An efficient synthesis of flavans from salicylaldehyde and acetophenone derivatives

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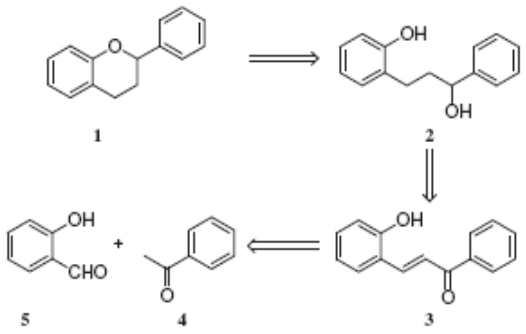
ABSTRACT

An efficient total synthesis of flavans from the reactions of salicylaldehyde and acetophenone derivatives is reported. The synthesis involves preparation of chalcones through an aldol reaction followed by reduction of both the double bond and the ketone using $NaBH_4$ and an acetic acid mediated cyclization. Methoxy groups on the aromatic rings did not affect significantly the yields of the procedure.

Flavans are a group of flavanoids possessing a 2-phenylchroman nucleus. They exist widely in the plant kingdom and exhibit many important biological and pharmacological activities.[1–3] Flavans have attracted the attention of many synthetic chemists and a number of general procedures have been developed for their synthesis. These include intramolecular Mitsunobu reaction,[4] cyclization of chalcones and the reduction of flavanones,[5] flav-2-enes[6] and flavones.[7] Most of these procedures suffer from long reactions times, poor yields and harsh conditions.

Herein, we report a short and efficient procedure for the total synthesis of flavans which involves the reduction of 2-hydroxychalcones with $NaBH_4$ and subsequent cyclization using acetic acid. 2-Hydroxychalcones are commonly synthesized via Claisen or aldol condensation between 2-hydroxyacetophenone and benzaldehyde.[8,9] This reaction suffers from long reaction times and low yields for polyhydroxylated benzaldehydes or acetophenones contrary to our method which used salicyladehyde and acetophenone for the synthesis of 2-hydroxychalcone. The general strategy for the construction of flavan **1** was based on the retrosynthetic analysis shown in Scheme 1. Disconnection of flavan **1** at the ether bond furnished advanced intermediate **2**. Functional group interconversions gave chalcone **3** and further disconnection identified commercially available salicylaldehyde (**5**) and acetophenone (**4**) as the starting materials. For most of the reported procedures for the synthesis of the 2-phenylchroman nucleus, the oxygen which forms the ether is introduced as 2-hydroxyacetophenone, while in our procedure it is introduced as salicylaldehyde.

In the event, efficient access to intermediate chalcone **3** was achieved through an aldol condensation between acetophenone (**4**) and salicylaldehyde (**5**) in a mixture of 40% $NaOH_{(aq)}$ and ethanol at 60 °C for 2 h. This reaction afforded chalcone **3** in 85% yield (Scheme 2). The successful preparation of chalcone **3** set the stage for the crucial cyclization reaction. Consequently, treatment of a solution of chalcone **3** in methanol with $NaBH_4$ gave derivative **2** in 88% yield. It is noteworthy that the carbon–carbon double bond was also reduced under these conditions and there is literature precedence to such a reduction.[10] Subsequent dissolution of **2** in



Scheme 1. Reterosynthetic analysis of flavan **1**.

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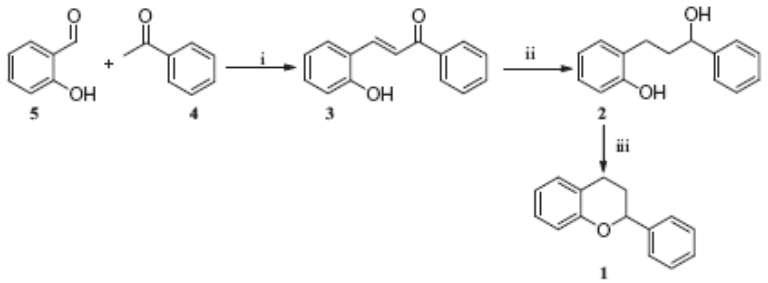
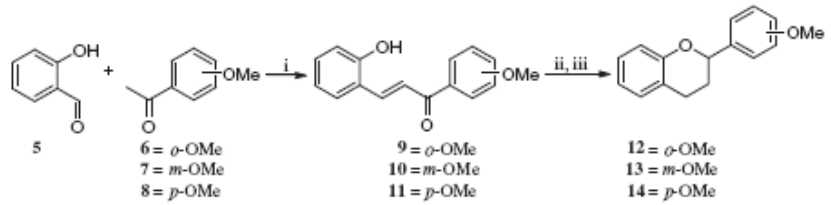
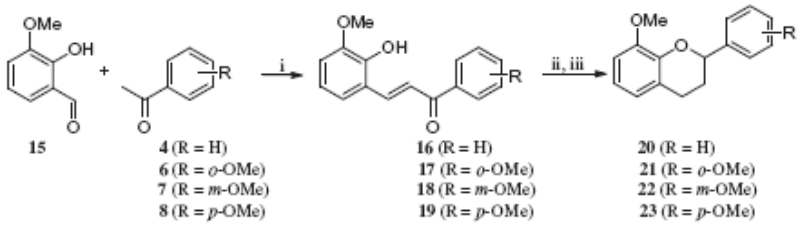


Scheme 2. Reagents and conditions: (i) 40% $NaOH_{(aq)}$, EtOH, 60 °C, 2 h, 85%; (ii) $NaBH_4$, MeOH, 25 °C, 10 min, 88%; (iii) AcOH, reflux, 30 min, 71%.



Scheme 3. Reagents and conditions: (i) 40% $NaOH_{(aq)}$, EtOH, 60 °C, 2 h, 83% [**9**], 66% [**10**], 78% [**11**]; (ii) $NaBH_4$, MeOH, 25 °C, 10 min; (iii) AcOH, reflux, 30 min, 70% [**12**], 38% [**13**], 78% [**14**].



Scheme 4. Reagents and conditions: (i) 40% $NaOH_{(aq)}$, EtOH, 60 °C, 2 h, 76% [**16**], 72% [**17**], 56% [**18**], 87% [**19**]; (ii) $NaBH_4$, MeOH, 25 °C, 10 min; (iii) AcOH, reflux, 30 min, 64% [**20**], 58% [**21**], 63% [**22**], 85% [**23**].

acetic acid and refluxing for 30 min gave flavan **1**[11,12] in 71% yield. It was found that the synthesis of **1** proceeded without having to purify intermediate **2**.

To test the generality of this synthetic route, a variety of methoxyacetophenones **6–8** and salicylaldehyde (**5**) were reacted under the conditions described above to give the corresponding chalcones **9–11** in 66–83% yields. The carbon–carbon double bonds and ketones of these chalcones were reduced using $NaBH_4$ and allowed to undergo the acetic acid mediated cyclization to give the corresponding flavans **12–14** in 38–78% yields from the chalcones, Scheme 3.

Next we decided to study the effects of a methoxy group attached to the salicyladehyde on our procedure. To this end, salicylaldehyde derivative **15** was treated with a solution of acetophenone (**4**) in a mixture of 40% $NaOH_{(aq)}$ and ethanol to give chalcone **16** in 76% yield. Subsequent reduction of the alkene and ketone groups of **16** followed by cyclization gave flavan **20** in 88% yield from chalcone **16**. Further reactions of acetophenone methoxy derivatives **6–8** afforded the corresponding chalcones **17–19** in 56–87% yields. Reduction and cyclization of chalcones **17–19** gave the corresponding flavans **21–23** in overall yields of 58–85%, Scheme 4.

In summary, we have reported a general method for the synthesis of flavans which involved reduction of both the ketone and double bond of chalcones using $NaBH_4$ and subsequent cyclization. The reaction is not affected by the presence of methoxy group substituents on either of the aromatic rings.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.09.147.

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11. Typical experimental procedure: To a solution of acetophenone (40 mmol) and salicylaldehyde (40 mmol) in EtOH (50 mL) was added 40% NaOH (10 mL) aqueous solution dropwise and the reaction was refluxed at 60 °C for 2 h. The solution/suspension was poured onto cold H_2O and the mixture neutralized with 2 M HCl until the solution was acidic. The resulting yellow precipitate was collected, washed with H_2O and recrystallized from EtOH to yield a yellow solid (4.2 g, 85% yield of **3**). $NaBH_4$ powder (5 equiv, 33.5 mmol) was added slowly to a stirred methanolic solution of **3** (6.7 mmol) at 25 °C. The resulting suspension was stirred for 10 min and after cooling the mixture was quenched with 2 M HCl. The organic layer was separated and the aqueous phase extracted with EtOAc (3 × 15 mL). The combined organic phase was dried ($MgSO_4$) and concentrated to a brown gum (1.3 g, 88% yield of **2**). Glacial AcOH (10 ml) was added to **2** (4.4 mmol). The solution was heated at reflux for 30 min, then cold H_2O (15 mL) followed by saturated $NaHCO_3$ (30 mL) were added, and the solution extracted with EtOAc (2 × 20 mL). The combined organic layer was washed with H_2O (20 ml) and brine (20 ml), dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography eluting with petroleum ether–EtOAc (v/v, 4:1) to give flavan **1** (710 mg, 71%).
12. Spectral data for **1**. Yellow gum; υ_{max} (neat): 2985, 2924, 1619, 1511, 1457, 1371, 1152, 1110, 839, 771 cm^{-1}; δ_H (300 MHz, acetone-d_6): 2.03 (1H, m, H-3a), 2.20 (1H, m, H-3b), 2.77 (1H, m, H-4a), 2.98 (1H, m, H-4b), 5.08 (1H, dd, J = 2.4, 10.2 Hz, H-2), 6.79 (1H, ddd, J = 0.9, 7.2, 8.1 Hz, H-6), 6.87 (1H, dd, J = 0.9, 8.1 Hz, H-8), 7.05 (1H, ddd, J = 1.5, 7.5 Hz, H-4′), 7.13 (1H, dd, J = 1.5, 7.2 Hz, H-5), 7.24 (1H, dt, J = 1.5, 8.1 Hz, H-7), 7.33 (2H, dt, J = 1.5, 7.5 Hz, H-3′ and 5′), 7.40 (2H, dd, J = 1.5, 7.5 Hz, H-2′ and 6′); δ_C (75 MHz, acetone-d_6): 26.4 (C-4), 39.7 (C-3), 73.0 (C-2), 115.1 (C-8), 119.5 (C-6), 125.9 (C-2′ and 6′), 128.4 (C-4a), 128.8 (C-4′), 126.9 (C-7), 128.0 (C-3′ and 5′), 130.1 (C-5), 145.9 (C-1′), 155.1 (C-8a); HRMS (EI) found M^+, 210.1049. $C_{15}H_{14}O$ requires 210.1045.