SiO₂/ZnCl₂-Catalyzed Heterocyclic Synthesis: Green, Rapid and Efficient One-Pot Synthesis of 14-H-dibenzo [a, j]Xanthenes, 1,8-Dioxo-octahydroxanthenes and 1,8-Dioxo-Decahydroacridines Under Solvent-Free Conditions

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Abstract: A green and highly efficient protocol for the one-pot synthesis of a variety of 14-aryl-14-H-dibenzo [a, j]xanthenes and 9-aryl-1,8-dioxo-octahydroxanthenes has been developed via cyclocondensation of aryl aldehydes with 2-naphthol or dimedone using SiO₂-ZnCl₂ (silzic) as a reusable heterogeneous catalyst under solvent-free reaction conditions. In addition, a one-pot, three-component condensation of aryl aldehydes, dimedone and ammonium acetate or aryl amines has been developed to furnish 9-aryl-1,8-dioxo-decahydroacridines in good to excellent yields under the same reaction conditions.

Keywords: Xanthenes, Acridine, Silzic, One-pot synthesis, Solvent-free, Heterogeneous catalyst, Multi-component reaction

Introduction

Xanthene derivatives are important O-heterocycles in medicinal chemistry field as well as in industry. In particular, 14H-dibenzo[a, j]xanthenes and 1,8-dioxo-octahydroxanthenes have gained remarkable interest due to their various synthetic and industrial applications. For example, they possess a large array of pharmacological activities such as anti-inflammatory1, anti-bacterial2 and antiviral properties3. Besides, some of them are served as leuco-dyes4, intracellular pH indicators and as fluorescent materials5. Moreover, application of such compounds in photodynamic therapy as well as in laser technologies has also been reported6,7. 14H-Dibenzo[a, j]xanthene derivatives are generally synthesized either by dehydration of bis(2-hydroxy-1-naphthyl)methane derivatives8 or by condensation of 2-naphthol with aromatic aldehydes in the presence of H₂SO₄ using acetic acid as solvent9. Using of environmentally hazardous and toxic acidic catalysts under harsh conditions, long reaction time, and tedious experimental procedures are serious disadvantages of these
traditional methods. Therefore, efforts for improving this synthesis via milder catalyzed-protocols have been reported. Synthesis of aryl-14H- dibenzo[a,j]xanthenes via condensation of aldehydes and 2-naphthol has been developed in the presence of various catalysts such as p-TSA (in boiling 1,2-dichloroethane for 20 h)\textsuperscript{10}, cyanuric chloride\textsuperscript{11}, LiBr\textsuperscript{12}. Greener approaches for synthesis of aryl-14H-dibenzo[a,j]xanthenes and 1,8-dioxo-octahydroxanthenes through condensation of aldehydes and 2-naphthol or 5,5-dimethyl-1,3-cyclohexanedicarboxaldehyde (dimedone) using ionic liquids as well as inorganic solid support catalysts under solvent-free conditions have also been developed\textsuperscript{13-19}. Nevertheless, some of these protocols are disadvantageous in terms of readily unavailability of catalyst (Yb(OTf)\textsubscript{3}/[BPy]BF\textsubscript{4}), or long reaction times under thermal conditions at elevated temperature\textsuperscript{20}. Also 1,8-dioxo-decahydroacridines are polyfunctionalized 1,4-dihydropyridine derivatives (DHPs), a class of nitrogen heterocycles of broad spectrum of important biological properties and pharmaceutical applications\textsuperscript{21-25}.

So, the development of novel synthetic strategies for heterocycles which have advantages with respect to using, less expensive and readily available catalysts or reagents, cleaner reactions, and simple isolation of the product are of interest\textsuperscript{26}. The protocol involves the employment of SiO\textsubscript{2}-ZnCl\textsubscript{2} as an efficient catalyst in achieving cyclocondensation of aryl aldehydes with 2-naphthol or dimedone resulting in formation of aryl-14H- dibenzo[a,j] xanthen derivatives or aryl-1,8-dioxo-octahydroxanthenes respectively, in good to excellent yields under solvent-free conditions. Under the same conditions, a variety of aryl-1,8-dioxo-decahydroacridines has also been efficiently synthesized through a one-pot, three-component condensation of aromatic aldehydes, dimedone and ammonium acetate or aryl amines.

**Experimental**

Melting points were determined using a Griffin melting point apparatus. The IR spectra were recorded with Mattson FTIR spectrometer 5000. Absorption maxima were measured in cm\textsuperscript{-1}. The \textsuperscript{1}H NMR and \textsuperscript{13}C NMR spectra were recorded with Bruker 200, 300 MHz spectrometer instruments in CDCl\textsubscript{3}. The chemical shifts (\(\delta\)) were measured in ppm and with the solvents as references (For CDCl\textsubscript{3}, 1H: \(\delta = 7.26\) ppm, 13C: \(\delta = 77.0\) ppm). MS spectra were recorded on GC-MS QP-1000 EX Shimadzu mass spectrometer. Thin layer chromatography (TLC) was performed on Merck silica gel GF254 plates and visualized by UV-light (254 nm).

**General procedure for the synthesis of aryl-14H- dibenzo[a,j]xanthenes (3) and 9-aryl-1,8-dioxo-octahydroxanthenes (5)**

To a mixture of aldehyde 2 (1 mmol) and 2-naphthol or dimedone (2 mmol) was added Silicic (which prepared as reported\textsuperscript{35}) (0.2 g mol%) and the mixture was allowed to stir at 100 °C for the total recorded time. After completion (the reaction was monitored by TLC), was added EtOAc (20 mL) to the reaction mixture. Then, the mixture was filtered off, the extract was vaporized, and the residue was subjected to short column chromatography using pet.ether-EtOAc (9:1) to give pure 3 or 5. The products are known compounds and all spectroscopic data were in agreement with literature.

**Selected spectral data for some products**

**14-(3,4-Dimethoxyphenyl)-14H-dibenzo[a,j]xanthenes**

(3 g, Table 1): Mp=198 IR (KBr, cm\textsuperscript{-1}): v 3064, 2932, 2832, 1622, 1592, 1514, 1457, 1433,1401, 1239, 1140, 1072, 1020, 961, 859,819, 748 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta \) = 8.21 (d, J=6.0 Hz, 2H), 7.22-7.70 (m, 12H ), 6.93 (d, J=8.0 Hz, 1H), 6.72 (s, 1H), 6.46 (d, J=8.0 Hz, 1H), 6.26 (s, 1H),3.49 (s, 6H) ppm.
3,3,6,6-Tetramethyl-9(3,5-dimethoxy-phenyl)-1,8-dioxo-octahydroxanthene
(5 h, Table 2) Mp. = 200 °C; IR (KBr, cm⁻¹): ν 3061, 2981, 2890, 1666, 1628, 1510, 1358, 1261, 841, 573, 1H NMR (300 MHz, CDCl₃): δ 6.51-7.3 (m, 3H, Ar-H), 4.72 (s, 1H, CH), 3.81 (s, 3H, OCH₃), 3.77 (s, 3H, OCH₃), 2.47 (s, 4H, 2x CH2), 2.23 (s, 4H, 2xCH₂), 1.12 (s, 6H, 2xCH₃), 1.03 (s, 6H, 2xCH₃). EI-MS: 410 (M⁺); Anal. Calcd. For C₂₅H₃₀O₅: C, 73.17; H, 7.32; Found: C, 73.26; H, 7.45.

Typical procedure for the synthesis of 1,8-dioxo-decahydroacridine derivatives
To a stirred mixture of aldehyde (5 mmol), dimedone (10 mmol) and aryl amine (6 mmol), was added Silizic (0.2 g mol%) and the mixture was allowed to stir at 100 °C for the total recorded time. After completion (the reaction was monitored by TLC), was added EtOAc (20 mL) to the reaction mixture. Then, the mixture was filtered off, the extract was vaporized, and the residue was subjected to short column chromatography using pet.ether-EtOAc (9:1) to give pure 6. The decahydroacridinediones 6 except for 6f, are known compounds and all spectroscopic data were in agreement with literature.

Data for 6f
Mp = 226 °C; IR (KBr, cm⁻¹): ν 3043, 2955, 2936, 1641, 1574, 1508, 1361, 1218, 1096, 921, 734; ¹H NMR (300 MHz, CDCl₃): δ 7.33 (d, J = 9 Hz, 2H, Ar-H), 7.05 (d, J = 9 Hz, 2H, Ar-H), 6.69 (s, 2H, Ar-H), 5.26 (s, 1H, CH), 3.81 (s, 3H, OCH₃), 3.77 (s, 3H, OCH₃), 2.48 (s, 3H, CH₃), 0.96 (s, 6H, 2xCH₃), 0.86 (s, 6H, 2xCH₃); EI-MS: 552 (M⁺Na)+; Anal. Calcd. For C₃₃H₃₉NO₅ (529.28): C, 74.83; H, 7.42; N, 2.64. Found: C, 74.97; H, 7.31, N, 2.49.

Results and Discussion
A convenient one-pot synthesis of aryl-14H- dibenzo[a,j]xanthenes through the reaction of 2-naphthol with aromatic aldehydes in the presence of SiO₂-ZnCl₂ (silzic) under solvent-free conditions has been achieved. Stirring a mixture of 2-naphthol (2 equiv) and aromatic aldehyde (1 equiv.) in the presence of SiO₂-ZnCl₂(0.2 g mol%) at 100 °C led to the formation of aryl-14H- dibenzo[a,j]xanthenes 3a-i in excellent yield (Scheme 1, Table 1).

<table>
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<tr>
<th>Entry</th>
<th>Substrate 2</th>
<th>Time, min</th>
<th>Product</th>
<th>Yield, %a</th>
<th>mp, °C</th>
<th>Lit. mp, °C</th>
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</thead>
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<td>181</td>
<td>182</td>
</tr>
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<td>4-OMe</td>
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<td>3b</td>
<td>83</td>
<td>185</td>
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<td>3c</td>
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<td>3d</td>
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<td>224-6</td>
<td>226</td>
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<td>4-NO₂</td>
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<td>3e</td>
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<td>295</td>
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<td>40</td>
<td>3h</td>
<td>77</td>
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</tr>
<tr>
<td>9</td>
<td>3,4,5-triOMe</td>
<td>40</td>
<td>3i</td>
<td>80</td>
<td>195-7</td>
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</tr>
</tbody>
</table>

*aIsolated yield
Also one-pot synthesis of 1,8-dioxo-octahydroxanthenes through the reaction of dimerone with aromatic aldehydes in the presence of SiO\textsubscript{2}-ZnCl\textsubscript{2} (silicic) under solvent-free conditions has been achieved. Stirring a mixture of dimerone (2 equiv.) and aromatic aldehyde (1 equiv.) in the presence of SiO\textsubscript{2}-ZnCl\textsubscript{2} (0.2 g mol\%) at 100 °C led to the formation of 1,8- dioxoctahydroxanthenes 5a-k in excellent yield (Scheme 2, Table 2).

\[ \text{O} \quad \text{Ar} \quad \text{H} \quad \text{SiO}_2\text{-ZnCl}_2 \quad \text{100}^\circ\text{C} \]

\[ \text{5a; Ar =Ph, 5b; Ar =4- OMeC}_6\text{H}_4, 5c; Ar=4-ClC}_6\text{H}_4, 5d; Ar =4-MeC}_6\text{H}_4, 5e; Ar=4-NO}_2\text{C}_6\text{H}_4, 5f; Ar=4-BrC}_6\text{H}_4, 5g; Ar=2,4-diOMeC}_6\text{H}_4, 5h; Ar=3,5-diOMeC}_6\text{H}_4, 5i; Ar=3,4,5-triOMeC}_6\text{H}_2, 5j; Ar=3-Ome,4-OH-C}_6\text{H}_3, 5k; Ar=4-CN C}_6\text{H}_4 \]

\[ \text{Scheme 2} \]

\[ \text{Table 2. SiO}_2/\text{ZnCl}_2\text{-Catalyzed one-pot synthesis of 1,8-dioxoctahydroxanthenes} \]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde/Ar</th>
<th>Time, min</th>
<th>Product</th>
<th>Yield, %\textsuperscript{a}</th>
<th>mp, °C</th>
<th>Lit. mp, °C</th>
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<td>25</td>
<td>5a</td>
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<td>202-204</td>
<td>204-206\textsuperscript{15}</td>
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<td>4-Cl</td>
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<td>4-Me</td>
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<td>4-NO\textsubscript{2}</td>
<td>27</td>
<td>5e</td>
<td>85</td>
<td>225-226</td>
<td>222-224\textsuperscript{14}</td>
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<tr>
<td>6</td>
<td>4-Br</td>
<td>25</td>
<td>5f</td>
<td>86</td>
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<td>2,4-diOMe</td>
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<td>5g</td>
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<td>207-208</td>
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<td>8</td>
<td>3,5-diOMe</td>
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<td>5h</td>
<td>80</td>
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</tr>
<tr>
<td>9</td>
<td>3,4,5-triOMe</td>
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<td>5i</td>
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<td>204-205</td>
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<tr>
<td>10</td>
<td>Vanillin</td>
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<td>11</td>
<td>4-CN</td>
<td>28</td>
<td>5k</td>
<td>85</td>
<td>214-216</td>
<td>217-218\textsuperscript{14}</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Isolated yield

The results summarized in Table 1 and Table 2 showed that the formation of aryl-14\textsubscript{H}-dibenzo[a,j]xanthenes and 1,8-dioxo-octahydroxanthenes proved to be general and quite efficient for aryl aldehydes and tolerated a variety of functional groups on the phenyl ring regardless of whether electron-donating or electron-withdrawing in character. Thus, chloro, bromo, nitro, methyl and methoxy containing aromatic aldehydes were reacted smoothly to give the respective aryl-14\textsubscript{H}-dibenzo[a,j]xanthenes and 1,8-dioxo-octahydroxanthenes in excellent yields. Identification of 3-aryl-14\textsubscript{H}-dibenzo[a,j]xanthenes and 1,8-dioxooctahydroxanthenes was carried out by spectroscopic analyses as well as by comparing their properties to those reported. For example, the \textsuperscript{1}H NMR spectra of the benzoxanthenes 3 obtained by the present method showed, no absorption bands for the hydroxyl group protons was observed, In the IR spectra, no any absorption for hydroxyl group (OH) was observed but, rather, all products displayed a characteristic ether-linkage (C-O) stretching band at \( \nu_{\text{max}} \) 1213-1227 cm\textsuperscript{-1}, indicating the cyclization step clearly.

The multi-component reaction of dimerone (2 mole), benzaldehyde (1 mole) and aromatic amine (or ammonium acetate) (1.2 mole) in the presence of Silicic (0.2 g mol\%) at 100 °C to produce 1,8-dioxo-decahydroacridines under solvent-free conditions, was studied. (Scheme 3, Table 3).
Table 3. SiO2/ZnCl2-Catalyzed one-pot synthesis of 1,8-dioxodecahydroacridines

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde/Ar</th>
<th>Amine/ NH4OAc</th>
<th>Time, min</th>
<th>Product</th>
<th>Yield, %a</th>
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<td>27</td>
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<td>85</td>
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<td>220-22235</td>
</tr>
<tr>
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<td>3,4,5-(OMe)C6H2+ 4-MeC6H4NH2</td>
<td>25</td>
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<td>NH2OAc</td>
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<td>82</td>
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<td>3,5-(OMe)2C6H3</td>
<td>NH2OAc</td>
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</table>

*aIsolated yield

In all cases, aromatic aldehydes with substituents caring either electron-donating or electron-withdrawing groups reacted successfully and gave the expected products in good yields and short reaction times.

The structure elucidation of acridine derivatives 6 was assigned on the basis of both elemental and spectral analyses. Also by comparison of their physical and spectroscopic data with those of authentic samples27-32.

**Conclusion**

In summary, we have developed a simple, mild and efficient protocol for the one-pot syntheses of various 14H-dibenzo[a,j]xanthenes, 1,8-dioxooctahydroxanthenes and 1,8-dioxodecahydroacridines, employing the cheap SiO2-ZnCl2 mixture. Under solvent-free, by condensation of aryl aldehyde with 2-naphthol, dimeredone and with dimedone in presence of amine. High yields, short reaction times and easy work up are some advantages of this reaction. Exploring this protocol for the condensation of mixed nucleophiles with aldehydes for synthesizing an array of novel heterocycles for biological evaluation is on-going project in our laboratory.

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**References**