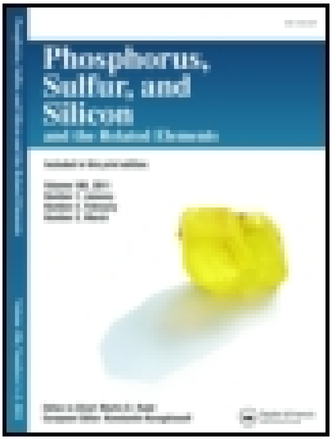

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An Effective Bismuth Trichloride-Catalyzed Synthesis of 1,8-Dioxo-Octahydroxanthenes

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An Effective Bismuth Trichloride-Catalyzed Synthesis of 1,8-Dioxo-Octahydroxanthenes

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Bismuth trichloride has been found to be an efficient catalyst for the synthesis of 1,8-dioxo-octahydroxanthenes from aromatic aldehydes and 5,5-dimethyl-1,3-cyclohexanedione under solvent-free conditions in high yields.

Keywords Aldehyde; bismuth trichloride; solvent-free; xanthene

INTRODUCTION

Heterocycles play an important role in the design and discovery of new physiological/pharmacologically active compounds.[1] Chemically, 1,8-dioxo-octahydroxanthenes are heterocyclic compounds with the xanthene framework. Xanthene derivatives are very useful and important organic compounds widely used as dye,[2] in laser technologies,[3] and fluorescent materials for visualization of biomolecules.[4] Furthermore, these compounds have shown promising activities such as antibacterial, antiviral and anti-inflammatory activities.[5] They are also valuable synthons because of the inherent reactivity of the inbuit pyran ring.[6]

Thus, the synthesis of these heterocyclic compounds is interesting for both organic synthesis and medicinal chemistry. Many methods are disclosed for the synthesis of xanthenes.[7] Recently, the condensation of aldehydes with 1,3-cyclohexanedione or 5,5-dimethyl-1,3-cyclohexanedione to the corresponding xanthenes has attracted much attention, which was conducted in the presence of strong protonic acids,[5] Lewis acids such as $InCl_3 \cdot 4H_2O$,[8] $FeCl_3 \cdot 8H_2O$,[9] $NaHSO_4$,[10]

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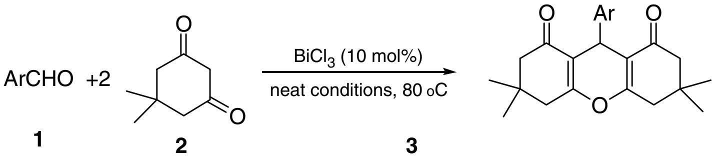
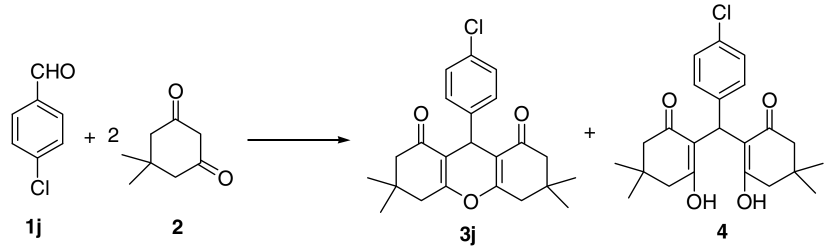
and heterogeneous catalysts like Dowex-50W,[11] $NaHSO_4{\cdot}SiO_2$,[12] silica sulfuric,[13] polyaniline-*p*-toluenesulfonate,[14] PPA-SiO_2,[15] TiO_2/SO_4^{2-},[16] and Amberlyst-15.[17] Other catalysts, such as trimethylsilyl chloride,[18] *p*-dodecylbenzenesulfonic acid,[19,20] trienthylbenzylammonium chloride,[21] and NH_2SO_3/SDS[22] have also been used for this transformation. It has also reported that the above condensation process could proceed in ionic liquid[23] or ethylene glycol.[24–25] However, some of these methodologies have not been entirely satisfactory, with disadvantage such as low yields, prolonged reaction time, harsh reaction conditions, and requirement of excess of catalysts, special apparatus. Consequently, there is still need to develop a more efficient, simple, milder and high yielding protocol for the synthesis of xanthene derivatives.

In recent years, bismuth compounds have been used as catalysts in organic synthesis because these compounds are relatively nontoxic, easy to handle, low cost, and good stability.[26] Among these, bismuth (III) trichloride has gain special attention because this compound not only is commercially available and inexpensive, but also of high stability. Bismuth (III) trichloride has been reported to be an efficient reagent for many important organic transformations, including intramolecular hetero-Diels-Alder reactions,[27] selective hydroarylation of styrenes with electron-rich arenas,[28] propargylic substitution reaction,[29] C-alkylation of pyrroles with electron-deficient olefins,[30] Pechmann condensation,[31] chemoselective deprotection of *N*-Boc group in amino acids and peptides,[32] regioselective ring opening of epoxides[33–34] and aziridines,[35] direct deoxygenative allylation of substituted benzylic alcohols with allyltrimethylsilane,[36] the synthesis of quinolines,[37] 4-substituted coumarins,[38] α-amino phosphonates.[39] In continuation of our previous work on the applications of cheap and ecofriendly materials as catalysts for development of new synthetic methodologies,[40] in this paper, we would like to report a mild and high yielding solvent-free method to prepare 1,8-dioxo-octahydroxanthene derivatives using a catalytic amount of $BiCl_3$ (Scheme 1).



SCHEME 1

TABLE I The Condensation Reaction of 4-Chlorobenzaldehyde and 5,5-Dimethyl-1,3-cyclohexanedione under Different Reaction Conditions



Entry	$BiCl_3$(mol%)	Temperature (°C)	Time (h)	Yield (%)[a]
1	0	25	10	—[b]
2	0	80	2	—[c]
3	10	25	6	15
4	10	60	2	71
5	10	80	2	93
6	5	80	4	80
7	15	80	2	90
8	20	80	2	92

[a]Isolated yield; [b]compound **4** was formed in 32% yield; and [c]compound **4** was formed in 90% yield.

RESULTS AND DISCUSSION

Initially, 4-chlorobenzaldehyde (**1j**) was selected as probe aldehyde to optimize the reaction conditions, and the results are listed in Table I. Obviously, the temperature and the amount of catalyst had important effects on the reaction. The reaction in absence of catalyst afforded only intermediate **4** as a lone product (Table I, entries 1 and 2). However, the addition of a catalytic amount of $BiCl_3$ resulted in the product **3j**. The result showed that $BiCl_3$ had catalytic effect on the synthesis **3j**. With 10 mol% of catalyst, the yield of **3j** increased from 15% to 93% as the temperature increased from 25°C to 80 °C (Table I, entries 3–5). Similar changes in the yields with the catalyst amount at a constant temperature were also observed. Therefore, it was reasonable to conclude that the best conditions were 10 mol% of $BiCl_3$ at 80°C, where the maximum yield of 93% could be obtained within 2 h. Higher amounts of the catalyst did not improve the results to a greater extent.

Having established the optimized experimental conditions, various aldehydes (**1**) were subjected to react with 5,5-dimethyl-1,3-cyclohexanedione (**2**) in order to investigate the reaction scope and

TABLE II BiCl$_3$-Catalyzed Synthesis of 1,8-Dioxo-octahydroxanthene Derivatives at 80 °C

Entry	Aldehydes	Time (h)	Yield (%)[a]	Found M.P. (°C) (Lit.)
a	PhCHO	3	90	200–202 (201–203)[18]
b	4-MeC$_6$H$_4$CHO	4	86	210–211 (210–212)[8]
c	4-MeOC$_6$H$_4$CHO	5	88	224–226 (224–226)[24]
d	3-MeOC$_6$H$_4$CHO	5	90	161–162 (160–162)[18]
e	3,4-(MeO)$_2$C$_6$H$_3$CHO	6	75	182–183 (184–185)[41]
f	3-MeO-4-OHC$_6$H$_3$CHO	6	78	225–227(226–228) [19]
g	4-OHC$_6$H$_4$CHO	6	80	247–248 (246–249) [42]
h	3,4-(OCH$_2$O)C$_6$H$_3$CHO	4	85	224–225 (224–226)[19]
i	4-FC$_6$H$_4$CHO	2	90	226–227 (225–227)[21]
j	4-ClC$_6$H$_4$CHO	2	93	228–230 (230–232)[18]
k	2-ClC$_6$H$_4$CHO	6	80	225–227 (228–230)[19]
l	3-ClC$_6$H$_4$CHO	3	91	183–185 (182–184)[20]
m	2,4-Cl$_2$C$_6$H$_3$CHO	6	82	253–254 (254–255)[18]
n	4-BrC$_6$H$_4$CHO	2	85	238–239 (240–242)[18]
o	3-NO$_2$C$_6$H$_4$CHO	4	85	145–146 (145–147)[8]
p	4-NO$_2$C$_6$H$_4$CHO	4	88	222–224 (223–224)[42]
q	Thiophene-2-carbaldehyde	4	91	162–164
r	Pyridine-2-carbaldehyde	9	75	203–204

[a] Isolated yield.

several representative results are summarized in Table II. As shown in Table II, benzaldehyde, and other aromatic aldehydes containing electron-withdrawing groups (such as halide, nitro) or electron-donating groups (such as methyl, methoxy, hydroxyl) were employed and reacted well to give the corresponding 1,8-dioxo-octahydroxanthene derivatives in good to excellent yields. Generally, *ortho*-substituted benzaldehydes required longer reaction times due to the steric hindrance (Table II, entries **k** and **m**). Thiophene-2-carbaldehyde (Table II, entry **q**) was also a good partner and excellent yield was obtained, whereas reaction of pyridine-2-carbaldehyde (Table II, entry **r**) afforded only 75% yield and long reaction time was required. Structures of synthesized compounds were assigned on the basis of their IR, ^{1}H NMR, elemental analyses, and also by comparison with authentic samples.[17] The IR spectra of products **3a–3r** showed two absorption bands at 1580–1622 and 1640–1662 cm^{-1}, corresponding to the stretching vibrations of the conjugated system of bonds C=C—C=O. The disappearance of the band at 1705–1725 due to C=O group of aldehydes confirmed the formation of product. In addition, **3r** showed the absence of a band at 3500–3000 cm^{-1} corresponding to a hydroxyl group, thus confirming the ring closure. The appearance of a singlet at δ4.86 due to the CH proton in the ^{1}H NMR spectrum of **3r** further confirmed the formation of product.

In summary, we have demonstrated that $BiCl_3$ is an efficient catalyst for the synthesis of 1,8-dioxo-octahydroxanthene derivatives by condensation of aldehydes with 5,5-dimethyl-1,3-cyclohexanedione. This method is bestowed with several unique merits, such as high conversions, simplicity in operation, solvent-free conditions, and use of low cost and commercially available bismuth chloride as catalyst.

EXPERIMENTAL

Melting points were recorded on X-4 apparatus. IR spectra were obtained using Shimadzu FTIR-8900 spectrometer. ^{1}H NMR spectra were recorded with a Bruker AV 300 or a Varain Mercury Plus 400 spectrometer using TMS as internal standard. Elemental analyses were carried out on Vario EL III CHNOS Elemental Analyzer.

Representative Procedure for the Synthesis of 1,8-Ddioxo-octahydroxanthene Derivatives

Thiophene-2-carbaldehyde (0.112 g, 1 mmol), 5,5-dimethyl-1,3-cyclohexanedione (0.280 g, 2 mmol) and $BiCl_3$ (0.031 g, 0.1 mmol) were added to a mortar. The mixture was ground by pestle and heated at 80°C for an appropriate time (monitored by TLC). After completion of the reaction, mixture was cooled to room temperature, extracted with 3 × 10 ml dichloromethane. The organic layer was washed with water, dried over $MgSO_4$, and concentrated to obtained crude product. The crude product was purified by silica gel column chromatography (40% ethyl acetate in *n*-hexane as eluent) to furnish the pure 3,3,6,6-Tetramethyl-9-thiophen-2-yl-1,8-dioxo-octahydroxanthene (0.323g, 91%) as white solid.

3,3,6,6-Tetramethyl-9-(4-bromophenyl)-1,8-dioxo-octahydroxanthene (3n)

White solid; IR (KBr): 2933, 1661, 1586, 1362, 1274, 1200, 1138, 1047, 694 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ1.00 (s, 6H), 1.11 (s, 6H), 2.26 (s, 6H), 2.15–2.47 (m, 8H), 4.70 (s, 1H), 7.18 (d, $J = 8.1$ Hz, 2H), 7.30 (d, $J = 8.1$ Hz, 2H) ppm; Anal. calcd. for $C_{23}H_{25}BrO_3$: C, 64.34; H, 5.87. Found: C, 64.08; H, 5.98.

3,3,6,6-Tetramethyl-9-thiophen-2-yl-1,8-dioxo-octahydroxanthene (3q)

White solid; IR (KBr): 2956, 2895, 2871, 1658, 1622, 1371, 1359, 1199 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ1.05 (s, 6H), 1.11 (s, 6H), 2.26 (s, 4H), 2.45 (s, 4H), 5.15 (s, 1H), 6.82 (dd, $J = 5.1, 3.6$ Hz, 1H), 6.96 (d, $J = 3.6$ Hz, 1H), 7.02 (dd, $J = 5.1, 0.9$ Hz, 1H) ppm; Anal. calcd. for $C_{21}H_{24}O_3S$: C, 70.75; H, 6.79; Found: C, 70.90; H, 6.62.

3,3,6,6-Tetramethyl-9-pyridin-2-yl-1,8-dioxo-octahydroxanthene (3r)

White solid; IR (KBr): 2958, 2930, 2874, 1681, 1657, 1623, 1199 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ1.00 (s, 6H), 1.09 (S, 6H), 2.15 (d, $J = 16$ Hz, 2H), 2.23 (d, $J = 16$ Hz, 2H), 2.44 (d, $J = 17.6$ Hz, 2H), 2.52 (d, $J = 17.6$ Hz, 2H), 4.86 (s, 1H), 6.94-7.00 (m ,1H), 7.45-7.61 (m 2H), 8.37 (d, $J = 4.4$ Hz, 1H); Anal. calcd. for $C_{22}H_{25}NO_3$: C, 75.19; H, 7.17; N, 3.99; Found: C, 75.45; H, 7.32; N, 3.78.

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