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Highly efficient multi component synthesis of xanthenes catalyzed by hydroxyapatite

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Abstract : A new protocol was established to synthesis xanthenes using hydroxyapatite (phosphates) as a catalyst through multi component reaction of arylaldehydes and 1,3-dicarbonyls, which afforded high yield with purity. All the newly synthesized xanthenes were characterized using NMR, IR and Mass spectral data. The required hydroxyapatite catalyst was synthesized by co-precipitation method and characterized using XRD, SEM and E-DAX analysis.

Keywords : Multi component reactions, hydroxyapatite, xanthenes.

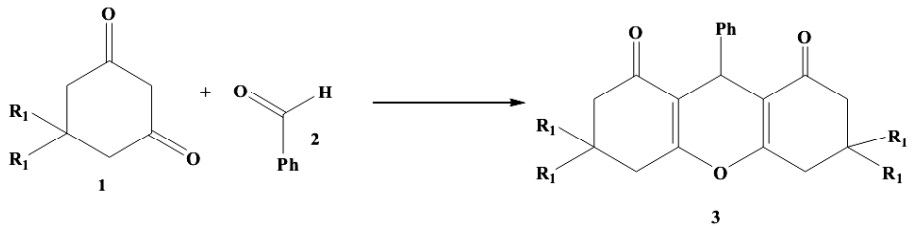
Introduction

The multi-component reactions (MCR) are extremely significant due to their broad range of applications in pharmaceutical chemistry for drug discovery. Such reactions provide a powerful tool for the synthesis of various organic compounds in a single step, thus avoiding isolation of intermediates and waste products. Xanthenes and its derivatives are important in the area of medicinal chemistry. Xanthene is an O-bridgehead heterocyclic ring system which has significant biological activities such as antifungal, antiviral, anti-inflammatory, antibacterial and herbicidal activities. Furthermore, these compounds are also used in laser technologies as dyes and in biotechnology as fluorescent materials[1–6]. Hydroxyapatite (HAP, $Ca_{10}(PO_4)_6(OH)_2$) is an important class of biomaterial which have chemical and structural similarity with the teeth and bone. It is a good heterogeneous catalyst due to its high adsorption capacity, acid-base properties and easily recoverable from the reaction medium. Moreover, it is used as macro-ligand for different catalytic active centers[7,8]. 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 of hydroxyapatite as heterogeneous catalyst under thermal conditions.

Results and discussion

The activity of the prepared catalyst as described in experimental section was first examined in the model reaction between trimethoxybenzaldehyde and dimedone in 0.1 g HAP (Scheme 1). Initially, different solvents were employed in this reaction and ethanol was chosen as suitable solvent which afforded maximum yield. We also examined different homogeneous and heterogeneous catalysts in this reaction, but compared to HAP all other catalysts afford only less yield. The amount of HAP on reaction rate was investigated for this reaction and it was discovered that by increasing the amount of catalyst more than 0.1 g, there is no gain in the yield. Thus, 0.1 g of HAP in ethanol is sufficient to catalyse this reaction. To show the scope of the developed protocol, different aryl aldehydes substituted with electron-withdrawing and electron-releasing groups were selected and the outputs are summarized in Table 1. After the reaction, the HAP catalyst recovered by simple filtration and reused after washing with acetone and ethyl acetate and calcined at 450 °C. The catalyst was found to be effective for four cycles without apparent loss of catalytic activity.

Proton chemical shift assignment : The careful examination of ^{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)** (Fig. 1) reveals that the singlets appeared at δ 1.01 ppm indicating the six protons for the methyl protons at C-11,11′. The signal at δ 1.12 ppm showing the six protons is due to the methyl protons at C-12,12′. The multiplet at 2.16–2.27 ppm integrating for



Sl. no	R_1	Ph	Time	Yield (%)
3a	CH_3	3,4-$(OCH_3)_2$-C_6H_3	45	82
3b	CH_3	3,4,5-$(OCH_3)_3$-C_6H_2	45	81
3c	H	4-(C_6H_5)-C_6H_4	40	87
3d	CH_3	3-(OH)-C_6H_4	45	83
3e	CH_3	4-(C_6H_5)-C_6H_4	45	82
3f	CH_3	2,2-$(Cl)_2$-C_6H_3	40	89

Scheme 1. Synthesis of xanthenes.

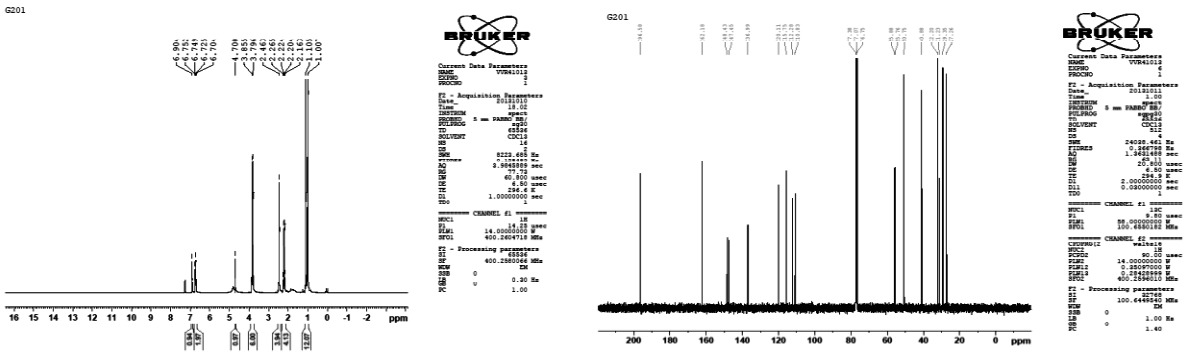


Fig. 1. ^1H and ^{13}C NMR spectrum of 3,4,6,7-tetrahydro-9-(3,4-dimethoxyphenyl)-3,3,6,6-tetramethyl-2*H*-xanthene-1,8(5*H*,9*H*)-dione (**3a**).

four protons is due to the protons of C-10,10′. Another multiplet at 2.47 ppm integrating for four protons is due to protons at C-8,8′. 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.

Carbon chemical shift assignment : The ^{13}C 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)** 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-f** have been characterized and included in the experimental section.

Experimental

Material :

All commercially available reagents were purchased from Sigma-Aldrich and Merck used without further purification. TLC was performed on preparative plates of silica gel (AVRA). Visualization was made by iodine chamber.

Instrumentation :

The IR spectra recorded on a Perkin-Elmer 781 Spectrophotometer using KBr pellets over the region 400–4000 cm^{-1}. The ^1H and ^{13}C NMR spectra were obtained by Bruker 400 MHz spectrometer using tetramethylsilane (TMS) as internal standard and chemical shifts are expressed in parts per million (ppm). Melting points were recorded on Elchem Microprocessor in open capillary tubes and uncorrected.

Synthesis of hydroxyapatite :

250 mL of a solution containing 7.92 g of diammonium hydrogen phosphate [$(NH_4)_2HPO_4$] was dissolved in 250 ml doubly distilled water and the pH adjusted to 11 with ammoniumhydroxide. It was added dropwise into 150 mL of a solution containing 23.6 g of calcium nitrate [$Ca(NO_3)_2.4H_2O$] under constant stirring and the resultant milky mixture was refluxed for 4 h. Filtration of the solid material followed by washing with double distilled water, dried overnight at 80 °C and calcined in air at 900 °C for 30 min provided hydroxyapatite catalyst.

General procedure for the synthesis of xanthenes :

The catalyst 0.1 g of hydroxyapatite was added to the stirred mixture of the aldehyde **1** (1 mmol), and cyclic diketone **3** (1 mmol) and the reaction mixture was refluxed in 5 mL ethanol. After completion of the reaction as indicated by TLC, the catalyst was recovered by simple filtration and washed with organic solvents. The residue was recrystallized leading to target compounds. The recovered hydroxyapatite catalyst was calcined for 2 h at 400 °C for subsequent reactions to demonstrate its reusability.

3,4,6,7-Tetrahydro-9-(3,4-dimethoxyphenyl)-3,3,6,6-tetramethyl-2H-xanthene-1,8(5H,9H)-dione (**3a**) : IR (KBr, cm^{-1}) : 1667, 1504, 1449, 999; ^1H NMR (400 MHz, $CDCl_3$) δ_H : 1.00 (6H, s, $-CH_3$), 1.10 (6H, s, $-CH_3$), 2.44 (2H, d, *J* 16.4 Hz, $-CH_2$ axial), 2.18 (2H, d, *J* 16.4 Hz, $-CH_2$ axial), 2.46 (4H, m, $-CH_2$ equatorial), 3.80 (3H, s, $-OCH_3$ of aryl), 3.86 (3H, s, $-OCH_3$ of aryl), 4.70 (1H, s, -CH), 6.71 (1H, d, *J* 8.4 Hz, aryl proton at C6′ *ortho*), 6.75 (1H, d, *J* 8.4 Hz, aryl proton at C5′ *meta*), 7.20 (1H, d, *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.

3,3,6,6-Tetramethyl-9-(3,4,5-trimethoxyphenyl)-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (**3b**) : IR (KBr, cm^{-1}) : 2816, 1667, 1504, 999; ^1H NMR (400 MHz, $CDCl_3$) δ_H : 1.03 (6H, s, $-CH_3$), 1.12 (6H, s, $-CH_3$), 2.24 (4H, m, CH_2), 2.47 (4H, m, CH_2), 3.77 (3H, s, $-OCH_3$), 3.85 (6H, s, $-OCH_3$), 4.71 (1H, s, CH), 6.51 (2H, d, 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-1H-xanthene-1,8(2H)-dione (**3c**) : IR (KBr, cm^{-1}) : 1667, 1483, 1360, 1011; ^1H NMR (400 MHz, $CDCl_3$) δ_H : 2.00–2.30 (4H, m, $-CH_2$), 2.33–2.42 (4H, m, $-CH_2$), 2.56–2.70 (4H, m, $-CH_2$), 4.85 (1H, s, CH), 7.26–7.52 (9H, m, ArH).

9-(3-Hydroxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (**3d**) : IR (KBr, cm^{-1}) : 2963, 1659, 1597, 1199; ^1H NMR (400 MHz, $CDCl_3$) δ_H : 1.00 (6H, s, $-CH_3$), 1.10 (6H, s, $-CH_3$), 2.20 (2H, d, *J* 16.4 Hz, $-CH_2$ axial), 2.25 (2H, d, *J* 16.4 Hz, $-CH_2$ axial), 2.46 (4H, m, CH_2 equatorial), 4.73 (1H, s, CH), 6.58 (1H, d, *J* 7.7 Hz, ArH), 6.70 (1H, d, *J* 7.7 Hz, ArH), 7.02 (1H, s, ArH), 7.05–6.58 (1H, t, *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-1H-xanthene-1,8(2H)-dione (**3e**) : IR (KBr, cm^{-1}) : 2955, 1668, 1412, 999; ^1H NMR (400 MHz, $CDCl_3$) δ_H : 1.02 (6H, s, $-CH_3$), 1.10 (6H, s, $-CH_3$), 2.16 (2H, d, *J* 16.2 Hz, $-CH_2$ axial), 2.35 (2H, d, *J* 16.4 Hz, $-CH_2$ axial), 2.44 (4H, m, CH_2 equatorial), 4.95 (1H, s, CH), 6.95 (2H, d, *J* 9.6 Hz, ArH), 7.02 (1H, m, *J* 9.6 Hz, ArH), 7.15 (2H, dd, *J* 8.4 Hz, 1.6 Hz, ArH), 7.26 (2H, dd, *J* 8.4 Hz, 1.6 Hz, ArH), 7.38 (2H, d, *J* 8.4 Hz, 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-hexahydro-1H-xanthene-1,8(2H)-dione (**3f**) : IR (KBr, cm^{-1}) : 1667, 1466, 1408, 567; ^1H NMR (400 MHz, $CDCl_3$) δ_H : 1.00 (6H, s, $-CH_3$), 1.09 (6H, s, $-CH_3$), 2.23 (8H, m, CH_2), 4.7 (1H, s, CH), 6.51 (3H, m, ArH).

Conclusion

An efficient synthesis of xanthenes was achieved be-

tween aromatic aldehydes and active methylene compounds by using hydroxyapatite as the catalyst and ethanol as the solvent in eco-friendly procedure. Moreover, the hydoxyapatite catalyst showed better yields and reusable for four cycles successfully.

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