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단 신

2'-하이드록시아세토페논으로부터 고리-A 하이드록시플라본의 효과적 합성

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An Efficient Synthesis of Ring-A Hydroxylated Flavones from 2'-Hydroxyacetophenones

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INTRODUCTION

The hydroxylated flavones (2-phenyl-4*H*-1-benzopyran-4-ones) are found naturally in plant tissues of berries, apple skins, celery, and red pepper and also widely consumed in dietary supplements by humans.[1] The ring-A hydroxylated flavones have attracted special attention due to biological activities such as antioxidative effect, potent inhibitor of cell proliferation, and chemotherapy of a retrovirus-associated human disease.[2] Currently some methods available for the synthesis of ring-A hydroxylated flavones have been developed.[3] The reaction of resacetophenone with benzoic anhydrides in the presence of potassium carbonate at reflux, followed by hydrolysis to afford hydroxyflavones, but the desired products are obtained in low to moderate yields with the corresponding coumarins as side products.[4] Although the direct synthesis of 5,7-dihydroxyflavones is accomplished by the microwave-assisted cyclocondensation of phloroglucinol with an excess of ethyl benzoylacetates at 240 °C, this method is limited to the symmetric phenol such as phloroglucinol.[5] The condensation of polylithiated enolates, generated from hydroxylated acetophenones and an excess of lithium diisopropylamide, with benzoyl chlorides or methyl benzoates gives the 1,3-diketone intermediates, which are cyclodehydrated with sulfuric acid in HOAc to afford hydroxyflavones.[6] 1,3-Diketones are also prepared by the reaction of 2'-hydroxyacetophenones and benzoyl chlorides with potassium carbonate using phase transfer catalyst[7] or the rearrangement of 2-acetylphenyl benzoates with bases such as KOH in pyridine[8] and K_2CO_3 in acetone,[9] but the former requires an excess of benzoyl chlorides and the latter proceeds in moderate yields or requires prolonged reaction time. The oxidative cyclization of 2'-hydroxychalcones, derived from the condensation of 2'-hydroxyacetophenones with benzaldehydes or the acylation of methoxy substituted phenols with cinnamoyl chloride, with $PhI(OAc)_2$/KOH in CH_3OH,[10] I_2-triethylene glycol,[11] and DDQ in toluene/dioxane[12] affords hydroxyflavones at high temperature. An alternative method includes the

Wittig olefination, in which phosphoranes, derived from *o*-hydroxyphenacyl chloride or *o*-benzoyloxyphenacyl bromide and triphenylphosphine, are condensed with benzoyl chlorides to afford hydroxyflavones after saponification in multiple steps from 2'-hydroxyacetophenones.[13] As part of our continuing studies of flavonoids,[14] we report an efficient synthesis of ring-A hydroxylated flavones by the concomitant cyclodehydration/hydrolysis of 1-(2-hydroxyphenyl)-3-phenyl-1,3-propanediones, derived from 2'-aroyloxyacetophenones and lithium diisopropylamide under mild conditions, with aq HBr in overall high yields.

EXPERIMENTAL

Preparation of 2',4'-di(benzoyloxy)acetophenone 3a <typical procedure>. To a solution of 2',4'-dihydroxyacetophenone (761 mg, 5.0 mmol) in methylene chloride (30 mL) was added triethylamine (1.42 mL, 10.2 mmol) and benzoyl chloride (1.41 g, 10.0 mmol) at 0 °C. After being stirred for 0.5 h between 0 °C and room temperature, the mixture was poured into saturated $NaHCO_3$ solution (40 mL) and extracted with methylene chloride (3 × 25 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography using 30% EtOAc/*n*-hexane as an eluant to afford **3a** (1.76 g, 98%), mp 80 °C (lit.[9] 80-81 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18-8.23 (m, 4H), 7.97 (d, J = 8.6 Hz, 1H), 7.64-7.69 (m, 2H), 7.49-7.56 (m, 4H), 7.29 (dd, J_1 = 8.6 Hz, J_2 = 2.2 Hz, 1H), 7.23 (d, J = 2.2 Hz, 1H), 2.56 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.3, 164.8, 164.3, 154.3, 150.4, 134.1, 134.0, 131.5, 130.4, 129.0, 128.8 (overlapped), 128.7, 128.3, 119.5, 117.7, 29.9; FT-IR (KBr) 3114, 1745 (COO), 1670 (C=O), 1599, 1450, 1358, 1241, 1050, 823, 703 cm^{-1}; MS *m/z* (%) 360 (M^+, 54), 106 (42), 105 (100), 77 (95).

Preparation of 1-(2-hydroxy-4-benzoyloxy)-3-phenyl-1,3-propanedione 4a <typical procedure>. To a solution of **3a** (1.44 g, 4.0 mmol) in THF (20 mL) was slowly added lithium diisopropylamide (2.0 M, 4.0 mL, 8.0 mmol) at -15 °C under argon atmosphere. After being stirred for 0.5 h between -15 °C and 0 °C, the resulting yellow mixture was quenched with 1 N-HCl (5 mL) and THF was evaporated *in vacuo*. The mixture was poured into 0.5 N-HCl (40 mL), 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 recrystallized twice in 20% EtOAc/*n*-hexane to afford **4a** (1.23 g, 85%) as a yellow solid, mp 164-165 °C (lit.[9] 167-169 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 15.50 (s, 1H), 12.40 (s, 1H), 8.17-8.23 (m, 2H), 7.94-7.97 (m, 2H), 7.86 (d, J = 8.8 Hz, 1H), 7.64-7.69 (m, 1H), 7.47-7.57 (m, 5H), 6.91 (d, J = 2.3 Hz, 1H), 6.85 (dd, J_1 = 8.8 Hz, J_2 = 2.3 Hz, 1H), 6.81 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.8, 177.5, 164.4, 164.0, 156.6, 134.0, 133.5, 132.5, 130.3, 129.8, 129.0, 128.8, 128.7, 126.9, 116.9, 113.2, 111.7, 92.3; FT-IR (KBr) 3060, 1742 (COO), 1625, 1589, 1241, 1208, 1140, 775, 698 cm^{-1}; MS *m/z* (%) 360 (M^-, 15), 106 (8), 105 (100), 77 (32).

Preparation of 7-hydroxyflavone 5a <typical procedure>. A solution of **4a** (1.08 g, 3.0 mmol) and hydrobromic acid (48 wt % in H_2O, 680 μL, 6.0 mmol) in glacial acetic acid (15 mL) was heated for 12 h at 80 °C. After evaporation of acetic acid, the mixture was poured into saturated $NaHCO_3$ solution (40 mL) and extracted with methylene chloride (3 × 20 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was recrystallized twice from 10% EtOAc/*n*-hexane to give **5a** (636 mg, 89%) as a pale yellow solid, mp 242-243 °C (lit.[6a] 241-243 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.90 (s, 1H), 8.05-8.10 (m, 2H), 7.91 (d, J = 8.7 Hz, 1H), 7.56-7.62 (m, 3H), 7.03 (d, J = 2.2 Hz, 1H), 6.95 (dd, J_1 = 8.7 Hz, J_2 = 2.2 Hz, 1H), 6.91 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 176.4, 162.7, 161.9, 157.4, 131.5, 131.2, 129.0, 126.5, 126.1, 116.1, 115.0, 106.5, 102.5; FT-IR (KBr) 3058, 1632 (C=O), 1609, 1388, 1263, 841, 685 cm^{-1}; MS *m/z* (%) 238 (M^-, 100), 237 (24), 210 (80), 136 (31), 108 (21).

7-Hydroxy-4'-methoxyflavone (5b): mp 261-263 °C (lit.[7] 264 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.81 (s, 1H), 8.02 (d, J = 8.9 Hz, 2H), 7.87 (d, J = 8.7 Hz, 1H), 7.11 (d, J = 8.9 Hz, 2H), 6.99 (d, J = 2.1 Hz, 1H), 6.91 (dd, J_1 = 8.7 Hz, J_2 = 2.2 Hz, 1H), 6.80 (s, 1H), 3.85 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 176.7, 163.0, 162.4, 162.3, 157.7, 128.3, 126.8, 123.8, 116.4, 115.2, 114.9, 105.5, 102.9, 55.8; FT-IR (KBr) 3107, 2969, 1622 (C=O), 1593, 1454, 1386, 1313, 1175, 1095, 815 cm^{-1}; MS m/z (%) 268 (M$^+$, 100), 267 (34), 240 (18), 225 (19), 132 (43).

7-Hydroxy-3',4',5'-trimethoxyflavone (5c): mp 280-281 °C (lit.[6a] 279-280 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.50 (s, 1H), 7.87 (d, J = 8.7 Hz, 1H), 7.33 (s, 2H), 7.04 (d, J = 2.1 Hz, 1H), 6.99 (s, 1H), 6.92 (dd, J_1 = 8.7 Hz, J_2 = 2.2 Hz, 1H), 3.91 (s, 6H), 3.74 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 176.8, 163.2, 162.1, 157.8, 153.6, 140.7, 127.0, 126.8, 116.4, 115.4, 106.9, 104.2, 103.1, 60.5, 56.6; FT-IR (KBr) 3054, 2997, 1629 (C=O), 1584, 1501, 1450, 1387, 1243, 1120, 1095, 826 cm^{-1}; MS m/z (%) 328 (M$^-$, 100), 313 (40), 257 (10), 137 (10).

6-Hydroxy-4'-chloroflavone (5d): mp 275-276 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.25 (s, 1H), 8.11 (d, J = 8.7 Hz, 2H), 7.65 (d, J = 8.9 Hz, 1H), 7.64 (d, J = 8.7 Hz, 2H), 7.32 (d, J = 2.9 Hz, 1H), 7.27 (dd, J_1 = 8.9 Hz, J_2 = 3.0 Hz, 1H), 7.00 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 177.4, 161.4, 155.4, 149.6, 136.8, 130.6, 129.5, 128.4, 124.5, 123.6, 120.2, 107.8, 106.5; FT-IR (KBr) 3050, 1641 (C=O), 1595, 1474, 1359, 1228, 1094, 912, 827 cm^{-1}; MS m/z (%) 274 (M$^+$+2, 30), 272 (M$^+$, 87), 244 (5), 136 (100), 108 (14).

6-Hydroxy-4'-methoxyflavone (5e): mp 249-250 °C (lit.[13a] 250 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.01 (s, 1H), 8.04 (d, J = 9.0 Hz, 2H), 7.64 (d, J = 9.0 Hz, 1H), 7.32 (d, J = 3.0 Hz, 1H), 7.25 (dd, J_1 = 9.0 Hz, J_2 = 3.0 Hz, 1H), 7.12 (d, J = 9.0 Hz, 2H), 6.87 (s, 1H), 3.86 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 177.2, 162.6, 162.3, 155.1, 149.6, 128.4, 124.5, 123.8, 123.2, 120.1, 114.9, 107.9, 104.9, 55.9; FT-IR (KBr) 3047, 2942, 1638 (C=O), 1599, 1472, 1359, 1265, 1183, 1019, 821 cm^{-1}; MS m/z (%) 268 (M$^+$, 100), 267 (21), 237 (5), 136 (44), 132 (36).

5-Hydroxyflavone (5f): mp 159-160 °C (lit.[7] 159 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.58 (s, 1H), 7.89-7.95 (m, 2H), 7.50-7.58 (m, 4H), 7.01 (dd, J_1 = 8.4 Hz, J_2 = 0.8 Hz, 1H), 6.82 (dd, J_1 = 8.3 Hz, J_2 = 0.6 Hz, 1H), 6.75 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.6, 164.6, 160.8, 156.5, 135.4, 132.1, 131.2, 129.1, 126.4, 111.5, 110.9, 107.1, 106.1; FT-IR (KBr) 3059, 1654 (C=O), 1613, 1450, 1225, 1078, 843, 752, 675 cm^{-1}; MS m/z (%) 238 (M$^+$, 100), 210 (17), 136 (34), 108 (28).

5-Hydroxy-4'-chloroflavone (5g): mp 188-189 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.50 (s, 1H), 7.86 (d, J = 8.7 Hz, 2H), 7.56 (dd, J_1 = 8.4 Hz, J_2 = 8.3 Hz, 1H), 7.52 (d, J = 8.7 Hz, 2H), 7.00 (d, J = 8.4 Hz, 1H), 6.83 (d, J = 8.3 Hz, 1H), 6.71 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.9, 163.8, 161.2, 156.7, 138.8, 136.0, 130.0, 129.9, 128.1, 112.1, 111.2, 107.4, 106.6; FT-IR (KBr) 3074, 1658 (C=O), 1619, 1475, 1265, 1094, 830, 746 cm^{-1}; MS m/z (%) 274 (M$^+$+2, 46), 272 (M$^+$, 100), 244 (9), 136 (36), 108 (26).

5,7-Dihydroxyflavone (5h): mp 275-277 °C (lit.[7] 273-274 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.85 (s, 1H), 10.94 (s, 1H), 8.03-8.10 (m, 2H), 7.53-7.66 (m, 3H), 6.98 (s, 1H), 6.53 (d, J = 2.0 Hz, 1H), 6.24 (d, J = 2.0 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 187.5, 170.0, 168.7, 167.0, 163.0, 137.6, 136.3, 134.7, 132.0, 110.7, 109.6, 104.6, 99.7; FT-IR (KBr) 3018, 1653 (C=O), 1612, 1577, 1498, 1358, 1168, 1032, 840, 781, 691 cm^{-1}; MS m/z (%) 254 (M$^-$, 100), 226 (21), 152 (16), 124 (14).

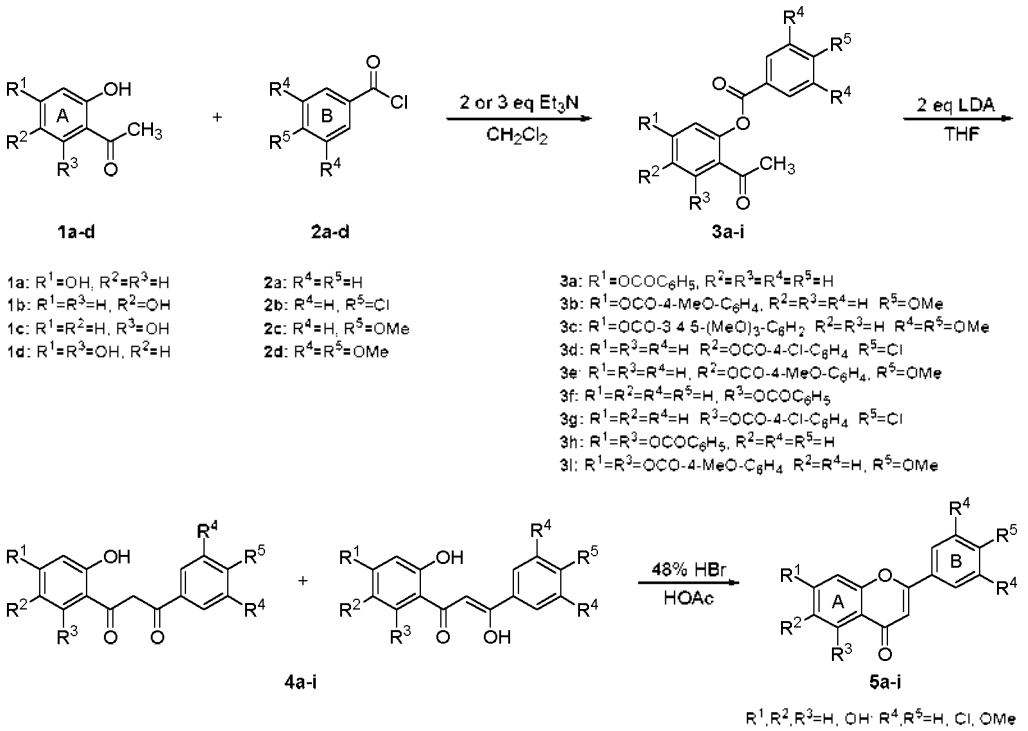
5,7-Dihydroxy-4'-methoxyflavone (5i): mp 263-265 °C (lit.[6a] 260-261 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.94 (s, 1H), 10.89 (s, 1H), 8.02 (d, J = 9.0 Hz, 2H), 7.10 (d, J = 9.0 Hz, 2H), 6.86 (s, 1H), 6.50 (d, J = 2.1 Hz, 1H), 6.21 (d, J = 2.1 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 182.1, 164.5, 163.6, 162.6, 161.8, 157.7, 128.6, 123.1, 114.9, 104.1, 103.8, 99.2, 94.4, 55.9; FT-IR (KBr) 3020, 1650 (C=O), 1608, 1510, 1430, 1369, 1165, 1033, 824, 759 cm^{-1}; MS m/z (%) 284 (M$^-$, 100), 283 (14), 256 (5), 241 (14), 132 (19).

RESULTS AND DISCUSSION

The *O*-aroylation of hydroxylated acetophenones **1a-d** with 2 or 3 equiv of aroyl chlorides **2a-d** in the presence of triethylamine proceeded readily in methylene chloride for 0.5-1 h between 0 °C and room temperature. After usual workup, the residue was subjected to silica gel chromatography to give 2'-aroyloxyacetophenones **3a-i** as colorless solids in 92-98% yields (*Scheme* 1).

The key step in ring-A hydroxylated flavone syntheses involves the intramolecular rearrangement of **3** to 1-(2-hydroxyphenyl)-3-phenyl-1,3-propanediones **4**. The rearrangement of 2',4'-di(benzoyloxy)acetophenone **3a** to 1-(2-hydroxyphenyl)-3-phenyl-1,3-propanedione **4a** was attempted by the treatment of **3a** with 2 equiv of lithium diisopropylamide in THF. The reaction proceeded rapidly between -15 °C and 0 °C and **4a** was obtained in 85% yield after 0.5 h. However, the reaction using 1 equiv of lithium diisopropylamide was not completed even after 24 h at room temperature. It seems that additive equimolar amount of lithium diisopropylamide abstracts the C_2 methylene proton of 1,3-dicarbonyl group in 1-(2-lithiumoxyphenyl)-3-phenyl-1,3-propanedione, produced by the intramolecular rearrangement of lithium enolate of **3a**, to shift equilibrium to more conjugated lithium dialkoxide intermediate. After acidic workup, the residue was recrystallized twice in 20% EtOAc/*n*-hexane to give **4** as yellow solids in 83-95% yields. All of **4** existed as enolic forms mostly by ^{1}H NMR analysis, which showed enolic OH signals of enol forms at the 15.31-15.90 ppm and C_2 proton signals of keto forms at the 4.50-4.64 ppm.

The conversion of **4** to ring-A hydroxylated flavones **5** was initially attempted using sulfuric acid according to our previous procedure.[14a] The treatment of 2-hydroxy-6-benzoyloxy-3-phenyl-1,3-propanedione **4f** as a model substrate with 1 equiv of sulfuric acid in acetonitrile for 2.5 h at room temperature afforded 5-benzoyloxyflavone in 96% yield, and thus the hydrolysis of 6-benzoyl



Scheme 1

Table 1. Preparation of ring-A hydroxylated flavones (**5**) from 1-(2-hydroxyphenyl)-3-phenyl-1,3-propanediones (**4**)

Entry **5**	R^1	R^2	R^3	R^4	R^5	Isolated yields, %[a]
a	OH	H	H	H	H	89 (74)
b	OH	H	H	H	OMe	83 (76)
c	OH	H	H	OMe	OMe	81 (62)
d	H	OH	H	H	Cl	85 (73)
e	H	OH	H	H	OMe	80 (68)
f	H	H	OH	H	H	91 (70)
g	H	H	OH	H	Cl	97 (78)
h	OH	H	OH	H	H	91 (76)
i	OH	H	OH	H	OMe	84 (69)

[a]The numbers in parentheses indicate the overall yields of three steps from the starting 2'-hydroxyacetophenones **1a-d**.

group in **4f** didn't occur. However, the reaction of **4f** with 1 equiv of 48% HBr in glacial acetic acid for 2.5 h at 80 °C afforded 5-hydroxyflavone **5f** in 91% yield. Under these conditions the cyclodehydration of **4f** proceeded at first and then followed by the hydrolysis of 5-benzoyl group to give **5f**. After evaporation of acetic acid, the mixture was washed with sat. $NaHCO_3$ solution and the residue was recrystallized twice from 10% EtOAc/*n*-hexane to give **5a-i** as pale yellow solids in high yields (80-97%).

As shown in *Table* 1, various ring-A hydroxylated flavones were synthesized in overall high yields (62-78%) from the starting **1**. The reaction worked well regardless of the kind and the position of aroyl group in A-ring of **4** under the present reaction conditions. The reaction also worked well both for the methoxy (**5b**, **5c**, **5e**, **5i**) and the chloro (**5d**, **5g**) substituent on the B-ring of **4**.

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