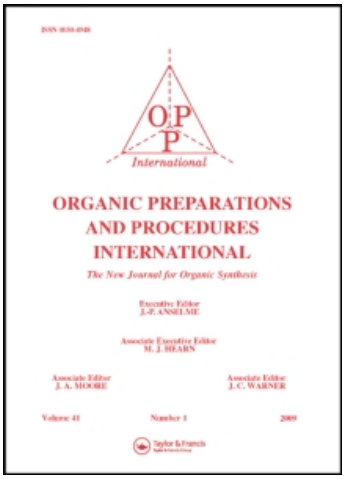

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

An Efficient Procedure for the Synthesis of Some New 9-Hydroxy-6-methyl-7*H*-benzo[*c*] chromene-7-one Derivatives

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Online publication date: 20 November 2009

To cite this Article Zonouzi, A. , Izakian, Z. and Biniaz, M.(2009) 'An Efficient Procedure for the Synthesis of Some New 9-Hydroxy-6-methyl-7*H*-benzo[*c*] chromene-7-one Derivatives', Organic Preparations and Procedures International, 41: 6, 543 — 548
To link to this Article: DOI: 10.1080/00304940903361897
URL: http://dx.doi.org/10.1080/00304940903361897

Organic Preparations and Procedures International, 41:543–548, 2009

ISSN: 0030-4948 print
DOI: 10.1080/00304940903361897

An Efficient Procedure for the Synthesis of Some New 9-Hydroxy-6-methyl-7*H*-benzo[*c*] chromene-7-one Derivatives

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Chromene (benzopyran) derivatives are an important class of compounds, widely present in plants, including edible vegetables and fruits.[1] Numerous bioactive natural products have been identified, and the presence of the chromene-based structure has been associated with the capacity to prevent disease.[2] Biologically active synthetic analogues of chromene were developed over the years, useful as anti-hypertensive,[3] hypoglycemic, cardio-protective,[4,5] antivirus, antitumor,[6] anti HIV agents[7] and as insecti- cides.[8] Some of their derivatives are utilized in the synthesis of new macrocyclic ligands [9,10] and others have shown photochromic properties.[11,12]

These interesting properties of chromene led us to investigate an efficient synthesis with the goal of obtaining more potent pharmacologically active compounds. Various methods are known to give chromene derivatives.[10–30] We have recently reported a simple and rapid procedure for the synthesis of some new 2*H*-chromenes[31] (**1**) and now describe a simple one-pot procedure for the synthesis of some new 9-hydroxy-6-methyl-7*H*-benzo[*c*]chromene-7-one derivatives (**2**) (*Scheme 1*).

Although the treatment of chromenes **1** with ethyl chloroacetate or methyl thioglycolate under basic conditions led to the desired products **2**, it was found that these compounds could be obtained in a one-pot reaction of the three-component *via* a Robinson-type annulation involving three components. There was no evidence for the presence of structures **3** and **4**. The intramolecular O-H hydrogen bonding in compounds **1** is so strong[32] that their carbonyl group is unreactive toward 2,4-dinitrophenylhydrazine.

Structures **2** were assigned on the basis of their elemental analysis, IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. The mass spectra of these compounds (**2a–f**) displayed molecular ion peaks at appropriate m/z values. Initial fragmentation involved the loss of the ring side chains (CH_3, OCH_3, CH_3OH, CH_3CO, CH_3COH and OH) and scission of the ring. Moreover fragment 43 in **2c**, **2d** is 100%. Fragment 107 which in **2e** appeared with intensity 60 and in **2f** with intensity 56, is related to M^+-CH_3CO, C_6H_3X (X = Cl, Br). The ^{1}H NMR

Submitted June 11, 2009.
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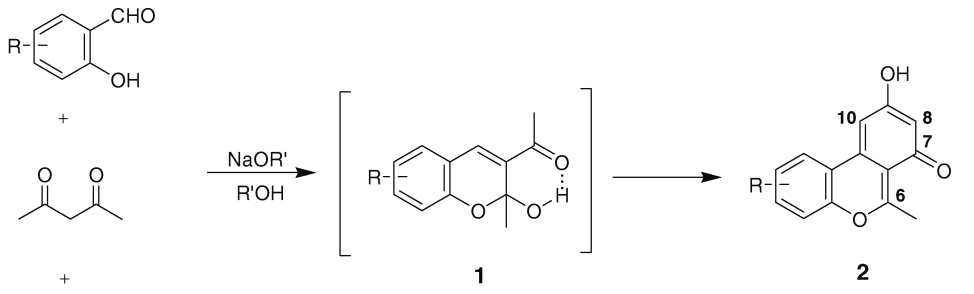
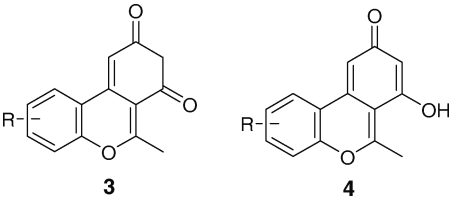


(HS)XCH_2CO_2R' (Me or Et)

a) R = H b) R = 6-OMe c) R = 4-OMe d) R = 3-OMe e) R = 5-Cl f) R = 5-Br

Scheme 1



spectrum of **2a** showed a single sharp line for the methyl group (δ 2.42), broad singlet for the OH proton at δ 6.6 and two doublets in 7.24, 7.26, J = 1.41 Hz for $H_{8,10}$ as well as a multiplet for the phenyl protons at δ 7.48–7.86 (see *Experimental Section*). The ^{1}H NMR spectra of **2b–f** were similar to that of **2a**, except for the signals of OCH_3 and for the changes in the multiplicity of signals of aromatic hydrogen atoms resulting from the presence of the R groups (OCH_3, Cl, Br). The ^{13}C NMR spectrum of **2a** displayed resonances in agreement with its structure, namely a signal for methyl group at δ 27.32 and a signal at δ 200.91 for the carbonyl group. The partial assignments of these resonances are given in the Experimental Section. The ^{13}C NMR spectral data for compounds **2b–f** confirm the proposed structures. The IR spectra of compounds **2a–f** showed a broad absorption for O-H (3348–3533 cm^{-1}) and carbonyl absorptions (1670–1741 cm^{-1}), there were also four sharp C-O absorptions (1022–1028, 1085–1148, 1191–1228, 1261–1280 cm^{-1}) for compounds **2b–d** and three absorptions (1126–1184, 1224–1251, 1248–1282 cm^{-1}) for compounds **2a**, **2e** and **2f**.

The reported procedure is a new modification of the Robinson annulation.[33] In addition, the newly highly functionalized fused 7*H*-benzo[*c*]-chromen-7-ones (**2a–f**) are synthesized by simple and easy approach in high yields. Further investigations of the present method are currently in progress to establish its scope and utility.

Experimental Section

Chemicals and solvents were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification. Column chromatography was performed on silica gel (0.015–0.04 mm, mesh-size) and TLC on precoated plastic sheets ($25DC_{UV\text{-}254}$) respectively. Melting points were measured on Branstead Electrothermal melting point

Table 1
Spectroscopic Data of **2a–f**

Cmpd	^{1}H NMR (δ)	^{13}C NMR (δ)	MS (m/z)
2a	2.42 (3H, s, CH_3) 6.6 (1H, brs, OH) 6.87, 7.48 (2H, 2d, J = 1.41 Hz, $H_{8,10}$), 6.92–7.49 (4H, Ar protons)	27.32 (CH_3) 116.90, 121.29, 122.02, 128.27, 129.90, 132.22, 140.46, 145.16, 156.05, 162.39 (Alkene and Aryl carbons) 200.91 (C = O)	226 (M^+, 30) 211 (M^+-CH_3, 36) 183 (M^+- CH_3CO^+, 100) 166 (M^+-CH_3CO^+, OH, 83), 43 (CH_3CO^+, 56)
2b	2.44 (3H, s, CH3) 3.88 (3H, s, OCH3) 6.26 (H, brs, OH proton) 6.45, 6.63 (2H, 2d, J = 2.35 Hz, H8, 10) 7.71–8.07 (3H, Ar protons)	27.65 (CH3) 59.17 (OCH3) 111.31, 119.42, 120.69, 121.11, 127.25, 137.81, 146.13, 147.74, 153.78 (Alkene and Aryl carbons) 200.19 (C = O)	256 (M+, 31) 241 (M+-CH3, 40) 213 (M+-CH3CO, 81) 183 (M+-CH3OH, CH3CO, 100) 43 (CH3CO+, 89)
2c	2.40 (3H, s, CH3) 3.80 (3H, s, OCH3) 6.07 (H, brs, OH proton) 6.48, 7.38 (2 H, 2d, J = 1.38 Hz, H8, 10) 6.97–7.80 (3H, Ar protons)	27.04 (CH3) 55.88 (OCH3) 100.81, 106.17, 107.62, 113.69, 124.25, 129.91, 130.31, 140.25, 156.95, 161.97 (Alkene and Aryl Carbons), 201.71 (C = O)	256 (M+, 25) 195 (M+-OH, CH_3CO, 48), 183 (M+-CH_3OH, CH_3CO, 72), 43 (CH_3 CO+, 100)
2d	2.39 (3H, s, CH_3) 3.92 (3H, s, OCH_3) 6.15 (1H, brs, OH proton) 6.88, 7.48 (2H, d of d, J = 1.40 Hz, $H_{8,10)}$ 6.92–7.86 (3H, Ar protons)	27.56 (CH_3) 56.61 (OCH_3) 112.36, 120.24, 120.65, 121.18, 128.52, 138.70, 145.75, 147.24, 154.95, 157.64 (Alkene and Aryl carbons), 199.69 (C = O)	256 (M^+, 37) 241 (M^+-CH_3, 45) 213 (M^+-CH_3CO, 78) 183 (M^+-CH_3COH, CH_3CO, 100) 43 (CH_3CO^+, 77)
2e	2.40 (3H, s, CH_3) 6.81 (1H, brs, OH proton) 6.82, 7.20 (2H, d of d, J = 1.57 Hz, $H_{8,10}$) 6.89–7.75 (3H, Ar protons)	27.56 (CH_3) 118.08, 123.15, 124.38, 127.72, 127. 87, 131.26, 138.22, 146.20, 151.05, 155.91 (Alkene and Aryl carbons), 198.94 (C = O)	260, 262 (M^+,M^+ + 2, 31, 10), 217, 219 (M^+, M^+ + 2-CH_3CO, 47,17) 175, 177 (M^+, M^++2 –CH_3, CO-CH=COH, 100, 39), 107 (M^+- CH_3 CO, C_6H_3Cl, 60)

(Continued on next page)

Table 1
Spectroscopic Data of **2a–f** *(Continued)*

Cmpd	^{1}H NMR (δ)	^{13}C NMR (δ)	MS (m/z)
2f	2.28 (3H, s, CH_3) 6.68 (1H,brs, OH) 6.75, 7.17 (2H, 2d, J = 1.66 Hz, $H_{8,10}$), 6.63–7.71 (3H, Ar protons)	27.64 (CH_3) 111.76, 118.61, 123.87, 126.01, 130.85, 134.23, 138.30, 149.92, 156.41 (Alkene and Aryl carbons) 199.20 (C = O)	304, 306 (M^+, M^++2, 35, 31), 261, 263 (M^+, M^++ 2-CH_3CO, 50, 48), 219, 221 (M^+, M^+ +2-CH_3, CO-CH= COH, 100, 98),107 (M^+-CH_3CO, C_6H_3Br, 56)

apparatus and are not corrected. Elemental analysis for C, H and N were performed using a Thermo Finnigan Flash EA1112 instrument. IR spectra were measured on a Shimadzu FT-IR-4300 spectrophotometer as KBr discs. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 500 MHz spectrometer in $CDCl_3$ and DMSO-d_6 solution and chemical shifts were recorded in δ units by using $SiMe_4$ as internal standard. Mass spectra were acquired on a Finnigan-MAT 8430 spectrometer at an ionization potential of 70ev.

9-Hydroxy-6-methyl-7H-benzo[c]chromene-7-ones (2a) from 1. General Procedure.

To a stirred (magnetically stirrer) mixture of 2*H*-chromene (**1a**, 0.40 g, 2 mmol)[31] and ethyl chloroacetate (0.20 mL, 2 mmol) in ethanol (25 mL) or methyl thioglycolate (0.18 mL, 2 mmol) in methanol (25 mL), a solution of sodium (0.09 g, 4 mmol) in

Table 2
Yields, mps and Elemental Analysis of **2a–f**

	Yields (%)							
	From 1		From one-pot				Elemental Analysis (Found)	
Cmpd	A	B	A	B	mp (°C)	Color	C	H
2a	89	87	88	86	127–129	Light yellow	74.33 (74.31)	4.42 (4.40)
2b	92	90	92	91	124–126	Yellow	70.37 (70.35)	4.72 (4.71)
2c	86	86	87	88	123–125	Yellow	70.37 (70.36)	6.02 (5.99)
2d	85	84	84	85	121–123	Pale green	70.37 (70.38)	4.72 (4.70)
2e	91	90	90	90	118–120	Light yellow	64.50 (64.51)	3.47 (3.46)
2f	91	88	89	86	120–122	Pale green	55.11 (55.10)	2.97 (2.94)

A: Yields from ethyl chloroacetate.
B: Yields from methyl thioglycolate.

absolute ethanol or methanol (15 mL) was added dropwise at 0° C over 1 h. The solution was stirred for 24 h and refluxed for 24–48 h; the progress of the reaction was monitored by TLC. When the 2*H*-chromene spot ($R_f = 0.6$ on silica gel, *n*-hexane/ethyl acetate 1:1) had disappeared, the precipitated product was collected and purified by PLC (silica gel, *n*-hexane/ethyl acetate 4:1) and recrystallized in dichloromethane. The product (0.4 g, 89% using ethyl chloroacetate and 0.39 g, 87% using methyl thioglycolate) was obtained as light yellow crystals, mp. 127–129°C. The same procedure was used to prepare **2b–f** in yields of 87–92%.

*9-Hydroxy-6-methyl-7*H-*benzo[c]chromene-7-ones (2a) by One-pot Reaction. General Procedure.*

To a stirred (magnetically stirrer) mixture of 2-hydroxybenzaldehyde derivatives (2 mmol) and 2,4-pentanedione (0.20 mL, 2 mmol) in dichloromethane (10 mL) at −15°C was added two drops of piperidine. The solution was stirred for 5–7 h at −15°C. The reaction mixture was allowed to stand in the refrigerator overnight. Then ethyl chloroacetate (0.20 mL, 2 mmol)/sodium ethoxide (0.09 gr, 4 mmol) in absolute ethanol (15 mL) or methyl thioglycolate (0.18 mL, 2 mmol)/sodium ethoxide (0.09 gr, 4 mmol) in dry methanol (15 mL) were added in this stage and the mixture was stirred at RT for1 h and refluxed for 24–48 hrs. After the reaction was complete, the products were purified as above.

Compound **1e** was not previously described in *ref*. *31* but could be obtained in 92% yield as yellow crystals (dichloromethane), mp. 87–89°C, according to the reported procedure.[31]

IR (KBr): 3412 (OH), 1649, 1623 (C=O), 1271, 1211, 1145 (C-O) cm^{-1}, ^{1}H NMR: δ 1.81, 2.46 (6H, 2s, $2CH_3$), 4.70 (1H, brs, OH), 6.88–6.90 (1H, d, $J = 6.68$ Hz, H_8), 7.21–7.22 (1H, d, $J = 2.35$ Hz, H_5), 7.20–7.30 (1H, d of d, $J = 8.6$ Hz, $J = 2.3$ Hz, H_7), 7.31 (s, 1H, olefinic protons). ^{13}C NMR: δ 27.02, 28.22 ($2CH_3$), 99.48 (^{13}C-OH), 118.80, 120.40, 127.00, 128.48, 133.04, 134.35 (Ar carbons), 134.61 (^{13}CH=C), 151.90 (^{13}C-C=O), 198.60 (C=O), MS: m/z, 238, 240 (M^+, M^++2), 223, 225 (M^+-CH_3), 206, 208 (M^+-CH_3OH), 128 (M^+-Cl, CH_3CO, CH_3OH).

Anal. Calcd. for $C_{12}H_{11}ClO_3$: C, 60.39, H, 4.65. Found: C, 60.38; H, 4.65.

Acknowledgements

We thank Research Council of University of Tehran for the financial support.

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