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MANGANESE PERCHLORATE-CATALYZED GREENER SYNTHESIS OF 12-ARYL OR 12-ALKYL-8,9,10,12-TETRAHYDROBENZO[α]XANTHEN-11-ONE DERIVATIVES UNDER ULTRASONICATION

Bhupinder Kaur,¹ Anupama Parmar,² and Harish Kumar¹

¹Department of Chemistry, Sant Longowal Institute of Engineering and Technology, Longowal, India ²Postgraduate Department of Chemistry, M. M. Modi College, Patiala, India

GRAPHICAL ABSTRACT



Abstract A greener and more efficient protocol for the synthesis of 12-aryl or 12-alkyl-8,9,10,12-tetrahydrobenzo[a]xanthen-11-one derivatives has been developed via one-pot, three-component reaction of aromatic aldehydes, 2-naphthol, and 1,3-cyclohexadione or 5,5-dimethyl 1,3-cyclohexadione using manganese perchlorate hydrate as a catalyst under ultrasonic irradiation. Good yield, shorter reaction time, simple workup procedure, and milder reaction conditions make this protocol efficient and environmentally benign.

Keywords Manganese perchlorate hydrate; multicomponent reaction; ultrasonic irradiation; xanthenes

INTRODUCTION

Xanthenes constitute an important class of biologically active heterocycles possessing analgesic,^[1] anti-inflammatory, antibacterial, and antiviral activities.^[2-4] These compounds are being utilized as antagonists for paralyzing action of zoxazolamine^[5] and in photodynamic therapy.^[6] Xanthenes have also been employed as dyes^[7] and pH-sensitive fluorescent material for visualization of biomolecules^[8] and in laser technologies.^[9] Many xanthene derivatives are potent nonpeptidic inhibitors of recombinant human calpain I.^[10] 12-Aryl or 12-alkyl-8,9,10,12tetrahydrobenzo[α]xanthen-11-one derivatives have been synthesized by the condensation of aromatic aldehydes, 2-naphthol, and 1,3-cyclohexadione or 5,5-dimethyl 1,3-cyclohexadione. Many reagents have been reported in the literature for this

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Address correspondence to Harish Kumar, Department of Chemistry, Sant Longowal Institute of Engineering and Technology, Longowal 148-106, India. E-mail: hk67@rediffmail.com

condensation including ceric ammonium nitrate (CAN),^[11] HBF₄/SiO₂,^[12] HClO₄/ SiO₂,^[13] dodecatungstophasphoric acid,^[14] sulfamic acid,^[15] cyanuric chloride,^[16] iodine,^[17] and silica chloride.^[18] Many of these processes suffer from one or more limitations such as longer reaction time, occurrence of some side reactions, use of hazardous solvents, drastic reaction conditions, poor yield, and tedious workup procedure. For example, synthesis of 12-aryl or 12-alkyl-8,9,10,12tetrahydrobenzo[a]xanthen-11-one derivatives with some of the recently used catalysts such as Sr(oTf)₂^[19], InCl₃/P₂O₅,^[20] or pTSA-[bmim]BF₄^[21] requires high temperature and longer reaction time as compared to reaction with manganese perchlorate. Comparison of reaction conditions of some important catalysts is given in Table 1. Thus, there is a need to develop a general protocol for the rapid and efficient synthesis of these types of xanthenes. Ultrasonication is a new trend in organic chemistry, offering a versatile and facile pathway for large varieties of syntheses. A large number of reactions can be carried out under ultrasonication in good yields, shorter reaction time, and milder conditions. Ultrasonication in combination with heterogeneous catalysts had been used in the synthesis of a variety of organic compounds. In continuation of our earlier efforts to develop a novel synthetic methodology and the use of transition-metal perchlorates^[22-24] as catalysts for the organic synthesis, we report herein a facile, greener, one-pot, three-component synthesis of 12-aryl or 12-alkyl-8,9,10,12-tetrahydrobenzo $[\alpha]$ xanthen-11-ones from condensation of aromatic aldehydes, 2-naphthol, and 1,3-dicarbonyl compounds (1,3-cyclohexadione or 5,5-dimethyl 1,3-cyclohexadione) using hydrated manganese perchlorate as catalyst under ultrasonic irradiations.

RESULTS AND DISCUSSION

The optimal condition for the synthesis of 12-aryl or 12-alkyl-8,9,10,12tetrahydrobenzo[α]xanthen-11-one was studied using benzaldehyde as a model substrate. In a typical experiment, mixtures of benzaldehyde (1.0 mmol), 5,5-dimethyl-1,3-cyclohexadione (1.2 mmol), and 2-naphthol (1.0 mmol) in ethanol were placed either under ultrasonic irradiation (Scheme 1) or without ultrasonic irradiation. To study the catalytic activity, hydrated manganese perchlorate was added in varying amounts. It was found that 4 mol% catalyst was optimal to carry out the reaction. Using more than 4 mol% of the catalyst did not affect the yield

Entry	Catalyst ^[ref.]	Temp. (°C)	Reaction time (h)	Yield (%)
1	$Sr(OTf)_2^{[22]}$	80	5–7	70–89
2	$NH_2SO_3H^{[15]}$	120	1.5-2.16	79-84
3	$InCl_3/P_2O_5^{[23]}$	120	0.30-0.75	63-85
4	pTSA in the presence of ionic liquid ($[bmim]BF_4$) ^[24]	80	2.5-3.5	84–96
5	pTSA in the absence of ionic liquid ($[bmim]BF_4$) ^[24]	120	0.35-0.45	82–92
6	Cyanuric chloride ^[16]	80	0.30 - 0.70	83–93
7	Hydrated Mn(ClO ₄) ₂	25	0.40-0.75	75–88

Table 1. Synthesis of 12-aryl or 12-alkyl-8,9,10,12-tetrahydrobenzo $[\alpha]$ xanthen-11-one derivatives in the presence of various catalysts



Scheme 1.

or time of the reaction. Further it was noted that under ultrasonic irradiation the reaction completed in 40 min with 87% yield. Without ultrasonic irradiation, only 20% yield was formed in 120 min. The results of the model experiment have been summarized in Table 2. To express the generality of the reaction, various aromatic aldehydes were condensed with 1,3-dicarbonyl compound (1,3-cyclohexadione or 5,5-dimethyl-1,3-cyclohexadione) in the presence of 2-naphthol using manganese perchloratate hydrate as catalyst under ultrasonic irradiation. After the completion of reaction, the solid product was formed, which was recrystallized from ethanol. The structures of the products **1a–t** formed were established on comparison with authentic samples prepared by other methods and from elemental analysis and spectroscopic analysis. The selected spectral and physical data are given in Table 3. The methodology was also applied to heterocyclic aldehydes such as thiophene-2-carbaldehyde, furfural, and N-formylpyrrolidine, but no reaction was observed in these cases.

EXPERIMENTAL

Material and Apparatus

All melting points recorded are uncorrected, open capillary measurements, using a sulfuric acid bath. Infrared (IR) spectra were recorded using KBr pellets on a Perkin-Elmer spectrophotometer, and NMR spectra were on measured AL-300 F (Bruker) Fourier transform (FT) NMR spectrophotometer using CDCl₃ as internal standard. Sonication was performed in Elma, Transsonic T 310/H ultrasonic cleaner (with a frequency of 35 KHz) (Hans Schmidbauer GmbH & Co., Germany). The reactions were performed in open vessels.

Table	2.	Effect	of	amount	of	catalyst	with	or	without	sonication	for	the	synthesis	of	12-aryl	or
12-alkyl-8,9,10,12-tetrahydrobenzo[a]xanthen-11-one derivatives at room temperature																

Entry		With s	onication	Without sonication			
	Mn(ClO ₄) ₂ (mol%)	Yield (%)	Time (min)	Yield (%)	Time (min)		
1	1	Nil	180	Nil	180		
2	2.5	40	130	Nil	180		
3	4	87	40	20	120		
4	6	85	60	22	140		

			With ultras	sonication	Without ultrasonication		
Entry	R	\mathbf{R}_1	Time (min)	Yield (%)	Time (min)	Yield (%)	Mp (lit. mp) (°C)
1a	C ₆ H ₅	CH ₃	40	87	120	20	148-151 (149-150)[14]
1b	$4-ClC_6H_4$	CH_3	45	88	150	25	185-188 (187-188)[14]
1c	$4-OHC_6H_4$	CH_3	55	82	160	35	147-150 (150-151)[14]
1d	2-NO ₂ C ₆ H ₄	CH_3	70	80	165	40	225-227 (223-225)[13]
1e	3-NO ₂ C ₆ H ₄	CH ₃	75	78	150	35	167-170 (166-167) ^[16]
1f	3-OHC ₆ H ₄	CH ₃	65	85	130	38	238-241 (240-241) ^[13]
1g	$4 - CH_3C_6H_4$	CH ₃	50	82	140	42	176-179 (175-176)[14]
1h	$2-ClC_6H_4$	CH ₃	65	88	150	43	180-183 (179-180) ^[13]
1i	$4-NO_2C_6H_4$	CH ₃	45	75	130	48	173-175 (175-176)[16]
1j	3,4-Cl ₂ C ₆ H ₃	CH ₃	40	78	130	30	180-182 (181-182)[14]
1k	4-OCH ₃ C ₆ H ₄	CH_3	50	85	145	5	205-207 (208-209)[14]
11	C ₆ H ₅	Н	55	83	150	25	186-189 (189-190)[16]
1m	4-ClC ₆ H ₄	Н	65	76	170	28	204-207 (205-206)[14]
1n	$4 - CH_3C_6H_4$	Н	60	85	180	35	203-205 (205-206) ^[14]
10	4-BrC ₆ H ₄	Н	65	75	155	24	205-207 (208-209)[14]
1p	3-ClC ₆ H ₄	Н	55	78	160	26	208-211 (209-210)[14]
1q	3-NO ₂ C ₆ H ₄	Н	70	75	180	35	235-237 (235-236) ^[13]
1r	4-NO ₂ C ₆ H ₄	Н	65	84	165	28	235-237 (234-235)[14]
1s	2-ClC ₆ H ₄	Н	70	80	175	35	246-249 (245-246)[14]
1t	$4\text{-OCH}_3\text{C}_6\text{H}_4$	Н	65	86	180	30	181–183 (181–182) ^[14]

Table 3. Manganese perchlorate–catalyzed synthesis of 12-aryl or 12-alkyl-8,9,10,12-tetrahydrobenzo- α xanthen-11-one derivatives at room temperature

General Procedure for the Synthesis of 12-Aryl or 12-Alkyl-8,9,10,12-tetrahydrobenzo[a]xanthen-11-one

A mixture of aromatic aldehyde (1 mmol), 2-naphthol (1 mmol), 1,3-dicarbonyl compounds (1.2 mmol) (1,3-cyclohexadione or 5,5-dimethyl-1,3-cyclohexadione) and manganese perchlorate hydrate (4 mol %) in ethanol was placed under ultrasonic irradiation for the time mentioned in Table 3. The reaction was monitored by thin-layer chromotography (TLC). After the completion of the reaction, the solid product was filtered. The solid product was recrystallized from ethanol.

Selected Spectral and Physical Data of Products

9,9-Dimethyl-12-(3-nitrophenyl)-8,9,10,12-tetrahydrobenzo[a]xanthen-11-one (1e). White solid, mp 166–167 °C; IR (KBr) 3139, 2958, 2912, 1649, 1618, 1597, 1400, 1375, 1348, 1224, 1176, 1085, 812 cm^{-1} ; ¹H NMR (400 MHz, CDCl₃): $\delta = 0.94$ (s, 3H), 1.12 (s, 3H), 2.23 and 2.31 (J = 16.4 Hz, 2H), 2.59 (s, 2H), 5.80 (s, 1H), 7.32–7.39 (m, 3H), 7.34 (d, J = 7.6 Hz, 1H), 7.77–7.80 (m, 3H), 7.85 (d, J = 8.4 Hz, 1H), 7.91 (d, J = 8.0 Hz, 1H), 8.14 (d, J = 8.0 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): $\delta = 27.1$, 29.3, 32.2, 34.7, 41.3, 50.7, 113.1, 116.0, 117.3, 121.6, 123.1, 123.2, 125.2, 127.4, 128.7, 129.1, 129.6, 130.9, 131.6, 134.8, 146.8, 147.8, 148.3, 164.6, 196.9; ESI-MS $m/z = 400 \text{ (M} + 1)^+$. Anal. calcd for C₂₅H₂₁NO₄: C, 75.17; H, 5.30; N, 3.51. Found: C, 75.32; H, 5.12; N, 3.70. **12-(3,4-Dichlorophenyl)-9,9-dimethyl-8,9,10,12-tetrahydrobenzo[a]xanthen-11-one (1j).** White solid, mp 181–182 °C; IR (KBr) 3138, 2962, 1649, 1637, 1618, 1596, 1558, 1398, 1384, 1373, 1234, 1202, 1070, 819 cm^{-1} ; ¹H NMR (400 MHz, CDCl₃): $\delta = 0.98$ (s, 3H), 1.12 (s, 3H), 2.24 and 2.30 (J = 16.4 Hz, 2H), 2.58 (s, 2H), 5.70 (s, 1H), 7.19–7.24 (m, 1H), 7.30–7.48 (m, 5H), 7.78–7.85 (m, 2H), 7.86 (d, J = 8.4 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃): $\delta = 27.2$, 29.2, 32.3, 34.1, 41.3, 50.7, 113.3, 116.3, 117.1, 123.2, 125.1, 127.3, 128.0, 129.4, 130.1, 130.3, 131.0, 131.5, 132.2, 144.9, 147.7, 164.3, 196.8; ESI-MS m/z = 423 (M + 1)+. Anal. calcd. for C₂₅H₂₀Cl₂O₂: C, 70.93; H, 4.76. Found: C, 71.05; H, 4.68.

12-(4-Bromophenyl)-8,9,10,12-tetrahydrobenzo[*a*]**xanthen-11-one (10)**. Colorless crystals, mp 208–209 °C; IR (KBr): 2823, 647, 1595, 1473, 1375, 1224, 1190, 1175, 1130, 1066, 954, 812, 746 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): 1.93–2.09 (m, 2H), 2.32–2.51 (m, 2H), 2.62–2.79 (m, 2H), 5.70 (s, 1H), 7.05 (t, J=8.0 Hz, 1H), 7.20 (d, J=8.0 Hz, 1H), 7.32–7.35 (m, 2H), 7.39 (t, J=7.6 Hz, 2H), 7.45 (t, J=8.0 Hz, 1H), 7.78 (d, J=8.4 Hz, 1H), 7.80 (d, J=8.0 Hz, 1H), 7.89 (d, J=8.4 Hz, Hz, 1H); Anal. calcd. for C₂₃H₁₇BrO₂: C, 68.16; H, 4.23. Found: C, 68.32; H, 4.05.

12-(4-Methoxyphenyl)-8,9,10,12-tetrahydrobenzo[*a*]**xanthen-11-one (1t).** Colorless crystals, mp 181–182 °C; IR (KBr): 2945, 2833, 1651, 1595, 1460, 1378, 1251, 1227, 1188, 1175, 1130, 1034, 952, 829, 748 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): 1.91–2.08 (m, 2H), 2.31–2.48 (m, 2H), 2.57–2.76 (m, 2H), 3.69 (s, 3H), 5.69 (s, 1H), 6.71 (d, J=8.0 Hz, 2H), 7.23–7.45 (m, 5H), 7.77 (t, J=8.4 Hz, 2H), 7.96 (d, J=8.4 Hz, 1H). Anal. calcd. for C₂₄H₂₀O₃: C, 80.88; H, 5.66. Found: C, 81.02; H, 5.53.

CONCLUSION

We describe here a manganese perchlorate hydrate–catalyzed green protocol for the synthesis of 12-aryl or 12-alkyl-8,9,10,12-tetrahydrobenzo[α]xanthen-11-one under ultrasonic irradiation in excellent yields. The present methodology gives several advantages such as simple procedure, easy workup, clean reaction profile, use of inexpensive catalyst, use of green solvents, and milder reaction conditions.

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