



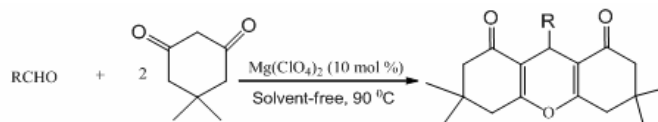
Mg(ClO₄)₂ CATALYZED PREPARATION OF XANTHENEDIONES UNDER SOLVENT-FREE CONDITIONS

Hamideh EMTIAZI and Mohammad A. AMROLLAHI*

Department of Chemistry, Yazd University, P.O.Box 89195-741, Yazd, Iran

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This report provides a description of an efficient and simple procedure for the synthesis of substituted xanthenediones via a one-pot three-component reaction of 5,5-dimethyl-1,3-cyclohexanedione and aldehydes in the presence of Mg(ClO₄)₂ under solvent-free conditions at 90 °C. This procedure offers several advantages such as simple methodology, high yield, and short reaction time.



INTRODUCTION

Xanthene derivatives are considered important because of their wide range of biological and pharmaceutical properties such as antibacterial,¹ antiviral,² anti-depressants, and antimalarial ones.³ These compounds are utilized in dyes,⁴ and fluorescent materials.⁵ Therefore, a variety of reagents and catalysts has been reported for the preparation of these compounds, such as amberlyst-15,⁶ p-TSA,⁷ polytungstozincate acid,⁸ [Hmim]TFA,⁹ Fe(HSO₄)₃,¹⁰ NaHSO₄-SiO₂ or silica chloride,¹¹ hexadecyltrimethylammonium bromide (HTMAB),¹² and InCl₃ or P₂O₅.¹³ Using each of these materials has its own advantages, but it also suffers from one or more disadvantages such as prolonged reaction time, low yields, use of toxic and costly catalysts, harsh reaction conditions, and complex work-up procedures. Therefore it would be highly desirable to avoid these limitations by using a new and efficient catalyst with high catalytic activity, short reaction time, suitability for green chemistry, and easy work-up for preparation of xanthenediones. Mg(ClO₄)₂, as a white crystal, is moisture-stable, non-toxic, cheap,

and commercially available. Previously, it has gained much interest in the synthesis of 1,5-benzodiazepines,¹⁴ the Diels-Alder reaction,¹⁵ the asymmetric reduction of carbonyl compounds,¹⁶ the Knoevenagel condensation,¹⁷ the synthesis of imines and phenyl hydrazine,¹⁸ and the synthesis of t-butyl ethers.¹⁹ In continuation of our research on organic synthesis,²⁰ we report the synthesis of 9-aryl-3,3,6,6-tetramethyl-tetrahydroxanthene-1,8-diones through the condensation of various aldehydes and 5,5-dimethyl-1,3-cyclohexanedione (dimedone) in the presence of Mg(ClO₄)₂ under solvent-free conditions.

RESULTS AND DISCUSSION

Initially, in order to optimize the reaction parameters, we investigated the reaction of benzaldehyde with dimedone in the presence of Mg(ClO₄)₂ under different conditions. We found that the best result was obtained with benzaldehyde (1 mmol), dimedone (2 mmol), and Mg(ClO₄)₂ (0.025 g) at 90 °C under solvent-free conditions (Table 1).

* Corresponding author: mamrollahi@yazd.ac.ir

Further increasing of catalyst loading did not affect the yield. When the same reaction was performed in the absence of the catalyst, only the trace amount of product was formed (Table 1, Entry 1). The reusability of the $\text{Mg}(\text{ClO}_4)_2$ catalyst was also examined. After each run, the product was dissolved in CHCl_3 and filtered. The catalyst residue was washed with CHCl_3 and reused. Treatment with CHCl_3 removes the tar from the catalyst surface more efficiently (Table 1, Entry 13, 14). We extended our study with different aromatic aldehydes to prepare a series of xanthenedione derivatives under optimized reaction conditions (Table 2).

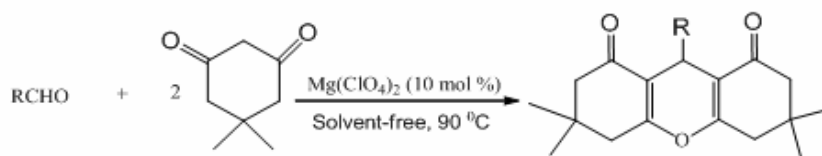
The results showed that the yields of the products and the reaction times are dependent on the substituent present on the aromatic rings. The aromatic aldehydes with electron-withdrawing groups as substrates reacted very well at a faster rate, and the reaction time was shorter compared with aromatic aldehydes with electron-donating groups (Table 2, Entries 2-4). The reaction was also investigated with heteroaromatic aldehydes

and α,β -unsaturated and the corresponding products were produced in good yields (Table 2, Entries 5,6). The reaction with acyclic diketone, such as 2,4-dioxopentane when treated with benzaldehyde, failed to give the expected products under this protocol. Attempts to perform the reaction with an aromatic ketone instead of an aromatic aldehyde failed, even with a prolonged reaction time.

Finally, in order to assess the efficiency and generality of this methodology, we compared the method with some reported results in the literature (Table 3). It was found that $\text{Mg}(\text{ClO}_4)_2$ is the most efficient catalyst with respect to reaction time, temperature, and catalyst nature.

The suggested mechanism of magnesium perchlorate catalyzed transformation is shown in Scheme 1. As it can be seen, the reaction proceeds *via* one-pot Knoevenagel condensation, Michael addition, and cyclodehydration. In this process, $\text{Mg}(\text{ClO}_4)_2$ acts the carbonyl groups of the aldehyde and intermediates.

Table 1

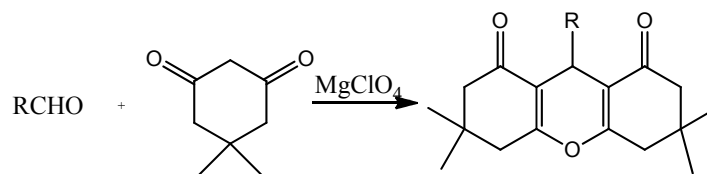
Optimization of reaction conditions ^{a)}

Entry	$\text{Mg}(\text{ClO}_4)_2$ (g)	Tem(°C)	Solvent	Yield(%) ^{b)}
1	-	60	-	10
2	0.020	60	-	60
3	0.020	80	-	73
4	0.020	90	-	83
5	0.020	100	-	83
6	0.010	90	-	72
7	0.025	90	-	90
8	0.030	90	-	92
9	0.025	90	Ethanol	90
10	0.025	90	Chloroform	80
11	0.025	90	Acetonitrile	70
12	0.025	90	Ethyl acetate	60
13	0.025 nd run	90	-	80
14	0.025 ^{ed} run	90	-	72

^{a)} Reaction conditions: benzaldehyde (1 mmol), dimesone (2 mmol), and solvent-free.

^{b)} Isolated yields

Table 2

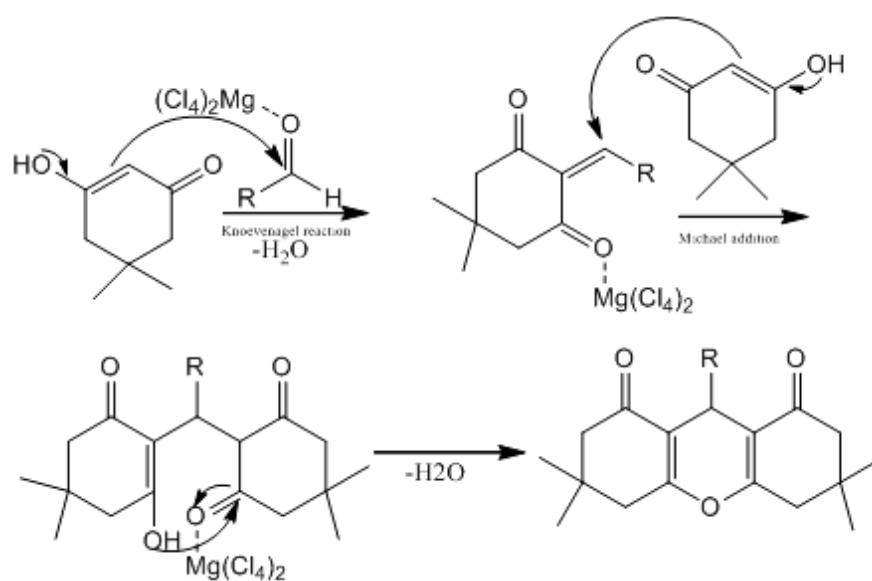
Synthesis of xanthenedione derivatives in the presence of $Mg(ClO_4)_2$ at 90 °C in solvent-free conditions

Entry	R	Time(min)	Yield(%)	Mp(°C)	Ref
1	C ₆ H ₅	25	90	200-202	10
2	3-NO ₂ C ₆ H ₄	22	92	173-174	11
3	4-NO ₂ C ₆ H ₄	17	94	254-255	11
4	Furan-2-yl	27	80	200-203	15
5	Pyridine-4-yl	25	78	208-210	-
6	Naphthalene-1-yl	35	83	236-237	13
7	C ₆ H ₅ CH=CH	40	72	178-179	13
8	3-FC ₆ H ₄	30	82	185-186	13
9	4-FC ₆ H ₄	25	84	229-230	13
10	2-ClC ₆ H ₄	32	89	228-230	10
11	4-BrC ₆ H ₄	35	84	242-243	11
12	3-OHC ₆ H ₄	50	70	207-209	16
13	4-OH,3-OMeC ₆ H ₃	50	75	198-200	13
14	2,5-diOMeC ₆ H ₃	40	82	183-184	13
15	4-OMeC ₆ H ₄	30	91	248-250	15
16	4-MeC ₆ H ₄	32	85	208-209	11

Table 3

Comparison of the efficiency of $Mg(ClO_4)_2$ with that of the reported catalysts for the synthesis of xanthenediones

Entry	Catalyst	Tem(°C)	Time (min/h)	Yield(%)	Ref
1	p-TSA	80	1-2.5 h	87-96	9
2	([Hmim]TFA)	80	3-4 h	82-93	12
3	NaHSO ₄ , SiO ₂ or Silica chloride	100	12-13 h	88-94	14
4	Amberlyst-15	125	35 min	80-94	8
6	$Mg(ClO_4)_2$	90	17-55 min	80-94	This work



Scheme 1 – A possible mechanism for the synthesis of xanthenedion.

EXPERIMENTAL

General

The products were characterized by ^1H -, ^{13}C -NMR, IR, and by comparison of their physical properties with those reported in the literature. IR spectra were run on a Bruker, Eqinox 55 spectrometer. ^1H - and ^{13}C -NMR spectra were obtained using a Bruker Avance 500 MHz spectrometer (DRX). Melting points were determined by a Buchi melting point B-540 B.V.CHI apparatus. Analytical TLC was performed on pre-coated plastic sheets of silica gel G/UV-254 with a thickness of 0.2 mm.

Typical procedure for the synthesis of xanthenedion derivatives

A mixture of an aldehyde (1 mmol), dimedone (2 mmol, 0.280 g), and $\text{Mg}(\text{ClO}_4)_2$ (0.025 g) was heated under solvent-free conditions at 90 °C for an appropriate time. After completion of the reaction, in order to isolate the catalyst, the mixture was dissolved in hot chloroform and filtered. The solvent of the resulting filtrate was evaporated and the pure product was obtained by recrystallization from ethanol.

Selected spectroscopic data

9-(Phenyl)-3,3,6,6-tetramethyl-1,2,3,4,5,6,7,8-octahydroxanthene-1,8-dione (Table 2, Entry 1). Yield: 90%, mp 200-202 °C. IR: 2960, 1679, 1654, 1640, 1469, 1350, 1195, 1165, 1139 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 1.03 (s, 12H), 1.98 (s, 4H), 2.12 (s, 4H), 4.20 (s, 1H), 7.14 (t, 1H), 7.37 (t, 2H), 7.50 (d, 2H). ^{13}C NMR (125 MHz, CDCl_3): δ 27.0, 31.9, 39.2, 40.1, 51.0, 113.9, 119.2, 131.8, 132.3, 143.7, 155.2, 198.2.

9-(4-Nitrophenyl)-3,3,6,6-tetramethyl-1,2,3,4,5,6,7,8-octahydroxanthene-1,8-dione (Table 2, Entry 3). Yield: 94%, mp 254-255 °C. IR: 2952, 1660, 1610, 1554, 1475, 1365, 1185, 1168 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 1.10 (s, 12H), 1.80 (s, 4H), 2.25 (s, 4H), 4.28 (s, 1H), 7.55 (d, $J = 8.3$ Hz, 2H), 7.90 (d, $J = 8.3$ Hz, 2H). ^{13}C NMR (125 MHz, CDCl_3): δ 27.7, 32.4, 38.9, 41.3, 52.1, 113.5, 119.0, 133.2, 133.9, 145.4, 156.5, 198.4.

9-(4-Pyridyl)-3,3,6,6-tetramethyl-1,2,3,4,5,6,7,8-octahydroxanthene-1,8-dione (Table 2, Entry 5). Yield: 78%, mp 208-210 °C. IR: 2962, 1681, 1655, 1624, 1591, 1467, 1361, 1197, 1165, 1139 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 1.16 (s, 12H), 2.25 (s, 4H), 2.82 (s, 4H), 4.77 (s, 1H), 7.77 (d, $J = 5.5$ Hz, 2H), 8.50 (d, $J = 5.5$ Hz, 2H). ^{13}C NMR (125 MHz, CDCl_3): δ 27.2, 30.1, 37.3, 39.9, 51.2, 114.1, 114.8, 124.7, 151.3, 156.4, 198.3.

9-(4-Fluorophenyl)-3,3,6,6-tetramethyl-1,2,3,4,5,6,7,8-octahydroxanthene-1,8-dione (Table 2, Entry 9). Yield: 84%, mp 229-230 °C. IR: 2956, 1681, 1657, 1627, 1507, 1467, 1360, 1222, 1196, 1140 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 1.20 (s, 12H), 2.29 (4H), 2.44 (s, 4H), 4.76 (s, 1H), 7.22 (d, $J = 8.5$ Hz, 2H), 7.36 (d, $J = 8.5$ Hz, 2H). ^{13}C NMR (125 MHz, CDCl_3): δ 27.9, 29.6, 37.9, 41.3, 51.2, 116.2, 126.5, 128.5, 141.7, 146.9, 162.5, 196.9.

9-(4-Bromophenyl)-3,3,6,6-tetramethyl-1,2,3,4,5,6,7,8-octahydroxanthene-1,8-dione (Table 2, Entry 11). Yield: 84%, mp 242-243 °C. IR: 2948, 1683, 1658, 1625, 1469, 1359, 1190, 1155 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 1.15 (s, 12H), 1.81 (s, 4H), 2.07 (s, 4H), 4.25 (s, 1H), 7.28 (d, $J = 8.5$ Hz, 2H), 7.37 (d, $J = 8.5$ Hz, 2H). ^{13}C NMR (125 MHz, CDCl_3): δ 26.7, 31.0, 39.6, 39.4, 51.9, 113.1, 118.9, 131.0, 132.1, 142.9, 155.8, 197.9.

9-(4-Methoxyphenyl)-3,3,6,6-tetramethyl-1,2,3,4,5,6,7,8-octahydroxanthene-1,8-dione (Table 2, Entry 15). Yield: 91%, mp 248-250 °C. IR: 2954, 1680, 1662, 1620, 1510, 1458, 1357, 1260, 1193, cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ 1.18 (s, 12H), 2.23 (s, 4H), 2.35 (s, 4H), 3.76 (s, 3H), 4.73 (s, 1H), 6.78 (d, $J = 6.5$ Hz, 2H), 7.23 (d, $J = 6.5$ Hz, 2H). ^{13}C NMR (125 MHz, CDCl_3): δ 26.9, 31.2, 38.1, 41.4, 50.7, 55.5, 113.8, 116.2, 129.7, 136.9, 141.5, 151.0, 196.8.

CONCLUSIONS

In this study, we have described a general and environmentally friendly procedure for the synthesis of xanthenediones in the presence of $\text{Mg}(\text{ClO}_4)_2$. The procedure reported here has the advantage of mild reaction conditions, high yields, short reaction time, operational simplicity, and use of cheap, commercially available, and non-corrosive catalysts.

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