



ONE-POT THREE-COMPONENT SYNTHESIS OF XANTHENE-1,8-DIONES UNDER CATALYST-FREE CONDITION

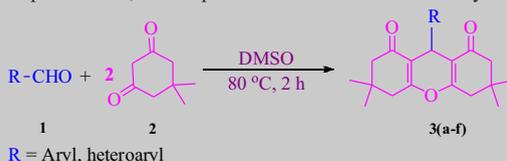
Mangalavathi

Department Of Studies In Chemistry, Jnanabharathi Campus, Bangalore University, Bengaluru 560056, India.

M. A. Pasha*

Department Of Studies In Chemistry, Jnanabharathi Campus, Bangalore University, Bengaluru 560056, India. *Corresponding Author

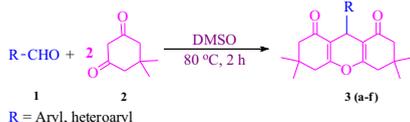
ABSTRACT An improved synthetic methodology for the preparation of medicinally important xanthene-1,8-diones by a catalyst free one-pot three-component condensation of electron rich and electron deficient aromatic/heteroaromatic aldehydes and dimedone in DMSO as a solvent, at 80 °C is reported. This new method has the advantage of a facile reaction condition, short reaction duration, absence of catalyst, absence of any workup and purification, and the products are formed in excellent yields.



KEYWORDS : 9-Aryl-hexahydro-xanthene-1,8-diones, aromatic/heteroaromatic aldehydes, dimedone, DMSO.

Introduction

Xanthene-1,8(2H)-diones exhibit a wide range of biological activities such as: Antioxidant [1], anti-inflammatory [2], antiviral [3] activities, and are found in a number of natural products [4]. A few one-pot MCRs, have been reported recently in the literature on the synthesis of xanthene-1,8(2H)-diones in the presence of various catalysts such as FeCl₃ [5], Boric acid [6], Kaolin/Ag Nanocomposite [7] and nano-ZnAl₂O₄ [8]. We have developed a solvent mediated catalyst-free synthesis of xanthene-1,8-diones 3(a-f) as shown in the Scheme 1.



Scheme 1: Synthesis of xanthene-1,8-diones 3(a-f).

Results and discussion

A model reaction of one equivalent of 4-hydroxybenzaldehyde, two equivalents of dimedone was chosen and noticed that, under solvent-free condition the reaction did not proceed to offer the desired product 3a (Table 1, entry 1). In order to understand viability of diverse solvents, the current reaction was carried out in n-hexane, benzene, toluene, xylene, THF, DMF, DMSO, EtOH and in H₂O (entries 2–10). From the results presented in the Table 1, it is clear that, in DMSO at 80 °C, the reaction proceeds to afford excellent yield of 3a (entry 10); hence, DMSO was selected as a solvent for all our further studies.

Table 1: Effect of solvent on the synthesis of 9-aryl-3,3,6,6-tetramethyl-2,4,5,7-tetrahydroxanthene-1,8(9H)-diones.

Entry	Solvent ^a	Temperature (°C)	Time (h)	Yield ^b (%)
1	No solvent	90	4	ND
2	EtOH	70	3	45
3	H ₂ O	95	3	58
4	n-hexane	60	4	50
5	Benzene	65	2	15
6	toluene	65	3	18
7	Xylene	50	3	20
8	THF	80	4	30
9	DMF	80	3	45
10	DMSO	80	2	98

^a2 mL; ^bIsolated yield; ND = Not detected.

The reaction in DMSO efficiently gave the preferred product 3a in 98% chemical yield. This excellent consequence prompted us to further

study the reaction conditions. In order to ascertain the amounts of solvent, we varied the amount and maximum yield was obtained in 2 mL DMSO (Table 2, entry 2), escalating the amount of the solvent had no considerable effect on the reaction (entries 3,4).

Table 2: Optimization of the amount of the solvent for the synthesis of 3a.

Entry	Solvent ^a (mL)	Time (h)	Yield ^b (%)
1	1.0	2	70
2	2.0	2	98
3	3.0	2	98
4	4.0	2	98

^aDMSO and ^b Isolated yield.

It was observed that, the use of DMSO as a solvent under different reaction temperatures also influenced the reaction rate and the yield of the target products as shown in the Table 3.

Table 3: Optimization of the reaction temperature for the synthesis of 3a.

Entry	Temperature (°C)	Time (h)	Yield ^a (%)
1	28	2	ND
2	40	2	20
3	50	2	40
4	60	2	75
5	80	2	98
6	100	2	90

^aIsolated yield.

After the standardization of the conditions, we then extended the method for the synthesis of different substituted xanthenediones, and carried out a series of reactions involving various aromatic and heteroaromatic aldehydes, dimedone in DMSO as a solvent at 80 °C as shown in the Table 4. All the synthesized xanthene-1,8-diones were characterized by the ¹H NMR, ¹³C NMR and mass spectral analysis.

Table 4: The synthesis of xanthenediones 3 (a-f) using DMSO at 80 °C.

Entry	Aldehyde	Product	Time (h)	Yield (%)	Mp (°C)
1	4-HOC ₆ H ₄ CHO	3a	2	98	184–186
2	Thiophene-2-CHO	3b	2	95	145–147
3	4-CH ₃ OC ₆ H ₄ CHO	3c	2	97	242–243
4	3,4-Di-CH ₃ OC ₆ H ₃ CHO	3d	2	98	175–176

5	4-NO ₂ C ₆ H ₄ CHO	3e	2	95	222–224
6	4-FC ₆ H ₄ CHO	3f	2	98	206–207

*** Isolated yield****Experimental****3.1. Materials and apparatus**

All the chemicals and reagents are commercial and were used as received, except liquid reagents which were distilled before use. Melting points were determined on a Raaga, INDIAN make melting point apparatus. The progress of the reactions was monitored by thin layer chromatography [(TLC) analytical silica gel plates (Merck 60 F₂₅₀), observed under ultraviolet (UV) light]. ¹H NMR and ¹³C NMR spectra were recorded on a Bruker Spectrophotometer in DMSO-d₆ and CDCl₃ at 400 MHz and 100 MHz respectively with TMS as an internal standard.

3.2. General procedure for the synthesis of 9-aryl-3,3,6,6-tetramethyl-2,4,5,7-tetrahydroxanthene-1,8(9H)-diones:

A 50 mL round bottom flask was charged with substituted benzaldehyde (1 mmol), dimedone (2 mmol), DMSO (2 mL, dropwise addition) and heated at 80 °C with continuous stirring for 2 h. The reaction was followed by thin layer chromatography (TLC) using hexane:ethyl acetate (7:3) as an eluent. After the completion of the reaction, the mixture was poured onto crushed ice. The solid thus precipitated was collected by filtration. Further purification was accomplished by recrystallization from absolute ethanol.

3.3. Spectral data**9-(4'-Hydroxyphenyl)-3,3,6,6-tetramethyl-2,4,5,7-tetrahydroxanthene-1,8(9H)-dione(3a):**

¹H NMR (400 MHz, DMSO-d₆): δ 0.88 (6H, s, 2 × CH₃), 1.01 (6H, s, 2 × CH₃), 2.02–2.49 (8H, m, 4 × CH₂), 4.33 (1H, s, CH), 6.55–6.58 (2H, d, J = 11.5 Hz, Ar-H), 6.91–6.94 (2H, d, J = 11.1 Hz, Ar-H), 9.40 (1H, s, OH) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 27.3, 29.9, 32.3, 41.6, 50.2, 113.8, 115.9, 130.4, 147.5, 150.6, 151.5, 196.1 ppm; Mass (m/z): [M] + 366.34.

9-(Thiophen-2-yl)-3,3,6,6-tetramethyl-2,4,5,7-tetrahydroxanthene-1,8(9H)-dione (3b):

¹H NMR (400 MHz, CDCl₃): δ 0.98 (6H, s, 2 × CH₃), 1.08 (6H, s, 2 × CH₃), 2.16–2.23 (8H, m, 4 × CH₂), 5.66 (1H, s, CH), 6.76–7.02 (3H, m, Ar-H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 26.7, 29.9, 32.3, 41.6, 50.2, 113.8, 122.5, 123.8, 126.8, 128.4, 130.4, 151.5, 196.1 ppm; Mass (m/z): [M] + 356.32.

9-(4-Methoxyphenyl)-3,3,6,6-tetramethyl-2,4,5,7-tetrahydroxanthene-1,8(9H)-dione (3c):

¹H NMR (400 MHz, CDCl₃): δ 0.80 (6H, s, 2 × CH₃), 0.94 (6H, s, 2 × CH₃), 1.87–2.02 (8H, m, 4 × CH₂), 3.73 (3H, s, OCH₃), 5.19 (1H, s, CH), 6.75–6.78 (2H, d, J = 12, Ar-H), 7.31–7.33 (2H, d, Ar-H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 26.74, 31.75, 32.28, 50.24, 55.08, 113.40, 114.46, 128.75, 138.93, 128.4, 151.01, 157.59, 196.26 ppm; Mass (m/z): [M] + 380.33.

9-(3,4-Dimethoxyphenyl)-3,3,6,6-tetramethyl-2,4,5,7-tetrahydroxanthene-1,8(9H)-dione (3d):

¹H NMR (400 MHz, DMSO-d₆): δ 0.98 (6H, s, 2CH₃), 1.09 (6H, s, 2CH₃), 1.98–2.46 (8H, m, 2CH₂), 3.65 (6H, s, OCH₃), 4.65 (1H, s, CH), 6.65 (1H, s, Ar-H), 6.73–6.74 (2H, d, J = 5.2, Ar-H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 27.0, 31.1, 40.7, 41.7, 50.6, 55.6, 55.7, 110.7, 112.1, 115.5, 120.0, 136.9, 147.3, 148.2, 162.2, 195.9, 196.5 ppm; Mass (m/z): [M] + 410.39.

9-(4-Nitrophenyl)-3,3,6,6-tetramethyl-2,4,5,7-tetrahydroxanthene-1,8(9H)-dione (3e):

¹H NMR (500 MHz, CDCl₃): δ 0.90 (s, 6H), 1.05 (s, 6H), 2.08–2.11 (2H, d, J = 6.5 Hz), 2.27–2.30 (2H, d, J = 6.5 Hz), 2.50–2.63 (4H, m), 4.63 (1H, s), 7.45–7.48 (2H, m), 8.10–8.12 (2H, m) ppm; ¹³C NMR (125 MHz, CDCl₃): δ: 27.2, 29.5, 32.1, 32.7, 50.9, 56.6, 60.8, 106.3, 115.1, 136.8, 140.7, 153.2, 163.8, 197.1 ppm.

9-(4-Fluorophenyl)-3,3,6,6-tetramethyl-2,4,5,7-tetrahydroxanthene-1,8(9H)-dione(3f):

¹H NMR (400 MHz, CDCl₃): δ 0.99 (s, 6H), 1.11 (6H, s), 2.15–2.26 (4H, dd, J = 16, 28.6 Hz), 2.46 (4H, s), 4.73 (1H, s), 6.88–6.92 (2H, t, J = 8.8 Hz), 7.24–7.27 (2H, d, J = 10.8 Hz) ppm; ¹³C NMR (125 MHz, CDCl₃): δ 27.2, 29.5, 32.0, 32.7, 50.0, 56.6, 60.7, 106.3, 115.1, 136.8, 140.7, 153.2, 163.5, 197.0 ppm.

Conclusions

In conclusion, we have herein, devised a simple, rapid and economical approach for the synthesis of a series of xanthene-1,8-diones having medicinal and pharmaceutical activities by using DMSO as polar aprotic solvent in high yields via a one-pot three component reaction through an easily accessible route. The products are readily obtained in excellent yields within 2 h.

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