

A Practical Approach to the Effective Synthesis of 1,8-Dioxoöctahydroxanthene Derivatives By The Use of ICl_3/SiO_2 and $In(CF_3SO_2)_3$ As Recyclable and Highly Efficient Catalysts

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ABSTRACT

Silica gel supported iodine trichloride and indium triflate were found as efficient and reusable catalysts to the synthesis of a series of xanthenes as potentially interesting biological active molecules in high rates and yields. A broad range of xanthene derivatives were efficiently prepared via a three component reaction between cyclic β -diketones and arylaldehydes (2:1 ratio) with high yield and purity by the use of a catalytic amount of ICl_3/SiO_2 and $In(CF_3SO_2)_3$ as Lewis acids under solvent-free and mild conditions. This newly achieved route has some advantage such as facile and simple handling, employing of neat and reusable catalysts, using readily available chemicals, short span of needed time, avoid of employing hazardous solvents, and including green chemistry aspects.

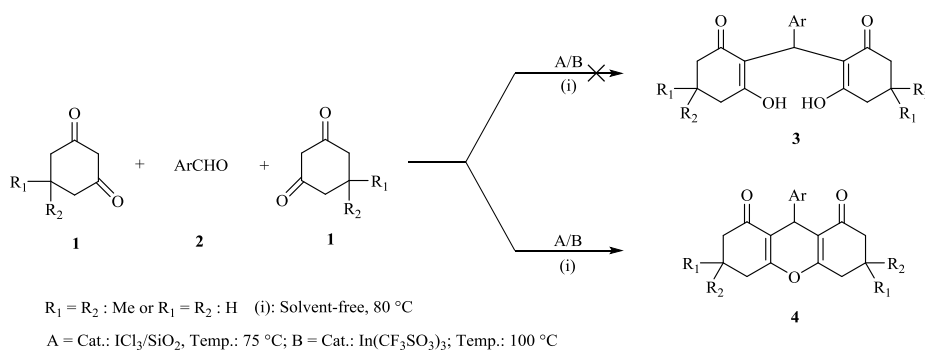
Keywords: Recyclable catalyst, Condensation reaction, Cyclic β -diketone, Solvent free, 1,8-dioxoöctahydroxanthene.

INTRODUCTION

Nowadays, the role of solid acids in environmentally safe and economical technologies, mainly in chemical manufacturing processes and green chemistry is inevitable and undeniable [1-5]. Furthermore, the key role of solid acids as catalyst in the synthesis of heterocycles and other organic compounds is well-known and well-recognized [6-9], especially, after completion of reaction, they can easily separate from reaction mixture [10,11]. Furthermore, considering green chemistry aspects, due to reducing of environment pollutions, use of eco-friendly technologies such as running organic reactions under green conditions is one of the more important perspective that nowadays has received the interest of chemists [12-18]. The use of solvent-free conditions in chemical reactions is one of these technologies. To the point of green chemistry view, loading chemical reactions under solvent-less conditions has significant advantages such as avoiding use of harmful solvents, reducing environmental pollution, bringing down handling costs, predigestion of experimental and, work up procedures, and also frugality in labor [12-18].

Among organic compounds, pharmacological and therapeutic virtues of xanthene derivatives make them more notable and important molecules. Therefore, they have recently received more attentions by chemists and pharmacologists [19,20]. In addition, the importance of xanthenes clearly is understood by their applications including, xanthene dyes [21], anti-cancer activity [22], applicable for the evaluation of biomolecules via its fluorescent activity [23], and also in laser and optic technologies [24]. As well as, some of the xanthene-based heterocycles have recognized as antagonists and in photodynamic therapy [25]. As a matter of fact cancer is the leading cause of death in the developed countries, and second leading cause of death in the developing countries, therefore improving and developing of new and more effective compounds to treat of cancer is inevitable [16]. Considering above, for instance, some derivatives of 1,8-dioxoöctahydroxanthene were synthesized and assessed for their anticancer activities in vitro [16]. The obtained results from this experiment, reveals this type of compounds have shown anti-proliferative properties against a number of cancer cell lines including, human neuroblastoma (IMR32), human colon carcinoma (Colo-205), and human chronic myeloid leukemia (K562) cells [16]. Despite, taking attempts to 1,8-dioxoöctahydroxanthene derivatives synthesis and

evaluation of their properties toward tumor and normal cell lines [26], the leishmanicidal assay of these compounds were evaluated. The results of this experiment, revealed that some derivatives of 1,8-dioxoöctahydroxanthenes would show anti-leishmanial activity [27]. Also Up to date several natural products and herbal medicines are isolated and characterized from natural sources which have xanthene motifs in their chemical structures [28]. Nowadays, there are numerous reported methods in which lead to produce of xanthenes and their derivatives, including the reaction between aryloxymagnesium halides and triethylorthoformate [29], cyclodehydration [30], reaction of benzynes with phenols [31], intramolecular condensation reactions between benzaldehydes and acetophenones [32], and cyclocondensation of ortho-hydroxyarylaldehydes and β -tetralone [33]. Turning to the matter of xanthene derivatives, some other procedures are well-known that cause to produce of these heterocycles, such as catalytic condensation between 2-naphthol with aldehydes or acetals by the use of silica sulfuric acid (SSA), $\text{HCl}/\text{CH}_3\text{COOH}$ or H_3PO_4 [34]. Because of some of these methods are possessed unfavourable effects such as having long times and harsh condition of reaction, and also low yields, modifying and improving of them have been endlessly sought. Therefore, following to our interest in highly efficient catalytic synthesis of a broad class of heterocycles and organic compounds via multicomponent and one pot reactions [35-38], in this work, an efficient, green adapted and new route to the synthesis of 1,8-dioxoöctahydroxanthenes (4) was reported via condensation reaction between 1,3-cyclohexanediones (1) with arylaldehydes (2) by employing $\text{ICl}_3/\text{SiO}_2$ (iodine trichloride supported on silicagel) and $\text{In}(\text{CF}_3\text{SO}_3)_3$ as powerful, cheap and recyclable catalysts (**Scheme 1**).



Scheme 1: Synthesis of xanthene derivatives catalyzed by $\text{ICl}_3/\text{SiO}_2$ or $\text{In}(\text{CF}_3\text{SO}_3)_3$.

MATERIALS AND METHODS

Experimental

Materials and methods

An electothermal KSB1N apparatus was applied to determine melting points (m.p.). JASCO FT-IR-680 plus spectrometer along with KBr as matrix was used to deduce IR spectra. FT-NMR Bruker Avance Ultra Shield Spectrometer at 400.13 and 100.62 MHz in CDCl_3 as solvent was used to determine ^1H NMR and ^{13}C NMR spectra respectively. A Heraeus Rapid analyzer was got for the measurement of elemental analyses (C, H, N, S) and the results were in good agreement with the calculated values ($\pm 0.3\%$). TLC-Grade silica gel-G/UV 254 nm plates (eluent: *n*-hexane, and ethyl acetate 2:1) was applied to control of reaction progress. All chemicals were also purchased from Merck and Sigma-Aldrich chemical companies.

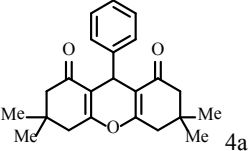
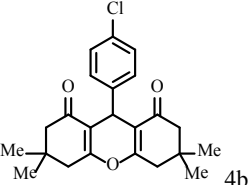
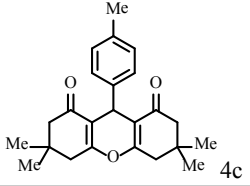
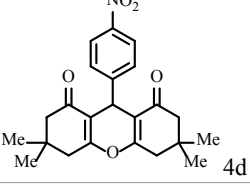
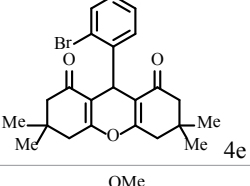
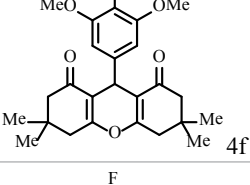
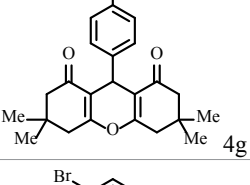
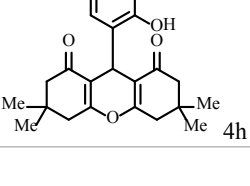
Preparation of $\text{ICl}_3/\text{SiO}_2$

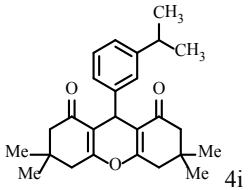
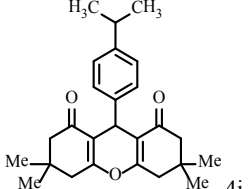
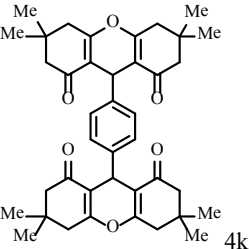
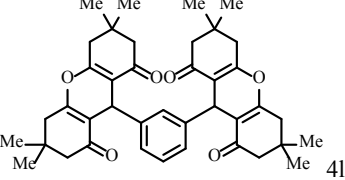
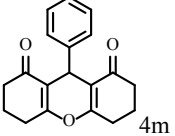
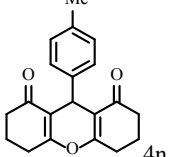
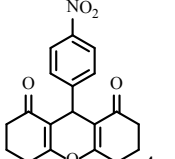
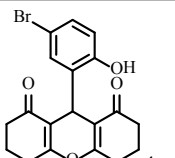
Firstly, the 5 g of silica gel [60 Å, 35-75 μm particle size] for 4 h was heated in oven at 140°C. Then dried silica gel (1 g) was stirred with iodine trichloride (0.117 g, 0.5 mmol) in chloroform (10 mL), and then was heated under reflux conditions for appropriate time (4 h). In continuous, the mixture was filtered, washed thoroughly with chloroform (3 \times 10 ml), and the obtained catalyst was dried at 70°C for 2 h.

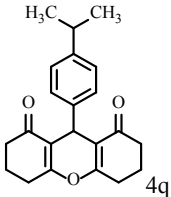
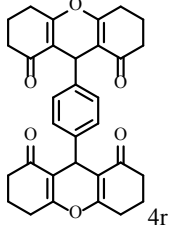
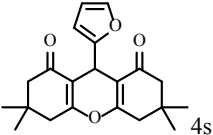
General Procedure for the Synthesis of 9-Aryl-Substituted 1,8-Dioxoöctahydro-xanthenes

Cyclic 1,3-diketone (2 mmol), was added to the mixture of arylaldehyde (1 mmol) and $\text{ICl}_3/\text{SiO}_2$ (0.117 g, 0.05 mmol) or $\text{In}(\text{CF}_3\text{SO}_3)_3$ (0.011 g, 0.02 mmol), and then the mixture was heated at 70°C for the time demonstrated in **Table 1**.

Table 1: Catalytic synthesis of 9-aryl-substituted-1,8-dioxooctahydroxanthenes by the use of $\text{ICl}_3/\text{SiO}_2$ and $\text{In}(\text{CF}_3\text{SO}_3)_3$ under solvent-free conditions.

Compound 4	$\text{ICl}_3/\text{SiO}_2$	$\text{In}(\text{CF}_3\text{SO}_3)_3$	M.P. (°C)/[lit.]
	Time (min)/Yield (%) ^a	Time (min)/Yield (%) ^a	
 4a	60/90	60/95	202-204 (201-202) [45]
 4b	70/90	70/92	230-232 (230-232) [45]
 4c	70/87	70/90	215-217 (216-217) [46]
 4d	40/88	40/90	219-221 (221-223) [46]
 4e	80/89	70/88	226-227 (226-228) [47]
 4f	60/88	60/92	209-211 (210-212) [48]
 4g	60/90	65/92	223-225 (224-226) [47]
 4h	60/84	70/89	250-252 (249-252) [49]

 <p>4i</p>	60/82	70/85	189-191 (190-191) [50]
 <p>4j</p>	70/88	70/90	238-239 (236-239) [30]
 <p>4k</p>	60/86	60/89	245-247 (>300) [51]
 <p>4l</p>	75/85	75/88	238-240 (236-238) [52]
 <p>4m</p>	60/92	70/95	271-273 (272-273) [53]
 <p>4n</p>	65/88	65/90	260-262 (262-263) [45]
 <p>4o</p>	60/91	55/95	224-227 (224-226) [54]
 <p>4p</p>	70/88	70/89	250-252 (249-252) [29]

 4q	80/84	60/88	170-172 (169-171) [55]
 4r	60/87	60/90	282-285 (280-282) [56]
 4s	90/81	80/85	141-143 (139-141) [13]

^a Refers to isolated yield

The progress of the reaction was controlled by TLC (eluent: *n*-hexane, and ethyl acetate 2:1). After confirming of reaction completion, CHCl₃ (10 mL) was poured to the reaction mixture, Afterwards, to separate catalyst, the mixture was filtered. In continuous, solvent was evaporated from the filtrate in vacuum to remain the crude product. Crude product was recrystallized by boiling EtOH to obtain the crystalline pure product. At the end, the separated catalyst from reaction mixture was washed with boiling ethanol, then dried at 120°C for 1 h (ICl₃/SiO₂; dried at 70°C for 8 h), and reused four more times in other reactions.

Typical procedure to the synthesis of product 4a

Compound 4a was synthesized based on the general procedure, by employing dimedone 1 (R₁, R₂=CH₃) (0.280 g, 2 mmol), benzaldehyde 2a (0.106 g, 1 mmol) and ICl₃/SiO₂ (0.117 g, 0.05 mmol) or In(CF₃SO₃)₃ (0.011 g, 0.02 mmol). The progress of the reaction was controlled by TLC. When the reaction progress was completed, CHCl₃ (10 ml) was poured to the mixture, and then the mixture was filtered to separate the catalyst. Removing solvent from filtrate by vacuum, lead to obtain crude product which was recrystallized by boiling EtOH to afford white crystals as pure product.

Representative spectral data

Compound 4a: mp 202-204°C; IR (KBr) ν_{\max} : 699, 742, 1200, 1468, 1624, 1662, 2958, 3059 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ (*J*, Hz): 0.79 (s, 6H, 2CH₃), 0.90 (s, 6H, 2CH₃), 2.00 (dd, ¹*J*=16.4, ⁴*J*=28.8, 4H, 2CH₂), 2.27 (s, 4H, 2CH₂), 4.55 (s, 1H, CH), 6.90-7.10 (m, 5H, CH_{Ar}) ppm; ¹³C NMR (100 MHz, CDCl₃) δ : 28.5, 30.4, 33.0, 33.4, 42.0, 51.9, 116.8, 127.5, 129.2, 129.5, 145.2, 163.4, 196.7 ppm; Anal. Calcd.: C, 78.83; H, 7.48, (C₂₃H₂₆O₃); Found: C, 78.79; H, 7.51.

Compound 4c: mp 260-262°C; IR (KBr) ν_{\max} : 827, 1125, 1175, 1466, 1615, 1658, 2955, 3049 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ (*J*, Hz): 2.01 (m, 4H, 2CH₂), 2.26 (s, 3H, CH₃), 2.35 (m, 4H, 2CH₂), 2.59 (m, 4H, 2CH₂), 4.78 (s, 1H, CH), 7.03 (d, *J*=7.2, 2H, Ar-H), 7.19 (2H, d, *J*=7.2, CH_{Ar}); ¹³C NMR (100 MHz, CDCl₃) δ : 20.3, 21.1, 27.1, 31.2, 37.0, 117.0, 128.2, 128.8, 135.8, 141.6, 163.8, 196.6 ppm; Anal. Calcd.: C, 79.09; H, 7.74, (C₂₄H₂₈O₃); Found: C, 79.12; H, 7.69.

Compound 4f: mp 209-211°C; IR (KBr) ν_{\max} : 844, 1089, 1189, 1375, 1479, 1620, 1659, 2995, 3049 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ (*J*, Hz): 1.04 (s, 6H, 2CH₃), 1.12 (s, 6H, 2CH₃), 2.24 (s, 4H, 2CH₂), 2.47 (s, 4H, 2CH₂), 3.78 (s, 3H, OCH₃), 3.81 (s, 6H, 2OCH₃), 4.72 (s, 1H, CH), 6.52 (s, 2H, CH_{Ar}); ¹³C NMR (100 MHz, CDCl₃) δ : 27.2, 29.4, 31.8, 32.2, 40.9, 50.7, 56.1, 60.7, 105.7, 115.6, 136.6, 139.7, 152.8, 162.3, 196.4; Anal. Calcd.: C, 70.89; H, 7.32, (C₂₆H₃₂O₆); Found: C, 70.91; H, 7.28.

Compound 4g: mp 223-225°C; IR (KBr) ν_{\max} : 1179, 1160, 1199, 1359, 1500, 1619, 1659, 2970, 2989, 3039 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ (*J*, Hz): 1.00 (s, 6H, 2CH₃), 1.11 (s, 6H, 2CH₃), 2.21 (q, *J*=16.4, 4H, 2CH₂), 2.47 (s,

4H, 2CH₂), 4.73 (s, 1H, CH), 6.91 (m, 2H, CH_{Ar}), 7.27 (m, 2H, CH_{Ar}); ¹³C NMR (100 MHz, CDCl₃) δ 27.3, 29.3, 32.2, 40.8, 50.7, 114.7, 114.9, 115.5, 129.9, 140.0, 160.1, 162.6, 196.3; Anal. Calcd.: C, 74.98; H, 6.84, (C₂₃H₂₅FO₃); Found: C, 74.91; H, 6.79.

Compound 4i: mp 189-191°C; IR (KBr) ν_{\max} : 1139, 1159, 1199, 1375, 1449, 1615, 1659, 2879, 2959, 3065 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ (J, Hz): 1.01 (s, 6H, 2CH₃), 1.10 (s, 6H, 2CH₃), 1.18 (d, *J*=5.2, 6H, 2CH₃), 2.21 (m, 4H, 2CH₂), 2.46 (s, 4H, 2CH₂), 2.79 (bb, 1H, CH), 4.73 (s, 1H, CH), 7.05 (d, *J*=6.8, 2H, CH_{Ar}), 7.19 (m, 2H, CH_{Ar}); ¹³C NMR (100 MHz, CDCl₃) δ: 23.9, 27.5, 29.2, 31.3, 32.2, 33.6, 40.9, 50.8, 126.1, 128.1, 141.4, 146.5, 162.1, 196.5; Anal. Calcd.: C, 79.56; H, 8.22, (C₂₆H₃₂O₃); Found: C, 79.61; H, 8.25.

Compound 4k: mp 245-247°C; IR (KBr) ν_{\max} : 809, 1004, 1161, 1199, 1364, 1424, 1461, 1619, 1665, 2956, 3039 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ (J, Hz): 0.97 (s, 12H, 4CH₃), 1.07 (s, 12H, 4CH₃), 2.18 (s, 8H, 4CH₂), 2.44 (dd, ¹*J*=36.4, ⁴*J*=17.6, 8H, 4CH₂), 4.71 (s, 2H, 2CH), 7.08 (s, 2H, CH_{Ar}), 7.27 (s, 2H, CH_{Ar}); ¹³C NMR (100 MHz, CDCl₃) δ: 25.0, 27.7, 29.0, 30.7, 32.2, 40.8, 50.6, 115.7, 127.9, 141.7, 162.4, 196.4; Anal. Calcd.: C, 77.14; H, 7.45, (C₄₀H₄₆O₆); Found: C, 77.09; H, 7.48.

Compound 4l: mp 238-240°C; IR (KBr) ν_{\max} : 769, 1158, 1203, 1462, 1629, 1660, 2958, 3094 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ (J, Hz): 1.03 (s, 12H, 4CH₃), 1.08 (s, 12H, 4CH₃), 2.15 (dd, ²*J*=24, ⁴*J*=16, 8H, 4CH₂), 2.48 (dd, ²*J*=45.2, ⁴*J*=17.6, 8H, 4CH₂), 4.72 (s, 2H, 2CH), 7.07-7.09 (m, 3H, CH_{Ar}), 7.15 (s, 1H, CH_{Ar}); ¹³C NMR (100 MHz, CDCl₃) δ 28.0, 29.6, 31.8, 32.6, 41.3, 51.3, 116.0, 126.8, 128.2, 144.0, 162.7, 196.7; Anal. Calcd.: C, 77.14; H, 7.45, (C₄₀H₄₆O₆); Found: C, 77.21; H, 7.39.

Compound 4n: mp 260-262°C; IR (KBr) ν_{\max} : 827, 1125, 1176, 1468, 1617, 1657, 2956, 3052 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ (J, Hz): 2.01 (m, 4H, 2CH₂), 2.26 (s, 3H, CH₃), 2.35 (m, 4H, 2CH₂), 2.59 (m, 4H, 2CH₂), 4.78 (s, 1H, CH), 7.03 (d, *J*=7.2, 2H, CH_{Ar}), 7.19 (d, *J*=7.2, 2H, CH_{Ar}); ¹³C NMR (100 MHz, CDCl₃) δ: 20.3, 21.1, 27.1, 31.2, 37.0, 117.0, 128.2, 128.8, 135.8, 141.6, 163.8, 196.6; Anal. Calcd.: C, 77.90; H, 6.54, (C₂₀H₂₀O₃); Found: C, 77.88; H, 6.59.

Compound 4o: mp 224-227°C; IR (KBr) ν_{\max} : 831, 1170, 1465, 1665, 2952, 3071 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ (J, Hz): 2.07 (m, 4H, 2CH₂), 2.35 (m, 4H, 2CH₂), 2.61 (m, 4H, 2CH₂), 4.88 (s, 1H, CH), 7.48 (d, *J*=8.8, 2H, CH_{Ar}), 8.10 (d, *J*=8.8, 2H, CH_{Ar}); ¹³C NMR (100 MHz, CDCl₃) δ: 20.2, 27.1, 32.2, 36.8, 115.7, 123.4, 129.4, 145.5, 151.7, 164.6, 196.4; Anal. Calcd.: C, 67.25; H, 5.05; N, 4.13, (C₁₉H₁₇NO₃); Found: C, 67.21; H, 5.11; N, 4.09.

Compound 4p: mp 250-252°C; IR (KBr) ν_{\max} : 649, 813, 1004, 1034, 1085, 1179, 1214, 1288, 1368, 1462, 1564, 1620, 2959, 3096 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ (J, Hz): 1.86 (s, 2H, CH₂), 2.05 (t, *J*=12.4, 2H, CH₂), 2.15 (d, *J*=8.4, 1H, CH), 2.43 (m, 2H, CH₂), 2.57 (t, *J*=9.2, 2H, CH₂), 2.75 (d, *J*=8.8, 1H, CH), 4.58 (s, 1H, CH), 6.91 (d, *J*=4.4, 1H, CH_{Ar}), 7.13 (s, 1H, CH_{Ar}), 7.26 (d, *J*=4.4, 1H, CH_{Ar}), 10.77 (s, 1H, OH); ¹³C NMR (100 MHz, CDCl₃) δ: 19.5, 19.9, 27.9, 28.0, 29.7, 35.9, 36.9, 112.0, 117.0, 117.3, 119.4, 126.9, 130.5, 130.7, 150.0, 170.7, 173.4, 197.1, 201.3; Anal. Calcd.: C, 58.63; H, 4.40, (C₁₉H₁₇BrO₄); Found: C, 58.59; H, 4.36.

Compound 4q: mp 170-172°C; IR (KBr) ν_{\max} : 827, 1129, 1199, 1449, 1619, 1659, 3049 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ (J, Hz): 1.19 (d, *J*=6.8, 6H, 2CH₃), 2.01 (m, 4H, 2CH₂), 2.34 (m, 4H, 2CH₂), 2.61 (m, 4H, 2CH₂), 2.81 (t, *J*=7.2, 1H, CH), 4.80 (s, 1H, CH), 7.06 (d, *J*=8, 2H, CH_{Ar}), 7.19 (2H, d, *J*=8, H Ar); ¹³C NMR (100 MHz, CDCl₃) δ 20.3, 23.9, 27.1, 31.0, 33.6, 37.0, 117.0, 126.2, 146.5, 163.9, 196.6; Anal. Calcd.: C, 78.54; H, 7.19, (C₂₂H₂₄O₃); Found: C, 78.55; H, 7.22.

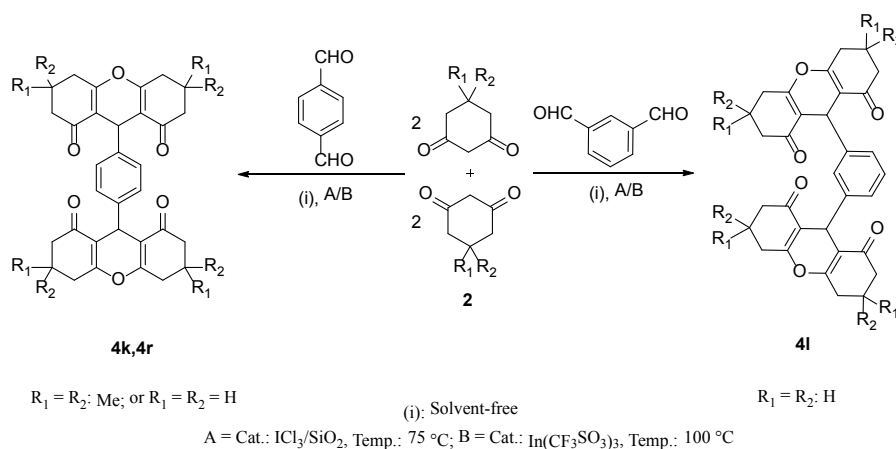
Compound 4r: 252-255°C; IR (KBr) ν_{\max} : 802, 1001, 1165, 1210, 1425, 1460, 1623, 1665, 2950, 3038 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ (J, Hz): 2.29 (m, 8H, 4CH₂), 2.39 (m, 8H, 4CH₂), 2.57 (m, 4H, 2CH₂), 2.67 (m, 4H, 2CH₂), 4.74 (s, 2H, 2CH), 7.18 (d, 4H, *J*=7.6, CH_{Ar}) ppm; ¹³C NMR (100 MHz, CDCl₃) δ: 20.1, 27.1, 30.8, 36.9, 116.9, 128.0, 141.9, 164.0, 196.7 ppm; Anal. Calcd.: C, 75.28; H, 5.92, (C₃₂H₃₀O₆); Found: C, 75.31; H, 5.89.

RESULTS AND DISCUSSION

In the first view, however, there are some reports from condensation reaction between cyclic 1,3-diketones 1 and arylaldehydes 2, that lead to synthesize 2,2'-(arylmethylene)bis(3-hydroxycyclohex-2-enone) (3) [26,39-41], but under given conditions, 2,2'-(arylmethylene)bis(3-hydroxycyclohex-2-enone) 3 wasn't obtained and reaction of cyclic 1,3-diketones 1 with arylaldehydes 2 leads to efficient synthesize of 9-aryl-substituted 1,8-dioxooctahydroxanthenes 4.

In the other investigation, using aryl-dialdehyde substrates, instead of monoaldehydes lead to condensation reaction with 1,3-cyclic diketones with 1:4 ratios respectively to afford bisxanthenes as target products. In this five component

reaction, 1,3-diketones (4 mmol) were reacted with dialdehyde (1 mmol) to afford bis(9-aryl-substituted-1,8-dioxoöctahydroxanthenes) (**Scheme 2**).



Scheme 2: Synthesis of bis(9-aryl-substituted-1,8-dioxoöctahydroxanthenes) by the use of catalytic amounts of $\text{ICl}_3/\text{SiO}_2$ and $\text{In}(\text{CF}_3\text{SO}_3)_3$.

The chemical structure of the product **4** was characterized from their IR, ^1H , and ^{13}C NMR spectroscopic data. Also the melting points of products were compared and confirmed with reported ones in the literatures.

We are directed to immobilize iodine trichloride onto the common solid support in order to combine the properties such as catalyst selectivity, high activity with the ease of separation and catalyst reuse. It may be considered notable that the support materials play a significant role on catalyst activity when they are supported catalysts on their surface. For instance, silica gel was chosen as solid support due to its high surface area, excellent stability (chemical and thermal), good accessibility, recyclability, and ease of functionalization of the surface groups [42,43]. Iodine trichloride supported on silica gel ($\text{ICl}_3/\text{SiO}_2$) does not need activation and is recycled many times under the same conditions with fresh reactants to yield similar results without significant loss of activity [44]. In following of our study, $\text{In}(\text{CF}_3\text{SO}_3)_3$ is handled as another effective and recoverable catalyst and is compared with $\text{ICl}_3/\text{SiO}_2$ in xanthene derivatives synthesis. However, a small part of this study, as an incomplete and partial results have been previously reported in a symposium [45], herein we wish to report developed and completed 1,8-dioxoöctahydroxanthenes synthesis protocol with highest yields in short reaction times under obtained best conditions.

To find the best conditions for catalytic ($\text{ICl}_3/\text{SiO}_2$ or $\text{In}(\text{CF}_3\text{SO}_3)_3$) synthesis of xanthene derivatives, at first, synthesis of compound **4a** was opted as a model.

By investigations on model reaction, the reaction carried out using $\text{ICl}_3/\text{SiO}_2$ or $\text{In}(\text{CF}_3\text{SO}_3)_3$ as catalyst in different solvents including H_2O , EtOH, CH_3OH , CH_3Cl , CH_3CN , and solvent-free conditions. These experiments showed that the reaction is performed with shortest time and highest yield under solvent-free conditions (**Table 2**). Therefore, the reaction carries out under solvent-free conditions. On the other hand, to the best of our knowledge solvent-free condition has some advantage for chemical reactions such as reduce pollution, avoiding the use of harmful and toxic solvents, decreasing costs of solvent handling, easy and facile work up technique, and leading to save in labour [46].

The affords to evaluation of required catalysts in the synthesis 1,8-dioxoöctahydroxanthene derivatives for the model reaction, was revealed that when the reaction was loaded with 5 mol% of $\text{ICl}_3/\text{SiO}_2$ and 2 mol% of $\text{In}(\text{CF}_3\text{SO}_3)_3$, the maximum yield of product is obtained (**Table 3**).

As the data of **Table 3** are shown, the best quantities of required catalysts for this reaction were found to be 5 mol% for $\text{ICl}_3/\text{SiO}_2$ and 2 mol% for $\text{In}(\text{CF}_3\text{SO}_3)_3$, whereas the use of larger amounts of the catalysts do not improve the yield.

In addition, the effect of temperature on reaction was studied. Examining of reactions progress at various temperatures in the presence of optimized amount of catalysts for model reaction, revealed that the maximum rate of reaction is achieved at 75°C when $\text{ICl}_3/\text{SiO}_2$ is used as catalyst, and at 100°C when $\text{In}(\text{CF}_3\text{SO}_3)_3$ is used as catalyst (**Table 4**).

By a looking at **Table 4**, it is found that the reaction is completed slowly at room temperature. When $\text{ICl}_3/\text{SiO}_2$ is used as catalyst, by increasing temperature to 75°C [when $\text{In}(\text{CF}_3\text{SO}_3)_3$ is used, it is 100°C], the yield of reaction is increased along with decreasing of the time of reaction. When, the reaction is heated above 75°C [above 100°C in the

Table 2: Evaluation of solvent effect for model reaction.

Entry	Solvent	A	B
		Time (min)/Yield (%)	Time (min)/Yield (%)
1	H ₂ O	130/trace	180/46
2	EtOH	130/60	130/50
3	MeOH	190/52	190/56
4	CHCl ₃	190/46	190/41
5	CH ₃ CN	190/33	190/27
6	DMF	190/35	190/30
7	Dioxane	65/76	65/81
8	Solvent-less	60/90	60/95

A) Reaction catalyzed by ICl₃/SiO₂
 B) Reaction catalyzed by In(CF₃SO₃)₃

Table 3: Optimization of required catalysts for model reaction.

ICl ₃ /SiO ₂ (mol%)	Time (min)	Yield ^a (%)	In(CF ₃ SO ₃) ₃ (mol%)	Time (min)	Yield ^a (%)
1	130	36	1	130	62
2	130	57	2	60	95
5	60	90	3	60	90
8	60	87	5	60	80
10	70	81	8	60	75

^aIsolated yield

Table 4: Evaluation of temperature effects on model reaction.

Temp. (°C) ^a	Time (min) ^a	Yield (%) ^a	Temp. (°C) ^b	Time (min) ^b	Yield (%) ^b
r.t.	120	25	r.t.	300	30
40	120	50	40	120	45
50	90	62	50	100	50
60	70	68	60	90	70
70	60	79	70	80	77
75	60	90	75	60	80
80	60	88	80	60	84
90	60	84	90	60	91
100	60	80	100	60	95
110	60	80	110	60	89

^aICl₃/SiO₂ as catalyst
^bIn(CF₃SO₃)₃ as catalyst

presence of In(CF₃SO₃)₃, so more high temperatures do not further improve the yield and the time of reaction. Based on obtained optimal conditions, we run the xanthenes derivatives synthesis in the presence of ICl₃/SiO₂ (5 mol%, at 75°C) or In(CF₃SO₃)₃ (2 mol%, at 100°C) in solvent-free conditions.

Considering optimal conditions, numerous arylaldehydes 2 bearing both electron-donating and electron-withdrawing groups were effectively condensed to give 9-aryl substituted 1,8-dioxooctahydroxanthene derivatives 4. In all cases, corresponding xanthenes were isolated with good to excellent yields (**Table 1**) [13,29,30,47-58].

At the end of each run, the separated catalysts by filtration, washed with diethyl ether, In(CF₃SO₃)₃ dried at 120°C for 1 h; and ICl₃/SiO₂ dried at 70°C for 8 h. The catalysts after drying reused in another reaction. It was found that both ICl₃/SiO₂ and In(CF₃SO₃)₃ represent high catalytic activity which lead to obtain products with good to excellent yields in short reaction times. Furthermore, the catalysts, can be recycled and reused four more times without considerable loss of their activity (**Figure 1**). All results of this evaluation for model reaction, are summarized in **Table 5**.

Results comparison for the synthesis of 4a (model reaction) between current protocol and others previously reported, could be found in **Table 6** [12-18,47,50,52,59-62]. As can be seen from **Table 6**, it was understood that, above used

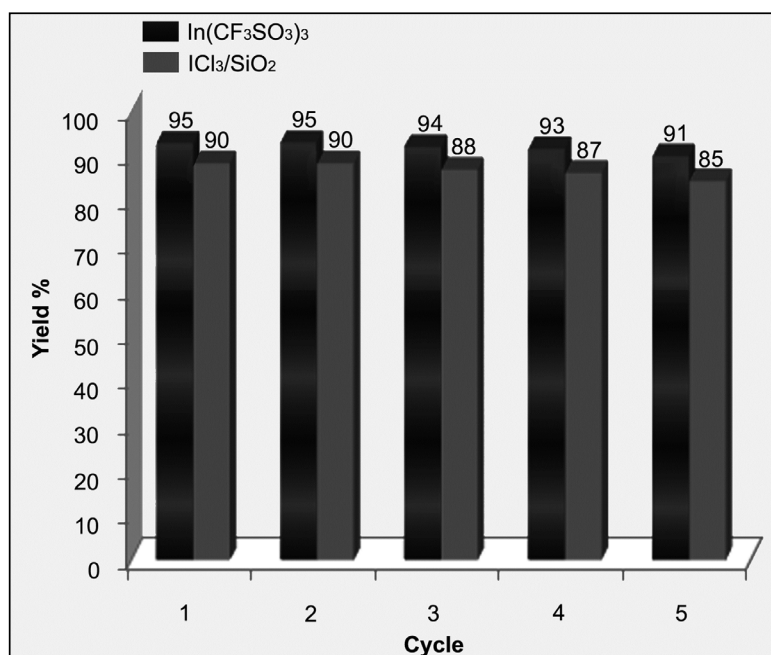
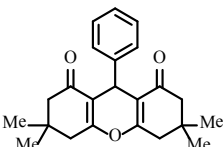


Figure 1: Recyclability results of ICl₃/SiO₂ and In(CF₃SO₃)₃ as catalysts in the synthetic procedure for model reaction.

Table 5: Evaluation of catalysts recyclability to the synthesis of 4a.

Product	Total reusability	ICl ₃ /SiO ₂	In(CF ₃ SO ₃) ₃
		Yield (%) ^a /Time (min)	Yield (%) ^a /Time (min)
	1	90/60	95/60
	2	90/60	95/60
	3	88/60	94/60
	4	87/60	93/60
	5	85/65	91/65
^a Isolated yield			

catalysts provided an excellent conditions to xanthenes synthesis than other that have been reported before. This protocol not only leads to obtain the xanthenes with high yields but also eludes the issues dependent with environmental pollution, catalysts prices, and handling. Considering **Table 6**, in the most cases, the yield of obtained product in our work is higher than others. However, in certain instances, it can be seen that the reported yields are higher than our procedure, but those tolerate some disadvantages than our procedure such as longer reaction times [13,47-49], need to higher temperature [13,47,50,62], necessity of organic solvent [14,16,60], high-cost of catalyst or high amount of required catalyst [13,15,16,18,47,50,60-62], and less or non-reusability of catalyst [14-16].

Table 6: Comparison of results obtained with $\text{In}(\text{CF}_3\text{SO}_3)_3$, and $\text{ICl}_3/\text{SiO}_2$ with other catalysts in xanthene synthesis (4a).

Entry	Catalyst	Catal. (mol %)	Solvent/Temp.(°C)	Time (min)/Yield%	[Ref.]
1	$\text{In}(\text{CF}_3\text{SO}_3)_3$	2	Solvent free/100	60/95	This work
2	$\text{ICl}_3/\text{SiO}_2$	5	Solvent free/75	60/90	This work
3	DBSA ^a	10	H_2O -Ultrasonic /30	60/89	[57]
4	TMSCl ^b	100	CH_3CN /Reflux	420/95	[58]
5	TBAHS ^c	10	Dioxane, H_2O /Reflux	210/88	[52]
6	DBSA ^a	20	H_2O /Reflux	180/91	[59]
7	Selectfluor ^{TM d}	10	Solvent free/120	60/95	[60]
8	PPA- SiO_2 ^e	10	Solvent free/140	30/93	[45]
9	HClO_4 - SiO_2	10	Solvent free/140	180/32	[45]
10	SbCl_5 - SiO_2	10	Solvent free/120	50/93	[48]
11	LUS-Pr- SO_3Hf	0.02 g	Solvent free/140	15/90	[12]
12	SmCl_3	20	Solvent free/120	540/98	[13]
13	CANg / ultrasound irradiation (40 kHz)	5	2-propanol/50	35/98	[14]
14	[Bmim]ClO ₄ ^h	200	Solvent free/100	40/92	[15]
15	I2	20	2-propanol/70-80	18/90	[16]
16	[cmim][BF ₄] ⁱ MW ^j	0.2 g	Solvent free/80	150/87	[17]
17	p-Toluene sulfonic acid	30	Solvent free/80	30/99	[18]

^ap-dodecylbenzenesulfonic acid; ^bTrimethylsilyl chloride; ^cTetrabutylammonium hydrogen sulfate; ^d1 (chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2,2,2]octane bis(tetrafluoroborate); ^epolyphosphoric acid supported on silica; ^fPropylsulfonic acid functionalized mesoporous Laval University silica; ^gceric ammonium nitrate; ^hIonic liquid 1-butyl, 3-methylimidazolium perchlorate; ⁱ1-carboxymethyl-3 methylimidazolium tetrafluoroborate; ^jMicrowave irradiation at 40% power level (280 W)

CONCLUSION

To conclude, a new protocol, green, and highly efficient method using ICl_3 supported on silica and $\text{In}(\text{III})$ triflate as highly efficient and recyclable catalysts to 9-arylsubstituted-1,8-dioxooctahydroxanthene synthesis was introduced. It is notable that, all obtained products by the use of catalytic amount of $\text{ICl}_3/\text{SiO}_2$ or $\text{In}(\text{CF}_3\text{SO}_3)_3$ were achieved in excellent yields. The progress of reaction is strongly dependent in Lewis acidic virtues of $\text{ICl}_3/\text{SiO}_2$ and $\text{In}(\text{CF}_3\text{SO}_3)_3$ as a key factor which efficiently catalysed reaction between cyclic 1,3-diketones and arylaldehydes. Using this highly efficient route without using any solvent not only provide an inexpensive and simple method but also lead to expanding the green chemistry aspects. The facile experimental procedure, short span of reaction times, use of neat procedure, recyclable catalysts, and readily available substrate are other advantages of this protocol.

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