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The Direct Preparation of Flavones from 2′-Hydroxychalcones Using Disulfides

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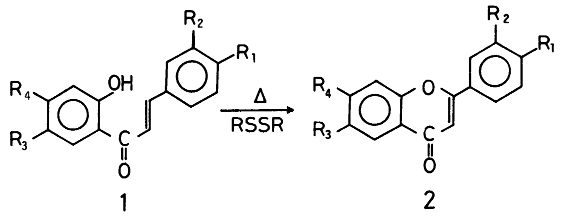
Synopsis. Flavone was obtained by a reaction of 2′-hydroxychalcone with disulfides in good yield. Among several disulfides, diphenyl disulfide gave the best result. Under the same conditions, some flavones were obtained from the corresponding 2′-hydroxychalcones in satisfactory yields.

A synthesis of flavones(**2**), which are the main materials of naturally occurring flavonoids, is usually based on the dehydrogenation of flavanones obtained by the cyclization of 2′-hydroxychalcones(**1**).[1)] Flavones can also be obtained directly from **1** by use of selenium dioxide,[2)] Pd-black[3)] or Pd(II).[4)] In a previous paper,[5)] we reported that **2** could be obtained by a reaction of **1** with sulfur in *N,N*-dimethylformamide (DMF) in good yields.

We now report the new synthesis of **2** from **1** using disulfides. In this reaction a mixture of **1a** and disulfides was heated at 260—290 °C under a nitrogen atmosphere.



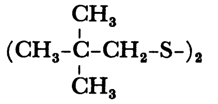
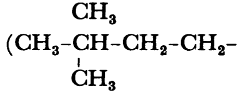
a $R_1=R_2=R_3=R_4=H$
b $R_1=Ph$, $R_2=R_3=R_4=H$
c $R_1=R_2=R_4=H$, $R_3=CH_3$
d $R_1=R_2=R_3=H$, $R_4=CH_3$
e $R_1=R_3=R_4=H$, $R_2=CH_3$
f $R_1=OCH_3$, $R_2=R_3=R_4=H$
g $R_1=R_3=R_4=H$, $R_2=OCH_3$
h $R_1=R_2=R_3=H$, $R_4=OCH_3$
i $R_1=Cl$, $R_2=R_3=R_4=H$
j $R_1=NO_2$, $R_2=R_3=R_4=H$

The effects of the disulfides on the formation of **2a** are shown in Table 1. Among four disulfides, diphenyl disulfide gave the best result. In the case of aliphatic disulfides, the low yields of **2a** may be due to the bulky carbon chains of thiyl radicals which are presumed to be formed in the course of the reaction.

Using diphenyl disulfide, nine flavone derivatives(**2b**—**j**) were prepared from the corresponding chalcones(**1b**—**j**) under the same conditions in various yields. The results are summarized in Table 2. In this and the above tables, the yields of **2** were determined by means of HPLC or GLC analyses using an absolute calibration method. For a comparison, the results of a run using flavanone(**3a**) as the starting material is also shown in Table 2.

In all cases, the conversions were complete and there was no isolable material in addition to the flavones. Table 2 shows that substituents having an electron-withdrawing effect tend to decrease the yields to a large extent. The nitroderivative(**1j** or **2j**) resinated considerably in these reaction conditions, and resulted in the lowest yield of **2j**. Although a slight increase in the yield of **2a** was observed in the case of **3a**, it can not be concluded in view of the

Table 1. Comparison of Reactivities of Disulfides for the Formation of flavone **2a** at 260—290 °C

Disulfide	Reaction time h	Yield %
 $(CH_3\text{-}C(CH_3)_2\text{-}CH_2\text{-}S\text{-})_2$	5	37[a)]
 $(CH_3\text{-}CH(CH_3)\text{-}CH_2\text{-}CH_2\text{-}S\text{-})_2$	5	40[a)]
$(CH_3\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}S\text{-})_2$	5	47[a)]
$(C_6H_5\text{-}S\text{-})_2$	2.5	80[b)]

a) GLC analysis. b) HPLC analysis.

Table 2. Yields of Flavones(**2a**—**j**) in the Reaction of 2′-Hydroxychalcones(**1a**—**j**) with Diphenyl Disulfide at 260—290 °C

Compound No.	Reaction time h	Product	Yield[a)] %
1a	2.5	**2a**	80
1b	2.5	**2b**	82
1c	3	**2c**	79[b)]
1d	3	**2d**	74[b)]
1e	3	**2e**	69[b)]
1f	1.5	**2f**	63
1g	3	**2g**	52
1h	2.5	**2h**	40
1i	2.5	**2i**	31
1j	3	**2j**	19
flavanone (3a)	2.75	**2a**	87

a) HPLC analysis. b) GLC analysis.

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reaction time that there is the difference in the reactivity between **1a** and **3a**. Eventually, the varieties of the yields of **2** may depend on the stabilities or the presence of secondary decompositions of the substrates and/or the products.

Although the mechanism of this reaction is not clear at present, we believe that the reaction provides a useful route to a one-step synthesis of flavones.

Experimental

Materials and Instruments. Disulfides were of a commercial grade and were used without further purification. 2′-Hydroxychalcones were prepared according to known procedures[6] from the corresponding 2′-hydroxyacetophenones and benzaldehydes. Those physical data have already been reported,[5] except **1b**, **1g**, and **1i**. All melting points are uncorrected and ^{1}H NMR spectra were obtained with a Hitachi R-22(90 MHz) spectrometer using tetramethylsilane as an internal standard.

4-Phenyl-2′-hydroxychalcone(1b): Mp 149.5—151.0 °C, ^{1}H NMR (CCl_4) δ=6.74—7.98 (15H, m, Olefin and Aromatic), 12.60 (1H, s, 2′-OH); Found: C, 84.20; H, 5.37%. Calcd for $C_{21}H_{16}O_2$: C, 83.98; H, 5.37%.

3-Methoxy-2′-hydroxychalcone(1g): Mp 91.5—92.5 °C, ^{1}H NMR (CCl_4) δ=3.81 (3H, s, 3-OCH_3), 6.73—7.88 (10H, m, Olefin and Aromatic), 12.59 (1H, s, 2′-OH); Found: C, 75.79; H, 5.42%. Calcd for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55%.

4-Chloro-2′-hydroxychalcone(1i): Mp 155—156 °C, ^{1}H NMR (CCl_4) δ=6.73—7.91 (10H, m, Olefin and Aromatic), 12.48 (1H, s, 2′-OH); Found: C, 69.26; H, 4.15; Cl, 13.64%. Calcd for $C_{15}H_{11}O_2Cl$: C, 69.64; H, 4.29; Cl, 13.70%. Flavones as authentic samples were also obtained by known procedures[1] and those physical data have already been reported.[7]

HPLC and GLC analyses were conducted using instruments by Yanagimoto High Speed Liquid Chromatograph L-2000 and Shimazu Gas Chromatograph GC-3BT, respectively.

General Reaction and Purification Procedure. In a 50 ml three-necked round-bottom flask equipped with nitrogen inlet and outlet tubes at both side necks, a mixture of chalcones(4.46 mmol) and disulfides(4.66 mmol) was placed and the center neck was sealded by a Uni-stopper. The flask was then dipped into a silicone oil bath and heated at 260—290 °C under a nitrogen atmosphere until the distilling of the formed thiols through the outlet tube ceased. The reaction mixture was then cooled at room temperature and solved in 50 ml chloroform. The yields of the flavones were determined by HPLC or GLC analyses. Then, the solvent was removed and the residue was purified by silica-gel column chromatography using dichloromethane as an eluent and crystallized from ligroin or benzene. All flavones were identified by a comparison of melting points and the IR and ^{1}H NMR spectra with those of authentic samples.

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