ACETIC ACID AS A CATALYST IN THE SYNTHESIS OF BENZOXANTHENES

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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 ^{1}H NMR, ^{13}C 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 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) / dimethyldione 0.28g(2 mmol) and arylaldehydes in acetic acid was heated at 60C. 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% $NaHCO_3$ solution, solids are filtered, purified through crystallisation using pet. ether. 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-2*H*-xanthene-1,8(5*H*,9*H*)-dione (3a)

IR (KBr,cm^{-1}) ν_{max}: 1667, 1504, 1449, 999; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.00 (s, 6H, -CH_3),1.10 (s, 6H, -CH_3), 2.18 (d, 2H, *J* = 16.4 Hz, -$CH_{2\ axial}$), 2.44 (d, *J* = 16.4 Hz, 2H, -CH_2 axial), 2.46 (m, 4H, -CH_2 equatorial), 3.80 (s, 3H, -OCH_3 of aryl), 3.86 (s, 3H, -OCH_3 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 C5′ *meta*), 7.20 (d, 1H, *J* = 4 Hz, aryl proton at C2′ *ortho*); ^{13}C NMR (100 MHz, $CDCl_3$) 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-2*H*-xanthene-1,8(5*H*,9*H*)-dione (3b)

IR (KBr,cm^{-1}) ν_{max}: 2816, 1667, 1504, 999; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.03 (s, 6H, -CH_3), 1.12 (s, 6H, -CH_3), 2.24 (m, 4H, CH_2), 2.47 (m, 4H, CH_2), 3.77 (s, 3H,-OCH_3), 3.85 (s, 6H,-OCH_3), 4.71 (s, 1H, CH), 6.51 (d, 2H, aryl

protons); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 27.2, 28.9, 32.2, 40.9, 50.7, 56.1, 60.3, 105.1, 115.6, 136.6, 139.8, 152.8, 162.4, 196.6.

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

IR (KBr,cm^{-1}) ν_{max} 1667, 1483, 1360, 1011; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.00-2.30 (m, 4H, -CH_2), 2.33-2.42 (m, 4H, -CH_2), 2.56-2.70 (m, 4H, -CH_2), 4.85 (s, 1H, CH), 7.26-7.52 (m, 9H, ArH).

3,4,6,7-tetrahydro-9-(3-hydroxyphenyl)-3,3,6,6-tetramethyl-2*H*-xanthene-1,8(5*H*,9*H*)-dione (3d**)**

IR (KBr,cm^{-1}) ν_{max} 2963, 1659, 1597, 1199; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.00 (s, 6H, -CH_3), 1.10 (s, 6H, -CH_3), 2.20 (d, 2H, J = 16.4 Hz, -$CH_{2\ axial}$), 2.25 (d, 2H, J = 16.4 Hz, -$CH_{2\ axial}$), 2.46 (m, 4H, $CH_{2equatorial}$) 4.73 (s, 1H, CH), 6.58 (d, 1H, J = 7.7 Hz, ArH), 6.70 (d, 1H, J = 7.7 Hz, ArH), 7.02 (s, 1H, ArH), 7.05 6.58 (t, 1H, J = 7.7 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 27.4, 29.2, 31.7, 32.3, 40.9, 50.7, 77.4, 113.6, 115.6, 116.3, 119.7, 129.2, 145.6, 156.0, 162.7, 197.0.

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

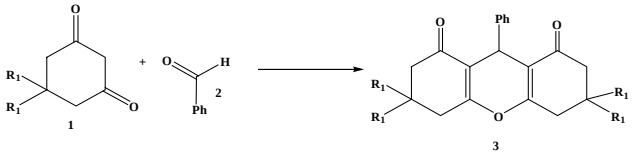
IR(KBr,cm^{-1}) ν_{max} 2955, 1668, 1412, 999; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.02 (s, 6H, -CH_3), 1.10 (s, 6H, -CH_3), 2.16 (d, 2H, J = 16.2 Hz, -$CH_{2\ axial}$), 2.35 (d, 2H, J = 16.4 Hz, -$CH_{2\ axial}$), 2.44 (m, 4H, $CH_{2equatorial}$) 4.95 (s, 1H, CH), 6.95 (d, J = 9.6 Hz, 2H, ArH), 7.02 (m, J = 9.6 Hz, 1H, ArH), 7.15 (dd, J = 8.4 Hz, 1.6 Hz, 2H, ArH), 7.26 (dd, J = 8.4 Hz, 1.6 Hz, 2H, ArH), 7.38 (d, J = 8.4 Hz, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 27.4, 29.3, 32.1, 40.8, 50.7, 76.7, 113.3, 126.8, 129.9, 132.8, 134.0, 163.2, 196.6.

9-(2,4-dichlorophenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexa hydro-1*H*-xanthene-1,8(2*H*)-dione (3f**)**

IR (KBr,cm^{-1}) ν_{max} 1667, 1466, 1408, 567; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.00 (s, 6H, -CH_3), 1.09 (s, 6H, -CH_3), 2.23 (m, 8H, CH_2), 4.7 (s, 1H, CH), 6.51 (m, 3H, ArH).

Results and Discussion

The benzoxanthenes (**3a-e**) were synthesized through the cyclocondensation reaction of 5,5-dimethylcycloheaxan-1,3-dione (**1**) (2mmol), arylaldehyde (**2a-e**) (1 mmol) in acetic acid (Scheme 1). The progress of the reaction was monitored by TLC. The attempt was found to be successful since it affords the desired product. To improve the yield the same reaction was attempted under different solvents such as ethanol, chloroform, acetic acid and found that acetic acid act as better solvent as well as the catalyst. All the synthesized compounds have been characterized using IR, ^{1}H 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-1*H*-xanthene-1,8(2*H*)-dione (**3a**) was considered as a representative example and its spectral characterization described below.



Cpd	-R_1	-Ph
3a	-CH_3	-3,4-$(OCH_3)_2$-C_6H_3
3b	-CH_3	-3,4,5-$(OCH_3)_3$-C_6H_2
3c	-H	-4-(C_6H_5)-C_6H_4
3d	-CH_3	-3-(OH)-C_6H_4
3e	-CH_3	-4-(C_6H_5)-C_6H_4
3f	-CH_3	-2,2-$(Cl)_2$-C_6H_3

Scheme 1. Synthesis of Benzoxanthenes

Proton Chemical Shift Assignment: The careful examination of ^{1}H 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 at C-11, 11′ and C-12, 12′.

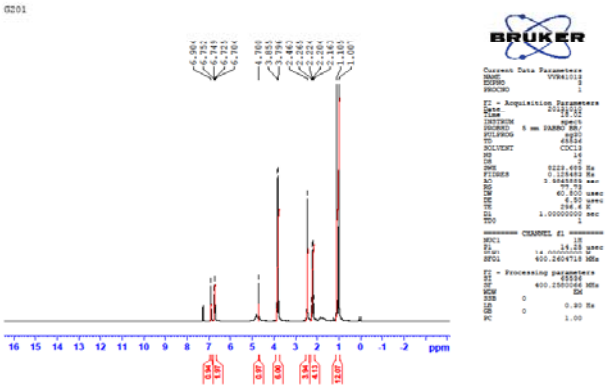


Figure 1. ^{1}H NMR spectrum of 3,4,6,7-tetrahydro-9-(3,4-dimethoxyphenyl)-3,3,6,6-tetramethyl-2*H*-xanthene-1,8(5*H*,9*H*)-dione (3a).

The doublets at 2.18 ppm and 2.44 ppm integrating for two protons each with the coupling constant of 16.4 Hz were due to the axial protons of the cyclohexane ring part (at C-8, C-8′, C-10, C-10′), whereas its equatorial protons appeared as multiplet at 2.46 integrating for four protons. The singlet appeared at 3.80 ppm and 3.86 ppm integrating for three protons each is due to the methyl protons of methoxyl group on aryl ring. The signal at δ 4.70 ppm appeared as singlet integrating for one proton has been assigned as proton at C-4. The three signals appeared between δ 6.70-6.90 ppm is due to the aryl protons and assigned as follows; The doublet at 6.71 ppm integrating for one proton with the coupling constant of 8.4 Hz is due to the C6′ *ortho* of aryl ring, The another doublet integrating for one proton at 6.75 ppm with the J = 8.4 Hz was assinged as aryl proton at C5′ *meta*. The remaining doublet at 7.20 which also integrates for one proton was due to the C2′ *ortho* of the aryl ring.

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 carbons at C-10, C-10′ and C-9 and C-9′ respectively. Signal at 50.75 ppm may be bue to the carbons at C-8 and C-8′. Signals at 55.76 and 55.88 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 carbons at C-2 and C-6. The signal at 196.50 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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