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SYNTHESIS OF RING-A HYDROXYLATED FLAVONES BY SODIUM HYDROXIDE-CATALYZED CYCLIZATION OF 1,3-DIKETONES IN WATER

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SYNTHESIS OF RING-A HYDROXYLATED FLAVONES BY SODIUM HYDROXIDE-CATALYZED CYCLIZATION OF 1,3-DIKETONES IN WATER

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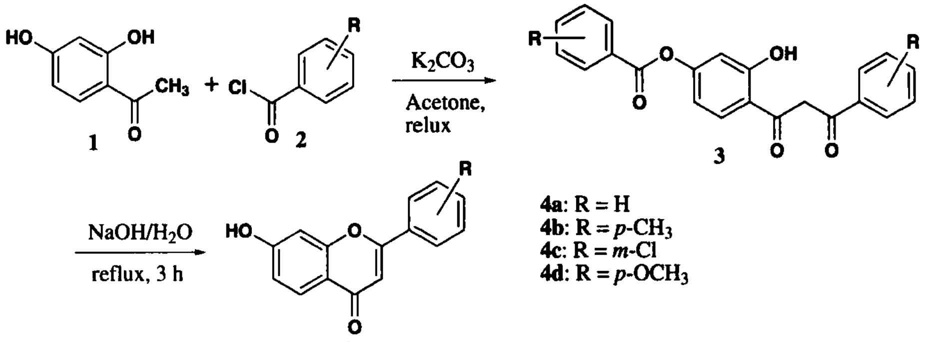
Flavonoids are a group of naturally occurring phenolic compounds widely distributed in the plant kingdom, the most abundant being the flavones. Members of the flavone class have been associated with a wide variety of biological properties, such as antitumor,[1-3] biocidal[4] and antioxidant[5,6] activities. Owing to their importance, the synthesis of flavones and their derivatives have attracted the attention of chemists for many years.

Currently there are a number of methods available to synthesize flavones,[7] including the Allan-Robinson synthesis,[8] the Baker-Venkataraman method,[9] synthesis from chalcones,[10] and synthesis *via* an intramolecular Wittig strategy,[11] etc. We would like to report herein that 6- and 7-hydroxyflavones can be synthesized by sodium hydroxide-catalyzed cyclization of the corresponding 1,3-diketone in water, the procedures are shown in *Schemes 1* and *2*, respectively.

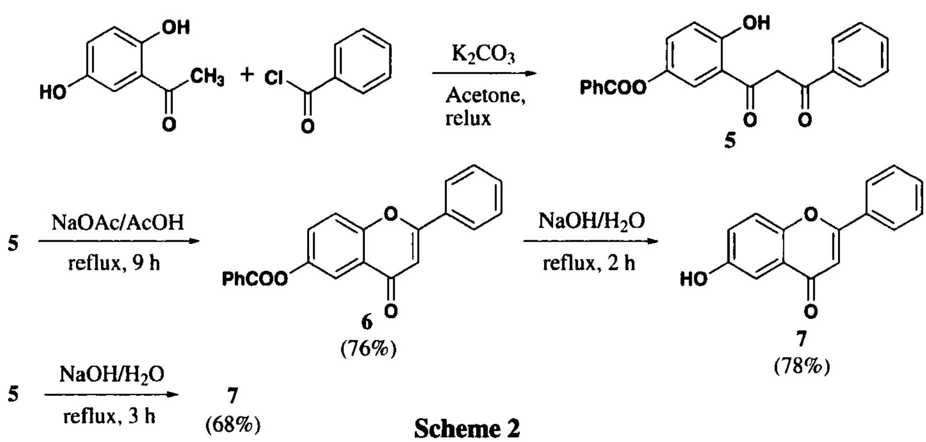


4a: R = H
4b: R = p-CH_3
4c: R = m-Cl
4d: R = p-OCH_3

Scheme 1

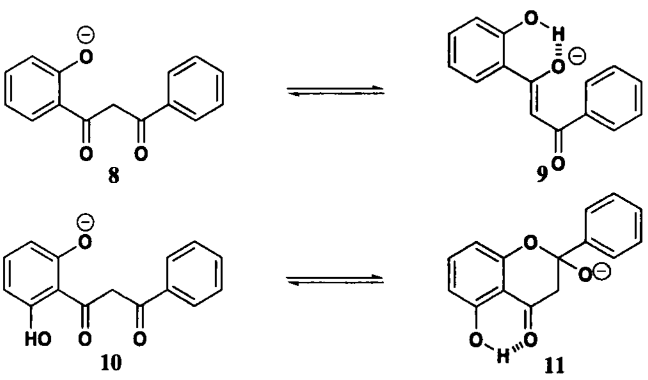
Among the reported methods for flavone synthesis, the Baker-Venkataraman approach is usually preferred. It is worth noting that during the cyclization process of the 1,3-diketone to form the corresponding flavone, the reaction medum is usually acidic, such as $AcOH/H_2SO_4$,[12-15] AcONa/AcOH[11], TosOH,[17] and AcOH/HCl,[18] etc. However, studies on base-catalyzed cyclization of 1,3-diketones to form flavones were rare, and are limited to *t*-BuOK[19] and K_2CO_3,[20] the latter is limited to the synthesis of 5-hydroxyflavones. The utilization of aqueous sodium hydroxide in the cyclization process of 1,3-diketones has not been reported so far.

In our initial experiments, the Baker-Venkataraman method was reinvestigated in which AcONa/AcOH was used in the cyclization step. While it is interesting to note that 7-hydroxyflavone (**4a**) could be obtained in good yield from 1,3-diketone **3a**, 6-hydroxyflavone (**7**) was formed when 1,3-diketone **5** was treated with AcONa/AcOH as for **3a**, followed by hydrolysis of compound **6** (*Scheme 2*). This also demonstrated that the 6-hydroxyflavone backbone is stable in the prevailing alkaline condition. The result prompted us to combine the cyclization and hydrolysis steps in one pot by a base-catalyzed process. Thus, 1,3-diketone **5** was treated in refluxed aqueous sodium hydroxide (1%) for 3 h, then the mixture was cooled to room temperature and acidified with dilute hydrochloride. The precipitate was collected by filtration and washed successively with water, 5% sodium bicarbonate and water. The crude product was dried and recrystallized from ethanol, yielding 6-hydroxyflavone as pale yellow needles. 7-Hydroxyflavones were also prepared in reasonable yield when the similar procedure was employed.



Scheme 2

Bois *et al.* reported a one-pot synthesis of 5-hydroxyflavones[20] *via* treatment of 2,6-dihydroxyacetophenone with aroyl chlorides in refluxing acetone in the presence of K_2CO_3. They also reported that 2-hydroxyacetophenone did not give flavones when subjected to the same experimental conditions. It was postulated that the 1,3-diketone intermediate **8** prepared from 2-hydroxyacetophenone might adopt the more stable enol form **9**, thus the cyclization process was inhibited. 1,3-Diketone **10** derived from 2,6-dihydroxyacetophenone can exist in equilibrium with the cyclic intermediate **11** (*Fig. 1*). When **11** is acidified, the protonated hydroxyl group formed can be eliminated to give 5-hydroxyflavone.



The Proposed Form of 1,3-Diketone Intermediates in Acetone

Fig. 1

In this study, each of the 1,3-diketones **3** and **5** has only one hydroxyl group adjacent to the carbonyl group, but the desired flavones **4** and **7** were obtained in reasonable yield by sodium hydroxide-catalyzed cyclization of the corresponding 1,3-diketones, respectively. This can be attributed to that the diketone form of **3** and **5** are more stable than the enol form in the polar and protic solvent, *i.e.*, water, thus the cyclodehydration process could proceed.

Table 1. Physical and Spectroscopic Data of Compounds **4** and **7**

Entry	Yield (%)	IR (cm^{-1})	MS m/z ($M+H^+$)	Melting Point (°C) Observed	*lit.*
4a	76	1626, 1560, 1574, 1549	239	240-243	240-243[21]
4b	52	1626, 1593, 1576, 1560	253	278-280	278-280[22]
4c	46	1624, 1572	273	267-269	269-271[22]
4d	38	1627, 1577, 1546	269	261-263	262-264[22]
7	68	1625, 1593, 1581, 1567	239	231-233	231-232[21]

All products were identified by IR, ^1H NMR and MS analysis.

In summary, a convenient preparation of 6- and 7-hydroxyflavones has been developed. In view of the variation of the aroyl chloride used, a number of ring-B substituted 6- and 7-hydroxyflavones can be synthesized by this method.

EXPERIMENTAL SECTION

1,3-Diketones **3a-3d** and **5** were prepared according to literature method.[22] ^1H NMR spectra were recorded on a Varian INOVA 400 NMR spectrometer in $CDCl_3$ or DMSO-d_6 using TMS as internal standard. IR spectra were measured with a FT/IR-430 spectrophotometer. Mass spectra were recorded on a HP1100 system of HPLC/MS spectrometer (HEWLETT PACKARD Ltd. Co., USA) by using atmospheric pressure chemical ionization (APCI) technique. Melting points were measured on an X-6 micro-melting point apparatus and are uncorrected.

Typical Procedure.- To a stirred solution of aqueous sodium hydroxide (1%, 40 mL) was added **3a** (1.80 g, 0.005 mole), and the mixture was heated to reflux for 3 h. After cooling to room temperature, the mixture was acidified with 2M hydrochloric acid, the precipitate formed was collected and washed successively with water, 5% sodium bicarbonate and water. The crude product was dried and recrystallized from ethanol to give 7-hydroxyflavone (**4a**) as off-white needles.

Compounds **4b**, **4c**, **4d** and **7** were prepared by the same procedure.

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