022; ^1H NMR (400MHz, CDCl_3) δ : 1.99-2.03 (m, 4H), 2.32-2.42 (m, 4H), 2.54-2.68 (m, 4H), 3.80 (s, 3H), 3.88 (s, 3H), 4.76 (s, 1H), 6.72 (d, 2H, $J = 8.4$ Hz), 7.00 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ c: 20.34, 27.16, 30.95, 36.99, 55.80, 55.96, 110.94, 112.70, 116.97, 118.78, 119.62, 120.93, 137.27, 147.55, 148.45, 163.88, 196.75.

9-(4-Fluorophenyl)-3,4,6,7-tetrahydro-2H-xanthene-1,8(5H,9H)-dione (**3b**): IR ($\text{KBr}\cdot\text{cm}^{-1}$) ν_{max} : 2955, 1721, 1649, 1598; ^1H NMR (400 MHz, CDCl_3) δ : 1.99-2.04 (m, 4H), 2.32-2.41 (m, 4H), 2.55-2.64 (m, 4H), 4.78 (s, 1H), 6.88-6.96 (m, 2H), 7.04-7.14 (m, 1H), 7.24-7.26 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ : 20.30, 27.15, 31.05, 36.94, 114.99, 115.55, 129.92, 132.71, 164.00, 196.64.

Decahydro-9-(3-nitrophenyl)-8aH-xanthene-1,8-dione (**3c**): IR ($\text{KBr}\cdot\text{cm}^{-1}$) ν_{max} : 2918, 1721, 1602, 1379; 9-(4-chlorophenyl)-decahydro-8aH xanthene-1,8-dione (**3d**):IR ($\text{KBr}\cdot\text{cm}^{-1}$) ν_{max} : 2922, 1720, 1088, 827. Decahydro-9-(3,4,5-trimethoxyphenyl)-8aH-xanthene-1,8-dione (**3e**): IR ($\text{KBr}, \text{cm}^{-1}$) ν_{max} : 2995, 1718, 1651, 1233.



Physical data of the synthesised compounds 3a-d in presence of potash alum (0.5 mmol) in water.

ENTRY	R	TIME (hours)	YIELD (%)	M. Pt ($^\circ\text{C}$)
3a	-3,4-(OCH_3) $_2$ - C_6H_3	6	78	171-178
3b	-4-F- C_6H_4	6	85	234-240
3c	-3- NO_2 - C_6H_4	10	77	190-195

3d	-4-Cl-C ₆ H ₄	6	83	160-165
3e	-3,4,5-(OCH ₃) ₂ -C ₆ H ₂	6	86	169-175

Result And Discussion:

The benzoxanthenes (**3a-e**) were synthesized through the cyclocondensation reaction of cyclohexan-1,3-dione (**1**) (2 mmol), arylaldehyde (1 mmol), potash alum (0.5 mmol) and 15 mL of millipore water (Scheme 1). TLC was performed to monitor the progress of the reaction. IR, ¹H NMR spectral data was used to characterize the synthesized compounds (included in experimental section). The compound Decahydro-9-(3,4-dimethoxyphenyl)-8aH-xanthene-1,8-dione (**3a**) was regarded as a representative example and its spectral characterizations were discussed below.

Proton Chemical Shift Assignment: The ¹H NMR spectrum of **3a** (Fig. 1) reveals that a multiplet between δ 1.99-2.03 ppm integrating for four protons. The other two multiplets appeared in the range of δ 2.32-2.42 ppm, δ 2.54-2.68 ppm also integrating for four protons each. The above three multiplets integrating for total of twelve protons are due to the protons at C-2, C-3, C-4, C-5, C-6 and C-7 carbons. The two singlets appeared at δ 3.80 ppm and 3.88 ppm integrating for three protons each are due to the protons of methoxyl groups of aryl substituent. The singlet at δ 4.77 ppm is due to the benzylic proton. The three aryl protons appeared as doublet at δ 6.72 ppm [*J* = 8.4 Hz] is integrating for two protons] and singlet at δ 7.00 ppm (integrating for one proton).

Carbon Chemical Shift Assignment: The ¹³C NMR spectrum of **3a** revealed that signals at signals at 20.34, 27.16, 30.95 and 36.99 ppm are due to the aliphatic carbons. The signal at δ 20.34 ppm is due to the C-3 & C-6 carbons. The chemical shift at δ 27.16 ppm is assigned to the C-4 & C-5 carbons, while the signal at δ 30.95 ppm was assigned to C-2 & C-7 atoms. The signal at δ 36.99 ppm is due to the C-9. The signals at δ 55.80 and 55.96 ppm are due to the methoxyl carbons of aryl substituent. The chemical shift values at δ 110.94 & 112.70 ppm are assigned to alkene carbons adjacent to the carbonyl functions. On the other hand the alkene carbons adjacent to the oxygen are appeared at δ 147.55 & 148.55 ppm. The aryl carbons are appeared at δ 116.97, 118.78, 119.62, 120.93, 137.27 and 163.88 ppm. The extreme down field signal at δ 196.75 ppm, was assigned to carbonyl carbon. Similarly for other compounds in the series was assigned and included in the experimental section. The compounds **3d** and **3e** are not soluble in the normal NMR solvents and hence IR spectral data only added for those samples.

Conclusion:

The use of water as a green solvent and alum as a green catalyst offers a convenient, nontoxic, inexpensive approach for the synthesis of benzoxanthenes. This procedure is simpler, economical and faster, consistent with the green chemistry theme which affords good yield.

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