ACETIC ACID AS A CATALYST IN THE SYNTHESIS OF BENZOXANTHENES


Keywords: Multicomponent reactions; acetic acid; benzoxanthenes.

Multi-functionalized xanthenes were synthesised using arylaldehydes and 1,3-dicarbonyl compounds through multi-component reactions using acetic acid as the catalyst and all these newly synthesized compounds have been characterized using 1H NMR, 13C NMR and IR spectral data.

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Introduction

The multicomponent reactions (MCR) are extremely significant due to their broad range of applications in pharmaceutical chemistry for drug discovery. MCRs are extremely convergent, producing a remarkably high increase of molecular complexity in just one step. Xanthenes and its derivatives are important in the area of medicinal chemistry. Xanthenes have wide range of biological and therapeutic properties such as antibacterial, antiviral and anti-inflammatory actions as good as in Photodynamic therapy. Furthermore, due to their useful spectroscopic properties, they were used as dyes in laser technologies and in fluorescent materials for visualization of bio molecules. It generated great attention due to its interesting biological activity.1-8

Acetic acid is one of the simplest carboxylic acid, which has more applications in industrial chemical, mainly used in the production of cellulose acetate for photographic film and polyvinyl acetate for wood glue, as well as synthetic fibres and fabrics.9 In the continuation of our earlier interest on xanthenes,10-13 in the present work, we report an efficient and convenient procedure for the synthesis of xanthenes employed by the union of aldehyde and 1,3-dicarbonyl compounds in the presence acetic acid as homogeneous catalyst under thermal conditions.

Experimental

Material

All the chemicals were purchased from Sigma Aldrich and used without further purification. TLC was performed on preparative plates of silica gel (s.d.fine). Visualization was made with iodine chamber. The purity of the products was also confirmed by TLC.

Instrumentation

Melting points were recorded on Elchem Microprocessor in open capillary tubes and uncorrected. The IR spectra were recorded on a Perkin Elmer 781 Spectrophotometer using KBr pellets, and only noteworthy absorption levels (reciprocal centimeters) were listed. The NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer using TMS as internal standard (chemical shifts δ in ppm).

General procedure for the synthesis of xanthenes

A mixture of cyclodione 0.25g(2 mmol) / dimethylidione 0.28g(2 mmol) and arylaldehydes in acetic acid was heated at 60°C. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature. The crude product was quenched into crushed ice mixture and further it was neutralized with 10% NaHCO3 solution. The products were characterized by IR, NMR spectroscopic data and the melting point of compounds was noted.

3,4,6,7-tetrahydro-9-(3,4-dimethoxyphenyl)-3,3,6,6-tetra methyl-2H-xanthen-1,8(5H,9H)-dione (3a)

IR (KBr, cm⁻¹) ν max: 1667, 1504, 1449, 999; 1H NMR (400 MHz, CDCl₃) δ_H: 1.00 (s, 6H, -CH₃), 1.10 (s, 6H, -CH₃), 2.18 (d, 2H, J = 16.4 Hz, -CH₂axial), 2.44 (d, J = 16.4 Hz, 2H, -CH₂ equatorial), 3.80 (3H, -OCH₃ of aryl), 3.86 (s, 3H, -OCH₃ of aryl), 4.70 (s, 1H, -CH), 6.71 (d, 1H, J = 8.4 Hz, aryl proton at C6’ ortho), 6.75 (d, 1H, J = 8.4 Hz, aryl proton at CS’ meta), 7.20 (d, 1H, J = 4 Hz, aryl proton at C2’ ortho); 13C NMR (100 MHz, CDCl₃) δ_C: 27.3, 29.4, 31.2, 32.2, 40.9, 50.8, 55.8, 55.9, 110.8, 112.3, 115.8, 120.1, 134.0, 147.4, 148.4, 162.2, 196.6.

3,4,6,7-tetrahydro-9-(3,4,5-trimethoxyphenyl)-3,3,6,6-tetra methyl-2H-xanthen-1,8(5H,9H)-dione (3b)

IR (KBr, cm⁻¹) ν max: 2816, 1667, 1504, 999; 1H NMR (400 MHz, CDCl₃) δ_H: 1.03 (s, 6H, -CH₃), 1.12 (s, 6H, -CH₃), 2.24 (m, 4H, CH₂), 2.47 (m, 4H, CH₂), 3.77 (3H, -OCH₃), 3.85 (s, 6H, -OCH₃), 4.71 (s, 1H, CH), 6.51 (d, 2H,
The carefully synthesized compounds have been characterized using IR, NMR (1H, 13C), and mass spectral methods. Two solvents, ethanol and acetic acid, were used to study the effect of solvents on the reaction. The cyclocondensation reaction was monitored by TLC. The careful examination of the IR spectra and NMR data indicated that the doublets at 2.18 ppm and 2.44 ppm integrating for two protons each were due to the methyl protons on C-11 and C-12.

The benzoxanthenes (3a-e) were synthesized through the cyclocondensation reaction of 5,5-dimethylcyclohexan-1,3-dione (1) with arylaldehyde (2a-e) in acetic acid (Scheme 1). The product was isolated by column chromatography and characterized by IR, 1H NMR, and mass spectral methods. The compound 9-(4-hydroxy-3,5-dimethoxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (3a) was considered as a representative example and its spectral characterization described below.

**Results and Discussion**

The benzoxanthenes (3a-e) were synthesized through the cyclocondensation reaction of 5,5-dimethylcyclohexan-1,3-dione (1) and arylaldehyde (2a-e) in acetic acid (Scheme 1). The progress of the reaction was monitored by TLC. The attempt was found to be successful since it afforded the desired product. The IR, 1H NMR spectral data (included in experimental section). The compound 9-(4-hydroxy-3,5-dimethoxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (3a) was considered as a representative example and its spectral characterization described below.

**Scheme 1. Synthesis of Benzoxanthenes**

*Proton Chemical Shift Assignment:* The careful examination of the 1H NMR spectrum of 3a (Fig. 1) reveals that the two singlets appeared at δ 1.00 ppm and 1.10 ppm integrating for six protons each were due to the methyl protons on C-11, C-11′ and C-12, C-12′.

**Figure 1.** 1H NMR spectrum of 3,4,6,7-tetrahydro-9-(3,4-dimethoxyphenyl)-3,3,6,6-tetramethyl-2H-xanthen-1,8(5H,9H)-dione (3a).
Carbon Chemical Shift Assignment: The $^{13}$C NMR spectrum of 3a revealed that signals at 27.26 ppm and 29.35 ppm correspond to the carbons at C-11, 11' and C-12, 12' respectively. The signals at 31.23 and 32.20 ppm are due to the methoxyl carbon of aryl ring. Signals at 110.83 and 162.10 ppm are due to the C3, C5 and C2, C6 carbons respectively. The signals at 120.11, 136.99, 147.45 and 148.43 are due to the aryl carbons. The signal at 162.19 ppm correspond to carbonyl carbons. Similarly all other compounds in the series 3b-e also be characterized and included in the experimental section. The above discussion clearly revealed the formation of the desired compounds.

Conclusion

In conclusion the acetic acid was found to be a best solvent cum catalyst in the synthesis of benzoxanthenes and afford the better yield than other methods.

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References


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