

A Novel Approach to the Synthesis of 6-Amino-7-hydroxy-flavone

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Abstract: A novel approach to the synthesis of 6-amino-7-hydroxyflavone (**1**) is described. Reaction in acetone of 2',4'-dihydroxy-5'-nitroacetophenone and benzoyl chloride in the presence of potassium carbonate affords 3-benzoyl-7-hydroxy-6-nitroflavone, which is cleaved in 5% ethanolic potassium hydroxide to give 1-(2,4-dihydroxy-5-nitrophenyl)-3-phenyl-1,3-propanedione. The 1,3-diketone thus formed is then transformed into 7-hydroxy-6-nitroflavone, followed by reduction to afford the title compound.

Keywords: Flavones; 4*H*-1-benzopyran-4-one; aminoflavones; chromones.

Introduction

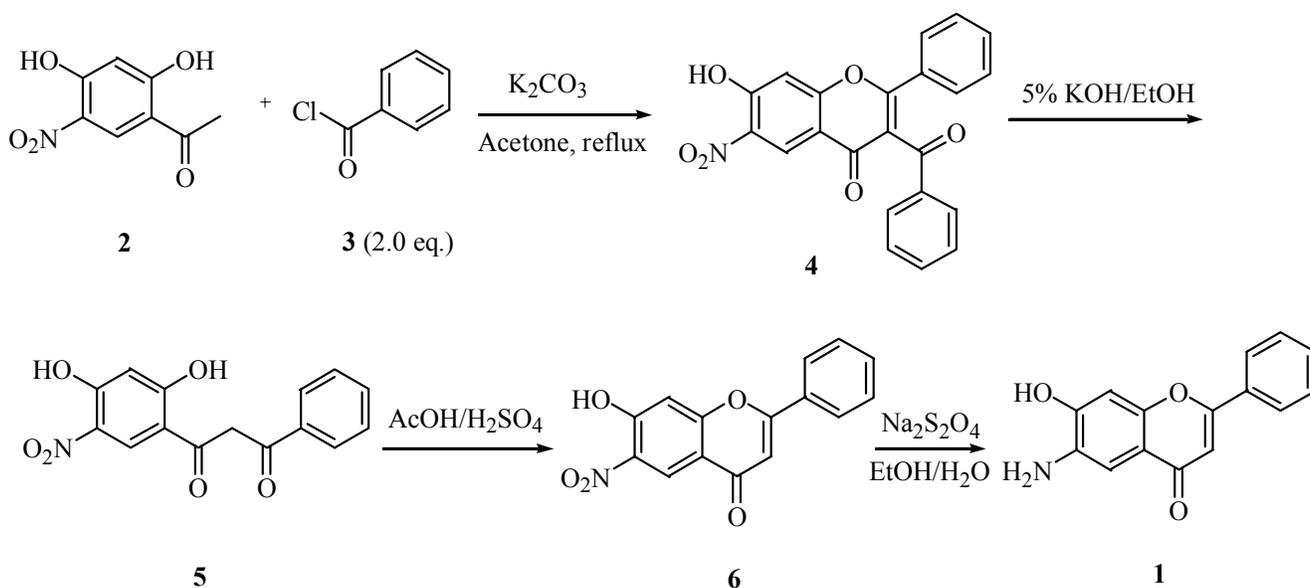
Flavones constitute one of the major classes of naturally occurring products. Synthesis of flavones and their derivatives have attracted considerable attention due to their significant biocidal [1-3], pharmaceutical [4-7] and antioxidant [8-10] activities. It has been observed that the presence of hydroxyl groups at position 5 or 7 is frequently required for higher biological activities [11,12]. On the other hand, aminoflavones have been studied as tyrosine kinase inhibitors [13] and as antimetabolic agents [14]. In light of these results we became interested in the synthesis of flavones bearing both hydroxyl and amino groups on the A-ring. We would now like to report that the title compound **1** could be prepared from 2',4'-dihydroxy-5'-nitroacetophenone (**2**) and benzoyl chloride via 3-

aroylflavone and 1,3-diketone intermediates (Scheme 1). The method presented provides an alternate synthesis of the useful 1,3-diketone intermediate, which can be easily induced to form nitro group-containing flavones by acid treatment.

Results and Discussion

It would seem that 7-hydroxy-6-nitroflavone (**6**), a potential precursor of the title compound, could be easily synthesized via the chalcone route, but the preparation of required 2',4'-dihydroxy-5'-nitrochalcone is known to be very time-consuming (10 days) [15]. A synthesis of compound **6** by a modified Baker-Venkataraman method has also been reported recently [16]. In this process, the 1,3-diketone intermediate **5** was prepared in one step by the reaction of **2** and benzoyl chloride, but this route required the use of relatively expensive lithium bis(trimethylsilyl)amide (LiHMDS) and low temperature (-78°C) conditions. Furthermore, compound **5** was not isolated nor fully characterized. The method presented herein for the preparation of compound **6** avoids both the lengthy synthesis of the corresponding chalcone precursor and the less convenient low temperature preparation of the 1,3-diketone intermediate **5**.

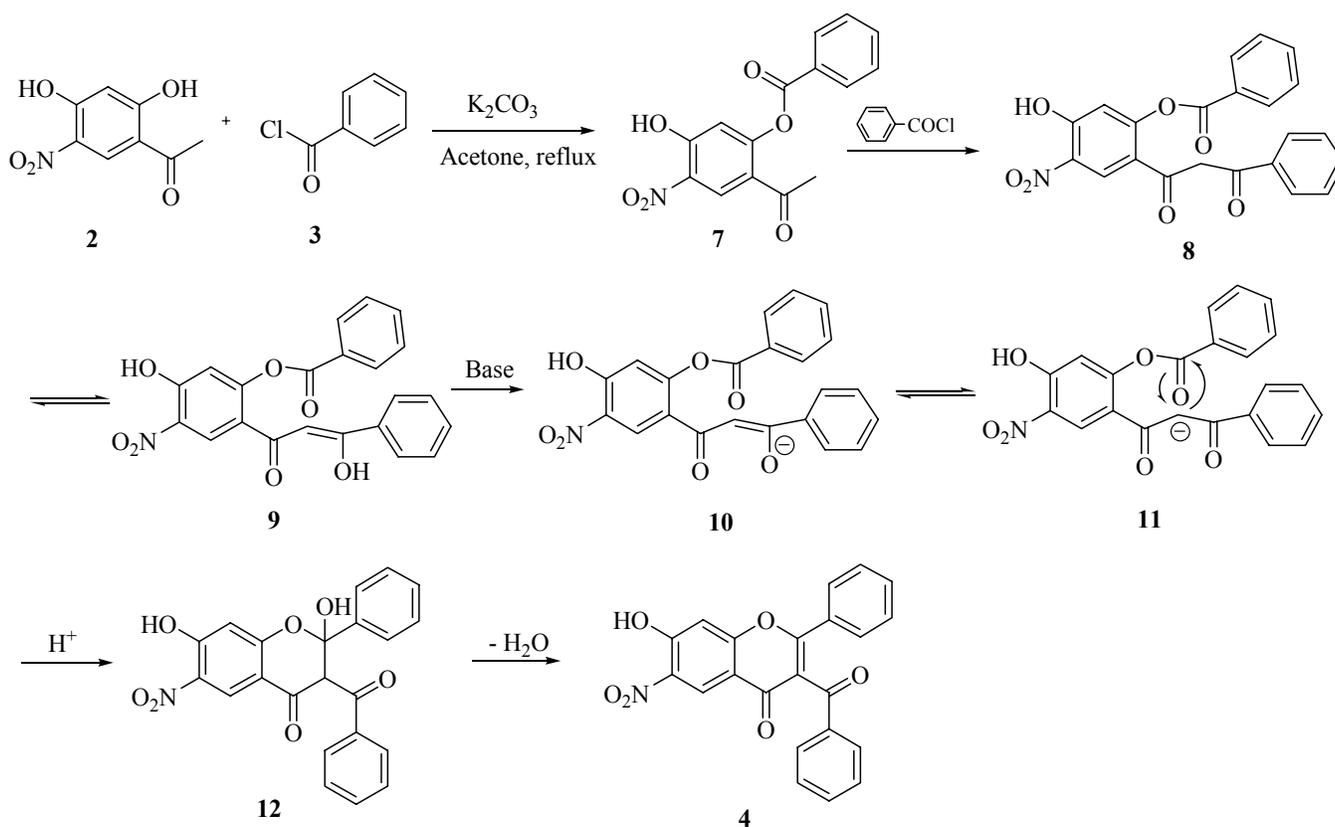
Scheme 1.



In the first attempt we reinvestigated a modified Baker-Venkataraman rearrangement, the commonly used approach. We thus tried to synthesize 1-(4-benzoyloxy-2-hydroxy-5-nitrophenyl)-3-phenyl-1,3-propanedione from 2',4'-dihydroxy-5'-nitroacetophenone (**2**) and 2.0 equivalents of benzoyl chloride in refluxing dry acetone in the presence of anhydrous potassium carbonate. However, none of the expected 1,3-diketone was observed in the obtained reaction mixture. Consequently, each

component in the mixture was separated by preparative thin layer chromatography and subsequent spectroscopic analysis revealed that they were, in order of increasing R_f values, 3-benzoyl-7-hydroxy-6-nitroflavone (**4**) (43%), 2'-benzoyloxy-4'-hydroxy-5'-nitroacetophenone (**7**) (19%) and 1-(2,4-dihydroxy-5-nitrophenyl)-3-phenyl-1,3-propanedione (**5**) (13%) respectively. These results show that the hydroxyl group adjacent to the nitro group in compound **2** cannot be acylated under the selected reaction conditions. We attribute this fact to the strong intramolecular hydrogen bonding between the nitro and hydroxyl groups, which hinders the acylation of the latter. The formation of 3-aryoylflavone **4** may be interpreted according to the mechanism proposed in Scheme 2. The initially formed monoester **7** undergoes carbanion benzylation to afford 1-(2-benzoyloxy-4-hydroxy-5-nitrophenyl)-3-phenyl-1,3-propanedione (**8**), which can exist in equilibrium with the corresponding enol form **9**. In this second step, formation of **9** takes precedence over the intramolecular Claisen condensation (Baker-Venkataraman rearrangement) because the acetyl carbanion has less nucleophilicity due to the presence of the nitro group and the acyl chloride is more activated than the ester. Compound **9** then undergoes *in situ* cyclodehydration via intermediates **10**, **11** and **12** to give the observed product **4**.

Scheme 2.



It is worth mentioning that compound **4** had been synthesized once before by the reaction of **2** with benzoic anhydride (acting as both acylating reagent and solvent) in the presence of sodium benzoate following the Kostanecki-Robinson procedure [17]. The method presented herein has the dual

advantages of requiring mild reaction conditions and affording higher yields. Our attempt to debenzoylate the benzoyl group in compound **4** by heating with potassium carbonate in dry pyridine (120-130°C) was unsuccessful, but when compound **4** was treated with 5% ethanolic KOH, TLC monitoring showed that the starting material disappeared after refluxing for 1 h, leaving two spots on the plate. These products were separated and characterized as 1-(2,4-dihydroxy-5-nitrophenyl)-3-phenyl-1,3-propanedione (**5**) and 1-(2-benzoyloxy-4-hydroxy-5-nitrophenyl)-3-phenyl-1,3-propanedione (**9**). 3-Aroylflavone **4** was converted quantitatively into the 1,3-diketone **5** when the reaction time was increased to 24 h.

Conclusions

In summary, a novel approach has been developed for the synthesis of 6-amino-7-hydroxyflavone (**1**). A convenient and readily applicable method for the synthesis of 3-benzoyl-7-hydroxy-6-nitroflavone (**4**) and 1-(2,4-dihydroxy-5-nitrophenyl)-3-phenyl-1,3-propanedione (**5**) intermediates has also been presented.

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Experimental

General

¹H-NMR spectra were recorded employing a Varian INOVA 400 NMR Spectrograph (Varian Inova Co. Ltd., USA) and chemical shifts (δ) are expressed in ppm relative to TMS used as internal standard. Infrared spectra were measured as KBr pellets with an FT/IR-430 spectrophotometer (JASCO Co. Ltd., Japan). Mass spectra were determined on a HP1100 system of HPLC/MS spectrometer (Hewlett Packard Ltd. Co., USA). High resolution mass spectra were recorded on a Mariner System 5303 (Applied Biosystems Co. Ltd., USA). Melting points were measured on an X-6 micro-melting point apparatus (Beijing Tech Instrument Co. Ltd., China) and are uncorrected. Thin layer chromatography (TLC) was carried out on silica coated glass sheets (Merck silica gel 60 F-254). 2',4'-Dihydroxy-5'-nitroacetophenone (**2**) was prepared according to a literature method [13]. Other reagents were commercial analytical grade and used as received, except for the acetone, which was dried over K₂CO₃ and distilled before use.

Synthesis of 3-benzoyl-7-hydroxy-6-nitroflavone (**4**).

Anhydrous potassium carbonate (27.0 g, 0.194 mol) was added to a stirred solution of 2',4'-dihydroxy-5'-nitroacetophenone (**2**, 5.30 g, 27.0 mmol) in dry acetone (300 mL). The mixture was

stirred at room temperature for 10 min and then benzoyl chloride (7.59 g, 54.0 mmol) was added dropwise and the mixture was stirred at room temperature for an additional 0.5 h. After refluxing for 24 h, the solvent was evaporated under reduced pressure. The residue was cooled to room temperature and acidified in a beaker with dilute hydrochloric acid to weak acidity. The precipitate formed was filtered off, dried and then recrystallized from acetic acid, affording **4** as off-white needles in 36% yield, mp. 279–281 °C (lit. [17] mp 272–273 °C); ¹H-NMR (CDCl₃) δ: 10.920 (s, 1H), 9.066 (s, 1H), 7.892 (d, 2H, J = 7.6 Hz), 7.633 (d, 2H, J = 7.6 Hz), 7.550 (m, 1H), 7.354–7.473 (m, 5H), 7.270 (s, 1H); IR: 3170, 3060, 1672, 1637, 1614, 1577, 1556, 1529, 1367, 1267, 1253, 1190 cm⁻¹; API-ES-MS (negative) m/z (%): 386 ([M-H]⁻, 100), 387 ([M]⁻, 25).

Synthesis of Compounds **5** and **9**.

Compound **4** (1.50 g, 3.88 mmol) was added to 5% ethanolic KOH (50 mL) at room temperature, and the mixture was stirred and heated to reflux for 1 h. After cooling to room temperature, the mixture was diluted with ice cold water and acidified. The precipitated products were filtered, washed with water, dried and then purified on preparative thin layer chromatographic plates (eluent: 1:7 ethyl acetate/petroleum ether) to afford compounds **5** and **9** in 32% and 64% yield, respectively. Compound **5** was obtained in 97% yield when the reaction time was increased to 24 h.

1-(2,4-dihydroxy-5-nitrophenyl)-3-phenyl-1,3-propanedione (5): Yellow needles, mp 220–222 °C (recrystallization from acetone); ¹H-NMR (CDCl₃) δ: 15.119 (s, 1H), 12.944 (s, 1H), 10.991 (s, 1H), 8.683 (s, 1H), 7.973 (d, 2H, J = 7.6 Hz), 7.525–7.600 (m, 3H), 6.773 (s, 1H), 6.626 (s, 1H) (this species exists completely in enolic form); IR: 1604, 1560, 1492, 1297, 1220, 1196, 1078 cm⁻¹; HRMS (ESI) for C₁₅H₁₀NO₆ ([M-H]⁻): Calcd. 300.0508; Found 300.0508.

1-(2-benzoyloxy-4-hydroxy-5-nitrophenyl)-3-phenyl-1,3-propanedione (9): Yellow needles, mp 180–182 °C (recrystallization from acetone); ¹H-NMR (CDCl₃) δ: 16.535 (s, 1H), 10.898 (s, 1H), 8.805 (s, 1H), 8.237 (d, 2H, J = 8.4 Hz), 7.654–7.724 (m, 3H), 7.468–7.563 (m, 3H), 7.302–7.341 (m, 2H), 7.157 (s, 1H), 6.719 (s, 1H); IR: 3444, 1745, 1633, 1242, 1157, 1054 cm⁻¹; HRMS (ESI) for C₂₂H₁₄NO₇ ([M-H]⁻): Calcd. 404.0770; Found 404.0754.

Preparation of 7-hydroxy-6-nitroflavone (**6**)

Compound **5** (0.301 g, 1.0 mmol) was added to glacial acetic acid (10 mL) containing two drops of concentrated sulfuric acid and the resulting mixture was heated at 100 °C for 1 h. After cooling the reaction mixture to ambient temperature, water (20 mL) was added and the precipitate formed was collected by filtration, washed with water, dried and then recrystallized from acetone, affording 0.255 g of compound **6** (90%) as pale yellow plates, mp: 237–238 °C (lit. [16] mp 220–222 °C); ¹H-NMR (DMSO-*d*₆) δ: 12.340 (s, broad, 1H), 8.477 (s, 1H), 8.119 (d, 2H, J = 7.2 Hz), 7.603 (m, 3H), 7.327 (s, 1H), 7.050 (s, 1H); IR: 3444, 1653, 1630, 1531, 1450, 1355 cm⁻¹.

Synthesis of 6-amino-7-hydroxyflavone (1).

Compound **6** (0.528 g, 1.87 mmol) was taken up in ethanol/water (36 mL, 2:1 v/v) and heated under reflux. Sodium dithionite (0.422 g, 2.43 mmol) was added portionwise into the flask till the compound dissolved completely to give a yellow colored solution. An excess of approximately 0.10 g sodium dithionite was then added and the solution was refluxed for further 2 h. The ethanol was distilled under reduced pressure and the remaining solution was poured into cold water (30 mL). The precipitate formed was filtered, air dried and recrystallized from toluene, giving **1** as yellow needles (64%), mp: 253-256°C (decomposed); ¹H-NMR (DMSO-*d*₆) δ: 8.003-8.026 (m, 2H), 7.553-7.568 (m, 3H), 7.144 (s, 1H), 6.950 (s, 1H), 6.782 (s, 1H); IR: 3399, 3322, 1624, 1579, 1375 cm⁻¹; HRMS (ESI) for C₁₅H₁₂NO₃ ([M+H]⁺): Calcd. 254.0817; Found 254.0795.

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Sample Availability: Samples of compounds **1**, **4**, **5**, **6** and **9** are available from the authors.

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