A Quick and Advantageous Synthesis of 2*H*-1-Benzopyran-2-ones Unsubstituted on the Pyranic Nucleus

George Bratulescu*

Faculty of Chemistry, University of Craiova, 13 A.I. Cuza, 200396 Craiova, Romania
E-mail: georgebratulescu@yahoo.com

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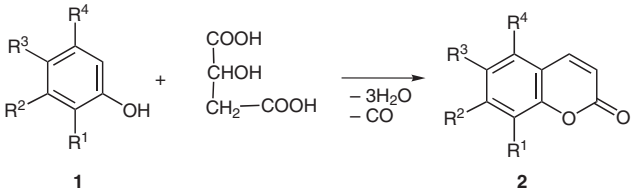
Abstract: The synthesis of 2*H*-1-benzopyran-2-ones (coumarins) unsubstituted on the pyranic nucleus was realized by condensation of malic acid and phenols under mild conditions. A short reaction time, improved yields, good purity of the products, and an easy clean experimental protocol are the advantages of this procedure.

Key words: coumarin, 2*H*-1-benzopyran-2-one, malic acid, phenols, condensation



1 2

Scheme 1

A large number of natural products bear a 2*H*-1-benzopyran-2-one (coumarin) as part of in their structure.[1] 2*H*-1-Benzopyran-2-ones show wide biological activity, e.g. as antioxidants,[2] anticoagulants,[3] antifungal agents,[4] anthelmintic, hypnotic, and cytotoxic agents,[1,5] They are widely used as agrochemicals,[6] additives in cosmetics and food,[5] optical brighteners, and dispersed fluorescent and tunable laser dyes optical agents.[7–10] Therefore, the synthesis of these heterocyclic compounds is of current interest.

2*H*-1-Benzopyran-2-one have been synthesized by several routes, including Perkin,[11,12] von Pechman,[13] Knoevenagel,[14,15] Reformatsky,[16] Wittig,[17] and combined Claisen rearrangement, ring-closing metathesis, and Diels–Alder[18] reactions. These methods all require specific organic or inorganic catalysts, organic solvents, long reaction times, or extensive purification operations to separate the products, which leads to extensive amounts of waste.[2]

Previously, we realized the synthesis of several organic compounds using a chemical paste medium and microwave irradiation.[19,20] In this medium, during microwave irradiation, hot points are created that function like catalytic centers and, hence, chemical reactions take place rapidly.[20]

The synthesis of 2*H*-1-benzopyran-2-ones unsubstituted on the pyranic heterocyclic nucleus constitutes a chemistry challenge because poor yields are frequently obtained.[5,15] Herein we report a new microwave-assisted synthesis of 2*H*-1-benzopyran-2-ones **2** from phenol derivatives **1** and malic acid (Scheme 1, Table 1).

The paste medium like chemical medium was obtained adding a few drops of pyridine. By this method the synthesis of 2*H*-1-benzopyran-2-ones **2a–l** was completed in a shorter time and with improved yields compared to conventional methods; the products were obtained with high purity. Moreover, the workup procedure is simple, the products only need to be recrystallized. These benefits make this method one of the cleanest for 2*H*-1-benzopyran-2-one synthesis.

Table 1 Synthesis of 2*H*-1-Benzopyran-2-ones

Entry	R^1	R^2	R^3	R^4	Temp (°C)	Time (min)	Product	Yield (%)
1	H	H	H	H	103	3	**2a**	68
2	H	H	H	Me	106	3	**2b**	71
3	Cl	H	H	H	114	2.5	**2c**	70
4	Br	H	H	H	111	2.5	**2d**	69
5	H	H	H	Cl	117	2.5	**2e**	84
6	H	H	H	NO_2	118	3	**2f**	62
7	H	Me	Me	H	101	3	**2g**	70
8	Me	H	H	Me	106	3	**2h**	72
9	H	Me	H	Me	104	3	**2i**	73
10	H	OMe	H	H	119	3	**2j**	79
11	H	H	H	OMe	121	3	**2k**	90
12	H	Me	H	OH	123	2.5	**2l**	93

[a] Satisfactory microanalysis obtained: C ±0.04, H ±0.03; **2f** N +0.01.

Malic acid, phenol derivatives, TsOH, and pyridine are commercially available reagents. The synthesized products were identified by TLC (silica gel, MeOH), elemental analysis, ^{1}H NMR, and IR spectra. The melting points were measured using a Böetius melting point apparatus. IR spectra were recorded on KBr disks using a Perkin-Elmer 1600 spectrophotometer. ^{1}H and ^{13}C NMR spectra were obtained in $CDCl_3$ solns with TMS as internal standard on a Bruker ARX 300 MHz spectrometer at 300 MHz (^{1}H) and 100 MHz

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(^{13}C). Elemental analyses were carried out with a Carlo Erba model 1106 apparatus. An Optiquick Y71 microwave device operating at 650 W was employed. The temperature during the microwave irradiation was determined with the help of a Novo Quick digital thermometer.

2*H*-1-Benzopyran-2-one Derivatives 2a–l; General Procedure
To a mixture of malic acid (2 mmol) and phenol derivatives **1** (2 mmol) was added 98% H_2SO_4 (0.7 mmol) in a 25-mL Erlenmeyer flask. A few drops of pyridine were added and the resulting paste was irradiated in a microwave oven (λ = 12.2 cm) for the required time. The resulting residue was purified by recrystallization (EtOH) to give the 2*H*-1-benzopyran-2-one derivatives.

2*H*-1-Benzopyran-2-one (2a)
Mp 70 °C (Lit.[21] 69–70 °C).

IR: 1729 (vs) (C=O), 1260 (s) (C–O^{as}), 1108 cm^{-1} (s) (C–O^{s}).

^{1}H NMR: δ = 6.38 (d, *J* = 9.5 Hz, 1 H, H3), 7.24 (ddd, *J* = 7.7, 7.4, 1.1 Hz, 1 H, H6), 7.31 (dd, *J* = 8.3, 1.1 Hz, 1 H, H8), 7.46 (dd, *J* = 7.7, 1.6 Hz, 1 H, H5), 7.52 (ddd, *J* = 8.3, 7.4, 1.6 Hz, 1 H, H7), 7.71 (d, *J* = 9.5 Hz, 1 H, H3).

^{13}C NMR: δ = 116.5, 116.8, 118.8, 124.4, 127.9, 131.7, 143.4, 153.9, 160.6.

5-Methyl-2*H*-1-benzopyran-2-one (2b)
Mp 82 °C.

IR: 1722 (vs) (C=O), 1254 (s) (C–O^{as}), 1101 cm^{-1} (s) (C–O^{s}).

^{1}H NMR: δ = 2.51 (s, 3 H, CH_3), 6.22 (d, *J* = 9.3 Hz, 1 H, H3), 6.83 (dd, *J* = 8.1, 1.2 Hz, 1 H, H8), 7.08 (dd, *J* = 7.4, 1.2 Hz, 1 H, H6), 7.28 (dd, *J* = 8.1, 7.4 Hz, 1 H, H7), 7.61 (d, *J* = 9.3 Hz, 1 H, H4).

^{13}C NMR: δ = 18.1 (MeO), 114.8, 116, 117.8, 125.9, 131.8, 136.4, 140.5, 154.9, 160.5.

8-Chloro-2*H*-1-benzopyran-2-one (2c)
Mp 146 °C.

IR: 1702 (vs) (C=O), 1221 (s) (C–O^{as}), 1005 cm^{-1} (s) (C–O^{s}).

^{1}H NMR: δ = 6.31 (d, *J* = 9.4 Hz, 1 H, H3), 7.19 (dd, *J* = 7.7, 7.2 Hz, 1 H, H6), 7.47 (dd, *J* = 7.7, 1.2 Hz, 1 H, H5), 7.38 (dd, *J* = 7.2, 1.2 Hz, 1 H, H7), 7.65 (dd, *J* = 9.4 Hz, 1 H, H4).

^{13}C NMR: δ = 113.8, 120.2, 123.9, 125.6, 127.8, 132.1, 143.7, 147.3, 159.5.

8-Bromo-2*H*-1-benzopyran-2-one (2d)
Mp 135 °C.

IR: 1719 (vs) (C=O), 1247 (s) (C–O^{as}), 1024 cm^{-1} (s) (C–O^{s}).

^{1}H NMR: δ = 6.37 (d, *J* = 9.4 Hz, 1 H, H3), 7.24 (dd, *J* = 7.8, 7.2 Hz, 1 H, H6), 7.52 (dd, *J* = 7.8, 1.3 Hz, 1 H, H5), 7.61 (dd, *J* = 7.2, 1.3 Hz, 1 H, H7), 7.72 (d, *J* = 9.4 Hz, 1 H, H4).

^{13}C NMR: δ = 113.5, 124.2, 124.6, 126.1, 129.2, 130.3, 143.4, 146.1, 160.2.

5-Chloro-2*H*-1-benzopyran-2-one (2e)
Mp 91 °C.

IR: 1710 (vs) (C=O), 1239 (s) (C–O^{as}), 1019 cm^{-1} (s) (C–O^{s}).

^{1}H NMR: δ = 6.31 (d, *J* = 9.5 Hz, 1 H, H3), 6.87 (dd, *J* = 8.2, 1.2 Hz, 1 H, H8), 6.94 (dd, *J* = 7.1, 1.2 Hz, 1 H, H6), 7.13 (dd, *J* = 8.2, 7.1 Hz, 1 H, H7), 7.55 (d, *J* = 9.5 Hz, 1 H, H4).

^{13}C NMR: δ = 115.9, 120.6, 125.1, 129.1, 130.8, 132.4, 142.8, 152.3, 160.3.

5-Nitro-2*H*-1-benzopyran-2-one (2f)
Mp 178 °C.

IR: 1741 (vs) (C=O), 1524 (s) (NO_2^{as}), 1327 (vs) (NO_2^{s}), 1277 (s) (C–O^{as}), 1119 cm^{-1} (s) (C–O^{s}).

^{1}H NMR: δ = 6.28 (d, *J* = 9.6 Hz, 1 H, H3), 7.62 (dd, *J* = 7.8, 6.9 Hz, 1 H, H7), 7.71 (dd, *J* = 7.8, 0.9 Hz, 1 H, H8), 7.92 (d, *J* = 9.6 Hz, 1 H, H4), 8.12 (dd, *J* = 6.9, 0.9 Hz, 1 H, H6).

^{13}C NMR: δ = 116.7, 118.6, 123.8, 128.3, 130.7, 143.9, 147.9, 152.1, 160.7.

6,7-Dimethyl-2*H*-1-benzopyran-2-one (2g)
Mp 147 °C.

IR: 1721 (vs) (C=O), 1239 (s) (C–O^{as}), 1110 cm^{-1} (s) (C–O^{s}).

^{1}H NMR: δ = 2.39 (s, 3 H, CH_3), 2.48 (s, 3 H, CH_3), 6.19 (d, *J* = 9.4 Hz, 1 H, H3), 6.98 (s, 1 H, H8), 7.12 (s, 1 H, H5), 7.63 (d, *J* = 9.4 Hz, 1 H).

^{13}C NMR: δ = 16.2 (7-Me), 18.4 (6-Me), 115.9, 119.8, 120.3, 128.1, 134.2, 137.3, 143.7, 148.2, 160.2.

5,8-Dimethyl-2*H*-1-benzopyran-2-one (2h)
Mp 121 °C.

IR: 1719 (vs) (C=O), 1246 (s) (C–O^{as}), 1106 cm^{-1} (s) (C–O^{s}).

^{1}H NMR: δ = 2.49 (s, 3 H, CH_3), 2.31 (s, 3 H, CH_3), 6.23 (d, *J* = 9.4 Hz, 1 H, H3), 7.09 (d, *J* = 7.3 Hz, 1 H, H6), 7.28 (d, *J* = 7.3 Hz, 1 H, H7), 7.63 (d, *J* = 9.4 Hz, 1 H, H4).

^{13}C NMR: δ = 14.3 (8-Me), 18.7 (5-Me), 115.9, 124.9, 128.2, 128.9, 130.2, 133.8, 142.8, 152.5, 160.4.

5,7-Dimethyl-2*H*-1-benzopyran-2-one (2i)
Mp 132 °C.

IR: 1722 (vs) (C=O), 1257 (s) (C–O^{as}), 1103 cm^{-1} (s) (C–O^{s}).

^{1}H NMR: δ = 2.50 (s, 3 H, CH_3), 2.67 (s, 3 H, CH_3), 6.22 (d, *J* = 9.3 Hz, 1 H, H3), 6.87 (d, *J* = 1.1 Hz, 1 H, H6), 7.92 (d, *J* = 1.1 Hz, 1 H, H8), 7.59 (d, *J* = 9.3 Hz, 1 H, H4).

^{13}C NMR: δ = 18.6 (5-Me), 24.4 (7-Me), 115.9, 116.9, 128.1, 128.3, 136.1, 137.2, 143.7, 150.7, 160.8.

7-Methoxy-2*H*-1-benzopyran-2-one (2j)
Mp 117 °C.

IR: 1706 (vs) (C=O), 1233 (vs) (C–O^{as}), 1025 cm^{-1} (vs) (C–O^{s}).

^{1}H NMR: δ = 3.87 (s, 3 H, CH_3), 6.24 (d, *J* = 9.4 Hz, 1 H, H3), 6.80 (d, *J* = 1.4 Hz, 1 H, H8), 6.84 (dd, *J* = 5.8, 1.4 Hz, 1 H, H6), 7.37 (d, *J* = 5.8 Hz, 1 H, H5), 7.64 (d, *J* = 9.4 Hz, 1 H, H4).

^{13}C NMR: δ = 56 (MeO), 104.7, 112.5, 113.1, 114.9, 132.1, 138.2, 154.5, 156.0, 160.6.

5-Methoxy-2*H*-1-benzopyran-2-one (2k)
Mp 82 °C.

IR: 1712 (vs) (C=O), 1240 (s) (C–O^{as}), 1019 cm^{-1} (vs) (C–O^{s}).

^{1}H NMR: δ = 3.82 (s, 3 H, CH_3), 6.23 (d, *J* = 9.3 Hz, 1 H, H3), 6.69 (dd, *J* = 6.9, 1 Hz, 1 H, H6), 6.73 (dd, *J* = 8.1, 1 Hz, 1 H, H8), 7.19 (dd, *J* = 8.1, 6.9 Hz, 1 H, H7), 7.60 (d, *J* = 9.3 Hz, 1 H, H4).

^{13}C NMR: δ = 56.1 (MeO), 104.5, 109.3, 109.9, 114.2, 132.4, 138.9, 154.5, 156.1, 161.6.

5-Hydroxy-7-methyl-2*H*-1-benzopyran-2-one (2l)
Mp 217 °C.

IR: 3154 (m) (OH), 1712 (vs) (C=O), 1251 (s) (C–O^{as}), 1067 cm^{-1} (s) (C–O^{s}).

^{1}H NMR: δ = 2.71 (s, 3 H, CH_3), 6.27 (d, *J* = 9.2 Hz, 1 H, H3), 6.58 (d, *J* = 1.3 Hz, 1 H, H6), 6.67 (d, *J* = 1.3 Hz, 1 H, H8), 7.57 (d, *J* = 9.2 Hz, 1 H, H4), 10.04 (br s, 1 H, OH).

^{13}C NMR: δ = 25.8 (7-Me), 112.7, 113.1, 116.2, 116.8, 140.2, 143.7, 152.6, 159.2, 160.1.

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