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Research Article

Convenient Synthesis of a Novel Flavonoid with Extended π-System: Active Agent for UVA Protection

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Flavonoid derivative with extended cinnamic acid moiety was synthesized using Baker-Venkataraman reaction. The compound shows interesting UV absorption properties which make it a good UVA absorber. A bathochromic shift of 18 nm was observed when the size of cinnamic acid segment was increased by one styrylogous extension.

1. Introduction

Flavonoids play an important role in biological processes in plants and other biological species [1]. Human diet contains trace amount of flavonoids which have been reported to exhibit a wide range of biological activities. These biological properties include anti-inflammatory [2], antibacterial, anti-tumor [3], antioxidant [4], antiviral [5], antiallergenic [6], and protein kinase C inhibitors [7]. Besides, it is known that some flavonoids have antifeedant activity against some phytophagous and a subterranean termite (*Coptotermes* sp.) [8]. Recently, flavonoids were recommended for the treatment of allergic and inflammatory diseases [9].

In addition, flavonoids are known for their ability to act as UV-absorbers and radical quenching compounds [10, 11]. Because of this important property, flavonoids are exploited by plants to protect them from the sun UV radiation. This use could be utilized in the protection of human hair and skin from UV radiation. It is well known that exposure to UV radiation can damage skin and hair fibers [12, 13]. UVB radiation is the principal radiation responsible for inducing skin cancer and hair protein loss (causing dryness, reduced strength, rough surface texture, and decreased luster) [14]. On the other hand, UVA radiation is responsible for premature photoaging of the skin and for color changes of hair [15]. Structurally, flavonoids can be divided into two main segments: the cinnamic acid subchromophore and the benzoyl subchromophore (Figure 1).

By altering the chromone substitution pattern, the UV absorption properties can be adjusted to individual needs. For example, a bathochromic shift was observed (from 294 nm to 330 nm) when the size of the cinnamic acid fragment was increased by introducing one vinylogous extension in the π-system (Figure 2) [16]. This means that flavone **1** would protect better against UVB and thus against hair protein loss, whilst 2-styryl-4H-chromen-4-one **2** would protect better against UVA radiation and hair color changes.

On the other hand, introducing an electron donating group such as hydroxyl group to the benzoyl subchromophore caused a hypsochromic shift from 294 nm to 265 nm (Figure 3) which means that 5-hydroxyflavone **3** would protect better against UVC [13].

Several methods have been applied for the synthesis of flavonoids for example, Allan-Robinson strategy, cyclization of chalcones, and via an intramolecular Wittig reaction [17, 18]. One of the most common methods used to prepare flavonoids involves acylation of *o*-hydroxyacetophenone with an aromatic acid chloride yielding an aryl ester. The ester is then rearranged by a base (the Baker-Venkataraman reaction) to a 1,3-diaryl-1,3-diketone [19]. The later compound gives 2-arylchromone (flavone) *via* acid-catalyzed cyclization. Here, we report the synthesis of a novel flavone derivative **4** in which the cinnamic acid fragment is increased by introducing a styryl extension in the π-system and to study its UV absorption properties.

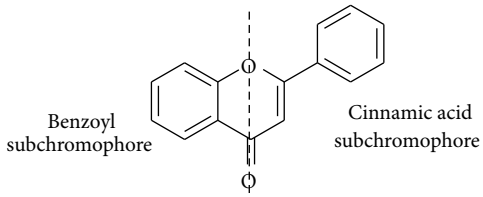


Figure 1: Benzoyl versus cinnamic acid subchromophores.

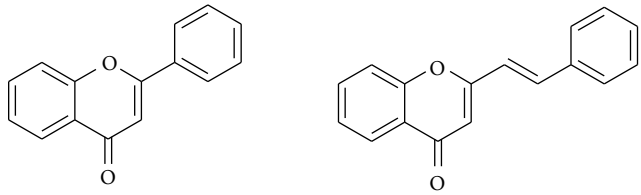


Figure 2: UV absorption of flavone and 2-styryl-4H-chromen-4-one.

2. Results and Discussion

Our strategy to make compound **4** started from the phosphonium salt **5** which was prepared by the reaction of 4-(bromomethyl)benzoic acid with triphenylphosphine in acetone (Scheme 1). We envisaged that the double bond between the two phenyl groups in the target compound **4** can be constructed via Wittig reaction between a suitable phosphorus ylide and benzaldehyde. So, the reaction of the salt **5** with benzaldehyde in H_2O/CH_2Cl_2 system in the presence of NaOH yielded the alkene as a mixture of *Z*- and *E*-isomers which was isomerized to the *E*-isomer **6** by treatment of the product mixture with a trace of iodine. The conversion of **6** into the acid chloride **7** was afforded using thionyl chloride following literature procedures [20]. The crude acid chloride **7** was subsequently reacted with 2-hydroxyacetophenone in pyridine to give ester **8** in 50% yield. Next, we turned our attention to construct the heterocyclic ring in the desired flavonoid derivative **4** using Baker-Venkataraman rearrangement of ester **8**. Thus, upon refluxing a pyridine solution of **8** in the presence of KOH followed by treatment with H_2SO_4 afforded successfully flavonoid derivative **4** in 63%.

The UV absorption properties of compound **4** and flavone **1** were measured. A bathochromic shift was observed when the cinnamic acid fragment was extended by styryl group. The maximum absorption of flavonoid derivative **4** is at 312 nm (UVA) compared to 294 nm (UVB) for flavone **1**. We believe that flavonoid derivative **4** is much better UVA absorber than flavonoid derivative **2** since it absorbs at a wide UVA range.

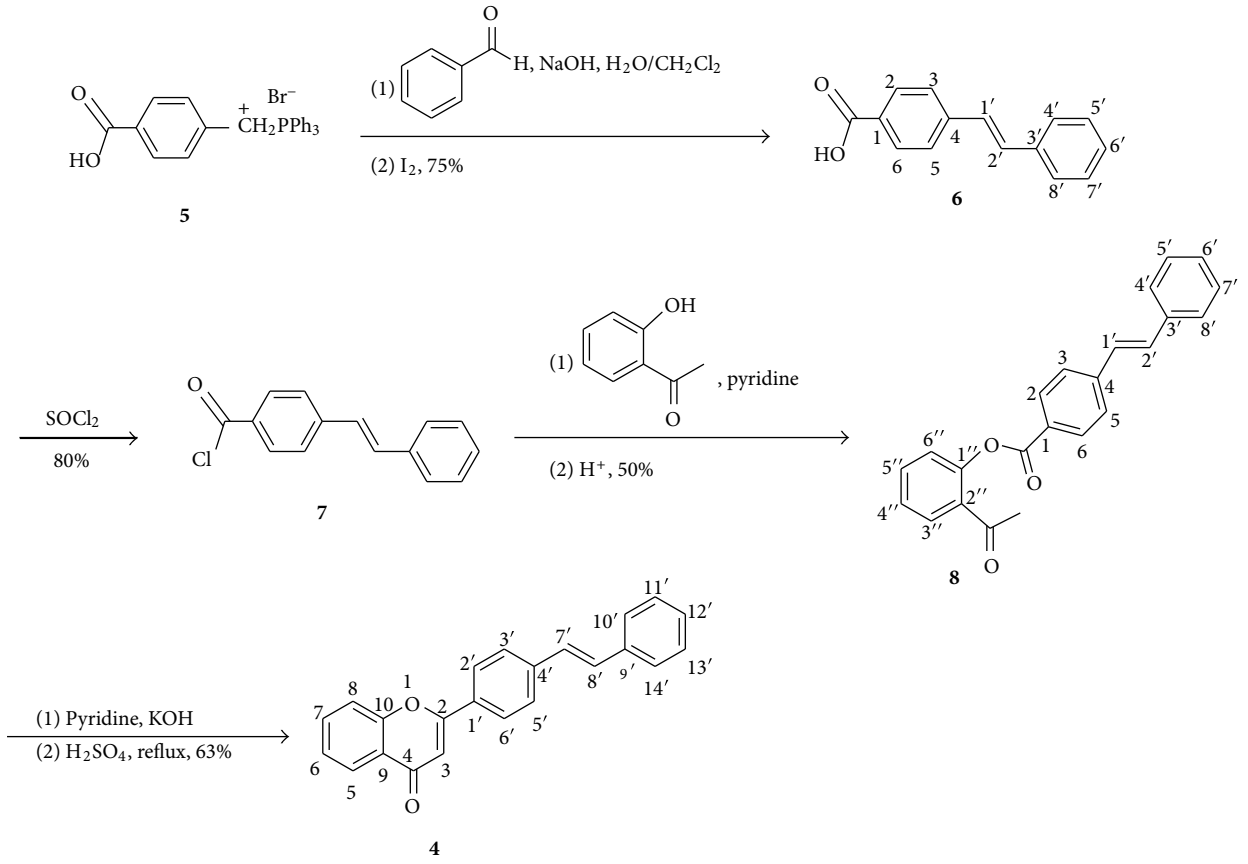
3. Experimental

The reagents and solvent were obtained from Aldrich and used without further purification. UV-vis spectra were measured using a Shimadzu, Model UV-1650PC spectrophotometer and reported as λ_{max} in nm (ε). IR spectra were obtained with a Nicolet model Magna 560 spectrometer; absorption bands are recorded in wave number (cm^{-1}). NMR spectra were recorded on a Bruker Avance 400 (^1H: 400 MHz, ^{13}C: 100.6 MHz). The chemical shifts are in δ-values (ppm) relative to the internal standard TMS and reported as chemical shift (multiplicity, coupling constant, and number of protons, assignment). Mass spectra were measured using HPLC-MS.

3.1. Synthesis of E-4-Styrylbenzoic Acid **6**. 4-Carboxybenzyltriphenylphosphonium bromide **5** (7.30 g, 15.3 mmol) was suspended in dichloromethane (175 mL) in an Erlenmeyer flask. 75 mL of aqueous solution of sodium hydroxide (50 g) and benzaldehyde (2.0 mL) were added to the reaction mixture. The neck of the flask was plugged with cotton wool and the yellow mixture stirred for 30 minutes. The organic layer was separated and the aqueous layer was extracted with (2 × 20 mL) dichloromethane. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Petroleum ether (50 mL) and few crystals of iodine were added to the residue and the mixture was refluxed for 3 h. The reaction mixture was washed with 25% sodium metabisulfite and the organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to give a white solid. The solid was recrystallised from ethanol to yield white needles (7.39 g, 0.033 mol, 75%). Mp 105.1°C; IR (KBr): ν_{max} (cm^{-1}) = 3500-2496, 3054, 1714, 1611, 752; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.15 (d, 1H, J = 16.6 Hz, H-2′), 7.21 (m, 1H, H-6′), 7.29 (d, 1H, J = 16.6 Hz, H-1′), 7.47 (m, 2H, H-5′ and H-7′), 7.54 (d, 2H, J = 8.1 Hz, H-3 and H-5), 7.67 (m, 2H, H-4′ and H-8′), 7.70 (d, J = 8.1 Hz, 2H, H-2 and H-6); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 124.4 (C-2′), 126.8 (C-1′), 128.9 (C-3 and C-5), 130.0 (C-4′ and C-8′), 130.8 (C-5′ and C-7′), 131.9 (C-6′), 132.9 (C-2 and C-6), 133.7 (C-1), 145.2 (C-3′), 149.9 (C-4), 165.6 (C=O).

3.2. Synthesis of E-4-Styrylbenzoyl Chloride **7**. A mixture of *E*-4-styrylbenzoic acid 6 (3.57 g, 16.0 mmol) and thionyl chloride (1.65 mL, 22.5 mmol) was heated under reflux for 1 h. Excess thionyl chloride was removed under reduced pressure and the crude solid (3.10 g, 12.8 mmol, 80%) was used for the next step.

3.3. Synthesis of E-2-Acetylphenyl 4-Styrylbenzoate **8**. To a solution of 2-hydroxyacetophenone (1.25 g, 9.25 mmol) in pyridine (2.3 mL) was added *E*-4-styrylbenzoyl chloride 7 (2.24 g, 9.25 mmol). The reaction mixture was stirred briefly at room temperature. The temperature of the reaction increased spontaneously. After cooling, the reaction mixture was poured into a mixture of 60 mL HCl (3%) and 30 g crushed ice. The product was extracted with chloroform



Scheme 1: Synthesis of flavone derivative **4**.

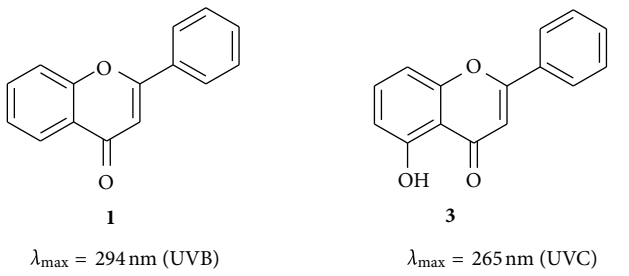


Figure 3: UV absorption of flavone and 5-hydroxyflavone.

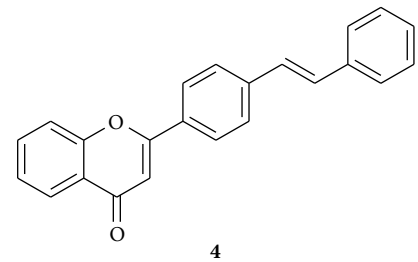


Figure 4

(3 × 10 mL) and the combined organic layer was dried over $MgSO_4$ and evaporated to give yellowish oil. The product was purified by column chromatography on silica gel eluting with hexane: ethyl acetate (9 : 1) (1.58 g, 4.63 mmol, 50%). IR (Nujol oil): ν_{max} (cm^{-1}) = 3031, 2900, 1715, 1637, 810; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) = 2.55 (s, 3H, CH_3), 7.23 (d, 1H, J = 15.8 Hz, H-2′), 7.26 (m, 1H, H-4″), 7.32 (d, 2H, J = 8.3 Hz, H-3 and H-5), 7.34 (m, 1H, H-6″), 7.36 (d, 1H, J = 15.8 Hz, H-1′), 7.45 (m, 3H, H-5′, H-6′, H-7′), 7.55 (m, 2H, H-4′ and H-8′), 7.57 (m, 1H, H-5″), 7.85 (m, 1H, H-3″), 8.10 (d, 2H, J = 8.3 Hz, H-2 and H-6); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 30.3 (CH_3), 124.3 (C-6″), 126.4 (C-2″), 126.5 (C-4″), 126.9 (C-1′ and C-2′), 129.1 (C-1), 129.8 (C-3,C-5,C-4′,C-8′), 130.6 (C-6′), 130.7 (C-3′), 130.8 (C-2 and C-6), 130.9 (C-5″), 131.9 (C-3″), 133.7 (C-5′ and C-7′), 145.2 (C-4), 149.9 (C-1″), 165.6 (COO), 198.0 (CO).

3.4. Synthesis of Flavonoid Derivative **4**. To a solution of *E*-2-acetylphenyl 4-styrylbenzoate **8** (0.25 g, 0.73 mmol) in pyridine (0.85 mL) at 50°C was added potassium hydroxide (0.062 g, mmol) and the mixture was stirred for 15 min. Acetic acid solution (10%, 1.3 mL) was added to the cooled mixture and the solid intermediate was collected by filtration (Figure 4). To a solution of the solid intermediate in acetic acid was added concentrated sulfuric acid (0.03 mL) and

the mixture was refluxed for 1 hour. The cooled mixture was poured into ice and the product was collected by suction filtration and washed with water. The product was recrystallized from petroleum (0.13 g, 63%). IR (Nujol oil): $\nu_{max}(cm^{-1})$ = 1706, 1637, 1577, 1259; λ_{max} (nm) (log ε) 252 (3.87), 288 (4.22), 312 (4.67), 455 (1.45); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 6.82 (s, 1H, H-3), 7.28 (d, 1H, J = 13.6 Hz, H-7′), 7.33 (d, 2H, J = 8.2 Hz, H-2′ and H-6′), 7.43 (m, 4H), 7.57 (m, 3H), 7.71 (m, 1H, H-7), 7.83 (d, 2H, J = 8.2 Hz, H-3′ and H-5′), 8.02 (d, 1H, J = 13.6 Hz, H-8′), 8.23 (m, 1H, H-5); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 108.0 (C-3), 118.5 (C-8), 124.4 (C-6), 125.6 (C-9), 125.7 (C-7′, C-8′), 126.2 (C-2′, C-6′), 126.7 (C-10′, C-14′), 129.4 (C-1′), 129.5 (C-12′), 129.6 (C-3′, C-5′), 130.2 (C-11′, C-13′), 132.0 (C-5), 132.2 (C-4′), 134.2 (C-9′), 142.7 (C-7), 156.7 (C-10), 164.1 (C-2), 179.0 (C-4).

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