Syntheses of Flavones via the Iodine-Mediated Oxidative Cyclization of 1,3-Diphenylprop-2-en-1-ones

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The syntheses of flavones from 1,3-diphenylporp-2-ene-1-ones are described. When 1,3-diphenylprop-2-en-1-ones were heated with iodine in triethylene glycol, oxidative cyclization underwent to obtain flavones in good yields.

Flavones play important roles in plants, and many methods to prepare them have been reported. Syntheses from 1-(2-hydroxyphenyl)ethan-1-one and benzoyl chloride are well-established methods.[1] However, they are not applicable for the syntheses of flavones having hydroxy groups on an A-ring, because a regioselective benzoylation of 1-(di- or trihydroxyphenyl)ethan-1-one is required, which is rather laborious in many cases. Although many modified methods have been reported, most of them are not satisfactory in terms of cost or generality.[2–4] Flavone syntheses from flavanones have also been reported,[5–11] and are useful only when the flavanones are readily available. In order to avoid these problems, we studied the direct syntheses of flavones from 1,3-diphenylprop-2-en-1-one **1**, which are often used as precursors of flavanones. Several methods for the transformation to flavones have already been reported. Although most of them are not satisfactory in terms of cost or yield,[12–19] a method using DMSO in the presence of a catalytic amount of iodine is promising.[17–19] In this paper, we report on an alternative inexpensive method for the transformation of **1** to flavone **2** (Scheme 1).

The 1,3-diphenylprop-2-en-1-one **1** can be easily prepared, by a base-catalyzed condensation between 1-(2-hydroxyphenyl)-ethan-1-one or 1-(2,4-dihydroxyphenyl)ethan-1-one and appropriate benzaldehydes.[20] The hydroxy groups of 1-(2-hydroxyphenyl)ethan-1-one or 1-(2,4-dihydroxyphenyl)ethan-1-one are not necessarily protected; the condensation proceeded smoothly in good yield. The transformation of **1** to **2** needs some oxidant, and iodine is suitable for this purpose. When **1** was heated with I_2, the oxidative cyclization of **1** proceeded smoothly to give **2**. Selecting of the solvent is important in this transformation. Of all the solvents that we studied, triethylene glycol gave the best result for the synthesis of **2a** from **1a**. Other solvents, such as DMF, DMSO, and acetic acid, gave a considerable amount of unidentified products together with a minor amount of **2a** (Table 1). However, the reaction in triethylene glycol proceeded in good yield. The results of the oxidative cyclization of **1b–1f**, which are precursors of substituted flavones **2b–2f**, are summarized in Table 2. Substituted flavones **2b–2f** as well as **2a** can be synthesized by this method. Methyl, chloro, and methoxy substituents in benzene rings do not disturb the transformation, and **2b–2d** were obtained in good yield. On the other hand, during the courses of the reaction of **1e**, which has a methoxymethyl protecting group, deprotection occurred to give a hydroxy group. The yield of the hydroxylated flavones, such as **2e** and **2f**, was lower, probably because they are oxidized more easily than **2a–2d**. This seems to be a common drawback for a similar transformation using oxidative cyclization of 1,3-diphenylprop-2-en-1-one, such as **1f**.

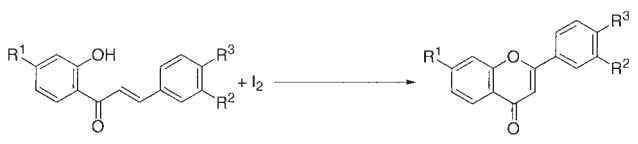
The mechanism of this reaction is still not clear. However, we tentatively propose the pathway of this reaction to be as shown in Scheme 2. Initially, the addition of iodine to enone occurred to

Table 1. Solvent Effect of the Syntheses of **2a** from **1a**

I_2 (mol amt)	Solvent	Temp/°C	Time/h	Yield/%
1.2	DMF	150	3	40
1.2	DMSO	120	3.5	45
1.2	CH_3COOH	120	4	45
1.2	triethylene glycol	150	4	83

Table 2. Syntheses of **2** from **1** in Triethylene Glycol

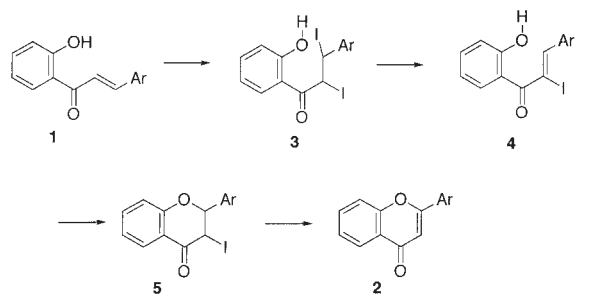
Substrate	Temp/°C	Time/h	Product	Yield/%
1a	150	4	**2a**	83
1b	150	2	**2b**	72
1c	150	3.5	**2c**	71
1d	150	4	**2d**	75
1e	140	1	**2e**	50
1f	150	2	**2f**	41
1g	120	10	**2g**	25



1a R^1=R^2=R^3=H
1b R^1=R^2=H, R^3=Me
1c R^1=H, R^2=R^3=OMe
1d R^1=R^2=H, R^3=Cl
1e R^1=R^2=H, R^3=OMOM
1f R^1=OH, R^2=R^3=H

2a R^1=R^2=R^3=H
2b R^1=R^2=H, R^3=Me
2c R^1=H, R^2=R^3=OMe
2d R^1=R^2=H, R^3=Cl
2e R^1=R^2=H, R^3=OH
2f R^1=OH, R^2=R^3=H

Scheme 1.



Scheme 2.

give **3**. The β-elimination of HI, yielding **4**, followed by the conjugate addition of a hydroxy group (**3** → **4** → **5**), or a replacement of the β-iodine by an aryloxy group (**3** → **5**), gave **5**. The β-elimination of HI gave flavones.

Experimental

General Procedure for the Preparation of Flavones (2). A solution of 1.0 mmol of **1** and 1.2 mmol of I_2 in triethylene glycol (2 mL) was stirred at 150 °C for 4 hours. After the mixture was cooled to room temperature, it was poured into water, and extracted with ethyl acetate. The organic layer was washed with a $Na_2S_2O_3$ solution, and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the product was purified by column chromatography on silica gel to give flavone (**2**).

Flavone (2a). ^{1}H NMR ($CDCl_3$) δ 6.82 (s, 1H), 7.36–7.44 (m, 1H), 7.51–7.58 (m, 4H), 7.64–7.73 (m, 1H), 7.90–7.93 (m, 2H), 8.23 (d, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 107.6, 118.1, 124.0, 125.2, 125.9, 126.3, 129.0, 131.6, 131.8, 133.8, 156.3, 163.4, 178.4; IR (nujol) 1660, 1320, 1240, 1140, 1060, 920, 860, 790, 770 cm^{-1}; mp 95–98 °C (lit. 97–98 °C).[1]

4′-Methylflavone (2b). ^{1}H NMR ($CDCl_3$) δ 2.37 (s, 3H), 6.74 (s, 1H), 7.24 (d, J = 8.0 Hz, 2H), 7.36 (dd, J = 7.5, 7.6 Hz, 1H), 7.49 (d, J = 8.3 Hz, 1H), 7.64 (ddd, J = 0.8, 7.6, 8.3 Hz, 1H), 7.74 (d, J = 8.0 Hz, 2H), 8.18 (dd, J = 0.8, 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.5, 106.7, 118.0, 123.8, 125.1, 125.5, 125.9, 126.1, 129.7, 133.6, 142.2, 156.1, 163.5, 178.4; IR (nujol) 1160, 1040, 960, 910, 820, 780, 760, 730 cm^{-1}; mp 109–111 °C (lit. 110–112 °C).[5]

3′,4′-Dimethoxyflavone (2c). ^{1}H NMR ($CDCl_3$) δ 3.95 (s, 3H), 3.97 (s, 3H), 6.73 (s, 1H), 6.96 (d, J = 8.1 Hz, 1H), 7.36 (d, J = 1.8 Hz, 1H), 7.40 (dd, J = 7.2, 7.5 Hz, 1H), 7.52 (dd, J = 1.8, 8.1 Hz, 1H), 7.53 (d, J = 7.5 Hz, 1H), 7.67 (ddd, J = 1.5, 7.2, 7.8 Hz, 1H), 8.20 (dd, J = 1.5, 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 56.1, 106.4, 108.8, 111.2, 118.0, 111.2, 118.0, 120.0, 123.9, 124.2, 125.6, 133.6, 149.3, 152.1, 156.1, 163.3, 178.3; IR (nujol) 1670, 1610, 1280, 1160, 1040, 890 cm^{-1}; mp 153–154 °C (lit. 154–155 °C).[15]

4′-Chloroflavone (2d). ^{1}H NMR ($CDCl_3$) δ 6.73 (s, 1H), 7.32–7.58 (m, 4H), 7.61–7.70 (m, 1H), 7.77–7.88 (m, 2H), 8.12–8.22 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 107.6, 117.8, 123.9, 125.3, 125.7, 127.5, 129.3, 130.2, 133.9, 137.8, 156.1, 162.8, 178.2; IR (nujol) 1630, 1450, 1365, 1080, 820, 750 cm^{-1}; mp 186–188 °C (lit. 188–189 °C).[5]

4′-Hydroxyflavone (2e). ^{1}H NMR ($CDCl_3$) δ 6.69 (s, 1H), 6.97 (d, J = 8.7 Hz, 2H), 7.39–7.44 (m, 1H), 7.57–7.62 (m, 1H), 7.69–7.74 (m, 1H), 7.83 (d, J = 8.7 Hz, 2H), 8.14–8.16 (m, 1H), 9.83 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 103.1, 114.2, 116.3, 119.9, 121.7, 123.1, 123.2, 126.4, 131.9, 153.9, 159.3, 161.5, 175.3; IR (nujol) 1640, 1580, 1310, 1270, 1190, 1050, 850, 790, 770 cm^{-1}; mp 270–271 °C (lit. 270–271 °C).[4]

7-Hydroxyflavone (2f). ^{1}H NMR ($CDCl_3$) δ 6.91 (s, 1H), 6.95 (dd, J = 1.8, 9.0 Hz, 1H), 7.02 (d, J = 1.8 Hz, 1H), 7.57–7.59 (m, 3H), 7.91 (d, J = 9.0 Hz, 1H), 8.05–8.08 (m, 2H), 10.8 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 102.6, 106.6, 115.1, 116.2, 126.2, 126.5, 129.1, 131.3, 131.5, 157.5, 161.2, 162.8, 176.4; IR (nujol) 2800, 1620, 1310, 1270, 1170, 850, 780 cm^{-1}; mp 240–243 °C (lit. 240 °C).[16]

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