$CeCl_3 \cdot 7H_2O$ AS MILD AND EFFICIENT CATALYST FOR THE ONE-POT MULTICOMPONENT SYNTHESIS OF 8-ARYL-7,8-DIHYDRO[1,3]DIOXOLO[4,5-*g*]CHROMEN-6-ONES

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Received November 22, 2010
Accepted February 2, 2011

A series of new 8-aryl-7,8-dihydro[1,3]dioxolo[4,5-*g*]chromen-6-ones were synthesized via a three-component reaction of 3,4-methylenedioxyphenol, aromatic aldehydes and Meldrum's acid in the presence of $CeCl_3 \cdot 7H_2O$ under solvent-free conditions. The method provided several advantages such as easy work-up, high yields and environmentally benign procedure.

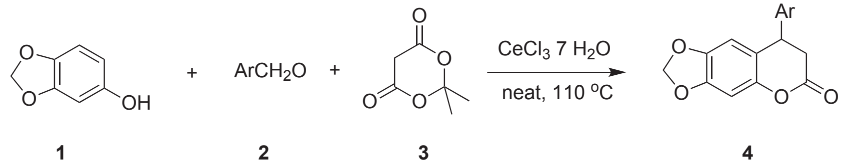
Keywords: [1,3]Dioxolo[4,5-*g*]chromen-6-one; Meldrum's acid; $CeCl_3 \cdot 7H_2O$; Solvent-free.

Multi-component, one-pot synthesis has received considerable attention because of their wide range of applications in pharmaceutical chemistry for creation of structural diversity and combinatorial libraries for drug discovery[1]. MCRs are extremely convergent, producing a remarkably high increase of molecular complexity in just one step[2]. The ready availability, potential biological activity and high reactivity of 2-chromanone makes it attractive molecule in pharmaceutical chemistry[3]. Consequently, a large number of 3,4-methylenedioxyphenol derivatives have been prepared for biological evaluation[4].

$CeCl_3 \cdot 7H_2O$ is a relatively cheap, water and air stable, and non-toxic reagent[5]. Due to the hardness of the cerium cation, it is able to activate carbonyl functionalities for nucleophilic attack and has been used as a Lewis acid for several transformations[6]. Herein, we report a mild and efficient protocol for the preparation of 8-aryl-7,8-dihydro[1,3]dioxolo[4,5-*g*]-chromen-6-ones by three-component reactions of an aromatic aldehyde, 3,4-methylenedioxyphenol and Meldrum's acid catalyzed by $CeCl_3 \cdot 7H_2O$ at 110 °C under solvent-free conditions (Scheme 1).

Collect. Czech. Chem. Commun. 2011, Vol. 76, No. 4, pp. 235–241

doi:10.1135/cccc2010139



SCHEME 1

RESULTS AND DISCUSSION

Initially, we conducted the reaction of 3,4-methylenedioxyphenol, benzaldehyde and Meldrum's acid in the presence of various metal halides such as LiBr, $FeCl_3$, $ZnCl_2$, $InBr_3$ and $CeCl_3\cdot7H_2O$ separately at 110 °C under solvent-free conditions. The corresponding 8-phenyl-7,8-dihydro[1,3]dioxolo[4,5-*g*]chromen-6-one was formed in 42, 35, 65, 72 and 88% yield, respectively (Table I). When reactions were carried out in the absence of a catalyst for long period of time (4–6 h), yield of the product was low. $CeCl_3\cdot7H_2O$ was thus selected as the most effective catalyst to carry out this reaction.

Next, to optimize the amount of the catalyst and the reaction temperature, the reaction of 3,4-methylenedioxyphenol, benzaldehyde and Meldrum's acid was studied under solvent-free conditions in the presence of $CeCl_3\cdot7H_2O$ at different temperatures. The results are summarized in Table II, and show that the reaction using 10 mole % $CeCl_3\cdot7H_2O$ at 110 °C proceeded in the highest yield.

TABLE I
Synthesis of 8-phenyl-7,8-dihydro[1,3]dioxolo[4,5-*g*]chromen-6-one using metal halides[a]

Entry	Metal halide	Time, h	Yield, %[b]
1	–	6	0
2	LiBr	4	42
3	$FeCl_3$	5	35
4	$ZnCl_2$	3	65
5	$InBr_3$	2	72
6	$CeCl_3\cdot7H_2O$	2	88

[a] Reaction conditions: 3,4-methylenedioxyphenol (1 mmol), benzaldehyde (1 mmol), Meldrum's acid (1 mmol), metal halides (0.1 mmol); neat, 110 °C. [b] Isolated yield.

TABLE II
Synthesis of 8-phenyl-7,8-dihydro[1,3]dioxolo[4,5-*g*]chromen-6-one under various conditions[a]

Entry	$CeCl_3·7H_2O$, mole %	Temperature, °C	Time, h	Yield, %[b]
1	0	110	6	0
2	1	110	4	48
3	2	110	4	56
4	5	110	3	67
5	10	25	6	0
6	10	50	6	28
7	10	90	4	65
8	10	100	3	76
9	10	110	2	88
10	10	120	2	88
11	10	130	2	87
12	15	100	2	82
13	15	110	1.5	88
14	20	110	1.5	87
15	25	110	1.5	86

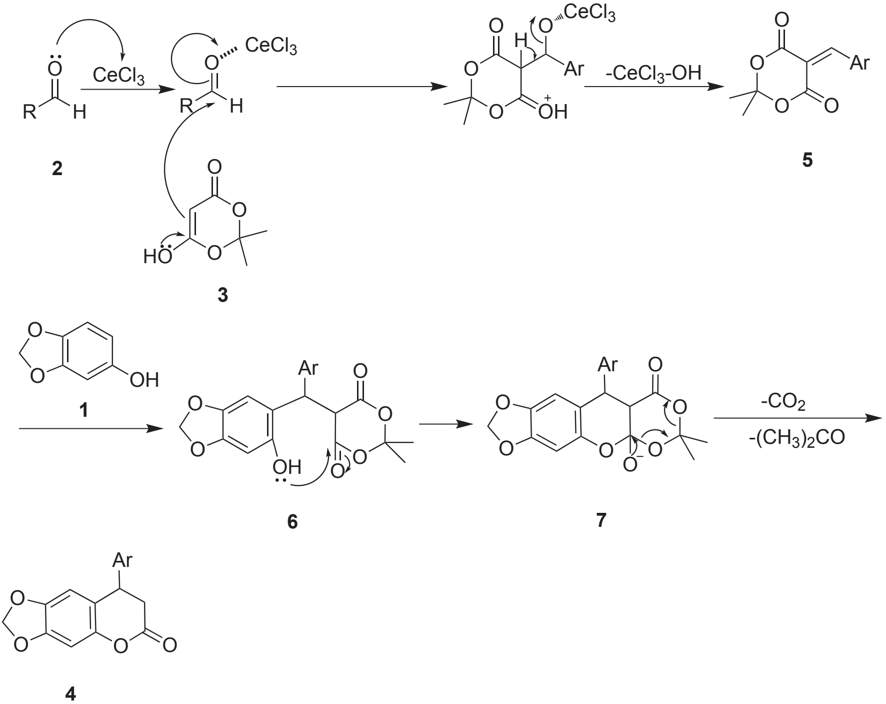
[a] Reaction conditions: 3,4-methylenedioxyphenol (1 mmol), benzaldehyde (1 mmol), Meldrum's acid (1 mmol); neat. [b] Isolated yield.

TABLE III
Preparation of 8-aryl-7,8-dihydro[1,3]dioxolo[4,5-*g*]chromen-6-ones[a]

Entry	Ar	Time, h	Product	Yield, %[b]
1	C_6H_5	2	**4a**	88
2	4-Cl-C_6H_4	1.5	**4b**	92
3	4-F-C_6H_4	1.5	**4c**	86
4	4-Me-C_6H_4	3	**4d**	82
5	4-NO_2-C_6H_4	1.5	**4e**	92
6	3-NO_2-C_6H_4	2	**4f**	85
7	2,4-diCl-C_6H_3	2.5	**4g**	88
8	4-MeO-C_6H_4	3.5	**4h**	85
9	2,5-diMeO-C_6H_3	3.5	**4i**	86
10	2-Cl-C_6H_4	2	**4j**	87

[a] Reaction conditions: 3,4-methylenedioxyphenol (1 mmol), aldehyde (1 mmol), Meldrum's acid (1 mmol), $CeCl_3·7H_2O$ (0.1 mmol); neat, 110 °C. [b] Isolated yield.

With this optimized procedure in hand, the scope of application of this three-component reaction was examined using different aldehydes as starting materials. As seen from Table III, aromatic aldehydes having electron-donating as well as electron-withdrawing groups were uniformly transformed into the corresponding 8-aryl-7,8-dihydro[1,3]dioxolo[4,5-*g*]-chromen-6-ones in high to excellent yields within 3.5 h. Substituents on the aromatic ring had no obvious effect on yield or reaction time under the above mentioned optimal conditions (Table III). All of the products **4** exhibited a triplet in their ^{1}H NMR spectra at δ 4.08–4.74 ppm for H-8, two doublets at δ 5.94–5.99 ppm for –OCH$_2$O–, two singlets at δ 6.38–6.69 ppm for H-4,9. A distinguishing peak at δ 37.0–40.6 ppm for C-8 in their ^{13}C NMR spectra, a distinguishing peak at δ 166.4–168.0 ppm carbonyl group and a distinguishing peak at δ 99.1–99.5 ppm for –OCH$_2$O– have been observed.



SCHEME 2

The formation of products **4a–4i** can be rationalized by initial formation of heterodiene **5** by standard Knoevenagel condensation of 2-hydroxynaphthalene-1,4-dione **3** and aromatic aldehyde **2** in the presence of a catalytic amount of $CeCl_3 \cdot 7H_2O$. Subsequent Michael-type addition of 3,4-methylenedioxyphenol **1** to the heterodienes **5** followed by cyclization, dehydration and air oxidation affords the corresponding products **4a–4j** (Scheme 2).

CONCLUSION

In conclusion, we have developed a highly efficient methodology for a three-component reaction of 3,4-methylenedioxyphenol, aromatic aldehydes and Meldrum's acid catalyzed by safe $CeCl_3 \cdot 7H_2O$, furnishing a class of 8-aryl-7,8-dihydro[1,3]dioxolo[4,5-*g*]chromen-6-ones in high yield. This method is advantageous in terms of simplicity and mildness, and hopefully could Þnd wide application in synthesis of complex chromene-containing compounds.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were determined on a Bruker AV-400 spectrometer (100 MHz for ^{13}C NMR) at room temperature using tetramethylsilane (TMS) as an internal standard ($CDCl_3$ solution). Chemical shifts are given in ppm (δ-scale), coupling constants (*J*) in Hz. IR spectra were determined on a FTS-40 infrared spectrometer. Elemental analysis were performed by a Vario-III elemental analyzer. Mass spectra were taken on a Macro mass spectrometer (Waters) by electro-spray method (ES). Melting points were determined on a XT-4 binocular microscope and were uncorrected. Commercially available reagents were used without further purification unless otherwise stated.

General Procedure for Preparation of **4**

A mixture of 3,4-methylenedioxyphenol (1 mmol), aldehyde (1 mmol), Meldrum's acid (1 mmol) and $CeCl_3 \cdot 7H_2O$ (0.1 mmol) were heated at 110 °C for an appropriate time (TLC). After completion, the reaction mixture was washed with water (15 ml), and the crude product purified by silica gel column chromatography using CH_2Cl_2 as an eluent to afford the pure product **4**.

8-Phenyl-7,8-dihydro[1,3]dioxolo[4,5-g]chromen-6-one (**4a**). White powder, m.p. 133–134 °C. ^{1}H NMR: 7.37–7.26 (m, 3 H), 7.16–7.14 (m, 2 H) 6.68 (s, 1 H), 6.39 (s, 1 H), 5.95 (d, 1 H, *J* = 1.2), 5.94 (d, 1 H, *J* = 1.2), 4.22 (t, *J* = 7.2, 1 H), 3.07–2.93 (m, 2 H). ^{13}C NMR: 167.7, 147.5, 146.2, 144.4, 140.4, 129.2, 128.6, 127.7, 127.5, 117.9, 107.3, 101.7, 99.1, 40.6, 37.0. MS (ESI): *m/z* 269 $[M + H]^+$. For $C_{16}H_{12}O_4$ (268.27) calculated: 71.64% C, 4.51% H; found: 71.60% C, 4.36% H.

8-(4-Chlorophenyl)-7,8-dihydro[1,3]dioxolo[4,5-g]chromen-6-one (**4b**). White powder, m.p. 205–206 °C. ^{1}H NMR: 7.32 (d, 2 H, *J* = 8.4), 7.08 (d, 2 H, *J* = 8.4), 6.66 (s, 1 H), 6.38 (s, 1 H), 5.97 (d, 1 H, *J* = 0.8), 5.96 (d, 1 H, *J* = 0.8), 4.21 (t, *J* = 6.8, 1 H), 3.06–2.89 (m, 2 H).

^{13}C NMR: 167.8, 148.1, 146.7, 144.8, 136.4, 134.2, 134.1, 130.0, 129.4, 127.9, 115.7, 107.1, 101.9, 99.3, 37.0, 35.3. MS (ESI): *m/z* 303 $[M + H]^+$. For $C_{16}H_{11}ClO_4$ (302.72) calculated: 63.48% C, 3.66% H; found: 63.39% C, 3.71% H.

8-(4-Fluorophenyl)-7,8-dihydro[1,3]dioxolo[4,5-g]chromen-6-one (**4c**). White semi-solid. ^{1}H NMR: 7.13–7.09 (m, 2 H), 7.05–7.01 (m, 2 H), 6.66 (s, 1 H), 6.38 (s, 1 H), 5.96 (d, 2 H, *J* = 1.2), 4.22 (t, *J* = 6.8, 1 H), 3.06–2.89 (m, 2 H). ^{13}C NMR: 167.3, 147.7, 146.2, 144.5, 136.2, 136.1, 129.1, 129.0, 117.6, 116.2, 116.0, 107.1, 101.8, 99.2, 39.9, 37.2. MS (ESI): *m/z* 287 $[M + H]^+$. For $C_{16}H_{11}FO_4$ (286.26) calculated: 67.13% C, 3.87% H; found: 67.09% C, 3.92% H.

8-(4-Methylphenyl)-7,8-dihydro[1,3]dioxolo[4,5-g]chromen-6-one (**4d**). White powder, m.p. 143–144 °C. ^{1}H NMR: 7.15 (d, 2 H, *J* = 7.6), 7.03 (d, 2 H, *J* = 8.0), 6.65 (s, 1 H), 6.39 (s, 1 H), 5.95 (d, 1 H, *J* = 1.2), 5.94 (d, 1 H, *J* = 1.2), 4.08 (t, *J* = 7.6, 1 H), 3.05–2.91 (m, 2 H), 2.34 (s, 3 H). ^{13}C NMR: 167.7, 147.4, 146.1, 144.4, 137.4, 129.8, 127.3, 118.2, 107.3, 101.7, 99.1, 40.2, 37.0, 31.0. MS (ESI): *m/z* 283 $[M + H]^+$. For $C_{17}H_{14}O_4$ (282.30) calculated: 72.33% C, 5.00% H; found: 72.40% C, 4.97% H.

8-(4-Nitrophenyl)-7,8-dihydro[1,3]dioxolo[4,5-g]chromen-6-one (**4e**). White powder, m.p. 225–226 °C. ^{1}H NMR: 8.21 (d, 2 H, *J* = 8.8), 7.33 (d, 2 H, *J* = 8.8), 6.69 (s, 1 H), 6.40 (s, 1 H), 5.99 (d, 1 H, *J* = 1.2), 5.98 (d, 1 H, *J* = 1.2), 4.30 (t, *J* = 6.0, 1 H), 3.14–2.95 (m, 2 H). ^{13}C NMR: 166.4, 148.2, 147.9, 147.4, 146.3, 144.8, 128.4, 124.4, 115.8, 107.0, 102.0, 99.5, 40.5, 36.7. MS (ESI): *m/z* 314 $[M + H]^+$. For $C_{16}H_{11}NO_6$ (313.27) calculated: 61.35% C, 3.54% H, 4.47% N; found: 61.28% C, 3.60% H, 4.52% N.

8-(3-Nitrophenyl)-7,8-dihydro[1,3]dioxolo[4,5-g]chromen-6-one (**4f**). White powder, m.p. 142–143 °C. ^{1}H NMR: 8.17–8.15 (m, 1 H), 8.03 (s, 1 H), 7.56–7.46 (m, 2 H), 6.69 (s, 1 H), 6.40 (s, 1 H), 5.99 (d, 2 H, *J* = 0.8), 4.37 (t, *J* = 6.4, 1 H), 3.14–2.97 (m, 2 H). ^{13}C NMR: 166.6, 148.7, 148.2, 146.3, 144.8, 142.7, 133.5, 130.3, 122.9, 122.6, 115.9, 107.0, 102.0, 99.5, 40.4, 36.9. MS (ESI): *m/z* 314 $[M + H]^+$. For $C_{16}H_{11}NO_6$ (313.27) calculated: 61.35% C, 3.54% H, 4.47% N; found: 61.33% C, 3.59% H, 4.49% N.

8-(2,4-Dichlorophenyl)-7,8-dihydro[1,3]dioxolo[4,5-g]chromen-6-one (**4g**). White powder, m.p. 179–180 °C. ^{1}H NMR: 7.45 (d, 1 H, *J* = 2.0), 7.16 (dd, 1 H, *J* = 2.0, 8.4), 6.81 (d, 1 H, *J* = 8.4), 6.69 (s, 1 H), 6.44 (s, 1 H), 5.98 (d, 2 H, *J* = 1.2), 4.68 (t, *J* = 6.0, 1 H), 3.02–2.97 (m, 2 H). ^{13}C NMR: 166.5, 148.7, 148.2, 146.3, 144.8, 142.7, 136.4, 133.5, 130.3, 122.6, 115.7, 106.9, 101.9, 99.3, 40.4, 36.9. MS (ESI): *m/z* 337 $[M + H]^+$. For $C_{16}H_{10}Cl_2O_4$ (337.16) calculated: 57.00% C, 2.99% H; found: 57.03% C, 3.02% H.

8-(4-Methoxyphenyl)-7,8-dihydro[1,3]dioxolo[4,5-g]chromen-6-one (**4h**). White powder, m.p. 129–130 °C. ^{1}H NMR: 7.06 (d, 2 H, *J* = 8.8), 6.87 (d, 2 H, *J* = 8.8), 6.65 (s, 1 H), 6.40 (s, 1 H), 5.95 (d, 2 H, *J* = 1.2), 4.17 (t, *J* = 6.0, 1 H), 3.80 (s, 3 H), 3.00–2.93 (m, 2 H). ^{13}C NMR: 167.8, 159.0, 147.4, 146.1, 144.4, 132.3, 128.5, 118.4, 114.5, 107.2, 101.7, 99.1, 55.3, 39.8, 37.2. MS (ESI): *m/z* 299 $[M + H]^+$. For $C_{17}H_{14}O_5$ (298.30) calculated: 68.45% C, 4.73% H; found: 68.51% C, 4.77% H.

8-(2,5-Dimethoxyphenyl)-7,8-dihydro[1,3]dioxolo[4,5-g]chromen-6-one (**4i**). White powder, m.p. 121–122 °C. ^{1}H NMR: 6.82 (d, 1 H, *J* = 8.8), 6.76 (d, 1 H, *J* = 3.2), 6.64 (s, 1 H), 6.46 (s, 1 H), 6.43 (d, 1 H, *J* = 3.2), 5.95 (d, 1 H, *J* = 1.2), 5.94 (d, 1 H, *J* = 1.2), 4.51 (t, *J* = 6.0, 1 H), 3.79 (s, 3 H), 3.69 (s, 3 H), 3.03–2.95 (m, 2 H). ^{13}C NMR: 168.0, 153.6, 150.9, 147.4, 146.5, 144.4, 129.9, 116.8, 115.2, 112.1, 116.7, 107.3, 101.6, 99.0, 55.6, 55.6, 35.4, 35.0. MS (ESI): *m/z* 329 $[M + H]^+$. For $C_{18}H_{16}O_6$ (328.32) calculated: 65.85% C, 4.91% H; found: 65.88% C, 4.87% H.

8-(Chorophenyl)-7,8-dihydro[1,3]dioxolo[4,5-g]chromen-6-one (**4j**). White powder, m.p. 160–161 °C. ^{1}H NMR: 7.43 (dd, 1 H, *J* = 0.8, 7.6), 7.25–7.17 (m, 2 H), 6.88 (dd, 1 H, *J* = 0.8, 7.2), 6.69 (s, 1 H), 6.45 (s, 1 H), 5.98 (d, 1 H, *J* = 1.2), 5.97 (d, 1 H, *J* = 1.2), 4.74 (t, *J* = 6.4, 1 H), 3.05–3.02 (m, 2 H). ^{13}C NMR: 167.2, 147.8, 146.7, 144.7, 137.7, 133.4, 130.1, 129.0, 128.5, 127.6, 116.3, 107.2, 101.8, 99.2, 37.3, 35.4. MS (ESI): *m/z* 303 [M + H]$^+$. For $C_{16}H_{11}ClO_4$ (302.72) calculated: 63.48% C, 3.66% H; found: 63.44% C, 3.70% H.

We are pleased to acknowledge the financial support from Xinxiang Medical University.

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