

SelectfluorTM Promoted Synthesis of 9-Aryl-1,8-dioxooctahydroxanthene Derivatives under Solvent-Free Conditions

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(Received 6 April 2008, Accepted 5 July 2008)

A novel and efficient procedure for the synthesis of 1,8-dioxo-octahydro-xanthenes through one-pot condensation of 5,5-dimethyl-1,3-cyclohexadione with aryl aldehydes in the presence of selectfluorTM [1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2,2,2]octane bis(tetrafluoroborate) as catalyst under solvent free conditions was applied. It demonstrated several advantages such as good yields of products, simple operation, convenient separation, and inexpensive catalyst.

Keywords: Dioxooctahydroxanthene, Xanthenes, Solvent-free, Condensation, SelectfluorTM

INTRODUCTION

Research on xanthenes, especially benzoxanthenes, has attracted attention in organic synthesis due to their wide range of biological and therapeutic properties like antiviral [1], antibacterial [2] and anti-inflammatory activities [3]. They have been used as sensitizers in photodynamic therapy [4], as antagonists of the paralyzing action of zoxazolamine [5] as leuco-dyes [6], and in laser technology [7].

Many procedures have been adopted to synthesize xanthenes and benzoxanthenes, including cyclodehydration [8], trapping of benzynes by phenol [9], as well as the cyclocondensation of 2-hydroxy aromatic aldehydes and 2-tetralone [10].

To develop an alternate procedure for the synthesis of octahydro-xanthenes derivatives, we used SelectfluorTM [1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)] as catalyst. Recently, SelectfluorTM has been introduced commercially as an electrophilic fluorinating reagent. SelectfluorTM is a low-cost readily available acidic

material. Recently it has been employed as an efficient Lewis acid catalyst for the one pot allylation of imines, hydrolysis of acetals, dithio acetals, as well as tetrahydropyranyl ethers, and for the synthesis of β -hydroxy thiocyanates [11].

EXPERIMENTAL

Reagents and Apparatus

The chemicals used in this experiment were purchased from Merck (Germany). Melting points were measured by an Electro thermal 9100 apparatus and were uncorrected. Mass spectra were recorded on a Finnigan-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. ¹H and ¹³C NMR spectra were recorded on a Bruker DRX-400. IR spectra were recorded on a Bomem MB-Series FT-IR spectrophotometer.

General Procedure for the Preparation of 9-Aryl-1,8-dioxooctahydroxanthene Derivatives (3)

A mixture of arylaldehyde (1 mmol), dimedone (2 mmol) and SelectfluorTM (0.1 mmol) was stirred at 120 °C for the appropriate time (Table 1). Completion of the reaction was

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Table 1. Effect of Temperature on the Synthesis of **3I**^a

Temperature (°C)	Yield (%)
50	65
80	78
100	89
120	91

^a4-Bromo-benzaldehyde (1 mmol), dimedone (2 mmol), catalyst (0.1 mmol), 2 h.

monitored by TLC (thin layer chromatography). The material was cooled to 25 °C, and after addition of water the mixture was stirred for 5 min. The solid so obtained was filtered off and recrystallized from ethanol. All the products obtained were fully characterized by spectroscopic methods such as IR, ¹H NMR, ¹³C NMR and mass spectroscopy, and also by comparison of their spectra data with those reported.

RESULTS AND DISCUSSION

Herein, a simple, efficient and high-yielding method for the synthesis of 9-aryl-1,8-dioxooctahydroxanthane derivatives under solvent-free conditions is described (Scheme 1).

The optimum temperature was examined using the reaction of 4-bromo-benzaldehyde **2I** and dimedone **1** in the presence of the optimum quantity of SelectfluorTM under solvent free conditions. As can be seen from Table 1, it was possible to carry out the reaction at much lower temperature, 120 °C, in similar yield.

In terms of the amount of catalyst required for the reaction of 4-bromo-benzaldehyde **2I** and dimedone **1** to afford **3I** under solvent-free conditions, at 120 °C, the best results were obtained using 0.035 g of catalyst (see Fig. 1).

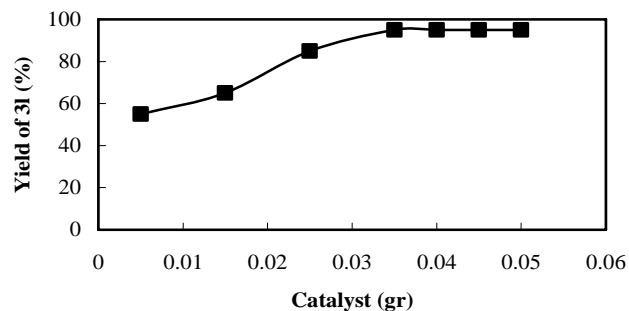


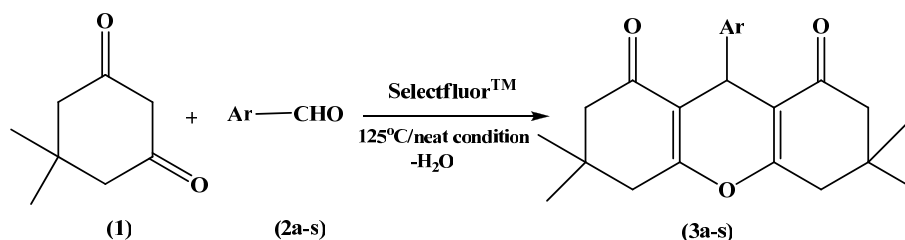
Fig. 1. Effect of catalyst on the synthesis of **3I** (reaction conditions: 4-bromo-benzaldehyde (1 mmol), dimedone (2 mmol), catalyst (0.1 mmol), and 2 h.

The condensation of dimedone **1** and aromatic aldehydes **2** gave only 9-aryl-1,8-dioxooctahydroxanthane derivatives (**3a-s**). Several functionalities present in the aryl aldehydes such as halogen, methoxy and nitro group tolerated the reaction conditions. In all of the cases, the corresponding 9-aryl-1,8-dioxooctahydroxanthane derivatives (**3a-s**) were obtained in good/excellent yields after 1-3.5 h (Table 2).

The analytical data for selected compounds (**3a-s**) are given below:

3,3,6,6-Tetramethyl-9-phenyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (3a). (White solid), m.p.: 205 °C; IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 3033, 1618, 1580; ¹H NMR (CDCl₃): δ_{H} 1.03 (6H, s, 2 × CH₃); 1.14 (6H, s, 2 × CH₃); 2.24 (4H, s); 2.50 (4H, s); 4.79 (1H, s); 7.13-7.35 (5H, m, ArH.); LC-MS: 373 [M+23]; Elemental analysis: Found (%): C, 78.63; H, 7.32; Calcd. for C₂₃H₂₆O₃ (350.54): C, 78.83, H, 7.48.

9-(2-Chlorophenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (3c). (White solid), m.p.: 228-230 °C; IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 3392, 3064, 2960, 2929, 1719, 1664, 1595, 1380, 1166; ¹H NMR (CDCl₃): δ_{H}



Scheme 1

SelectfluorTM Promoted Synthesis of 9-Aryl-1,8-dioxooctahydroxanthanes

Table 2. Synthesis of Various 9-Aryl-1,8-dioxooctahydroxanthane Derivatives **3** Catalysed by SelectfluorTM

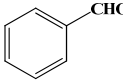
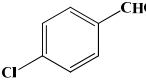
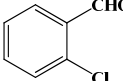
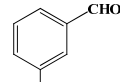
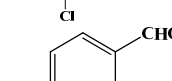
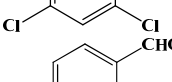
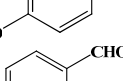
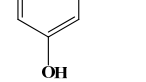
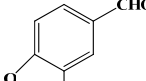
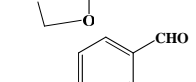
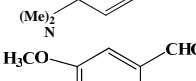
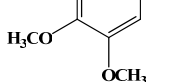
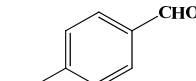
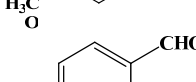
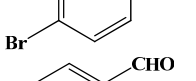
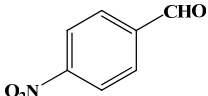
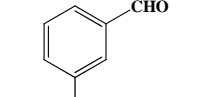
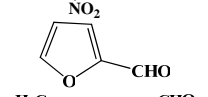
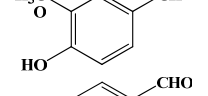
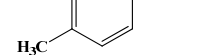
Entry	Aldehyde (2)	Time (h)	Yield (%) ^a	Mp (°C)	
				Obtained	Reported
3a		1	95	201-202	205 [12]
3b		1.5	93	230-232	228-230 [13]
3c		2	93	229-230	228-230 [13]
3d		1.5	93	190-192	193 [13]
3e		3	91	247-249	248-250 [13]
3f		2.5	90	250-251	246 [14]
3g		3	91	225-227	226 [13]
3h		2.5	88	221-222	224-226 [12]
3i		3	89	222-225	224-226 [12]
3j		3	90	186-188	187-189 [13]
3k		3	89	242-244	241-243 [13]
3l		3	89	242-244	241-243 [13]
3m		2	91	240-242	245-250 [13]
3n		3	95	162-164	164-165 [13]
3n		3	98	259-261	258-262 [13]

Table 2. Continued

3o		2.5	96	225-226	221-223 [13]
3p		3	92	170-171	168-170 [13]
3q		2	90	62-63	62-64 [13]
3r		2	91	227-230	226-228 [13]
3s		1.5	89	216-217	217-218 [13]

^aIsolated yields.

1.02-1.19 (12H, s, br, 4 × CH₃); 2.25-2.44 (8H, m); 5.62 (1H, s); 7.09-7.44 (4H, m, ArH.); LC-MS: 406 [M+23]; Elemental analysis: Found (%): C, 71.66; H, 6.41; Calcd. for C₂₃H₂₅ClO₃ (384.15): C, 71.77; H, 6.55.

9-(2,4-Dichlorophenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (3e). (White solid), m.p.: 247-249 °C; IR (KBr) (ν_{max}/cm⁻¹): 3387, 3056, 2943, 2930, 1717, 1657, 1587, 1383, 1169; ¹H NMR (CDCl₃): δ_H 1.03 (6H, s, CMe₂); 1.11 (6H, s, CMe₂); 2.10-2.22 (4H, dd, J = 1.6 Hz, J = 2.4, 2 × CH₂); 2.40 (4H, s, 2 × CH₂); 4.85 (1H, s, CH); 7.13-7.43 (3H, m, ArH.); LC-MS: 441 [M+23]; Elemental analysis: Found (%): C, 65.43; H, 5.89; Calcd. for C₂₃H₂₄Cl₂O₃ (419.34): C, 65.88; H, 5.77.

9-(4-Hydroxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (3f). (White solid), m.p.: 250-251 °C; IR (KBr) (ν_{max}/cm⁻¹): 3498, 3078, 2933, 2929, 1719, 1645, 1577, 1384, 1166; ¹H NMR (CDCl₃): δ_H 1.00 (6H, s, CMe₂); 1.11 (6H, s, CMe₂); 2.12-2.24 (4H, q, J = 16.6 Hz, 2 × CH₂); 2.45 (4H, s, 2 × CH₂); 4.61 (1H, s, CH); 6.77 (2H, m, ArH.); 6.93 (2H, m, ArH); LC-MS: 389 [M+23]; Elemental analysis: Found (%): C, 75.21; H, 7.20; Calcd. for C₂₃H₂₆O₄ (366.18): C, 75.38; H, 7.15.

9-(4-(Dimethylamino)phenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (3i). (Yellow solid), m.p.: 222-225 °C; IR (KBr) (ν_{max}/cm⁻¹): 3087, 3010, 2923, 2901, 1709, 1643, 1573, 1376, 1133; ¹H NMR (CDCl₃): δ_H 1.01 (6H, s, CMe₂); 1.11 (6H, s, CMe₂); 2.11-2.22 (4H, q,

J = 16.05 Hz, 2 × CH₂); 2.42 (4H, s, 2 × CH₂); 4.61 (1H, s, CH); 7.13 (2H, m, ArH.); 7.25 (2H, m, ArH); LC-MS: 418 [M+23]; Elemental analysis: Found (%): C, 76.21; H, 7.90; Calcd. for C₂₃H₃₁NO₃ (393.52): C, 76.30; H, 7.94.

3,3,6,6-Tetramethyl-9-(2,3,4-trimethoxyphenyl)-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (3J). (Pale yellow solid); m.p.: 187-189 °C; IR (KBr) (ν_{max}/cm⁻¹): 3008, 2956, 2920, 1668, 1643, 1580, 1370; ¹H NMR (CDCl₃): δ_H 1.12 (6H, s, CMe₂); 1.24 (6H, s, CMe₂); 2.20 (4H, s, 2 × CH₂); 2.43 (4H, s, 2 × CH₂); 3.75 (3H, s, OMe); 4.63 (1H, s, CH.); 6.45 (2H, s, ArH); LC-MS: 463 [M+23]; Elemental analysis: Found (%): C, 70.63; H, 7.23; Calcd. for C₂₆H₃₂O₆ (440.53): C, 70.89; H, 7.32.

9-(4-Bromophenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (3I). (White solid); m.p.: 187-189 °C; IR (KBr) (ν_{max}/cm⁻¹): 3078, 2946, 2910, 1701, 1623, 1545, 1376; ¹H NMR (CDCl₃): δ_H 1.00 (6H, s, CMe₂); 1.12 (6H, s, CMe₂); 2.10-2.23 (4H, q, J = 16.6 Hz, 2 × CH₂); 2.41 (4H, s, 2 × CH₂); 4.63 (1H, s, CH); 7.12 (2H, d, J = 8.30 Hz, ArH); 7.29 (2H, d, J = 8.30 Hz, ArH); LC-MS: 452 [M+23]; Elemental analysis: Found (%): C, 64.12; H, 5.45; Calcd. for C₂₆H₂₅BrO₃ (429.35): C, 64.34; H, 5.87.

3,3,6,6-Tetramethyl-9-(2-nitrophenyl)-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (3n). (white solid); m.p.: 258-262 °C; IR (KBr) (ν_{max}/cm⁻¹): 3095, 2932, 2920, 1707, 1643, 1556, 1366; ¹H NMR (CDCl₃): δ_H 1.00 (6H, s, CMe₂); 1.11 (6H, s, CMe₂); 2.05-2.25 (4H, q, J = 16.2 Hz, 2 ×

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CH₂); 2.47 (4H, s, 2 × CH₂); 5.48 (1H, s, CH); 7.27-7.78 (4H, m, ArH); LC-MS: 418 [M+23]; Elemental analysis: Found (%): C, 69.67; H, 6.23; Calcd. for C₂₃H₂₅NO₅ (395.45): C, 69.86; H, 6.37.

9-(Furan-2-yl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (3q). (Brown solid); m.p.: 62-64 °C; IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 3020, 2952, 2890, 1669, 1601, 1354, 1206, 1160, 920, 765, 668; ¹H NMR (CDCl₃): δ_{H} 1.03 (6H, s, CMe₂); 1.11 (6H, s, CMe₂); 2.37 (8H, s, broad); 4.95 (1H, s, CH); 5.38 (1H, s, CH); 5.85-6.27 (2H, m, ArH); LC-MS: 363 [M+23]; Elemental analysis: Found (%): C, 74.23; H, 7.03; Calcd. for C₂₁H₂₄NO₄ (340.41): C, 74.09; H, 7.11.

9-(4-Hydroxy-3-methoxyphenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (3r). (Colorless solid); m.p.: 226-228 °C; IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 3694, 3565, 3151, 2972, 1665, 1508, 1355, 1169; ¹H NMR (CDCl₃): δ_{H} 1.00 (6H, s, CMe₂); 1.09 (6H, s, CMe₂); 2.20 (4H, s, 2 × CH₂); 2.44 (4H, s, 2 × CH₂); 3.88 (3H, s, CH₃); 4.65 (1H, s, CH); 5.46 (1H, s, br); 6.53-6.58 (1H, dd, J = 2.0, 8.1 Hz); 6.71 (1H, d, J = 8.2 Hz); 7.00 (1H, d, J = 2.0 Hz); LC-MS: 419 [M+23]; Elemental analysis: Found (%): C, 74.45; H, 7.22; Calcd. for C₂₄H₂₈O₅ (340.41): C, 72.70; H, 7.12.

3,3,6,6-Tetramethyl-9-p-tolyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (3s). (White solid); m.p.: 217-218 °C; IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 3143, 2954, 1720, 1587, 1375, 1199; ¹H NMR (CDCl₃): δ_{H} 1.00 (6H, s, CMe₂); 1.09 (6H, s, CMe₂); 2.20 (4H, d, J = 3.43 Hz, 2 × CH₂); 2.24 (3H, s, CH₃); 2.45 (4H, s, 2 × CH₂); 4.70 (1H, s, CH); 7.00 (2H, s, J = 8.1 Hz, ArH); 7.15 (2H, d, J = 8.1 Hz); LC-MS: 387 [M+23]; Elemental analysis: Found (%): C, 79.23; H, 7.262; Calcd. for C₂₄H₂₈O₃ (364.48): C, 79.09; H, 7.74.

A plausible mechanism for the synthesis of various 9-aryl-1,8-dioxooctahydroxanthane derivatives (**3a-s**) catalysed by SelectfluorTM is shown in Fig. 2.

CONCLUSIONS

We have developed a simple, efficient and green protocol for the synthesis of 9-aryl-1,8-dioxooctahydroxanthane derivatives using SelectfluorTM under solvent-free conditions. The short reaction times, simple work-up in isolation of the products in good yields with high purity, and mild reaction conditions are features of this new procedure.

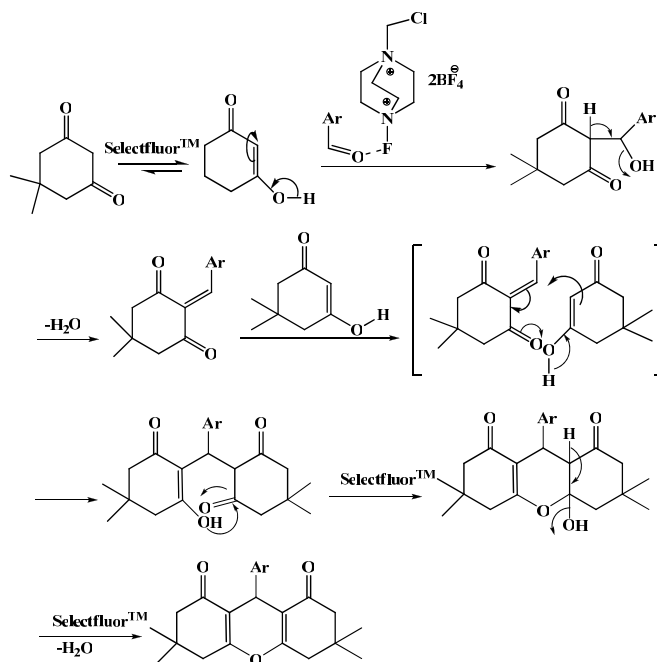


Fig. 2. Plausible mechanism for the one-pot synthesis of 9-aryl-1,8-dioxooctahydroxanthane derivatives (**3a-s**), catalyzed by SelectfluorTM.

ACKNOWLEDGEMENTS

I gratefully acknowledge the financial support from the Research Council of Payame Noor University (PNU), Iran. Thanks are also due to Prof. Jackson of Sheffield University, UK for ¹H, ¹³C NMR and High Resolution Mass spectra.

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