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Note

A facile microwave assisted synthesis of flavones

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Chalcones **3a-f** on irradiation under microwave in DMSO in presence of catalytic amount of I_2 provides flavones **4a-f** in high yield. The corresponding chalcones **3a-f** are obtained by Claisen-Schimdt condensation of aromatic aldehydes with *o*-hydroxy acetophenone.

Keywords: Microwave irradiation, flavones, chalcones

The flavones (2-phenylchromones) are naturally occurring heterocyclic compounds belonging to the flavanoid group. These are widely distributed in vascular plants[1]. Though their presence being a century old[2], isolation[3] of new flavones and newer methods[4] of synthesis continue to appear. Their attraction as synthetic targets is due to the wide range of biological activities exhibited by them. These include leishmanicidal activity, oviposter stimulant phytoalexins, anti-HIV, vasodilator, antiviral, anti-oxidants, bactericidal, DNA clevage, antiinflamatory, antimutagenic, antiallergic, and anticancer[5]. Some flavonoids inhibit the histamine release from human basophils and rat mast cells[6]. Moreover, it is known that some flavonoids have a repelling property against some phytophagous insects and a subterranean termite (*Coptotermes sp*.) acting as antifeedant[7,8].

The main synthetic methods known for flavones are oxidative cyclization[9] of 2'-hydroxy chalcones, the cyclodehydration[10] of 1-(2-hydroxyphenyl-3-phenyl-1,3-propanedione) and *via* intermolecular Wittig reaction[11].

Recently, there is a surge to employ microwave in organic synthesis. Microwave synthesis[12] offers advantages over conventional heating due to rapid heating and increased rate of reaction. Also, cleaner reactions together with improvement in yield and selectivity are mostly observed. There are several reports[5,10,13] for the syntheses of flavanoids and neoflavanoids by using microwave irradiation.

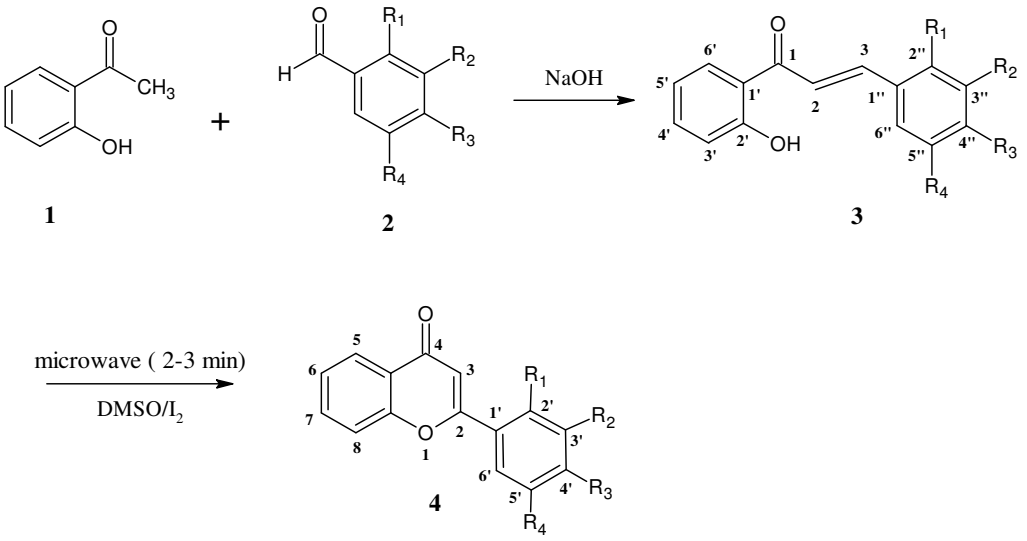
One of the methods for oxidative cyclization of 2'-hydroxy chalcone uses catalytic amount of iodine in refluxing DMSO by conventional heating[9a]. The method is very effective except for the large volume of DMSO required for its application. It was envisaged that by using microwave irradiation the reaction can be done by reduced volume of DMSO. Also, it would reduce the time required for the reaction and may improve the yield. Thus, different volumes of DMSO and iodine were tried under microwave irradiation. Optimum results were obtained when 1 mmole of 2'-hydroxy chalcone **3a** was placed in 2 mL of DMSO and 0.2 eq of iodine was irradiated for 2 min. The other chalcones **3b-f** similarly gave flavones in 80-92% yield in 2-3 minutes. While conventional heating in refluxing DMSO (20 mL) with 0.1 eq of iodine for 20-40 min provided flavones in slightly less yield 60-70%. Reduction in volume of DMSO for conventional heating resulted in lower yields. The required chalcones **3a-f** (**Scheme I**) were prepared by slightly modified reaction condition of Claisen Schmidt condensation reported[14] for 2'-hydroxy chalcone. When 2',4'-dihydroxy chalcone was subjected for oxidative cyclization, it failed to provide the corresponding flavone in our hands either by conventional heating or microwave irradiation.

In conclusion, an efficient general microwave method has been developed for the synthesis of alkoxy substituted flavones. The products are obtained in shorter time and in excellent yield. The microwave method reduces the volume of DMSO required drastically.

Experimental Section

IR spectra were recorded on a Shimadzu FT-IR, Prestige-21. ^{1}H NMR spectra were recorded on a Bruker spectrometer at 300 MHz in $CDCl_3$. IFB-2450 MHz (900 W) microwave oven was used for microwave irradiation. The silica gel used for column chromatography was of 60-120 mesh size.

General procedure for the preparation of chalcone 3: A solution of NaOH (2.5 mmole in 10 mL) in ethanol (20 mL) was added to a mixture of aromatic benzaldehyde and *o*-hydroxy acetophenone (1 mmole each) in a conical flask. After heating on



Scheme I

the water-bath for about 15 minutes, the reaction-mixture was quenched into the ice and then Conc. HCl was added slowly with stirring till the reaction becomes acidic. A pale yellow solid separated was filtered and washed with ice-cold water followed by recrystallisation using absolute ethanol to afford chalcone-2'-ol **3a-f**.

Chalcone-2'-ol 3a (Ref. 14a): Light yellow solid, m.p. 86°C, IR (KBr): 3200 (OH), 1643 (C=O), 1571, 975 cm^{-1}; ^1H NMR: δ 6.98 (t, 1H, *J* = 7.65 Hz, 5'-H), 7.06 (d, 1H, *J* = 8.4 Hz, 3'-H), 7.47 (m, 3H, 3", 4" & 5"-H), 7.53 (t, 1H, *J* = 7.8 Hz, 4'-H), 7.67 (d, 1H, *J* = 15.3 Hz, -CO-C*H*=CH-), 7.69 (m, 2H, 2" & 6"-H), 7.96 (d, 1H, *J* = 15.3 Hz, -CO-CH=C*H*-), 7.97 (d, 1H, *J* = 8.4 Hz, 6'-H), 12.73 (s, 1H, OH).

2-Chlorochalcone-2'-ol 3b (Ref. 14b): Light yellow solid, m.p. 54°C, IR (KBr): 3100 (OH), 1693 (C=O), 1643, 1485, 1205, 760 cm^{-1}; ^1H NMR: δ 6.97 (t, 1H, *J* = 7.8 Hz, 5'-H), 7.07 (d, 1H, *J* = 8.4 Hz, 3'-H), 7.39 (m, 2H, 4" & 5"-H), 7.52 (m, 2H, 3" & 4'-H), 7.67 (d, 1H, *J* = 15.6 Hz, -CO-C*H*=CH-), 7.78 (m, 1H, 6"-H), 7.94 (d, 1H, *J* = 8.1 Hz, 6'-H), 8.33 (d, 1H, *J* = 15.6 Hz, -CO-CH=C*H*-), 12.73 (s, 1H, OH).

4-Chloro chalcone-2'-ol 3c (Ref. 14c): Brilliant yellow solid, m.p. 149°C, IR (KBr): 3100 (OH), 1640 (C=O), 1564, 1487, 1205, 760 cm^{-1}; ^1H NMR: δ 6.98 (t, 1H, *J* = 7.2 Hz, 5'-H), 7.06 (d, 1H, *J* = 8.4 Hz, 3'-H), 7.44 (d, 2H, *J* = 8.4 Hz, 3" & 5"-H), 7.54 (dt, 1H, *J* = 7.2 & 2.1 Hz, 4'-H), 7.63 (d, 2H, *J* = 8.4 Hz, 2" & 6"-H), 7.65 (d, 1H, *J* = 15.6 Hz, -CO-C*H*=CH-), 7.89 (d, 1H, *J* = 15.6 Hz, CO-CH=C*H*-), 7.95 (d, 1H, *J* = 8.4 Hz, 6'-H), 13.00 (s, 1H, OH).

4-Methoxychalcone-2'-ol 3d (Ref. 14c): Orange yellow solid, m.p. 83-85°C, IR (KBr): 3200 (OH), 1635 (C=O), 1558, 1207, 764 cm^{-1}; ^1H NMR: δ 3.94 (s, 3H, OCH_3), 6.95 (d, 1H, *J* = 7.8 Hz, 5'-H), 6.98 (d, 2H, *J* = 8.7 Hz, 3"-H & 5"-H), 7.05 (d, 1H, *J* = 8.4 Hz, 3'-H), 7.50 (t, 1H, *J* = 6.9 Hz, 4'-H), 7.57 (d, 1H, *J* = 15.6 Hz, CO-C*H*=CH-), 7.66 (d, 2H, *J* = 9.0 Hz, 2" & 6"-H), 7.93 (d, 1H, *J* = 15.6 Hz, CO-CH=C*H*), 7.95 (d, 1H, *J* = 6.9 Hz, 6'-H), 12.96 (s, 1H, OH).

3,4-Dimethoxychalcone-2'-ol 3e (Ref. 14d) : Orange solid, m.p. 115-17°C, IR (KBr): 3100 (OH), 1638 (C=O), 1558, 1207, 764 cm^{-1}; ^1H NMR: δ 3.97 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 6.96 (m, 2H, 3' & 5'-H), 7.05 (d, 1H, *J* = 8.4 Hz, 5"-H), 7.20 (d, 1H, *J* = 1.2 Hz, 2"-H), 7.31 (m, 1H, 6"-H), 7.53 (t, 1H, *J* = 7.5 Hz, 4'-H), 7.54 (d, 1H, *J* = 15.3 Hz, CO-C*H*=CH-), 7.92 (d,1H, *J* = 15.3 Hz, CO-CH=C*H*), 7.96 (d, 1H, *J* = 9.6 Hz, 6'-H), 12.94 (s, 1H, OH).

3,4,5-Trimethoxychalcone-2'-ol 3f: (Ref. 14e) Orange yellow solid, m.p. 142°C, IR (KBr) 3200 (OH), 1648 (C=O), 1504, 1128, 835, 770 cm^{-1}; ^1H NMR: δ 3.94 (s, 3H, OCH_3), 3.96 (s, 6H, 2 × OCH_3), 6.91 (s, 2H, 2" & 6"-H), 6.98 (t, 1H, *J* = 7.5 Hz, 5'-H), 7.06 (d, 1H, *J* = 6 Hz, 3'-H), 7.53 (t, 1H, *J* = 7.8 Hz, 4'-H), 7.56 (d, 1H, *J* = 15.3 Hz, CO-C*H*=CH-), 7.87 (d, 1H, *J* = 15.3 Hz, CO-CH=C*H*), 7.96 (d, 1H, *J* = 8.7 Hz, 6'-H),12.85 (s, 1H, OH).

General procedure for the preparation of flavone by microwave irradiation 4: The chalcone-2'-ol (1 mmole) was suspended in (DMSO, 2 mL) and to this solution iodine (0.02 mmole) was added. The mixture was subjected to microwave irradiation for two minutes at level five. The mixture was diluted

Table I — Synthesis of 2'-hydroxy chalcone and flavones

Entry	R_1	R_2	R_3	R_4	Yield of **3** (%)	Yield of **4** (%)by conventional method	(%)by MW
a	H	H	H	H	78	68	87
b	Cl	H	H	H	86	67	88
c	H	H	Cl	H	80	70	80
d	H	H	OMe	H	70	60	87
e	H	OMe	OMe	H	68	59	83
f	H	OMe	OMe	OMe	60	64	92

with water (excess) and extracted with diethyl ether (3 × 20 mL). The organic layer was washed with aqueous 20% sodium thiosulphate, water and dried over anhydrous sodium sulphate. The crude solid obtained was subjected to column chromatography over silica gel using hexanes:EtOAc (80:20 v/v). The solid flavones (**Table I**) obtained were recrystallised using ethyl alcohol.

Flavone 4a: (Ref. 14f) m.p. 97°C, IR (KBr): 1660 (C=O), 1465, 1377, 770 cm^{-1}; UV λmax (MeOH, 27°C) nm (ε): 249.5 (19866), 294 (23545); ^{1}H NMR: δ 6.86 (s, 1H, 3-H), 7.45 (t, 1H, *J* = 7.5 Hz, 6-H), 7.57 (m, 3H, 3', 4' & 5'-H), 7.60 (d, 1H, *J* = 9.3 Hz, 8-H), 7.73 (dt, 1H, *J* = 7.4 & 1.5 Hz, 7-H), 7.96 (m, 2H, 2' & 6'-H), 8.27 (dt, 1H, *J* = 8.1 & 1.5 Hz, 5-H).

2'-Chloroflavone 4b (Ref. 14g): m.p. 118°C, IR (KBr); UV λmax (MeOH, 27°C) nm (ε): 246 (16834), 295 (10904); 1658 (C=O), 1467, 1370, 768 cm^{-1}; ^{1}H NMR: δ 6.81 (s, 1H, 3-H), 6.9 (m, 2H, 6 & 8-H), 7.50 (m, 5H, 3', 4', 5', 6' & 7-H), 8.29 (d, 1H, *J* = 8.1 Hz, 5-H).

4'-Chloroflavone 4c (Ref. 14f): m.p. 185°C; IR (KBr): 1639 (C=O), 1469, 1409, 1375, 1091, 773 cm^{-1}; UV λmax (MeOH, 27°C) nm (ε): 257.5 (13368), 298.5 (15989); ^{1}H NMR: δ 6.82 (s, 1H, 3-H), 7.46 (t, 1H, *J* = 7.5 Hz, 6-H), 7.53 (d, 2H, *J* = 8.7 Hz, 3' & 5'-H), 7.59 (d, 1H, *J* = 8.4 Hz, 8-H), 7.74 (dt, 1H, *J* = 7.8 & 2.1 Hz, 7-H), 7.89 (d, 2H, *J* = 8.7 Hz, 2' & 6'-H), 8.25 (dd, 1H, *J* = 7.8 & 2.1 Hz, 5-H).

4'-Methoxyflavone 4d (Ref. 14f): m.p. 155°C; IR (KBr): 1651 (C=O), 1465, 1379, 827,768 cm^{-1}; UV λmax (MeOH, 27°C) nm (ε): 271 (3969), 319 (26443); ^{1}H NMR: δ 3.92 (s, 3H, OCH_3), 6.78 (s, 1H, 3-H), 7.05 (d, 2H, *J*= 8.7 Hz, 3' & 5'-H), 7.43 (t, 1H, *J* = 7.8 Hz, 6-H), 7.58 (d, 1H, *J* = 8.4 Hz, 8-H), 7.74 (dt, 1H, *J* = 8.6 & 1.5 Hz, 7-H), 7.92 (d, 2H, *J* = 9 Hz, 2' & 6'-H), 8.25 (dd, 2H, *J* = 8.1 & 1.5 Hz, 5-H).

3',4'-Dimethoxyflavone 4e: (Ref. 14a) m.p. 154°C, IR (KBr): 1651 (C=O), 1514, 1466, 1147, 762 cm^{-1}; UV λmax (MeOH, 27°C) nm (ε): 242 (16740), 334 (18176); ^{1}H NMR: δ 3.99 (s, 3H, OCH_3), 4.01 (s, 3H, OCH_3), 6.80 (s, 1H, 3-H), 7.02 (d, 1H, *J* = 8.4Hz, 5'-H), 7.41 (d, 1H, *J* = 1.2 Hz, 2'-H), 7.45 (d, 1H, *J* = 7.8 Hz, 6-H), 7.58 (dd, 2H, *J* = 8.4 & 1.0 Hz, 8-H), 7.72 (dt, 1H, *J* = 8.5 & 1.5 Hz, 7-H), 8.25 (dd, 1H, *J* = 7.8, 1.5 Hz, 5-H).

3',4',5'-Trimethoxyflavone 4f: (Ref. 14g) m.p. 174°C; IR (KBr): 1640 (C=O), 1468, 1373, 770 cm^{-1}; UV λmax (MeOH, 27°C) nm (ε): 271 (3642), 312 (24768); ^{1}H NMR: δ 3.97 (s, 3H, OCH_3), 3.99 (s, 6H, 2 × OCH_3), 7.08 (s, 1H, 3-H), 7.20 (s, 2H, 2' & 6'-H), 7.50 (t, 1H, *J* = 7.4 Hz, 6-H), 7.66 (d, 1H, *J* = 8.4 Hz, 8-H), 7.78 (d, 1H, *J* = 7.4 Hz, 7-H), 8.28 (d, 1H, *J* = 7.8 Hz, 5-H).

General procedure for the preparation of flavone by conventional method 4: Iodine (0.1 mmole), was added to the solution of chalcone–2′-ol **3** (1 mmole) in DMSO (20 mL). The mixture was refluxed for 20-40 minutes. The solid obtained after dilution with excess of water was filtered, washed with aqueous 20% sodium thiosulphate till the product become colourless. Futher purified by column chromatography using hexane:EtOAc (80:20 v/v) as an eluent.

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