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


Keywords: Solvent-free reaction; 1,8-dioxooctahydroxanthene; 3,3-arylindene bis (4-hydroxycoumarin) derivatives ; reusable promoting material

A rapid, green and efficient method for the synthesis of 1,8-dioxooctahydroxanthene and 3,3-arylindenebis(4-hydroxycoumarin) derivatives through a one-pot condensation from various aromatic aldehydes is described using manganese ferrite (MnFe₂O₄) and cobalt ferrite (CoFe₂O₄) 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 antiviral1 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-arylindene 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 benzoanthenes have been reported in the literature, including the reaction of For this purpose, react two molecules of dimedone (5,5-dimethyl-1,3-cyclohexanedione) with various aromatic aldehydes,3 by using of different Lewis acid catalysts such as triethylbenzyl ammonium chloride3, p-dodecyl benzenesulfonic acid8, dianion hydrogen phosphate under various conditions,7 sulfonic acid under ultrasonic irradiation,8 ionic liquids,9 Amberlyst-15,10 NaHSO₄-SiO₂ or silica chloride.11

In continuation of our work,12-17 we have developed the new protocol that using nanosized manganese ferrite (MnFe₂O₄) is an efficient and reusable promoter for the synthesis of 3,3,6,6-tetramethyl-9-aryl-1,8-dioxooctahydroxanthene derivatives. The salient features of this protocol include the use of a small amount of the MnFe₂O₄, 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 MnFe₂O₄ was applied the corresponding products obtained in lower yields and require more time, whereas use of more than 1 mmol MnFe₂O₄ 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 MnFe₂O₄ sites over what is actually required by the reactant molecules and hence, the additional MnFe₂O₄ does not increase the rate of reaction. Therefore, in all further reactions 1 mmol of MnFe₂O₄ 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 MnFe₂O₄ (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 MnFe₂O₄. 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 MnFe₂O₄ promoted synthesis of 1,8-dioxooctahydroxanthene is shown in Scheme. Concerning the reaction mechanism, we suggest that, initially activation of the carbonyl group of aldehyde by MnFe₂O₄ 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.

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 CoFe₂O₄ and followed by Michele addition of the second 4-hydroxycoumarin (Scheme 2).

Table 1. Synthesis of 1,8-dioxooctahydroxanthene by condensation of aldehydes and 5,5-dimethyl-1,3-cyclohexanedione using MnFe₂O₄

<table>
<thead>
<tr>
<th>R</th>
<th>Product</th>
<th>Time, min</th>
<th>Yield, %</th>
<th>M.P. °C Found</th>
<th>M.P. °C Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>1a</td>
<td>45</td>
<td>90</td>
<td>203-204</td>
<td>204-205*</td>
</tr>
<tr>
<td>3-Cl</td>
<td>1b</td>
<td>45</td>
<td>95</td>
<td>180-182</td>
<td>182-184*</td>
</tr>
<tr>
<td>4-Cl</td>
<td>1c</td>
<td>60</td>
<td>92</td>
<td>225-227</td>
<td>226-228*</td>
</tr>
<tr>
<td>4-NO₂</td>
<td>1d</td>
<td>50</td>
<td>94</td>
<td>223-225</td>
<td>224-225*</td>
</tr>
<tr>
<td>4-OH</td>
<td>1e</td>
<td>60</td>
<td>92</td>
<td>245-246</td>
<td>247-248*</td>
</tr>
</tbody>
</table>

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 CoFe₂O₄. Initially, the systematic evaluation of different solvents for the model reaction of 3-nitro benzaldehyde and 4-hydroxycoumarin in the presence of CoFe₂O₄ 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 H₂O 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.

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 CoFe₂O₄ and followed by Michele addition of the second 4-hydroxycoumarin (Scheme 2).

Table 2. Synthesis of 3,3-arylidene bis(4-hydroxycoumarin) derivatives by condensation of aldehydes and 4-hydroxycoumarin using CoFe₂O₄

<table>
<thead>
<tr>
<th>R</th>
<th>Product</th>
<th>Time, min</th>
<th>Yield, %</th>
<th>M.P., °C Found</th>
<th>M.P., °C Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>2a</td>
<td>45</td>
<td>96</td>
<td>232-234</td>
<td>230-232*</td>
</tr>
<tr>
<td>4-OMe</td>
<td>2b</td>
<td>45</td>
<td>95</td>
<td>249-251</td>
<td>246-248*</td>
</tr>
<tr>
<td>4-Cl</td>
<td>2c</td>
<td>45</td>
<td>92</td>
<td>258-260</td>
<td>256-258*</td>
</tr>
<tr>
<td>4-NO₂</td>
<td>2d</td>
<td>45</td>
<td>90</td>
<td>237 - 240</td>
<td>232-234*</td>
</tr>
</tbody>
</table>

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-dioxooctahydroxanthene Derivatives:

The 5,5-dimethyl-1,3-cyclohexanedione (2 mmol), an aromatic aldehyde (1 mmol) and MnFe₂O₄ (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 MnFe₂O₄ was recovered from filtrate. The residue was washed with ethanol (95%) to give compounds 3a-1 in high yields. Recovered MnFe₂O₄ 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).

\[ \text{H NMR (CDCl₃, 500 MHz): 0.99 (s, } 12\text{H), 1.90 (s, } 4\text{H), 1.92 (s, } 4\text{H), 3.90 (s, } 1\text{H), 7.11–7.32 (m, } 5\text{H, Ar-H); IR (KBr): 1710, 1622, 1545, 1509, 1120 cm}^{-1}; \text{ MS (70 eV) } m/z (\%): 351.45 (M}^+1, 100)\]
9-(3-Chlorophenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (1b).

\[ \text{1H NMR (CDCl}_3\text{, 500 MHz): 0.98 (s, 12H), 1.92 (s, 4H)} \]
\[ , 1.94 (s, 4H), 3.93 (s, 1H), 7.11–7.13 (d, 2H, Ar-H); 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).

\[ \text{1H NMR (CDCl}_3\text{, 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).

\[ \text{1H NMR (CDCl}_3\text{, 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).

\[ \text{1H NMR (CDCl}_3\text{, 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, 1545, 1509, 1120 cm\(^{-1}\); MS (70 eV) m/z (%): 367.45 (M\(^++1\), 100). \]

CONCLUSION

In conclusion, manganese ferrite (MnFe\(_2\)O\(_4\)) and cobalt ferrite (CoFe\(_2\)O\(_4\)) were proved to be efficient promoter for the synthesis of dicumarols 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


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Section A Research paper


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