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A Practical Synthesis of Flavones from Methyl Salicylate

Dhanapalan Nagarathnam and Mark Cushman*

Department of Medicinal Chemistry and Pharmacognosy, Purdue University, West Lafayette, Indiana 47907, USA

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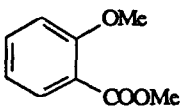
Abstract: A facile synthetic method has been developed for the conversion of methyl salicylate (5) into flavones 1a-i in high yields. Compound 5 on treatment with t-butyldimethylsilyl chloride (6) gave the O-silyl protected ester 7. Condensation of this ester 7 with the lithium anion generated from acetophenones 3a-i yielded the 1,3-diarylpropane-1,3-diones 8a-i, which on treatment with glacial acetic acid containing 0.5% H_2SO_4 for 3 h at 95-100 °C provided the desired flavones 1a-i in 83-94% yields.

Flavones constitute one of the major classes of the natural products. They have been of interest in the area of drug development because of their broad spectrum of pharmacological activities.[1-3] The chemistry of these compounds has been reviewed repeatedly.[4,5] The main synthetic methods include the Kostanecki reaction, the Baker-Venkataraman rearrangement, synthesis *via* chalcones, and several other more recent methods.[6,7] A common feature in all these methods is that they invariably use 2'-hydroxyacetophenones as the starting material. However, there are a few reports of the synthesis of the parent flavone (**1a**) from methyl 2'-methoxybenzoate (**2**) in poor yield.[8,9] This method involves the condensation of compound **2** with acetophenone (**3a**) using metallic sodium to give 1-(2-methoxyphenyl)-3-phenylpropane-1,3-dione (**4**), which on treatment with boiling aqueous HI gave flavone (**1a**) in 17.5% overall yield from compound **2**.[9] We decided

to attempt an improvement of this approach by employing the lithium anion of the acetophenone instead of the sodium salt and by employing a *t*-butyldimethylsilyl protecting group in place of the methyl ether.[7,10]



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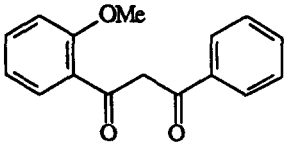

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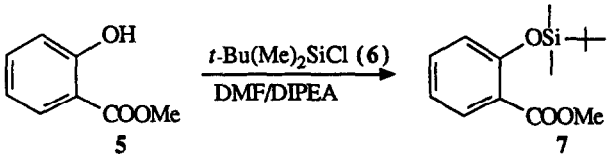
This report discloses a high yielding procedure for synthesis of flavone (**1a**) and its derivatives **1b-i**, including the rare natural product 2'-hydroxyflavone (**1i**).[9] The *t*-butyldimethylsilyl protecting group has been utilized due to its easy introduction and subsequent cleavage in high yield.[11,12] Reaction of methyl salicylate (**5**) with *t*-butyldimethylsilyl chloride (**6**) in DMF in the presence of *N,N*-diisopropylethylamine provided methyl 2-{(*t*-butyldimethylsilyl)-oxy}-benzoate (**7**) in quantitative yield (Scheme I). Compound **7** on condensation with acetophenone (**3a**) in the presence of two equivalents of lithium hexamethyldisilylamide (LiHMDS) afforded 1-[2-{(*t*-butyldimethylsilyl)-oxy}-phenyl]-3-phenylpropane-1,3-dione (**8a**). This reaction required about 48 h for completion. The ^{1}H NMR analysis of product **8a** showed that it exists as a tautomeric mixture[13,14] and it was used as such in subsequent reactions without any further characterization. Treatment of propane-1,3-dione **8a** with glacial acetic acid containing 0.5% H_2SO_4 at 95-100 °C for 3 h resulted in cleavage of the silyl protecting group followed by cyclization to provide flavone (**1a**) in 83% yield. The general utility of this method was studied with several other methoxy substituted acetophenones **3b-f** and in all these cases the corresponding flavones **1b-f** were obtained in good yields (Scheme II). This method has also been utilized for the preparation of ring-C hydroxylated flavones.[10] The technique of generating polyanions from hydroxyacetophenones with excess LiHMDS has been adopted to make high yields of C-acylated products for the preparation of 3-methoxycarbonylated and ring-A hydroxylated flavones.[10,15] Accordingly, reaction of hydroxyacetophenones **3g-i** with three equivalents of LiHMDS and one equivalent of *O*-silyl protected ester **7** followed by treatment of the intermediates **8g-i** with 0.5% H_2SO_4 in acetic acid at 95-100 °C for 3 h gave the desired ring-C hydroxylated flavones (**1g-i**), also in high yields.

Scheme I



5 **7**

Scheme II

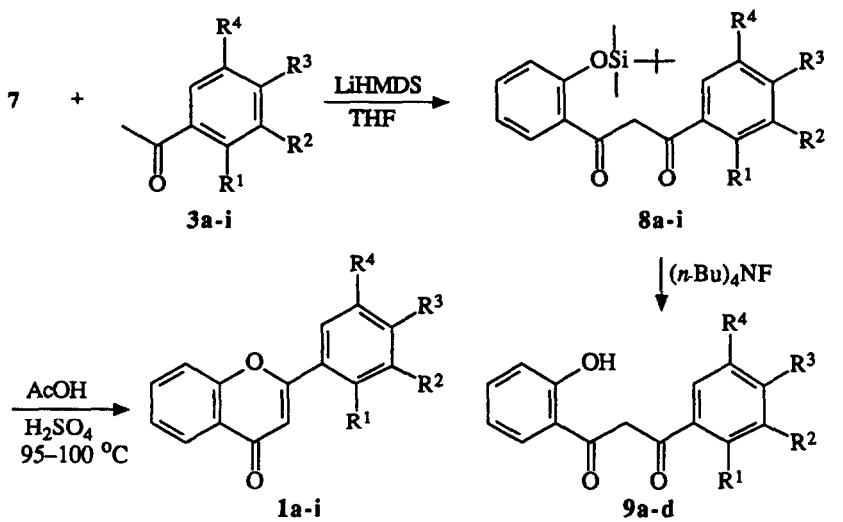


Table I. Physical characteristics and yields of flavones **1a-i**.

Compd	R^1	R^2	R^3	R^4	Yield	mp. °C (Lit. mp. °C)
1a	H	H	H	H	83	96-97 (96-97)[9,16]
1b	H	H	OMe	H	88	157-158 (156-158)[16,17]
1c	H	OMe	OMe	H	85	156 (155-156)[16]
1d	H	OMe	OMe	OMe	94	176 (174-175)[16]
1e	H	OMe	H	H	94	131-132 (131-132)[17,18]
1f	OMe	H	H	H	92	104 (103-104)[9,16-18]
1g	H	H	OH	H	92	269-270 (269-271)[17,18]
1h	H	OH	H	H	88	209-210 (209-211)[17]
1i	OH	H	H	H	83	249-250 (246-251)[9,16-18]

1-(2-Hydroxyphenyl)-3-phenylpropane-1,3-diones are also potential intermediates for the synthesis of several other heterocyclic systems[19-25] including coumaran-3-ones,[19] isoxazoles,[20] 1,5-benzodiazepenes,[21,22] pyrimidines,[23] and pyrazolines,[24] which are of pharmacological interest.[20-23] Preparation of these 1-(2-hydroxyphenyl)-3-phenylpropane-1,3-diones from salicylic acid derivatives would be a new and economical

method to prepare these substances. The *O*-silyl protected propane-1,3-diones **8a-d** were therefore treated with tetra-*n*-butylammonium fluoride and the corresponding 1-(2-hydroxyphenyl)-3-arylpropane-1,3-diones **9a-d** were obtained in high yields (Scheme II). The physical characteristics of these compounds are in agreement with the data reported in literature.[9,16-18,26]

Experimental Section

Melting points were determined in capillary tubes on a Mel-Temp apparatus and are uncorrected. Chemical ionization (CI) mass spectra were obtained on a Finnegan 4000 spectrometer. ^{1}H NMR spectra were run on a Varian VXR-500S spectrometer with TMS as the internal standard in $CDCl_3$. Microanalyses were performed at the Purdue Microanalysis Laboratory. Acetophenones **3a-i** and solutions of lithium hexamethyldisilylamide in THF and tetra-*n*-butylammonium fluoride in THF were obtained from commercial sources.

Methyl 2-[(*t*-butyldimethylsilyl)-oxy]-benzoate (7). A solution of methyl 2-hydroxybenzoate (**5**, 3.80 g, 25 mmol) in dry DMF (150 mL) under argon atmosphere was cooled to 0 °C and *N,N*-diisopropylethylamine (6.50 g, 50 mmol) was added. *t*-Butyldimethylsilyl chloride (**6**, 4.22 g, 28 mmol) was added during 30 min and the reaction mixture was allowed to warm to room temperature over a period of 1 h. After 4 h, the reaction mixture was poured into ice water (500 mL) and extracted with ethyl ether (3 x 50 mL). The combined extracts were washed with brine (3 x 50 mL) and dried (Na_2SO_4). Evaporation of solvent and drying the residue at reduced pressure for 24 h at room temperature gave methyl 2-[(*t*-butyldimethylsilyl)-oxy]-benzoate (**7**, 6.67 g, 100%) as a single product. An analytical sample was prepared by passing a solution of a small amount of it in hexane through a bed of neutral alumina, followed by evaporation of the solvent to afford an oil: ^{1}H NMR ($CDCl_3$) δ 7.79 (dd, J = 8.0 and 2.0 Hz, 1 H), 7.38 (m, 1 H), 7.00 (m, 1 H), 6.90 (dd, J = 8.0 and 2.0 Hz, 1 H), 3.88 (s, 3 H), 1.03 (s, 9 H), 0.24 (s, 6 H); CIMS (isobutane) *m/e* 267 (MH^+, 100). Anal. Calcd for $C_{14}H_{22}O_3Si$: C, 63.12; H, 8.32. Found: C, 63.34; H, 8.40.

Preparation of Flavones 1a-f: General Procedure. A solution of LiHMDS in THF (1 M, 20 mL, 20 mmol) was added to a well-stirred solution of acetophenones (**3a-f**, 10 mmol) in THF (50 mL) under argon atmosphere at -78 °C in 15 min. After 30 min, a solution of methyl 2-[(*t*-butyldimethylsilyl)-oxy]-benzoate (**7**, 2.66 g, 10 mmol) in THF (5 mL) was added. Stirring was continued at -78 °C for 1 h and at room temperature for 36-48 h (until the disappearance of the starting materials as indicated by ^{1}H NMR). The reaction mixture was poured into a mixture of ice (200 g) and conc. HCl (10 mL) and extracted with $CHCl_3$ (3 x

25 mL). Solvents were evaporated from the combined, dried (Na_2SO_4) extracts and the residue was dried under vacuum for 24 h. It was mixed with glacial acetic acid (40 mL) and H_2SO_4 (0.2 mL) and heated at 95-100 °C under argon atmosphere for 3 h. About 30 mL of acetic acid was distilled off at reduced pressure and the residue was poured into water (300 mL). It was extracted with $CHCl_3$ (3 x 25 mL) and the combined extracts were dried (Na_2SO_4). Evaporation of solvents and recrystallization of the residue from EtOAc/hexane gave flavones **1a-f**. The physical characteristics and yields of these compounds are summarized in Table I.

Preparation of Hydroxyflavones 1g-i: General Procedure. A well-stirred solution of LiHMDS in THF (1 M, 30 mL, 30 mmol) was cooled to -78 °C under a dry argon atmosphere and a solution of hydroxyacetophenones **3g-i** (10 mmol) in dry THF (100 mL) was added in 20 min. The resulting orange solution was stirred at -78 °C for 1 h and at -10 °C for 2 h. It was cooled again to -78 °C and a solution of methyl 2-[(*t*-butyldimethylsilyl)-oxy]-benzoate (**7**, 2.66 g, 10 mmol) in THF (5 mL) was added. The procedure was continued as reported above. About 80% of the acetic acid was removed from the reaction mixture at reduced pressure and the residue was poured into ice water (500 mL). The product precipitated and was filtered and recrystallized from acetone-hexanes. The physical characteristics and yields of hydroxyflavones **1g-i** are listed in Table I.

Preparation of 1-(2-Hydroxyphenyl)-3-arylpropane-1,3-diones (9a-d). A solution of tetra-*n*-butylammonium fluoride in THF (1 M, 15 mL, 15 mmol) was added to a solution of the crude products **8a-d** (5 mmol, prepared from acetophenones **3a-d** in 5 mmol scale) in THF (30 mL) at 0 °C and stirring was continued for 45 min. THF was distilled off at reduced pressure and the residue was treated with water (100 mL). The precipitated product was filtered, washed with water and dried.

1-(2-Hydroxyphenyl)-3-phenylpropane-1,3-dione (9a): 1.10 g; 92% yield; mp 118-121 °C (lit.[26] mp 117-120 °C).

1-(2-Hydroxyphenyl)-3-(4-methoxyphenyl)-propane-1,3-dione (9b): 1.20 g; 89% yield; mp 115-116 °C (lit.[16] mp 114 °C).

3-(3,4-Dimethoxyphenyl)-1-(2-hydroxyphenyl)-propane-1,3-dione (9c): 1.38 g; 92% yield; mp 129-130 °C (lit.[16] mp 130 °C).

1-(2-Hydroxyphenyl)-3-(3,4,5-trimethoxyphenyl)-propane-1,3-dione (9d): 1.45 g; 88% yield; mp 138 °C (lit.[16] mp 136 °C).

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