SYNTHESIS OF 1,8-DIOXOOCTAHYDROXANTHENE AND 3,3-ARYLIDENE BIS(4-HYDROXYCOUMARIN) DERIVATIVES

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A rapid, green and efficient method for the synthesis of 1,8-dioxooctahydroxanthene and 3,3-arylidenebis(4-hydroxycoumarin) derivatives through a one-pot condensation from various aromatic aldehydes is described using manganese ferrite ($MnFe_2O_4$) and cobalt ferrite ($CoFe_2O_4$) as promoting material under solvent-free conditions which can easily be recovered and reused. Compared with other synthetic methods, this new method has advantages such as milder reaction conditions, good to excellent yields, short reaction times, and environmentally benign procedure.

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INTRODUCTION

Synthesis of heterocyclic compound has a huge importance in chemistry, biochemistry, modern drug design, and these compounds are widely distributed in nature. Nowadays there are a lot of heterocyclic pharmaceuticals, these are used widely as antitumor, antiviral, antibiotic, anti-HIV pharmaceuticals although there is a large number of literatures about the synthesis of heterocyclic compounds have potential biological activity, but preparation of novel compounds and more efficient and economic methods means challenge for organic chemists.

Xanthenes and their substituted derivatives are useful targets for chemical synthesis as they have been associated with a diverse range of therapeutic and pharmacological properties such as antiviral[1] and antibacterial activity.[2] Apart from these applications, they are used in photodynamic therapy.[3] view of the general observation that the biological activities are invariably associated with1,8-dioxooctahydroxanthenes and 3,3-arylidene bis(4-hydroxycoumarin) derivatives, in this work we describe a new method and promoter to prepare some derivatives belong to these compound classes.

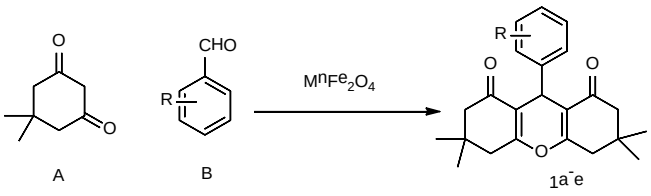
RESULT AND DISCUSSION

Synthesis of 1,8-dioxooctahydroxanthene derivatives

Many procedures for the synthesis of xanthenes and benzoxanthenes have been reported in the literature, including the reaction of For this purpose, react two molecules of dimedone (5,5-dimethyl-1,3-cyclohexane dione) with various aromatic aldehydes,[4] by using of different Lewis acid catalysts such as triethylbenzyl ammonium chloride[5], p-dodecyl benzenesulfonic acid[6], diammonium hydrogen phosphate under various conditions,[7] sulfonic acid under ultrasonic irradiation,[8] ionic liquids,[9] Amberlyst-15,[10] $NaHSO_4$-SiO_2 or silica chloride.[11]

In continuation of our work,[12-17] we have developed the new protocol that using nanosized manganese ferrite ($MnFe_2O_4$) is an efficient and reusable promoter for the synthesis of 3,3,6,6-tetramethyl-9-aryl-1,8-dioxooctahydro xanthene derivatives. The salient features of this protocol include the use of a small amount of the $MnFe_2O_4$, good yields, operational simplicity, short reaction times, promoter separation from the reaction medium. Moreover, the use of environmentally benign catalyst and avoidance of hazardous organic solvents are important features of this method.

To optimize the reaction conditions, the reaction of 5,5-dimethyl-1,3-cyclohexanedione (2 mmol) and benzaldehyde (1 mmol) under solvent-free conditions was selected as a model. After many studies on the above model reaction, we found that when less than 1 mmol of $MnFe_2O_4$ was applied the corresponding products obtained in lower yields and require more time, whereas use of more than 1 mmol $MnFe_2O_4$ did not improve the yield and require the same time. This was due to the fact that beyond a certain concentration, there exist an excess of $MnFe_2O_4$ sites over what is actually required by the reactant molecules and hence, the additional $MnFe_2O_4$ does not increase the rate of reaction. Therefore, in all further reactions 1 mmol of $MnFe_2O_4$ was used.



Scheme 1. Synthesis of 1,8-dioxooctahydroxanthene

In order to evaluate the generality of the process, we carried out a series of reactions using 5,5-dimethyl-1,3-cyclohexanedione (2 mmol) and various aromatic aldehydes

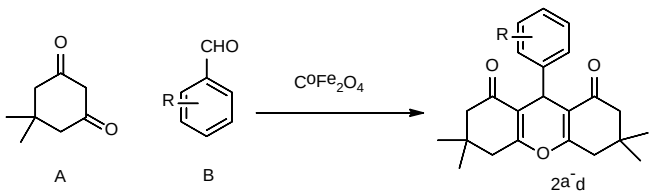
(1 mmol) in presence of $MnFe_2O_4$ (1 mmol) at 110 °C under solvent-free conditions. Most importantly, aromatic aldehydes with substituent's bearing either electron-donating or electron-withdrawing groups as well as heterocyclic aldehydes reacted successfully in the presence of $MnFe_2O_4$. In all these reactions expected products were obtained in good to excellent yields. The results are shown in Table 1. The suggested mechanism for the $MnFe_2O_4$ promoted synthesis of 1,8-dioxooctahydro xanthenes is shown in Scheme. Concerning the reaction mechanism, we suggest that, initially activation of the carbonyl group of aldehyde by $MnFe_2O_4$ facilitates nucleophilic attack of dimedone in its enol form and form the corresponding carbocation. This carbocation then reacts with these activated dimedone to give intermediate, which then undergo dehydration to give the final product.

Table 1. Synthesis of 1,8-dioxooctahydroxanthene by condensation of aldehydes and 5,5-dimethyl-1,3-cyclohexanedione using $MnFe_2O_4$.

R	Product	Time, min	% Yield	M.P., ^{0}C	
				Found	Reported
H	1a	45	90	203-204	204-205*
3-Cl	1b	45	95	180-182	182-184*
4-Cl	1c	60	92	225-227	226-228*
4-NO_2	1d	50	94	223-225	224-225*
4-OH	1e	60	92	245-246	247-248*

Synthesis of 3,3-arylidene bis(4-hydroxycoumarin) derivatives

An efficient method was proposed for the condensation of aldehydes with 4-hydroxycoumarin, which led to the corresponding 3,3-arylidene bis-(4-hydroxycoumarin) and different aldehydes in the presence of $CoFe_2O_4$. Initially, the systematic evaluation of different solvents fo rthe model reaction of 3-nitro benzaldehyde and 4-hydroxycoumarin in the presence of $CoFe_2O_4$ in water at reflux was focused on. Attempts were made to study and optimize the reaction conditions in order to show that performing the reaction in H_2O with low yield while using the amounts of EtOH in the media produced satisfactory results. These results revealed that the highest yield was obtained with the water/ethanol (1:1) solvent system.



Scheme 2. Synthesis of 1,8-dioxooctahydroxanthenes in the presence of cobalt ferrite ($CoFe_2O_4$)

In order to check the viability of this protocol in obtaining a series of 3,3-arylidene bis (4-hydroxycoumarin) derivatives, arrange of dicoumarols was synthesized using different aldehydes and 4-hydroxycoumarin under the standardized reaction condition (Table 2). Regardless of the nature of the substitution (electron donating and electron withdrawing) of the aromatic aldehydes, the products were obtained in good to excellent yields. In these reactions, there was no need for the column purification of the products. The obtained solid products were just filtered off from the reaction mixture, dissolved in hot ethanol, refiltered to separate solid mixed oxide residue and finally recrystallized from the filtrate to obtain pure dicoumarols.[6]

According to the proposed mechanism, the formation of 3,3-arylidene bis(4-hydroxycoumarin) could be rationalized. From the Knoevenagel condensation of aromatic aldehydes with 4-hydroxycoumarin in the presence of $CoFe_2O_4$ and followed by Michele addition of the second 4-hydroxycoumarin (Scheme 2).

Table 2. Synthesis of 3,3-arylidene bis(4-hydroxycoumarin) derivatives bycondensationofaldehydes and 4-hydroxycoumarin using $CoFe_2O_4$

R	Pro-duct	Time, min	Yield, %	M.P., ^{0}C	
				Found	Reported
H	**2a**	45	96	232-234	230-232*
4-OMe	**2b**	45	95	249-251	246-248*
4-Cl	**2c**	45	92	258-260	256-258*
4-NO_2	**2d**	45	90	237 - 240	232-234*

EXPERIMENTAL

Melting points were determined on an electrothermal apparatus, and the temperature was not calibrated. IR spectra were recorded as thin films on KBr using a Perkin-Elmer 1700 spectrophotometer. The NMR spectra were recorded on a Bruker ARX-300 spectrometer. Sample solutions were prepared in dimethylsulfoxide (DMSO) containing tetramethylsilane (TMS) as an internal reference. Mass spectra were recorded on a JMS-DX300 at 70 eV.
All chemical reagents were commercially available and purified with standard methods before use. Solvents were dried in routine ways and redistilled.

General procedure for the synthesis of 1,8-dioxooctahydro-xanthene Derivatives:

The 5,5-dimethyl-1,3-cyclohexanedione (2 mmol), an aromatic aldehyde (1 mmol) and $MnFe_2O_4$ (1 mmol) was heated in the oil bath at 110°C for the appropriate time. The progress of reaction was monitored by thin layer chromatography (TLC). Upon completion, the reaction mixture was cooled to room temperature and ethanol (10 ml) was added. The $MnFe_2O_4$ was recovered from filtrate. The residue was washed with ethanol (95%) to give compounds **3a-l** in high yields. Recovered $MnFe_2O_4$ was washed with diethyl ether (10 ml) and calcined at 120 °C for 1 h, before reusing.

3,3,6,6-Tetramethyl-9-phenyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (1a).

^{1}H NMR ($CDCl_3$, 500 MHz): 0.99 (s, 12H), 1.90 (s, 4H), 1.92 (s, 4H), 3.90 (s, 1H), 7.11–7.32 (m, 5H, Ar-H); IR (KBr) : 1710, 1622, 1545, 1509, 1120 cm^{-1}; MS (70 eV) m/z (%): 351.45 (M^++1, 100).

9-(3-Chlorophenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (1b).

^{1}H NMR ($CDCl_3$, 500 MHz): 0.98 (s, 12H), 1.92 (s, 4H), 1.94 (s, 4H), 3.93 (s, 1H), 7.11–7.13 (d, 2H, Ar-H); 7.30–7.32 (d, 2H, Ar-H); IR (KBr): 1712, 1620, 1542, 1504, 1122 cm^{-1}; MS (70 eV) m/z (%):385.90 (M^++1, 100).

9-(4-Chlorophenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (1c).

^{1}H NMR ($CDCl_3$, 500 MHz): 0.98 (s, 12H), 1.92 (s, 4H), 1.94 (s, 4H), 3.92 (s, 1H), 7.30–7.32 (m, 4H, Ar-H); IR (KBr): 1710, 1622, 1545, 1509, 1120 cm^{-1}; MS (70 eV) m/z (%): 385.90 (M^++1, 100).

3,3,6,6-Tetramethyl-9-(4-nitrophenyl)-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (1d).

^{1}H NMR ($CDCl_3$, 500 MHz): 0.99 (s, 12H), 1.90 (s, 4H), 1.92 (s, 4H), 3.91 (s, 1H), 7.48–7.50 (d, 2H, Ar-H); 8.14–8.16 (d, 2H, Ar-H); IR (KBr): 1710, 1622, 1545, 1509, 1120 cm^{-1}; MS (70 eV) m/z (%): 396.45 (M^++1, 100).

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

^{1}H NMR ($CDCl_3$, 500 MHz): 0.99 (s, 12H), 1.90 (s, 4H), 1.92 (s, 4H), 3.88 (s, 1H), 5.50 (s, 1H), 6.80–6.82 (d, 2H, Ar-H); 7.14–7.16 (d, 2H, Ar-H); IR (KBr): 1710, 1622, 1540, 1506, 1115 cm^{-1}; MS (70 eV) m/z (%): 367.45 (M^++1, 100).

General procedure for the synthesis of 3,3-arylidene bis(4-hydroxycoumarin) Derivatives

A mixture of 4-hydroxycoumarin (2 mmol, 0.324 g), substituted benzaldehydes (1 mmol, 0.106 g), and cobalt ferrite ($CoFe_2O_4$, 1 mmol, 0.326 g) was stirred at reflux in 5 ml ethanol-water mixture (1:1). The progress of the reaction was monitored by TLC. After the reaction completion and upon its cooling, the solid material was precipitated from the solution. The precipitates were filtered off, washed with water, and were recrystallized from EtOH to obtain pure 3,3-arylidenebis(4-hydroxy-*2H*-chromen-2-ones) derivatives as yellow-white solids.[8]

3,3,6,6-Tetramethyl-9-phenyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (2a).

^{1}H NMR ($CDCl_3$, 500 MHz): 0.99 (s, 12H), 1.90 (s, 4H), 1.92 (s, 4H), 3.90 (s, 1H), 7.11–7.32 (m, 5H, Ar-H); IR (KBr) : 1710, 1622, 1545, 1509, 1120 cm^{-1}; MS (70 eV) m/z (%): 351.45 (M^++1, 100).

9-(4-Methoxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (2b).

^{1}H NMR ($CDCl_3$, 500 MHz): 0.98 (s, 12H), 1.92 (s, 4H), 1.94 (s, 4H), 3.80 (s, 3H), 3.92 (s, 1H), 7.10–7.12 (d, 2H, Ar-H); 7.30–7.32(d, 2H, Ar-H); IR (KBr): 1710, 1622, 1545, 1509, 1120 cm^{-1}; MS (70 eV) m/z (%): 381.50 (M^++1, 100).

9-(4-Chlorophenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (2c).

^{1}H NMR ($CDCl_3$, 500 MHz): 0.98 (s, 12H), 1.92 (s, 4H), 1.94 (s, 4H), 3.92 (s, 1H), 7.30–7.32 (m, 4H, Ar-H); IR (KBr): 1710, 1622, 1545, 1509, 1120 cm^{-1}; MS (70 eV) m/z (%): 385.90 (M^++1, 100).

3,3,6,6-Tetramethyl-9-(4-nitrophenyl)-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (2d).

^{1}H NMR ($CDCl_3$, 500 MHz): 0.99 (s, 12H), 1.90 (s, 4H), 1.92 (s, 4H), 3.91 (s, 1H), 7.48–7.50 (d, 2H, Ar-H); 8.14–8.16 (d, 2H, Ar-H); IR (KBr): 1710, 1622, 1545, 1509, 1120 cm^{-1}; MS (70 eV) m/z (%): 396.45 (M^++1, 100).

CONCLUSION

In conclusion, manganese ferrite ($MnFe_2O_4$) and cobalt ferrite ($CoFe_2O_4$) were proved to be efficient promoter for the synthesis of dicoumarols and 1,8-dioxooctahydroxanthenes, respectively. These conditions had advantages such as shorter reaction time, simpler work-up, inexpensive and non-toxic promoter, environmental benignity and excellent yields. The protocol described herein is advantageous in terms of preclusion of hazardous organic solvents, low amount of prooter, shorter reaction time, good yields, recovery and reusability of the promoter.

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REFERENCES

[1]Lambert, R. W., Martin, J. A., Merrett, J. H., Parkes, K. E. B., Thomas, G. J., PCT Int. Appl. WO 9706178; *Chem. Abstr*., **1997**, *126*, 212377y. http://dx.doi.org/10.4236/me.2014.51005

[2]Hideo, T., Tokkyo Koho JP 56005480; *Chem. Abstr*., **1981**, *95*, 80922b. https://doi.org/10.1080/17518253.2011.584217

[3]Ion, R. M., Frackowiak D., Planner, A., Wiktorowicz, K., The incorporation of various porphyrins into blood cells measured via flow cytometry, absorption and emission spectroscopy. *Acta. Biochim. Pol*., **1998**, *45*, 833-845. http://www.actabp.pl/pdf/3_1998/833.pdf

[4](a)Horning, E. C., Horning, M. G., Methone derivatives of aldehydes *J. Org. Chem*., **1946**, *11*, 95-99 https://doi.org/10.1021/jo01171a014 ; (b) Tu, S. J., Zhou, J. F., Lu, Z. S., Deng, X., Shi, D. Q. Wang, S. H., Condensation of aromatic aldehydes with 5,5-dimethyl- 1,3-cyclohexanedione without catalyst *Synth. Commun*., **2002**, *32*, 3063-3067 DOI:10.1081/SCC-120012999; (c) Jin, T. S., Zhang, J. S., Wang, A. Q., Li, T. S., Solid ‐ State Condensation Reactions Between Aldehydes and 5,5 ‐ Dimethyl ‐ 1,3 ‐ cyclohexanedione by Grinding at Room Temperature *Synth. Commun*., **2005**, *35*, 2339. DOI:10.1080/00397910500187282

[5]Wang, X. S., Shi, D. Q., Li, Y. L., Chen, H., Wei, X. Y., Zong, Z. M., A Clean Synthesis of 1 ‐ Oxo ‐ hexahydroxanthene Derivatives in Aqueous Media Catalyzed by TEBA *Synth. Commun*., **2005**, *35*, 97. DOI:10.1081/SCC-200046510

[6]Jin, T. S., Zhang, J. S., Xiao, J. C., Wang, A. Q., Li, T. S., Clean Synthesis of 1,8-Dioxo-octahydroxanthene Derivatives Catalyzed by p-Dodecylbenezenesulfonic Acid in Aqueous Media *Synlett*., **2004**, *5*, 866. DOI:10.1055/s-2004-820022

[7]Darvish, F., Balalaei, S., Chadegani, F., Salehi, P., Diammonium Hydrogen Phosphate as a Neutral and Efficient Catalyst for Synthesis of 1,8-Dioxooctahydroxanthene Derivatives in Aqueous Media *Synth. Commun*., **2007**, *37*, 1059-1067. DOI:10.1080/00397910701196520

[8]Jin, T. S., Zhang, J. S., Wang, A. Q. and Li, T. S., Ultrasound-assisted synthesis of 1,8-dioxo-octahydroxanthene derivatives catalyzed by p-dodecylbenzenesulfonic acid in aqueous media *Ultrason Sonochem*., **2006**, *13*, 220. DOI:10.1016/j.ultsonch.2005.04.002

[9]Dabiri, M., Baghbanzadeh, M., Arzroomchilar, E., 1-Methylimidazolium triflouroacetate ([Hmim]TFA): An efficient reusable acidic ionic liquid for the synthesis of 1,8-dioxo-octahydroxanthenes and 1,8-dioxo-decahydroacridines *Catal. Commun*., **2008**, *9*, 939-942. DOI:10.1016/j.catcom.2007.09.023

[10]Das, B., Thirupathi, P., Mahender, I., Reddy, V. S., Rao, Y. K., mberlyst-15: An efficient reusable heterogeneous catalyst for the synthesis of 1,8-dioxo-octahydroxanthenes and 1,8-dioxo-decahydroacridines *J. Mol. Catal. A. Chem*., **2006**, *247*, 233. DOI:10.1016/j.molcata.2005.11.048

[11]Das, B., Thirupathi, P., Mahender, I., Reddy, K. R., Ravikanth, B., Nagarapu, L., An efficient synthesis of 1,8-dioxo-octahydroxanthenes using heterogeneous catalysts *Catal. Commun*., **2007**, *8*, 535. DOI:10.1016/j.catcom.2006.02.023

[12]Pansare, D. N., Shelke, R. N., Pawar, C. D., A facile synthesis of (Z)-2-((5-(4-chlorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino)substituted acid using microwave irradiation and the conventional method. *Lett. Org. Chem*., **2017,** *14(7)*, 517. DOI: 10.2174/1570178614666170524142722

[13]Pansare, D. N., Shelke, R. N., Shinde, D. B., A facial synthesis and anticancer activity of (Z)-2-((5-(4-nitrobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino)-substituted acid, *J. Het. Chem*., **2017**, *54(6)*, 3077. DOI: 10.1002/jhet.2919

[14]Pansare, D. N., Shinde, D. B., A facile synthesis of novel series (Z)-2-((4-oxo-5-(thiophen-2-yl methylene)-4,5-dihydro thiazol-2-yl)amino) substituted acid, *J. Saudi. Chem. Soc*., **2017**, *21*, 434. https://doi.org/10.1016/j.jscs.2015.10.005

[15]Pansare, D. N., Shelke, R. N., Khade, M. C., Jadhav, V. N., Pawar, C. D., Jadhav, R. A., Bembalkar, S. R., New thiazolone derivatives: design, synthesis, anticancer and antimicrobial activity. *Eur. Chem. Bull.* **2019**, *8(1)*, 7-14. DOI: 10.17628/ecb.2019.8.7-14

[16]Pansare, D. N., Shelke, R. N., Khade, M. C., Jadhav, V. N., Pawar, C. D., Deshmukh, S.U., Dhas, A. K., Chavan, P. N., Sarkate, A. P., Pawar, R. P., Shinde, D. B., Thopate, S. R., Synthesis and anticancer evaluation of new benzenesulfonamide derivatives. *Eur. Chem. Bull*. **2019**, *8(1)*, 1-6. DOI: 10.17628/ecb.2019.8.1-6

[17]Shelke, R. N., Pansare, D. N., Khade, M. C., Jadhav, V. N., Pawar, C. D., Deshmukh, S.U., Sarkate, A. P., Gore N. S., Pawar, R. P., Shinde, D. B., Thopate, S. R., Synthesis of 2-((5-benzylidene-4-oxo-4,5-dihydrothiazol-2-yl)-substituted amino acids as anticancer and antimicrobial agents. *Eur. Chem. Bull.* **2019**, *8(2)*, 63. DOI: 10.17628/ecb.2019.8.63-70

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