SYNTHESIS OF HYDROXYFLAVANONES FROM SUBSTITUTED ACETOPHENONES AND BENZALDEHYDES IN THE PRESENCE OF SILICA GEL, BORIC ACID AND PIPERIDINE

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Abstract- Direct synthesis of hydroxyflavanones from appropriately substituted acetophenones and benzaldehydes was achieved in the presence of boric acid, silica gel and piperidine. The formation of flavanones presumably involved the reaction between the acetophenone-boric acid complex (**1**) and the piperidino-aldehyde adduct (**2**) to yield the piperidino ketone (**3**). Elimination of piperidine from **3** gave the chalcone (**4**), which cyclized to flavanone (**5**).

INTRODUCTION

The most common method in flavanone synthesis is the condensation of hydroxyacetophenone with suitably substituted benzaldehyde in alkaline condition to give the chalcone and then the flavanone.[1] Acid condensation of ketones and aldehydes,[2,3] are less effective in the synthesis of flavanones.[4] Other less commonly used approaches include condensation of aromatic aldehydes with malondinitrile,[5] transformation of appropriate substituted 3-bromo-1-phenylprop-2-ynyl aryl ethers to flavanone,[6] and the formation of flavanone *via* an isoxazoline route.[7] It should be noted that none of these methods are a single step reaction process. In our previous study, boric acid was used to couple the hydroxyacetophenone with hydroxybenzaldehyde successfully to give polyhydroxyflavanone,[8] however, the yields of the reaction were not satisfactory, ~ 30%. In this study,

in order to increase the yield of flavanone, silica gel was used as adsorbent to promote the cyclization of chalcones to give flavanones according to the documented method.[9] Furthermore, the activity of the aldehyde in the reaction was enhanced with piperidine. This activated reactivity between acetophenone and aldehyde should be in a similar manner as reported in the preparation of α-azidochalcones.[10]

RESULTS AND DISCUSSION

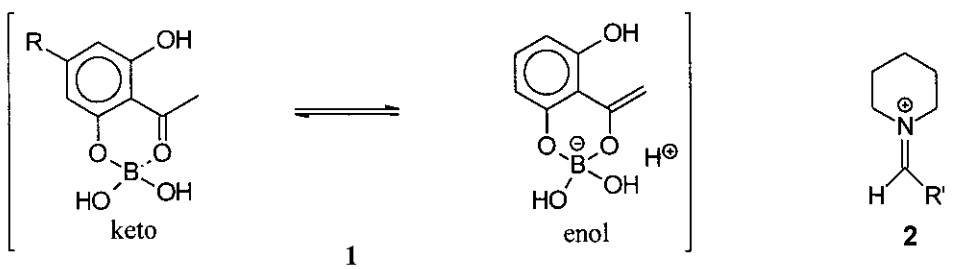
This article reports on the synthesis of nine hydroxyflavanones using 2,6-dihydroxyacetophenone/2,6-dihydroxy-4-methoxyacetophenone and suitably substituted benzaldehydes in the presence of silica gel, piperidine and boric acid. The yields of flavanones in this single step process ranged from 50 to 80% (Table 1).

Table 1. Preparation of flavanones

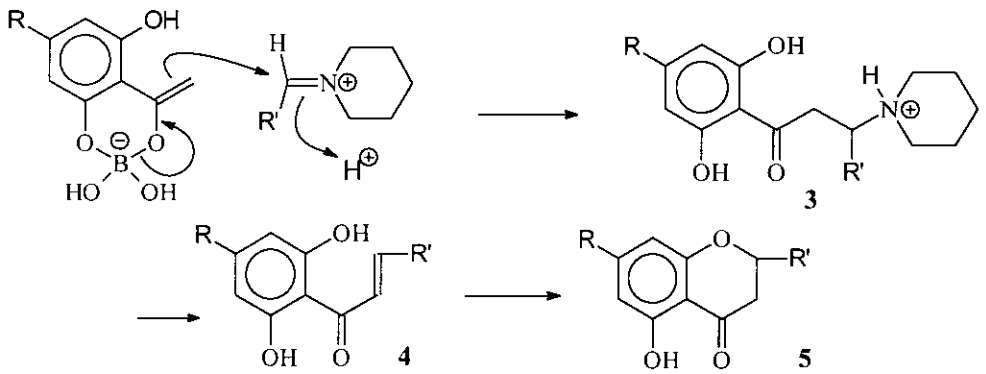
Flavanone	time/h	mp/°C	yield(%)
*5,4'-dihydroxy-3'-methoxy-	12	159-161 (lit., 163-165)[12]	74
2'-chloro-5-hydroxy-	6	80-82	76
*5,4'-dihydroxy-	12	206-207 (lit., 206-208)[12]	78
4'-cyano-5-hydroxy-	12	115-117	72
*5-hydroxy-	6	[a]50-52 (lit., 62-63)[13]	80
5-hydroxy-4'-nitro-	11	118-120	74
*5,3',4'-trihydroxy-[14]	8	[b]197-199	56
*5,3',5'-trihydroxy-7-methoxy-	10	151-152 (lit., 151-152)[8]	50
*5,3',4'-trihydroxy-7-methoxy-	10	220-222 (lit., 220-222)[8,11,15]	60

*Known compound; [a]mp does not match with the reported value; [b]mp was not reported before.

In the presence of boric acid, acetophenone-boric acid complex (**1**) was formed. The concentration of enol form in the complex should be higher than in the free acetophenone due to the formation of boron-oxygen bond, and it is the enol form reacted with the activated aldehyde adduct (**2**) to give the intermediate (**3**).



The proposed mechanisms of formation of flavanone is depicted in Scheme 1.



Scheme 1

In order to study the effects of silica gel, boric acid and piperidine on the synthesis of flavanone, a series of preparations of 5,4'-dihydoxyflavanone (**5**. R=H, R'=4-hydroxy-phenyl) have been carried out. The results are presented in Table 2.

Table 2. Synthesis of 5,4'-dihydroxyflavanone:
2,6-dihydroxyacetophenone (10 mmol) : 4-hydroxybenzaldehyde (10 mmol)

SiO_2/(mmol)	H_3BO_3/(mmol)	piperidine/(mmol)	solvent	time/h	yield(%)
10	15	0	diglyme	24	30
10	15	2.5	toluene	18	43
10	15	2.5	DMF	12	74
10	0	2.5	diglyme	24	20
10	15	2.5	diglyme	12	78
0	15	2.5	diglyme	18	64

Our results clearly indicated the significance of the presence of boric acid and piperidine, while the silica gel was found to be less important. Low yield of the product in toluene was ascribed to the low solubility of the reactants. On the other hand, the yield of flavanone in DMF was lower than the yield in diglyme, which was due to the high solubility of the reactants in DMF. In DMF the adsorption of chemicals on silica gel was much reduced. In summary, this is a facile route to the synthesis of flavanone with high yield by the direct coupling of hydroxyacetophenone with substituted benzaldehyde.

EXPERIMENTAL

Appropriate acetophenone (10 mmol) and benzaldehyde (10 mmol) were added to a mixture of H_3BO_3 (0.93 g, 15 mmol), piperidine (0.22 g, 2.5 mmol) and SiO_2 (5 g) in diglyme (20 ml). The content was stirred and heated at 120 °C under nitrogen for 6-12 h. The mixture was then cooled to room temperature and diluted with acetone (20 ml) and filtered. The SiO_2 was rinsed with acetone (10 ml) three times. The acetone solution was combined with the filtrate and evaporated at reduced pressure to dryness. The residue was dissolved in a small amount of ethanol (10 ml) and poured into 0.0004% HCl solution(150 ml). The precipitate obtained was filtered and purified upon chromatography (silica gel) with petroleum ether/ethyl acetate (4 : 6) as eluent.

Nine hydroxyflavanones were prepared and the following are the analytical data of new compounds and compounds of physical data which were not matched with the reported or untraceable.

2'-Chloro-5-hydroxyflavanone (**5**, R=H, R'=2-chlorophenyl): ^{1}H Nmr (400 MHz, acetone-d_6): δ 11.80 (s, 1H), 7.82 (m, 1H), 7.55-7.45 (m, 4H), 6.56-6.53 (m, 2H), 5.98 (dd, C_2-H, J=13.5; 2.8 Hz), 3.28 (dd, C_3-H, J=17.5; 13.5 Hz), 2.98 (dd, C_3-H, J=17.5; 2.8 Hz). Anal. Calcd for $C_{15}H_{11}O_3Cl$: C, 65.58; H, 4.04. Found: C, 65.25; H, 3.84; ms (EI) (274, 276 M). 4'-Cyano-5-hydroxyflavanone (**5**, R=H, R'=4-cyanophenyl): ^{1}H Nmr (400 MHz, acetone-d_6): δ 11.75 (s, 1H), 7.90, (d, $C_{3'}$, $C_{5'}$-H, J=8.0 Hz), 7.84 (d, $C_{2'}$,$C_{6'}$-H, J=8.0 Hz), 7.50 (t, C_7-H, J=8.0 Hz), 6.58, 6.54 (d, C_6, C_8-H, J=8.0 Hz), 5.82 (dd, C_2-H, J=13.0, 3.0 Hz), 3.29 (dd, C_3-H, J=17.0, 13.0 Hz), 3.04 (dd, C_3-H, J=17.0, 3.0 Hz). Anal. Calcd for $C_{16}H_{11}NO_3$: C, 72.45; H, 4.18; N, 5.28. Found: C, 72.10; H, 3.90; N, 5.40; ms (EI) (265 M). 5-Hydroxyflavanone (**5**, R=H, R'=phenyl): ^{1}H Nmr (400 MHz, $CDCl_3$): δ 11.70 (s, 1H), 7.49-7.40 (m, 6H), 6.57-6.51 (m, 2H), 5.46 (dd, C_2-H, J=12.5; 3.0 Hz), 3.15 (dd, C_3-H, J=17.5; 12.5 Hz), 2.89 (dd, C_3-H, J=17.5; 3.0 Hz). Anal. Calcd for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03. Found: C, 75.20; H, 4.77; ms (EI) (240 M). 5-Hydroxy-4'-nitroflavanone (**5**, R=H, R'=4-nitrophenyl): ^{1}H Nmr (400 MHz, acetone-d_6): δ 11.75 (s, 1H), 8.35 (d, $C_{3'}$,$_{5'}$-H, J=8.7 Hz), 7.91 (d, $C_{2'}$,$_{6'}$-H, J=8.7 Hz), 7.51 (dd, C_7-H, J=8.5, 8.5 Hz), 6.59, 6.54(d, C_6, C_8-H, J=8.5 Hz), 5.89 (dd, C_2-H, J=13.0, 3.0 Hz), 3.32 (dd, C_3-H, J=17.2, 13.0 Hz), 3.08 (dd, C_3-H, J=17.2,

3.0 Hz). Anal. Calcd for $C_{15}H_{11}NO_5$: C, 63.16; H, 3.89; N, 4.91. Found: C, 63.39; H, 4.18; N, 5.30; ms (EI) (285 M).

REFERENCES AND NOTES

1. H. Wagner and L. Farkas, "The Flavonoids", ed. by J. B. Harborne, T. J. Mabry, and H. Mabry, Academic Press Inc., 1975, p .133.
2. L. Claisen, Ber., 1887, **20**, 657.
3. D. N. Dhar, J. Proc. Inst. Chem., 1959, **31**, 297.
4. T. A. Geissman, "The Chemistry of Flavanoids Compounds", Macmillan and Co., New York, N. Y., 1962, p. 308.
5. J. Chen, W. Yang, X. Pan, Y. Li, and Z. Tan, Gaodeng Xuexiao Huaxue Xuebao, 1987, **8**, 914.
6. R. S. Subramanian and K. K. Balasubramanian, J. Chem. Soc., Chem. Commun., 1990, **21**, 1469.
7. J. T. Almtorp, Acta Chem. Scand., 1991, **45**, 212.
8. W. L. Chan, Y. C. Lin, W. H. Zhang, P. L. Tang, and Y. S. Szeto, Heterocycles, **1996**, *43*, 551 .
9. M. B. Bagade, A. W. Thool, and P. D. Lokhande, Indian J. Chem., Sect. B, 1991, **30B**, 973.
10. D. Knittel, H. Hemetsberger, and H Wheidmann, Monatsh fur Chem., 1970, **101**, 157.
11. S. Babber, S. Chandra, and A. K. Aggarwal, Indian J. Chem., 1987, **26B**, 797.
12. M. Yamato, K. Hashigaki, K. Mito, and T. Koyama, Chem. Pharm. Bull., 1978, **26**, 2321.
13. F. Kally and G. Janzso, Indian J. Chem., 1969, **7**, 524.
14. E. M. Suolinna, R. N. Buchsbaum, and E Racker, Cancer Research, 1975, **35**, 1865 .
15. C. Zdero, F. Bohlmann, and H. M. Niemeyer, Phytochemistry, 1990, **29**, 3247.

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