A New One-Pot Synthesis of Isoflavanones

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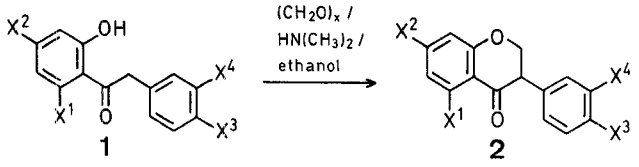
We report here a new, convenient one-step synthesis of isoflavanones **(2)** by the reaction of benzyl 2-hydroxyphenyl ketones **(1)** with paraformaldehyde in boiling ethanol in the presence of secondary amines such as piperidine, dimethylamine, or diethylamine.



	X¹	X²	X³	X⁴
a	H	OCH_3	H	H
b	OCH_3	OCH_3	H	H
c	H	OCH_3	OCH_3	H
d	OCH_3	OCH_3	OCH_3	H
e	H	OCH_3	$-O-CH_2-O-$	

Except for the 2-hydroxy group which is involved in the cyclization, all other hydroxy groups present in the benzyl 2-hydroxyphenyl ketone **(1)** should be protected.

Isoflavanones are usually obtained by hydrogenation of isoflavones using noble metal catalysts[1-4]. Other methods starting from the preformed ring skeleton are the hydroboration of 3-phenylcoumarin or 4-hydroxy-3-phenylcoumarin followed by chromic acid oxidation[5] and the palladium(II) acetate-catalyzed arylation of 4-acyloxy-2*H*-chromenes (4-chromanone enol esters) with arylmercury(II) compounds[6]. Earlier methods for the conversion of benzyl 2-hydroxyphenyl ketones **(1)** into isoflavanones **(2)**[7,8] involve the use of formaldehyde in alkaline medium (hydrogen carbonate or alkali metal hydroxides); however, the reports on these methods either do not give experimental details and yields[7] or are limited to the preparation of only one isoflavanone in the form of its enol ester, the scope of the method not being studied[8]. In a related cyclocondensation, isoflavanones **(2)** have been prepared from compounds of the type **1** and diiodomethane[9].

Isoflavanones (2); General Procedure:

The benzyl 2-hydroxyphenyl ketone (**1**; 2 mmol), paraformaldehyde (0.12 g, corresponding to 4 mmol of formaldehyde), and aqueous 25% dimethylamine solution (0.38 ml, 2 mmol) are heated in boiling ethanol (25 ml) for 3 h (water bath). Ethanol is then evaporated in vacuo, water (10 ml) is added, and the mixture acidified with hydrochloric acid. The insoluble isoflavanone **2** is isolated by suction and recrystallized from methanol.

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Table. Isoflavanones **(2)** from Benzyl 2-Hydroxyphenyl Ketones **(1)** and Paraformaldehyde

Reaction	Yield [%]	m.p. [°C] found	m.p. [°C] reported	I.R. (KBr) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS_{int})[a] δ [ppm]
1a[10] → **2a**	61	91–92°	92°[2]	1680, 1610, 1575	3.84–3.97 (distorted t, 4H, 3-H and OCH_3); 4.65 (d, 2H, J=6 Hz, 2,2-H_2); 6.44–6.88 (m, 2H, 6-H, 8-H); 7.35 (s, 5H: 2′,3′,4′,5′,6′); 7.94 (d, 1H, J=9 Hz, 5-H)
1b[11] → **2b**	51	149–150°	151°[2]	1685, 1670, 1610, 1572	3.78–3.91 (distorted t, 7H, 3-H and 2 OCH_3); 4.64 (d, 2H, J=6 Hz, 2,2-H_2); 6.13 (s, 2H, 6-H, 8-H); 7.37 (s, 5H: 2′,3′,4′,5′,6′)
1c[12] → **2c**	67	134–135°	125–126°[3] 128–129°[6]	1675, 1610, 1576	3.81–3.95 (distorted t, 7H, 3-H and 2 OCH_3); 4.64 (d, 2H, J=6 Hz, 2,2-H_2); 6.48–6.72 (m, 2H, 6-H, 8-H); 6.88–7.31 (A_2B_2, 4H: 2′,3′,5′,6′); 7.97 (d, 1H, J=9 Hz, 5-H)
1d[13] → **2d**	54	155–156°	156–157°[3]	1674	3.78–3.88 (distorted t, 10H, 3-H and 3 OCH_3); 4.60 (d, 2H, J=6 Hz, 2,2-H_2); 6.11 (s, 2H, 6-H, 8-H); 6.83–7.32 (A_2B_2, 4H: 2′,3′,5′,6′)
1e[14] → **2e**	65	118–119°	120°[2]	1673	3.73–3.89 (distorted t, 4H, 3-H and OCH_3); 4.60 (d, 2H, J=6 Hz, 2,2-H_2); 5.91 (s, 2H, O—CH_2—O); 6.42–6.76 (m, 5H: 6,8,2′,5′,6′); 7.88 (d, 1H, J=9 Hz, 5-H)

[a] In a number of natural isoflavanones, the usually expected diastereotopism of the H-atom at C-2 of the pyrone ring is absent and only a doublet is observed[15,16]. In the presently studied cases of this type, this diastereotopism is not observed, the compounds being synthetic, and only a doublet is observed. The methoxy signals often merge with the triplet expected for 3-H and hence only a distorted triplet is observed.

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