

## Silica-Supported Phosphorus-Containing Catalysts Efficiently Promoted Synthesis of 1,8-Dioxo-octahydroxanthenes under Solvent-Free Conditions

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**Abstract:** Synthesis of 1,8-dioxo-octahydroxanthene derivatives from dimedone and aldehydes using silica-supported phosphorus pentoxide ( $P_2O_5/SiO_2$ ) or Silicaphosphine (Silphos,  $[PCl_{3-n}(SiO_2)_n]$ ) as efficient and heterogeneous catalysts is described in this paper. The reactions were completed in relatively short reaction times under solvent-free conditions at 80 °C and the products were obtained in good to excellent yields.

**Keywords:**  $P_2O_5/SiO_2$ , Silphos, 1,8-Dioxo-octahydroxanthene, Dimedone, Aldehyde, Solvent-free

### Introduction

Recently, the use of catalysts and reagents supported on solid supports especially those based on silica and also solvent-free conditions have been extensively developed because such reagents not only cause to simplify the purification processes but also help to prevent the releasing of toxic reaction residues into the environment<sup>1-3</sup>. Moreover, due to moisture sensitivity of some reagents, application of them in organic reactions is difficult. This problem can be solved by their immobilization onto solid supports<sup>1-3</sup>. Silica-supported phosphorus-containing catalysts are one class of the most interesting solid-supported catalysts and are inexpensive, commercially available and environmentally benign which has been used in various organic transformations<sup>3,4</sup>.

Xanthene derivatives are of importance as they have been used as dyes, fluorescent materials and laser technologies due to their useful spectroscopic properties<sup>5</sup>. These compounds have also received significant attention due to their useful biological and pharmaceutical properties such as antiviral<sup>6</sup>, antibacterial<sup>7</sup> and antinociceptive activities<sup>8</sup> as well as their efficiency in photodynamic therapy<sup>9</sup> and anti-inflammatory activities<sup>10</sup>. Some procedures have been reported for the synthesis of 1,8-dioxo-octahydroxanthene derivatives employing dimedone and aromatic aldehydes in the presence of acidic catalysts such as

SbCl<sub>3</sub>/SiO<sub>2</sub><sup>11</sup>, HClO<sub>4</sub>/SiO<sub>2</sub><sup>12</sup>, silica chloride<sup>13</sup>, FeCl<sub>3</sub>/SiO<sub>2</sub><sup>14</sup>, silica sulfuric acid<sup>15</sup>, Dowex-50w<sup>16</sup>, Amberlyst-15<sup>17</sup>, [bmim][TFA]<sup>18</sup> and TMSCl<sup>19</sup>. However, the reported methods suffer from drawbacks such as long reaction times, moderate yields, the use of toxic reagents, formation of by-products and no agreement with the green chemistry protocols.

In continuation of our interest on synthesis of heterocyclic compounds<sup>20</sup>, we report here a new, green and highly efficient method for the synthesis of 1,8-dioxo-octahydroxanthenes via the condensation of dimedone with aldehydes using P<sub>2</sub>O<sub>5</sub>/SiO<sub>2</sub> or silphos as non-toxic, readily producible and heterogeneous catalysts under solvent-free conditions at 80 °C (Scheme 1). Interestingly, our method has none of the above-mentioned disadvantages at all.

## Experimental

All chemicals were purchased from Merck or Fluka Chemical Companies. All compounds are known and their structures were identified by comparing their melting points and <sup>1</sup>H and <sup>13</sup>C NMR data with those reported in the literature. The <sup>1</sup>H NMR (500 MHz) and <sup>13</sup>C NMR (125 MHz) were run on a Bruker Avance DPX-250, FT-NMR spectrometer (δ in ppm). Melting points were recorded on a Büchi B-545 apparatus in open capillary tubes.

### *Preparation of P<sub>2</sub>O<sub>5</sub>/SiO<sub>2</sub> (30% w/w)*

A mixture of SiO<sub>2</sub> [silica gel 60, 0.063-0.200 mm (70-230 mesh ASTM), 3.5 g] and P<sub>2</sub>O<sub>5</sub> (1.5 g) was ground vigorously to give the catalyst, P<sub>2</sub>O<sub>5</sub>/SiO<sub>2</sub>, as a white powder (5.0 g)<sup>3</sup>. This catalyst can be kept without any change for months in a capped bottle.

### *Preparation of silphos*

Under an argon atmosphere, to a flask containing dried silica gel (type 60, 15-40 μm) (18.0 g, 300 mmol) was added PCl<sub>3</sub> (13.8 g, 100 mmol) at room temperature and stirred slowly with a mechanical stirrer for 30 min. The mixture was then heated to 60 °C while it was stirring (400 cycle/min) under pressure of argon for 3 h to remove all HCl. The reaction mixture was washed with 50 mL of dry CH<sub>2</sub>Cl<sub>2</sub> and dried under vacuum. Silphos was obtained as a white solid (21.6-22.3 g), which was stored in a capped bottle<sup>4</sup>. The catalyst can be kept without any change for months.

### *General procedure for the preparation of 1,8-dioxo-octahydroxanthenes using P<sub>2</sub>O<sub>5</sub>/SiO<sub>2</sub> or silphos*

A mixture of dimedone (2 mmol), aldehyde (1 mmol) and P<sub>2</sub>O<sub>5</sub>/SiO<sub>2</sub> (0.12 g) or silphos (1.0 g), in a round-bottomed flask connected to a reflux condenser, was heated and stirred in an oil-bath (80 °C). After completion the reaction as monitored by TLC, EtOAc (10 mL) was added to the reaction mixture, stirred for 2 min and filtered. The solvent of the filtrate was evaporated and the resulting solid (crude product) was recrystallized from EtOH (97%) to afford the pure product.

## Selected spectral data of the products

### *3,3,6,6-Tetramethyl-9(phenyl)-1,8-dioxo-octahydroxanthene (Table 3, Entry 1)*

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz): δ 0.90 (s, 6H), 1.04 (s, 6H), 2.09 (d, *J* = 16.1 Hz, 2H), 2.27 (d, *J* = 16.2 Hz, 2H), 2.53 (d, *J* = 17.1 Hz, 2H), 2.58 (d, *J* = 17.7 Hz, 2H), 4.53 (s, 1H), 7.10 (t, *J* = 7.0 Hz, 1H), 7.18 (d, *J* = 7.0 Hz, 2H), 7.21 (t, *J* = 7.20 Hz, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz): δ 27.7, 29.6, 32.3, 32.6, 41.3, 51.2, 116.1, 126.8, 128.4, 128.8, 144.5, 162.7, 196.8.

*3,3,6,6-Tetramethyl-9(4-chloro-Phenyl)-1,8-dioxo-octahydroxanthene* (Table 3, Entry 2)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz): δ 0.90 (s, 6H), 1.04 (s, 6H), 2.09 (d, *J* = 16.1 Hz, 2H), 2.27 (d, *J* = 16.1 Hz, 2H), 2.52 (d, 2H), 2.57 (d, *J* = 17.6 Hz, 2H), 4.51 (s, 1H), 7.19 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.2 Hz, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz): δ 27.7, 29.7, 31.8, 32.6, 41.3, 51.1, 115.6, 128.6, 130.2, 132.4, 143.1, 162.8, 196.7.

*3,3,6,6-Tetramethyl-9(3-nitro-Phenyl)-1,8-dioxo-octahydroxanthene* (Table3, Entry 6)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz): δ 0.91 (s, 6H), 1.04 (s, 6H), 2.11 (d, *J* = 16.1 Hz, 2H), 2.29 (d, *J* = 16.1 Hz, 2H), 2.57 (d, *J* = 17.9 Hz, 2H), 2.60 (d, *J* = 17.9 Hz, 2H), 4.65 (s, 1H), 7.56 (t, *J* = 7.7 Hz, 1H), 7.66 (d, *J* = 7.6 Hz, 1H), 8.00 (d, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz): δ 27.2, 29.6, 32.0, 32.7, 50.9, 56.6, 60.7, 106.3, 115.1, 136.8, 140.7, 153.2, 163.9, 197.0.

*3,3,6,6-Tetramethyl-9(3,4-dimethoxy-Phenyl)-1,8-dioxo-octahydroxanthene* (Table 3, Entry 17)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz): δ 0.92 (s, 6H), 1.04 (s, 6H), 2.10 (d, *J* = 16.1 Hz, 2H), 2.27 (d, *J* = 16.1 Hz, 2H), 2.51 (d, *J* = 17.6 Hz, 2H), 2.57 (d, *J* = 17.4 Hz, 2H), 3.68 (s, 6H), 4.48 (s, 1H), 6.67 (dd, *J* = 8.3, 1.9 Hz, 1H), 6.72 (d, *J* = 1.9 Hz, 1H), 6.80 (d, *J* = 8.31 Hz, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz): δ 27.2, 29.6, 31.4, 32.7, 50.9, 56.3, 56.3, 112.2, 112.9, 115.4, 120.9, 137.7, 148.1, 148.9, 163.6, 196.9.

*3,3,6,6-Tetramethyl-9(5-bromo-2-hydroxy-Phenyl)-1,8-dioxo-octahydroxanthene* (Table 3, Entry 19)

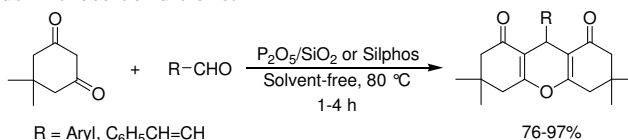
<sup>1</sup>H NMR(CDCl<sub>3</sub>, 500 MHz): δ 0.90 (s, 6H), 0.97 (s, 3H), 1.05 (s, 3H), 2.04 (d, *J* = 15.8 Hz, 2H), 2.25 (d, *J* = 15.9 Hz, 2H), 2.34 (d, *J* = 17.3 Hz, 2H), 2.55 (d, *J* = 17.4 Hz, 2H), 5.04 (s, 1H), 6.95 (d, *J* = 8.64 Hz, 1H), 7.04 (s, 1H), 7.28 (d, *J* = 8.60 Hz, 1H), 10.59 (s, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz): δ 26.9, 28.4, 30.0, 32.5, 51.2, 100.4, 111.3, 116.3, 129.1, 130.6, 131.4, 149.8, 165.3, 196.5.

*3,3,6,6-Tetramethyl-9(2-phenyl-ethylene)-1,8-dioxo-octahydroxanthene* (Table 3, Entry 20)

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz): δ 1.04 (s, 6H), 1.06 (s, 6H), 2.25 (d, *J* = 16.04 Hz, 2H), 2.31 (d, *J* = 16.02 Hz, 2H), 2.52 (s, 4H), 4.15 (d, *J* = 5.29 Hz, 1H), 6.19 (d, *J* = 16.05 Hz, 1H), 6.21 (dd, 1H), 7.19 (m, 1H), 7.27 (d, *J* = 3.7 Hz, 4H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz): δ 27.7, 28.3, 29.4, 32.8, 50.9, 114.1, 126.8, 128.2, 129.4, 130.4, 132.2, 137.5, 164.4, 197.1.

## Results and Discussion

Initially, we studied effect of amount of the catalysts on the reaction of dimedone (2 mmol) with benzaldehyde (1 mmol) under solvent-free conditions at 80 °C (Scheme1). The results are summarized in Table 1. As it can be seen in Table 1, the best amounts of P<sub>2</sub>O<sub>5</sub>/SiO<sub>2</sub> and silphos were 0.12 and 1.0 g, respectively. The reaction was also examined in the presence of P<sub>2</sub>O<sub>5</sub>, PCl<sub>3</sub> and SiO<sub>2</sub> separately (Table 1, entries 10-12); however, the product was obtained in moderate yields in these conditions.



**Scheme 1**

**Table 1.** The condensation of dimedone (2 mmol) with benzaldehyde (1 mmol) using different amounts of the catalysts under solvent-free conditions at 80 °C

Entry	Catalyst	Amount, g	Time, h	Yield <sup>a</sup> , %
1	-	-	8	-
2	P <sub>2</sub> O <sub>5</sub> /SiO <sub>2</sub>	0.04	5	62
3	P <sub>2</sub> O <sub>5</sub> /SiO <sub>2</sub>	0.08	2	90
4	P <sub>2</sub> O <sub>5</sub> /SiO <sub>2</sub>	0.12	1.5	97
5	P <sub>2</sub> O <sub>5</sub> /SiO <sub>2</sub>	0.15	1.5	96
6	Silphos	0.4	5	74
7	Silphos	0.8	2.5	83
8	Silphos	1.0	2	96
9	Silphos	1.2	2	96
10	P <sub>2</sub> O <sub>5</sub>	0.04	2	74
11 <sup>b</sup>	PCl <sub>3</sub>	0.05	3	52

<sup>a</sup>Isolated yield. <sup>b</sup>This reaction was carried out at 75 °C

In another study, the condensation of dimedone with benzaldehyde was checked at different temperatures in the presence of P<sub>2</sub>O<sub>5</sub>/SiO<sub>2</sub> and silphos under solvent-free conditions (Table 2). As Table 2 indicates, higher yields and shorter reaction times were observed at 80 °C using both reagents.

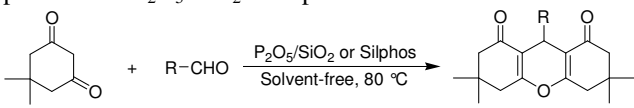
**Table 2.** The reaction of dimedone (2 mmol) with benzaldehyde (1 mmol) using P<sub>2</sub>O<sub>5</sub>/SiO<sub>2</sub> (0.12) or silphos (1.0 g) at different temperatures under solvent-free conditions

Entry	Catalyst	Temperature, °C	Time, h	Yield <sup>a</sup> , %
1	P <sub>2</sub> O <sub>5</sub> /SiO <sub>2</sub>	r.t.	20	Trace
2	P <sub>2</sub> O <sub>5</sub> /SiO <sub>2</sub>	60	5	67
3	P <sub>2</sub> O <sub>5</sub> /SiO <sub>2</sub>	70	3	81
4	P <sub>2</sub> O <sub>5</sub> /SiO <sub>2</sub>	80	1.5	97
5	P <sub>2</sub> O <sub>5</sub> /SiO <sub>2</sub>	90	1.5	97
6	Silphos	r.t.	20	Trace
7	Silphos	60	6	58
8	Silphos	70	4	82
9	Silphos	80	2	96
10	Silphos	90	2	96

<sup>a</sup>Isolated yield

To compare the efficiency as well as capacity of the solvent-free conditions with respect to solution conditions, the reaction of dimedone (2 mmol) with benzaldehyde (1 mmol) was tested in the presence of silica-supported P<sub>2</sub>O<sub>5</sub> (0.12) or silphos (1.0 g) in several solvents (5 mL), such as MeCN, CH<sub>2</sub>Cl<sub>2</sub>, CHCl<sub>3</sub>, THF and EtOH under reflux conditions. In these conditions, the product was produced in low yields and in long reaction times.

After optimization of the reaction conditions, dimedone was reacted with different types of aldehydes (including aromatic aldehydes possessing electron-releasing substituents, electron-withdrawing substituents and halogens on their aromatic rings as well as cinnamaldehyde) in the presence of the silica-supported phosphorus-containing catalysts. The results are displayed in Table 3. As it is shown in Table 3, all reactions were completed within 1-4 h and the desired products were obtained in good to excellent yields (76-98%). Thus, our method is highly efficient and general.

**Table 3.** The Synthesis of 1,8-doxo-octahydro-xanthene derivatives from dimedone and aldehydes in the presence of P<sub>2</sub>O<sub>5</sub>/SiO<sub>2</sub> or silphos under solvent-free conditions at 80 °C


Entry	R	P <sub>2</sub> O <sub>5</sub> /SiO <sub>2</sub>		Silphos		M.P., (lit)[Ref]
		Time, h/Yield <sup>a</sup> , %	Time, h/Yield <sup>a</sup> , %	Time, h/Yield <sup>a</sup> , %	Time, h/Yield <sup>a</sup> , %	
1	C <sub>6</sub> H <sub>5</sub>	1.5/97	2/96			199-201 (201-202) [12]
2	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	1.15/97	1.5/97			231-233 (230-232) [12]
3	<i>m</i> -ClC <sub>6</sub> H <sub>4</sub>	2/87	1.5/91			184-186 (183-185) [11]
4	<i>o</i> -ClC <sub>6</sub> H <sub>4</sub>	2/95	2/92			223-225 (226-227) [11]
5	<i>p</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	1/94	1.5/97			223-225 (222-224) [11]
6	<i>m</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	1.5/97	1/95			163-165 (165-166) [11]
7	<i>o</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	1.5/97	2.5/90			249-251 (252-254) [18]
8	<i>p</i> -Br C <sub>6</sub> H <sub>4</sub>	1.5/93	1.5/94			241-243 (240-242) [12]
9	<i>o</i> -BrC <sub>6</sub> H <sub>4</sub>	2/87	1.5/85			221-223 (226-229) [11]
10	<i>p</i> -CNC <sub>6</sub> H <sub>4</sub>	1.5/88	2/84			220-222 (217-218) [11]
11	<i>p</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	1/98	1.5/95			213-215 (215-216) [11]
12	<i>m</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	1/96	1.5/95			207-209 (208-210) [18]
13	<i>o</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	3/80	2.5/85			210-212 (210-212) [18]
14	<i>p</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	2/93	2/91			241-243 (242-243) [11]
15	<i>m</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	3/86	2.5/85			161-163 (161-162) [11]
16	<i>o</i> -OHC <sub>6</sub> H <sub>4</sub>	1/95	1.15/93			198-200 (194-196) [18]
17	3,4- (CH <sub>3</sub> O) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	3/87	2/90			178-180 (175-176) [11]
18	3,4,5- (CH <sub>3</sub> O) <sub>3</sub> C <sub>6</sub> H <sub>2</sub>	4/76	3.5/83			201-203 (205-208) [12]
19	5-Br -2- OHC <sub>6</sub> H <sub>3</sub>	1/97	1.5/97			250-252 (249-252) [18]
20	C <sub>6</sub> H <sub>5</sub> CH=CH	2.5/89	1.5/94			172-174 (174-176) [18]
21	<i>p</i> -OHCC <sub>6</sub> H <sub>4</sub>	4/95	3.5/92			>300 (>300) [18]

<sup>a</sup>Isolated yield

## Conclusion

In conclusion, we have developed a new method for the synthesis of 1,8-dioxo-octahydroxanthenes using two heterogeneous catalysts, P<sub>2</sub>O<sub>5</sub>/SiO<sub>2</sub> and silphos. The simple experimental and work-up procedures, efficiency, high yields, relatively short reaction times, generality, application of inexpensive catalysts and compliance with the green chemistry protocols are the advantages of the present method.

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