A Facile Preparation of Flavones Using Nonaqueous Cation-Exchange Resin

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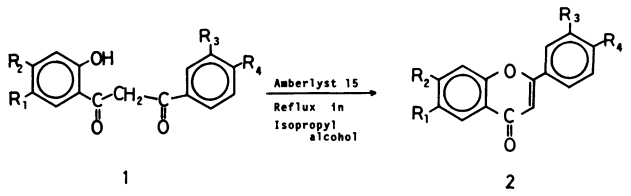
Synopsis. Flavone was prepared from 1-(2-hydroxyphenyl)-3-phenyl-1,3-propanedione by using nonaqueous cation-exchange resin in a nearly quantitative yield. Of several reaction media, isopropyl alcohol gave the best result. Eight substituted flavones were also synthesized from the corresponding diketones in satisfactory yields.

Organic syntheses using ion-exchange resins have long been known, which are exemplified by esterification of acids and alcohols,[1] addition of acids to olefins,[2] Knoevenagel condensation,[3] and von Pechmann reaction.[4] Recently, the utilization of ion-exchange resins is in rapid progress. The use of the resin as catalyst has the following advantages: (1) Products can be stripped of catalyst resin simply by filtering reaction mixtures; (2) the resin can be recovered simply by filtration; (3) it is possible to minimize side reactions. But, hitherto, only few examples using ion-exchange resin have been known in the field of flavonoid synthesis. On the other hand, Baker–Venkataraman's method[5] is one of the best known procedures of a number of synthetic methods for flavones. In this method flavone (**2a**) is usually prepared by intramolecular dehydration, followed by cyclization, of 1-(2-hydroxyphenyl)-3-phenyl-1,3-propanedione (**1a**) with sulfuric acid in glacial acetic acid; **1a** is obtained from *o*-(benzoyloxy)acetophenone by the Baker–Venkataraman transformation.



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Now we attempted this cyclization by using a nonaqueous cation-exchange resin, Amberlyst 15, instead of sulfuric acid, and succeeded in obtaining satisfactory results. In this work, flavones (**2**) were also obtained in high yields by very simple procedures and under comparatively mild conditions. When a mixture of **1a** and a resin in a solvent was heated at the reflux temperature for several hours, a crude product was obtained almost quantitatively simply by filtering off the resin.

Reactions were carried out in benzene, chloroform, acetonitrile, or isopropyl alcohol. The results obtained are summarized in Table 1. We avoided using glacial acetic acid as the reaction medium, because its boiling point is close to the limiting temperature for the use of Amberlyst 15 (120 °C). The reactions were monitored by means of TLC analyses, and were taken as finished when the spot of starting material disappeared or when no change was observed in spots of substrate and product for more than three hours. In the case of chloroform, the reaction did not finish even after 27 h.

Amberlyst 15 is a macroreticular (MR) sulfonic acid type cation-exchange resin and has a huge network structure. When this kind of resin is used as an organic reaction catalyst, the key point is the rate of diffusion of substrate into the network of resin. The best yield of **2a** in the case of isopropyl alcohol may be due to the facility of the diffusion of substrate into the resin. Furthermore, it is remarkable that solvents having a comparatively high dielectric constant give high yields of **2a**. In those solvents the exchange groups in the resin might get more activated than in low dielectric solvents.

The total capacity of Amberlyst 15 is 4.6—5.0 meq/g-R, and accordingly one gram of resin is formally equivalent to ca. 5 mmol of substrate. But it is considered that in this reaction the resin acts as a catalyst for the substrate. This was confirmed by the following experimental result: When a recovered resin was used again for the same reaction without any regenerating treatment, **2a** reappeared and its yield did not extremely decrease (crude 90% and pure 75%; 3 h), although degradation of the resin was observed to

Table 1. Yields of Flavone (**2a**) and Reaction Times in Four Solvents[a]

Solvent[b]	Reaction Time / h	Yield[c] / %
Benzene	14	65[d]
Chloroform	>27	79[d]
Acetonitrile	6	83
Isopropyl alcohol	4	90

a) Substrate: 3.0 g (12.5 mmol); resin: 3.0 g (15.0 meq). b) 80 ml. c) Isolated yield. d) Isolated by column chromatography.

Table 2. Influence of Reaction Composion on the Yield of Flavone (**2a**) in Isopropyl Alcohol[a]

Composion (**1a** : Resin)	Reaction Time / h	Isolated Yield / %
1 : 0.33	14.5	90
1 : 1.20	4	90[b]
1 : 1.43	4	91
1 : 2.64	3	92
1 : 5.0	3	90

a) Solvent: 30 ml. b) From the value in Table 1.

Table 3. Reaction Times and Yields of Mono- or Disubstituted Flavones (**2b—i**) in Isopropyl Alcohol in the Presence of Amberlyst 15

Product No.	R_1	R_2	R_3	R_4	Reaction Time h	Isolated Yield %
2b	H	OCH_3	H	H	8.5	80
2c	H	H	H	OCH_3	2.5	78
2d	H	H	OCH_3	H	8	85
2e	H	OCH_3	OCH_3	H	19	83
2f	H	H	H	Cl	9	80
2g	H	H	Br	H	19.5	67
2h	CH_3	H	H	H	5	90
2i	H	CH_3	H	H	6	83

some extent.

In search for the optimum reaction conditions, reactions were repeated in isopropyl alcohol with several compositions of **1a** and resin. The results are shown in Table 2. Although there is not a great difference in the yield caused by changing the reaction composition, it can be concluded from the viewpoint of reaction time and economy that nearly equivalent composition of substrate and resin is optimum.

Eight mono- or disubstituted flavones (**2b—i**) were also prepared from the corresponding diketones (**1b—i**) by the same procedure. The results obtained are summerized in Table 3. Syntheses of a few 2′-substituted derivatives were also attempted in vain. This may be due to the steric hindrance by the introduction of the 2′-substituent close to the reaction center. From the results in Table 3, this method may be regarded as a general synthetic procedure for the flavones except the above-mentioned examples.

Thus we believe that this reaction allows a facile preparation of flavones, although the behavior of the substrate and product molecules in the network structure of the resin is not clear at present.

Experimental

All melting points were uncorrected. ^{1}H NMR spectra were obtained with a Hitachi R-22 (90 MHz) spectrometer by using tetramethylsilane as an internal standard. Physical data of isolated flavones agreed with those of independently synthesized authentic samples, which have already been reported.[6]

Materials. Solvents were of commercially available grade and were purified by ordinary procedures before use. Amberlyst 15 (Rohm and Haas Co., Ltd., U. S. A.) was employed without any treatment. Diketones were prepared according to known procedures,[5] and were identified on the basis of values in literatures[7] except for the following derivatives.

1-(2-Hydroxyphenyl)-3-(3-methoxyphenyl)-1,3-propanedione (1d): Mp 85.0—86.0 °C; ^{1}H NMR (CCl_4) δ=3.82 (3H, s, 3-OCH_3), 6.76 (2H, s, -CH_2-), 6.79—7.72 (8H, m, Aromatic), and 11.77 (1H, s, 2-OH). Found: C, 71.05; H, 5.10%. Calcd for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22%.

1-(2-Hydroxy-4-methoxyphenyl)-3-(3-methoxyphenyl)-1,3-propanedione (1e): Mp 102.0—103.0 °C; ^{1}H NMR (CCl_4) δ=3.78 (3H, s, 4-OCH_3), 3.80 (3H, s, 3-OCH_3), 6.56 (2H, s, -CH_2-), 6.27—7.59 (7H, m, Aromatic), and 12.22 (1H, s, 2-OH). Found: C, 67.95; H, 5.30%. Calcd for $C_{17}H_{16}O_5$: C, 67.99; H, 5.37%.

1-(2-Hydroxyphenyl)-3-(3-bromophenyl)-1,3-propanedione (1g): Mp 115.0—116.0 °C; ^{1}H NMR (CCl_4) δ=6.71 (2H, s, -CH_2-), 6.81—8.00 (8H, m, Aromatic), and 11.71 (1H, s, 2-OH). Found: C, 56.48; H, 3.50; Br, 25.01%. Calcd for $C_{15}H_{11}O_3Br$: C, 56.45; H, 3.47; Br, 25.04%.

1-(2-Hydroxy-5-methylphenyl)-3-phenyl-1,3-propanedione (1h): Mp 88.0—91.0 °C; ^{1}H NMR ($CDCl_3$) δ=2.32 (3H, s, 5-CH_3), 6.79 (2H, s, -CH_2-), 6.83—7.98 (8H, m, Aromatic), and 11.86 (1H, s, 2-OH). Found: C, 75.54, H, 5.61%. Calcd for $C_{16}H_{14}O_3$: C, 75.58; H, 5.55%.

1-(2-Hydroxy-4-methylphenyl)-3-phenyl-1,3-propandione (1i): Mp 83.0—84.5 °C; ^{1}H NMR (CCl_4) δ=2.30 (3H, s, 4-CH_3), 6.68 (2H, s, -CH_2-), 6.51—7.89 (8H, m, Aromatic), and 11.82 (1H, s, 2-OH). Found: C, 75.60; H, 5.50%. Calcd for $C_{16}H_{14}O_3$: C, 75.58; H, 5.55%.

General Procedure. In a 50 ml conical flask equipped with a reflux condenser, a mixture of diketone (3.0 g, 12.5 mmol) and resin (3.0 g, 15.0 meq) was placed. Then isopropyl alcohol (30 ml) was added and the flask was heated on a hot plate for several hours under reflux with magnetic stirring. During the reaction, trace amounts of the reaction solution were withdrawn at hourly intervals with a glass capillary and subjected to TLC analyses. When the reaction was taken as finished, the flask was cooled to room temperature and had 20 ml chloroform added. Then the resin was filtered off and washed with a small amount of chloroform. The solvent of filtrate was removed by using an evaporator and the residue was dried overnight in a desicator under reduced pressure. Then the pure product was obtained by recrystallization from hexane or ligroine and benzene.

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