An Efficient Synthesis of Flavones from 2-Hydroxybenzoic Acids

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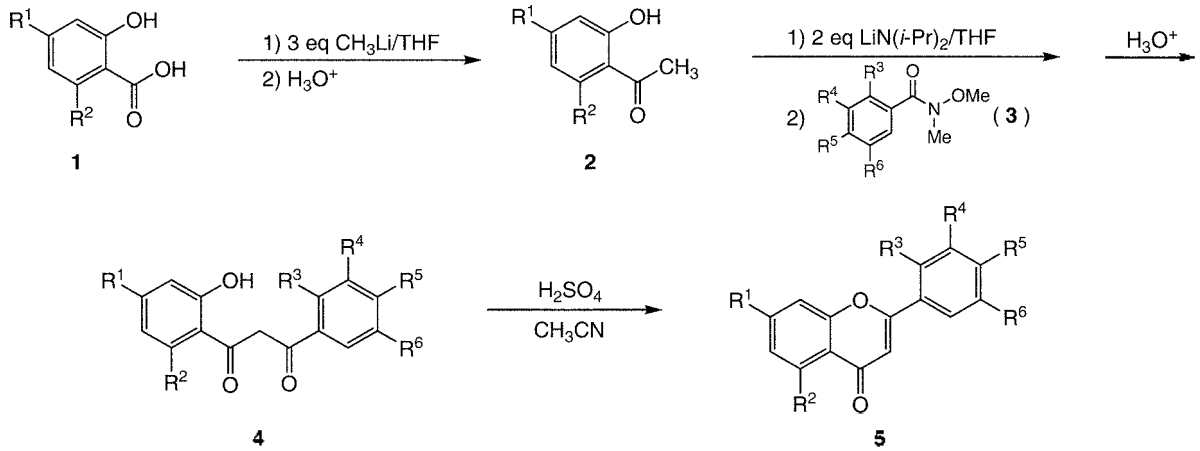
The flavones are a class of naturally occurring compounds that are widely distributed in vascular plants[1] and possess biological activities, such as antioxidant effect, inhibition of HIV-1 proteinase, and anticancer.[2] The general methods to obtain flavones are the cyclization of 1,3-diphenylpropane-1,3-diones or 2'-hydroxychalcones, which are prepared from 2'-hydroxyacetophenones and benzoylating reagents or benzaldehydes.[3] In the Baker-Venkataraman process,[4] 2'-hydroxyacetophenones are converted into benzoyl esters, which are rearranged with bases to form 1,3-diphenylpropane-1,3-diones, followed by cyclization with sodium acetate[4a] or sulfuric acid[4b,c] in acetic acid. I_2-DMSO,[5] and $Co^{III}(salpr)(OH)$[6] to yield flavones in three steps. Although the reaction of 2'-hydroxyacetophenones and benzoyl chlorides[7] or methyl benzoates[8] with bases affords 1,3-diphenylpropane-1,3-diones directy, these methods required excess benzoylating reagents or bases. The oxidative cyclodehydration of 2'-hydroxychalcones with $NiCl_2$/Zn/KI,[9] $NaIO_4$-DMSO,[10] and iodosobenzene diacetate[11] also leads to the formation of flavones, but this process requires high reaction temperature. Other methods to synthesize flavones include the coupling of 2-iodophenols with phenylacetylenes in the presence of secondary amine and $PdCl_2$(dppf).[12] but only a few examples of flavones from these techniques have been reported. An intramolecular Wittig reaction[13] of 2-acetoxyphenacyl bromides and benzoyl chlorides also gives flavones, a four step process from 2'-hydroxyacetophenones.

In the present paper we report that flavones can be efficiently synthesized in two steps *via* 1-(2-hydroxyphenyl)-3-phenylpropane-1,3-diones from 2'-hydroxyacetophenones in high yields. 2'-Hydroxyacetophenones **2**, pivotal starting materials for the synthesis of flavones **5**, were readily prepared by the treatment of 2-hydroxybenzoic acids **1** with 3 equiv of methyllithium in THF for 2 h between 0 °C and room temperature (Scheme 1). The reaction proceeded smoothly without protection of the 2-hydroxy group to give **2** free from tertiary alcohol after acidic hydrolysis (R^1=H, R^2=H; 88%, R^1=H, R^2=OMe; 74%, R^1=OMe, R^2=H; 90%).

The key step in flavones synthesis involves the condensation of the dianion of **2** with benzoylating reagent to give 1-(2-hydroxyphenyl)-3-phenylpropane-1,3-diones **4**. To investigate the optimum reagent for the benzoylation of **2**, we added benzoyl chloride, benzoyl cyanide, and 2-pyridyl benzoate to the lithium dianion at 0 °C, which was generated from 2'-hydroxyacetophenone and 2 equiv of lithium diisopropylamide in THF. 1-(2-Hydroxyphenyl)-3-phenylpropane-1,3-dione was obtained in 44%, 55%, and 53% yield, respectively, with the recovery of 2'-hydroxyaceto-



Scheme 1

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phenone. The moderate yields may be ascribed to the fact that the lithium dianion of 2'-hydroxyacetophenone abstracts an enolic proton of the product. However, the reaction of the lithium dianion of 2'-hydroxyacetophenone with *N*-methoxy-*N*-methylbenzamide[14] proceeded well to give 1-(2- hydroxyphenyl)-3-phenylpropane-1,3-dione in 82% yield after 24 h between 0 °C and room temperature. A 5-membered chelate between the lithium atom and the two oxygen atoms of *N*-methoxy-*N*-methylbenzamide seems to have suppressed the formation of enolic tautomer of the product.

The presence of the 2-hydroxy group in **2** is also requisite for the efficient condensation of **2** with *N*-methoxy-*N*-methylbenzamides **3**. Interestingly, no reaction of the lithium enolate of 2'-methoxyacetophenone with *N*-methoxy-*N*-methylbenzamide proceeded for 24 h at room temperature. This fact is compatible with the result that there was no condensation of the lithium enolate of acetophenone with *N*-methoxy-*N*-methylacetamide even when the mixture was refluxed in THF, whereas the condensation of the lithium dienolate of 1-phenyl-1,3-butanedione with *N*-methoxy-*N*-methylacetamide proceeded smoothly at room temperature.[15] Thus, the condensation of the lithium dianion of **2** with **3** proceeded well by the electron-donating participation of the 2-lithiumoxy group in **2**, producing **4** in 73-90% yields. The ^{1}H NMR analysis of **4** shows that all of products exist as enols or enol-keto tautomeric mixtures.

The cyclization of **4** has been accomplished mostly by heating in glacial acetic acid containing sulfuric acid at 95-100 °C. However, acetic acid is hard to handle because it is corrosive, irritant, and pungent. The cyclization of **4** was carried out using sulfuric acid in acetonitrile and various **5** products were obtained in 95-98% yields within 2 h at room temperature. During the cyclization no side product, such as acetamide, was obtained by the hydrolysis of acetonitrile with dehydrated H_2O. As shown in Table 1, various flavones were obtained in overall high yields (53-78%) from the starting **1**. The present method was generally applicable for the synthesis of **5** having methoxy and chloro substituents on the A- and/or B-ring. Thus, the reaction worked well both for the methoxy substituent (**5e-5h**) on the A-ring and methoxy (**5b**, **5d**, **5f**, **5g**, **5j**) or chloro substituent (**5c**, **5h**) on the B-ring of **5** under the present reaction conditions. Furthermore, the presence of 2-methoxy group (**5i**, **5j**) on the A-ring of **5** did not affect the efficiency of the condensation of **2** with **3** and the cyclization of **4** with sulfuric acid in acetonitrile.

Table 1. Preparation of Flavones from 2-Hydroxybenzoic Acids

Entry **5**	R^1	R^2	R^3	R^4	R^5	R^6	Isolated yield, %[a]
a	H	H	H	H	H	H	70
b	H	H	H	H	OMe	H	66
c	H	H	H	H	Cl	H	72
d	H	H	H	OMe	OMe	OMe	67
e	OMe	H	H	H	H	H	68
f	OMe	H	OMe	H	H	H	59
g	OMe	H	H	H	OMe	H	66
h	OMe	H	H	H	Cl	H	78
i	H	OMe	H	H	H	H	56
j	H	OMe	H	OMe	OMe	H	53

[a]Overall yields of three steps from the starting 2-hydroxybenzoic acids.

Experimental Section

Preparation of 2'-hydroxyacetophenone (General procedure). To a solution of 2-hydroxybenzoic acid (690.6 mg, 5.0 mmol) in THF (20 mL) was slowly added methyllithium (1.5 M in Et_2O, 10.0 mL, 15.0 mmol) at 0 °C. After being stirred for 2 h between 0 °C and room temperature, the mixture was quenched with 0.5 N-HCl (3 mL), and THF was evaporated *in vacuo*. The mixture was poured into 0.5 N-HCl (30 mL) and extracted with methylene chloride (3 × 25 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by vacuum distillation using Kugelrohr apparatus to give 2'-hydroxyacetophenone (599.1 mg, 88%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.27 (s, 1H), 7.74 (dd, J_1 = 8.1 Hz, J_2 = 1.5 Hz, 1H), 7.43-8.00 (m, 1H), 6.98 (dd, J_1 = 8.4 Hz, J_2 = 0.9 Hz, 1H), 6.88-6.94 (m, 1H), 2.64 (s, 3H); FT-IR (film) 3248 (O-H), 3049, 2976, 1642 (C=O), 1487, 1447, 1367, 1244, 754 cm^{-1}; Ms *m/z* (%) 136 (M^+, 54), 122 (8), 121 (100), 93 (18), 65 (16).

Preparation of 1-(2-hydroxyphenyl)-3-phenylpropane-1,3-dione (General procedure). To a solution of 2'-hydroxyacetophenone (544.6 mg, 4.0 mmol) in THF (10 mL) was added lithium diisopropylamide (2.0 M, 4.2 mL, 8.4 mmol) at −15 °C. The stirring was continued for 2 h at this temperature and then a solution of *N*-methoxy-*N*-methylbenzamide (660.8 mg, 4.0 mmol) in THF (8 mL) was added to the yellowish solution. After being stirred for 24 h and allowed to warm to room temperature, the mixture was quenched with 0.5 N-HCl (2 mL). After evaporation of THF, the mixture was poured into 0.5 N-HCl (40 mL), and the aqueous phase was extracted with methylene chloride (3 × 25 mL), and washed with brine (40 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography using 30% EtOAc/*n*-hexane to give 1-(2-hydroxyphenyl)-3-phenylpropane-1,3-dione (788.1 mg, 82%). M.p. 118-120 °C (lit.[6b] 122 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 15.54 (s, 1H), 12.11 (s, 1H), 7.93 (d, J = 8.4 Hz, 2H), 7.78 (dd, J_1 = 8.1 Hz, J_2 = 1.2 Hz, 1H), 7.46-7.55 (m, 4H), 7.00 (d, J = 8.4 Hz, 1H), 6.89-6.95 (m, 1H), 6.84 (s, 1H); FT-IR (KBr) 3435 (O-H), 3064, 1606, 1492, 1298, 1022, 730 cm^{-1}; Ms *m/z* (%) 240 (M^+, 47), 223 (11), 121 (28), 105 (100), 77 (30).

Preparation of flavone 5a (General procedure). To a solution of 1-(2-hydroxyphenyl)-3-phenylpropane-1,3-dione (720.8 mg, 3.0 mmol) in acetonitrile (15 mL) was added *conc.* H_2SO_4 (160 μL, 3.0 mmol) at room temperature. After being stirred for 2 h, acetonitrile was evaporated *in vacuo*. The reaction mixture was poured into sat. $NaHCO_3$ (30 mL), and the aqueous phase was extracted with methylene

chloride (3 × 25 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was washed with *n*-hexane to give **5a** (653.4 mg, 98%). M.p. 96-97 °C (lit.[8b] 96-97 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 (dd, J_1 = 8.1 Hz, J_2 = 1.5 Hz, 1H), 7.92-7.95 (m, 2H), 7.68-7.74 (m, 1H), 7.51-7.59 (m, 4H), 7.40-7.45 (m, 1H), 6.84 (s, 1H); FT-IR (KBr) 3071, 1646 (C=O), 1606, 1466, 1129, 769 cm^{-1}; Ms *m*/*z* (%) 222 (M^-, 100), 221 (37), 194 (51), 120 (44), 92 (31).

4'-Methoxyflavone (5b). M.p. 156-158 °C (lit.[8b] 157-158 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (dd, J_1 = 7.8 Hz, J_2 = 1.5 Hz, 1H), 7.89 (d, J = 9.0 Hz, 2H), 7.66-7.72 (m, 1H), 7.55 (d, J = 7.5 Hz, 1H), 7.39-7.44 (m, 1H), 7.03 (d, J = 9.0 Hz, 2H), 6.75 (s, 1H), 3.90 (s, 3H); FT-IR (KBr) 3050, 2992, 1647 (C=O), 1608, 1465, 1381, 1123, 827 cm^{-1}; Ms *m*/*z* (%) 252 (M^-, 100), 251 (33), 209 (13), 132 (49).

4'-Chloroflavone (5c). M.p. 185-189 °C (lit.[6b] 185-188 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (dd, J_1 = 8.0 Hz, J_2 = 1.5 Hz, 1H), 7.87 (d, J = 8.7 Hz, 2H), 7.69-7.75 (m, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.51 (d, J = 8.7 Hz, 2H), 7.41-7.46 (m, 1H), 6.80 (s, 1H); FT-IR (KBr) 3090, 1641 (C=O), 1606, 1466, 1220, 1090, 828 cm^{-1}; Ms *m*/*z* (%) 258 (M^-+2, 34), 256 (M^-, 100), 230 (14), 228 (41), 120 (57), 92 (33).

3',4',5'-Trimethoxyflavone (5d). M.p. 174-176 °C (lit.[8b] 176 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (dd, J_1 = 8.0 Hz, J_2 = 1.5 Hz, 1H), 7.68-7.74 (m, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.41-7.46 (m, 1H), 7.14 (s, 2H), 6.78 (s, 1H), 3.97 (s, 6H), 3.94 (s, 3H); FT-IR (KBr) 3080, 2943, 1644 (C=O), 1603, 1464, 1126 cm^{-1}; Ms *m*/*z* (%) 312 (M^-, 100), 297 (46), 269 (17), 121 (11).

7-Methoxyflavone (5e). M.p. 103-105 °C (lit.[6b] 104-106 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (d, J = 9.0 Hz, 1H), 7.88-7.91 (m, 2H), 7.48-7.53 (m, 3H), 6.96-6.99 (m, 2H), 6.76 (s, 1H), 3.93 (s, 3H); FT-IR (KBr) 3066, 2944, 1639 (C=O), 1606, 1449, 1375, 1162, 770, 750 cm^{-1}; Ms *m*/*z* (%) 252 (M^-, 100), 224 (45), 209 (57), 150 (22).

2',7-Dimethoxyflavone (5f). M.p. 177-180 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (d, J = 8.7 Hz, 1H), 7.88 (dd, J_1 = 7.8 Hz, J_2 = 1.5 Hz, 1H), 7.44-7.50 (m, 1H), 7.11 (d, J = 7.8 Hz, 1H), 7.07 (s, 1H), 7.04 (d, J = 8.4 Hz, 1H), 6.97 (dd, J_1 = 8.7 Hz, J_2 = 2.4 Hz, 1H), 6.92 (d, J = 2.4 Hz, 1H), 3.93 (s, 3H), 3.92 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.3, 164.0, 160.4, 158.2, 157.9, 132.2, 129.2, 126.9, 121.0, 120.9, 117.7, 114.2, 112.5, 111.7, 100.3, 55.8, 55.6; FT-IR (KBr) 3102, 2963, 1621 (C=O), 1603, 1435, 1251, 1017, 765 cm^{-1}; Ms *m*/*z* (%) 282 (M^-, 86), 239 (15), 151 (100), 132 (16).

4',7-Dimethoxyflavone (5g). M.p. 146-147 °C (lit.[7a] 145 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (d, J = 9.0 Hz, 1H), 7.86 (d, J = 9.0 Hz, 2H), 7.02 (d, J = 9.0 Hz, 2H), 6.95-6.99 (m, 2H), 6.80 (s, 1H), 3.93 (s, 3H), 3.89 (s, 3H); FT-IR (KBr) 3082, 2940, 1645 (C=O), 1605, 1441, 1376, 1267, 1163, 1029 cm^{-1}; Ms *m*/*z* (%) 282 (M^-, 100), 281 (33), 239 (28), 132 (36).

4'-Chloro-7-methoxyflavone (5h). M.p. 172-174 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (d, J = 8.7 Hz, 1H), 7.84 (d, J = 8.7 Hz, 2H), 7.50 (d, J = 8.7 Hz, 2H), 7.00 (dd, J_1 = 9.0 Hz, J_2 = 2.4 Hz, 1H), 6.96 (d, J = 2.1 Hz, 1H), 6.73 (s, 1H), 3.94 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.6, 164.3, 161.8, 157.9, 137.7, 130.3, 129.3, 127.4, 127.1, 117.8, 114.5, 107.7, 100.4, 55.9; FT-IR (KBr) 2903, 1656 (C=O), 1605, 1441, 1374, 1165, 1096 cm^{-1}; Ms *m*/*z* (%) 288 (M^-+2, 35), 286 (M^-, 100), 260 (16), 258 (47), 243 (54), 150 (29).

5-Methoxyflavone (5i). M.p. 126-128 °C (lit.[4b] 128-129 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88-7.91 (m, 2H), 7.57 (dd, J_1 = 8.4 Hz, J_2 = 8.4 Hz, 1H), 7.48-7.53 (m, 3H), 7.14 (d, J = 8.4 Hz, 1H), 6.83 (d, J = 8.4 Hz, 1H), 6.74 (s, 1H), 4.00 (s, 3H); FT-IR (KBr) 3069, 2971, 1633 (C=O), 1474, 1383, 1269, 1098, 755, 675 cm^{-1}; Ms *m*/*z* (%) 252 (M^+, 100), 251 (51), 223 (42), 206 (73), 120 (24).

3',4',5-Trimethoxyflavone (5j). M.p. 204-205 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51-7.59 (m, 2H), 7.34 (s, 1H), 7.13 (d, J = 8.4 Hz, 1H), 6.97 (dd, J_1 = 8.4 Hz, J_2 = 4.2 Hz, 1H), 6.82 (d, J = 8.4 Hz, 1H), 6.67 (s, 1H), 4.00 (s, 3H), 3.97 (s, 3H), 3.95 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.3, 161.0, 159.7, 158.2, 151.8, 149.2, 133.6, 123.9, 119.7, 114.5, 111.1, 110.1, 108.6, 108.0, 106.4, 56.5, 56.1 (overlapped C); FT-IR (KBr) 2941, 1633 (C=O), 1599, 1471, 1260, 1100, 1025 cm^{-1}; Ms *m*/*z* (%) 312 (M^-, 100), 311 (50), 295 (22), 283 (31), 266 (54).

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