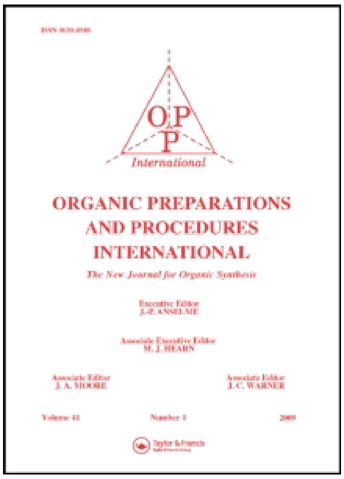


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

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

Lijun Tang[a][b]; Shufen Zhang[a]; Jinzong Yang[a]; Wentao Gao[b]; Jian Cui[a]
[a] State Key Laboratory of Fine Chemicals, Dalian University of Technology, Dalian, PR CHINA [b] Institute of Superfine Chemicals, Bohai University, Jinzhou, PR CHINA

To cite this Article Tang, Lijun , Zhang, Shufen , Yang, Jinzong , Gao, Wentao and Cui, Jian(2004) 'SYNTHESIS OF RING-A HYDROXYLATED FLAVONES BY SODIUM HYDROXIDE-CATALYZED CYCLIZATION OF 1,3-DIKETONES IN WATER', Organic Preparations and Procedures International, 36: 5, 453 — 457

To link to this Article: DOI: 10.1080/00304940409356629

URL: http://dx.doi.org/10.1080/00304940409356629

ORGANIC PREPARATIONS AND PROCEDURES INT., 36 (5), 453-457 (2004)

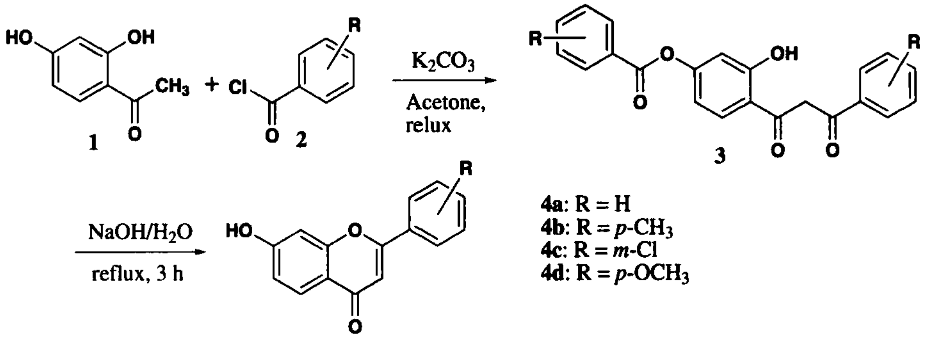
SYNTHESIS OF RING-A HYDROXYLATED FLAVONES BY SODIUM HYDROXIDE-CATALYZED CYCLIZATION OF 1,3-DIKETONES IN WATER

Lijun Tang[†,††], Shufen Zhang[*,†], Jinzong Yang[†], Wentao Gao[††] and Jian Cui[†]

[†] *State Key Laboratory of Fine Chemicals, Dalian University of Technology*
158-40 Zhongshan Road, Dalian 116012, P. R. CHINA
[††] *Institute of Superfine Chemicals, Bohai University*
5-27 Jiefang Road, Jinzhou 121003, P. R. CHINA

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.

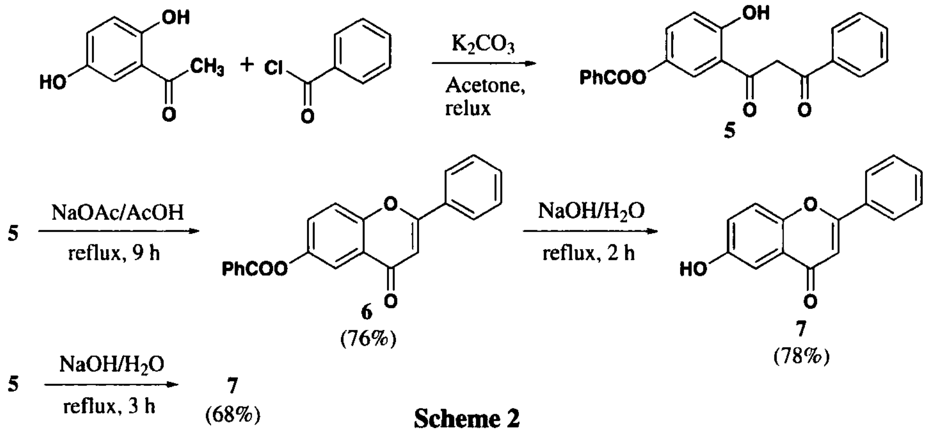
Currently there are a number of methods available to synthesize flavones,[7] including the Allan-Robinson synthesis,[8] the Baker-Venkataraman method,[9] synthesis from chalcones,[10] and synthesis *via* an intramolecular Wittig strategy,[11] etc. We would like to report herein that 6- and 7-hydroxyflavones 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.



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.

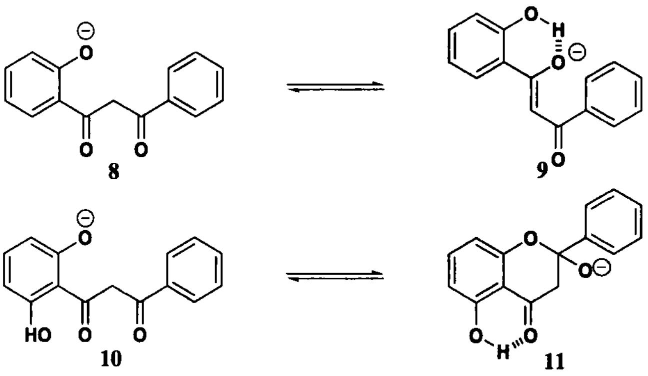
In our initial experiments, the Baker-Venkataraman method was reinvestigated in which AcONa/AcOH was used in the cyclization step. While it is interesting to note that 7-hydroxyflavone (**4a**) could be obtained in good yield from 1,3-diketone **3a**, 6-hydroxyflavone (**7**) was formed when 1,3-diketone **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



Scheme 2

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.

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.

Acknowledgement.- Sincere thanks are expressed to the National Natural Science Foundation of China (No. 20276009) and the Trans-Century Training Program Foundation for the Talents of the State Education Commission for financial support.

REFRENCES

1. H. K. Wang, Y. Xia, Z. Y. Yang, S. L. Natschke and K. H. Lee, *Adv. Exp. Med. Biol.*, **439**, 191 (1998).
2. M. Cushman and D. Nagarathnam, *J. Nat. Prod.*, **54**, 1656 (1991).
3. J. F. Post and R. S. Varma, *Cancer Lett.*, **67**, 207 (1992).
4. M. Weidenborner and H. C. Jha, *Pestic. Sci.*, **38**, 347 (1993).
5. S. V. Jovanovic, S. Steenken, M. Tosic, B. Marjanovic and M. G. Simic, *J. Am. Chem. Soc.*, **116**, 4846 (1994).
6. C. A. Rice-Evans, N. J. Miller and G. Paganga, *Free Radic. Biol. Med.*, **20**, 933 (1996).
7. L. M. Wang, *Chin. J. Pharm.*, **21**, 423 (1990); *Chem. Abstr.*, **114**, 101389 (1991).
8. J. Allan and R. Robinson. *J. Chem. Soc.*, 2192 (**1924**).
9. H. S. Mahal and K. Venkataraman. *J. Chem. Soc.*, 1767 (**1934**).
10. Y. Hoshino, T. Oohinate and N. Takeno. *Bull. Chem. Soc. Jpn.*, **59**, 2351 (1986).
11. Y. LeFloc'h and M. LeFeuvre. *Tetrahedron Lett.*, 5503 (1986).
12. S. Mahboobi and H. Pongratz, *Synth. Commun.*, **29**, 1645 (1999).
13. D. Nagarathnam and M. Cushman, *Tetrahedron*, **47**, 5071 (1991).
14. M. Cushman and D. Nagarathnam, *Tetrahedron Lett.*, **31**, 6497 (1990).
15. D. Nagarathnam and M. Cushman, *J. Org. Chem.*, **56**, 4884 (1991).

16. P. E. Kumar and K.J. Rajendra Prasad, *Indian. J. Chem.,* **38B**, 1277 (1999).

17. P. K. Jain, J. K. Makarandi and S. K. Gover, *Synthesis*, 221 (**1982**).

18. I. Hirao, M. Yamaguchi and M. Hamada, *Synthesis*, 1076 (**1984**).

19. N. Z. Deka, M. Hadjeri, M. Lawson, C. Beney and A. Boumendjel, *Heterocycles,* **57**, 123 (2002).

20. F. Bois, C. Beney, A. M. Mariotte and A. Boumendjel, *Synlett*, 1480 (**1999**).

21. J. Buckingham and F, Macdonald, *Dictionary of Organic Compounds* (Sixth Edition), Chapman & Hall, 3648 (1996).

22. B. S. Yan, T. M. Sun and Z. Q. Wu, *Chin. J. Med. Chem.*, **4**, 36 (1994); *Chem. Abstr.*, **122**, 132909 (1995).

(Received April 14, 2004; in final form September 14, 2004)