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Green synthesis of chromene using *insitu* synthesis of 4-hydroxycumarines

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Abstract: An efficient synthesis of chromene derivatives *via* reaction of acetophenone, dimethylcarbonate, melderum acid and ketones in water as solvent and room temperatureis described.

Keywords: Chromene; Acetophenone derivatives; Aqueous media**;** Meldrum's acid**;** 4-Hydroxycoumarin, Dimethylcarbonate.

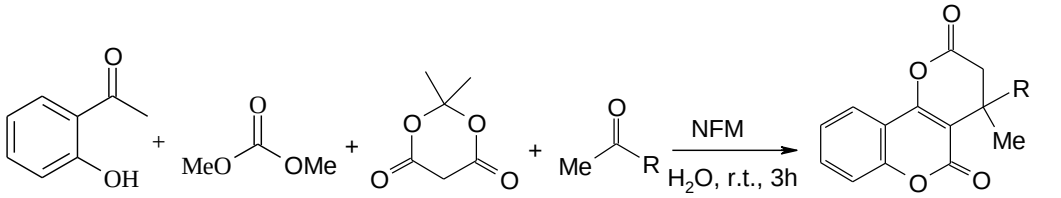
Introduction

Natural products containing chromene structure represent an important class of compounds [1-4]. The bicyclic ring system of chromenes has inspired a number of different synthetic approaches [5,6]. Also, substituted 4*H*-chromenes are a new set of anticancer compounds [7]. For these reasons, their synthesis is very importance to organic chemists and many studies have been reported on the synthesis of the chromene ring system [8,9]. Consequently, a number of synthetic strategies for the construction of pyrano[3,2-c]chromene derivatives have been reported [10]. Some of the reported procedures require long reaction times, multi-step reactions and complex synthetic pathways, afford products with only modest yields [11-13].

Therefore, the development of more effective methods for their preparation is still necessary.

Results and discussion

As part of our current studies [14-16] on the development of new routes to heterocyclic systems, we now report an efficient method to prepare functionalized chromenes. Thus the reaction of acetophenone **1**, dimethylcarbonate **2**, Meldrum's acid **3** and ketones **4** in the presence of *N*-formylmorpholine (NFM) at room temperature in water led to chromenes **5** in good yields (Scheme **1**).



1 **2** **3** **4**

5	R	Yield/%
a	Me	97
b	Et	87
c	^{n}Pr	78
d	Me_2CHCH_2	65

Scheme 1. Synthesis of chromene derivatives.

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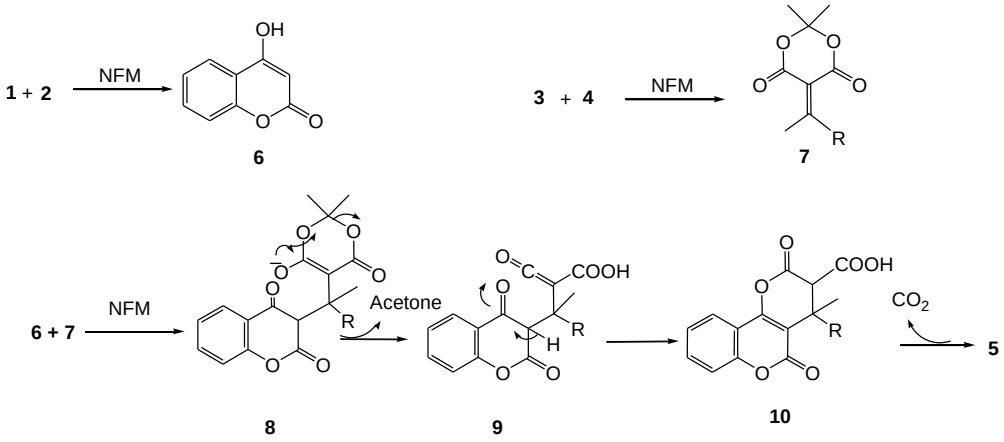
Structures of compounds **5a**–**5d** were assigned by IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. The ^{1}H NMR spectrum of **5a** showed two singlets arising from methyl and methylene protons, along with the aromatic protons. The ^{1}H NMR spectrum of **5a-5d** exhibited a characteristic AB system for the CH_2 moiety. The carbonyl group resonances in the ^{13}C NMR spectrum of **5a** appear at 159.5 and 164.8 ppm. The mass spectrum of **5a** displayed the molecular ion peak at *m*/*z* = 244.

A tentative mechanism for this transformation is proposed in Scheme **2**. It is conceivable that the initial event is the formation of **6** which undergoes Knoevenagel condensation with Meldrum's acid. This intermediate is subsequently attacked by 4-hydroxycoumarin **6** that is generated from the reaction of acetophenone and dimethyl carbonate to generate **8**. Intermediate **8** first loses acetone to give ketene **9**, which undergoes cyclization and decarboxylation to produce **5**.



Scheme 2. Proposed mechanism for the synthesis of chromene **5**

Investigation of antioxidant activity using DPPH:

Diphenyl-2-picrylhydrazyl (DPPH) radical scavenging test is broadly employed to estimate the ability of compounds to capture free radicals and their antioxidant activity in foods and biological systems. The DPPH analyze donating activity of the hydrogen atom (or one electron) and gives an evaluation of antioxidant activity because of free radical scavenging. The antioxidant activity of **5a-5d** was investigated by testing their ability to the DPPH radical. DPPH radical shows the absorption in area 517 nm but its absorption decreases when is reduced by an antioxidant or a radical species. In this study, the antioxidant activity of **54-5d** was compared to BHT and TBHQ at different concentrations from 200 mmol/L to 1000 mmol/L. At all concentrations, the new synthesized compound 5c had significant differences compared to BHT and TBHQ. Overall, the all compounds especially compound **5c** were shown excellent free radical scavenging performance compared to BHT and TBHQ at 1000 ppm concentration

Ferric ions (Fe3+) reducing potential (FRAP):

The ability of the synthesized compounds to reduce Ferric ions (Fe3+) was studied by measuring the amount of exchange of Fe3+/ferricyanide complex to the Fe2+/ ferrous shape at 700 nm. The ability of compound to reducing may act as a important indicator of its potential antioxidant activity. Compound **5b** and **5c** was displayed good reducing activity compared to standards (BHT and TBHQ).

Conclusion

In conclusion, we have described a convenient route to chromene derivatives from the reaction of acetophenone, dimethyl carbonate, Meldrum's acid, and ketones. The functionalized chromenes reported in this work may be considered as potentially useful synthetic intermediates because they possess atoms with different oxidation states. The advantage of the present procedure is that the reaction is performed under neutral conditions by simple mixing of the starting materials. The simplicity of the present

procedure makes it an interesting alternative to other approaches.

Material and methods

Mp: *Electrothermal-9100* apparatus; uncorrected. IR Spectra: *Shimadzu IR-460* spectrometer. ^{1}H- and ^{13}C-NMR spectra: Bruker DRX-500 AVANCE instrument; in $CDCl_3$ at 500.1 and 125.7 MHz, resp.; □ in ppm, *J* in Hz. EI-MS (70 eV): Finnigan-MAT-8430 mass spectrometer, in *m/z*. Elemental analyses (C, H, N) were performed with a Heraeus CHN-O-Rapid analyzer. All chemicals were used as-received from the appropriate suppliers.

General procedure:

To a stirred solution of Meldrum's acid **3** (0.29 g, 2 mmol) and methyl ketones **4** (2 mmol) was added NFM (2 mmol). The reaction mixture was stirred for 4 hours. After completion of the reaction (monitored by TLC), was added acetophenone **1** (2 mmol) and dimethyl carbonate **2** (2 mmol) mixture that is stirred for 30min. The reaction mixture was stirred for 12 h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (SiO_2; hexane/AcOEt) to afford **5.**

4,4-Dimethyl-3,4-dihydro-2H,5H-pyrano[3,2-c]chromene-2,5-dione (5a):

White powder, yield: 0.47 g (97%), m.p. 128-131°C. IR (KBr) (ν_{max}/cm^{-1}): 1794, 1712, 1626, 1358 cm^{-1}. ^{1}H NMR: 1.98 (s, 6 H, 2 Me), 3.23 (s, 2 H, CH_2), 7.80 (t, ^3J = 8.1 Hz, 1 H, CH), 7.81 (d, ^3J = 7.6 Hz, 1 H, CH), 8.06 (td, ^3J = 8.56 Hz, ^4J = 1.15 Hz, 1 H, 1 CH), 7.81 (d, ^3J = 7.8 Hz, 1 H, CH).^{13}C NMR: 26.5 (2 Me), 33.8 (C), 44.3 (CH_2), 111.1 (C), 114.0 (C), 116.4 (CH), 123.1 (CH), 124.4 (CH), 132.6 (CH), 152.7 (C), 156.0 (C), 159.5 (C=O), 164.8 (C=O). EI-MS: 245 (M^++1, 95), 244 (M^+, 85), 229 (65), 216 (45), 201 (100), 121 (50), 92 (40). Anal. Calcd for $C_{14}H_{12}O_4$ (244.24): C 68.85, H 4.95%. Found: C 68.10, H 5.01%.

4-Ethyl-4-methyl-3,4-dihydro-2H,5H-pyrano[3,2-c]chromene-2,5-dione (5b):

White powder, yield: 0.45 g (87%), m.p. 100-103 °C. IR (KBr) (ν_{max}/cm^{-1}): 1796, 1716, 1624, 1377 cm^{-1}. ^{1}H NMR: 1.33 (t, ^3J = 7.5 Hz, 3 H, Me), 1.92 (s, 3 H, Me), 2.06 (dq, ^2J = 6.7 Hz, ^3J = 7.4 Hz, 1 H, CH), 2.56 (dq, ^2J = 6.7 Hz, ^3J = 7.4 Hz, 1 H, CH), 3.07 (d, ^2J = 15.9 Hz, 1 H, CH), 3.30 (d, ^2J = 15.9 Hz, 1 H, CH), 7.74-7.77 (m, 2 H, 2 CH), 8.02 (td, ^3J = 7.35 Hz, ^4J = 1.55 Hz, 1 H, 1 CH), 8.26 (dd, ^3J = 8.1 Hz, ^4J = 1.45 Hz, 1 H, CH).^{13}C NMR: 8.90 (Me), 25.3 (Me), 31.7 (CH_2), 37.6 (C), 40.9 (CH_2), 109.6 (C), 113.6 (C), 116.3 (CH), 122.9 (CH), 124.3 (CH), 132.6 (CH), 152.7 (C), 156.8 (C), 159.5 (C=O), 165.3 (C=O). EI-MS: 259 (M^++1, 95), 258 (M^+, 85), 243 (74), 230 (42), 215 (100), 121 (44), 92 (42). Anal. Calcd for $C_{15}H_{14}O_4$ (258.27): C 69.76, H 5.46%. Found: C 69.22, H 5.40%.

4-Methyl-4-propyl-3,4-dihydro-2H,5H-pyrano[3,2-c]chromene-2,5-dione (5c):

White powder, yield: 0.42 g (87%), m.p. 87-93 °C. IR (KBr) (ν_{max}/cm^{-1}): 1794, 1710, 1622, 1358 cm^{-1}. ^{1}H NMR: 1.36 (t, ^3J = 7.3 Hz, 3 H, Me), 1.64-1.79 (m, 2 H, CH_2), 1.95 (s, 3 H, Me), 2.01 (dt, ^2J = 4.4 Hz, ^3J = 12.8 Hz, 1 H, CH), 2.48 (dt, ^2J = 4.4 Hz, ^3J = 12.8 Hz, 1 H, CH), 3.09 (d, ^2J = 15.9 Hz, 1 H, CH), 3.31 (d, ^2J = 15.9 Hz, 1 H, CH), 7.75-7.78 (m, 2 H, 2 CH), 8.02 (td, ^3J = 8.8 Hz, ^4J = 1.4 Hz, 1 H, 1 CH), 8.27 (dd, ^3J = 8.0 Hz, ^4J = 1.2 Hz, 1 H, CH). ^{13}C NMR: 14.3 (Me), 17.9 (Me), 25.7 (CH_2), 37.4 (C), 41.4 (CH_2), 41.5 (CH_2), 109.9 (C), 113.6 (C), 116.4 (CH), 123.0 (CH), 124.3 (CH), 132.5 (CH), 152.7 (C), 156.6 (C), 159.5 (C=O), 165.2 (C=O). EI-MS: 273 (M^++1, 95), 272 (M^+, 85), 257 (65), 244 (58), 229 (100), 121 (60), 92 (42). Anal. Calcd for $C_{16}H_{16}O_4$ (272.30): C 70.58, H 5.92%. Found: C 69.22, H 5.59%.

4-Isobutyl-4-methyl-3,4-dihydro-2H,5H-pyrano[3,2-c]chromene-2,5-dione (5d):

White powder, yield: 0.37 g (65%), m.p. 107-108°C. IR (KBr) (ν_{max}/cm^{-1}): 1797, 1710, 1620, 1359 cm^{-1}. ^{1}H NMR: 0.93 (d, ^3J = 6.6 Hz, 3 H, Me), 0.97 (d, ^3J = 6.6 Hz, 3 H, Me), 1.56 (s, 3 H, Me), 1.59 (dd, ^2J = 5.3 Hz, ^3J = 14.4 Hz, 1 H, CH), 1.70-1.75 (m, 1 H, CH), 2.04 (dd, ^2J = 5.3 Hz, ^3J = 14.4 Hz, 1 H, CH), 2.69 (d, ^2J = 15.9 Hz, 1 H, CH), 2.96 (d, ^2J = 15.8 Hz, 1 H, CH), 7.35-7.38 (m, 2 H, 2 CH), 7.62 (td, ^3J = 7.37 Hz, ^4J = 1.5 Hz, 1 H, 1 CH), 7.89 (dd, ^3J = 7.9 Hz, ^4J = 1.5 Hz, 1 H, CH). ^{13}C NMR: 24.7 (Me), 25.3 (CH), 25.6 (Me), 26.7 (Me), 37.9 (C), 42.4 (CH_2), 47.7 (CH_2), 111.2 (C), 114.0 (C), 116.9 (CH), 123.5 (CH), 124.7 (CH), 133.0 (CH), 153.1 (C), 156.7 (C), 160.1 (C=O), 165.7 (C=O). EI-MS: 287 (M^++1, 80), 244 (M^+, 68), 272 (65), 259 (45), 244 (100), 121 (50), 92 (30). Anal. Calcd for $C_{17}H_{18}O_4$ (286.32): C 71.31, H 6.34%. Found: C 71.0, H 6.22%.

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