A Novel Synthesis of Flavones from 2-Methoxybenzoic Acids

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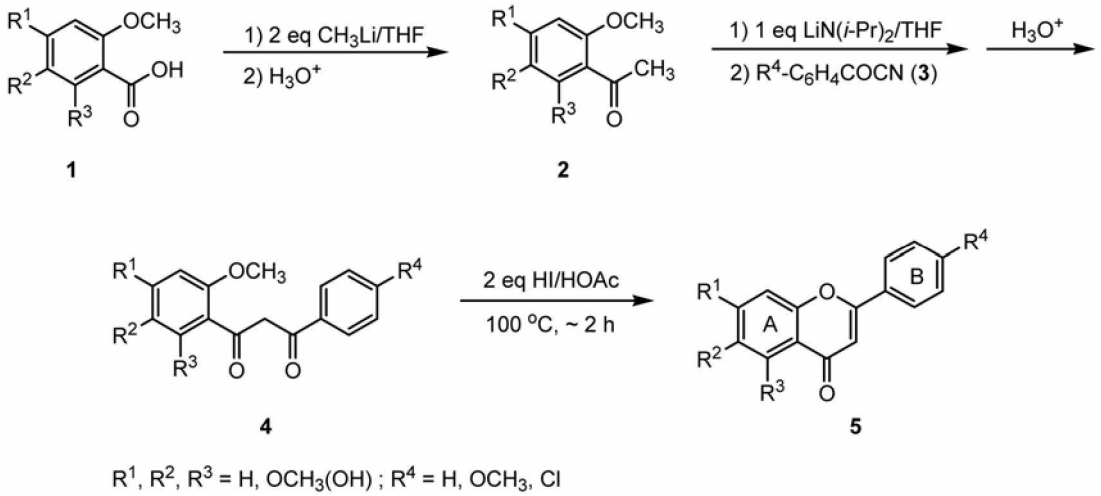
The flavones (2-phenylchromones) are widely distributed in vascular plants[1] and have attracted a lot of attention because they possess biological activities, such as antioxidant effect, antiviral activity, and anticarcinogenic effect.[2] The main synthetic methods known for the flavones are the cyclodehydration of 1-(2-hydroxyphenyl)-3-phenyl-1,3-propanediones, the oxidative cyclization of 2'-hydroxychalcones, and synthesis *via* an intramolecular Wittig reaction.[3] The rearrangement of benzoyl esters of 2'-hydroxyacetophenones (Baker-Venkataraman process[4]) and the direct benzoylation of 2'-hydroxyacetophenones with benzoyl chlorides[5] or methyl benzoates[6] affords 1-(2-hydroxyphenyl)-3-phenyl-1,3-propanediones, which are cyclodehydrated to give flavones in acidic conditions. The treatment of 2'-hydroxychalcones which are prepared from 2'-hydroxyacetophenones and benzaldehydes in the presence of 2 equiv of lithium diisopropylamide with oxidizing agents also affords flavones at high temperature.[7] Alternatively Wittig reaction[8] involves the intramolecular olefination of phosphoranes obtained from triphenylphosphine and 2-acetoxyphenacyl bromides, a four step process from 2'-hydroxyacetophenones. A common feature in all these methods is that they invariably use 2'-hydroxyacetophenones as the starting material.

However, there are no reports of the synthesis of flavones from 2'-methoxyacetophenones. Although 1-(2-methoxyphenyl)-3-methyl-1,3-propanedione is cyclized with boiling HI to give 2-methylchromone, the scope of the reaction is not fully investigated and there are no reports on the synthesis of flavones with 2-substituted phenyl group.[9] Furthermore, it has been reported that the condensation of 2'-methoxyacetophenone with methyl 2-methoxybenzoate using sodium or sodium hydride failed to produce the corresponding 1,3-diketone.[10]

As part of our continuing studies of flavonoids,[11] we report that flavones can be newly synthesized in two steps *via* 1-(2-methoxyphenyl)-3-phenyl-1,3-propanediones from 2'-methoxyacetophenones cheaper than 2'-hydroxyacetophenones in general. 2'-Methoxyacetophenones **2** were readily prepared by the treatment of 2-methoxybenzoic acids **1** with 2 equiv of methyllithium in THF for 2 h at −78 °C (Scheme 1). The reaction proceeded smoothly to give **2** free from the corresponding tertiary alcohols after acidic hydrolysis (R^1, R^2, R^3=H; 92%, R^1=OCH_3, R^2, R^3=H; 93%, R^1, R^3=H, R^2=OCH_3; 88%). However, the reaction of 2,6-dimethoxybenzoic acid with methyllithium proceeded sluggish due to the steric effect and thus 2',6'-dimethoxyacetophenone was prepared by the treatment of *N*-methoxy-*N*-methyl 2,6-dimethoxybenzamide with methyl magnesium bromide at room temperature in 75% yield.

The key intermediates, 1-(2-methoxyphenyl)-3-phenyl-1,3-propanediones **4**, for the synthesis of flavones **5** were readily prepared by the condensation of the lithium enolates of **2** with benzoyl cyanides. To find out the optimum reagent



1 **2** **4** **5**

R^1, R^2, R^3 = H, OCH_3(OH) ; R^4 = H, OCH_3, Cl

Scheme 1

for the benzoylation of **2**, benzoyl chloride, 2-pyridyl benzoate, and benzoyl cyanide were added to the lithium enolate solution in THF at −78 °C, which was generated from 2'-methoxyacetophenone and 1 equiv of lithium diisopropylamide for 2 h at −20 °C. The resulting yellow solution was allowed to warm to room temperature and 1-(2-methoxyphenyl)-3-phenyl-1,3-propanedione was obtained in 63%, 51%, 94% yield, respectively, after chromatographic separation. The condensation of the lithium enolate of **2** with **3** worked well regardless of the kind of substituents (methoxy, chloro) on both 2'-methoxyacetophenones and benzoyl cyanides under the present reaction conditions and **4** were obtained in high yields (80-95%). The ^{1}H NMR spectra of **4** showed the presence of enolic OH (δ 16.00-16.20) together with the vinyl protons (δ 7.09-7.20) and also indicated that enols are major tautomers in all of products.

The cyclization of **4** was successfully accomplished by heating with hydriodic acid in glacial acetic acid. The initial cyclization of 1-(2-methoxyphenyl)-3-phenyl-1,3-propanedione with sulfuric acid, hydrobromic acid, and hydriodic acid in acetonitrile didn't proceed at room temperature. However, the cyclization accompanied by the cleavage of the 2-methoxy group of 1-(2-methoxyphenyl)-3-phenyl-1,3-propanedione with 47% HI proceeded well in glacial acetic acid for 1.5 h at 100 °C to afford flavone in 78% yield. The use of 48% HBr was also effective, but the yield of flavone was decreased to 55%.

As shown in Table 1, various flavones were synthesized in overall high yields (47-67%) from the starting 2-methoxybenzoic acids. 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 (**5d-5g**) on the A-ring and the methoxy (**5b**, **5e**) or chloro substituent (**5c**, **5f**) on the B-ring of **5**. During the cyclization 6 or 7-methoxy group of A-ring and 4'-methoxy group of B-ring were not cleaved under the present reaction conditions. However, the treatment of 1-(2,6-dimethoxyphenyl)-3-(4'-chlorophenyl)-1,3-propanedione with 47% HI in glacial acetic acid at reflux resulted in the cleavage of the two methoxy groups and the successive cyclization to produce 5-hydroxy-4'-chloroflavone (**5h**) in 85% yield.

Table 1. Preparation of Flavones from 2-Methoxybenzoic Acids

Entry 5	R^1	R^2	R^3	R^4	Isolated yield, %[a]
a	H	H	H	H	67
b	H	H	H	OMe	55
c	H	H	H	Cl	63
d	OMe	H	H	H	66
e	OMe	H	H	OMe	47
f	OMe	H	H	Cl	53
g	H	OMe	H	H	54
h	H	H	OH	Cl	51

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

In conclusion, the present method provides some advantages over previous methods using 2'-hydroxyacetophenone derivatives with respect to (i) the cheapness of 2'-methoxyacetophenone derivatives in general (ii) the use of 1 equiv of lithium diisopropylamide for the benzoylation of **2** (iii) the high yield synthesis of **4** using benzoyl cyanides.

Experimental Section

Preparation of 2',4'-dimethoxyacetophenone (General procedure). To a solution of 2,4-dimethoxybenzoic acid (819.8 mg, 4.5 mmol) in THF (18 mL) was slowly added methyllithium (1.5 M in Et_2O, 6.0 mL, 9.0 mmol) under argon atmosphere at −78 °C. After being stirred for 1 h, 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), extracted with methylene chloride (3 × 25 mL), and washed with sat. $NaHCO_3$ (30 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by vacuum distillation using Kugelrohr apparatus to give 2',4'-dimethoxyacetophenone (754.1 mg, 93%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, J = 8.7 Hz, 1H), 6.49 (dd, J_1 = 8.7 Hz, J_2 = 2.3 Hz, 1H), 6.43 (d, J = 2.3 Hz, 1H), 3.86 (s, 3H), 3.82 (s, 3H), 2.56 (s, 3H); FT-IR (film) 3004, 2943, 1661 (C=O), 1598, 1465, 1358, 1269, 1027, 827, 734 cm^{-1}; Ms *m/z* (%) 180 (M^+, 61), 166 (29), 165 (100), 135 (14), 107 (22), 92 (15), 77 (18).

Preparation of 1-(2,4-dimethoxyphenyl)-3-phenyl-1,3-propanedione (General procedure). To a solution of 2',4'-dimethoxyacetophenone (630.7 mg, 3.5 mmol) in THF (12 mL) was added lithium diisopropylamide (2.0 M, 1.8 mL, 3.6 mmol) under argon atmosphere at −20 °C. The stirring was continued for 2 h at this temperature and a solution of benzoyl cyanide (459.0 mg, 3.5 mmol) in THF (6 mL) was added at −78 °C. After being stirred for 2 h between −78 °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), extracted with methylene chloride (3 × 25 mL), and washed with brine (30 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography using 30% EtOAc/*n*-hexane to give 1-(2,4-dimethoxyphenyl)-3-phenyl-1,3-propanedione (915.5 mg, 92%). M.p. 37-40 °C; ^{1}H NMR (300 MHz, $CDCl_3$) enolic form δ 16.20 (s, 1H), 8.01 (d, J = 8.4 Hz, 1H), 7.94-7.97 (m, 2H), 7.47-7.50 (m, 3H), 7.18 (s, 1H), 6.60 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H), 6.52 (d, J = 2.4 Hz, 1H), 3.95 (s, 3H), 3.88 (s, 3H); FT-IR (KBr) 3061, 3004, 2967, 1607, 1504, 1277, 1026, 775 cm^{-1}; Ms *m/z* (%) 284 (M^+, 20), 253 (81), 207 (49), 165 (100), 138 (25), 105 (16), 77 (20).

Preparation of 7-methoxyflavone 5d (General procedure). A solution of 1-(2,4-dimethoxyphenyl)-3-phenyl-1,3-propanedione (852.9 mg, 3.0 mmol) and hydriodic acid (47 wt.% in H_2O, 1.09 mL, 6.0 mmol) in glacial acetic acid (12 mL) was refluxed for 1.5 h at 100 °C. After evaporation of

acetic acid, the mixture was poured into sat. $NaHCO_3$ (30 mL), and the aqueous phase was extracted with methylene chloride (3 × 20 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 40% EtOAc/*n*-hexane to give **5d** (583.0 mg, 77%). M.p. 109-111 °C (lit.[7a] 110-112 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ8.11 (d, J = 8.7 Hz, 1H), 7.87-7.90 (m, 2H), 7.48-7.52 (m, 3H), 6.95-6.98 (m, 2H), 6.74 (s, 1H), 3.92 (s, 3H); FT-IR (KBr) 3065, 2985, 1641 (C=O), 1439, 1163, 770 cm^{-1}; Ms *m/z* (%) 252 (M^+, 100), 224 (42), 209 (55), 150 (22), 122 (19).

Flavone (5a). M.p. 95-96 °C (lit.[7c] 97-98 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ8.24 (dd, J_1 = 7.8 Hz, J_2 = 1.5 Hz, 1H), 7.91-7.95 (m, 2H), 7.68-7.73 (m, 1H), 7.52-7.59 (m, 4H), 7.41-7.45 (m, 1H), 6.83 (s, 1H); FT-IR (KBr) 3054, 1644 (C=O), 1422, 1129, 769 cm^{-1}; Ms *m/z* (%) 222 (M^+, 100), 221 (36), 194 (46), 120 (48), 92 (30).

4'-Methoxyflavone (5b). M.p. 158-159 °C (lit.[4b] 158-160 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ8.23 (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), 7.57 (d, J = 8.4 Hz, 1H), 7.39-7.44 (m, 1H), 7.03 (d, J = 9.0 Hz, 2H), 6.76 (s, 1H), 3.90 (s, 3H); FT-IR (KBr) 3050, 2992, 1641 (C=O), 1607, 1466, 1376, 837 cm^{-1}; Ms *m/z* (%) 252 (M^+, 100), 251 (33), 207 (31), 132 (51).

4'-Chloroflavone (5c). M.p. 185-187 °C (lit.[4b] 185-188 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ8.24 (dd, J_1 = 8.0 Hz, J_2 = 1.5 Hz, 1H), 7.86 (d, J = 8.7 Hz, 2H), 7.69-7.74 (m, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.51 (d, J = 8.7 Hz, 2H), 7.41-7.45 (m, 1H), 6.79 (s, 1H); FT-IR (KBr) 3090, 1645 (C=O), 1606, 1467, 1095, 834 cm^{-1}; Ms *m/z* (%) 258 (M^++2, 34), 256 (M^+, 100), 230 (14), 228 (41), 120 (57), 92 (33).

4',7-Dimethoxyflavone (5e). M.p. 143-144 °C (lit.[7a] 142-143 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ8.13 (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), 6.69 (s, 1H), 3.93 (s, 3H), 3.89 (s, 3H); FT-IR (KBr) 3080, 2940, 1641 (C=O), 1606, 1422, 1376, 1163 cm^{-1}; Ms *m/z* (%) 282 (M^+, 100), 281 (35), 239 (29), 132 (35).

4'-Chloro-7-methoxyflavone (5f). M.p. 171-173 °C (lit.[11] 172-174 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ8.13 (d, J = 8.7 Hz, 1H), 7.84 (d, J = 8.7 Hz, 2H), 7.49 (d, J = 8.7 Hz, 2H), 6.99 (dd, J_1 = 8.7 Hz, J_2 = 2.1 Hz, 1H), 6.95 (d, J = 2.1 Hz, 1H), 6.73 (s, 1H), 3.94 (s, 3H); FT-IR (KBr) 2986, 1656 (C=O), 1607, 1439, 1374, 1163, 837 cm^{-1}; Ms *m/z* (%) 288 (M^++2, 34), 286 (M^+, 100), 260 (14), 258 (42), 243 (51), 207 (31), 150 (30).

6-Methoxyflavone (5g). M.p. 161-163 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ7.91-7.94 (m, 2H), 7.50-7.61 (m, 5H), 7.26-7.32 (m, 1H), 6.83 (s, 1H), 3.92 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.7, 163.5, 157.4, 151.4, 132.2, 131.9, 129.4, 126.6, 124.9, 124.2, 119.9, 107.2, 105.2, 56.3; FT-IR (KBr) 3060, 2945, 1640 (C=O), 1485, 1362, 1030 cm^{-1}; Ms *m/z* (%) 252 (M^+, 100), 251 (83), 222 (25), 150 (39), 107 (18).

5-Hydroxy-4'-chloroflavone (5h). M.p. 190-191 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.50 (s, 1H), 7.84 (d, J = 8.8 Hz, 2H), 7.54 (dd, J_1 = 8.4 Hz, J_2 = 8.3 Hz, 1H), 7.50 (d, J = 8.8 Hz, 2H), 6.99 (dd, J_1 = 8.4 Hz, J_2 = 0.8 Hz, 1H), 6.82 (dd, J_1 = 8.3 Hz, J_2 = 0.8 Hz, 1H), 6.70 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ183.8, 163.7, 161.2, 156.7, 138.8, 135.9, 130.0, 129.9, 128.1, 112.0, 111.2, 107.4, 106.5; FT-IR (KBr) 3434 (OH), 3075, 1659 (C=O), 1621, 1265, 1113, 830, 746 cm^{-1}; Ms *m/z* (%) 274 (M^++2, 34), 272 (M^+, 100), 244 (14), 136 (55), 108 (55), 77 (12).

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