An Effective Synthesis of 5,4'-Disubstituted Flavones via a Cesium Enolate Assisted Intramolecular ipso-Substitution Reaction

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A variety of 5,4'-disubstituted flavones, which are anticipated to be androgen receptor antagonists to treat diseases mediated by the androgen receptor, were synthesized. It was found that an intramolecular ipso-substitution reaction via cesium enolate using 2-fluoro-6-hydroxyacetophenone and various benzoyl chlorides was effective in the preparation of 5-hydroxy-4'-alkylflavones.

Key words flavone; ipso-substitution; androgen; antagonist

The androgen receptor (AR), which is activated by androgenic hormones, functions as a DNA binding transcription factor that regulates gene expression.1,2) The androgen-regulated genes are important for the development and maintenance of the male sexual phenotype. It is known that isoflavones are similar to the estrogen hormone, and several studies using flavones as AR antagonists have been reported.3,4) We have already reported that some flavonoids act as novel androgen receptor ligands which interacts with the receptor in a different manner from known androgen receptor ligands.5) We also disclosed that 5-hydroxyflavone has extremely high AR antagonistic activity, and that the hydroxyl group at the 4'-position plays an important role in the interaction with the AR. Furthermore, the introduction of hydroxyl group at the 4'-position increases AR antagonistic activity as well. We report herein the syntheses of various 5,4'-disubstituted flavones, which are expected to be AR antagonist, using a novel intramolecular ipso-substitution method to construct the flavone-skeleton.

Results and Discussion

We planned to prepare a number of 5,4'-disubstituted flavones, shown in Table 1, and assay them for AR antagonistic activity. The compounds with asterisk are novel flavones and the others are flavones, with unknown AR antagonistic activity. These compounds were chosen because of the variation in the substituent constant6) and STERIMOL parameter5) of the 4'-position substituent as shown in Table 2.

At the outset, 5-hydroxyflavones (3a–h) in Table 3 were prepared according to the known method7) using 2,6-dihydroxyacetophenone and the corresponding benzoyl chlorides under basic conditions in acetone.8) The yields were low except for the 5-hydroxy-4'-trifluoromethylflavone (3e). The 1H-NMR of the crude products showed significant contamination with by-products. More importantly, the desired reaction did not proceed at all, when 4-alkylbenzoyl chlorides were used as substrate (Table 1, entries 9, 10). In this case, the major product was 4 even under high dilution conditions (Fig. 1).9)

Thus finding a new method to prepare 4'-alkylflavones was imperative. To prevent the double benzoylation of the alkylbenzoyl chloride to 2,6-dihydroxyacetophenone, 2-fluoro-6-hydroxyacetophenone 5 was used as an alternative substrate. We hypothesized that the electron-withdrawing effect of the fluoro-group on the aromatic ring would decrease the electron density of the corresponding phenoxy anion intermediate. And the various 5-hydroxyflavones would be...
obtained via the plausible mechanism shown in Fig. 2, if an intramolecular ipso-substitution reaction of an enolate proceeds.

Although there had been no report of flavone synthesis using intramolecular ipso-substitution reaction, we found that the treatment of 2-fluoro-6-hydroxyacetophenone 5, benzoyl chloride 2k, and potassium carbonate provided 5-hydroxyflavone in good yield (78% recryst. from ethyl acetate) (Table 4, entry 1). After exploring a variety of reaction conditions, we found that cesium carbonate was better as the base than other carbonates (Li2CO3, Na2CO3, and K2CO3) in terms of reaction rate, and either acetone or N,N-dimethylformamide (DMF) was suitable as solvent. We then tried to prepare 5-hydroxyflavones (3i, 3j, 3f, 3g), which were difficult to obtain in good yields with the reported method. The yields were improved as shown in Table 4 and enough amount of the target flavones were obtained for the assay. We believe that the ipso-substitution method will be one of the most effective synthetic methods for various 5-hydroxyflavones, if suitable substrates are available.

Attempts to utilize the intramolecular ipso-substitution method to prepare 5-fluoroflavones proved futile. Therefore we had to apply the known synthetic method to prepare the novel 5-fluoroflavones (7a—c) (Fig. 3). Similarly, 5-methoxyflavones (10a, b) were also prepared using another known method because the corresponding substrates for the intramolecular ipso-substituted protocol were difficult to obtain (Fig. 4).

Finally, novel 5-hydroxy-4'-aminoflavone derivatives (3l—n) were prepared from 5-hydroxy-4'-nitroflavone (3d) as shown in Fig. 5. The prepared novel flavones (3c, 3e, 3f, 3g, 3l—n) and the other flavones, which have not been examined for AR antagonist activity (3a, 3b, 3d, 3h, 3l, 3j, 3k, 10a, 10b, 10d, 10h), will be tested in an in-vitro reporter gene assay in the near future.

**Experimental**

Melting points are uncorrected. Infrared absorption spectra were recorded on a Bibby Scientific Ltd. Stuart® SMP 30. 1H-NMR spectra were measured in CDCl3 on JNM-EX270 (270 MHz) spectrometers with tetramethylsilane as the internal standard. Mass spectra were recorded on a Shimadzu Corp.,

![Fig. 1. By-products Dibenzoyleated](image1)

![Fig. 2. Synthetic Strategy for Flavone Synthesis via Intramolecular ipso-Substitution of an Enolate](image2)

**Table 4. Flavone Synthesis via Intramolecular ipso-Substitution**

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Base</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H: 3k</td>
<td>K2CO3</td>
<td>24</td>
<td>78%</td>
</tr>
<tr>
<td>2</td>
<td>Me: 3i</td>
<td>Cs2CO3</td>
<td>3</td>
<td>68%</td>
</tr>
<tr>
<td>3</td>
<td>CN: 3e</td>
<td>Cs2CO3</td>
<td>4</td>
<td>68%</td>
</tr>
<tr>
<td>4</td>
<td>tBu: 3j</td>
<td>Cs2CO3</td>
<td>2</td>
<td>54%</td>
</tr>
<tr>
<td>5</td>
<td>SMe: 3f</td>
<td>Cs2CO3</td>
<td>3</td>
<td>44%</td>
</tr>
<tr>
<td>6</td>
<td>NMe2: 3g</td>
<td>Cs2CO3</td>
<td>4</td>
<td>47%</td>
</tr>
</tbody>
</table>

a) Isolated yield after recrystallization from ethyl acetate.  b) Isolated yield after column chromatography.

![Fig. 3. Synthesis of Novel 5-Fluoroflavones](image3)

![Fig. 4. Synthesis of 5-Methoxyflavones, Which Were Not Examined for AR Antagonist](image4)

![Fig. 5. Synthesis of Novel 5-Hydroxy-4'-aminoflavone Derivatives](image5)
was added cesium carbonate (635 mg, 1.95 mmol) at room temperature. The reaction mixture was stirred at 70°C for 3 h, and quenched with 1 M HCl, then extracted with AcOEt. The organic layer was washed with brine, dried with sodium sulfate and concentrated in vacuo. The residue was purified by recrystallization from ethyl acetate to give 5-hydroxy-4'-methylflavone 3a (110 mg, 68% yield) as yellow crystals; mp 175.0—176.0°C. 1H-NMR δ: 6.79 (1H, s), 6.84 (1H, d, J = 6.7 Hz), 6.92 (1H, m), 7.49—7.60 (3H, m), 7.84—7.89 (2H, m), 12.50 (1H, s). MS m/z: 272 (M+), 274 (M+) + 2, 136, 108.

5-Hydroxy-4'-fluoroflavone 3b (3a) Yellow crystals; mp 185.0—186.0°C. 1H-NMR δ: 6.69 (1H, s), 6.83 (1H, d, J = 8.1 Hz), 7.00 (1H, d, J = 10.8 Hz), 7.22 (2H, J = 8.1 Hz), 7.56 (1H, t, J = 8.1 Hz), 7.91—7.96 (2H, m), 12.53 (1H, s). Anal. Calcd for C17H11O3F: C, 63.75; H, 3.46.

5-Hydroxy-4'-cyanoflavone 3c Yellow crystals; mp 195.0—196.0°C. 1H-NMR δ: 6.79 (1H, s), 6.86 (1H, d, J = 8.0 Hz), 7.03 (1H, d, J = 8.1 Hz), 7.60 (1H, t, J = 8.1 Hz), 7.85 (2H, J = 8.1 Hz), 8.04 (2H, J = 8.1 Hz), 12.37 (1H, s). MS m/z: 263 (M+), 136, 108. Anal. Calcd for C17H11NO: C, 73.00; H, 3.45; N, 5.32. Found: C, 72.64; H, 3.41; N, 5.28.

5-Hydroxy-4'-nitroflavone 3d (3a) Yellow crystals; mp 226.0—227.0°C. 1H-NMR δ: 6.83 (1H, s), 6.88 (1H, d, J = 8.1 Hz), 7.04 (1H, d, J = 7.6 Hz), 7.61 (1H, t, J = 8.1 Hz), 8.10 (2H, J = 7.0 Hz), 8.40 (2H, J = 7.0 Hz), 12.34 (1H, s). MS m/z: 283 (M+) + 2, 237, 108.

5-Hydroxy-4'-trifluoroacetylflavone 3e Yellow crystals; mp 138.0—139.0°C. 1H-NMR δ: 6.79 (1H, s), 6.85 (1H, d, J = 8.1 Hz), 7.03 (1H, d, J = 10.8 Hz), 7.59 (1H, t, J = 8.1 Hz), 7.81 (2H, J = 8.1 Hz), 8.04 (2H, J = 8.1 Hz), 12.43 (1H, s). Anal. Calcd for C17H11F3O: C, 60.75; H, 3.46.

5-Hydroxy-4'-methoxyflavone 3f Yellow crystals; mp 166.0—167.0°C. 1H-NMR δ: 2.56 (3H, s), 6.71 (1H, s), 6.82 (1H, d, J = 8.4 Hz), 6.98—7.01 (1H, m), 7.34—7.37 (2H, m), 7.55 (1H, t, J = 8.1 Hz), 7.81—7.85 (2H, m), 12.61 (1H, s). MS m/z: 284 (M+) + 2, 148. Anal. Calcd for C17H15NO2: C, 62.75; H, 4.25. Found: C, 62.70; H, 4.20.

5-Hydroxy-4'-dimethylaminoflavone 3g Yellow crystals; mp 184.0—185.0°C. 1H-NMR δ: 6.97 (1H, s), 6.75 (1H, d, J = 8.1 Hz), 7.12 (1H, d, J = 8.1 Hz), 6.96 (1H, d, J = 8.1 Hz), 7.49 (1H, d, J = 9.5 Hz), 7.50 (2H, d, J = 8.9 Hz), 12.87 (1H, s). MS m/z: 281 (M+) + 2, 207. Anal. Calcd for C17H15NO2: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.46; H, 5.41; N, 5.00.

5-Hydroxy-4'-phenylflavone 3h (3a) Pale yellow crystals; mp 177.0—178.0°C. 1H-NMR δ: 6.78 (1H, s), 7.01 (1H, d, J = 10.8 Hz), 7.37—7.57 (4H, m), 7.64 (2H, J = 8.1 Hz), 7.65 (2H, J = 8.1 Hz), 7.98 (2H, J = 8.1 Hz), 12.57 (1H, s). MS m/z: 314 (M+) + 2, 178.

5-Hydroxy-4'-tert-butylation 3j (3a) Yellow crystals; mp 155.0—156.0°C. 1H-NMR δ: 1.37 (9H, s), 6.72 (2H, s), 6.82 (1H, d, J = 8.4 Hz), 7.00 (1H, d, J = 7.8 Hz), 7.52—7.58 (3H, m), 7.86 (2H, J = 8.4 Hz), 12.63 (1H, s). MS m/z: 294 (M+) + 2, 279.

5-Hydroxyflavone 3k Yellow crystals; mp 145.0—146.0°C. 1H-NMR δ: 6.75 (1H, s), 6.83 (1H, d, J = 8.1 Hz), 7.01 (1H, d, J = 8.6 Hz), 7.53—7.59 (4H, m), 7.90—7.94 (2H, m), 12.57 (1H, s). MS m/z: 238 (M+) + 2, 136, 108.

5-Hydroxy-4'-aminoflavone 3l Yellow crystals; mp 195.0—196.0°C. 1H-NMR δ: 8.41—8.43 (2H, m), 6.60 (1H, s), 6.77 (1H, t, J = 8.5 Hz), 6.96, 12.81 (1H, s). MS m/z: 238 (M+) + 2, 137.

5-Hydroxy-4',N,N-diacyliminoflavone 3m Yellow crystals; mp 202.0—203.0°C. 1H-NMR δ: 2.05 (3H, s), 2.30 (3H, s), 6.72 (1H, s), 6.82 (1H, d, J = 8.1 Hz), 7.00 (1H, d, J = 8.1 Hz), 7.01 (1H, d, J = 8.1 Hz), 7.56 (1H, t, J = 8.1 Hz), 7.63—7.68 (2H, m), 7.92—7.97 (2H, m), 12.51 (1H, s). MS m/z: 295+ (M+) + 2, 253.

5-Hydroxy-4',N-acyliminoflavone 3n Yellow crystals; mp 230.0—231.0°C. 1H-NMR δ: 2.24 (3H, s), 6.70 (1H, s), 6.82 (1H, d, J = 8.1 Hz), 7.00 (1H, d, J = 8.1 Hz), 7.31 (1H, s), 7.55 (1H, t, J = 8.1 Hz), 7.70 (2H, d, J = 8.1 Hz), 7.90 (2H, d, J = 8.1 Hz), 12.61 (1H, s). MS m/z: 295 (M+) + 2, 253.


