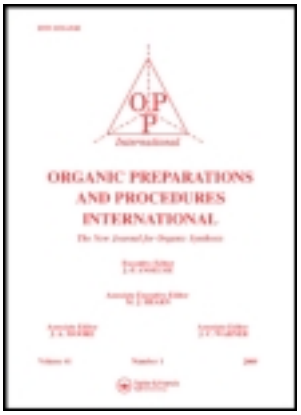

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Facile and Rapid Synthesis of 9-Aryl 1,8-dioxoöctahydroxanthenes Derivatives using Tungstate Sulfuric Acid

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Xanthenes and its derivatives have received significant attention in recent years due to their wide range of biological and therapeutic properties.[1–3] Xanthenes and its derivatives have been prepared by various methods such as the reaction of aryloxymagnesium halides with triethyl orthoformate,[4] cyclodehydration of a Mannich base (formed from piperidine, formaldehyde and 2-hydroxy-5,7,8-trimethoxy-1,4-naphtoquinone) with a phenol,[5] trapping of benzynes with phenols,[6] coupling of 3-(dimethoxymethyl)phenol with 2-bromoacetophenone, followed by intramolecular phenyl–carbonyl coupling reaction,[7] cyclocondensation between 2-hydroxy aromatic aldehydes with 2-tetralone,[8] and condensation of β-naphthol with aldehydes or acetals.[9] Furthermore xanthene derivatives may be obtained by reaction of aldehydes, β-naphthol and cyclic 1,3-diketones in the presence of catalysts such as tetra-(*n*-butyl) ammonium fluoride in various solvents.[10] However, some of these methods involve long reaction times, unsatisfactory yields, harsh reaction conditions and often expensive catalysts.

Solid acids play a significant role in green chemistry, especially in chemical manufacturing processes,[11–14] generally have high turnover numbers and can be easily separated from the organic components.[15] Tungstate sulfuric acid (TSA) has been reported as a new inorganic solid acid prepared by an improved, shorter and safer procedure from anhydrous sodium tungstate with chlorosulfonic acid (1:2 mole) in *n*-hexane (*Scheme 1*).[16–18]

We now describe the use of TSA for the synthesis of 1,8-dioxoöctahydroxanthenes **3** by condensation of 1,3-cyclohexanediones **1** with aromatic aldehydes **2** under solvent-free conditions (*Scheme 2*). The structures of the products were deduced from their IR, NMR spectroscopic data and their melting points.

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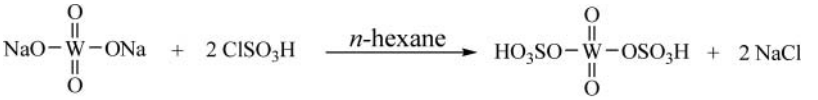
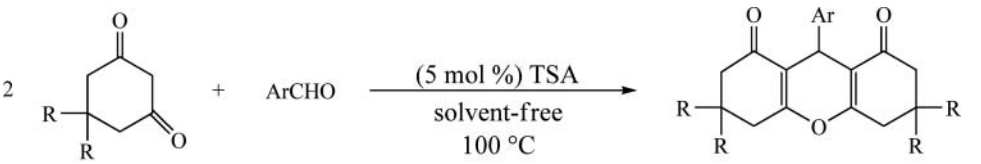


TSA

Scheme 1



1 **2** **3**

a) R = Me; b) R = H

Scheme 2

Under the given conditions several aromatic aldehydes **2** containing electron-donating as well as electron-withdrawing groups with different substitution patterns were effectively cyclized to give 9-aryl-substituted 1,8-dioxoöctahydroxanthenes **3**. No appreciable yields of products were obtained with aliphatic aldehydes and ketones, possibly due to enolization; cinnamaldehyde gave the expected xanthene in 95% yield product while other cyclic diketones such as 1,3-cyclopentane- and cycloheptanediones led to pyrans.

The best molar ratio of the catalyst for this reaction was found to be 5 mol% for the model reaction whereas larger amounts of the catalyst did not improve the results. Comparison of this catalyst with other methods for the synthesis of 3,3,6,6-tetramethyl-9-phenyl-1,2,3,4,5,6,7,8-octahydro-9H-xanthene-1,8-dione show that TSA provide the best yields for the synthesis of xanthene derivatives (*Table 1*).

This method provides a simple, efficient and practical approach for the synthesis of xanthene derivatives in the presence of tungstate sulfuric acid as an eco-friendly catalyst with high catalytic activity at 100°C under solvent-free conditions. The catalyst is recyclable (up to five times) without significant loss of activity.

Experimental Section

Melting points were measured on an elecrtothermal KSB1N apparatus. IR spectra were recorded in the matrix of KBr with JASCO FT-IR-680 plus spectrometer. ^{1}H NMR and ^{13}C NMR spectra were determined on a FT-NMR Bruker Avance Ultra Shield Spectrometer at 400.13 and 100.62 MHz in $CDCl_3$ as solvent in the presence of tetramethylsilane as internal standard. TLC was performed on TLC-Grade silica gel-G/UV 254 nm plates (*n*-hexane, ethyl acetate 2:1). Chemicals were purchased from Aldrich, Fluka and Merck chemical

Table 1
Comparison of the Results for the Synthesis of 3,3,6,6-Tetramethyl-9-phenyl-1,2,3,4,5,6,7,8-octahydro-9H-xanthene-1,8-dione (*Table 2, Entry 1*) with Other Catalysts

Catalyst	Mol (%)	Solvent/Temp. (°C)	Time (min.)	Yield (%)	[Ref.]
TSA	5	Solvent free/100	60	96	This work
p-TsOH[a]	5	MeOH, H_2O/50	20	80	[19]
DBSA[b]	10	H_2O-Ultrasonic/25–30	60	89	[20]
TMSCl[c]	100	CH_3CN/Reflux	420	95	[21]
TBAHS[d]	10	Dioxane, H_2O/Reflux	210	88	[22]
$NaHSO_4.SiO_2$	50	CH_3CN/reflux	390	90	[23]
Selectfluor™ [e]	10	Solvent free/120	60	95	[24]
PPA-SiO_2[f]	10	Solvent free/140	30	93	[25]
$HClO_4$-SiO_2	10	Solvent free/140	180	32	[25]
$SbCl_3$-SiO_2	10	Solvent free/120	50	93	[26]

a) *p*-Toluenesulfonic acid. b) *p*-Dodecylbenzenesulfonic acid. c) Trimethylsilyl chloride. d) Tetrabutylammonium bisulfate. e) 1-(Chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2,2,2]octane bis(tetrafluoroborate). f) Polyphosphoric acid supported on silica.

companies. All compounds were characterized by comparison with authentic samples and combustion analyses.

Preparation of Catalyst

[16–18] To 1 L of dry *n*-hexane in a 2 L round bottom flask, equipped with overhead stirrer and cooled in an ice bath, was added 59 g (0.2 mol) of anhydrous sodium tungstate; then 27 mL (0.4 mol) of chlorosulfonic acid (CAUTION) was added dropwise over 30 min. This mixture was stirred for 1.5 h. Afterwards the reaction mixture was gradually poured into 1 L of chilled distilled water with stirring. The yellowish catalyst which separated out was collected, washed with distilled water (100 mL) five times until the filtrate showed negative test for chloride ion. Drying at 120°C for 5 h gave 80 g (98%) of the yellowish catalyst, mp. 285°C (dec.). *lit.*[17] 285°C.

General Procedure for the Preparation of 9-Aryl 1,8-Dioxoöctahydroxanthenes

A mixture of dimedone (28 g, 0.2 mol), aldehyde (0.1 mol) and TSA (3 g, 0.005 mol) was heated at 100°C for the time indicated in *Table 2*. The progress of the reaction was monitored by TLC on silica gel (SILG/UV 254) plates (*n*-hexane, ethyl acetate 2:1). After completion of the reaction, the reaction mixture was cooled to room temperature and washed with $CHCl_3$ (0.5 L), then was filtered to remove the catalyst and the filtrate was concentrated in vacuum to afford the crude product which was recrystallized from EtOH to afford the crystalline pure product. The catalyst was washed with ethanol, dried at 120°C for 1 h, and reused five times in other reactions.

Table 2
TSA-catalyzed Synthesis of 9-Aryl Substituted 1,8-Dioxoöctahydroxanthenes

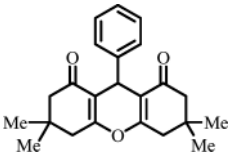
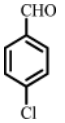
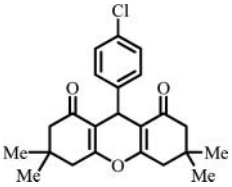
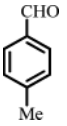
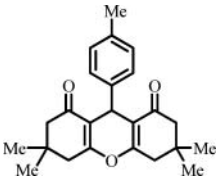
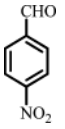
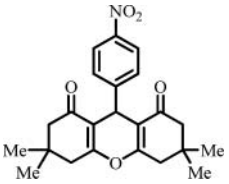
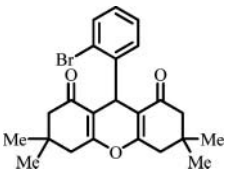
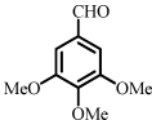
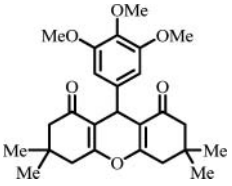
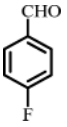
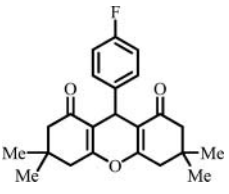
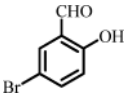
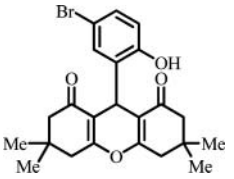
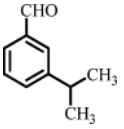
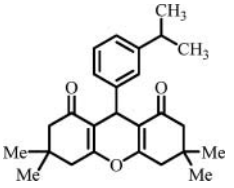
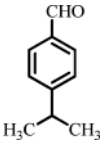
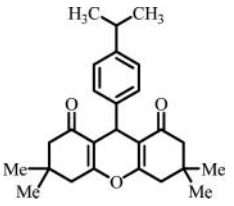
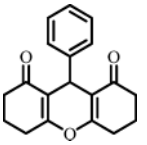
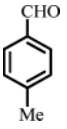
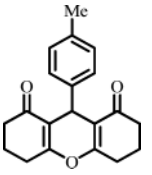
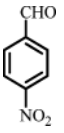
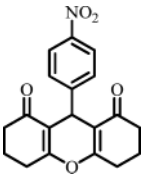
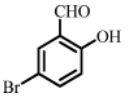
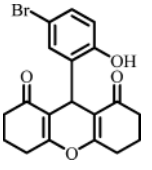
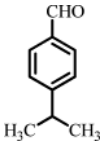
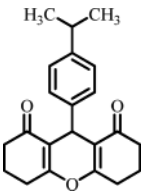
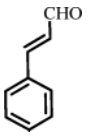
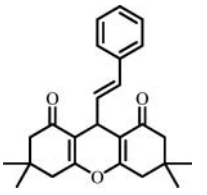
Entry	Aldehyde **2**	Product[a] **3**	Time (min)	Yield (%)/[lit.]	mp (°C)/[lit.]
1			60	96 (93)[25]	202–204 (201–202)[25]
2			45	90 (85)[25]	230–232 (230–232)[25]
3			90	88 (75)[27]	215–217 (216–217)[27]
4			30	95 (88)[27]	219–221 (221–223)[27]
5			60	89 (76)[28]	226–227 (226–228)[28]
6			60	93 (95)[26]	209–211 (210–212)[26]
7			35	92(90)[28]	223–225 (224–226)[28]

Table 2
TSA-catalyzed Synthesis of 9-Aryl Substituted 1,8-Dioxoöctahydroxanthenes
(Continued)

Entry	Aldehyde **2**	Product[a] **3**	Time (min)	Yield (%)/[lit.]	mp (°C)/[lit.]
8			50	90 (88)[29]	250–252 (249–252)[29]
9			110	86 (75)[30]	189–191 (190–191)[5,30]
10			90	88 (80)[5]	238–239 (236–239)[5]
11			45	95 (82)[31]	271–273 (272–273)[31]
12			65	89 (84)[25]	260–262 (262–263)[25]
13			30	92 (84)[32]	224–227 (224–226)[32]
14			55	88 (80)[4]	250–252 (249–252)[4]

(Continued on next page)

Table 2
TSA-catalyzed Synthesis of 9-Aryl Substituted 1,8-Dioxoöctahydroxanthenes
(Continued)

Entry	Aldehyde **2**	Product[a] **3**	Time (min)	Yield (%)/[lit.]	mp (°C)/[lit.]
15			60	86 (84)[33]	170–172 (169–171)[33]
16			50	95 (93)[20]	176–177 (175–177)[20]

a) Identified by comparison with authentic samples.

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