EFFICIENT SYNTHESIS OF 1,8-DIOXO-OCTAHYDROXANTHENES USING HClO₄/SiO₂ AS CATALYST

Gholam Hossein Mahdavinia, a Mohammad A. Bigdeli, b* Yaser Saeidi Hayeniaz, b and Firouzeh Nemati b

aDepartment of Chemistry, Islamic Azad University-Marvdasht Branch, Marvdasht, Iran. Fax: +98 728 3338686; E-mail: hmahdavinia@gmail.com.
bFaculty of Chemistry, Tarbiat Moalem University, 49 Mofateh St., Tehran, Iran. Fax: +98 21 88820993; E-mail: mabig397@yahoo.com

Abstract – Silica supported perchloric acid (HClO₄/SiO₂) is found to be a heterogeneous recyclable catalyst for rapid and efficient synthesis of 1,8-dioxo-octahydroxanthenes with good to excellent yields in solvent free conditions. The catalyst is easily prepared, stable, reusable and efficiently used under reaction condition.

INTRODUCTION

Xanthenes and benzoxanthenes are important classes of compounds that have found use as dyes, fluorescent materials for visualization of bio-molecules and laser technologies due to their useful spectroscopic properties. Xanthene-based compounds have also been investigated for agricultural bacterial activity, photodynamic therapy, anti-inflammatory effect and antiviral activity. Numerous references are available on the synthesis of xanthenes including palladium catalyzed cyclization of polycyclic aryltriflate esters, intramolecular trapping of benzenes by phenols and reaction of aryloxymagnesium halides with triethylorthofomate. These methodologies, however, have disadvantages such as low yields, lack of availability or difficulty in preparation of starting materials, prolonged reaction time (16 h to 5 days), and use of toxic organic solvents and excess employment of reagents or catalysts. p-Dodecylbenzenesulfonic acid (DBSA) in aqueous media, p-toluenesulfonic acid (p–TsOH) in organic solvents, heterogeneous catalysts (NaHSO₄-SiO₂ and silica chloride), InCl₃·4H₂O in ionic liquid, Amberlyst-15, polyaniline-p-toluensulfonate salt and PPA-SiO₂ are also reported. Many of these methods, however, have similar shortcoming to the previously mentioned methods. Hence it is important to be on the lack out for more convenient methods.
The leading contenders for environmentally acceptable processes are supported reagents. Use of silica-supported reagents in one-pot multi-component construction of heterocycles has received considerable attention in organic synthesis. Perchloric acid adsorbed on silica gel (HClO₄/SiO₂) has emerged as an extremely useful catalyst in various organic transformations.

In view of its inherent properties such as environmental compatibility, greater selectivity, operational simplicity, moisture-insensitively, noncorrosive nature and ease of isolation, we set out to find out more about the behavior of HClO₄ supported on silica gel (230-400 mesh) in the synthesis of 1,8-dioxo-octahydroxanthenes. To the best of our knowledge, there was only one example on the use of HClO₄/SiO₂ on the synthesis of 1,8-dioxo-octahydroxanthenes with a low yield.

In continuation of our work on the development of efficient protocols for the synthesis of xanthenes an intermediate for the preparation of an antibacterial drug and in view of importance of heterogeneous acid catalysts in organic synthesis, we now wish to report that HClO₄/SiO₂ efficiently catalyzes synthesis of 1,8-dioxo-octahydroxanthenes. By the condensation of 5,5-dimethyl-1,3-cyclohexanedione (dimedone) with wide variety of aromatic aldehydes under solvent free conditions (Scheme 1).

![Scheme 1](image)

**RESULTS AND DISCUSSION**

In continuation of our research on finding efficient and environmentally friendly catalysts for organic reactions we came across a report on the use of HClO₄/SiO₂ catalyst in preparation of 1,8-dioxo-octahydroxanthenes is claimed that the intermediate obtained is 2,2′-arylmethylene bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) in 68% yield and the cyclized product is obtained in 32% yield in the presence of 30 mol% of HClO₄/SiO₂.

We wish to dispute these results and present our findings which show the formation of cyclized products. We have used HClO₄/SiO₂ in condensation reaction of benzaldehydes with dimedone giving 1,8-dioxo-octahydroxanthenes in excellent yields. In order to elucidate the structure of these compounds, we examined the structure of one compound (3d) by X-ray crystallography. ORTEP (Oak Ridge Thermal Ellipsoid Plot) view of this structure (Figure 1) shows the three rings in the molecule cyclized and 1,8-dioxo-octahydroxanthene fully formed.
In order to determine the optimal reaction conditions and evaluate the catalytic efficiency of HClO$_4$/SiO$_2$ catalyst, a model study was carried out on the synthesis of 3a (Scheme 1). Various solvents as well as solvent free conditions were tested and it was found that condensation of benzaldehyde with dimeredone was proceeded to give the highest yield, under solvent free conditions (94% yield, 15 min).

Results in Table 1 show the generality of the reaction. The results also indicate that the reaction is not substituted sensitive. The yields obtained were good to excellent without formation of any side products giving xanthenediones 3 in 82-96% yields.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>Time (min)</th>
<th>Yield (%)$^a$</th>
<th>Product</th>
<th>Mp (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C$_6$H$_5$</td>
<td>15</td>
<td>94</td>
<td>3a</td>
<td>204-205</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>202-204$^{13}$</td>
</tr>
<tr>
<td>2</td>
<td>4-ClC$_6$H$_4$</td>
<td>15</td>
<td>94</td>
<td>3b</td>
<td>225-226</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>228-230$^{13}$</td>
</tr>
<tr>
<td>3</td>
<td>2-ClC$_6$H$_4$</td>
<td>20</td>
<td>85</td>
<td>3c</td>
<td>228-230</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>228-230$^{13}$</td>
</tr>
<tr>
<td>4</td>
<td>4-BrC$_6$H$_4$</td>
<td>15</td>
<td>94</td>
<td>3d</td>
<td>233-235</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>234-236$^{17}$</td>
</tr>
<tr>
<td>5</td>
<td>4-FC$_6$H$_4$</td>
<td>15</td>
<td>96</td>
<td>3e</td>
<td>224-225</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>224-226$^{17}$</td>
</tr>
<tr>
<td>6</td>
<td>4-MeC$_6$H$_4$</td>
<td>18</td>
<td>92</td>
<td>3f</td>
<td>218-220</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>217-218$^{13}$</td>
</tr>
<tr>
<td>7</td>
<td>4-MeOCC$_6$H$_4$</td>
<td>18</td>
<td>86</td>
<td>3g</td>
<td>243-245</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>242-244$^{13}$</td>
</tr>
<tr>
<td>8</td>
<td>2-MeOCC$_6$H$_4$</td>
<td>20</td>
<td>85</td>
<td>3h</td>
<td>184-185</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>190-191$^{44}$</td>
</tr>
<tr>
<td>9</td>
<td>3-MeOCC$_6$H$_4$</td>
<td>20</td>
<td>82</td>
<td>3i</td>
<td>177-180</td>
</tr>
</tbody>
</table>
All the products obtained were characterized by spectroscopic methods such as IR, $^1$H NMR, for unknown compound ($^{13}$C NMR and analytical data) and also by comparison with the reported spectral data and melting points.

**REUSABILITY OF CATALYST**

To investigate the reusability and recycling of HClO$_4$/SiO$_2$. $p$-Bromobenzaldehyde, dimedone and 0.01 mmol HClO$_4$/SiO$_2$ were mixed in neat condition. The mixture was stirred at 80 °C. When the reaction was completed, the reaction mixture was dissolved in hot ethanol and catalyst was separated by simple filtration and recovered. HClO$_4$/SiO$_2$ was reused in subsequent reactions. No significant decrease in activity up to five runs was observed (Table 2).

**Table 2.** The recycling of 0.01 mmol of HClO$_4$/SiO$_2$ in neat conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time (min)</th>
<th>Yield(%)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td>94</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td>92</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>90</td>
</tr>
</tbody>
</table>

$a$ Isolated yields.

**EXPERIMENTAL**

The products (3a-r) were isolated and characterized by comparison of physical and spectral data with those reported in literature. $^1$H NMR and $^{13}$C NMR spectra were recorded on Bruker Avance-300 MHz spectrometers with 7–10 mM solutions in CDCl$_3$ in the presence of tetramethylsilane as internal standard. IR spectra were recorded using a Perkin-Elmer 843 spectrometer with KBr plates. Melting points were determined on an Electro thermal 9100, and are not corrected.
PREPARATION OF HClO₄/SiO₂ CATALYST

70% Aqueous perchloric acid (1.8 g, 12.5 mmol) was added to a suspension of SiO₂ (230-400 mesh, 23.7 g) in ether (70 mL). The mixture was concentrated and the residue was heated at 100 °C for 72 h under vacuum to give HClO₄/SiO₂ (0.5 mmol/g) a free flowing powder (50 mg = 0.025 mmol of HClO₄).

GENERAL EXPERIMENTAL PROCEDURE

A solution of 1 mmol of aldehyde and 2 mmol of dimesone in CH₂Cl₂ (5 mL), was added the HClO₄/SiO₂ (20 mg, 0.01 mmol, 1 mol%) in a 20 mL glass vial. The solvent was allowed to evaporate and the dry residue was stirred at 80 °C for an appropriate time according to Table 1. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was dissolved in hot ethanol and the catalyst was separated by simple filtration. The filtrate was kept at rt to give the pure product.

The spectral (IR, ¹H NMR, ¹³C NMR) and analytical data of unknown compounds are given below:

**Compound 3i** (Table 1): with solid; IR (KBr): v max/cm⁻¹ 3005, 2959, 2873, 1674, 1660, 1625, 1605, 1584, 1486, 1447, 1360, 1274, 1201, 1164, 1139, 1047, 1001, 9001, 862, 801, 768, 691, 654, 574; ¹H NMR (300 MHz; CDCl₃; Me₄Si): δ 1.00 (s, 6H, 2CH₃), 1.10 (s, 6H, 2CH₃), 2.21 (ABq, 4H, J = 16.4 Hz, 2CH₂, H-4, H-5), 2.45 (s, 4H, 2CH₂, H-2, H-7), 3.77 (s, 3H, OCH₃), 4.74 (s, 1H, H-9), 6.63-6.67 (m, 1H, ArH), 6.86-6.89 (m, 2H, ArH), 7.10-7.15 (m, 1H, ArH); ¹³C NMR (75 MHz, CDCl₃): δ 27.41, 29.22, 31.76, 32.18, 40.85, 50.74, 55.09, 55.13, 111.80, 114.29, 115.54, 120.87, 128.87, 145.68, 159.31, 162.25, 196.39; Anal. Calcd for C₂₄H₂₈O₄: C, 69.33; H, 9.33. Found: C, 68.99; H, 9.41.

**Compound 3j** (Table 1): with solid; IR (KBr): v max/cm⁻¹ 3019, 2967, 2890, 1679, 1667, 1628, 1613, 1589, 1508, 1468, 1429, 1364, 1301, 1272, 1217, 1201, 1170, 1140, 1048, 1005, 933, 836, 578; ¹H NMR (300 MHz; CDCl₃; Me₄Si): δ 0.95 (s, 6H, 2CH₃), 1.09 (s, 6H, 2CH₃), 2.18 (ABq, 4H, J = 16.4 Hz, 2CH₂, H-4, H-5), 2.40 (ABq, 4H, J = 17.4 Hz, 2CH₂, H-2, H-7), 3.72 (s, 3H, OCH₃), 3.74 (s, 3H, OCH₃), 4.77 (s, 1H, H-9), 6.32 (d, 1H, J = 2.3 Hz, ArH), 6.43 (m, 1H, ArH), 7.3 (d, 1H, J = 8.3 Hz ArH); ¹³C NMR (75 MHz, CDCl₃): δ 26.67, 29.05, 29.54, 32.12, 40.93, 50.78, 54.99, 55.12, 98.53, 103.91, 113.71, 123.14, 132.55, 155.42, 159.44, 162.78, 196.73; Anal. Calcd for C₂₅H₃₀O₅: C, 73.17; H, 7.32. Found: C, 73.26; H, 7.45.

**Compound 3p** (Table 1): with solid; IR (KBr): v max/cm⁻¹ 3069, 2971, 2940, 2885, 1679, 1667, 1630, 1605, 1511, 1466, 1364, 1199, 1167, 1142, 1005, 829, 747, 484; ¹H NMR (300 MHz; CDCl₃; Me₄Si): δ 0.98 (s, 6H, 2CH₃), 1.10 (s, 6H, 2CH₃), 2.19 (ABq, 4H, J = 16.3 Hz, 2CH₂, H-4, H-5), 2.51 (s, 4H, 2CH₂, H-2, H-7), 4.92 (s, 1H, H-9), 7.36-7.40 (m, 2H, ArH), 7.44-7.47 (m, 1H, ArH), 7.69-7.75 (m, 4H, ArH); ¹³C NMR (75 MHz, CDCl₃): δ 27.32, 29.30, 31.98, 32.21, 40.89, 50.72, 115.59, 125.29, 125.58, 126.87, 127.13, 127.45, 127.68, 127.97, 132.34, 133.37, 141.62, 162.31, 196.40; Anal. Calcd for C₂₇H₂₈O₃: C, 81.00; H, 7.00. Found: C, 81.13; H, 7.07.
ACKNOWLEDGEMENTS
We thank the faculty of chemistry of Tarbiat Moalem University for supporting of this work.

REFERENCES
20. S. Kantevari, R. Bantu, and L. Nagarapu, J. Mol. Catal. A: Chem., 2007, 269, 53. In the ref. 20 A mixture of dinedone, aldehyde and catalyst HClO₄/SiO₂ was heated at 140 °C but in this work for completely homogenousing we dissolve a mixture of aldehyde, dinedone and HClO₄/SiO₂ in CH₂Cl₂ as a solvent then the solvent was allowed to evaporate. After this process the reaction was done.
2006, 47, 5573.