ONE STEP SYNTHESIS OF POLYHYDROXYFLAVANONES FROM HYDROXYACETOPHENONES AND HYDROXYBENZALDEHYDES

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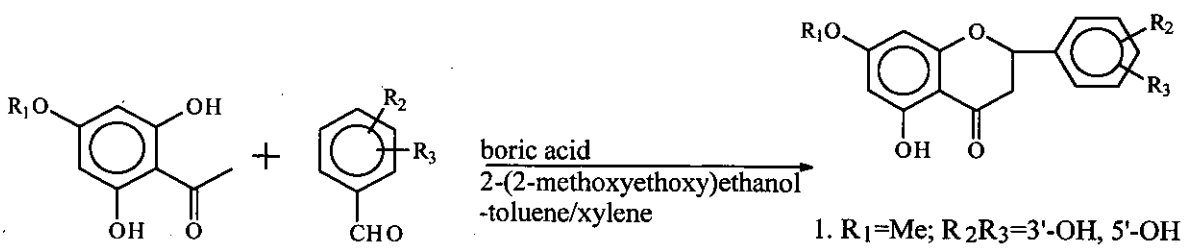
Abstract-Polyhydroxyflavanones were synthesized in a one-step process by reacting the appropriate hydroxyacetophenones and hydroxybenzaldehydes in the presence of boric acid, in a mixed solvent system.

INTRODUCTION

The most generally adopted method in the synthesis of flavanone is the condensation of an appropriate hydroxyacetophenone with a suitably substituted benzaldehyde in the presence of alkaline to give the chalcone which is then cyclized to produce the flavanone.[1] In the preparation of polyhydroxyflavanone, conversion of hydroxy groups which were not used in the formation of the ring, into appropriate derivatives are sometimes required,[2,3] in some case, the experimental work involved are laborious.[4] Direct coupling of polyhydroxy-aldehyde with acetophenone is difficult. The reaction is either prohibited by the formation of 'quinonemethide ion' of the aldehyde in the case of 2-/4- hydroxybenzaldehyde,[5] or stopped by Cannizzaro reaction to give the *dismutation products*[6] for 3,5-dihydroxybenzaldehyde. Although the acid catalysts, $AlCl_3$, BF_3, HF, HCl, H_2SO_4 and organic acids have been long used in the Claisen-Schmidt condensation of ketones and aldehydes,[7] their applications in flavanone synthesis are comparatively less suitable.[8] This paper reports the synthesis of polyhydroxyflavanones from di-/tri- hydroxyacetophenone and mono-/di- hydroxybenzaldehyde in the presence of boric acid in a mixed solvent system.

RESULTS AND DISCUSSION

The synthesis of polyhydroxylated flavanones (**1, 4, 5**) by coupling 2,6-dihydroxy-4-methoxyacetophenone with 3,5-, 2,4- and 3,4- dihydroxybenzaldehydes respectively is all unsuccessful, in our laboratory, under either acid or alkaline conditions. In the synthesis of 5,3',5'-trihydroxy-7-methoxyflavanone (**1**) using 3,5-dihydroxybenzaldehye in alkaline conditions, the only reaction observed was the Cannizzaro reaction of the aldehyde. Liang has reported the use of boric acid as catalyst in the synthesis of flavanone, either by heating the well mixed reactants and boric acid in solid state, with inconsistent results, or in ethanol or diglyme.[9] We have repeated the synthesis in the solid state with some success after several attempts, but were not successful in the solvent as reported. The study of aldehyde and ketone condensation reactions in the presence of boric acid indicated that the solubility of boric acid and the efficiency of water removal were important.[10] Thus we used a mixed anhydrous solvent system, in which both the solubility of reagents and boric acid were enhanced and water formed during the reaction was azeotropically removed by drying reagent packed in the side-arm of a mini Dean-Stark apparatus equipped on the reaction flask. By this simple method, direct coupling of hydroxy-benzaldehydes with hydroxyacetophenones can be achieved to give the desired polyhydroxyflavanones. Six differently substituted hydroxyflavavones were synthesized with this method.



1. R_1=Me; R_2R_3=3'-OH, 5'-OH
2. R_1=H; R_2R_3=3'-OH, 5'-OH
3. R_1=Me; R_2R_3=3'-OAc, 5'-OAc
4. R_1=Me; R_2R_3=2'-OH, 5'-OH
5. R_1=Me; R_2R_3=3'-OH, 4'-OH
6. R_1=Me; R_2R_3=3'-OMe, 4'-OH

Conditions and yield of the synthesis

flavanone	temperature/°C	time	solvent	yield(%)	mp/°C
1	145	48 hour	2-(2-methoxyethoxy)ethanol-xylene	25	151-152
2	145	48 hour	2-(2-methoxyethoxy)ethanol-xylene	22	186-188
3	120	48 hour	2-(2-methoxyethoxy)ethanol-toluene	29	101-103
4	120	48 hour	2-(2-methoxyethoxy)ethanol-toluene	31	165-167
5*	120	48 hour	2-(2-methoxyethoxy)ethanol-toluene	33	220-222
6*	120	48 hour	2-(2-methoxyethoxy)ethanol-toluene	24	146-147

*Known natural products: **5**[4, 10-13]; **6**[13]

EXPERIMENTAL

Appropriate hydroxybenzaldehyde and boric acid were added into a solvent mixture, 2-(2-methoxyethoxy)ethanol-xylene or -toluene, in a round bottom flask equipped with a mini Dean-Stark apparatus, with calcium oxide contained in the side-arm. The content was gently refluxed and to which hydroxy-acetophenone in the same solvent mixture was added *via* a dropping funnel, in 3 separated portions at about 6-10 hour intervals (aldehyde : acetophenone : boric aicd = 1:1:1.2 in mole ratio; 0.50 g : 0.38-0.61 g : 0.17 g; solvent mixture used ~35-40 ml 50/50). After addition was completed, the mixture was gently refluxed (20-25 hours) and monitored with tlc. When the reaction completed, the mixture was evaporated. The dark sticky residue was seperated on chromatograph (silica gel) using petroleum ether-ethyl acetate (50/50) as eluent.

5,3',5'-Trihydroxy-7-methoxyflavanone (**1**): ^{1}H Nmr (acetone-d_6, 90 MHz) δ 12.08 (s, 1H), 9.36 (s, 2H), 6.33 (s, 2H), 6.21 (s, 1H), 6.10 (s, 2H), 5.45 (dd, 1H, J 3.6, 11.7 Hz), 3.18 (dd, 1H, J 11.7, 17.1 Hz), 2.73 (dd, 1H, J 3.6, 17.1Hz), 3.78 (s, 3H). Anal. Calcd for $C_{16}H_{14}O_6$: C, 63.57; H, 4.67. Found: C, 63.28; H, 4.80; ms (EI) (302 M^+). 5,7,3',5'-Tetrahydroxyflavanone (**2**): ^{1}H Nmr (acetone-d_6, 90 MHz) δ 12.15 (s, 1H), 9.69 (s, 1H), 8.43 (s, 1H), 8.04 (s, 1H), 6.52 (d, 2H, J 1.8 Hz), 6.38 (d, 1H, J 1.8 Hz), 6.16 (s, 1H), 6.06 (s, 1H), 5.41 (dd, 1H, J 3.6, 11.7 Hz), 3.10 (dd, 1H, J 11.7, 17.1 Hz), 2.74 (dd, 1H, J 3.6, 17.1 Hz). Anal. Calcd for $C_{15}H_{12}O_6$: C, 62.50; H, 4.19. Found: C, 62.17; H, 4.31; ms (EI) (288 M^+). 5-Hydroxy-7-methoxy-3',5'-diacetyloxyflavanone (**3**): ^{1}H Nmr ($CDCl_3$, 90 MHz) δ 11.95 (s, 1H), 7.10 (d, 2H, J 1.8 Hz), 6.97 (d, 1H, J 1.8 Hz), 6.07 (d, 2H, J 1.5 Hz), 5.40 (dd, 1H, J 4.5, 11.7 Hz), 3.85 (s, 3H), 3.19 (dd, 1H, J 11.7, 18 Hz), 2.80 (dd, 1H, J 4.5, 18 Hz), 2.31 (s, 6H). Anal. Calcd for $C_{20}H_{18}O_8$:C, 62.17; H, 4.69. Found: C, 62.41; H, 4.84;

ms (FAB) (387 M^++1). 5,2',5'-Trihydroxy-7-methoxyflavanone (4): ^{1}H Nmr (acetone-d_6, 90 MHz) δ 12.15 (s, 1H), 8.20 (s, 1H), 7.92 (s, 1H), 7.02 (d, 1H, J 1.8 Hz), 6.75 (m, 2H), 6.10 (d, 1H, J 1.8 Hz), 6.05 (d, 1H, J 1.8 Hz), 5.76 (dd, 1H, J 3.6, 11.7 Hz), 3.87 (s, 3H), 3.11 (dd, 1H, J 11.7, 17.1 Hz), 2.72 (dd, 1H, J 3.6, 17.1 Hz). Anal. Calcd for $C_{16}H_{14}O_6$: C, 63.57; H, 4.67. Found: C, 63.37; H, 4.52; ms (FAB) (303 M^++1).

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