Utilization of "2-Pyrrolidone Hydrotribromide" in the Synthesis of Flavones

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Synopsis. The reaction of flavanone with "2-pyrrolidone hydrotribromide" in tetrahydrofuran gave 3-bromoflavanone in a good yield. On the other hand, flavone was obtained in 97% yield when this reaction was carried out in dimethyl sulfoxide at 80 °C. Under the same conditions, most flavones were obtained from the corresponding flavanones in high purity and good yields.

The most commonly used methods for the synthesis of flavones are the acid-catalyzed cyclodehydration of 1-(*o*-hydroxyphenyl)-1,3-diketone derivatives[1] and the dehydrogenation of flavanones by selenium dioxide,[2] phosphorus pentachloride,[3] and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.[4] Flavanones also can be converted into the corresponding flavones by bromination at the C_3 position, followed by the base-catalyzed dehydrobromination.[5]

We now report that flavones can be easily obtained from the corresponding flavanones and "2-pyrrolidone hydrotribromide" (2-pyrrolidone-hydrogen bromide–bromine complex $(C_4H_7NO)_3 \cdot HBr \cdot Br_2$,[6] abbreviated to PHT) by a one-pot procedure.

The results obtained are summarized in Table 1. The reaction was followed by TLC and the reaction time was determined by the disappearance of the flavanones. The reaction of flavanone(**1**) with PHT in tetrahydrofuran(THF) gave 3-bromoflavanone(**2**) in excellent yield, although the product was a mixture of *cis*- and *trans*-isomers: The ratio of the former to the latter was determined on the basis of the ^1H NMR spectrum,[7] since the isomers cannot be separated. The ratio of the *cis*-isomer to the *trans*-isomer strongly depends on the reaction temperature used. An attempt to prepare flavone(**3**) by the above method was unsuccessful, although **2** was obtained in a good yield.

The reaction of **1** with PHT in dimethyl sulfoxide (DMSO) at room temperature gave a mixture of **2** and **3**: the ratio of the former to the latter was also determined on the basis of ^1H NMR spectrum, as shown in Table 1. On the other hand, when the reaction was caried out at 80 °C, **1** gave exclusively **3**, which was easily isolated from the reaction mixture (97%). Similarly, the other flavones were also obtained by this procedure in excellent yields except for 4′-methoxyflavanone(**4**) and 4′,7-dimethoxyflavanone(**5**) (see below). The key for direct formation of flavones from the corresponding flavanones involves the use of DMSO as a solvent. Since DMSO is an effective dehydrobromination agent,[8] the results indicates that the conversion of flavanones to the corresponding flavones proceed *via* 3-bromoflavanones. **4** and **5** gave the corresponding flavones in somewhat decreased yields, for it gave the corresponding 3-bromoflavones as by-product. The decreased yields of flavones may be due to the presence of an electron-releasing methoxyl group at the *p*-position in the phenyl group. In this case, it

TABLE 1. THE REACTIONS OF FLAVANONES WITH "2-PYRROLIDONE HYDROTRIBROMIDE"

Entry	Starting material	Reaction conditions			Product(s)	Yield/%
		Solvent	Temp/°C	Time/h		
1	Flavanone	THF	Room	10.0	3-Bromoflavanone (*cis*:*trans*=4:6)[a]	98
2	Flavanone	THF	Reflux	1.5	3-Bromoflavanone (*cis*:*trans*=6:4)[a]	91
3	Flavanone	DMSO	Room	20.0	3-Bromoflavanone (*cis*:*trans*=1:9)[a]	34
					Flavone	60
4	Flavanone	DMSO	80	2.0	Flavone	97
5	7-Methoxyflavanone	DMSO	80	2.5	7-Methoxyflavone	98
6	3′-Methoxyflavanone	DMSO	80	2.0	3′-Methoxyflavone	98
7	3′,7-Dimethoxyflavanone	DMSO	80	2.5	3′,7-Dimethoxyflavone	97
8	4′-Methoxyflavanone	DMSO	80	2.0	4′,-Methoxyflavone	72
					3-Bromo-4′-methoxyflavone	25
9	4′,7-Dimethoxyflavanone	DMSO	80	2.5	4′,7-Dimethoxyflavone	67
					3-Bromo-4′,7-dimethoxyflavone	21

a) The ratio of *cis*-isomer to *trans*-isomer was determined on the basis of ^1H NMR spectrum.

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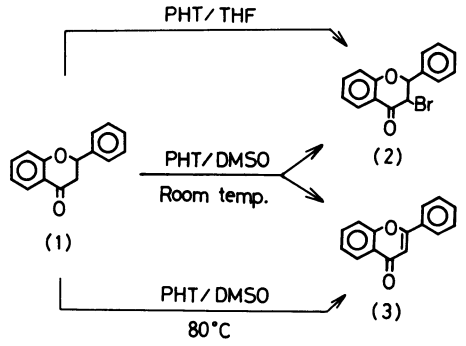
is natural to suppose that 2,3-dibromoflavanones, obtained by the addition of Br_2 to the previously produced flavones, underwent dehydrobromination by DMSO to give the corresponding 3-bromoflavones.

In conclusion, most flavones were easily obtained from the corresponding flavanones and PHT in high purity and good yields.



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^1H NMR spectra were obtained on a Hitachi R-22 with tetramethylsilane as internal reference. Mass spectra were measured with a JMS-D300 double-focusing mass spectrometer.

Materials. Flavanones were prepared according to a reported procedure.[9] Flavanones except for the new materials were identified by comparison with reported data.[10] *3'-Methoxyflavanone*: mp 76—77 °C. ^1H NMR (CCl_4) δ=2.62—3.10 (2H, m, C_3-H_{ax}, H_{eq}), 3.77 (3H, s, 3'-OCH_3), 5.34 (1H, dd, $J_{ax,ax}$=12.5 Hz, $J_{ax,eq}$=5.5 Hz, C_2-H_{ax}), 6.72—7.49 (7H, m, Aromatic), 7.86 (1H, dd, J_{ortho}=6.5 Hz, J_{meta}=1.5 Hz, C_5-H). Found: C, 75.78; H, 5.56. Calcd for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. *3',7-Dimethoxyflavanone*: mp 101—102 °C. ^1H NMR ($CDCl_3$) δ=2.66—3.20 (2H, m, C_3-H), 3.83 (6H, s, 2×OCH_3), 5.43 (1H, dd, $J_{ax,ax}$=11 Hz, $J_{ax,eq}$= 4 Hz, C_2-H), 6.49—7.42 (6H, m, Aromatic), 7.86 (1H, d, J_{ortho}=8 Hz, C_5-H). MS, Found: M^+=284. Calcd for $C_{17}H_{16}O_4$: M=284. *4'-Methoxyflavanone*: mp 87—88 °C [lit,[11] 96—97]. Though its melting point is different from the value in literature, we identified this material with 4'-methoxyflavanone from the following data. ^1H NMR (CCl_4) δ=2.58—3.13 (2H, m, C_3-H_{ax}, H_{eq}), 3.78 (3H, s, 4'-OCH_3), 5.33 (1H, dd, $J_{ax,ax}$=12 Hz, $J_{ax,eq}$=4.5 Hz, C_2-H_{ax}), 6.78—7.50 (7H, m, Aromatic), 7.83 (1H, dd, J_{ortho}=9 Hz, J_{meta}=2 Hz, C_5-H). Found: C, 75.60; H, 5.49. Calcd for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55.

Reaction Procedure. To a solution of flavanone (4.46 mmol) in the solvent (50 ml) was added a solution of PHT (4.84 mmol) in the solvent (50 ml). The mixture was stirred for a suitable time and temperature as indicated in Table 1. The reaction was followed by TLC (silica gel: benzene as sovent). Water was added to the cooled reaction mixture. The mixture was extracted with benzene and the organic extract was washed with brine, dried and evaporated.

Products of Reaction in THF. The residue was recrystallized from EtOH-H_2O: mp 85—105 °C. The product was a mixture of *cis*- and *trans*-3-bromoflavanone, indicated by integration of the ^1H NMR spectrum (see Table 1). ^1H NMR ($CDCl_3$) δ (ppm); *cis*-form: 4.54 (1H, d, J=2 Hz, β-H) [lit,[7] 4.53], 5.42 (1H, d, J=2 Hz, α-H) [lit,[7] 5.38], *trans*-form; 4.98(1H, d, J=8 Hz, β-H) [lit,[7] 4.98], 5.56 (1H, d, J=8 Hz, α-H) [lit,[7] 5.53].

Products of Reaction in DMSO. The product of reaction at room temperature was a mixture of 3-bromoflavanone and flavone as indicated by integration of ^1H NMR spectrum (see Table 1). Flavone: ^1H NMR ($CDCl_3$), δ=6.82 (1H, s, C_3-H), 7.31—7.99 (8H, m, Aromatic), 8.24 (1H, dd, J_{ortho}=8 Hz, J_{meta}=2 Hz, C_5-H). The residue of reaction at 80 °C was purified by silica-gel column chromatography (dichloromethane-diethyl ether, 5:1). Flavones and 3-bromo-4'-methoxyflavone, except for the new product, were identified by comparison with the reported data.[12] Satisfactory analysis was obtained for the new product, 3-bromo-4',7-dimethoxyflavone: mp 150—151 °C; ^1H NMR ($CDCl_3$) δ=3.91 (6H, s, 2×OCH_3), 6.85—7.90 (6H, m, Aromatic), 8.14 (1H, d, J_{ortho}=8 Hz, C_5-H); MS, Found: M^+=360, 362. Calcd for $C_{17}H_{13}O_4Br$: M=360, 362.

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