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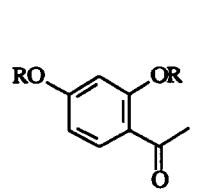
A METHOD FOR THE FACILE SYNTHESIS OF RING-A HYDROXYLATED FLAVONES

Mark Cushman* and Dhanapalan Nagarathnam
Department of Medicinal Chemistry and Pharmacognosy
Purdue University, West Lafayette, Indiana 47907

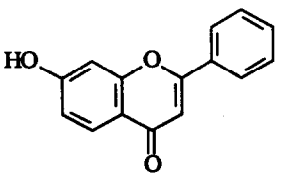
Abstract: A general method for the facile synthesis of ring-A hydroxylated flavones is described. Treatment of the hydroxylated acetophenones **6a-d** with enough lithium bis(trimethyl)silyl amide to deprotonate all of the phenols as well as to generate the lithium enolate of the ketone, followed by addition of the acid chlorides **7a-d,** gave the 1,3-diketones **8a-g**, which were cyclized to the desired products **9a-g** in high yield.

Recent interest in ring-A hydroxylated flavones stems from their ability to inhibit retroviral reverse transcriptases,[1,2,3] including HIV reverse transcriptase,[2,3] as well as their capacity to inhibit protein tyrosine kinases[4,5] and serine/threonine kinases.[4] In fact, a naturally occurring ring-A hydroxylated flavone and several related compounds have recently been shown to inhibit HIV-induced syncytium formation.[6] In addition, these substances have been found to possess anticancer[7,8] and chemopreventative activity.[8] Methods available for the synthesis of ring-A hydroxylated flavones include the Kostanecki reaction, in which e.g. resacetophenone (**1**) is heated with benzoic anhydride and sodium benzoate, followed by hydrolysis, to afford 7-hydroxyflavone (**2**).[9] However, the desired products of this method are isolated in low yields from complex reaction mixtures that often yield 3-aroylflavones as the main products.[9,10,11] An alternative method which often proceeds in better overall yield is the Baker-Venkataraman rearrangement pathway, in which e.g. resacetophenone dibenzoate (**3**) undergoes a base-catalyzed rearrangement to the 1,3-diketone **4**, followed by cyclodehydration and hydrolysis of the benzoate to yield **2**.[10,12,13,14] The main disadvantage of this method is that it requires multiple operations in which several benzoate groups must first be installed and then removed after the rearrangement and cyclodehydration steps. In addition, this method also often results in the formation of 3-aroylflavones instead of the desired 3-unsubstituted flavones.[11] A third method for the preparation of ring-A hydroxylated flavones involves an intramolecular Wittig reaction. Reaction of resacetophenone dibenzoate (**3**) with bromine followed by triphenylphosphine affords the triphenylphosphonium salt **5**, which on treatment with sodium carbonate followed by hydrolysis with sodium hydroxide gives flavone **2**.[15,16] This method effectively avoids the formation of 3-aroylflavones, but involves multiple steps.

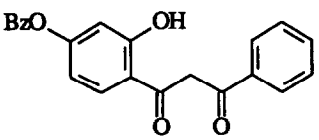
We have recently devised a method for hydroxyflavone synthesis that is short, avoids the intermediacy of *O*-aroylated intermediates, and provides the desired products in high yield without contamination from undesired side products (Scheme I). The key step in this process is the generation of lithium polyanions from the polyhydroxylated acetophenones **6** using enough lithium bis(trimethyl)silyl amide to ensure the generation of the



1, R = H
3, R = Bz



2



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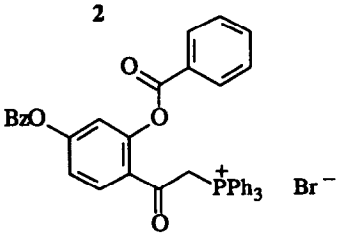
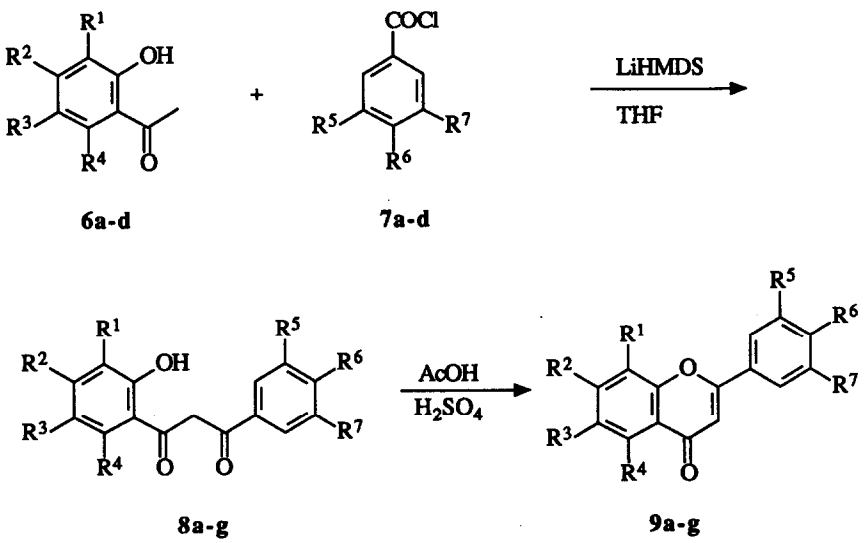


5

Scheme 1



lithium enolates from the acetyl groups. Treatment of these lithium polyanions with one equivalent of aroyl chlorides **7a-d** afforded the 1-(2-hydroxyphenyl)-3-phenyl-1,3-propanediones **8a-g**. An extensive study revealed that four and five equivalents of the base were required for optimal yields of the diketones **8** when di- and trihydroxyacetophenones were employed as starting materials, respectively. The ^{1}H NMR analysis of these intermediates showed that most of them exist as a mixture of tautomers.[17] They cyclized to the corresponding mono- and dihydroxyflavones **9a-g** upon heating in glacial acetic acid containing 0.5% sulfuric acid at 95-100 °C for 1 h.

The formation of the 1,3-diketones **8** from the polyanions derived from **6** and the aroyl chlorides **7** appears to involve direct acylation of the enolate as opposed to *O*-acylation followed by Baker-Venkataraman rearrangement. This was indicated by the observation that during the monitoring of aliquots of the reaction mixtures by ^{1}H NMR, only the starting materials **6** and **7** and the products **8** were detected. In addition, enolate formation from **6** was proven by quenching the polyanions derived from **6** with D_2O. ^{1}H NMR analysis of the deuterated products showed the replacement of the 3 H singlet of the methyl groups of the starting acetophenones with three lines of equal intensity for 2 H. In general, Baker-Venkataraman rearrangements require higher temperatures than were employed during the formation of the diketones **8** by the present method.

The scope of this reaction was studied using 2,4- and 2,5-dihydroxyacetophenones **6a** and **6b** and 2,3,4-trihydroxy- and 2,4,6-trihydroxyacetophenones **6c** and **6d**, as well as benzoyl, methoxyl, and nitro substituted benzoyl chlorides **7a-d**. All of these reactions gave the desired hydroxylated flavones in 89-96% yields. The yields of the product and their melting points are listed in Table I.

Table I. Physical characteristics and yields of flavones **9a-g**.

Compd	R^1	R^2	R^3	R^4	R^5	R^6	R^7	Yield	mp. °C (Lit. mp. °C)
9a	H	OH	H	H	H	H	H	92	241-243 (240)[10]
9b	OH	OH	H	H	H	H	H	89	250-251 (250)[16]
9c	H	OH	H	OH	H	OMe	H	91	260-261 (260, 261)[9,14]
9d	H	OH	H	H	OMe	OMe	OMe	96	279-280 (279-280)[18]
9e	H	OH	H	H	H	NO_2	H	96	308-309 (308-310)[13]
9f	H	H	OH	H	H	NO_2	H	94	318-320[19]
9g	OH	OH	H	H	H	NO_2	H	95	310-312[19]

Typical Experimental Procedure: 7-Hydroxy-4'-nitroflavone (9e). A solution of LiHMDS in THF (1 M, 80 mL, 80 mmol) was added to a well-stirred solution of 2,4-dihydroxyacetophenone (3.04 g, 20 mmol) in THF under argon atmosphere at -78 °C in 15 min. The reaction mixture 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 4-nitrobenzoyl chloride (3.70 g, 20 mmol) in THF (15 mL) was added in 10 min. Stirring was continued for 30 min at -78 °C and at room temperature for 4 h and the reaction mixture was poured into a mixture of ice water (500 g) and HCl (20 mL). It was extracted with $CHCl_3$ (3 x 50 mL) and the combined extracts were dried (Na_2SO_4). Solvent was evaporated, and the residue was

mixed with glacial acetic acid (100 mL) and H_2SO_4 (0.5 mL) and heated at 95-100 °C for 1 h. About 75% of the solvent was removed at reduced pressure and the residue was poured into ice water (500 mL). The product was filtered, washed with water and dried to give **9e** (5.43 g, 96%). An analytical sample was prepared by recrystallization from acetone.

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(19) ^1H NMR (DMSO-d_6, 500 MHz). **9f**: δ 13.55 (bs, 1 H, exchanges with D_2O), 8.34 (ABq, J = 7.9 Hz, 4 H), 7.50 (d, J = 9.15 Hz, 1 H), 7.07 (m, 2 H), 7.04 (s, 1 H); **9g**: δ 10.44 (bs, 1 H, exchanges with D_2O), 9.64 (bs, 1 H, exchanges with D_2O), 8.43 (d, J = 9.0 Hz, 2 H), 8.40 (d, J = 9.0 Hz, 2 H), 7.43 (d, J = 8.6 Hz, 1 H), 7.11 (s, 1H), 7.00 (d, J = 8.6 Hz, 1 H). Both of these compounds gave satisfactory microanalysis values for carbon and hydrogen.

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