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Selectfluor™ Promoted Synthesis of 9-Aryl-1,8-dioxooctahydroxanthane Derivatives under Solvent-Free Conditions

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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 selectfluor™ [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, Selectfluor™

INTRODUCTION

Research on xanthenes, especially benzoxanthanes, 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 Selectfluor™ [1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis (tetrafluoroborate)] as catalyst. Recently, Selectfluor™ has been introduced commercially as an electrophilic fluorinating reagent. Selectfluor™ 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].

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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. ^{1}H and ^{13}C 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-dioxooctahydroxanthane Derivatives (3)

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

Table 1. Effect of Temperature on the Synthesis of **3l**[a]

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

[a]4-Bromo-benzaldehyde (1 mmol), dimedone (2 mmol), catalyst (0.1 mmol), 2 h.

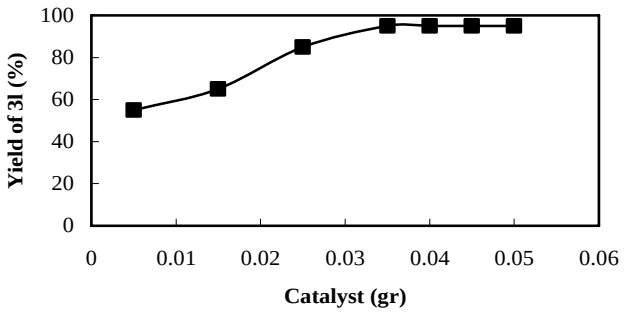


Fig. 1. Effect of catalyst on the synthesis of **3l** (reaction conditions: 4-bromo-benzaldehyde (1 mmol), dimedone (2 mmol), catalyst (0.1 mmol), and 2 h.

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, ^{1}H NMR, ^{13}C 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 **2l** and dimedone **1** in the presence of the optimum quantity of Selectfluor™ 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.

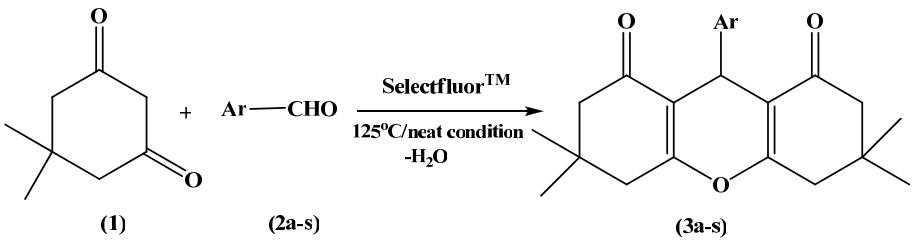
In terms of the amount of catalyst required for the reaction of 4-bromo-benzaldehyde **2l** and dimedone **1** to afford **3l** under solvent-free conditions, at 120 °C, the best results were obtained using 0.035 g of catalyst (see Fig. 1).

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) (ν_{max}/cm^{-1}): 3033, 1618, 1580; ^{1}H NMR ($CDCl_3$): δ_H1.03 (6H, s, 2 × CH_3); 1.14 (6H, s, 2 × CH_3); 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 $C_{23}H_{26}O_3$ (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) (ν_{max}/cm^{-1}): 3392, 3064, 2960, 2929, 1719, 1664, 1595, 1380, 1166; ^{1}H NMR ($CDCl_3$): δ_H



Scheme 1

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

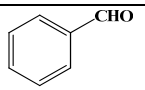
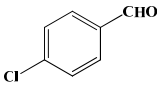
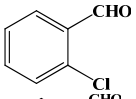
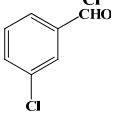
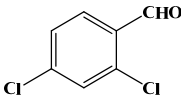
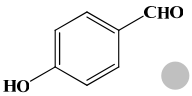
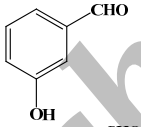
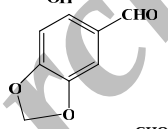
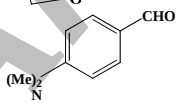
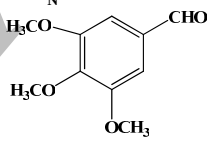
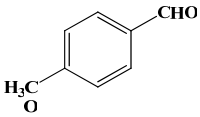
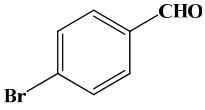
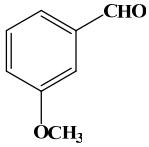
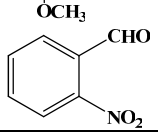
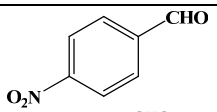
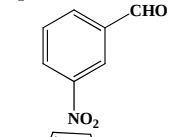
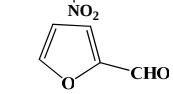
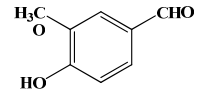
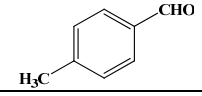
Entry	Aldehyde (**2**)	Time (h)	Yield (%)[a]	Mp (°C)	
				Obtained	Reported
3a		1	95	201-202	205 [12]
3b		1.5	93	230-232	228-230 [13]
3c		2	93	229-230	228-230 [13]
3d		1.5	93	190-192	193 [13]
3e		3	91	247-249	248-250 [13]
3f		2.5	90	250-251	246 [14]
3g		3	91	225-227	226 [13]
3h		2.5	88	221-222	224-226 [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		2	91	240-242	245-250 [13]
3m		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]

[a]Isolated yields.

1.02-1.19 (12H, s, br, 4 × CH_3); 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 $C_{23}H_{25}ClO_3$ (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; ^{1}H NMR ($CDCl_3$): δ_H 1.03 (6H, s, CMe_2); 1.11 (6H, s, CMe_2); 2.10-2.22 (4H, dd, J = 1.6 Hz, J = 2.4, 2×CH_2); 2.40 (4H, s, 2 × CH_2); 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 $C_{23}H_{24}Cl_2O_3$ (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; ^{1}H NMR ($CDCl_3$): δ_H 1.00 (6H, s, CMe_2); 1.11 (6H, s, CMe_2); 2.12-2.24 (4H, q, J = 16.6 Hz, 2 × CH_2); 2.45 (4H, s, 2 × CH_2); 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 $C_{23}H_{26}O_4$ (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; ^{1}H NMR ($CDCl_3$): δ_H 1.01 (6H, s, CMe_2); 1.11 (6H, s, CMe_2); 2.11-2.22 (4H, q, J = 16.05 Hz, 2 × CH_2); 2.42 (4H, s, 2 × CH_2); 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 $C_{23}H_{31}NO_3$ (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; ^{1}H NMR ($CDCl_3$): δ_H 1.12 (6H, s, CMe_2); 1.24 (6H, s, CMe_2); 2.20 (4H, s, 2 × CH_2); 2.43 (4H, s, 2×CH_2); 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 $C_{26}H_{32}O_6$ (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 (3l). (White solid); m.p.: 187-189 °C; IR (KBr) (ν_{max}/cm^{-1}): 3078, 2946, 2910, 1701, 1623, 1545, 1376; ^{1}H NMR ($CDCl_3$): δ_H 1.00 (6H, s, CMe_2); 1.12 (6H, s, CMe_2); 2.10-2.23 (4H, q, J = 16.6 Hz, 2 × CH_2); 2.41 (4H, s, 2 × CH_2); 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 $C_{26}H_{25}BrO_3$ (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; ^{1}H NMR ($CDCl_3$): δ_H 1.00 (6H, s, CMe_2); 1.11 (6H, s, CMe_2); 2.05-2.25 (4H, q, J = 16.2 Hz, 2 ×

CH_2); 2.47 (4H, s, 2 × CH_2); 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 $C_{23}H_{25}NO_5$ (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) (ν_{max}/cm^{-1}): 3020, 2952, 2890, 1669, 1601, 1354, 1206, 1160, 920, 765, 668; ^{1}H NMR ($CDCl_3$): δ_H 1.03 (6H, s, CMe_2); 1.11 (6H, s, CMe_2); 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 $C_{21}H_{24}NO_4$ (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) (ν_{max}/cm^{-1}): 3694, 3565, 3151, 2972, 1665, 1508, 1355, 1169; ^{1}H NMR ($CDCl_3$): δ_H 1.00 (6H, s, CMe_2); 1.09 (6H, s, CMe_2); 2.20 (4H, s, 2 × CH_2); 2.44 (4H, s, 2 × CH_2); 3.88 (3H, s, CH_3); 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 $C_{24}H_{28}O_5$ (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) (ν_{max}/cm^{-1}): 3143, 2954, 1720, 1587, 1375, 1199; ^{1}H NMR ($CDCl_3$): δ_H 1.00 (6H, s, CMe_2); 1.09 (6H, s, CMe_2); 2.20 (4H, d, J = 3.43 Hz, 2 × CH_2); 2.24 (3H, s, CH_3); 2.45 (4H, s, 2 × CH_2); 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 $C_{24}H_{28}O_3$ (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 Selectfluor™ 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 Selectfluor™ 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.

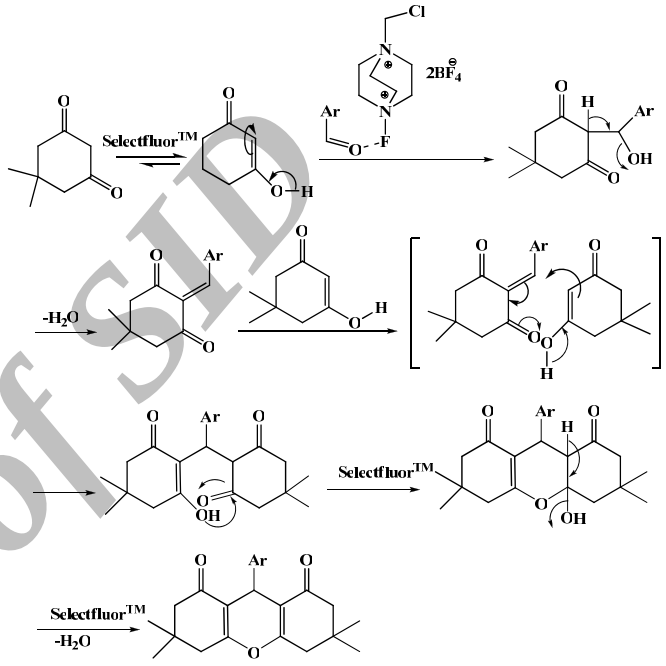


Fig. 2. Plausible mechanism for the one-pot synthesis of 9-aryl-1,8-dioxooctahydroxanthane derivatives (**3a-s**), catalyzed by Selectfluor™.

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