Synthesis of isoflavones via base catalysed condensation reaction of deoxybenzoin

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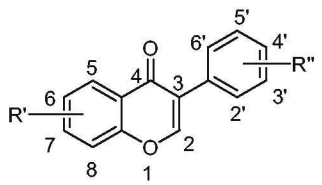
Base catalysed condensation reaction of o-hydroxyl-α-phenylacetophenones with formyl reagents affords various substituted isoflavones. Many bases were tested in the condensation reaction and DMAP was found to be the most effective catalysis.

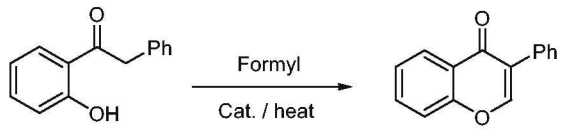
Keywords: isoflavones, base, condensation reaction, formyl reagents

Isoflavones are widely distributed in nature and exert a variety of biological effects on mammalian systems[1] that might be exploitable in medicine.[2-6]



isoflavone

The two most popular synthetic pathways to isoflavones are the deoxybenzoin (2-hydroxyphenylbenzyl ketones)[7-11] and the chalcone[12-16] routes. The beauty of the deoxybenzoin route is the simplicity of the reaction as there is no need for the protection of phenolic OH-groups. In the deoxybenzoin route, cyclisation is the key step, which can be carried out in many ways. The additional carbon atom needed for the ring formation can be introduced by treatment with one of the following combinations of reagents:- BF_3Et_2O/DMF/$MeSO_2Cl$,[7,9] BF_3Et_2O/DMF/PCl_5,[10,11] HCO_2Et/Na.[17] However, these methods often suffer from drawbacks such as low yields, harsh reaction conditions, lengthy reaction times, and the use of toxic reagents. The development of efficient methods for the synthesis of isoflavones is of interest. Herein, we report an effective combination of reagents for the synthesis of isoflavones from deoxybenzoin via a condensation reaction.



1a **2a**

Scheme 1

Formyl reagents to provide the additional carbon atom were tested in the model cyclisation of α-phenyl-*o*-hydroxyacetophenone (Scheme 1, **1a**). Many common inorganic and organic bases were also investigated. The results are listed in Table 1.

The results in Table 1 show that inorganic bases including NaOAc, NaOH, K_2CO_3 (entries 8, 9 and 10) showed poor reactivity. Many organic bases, especially DMAP (entries 13 and 14), exhibited good to excellent catalysis with up to 96% yield. If DMF was used as the formyl reagent without any other basic catalyst (entry 3), 38% yield of **2a** was obtained, while only trace of **2a** could be obtained under the same reaction condition when triethyl orthoformate was used (entry 4). This may be due to a base from DMF. The condensation reaction of **1a** with formyl reagent in the presence of DMAP was also performed in several organic solvents such as toluene, chloroform, THF, ethanol, acetonitrile, but the yields were not comparable to those in 1 ml formyl reagent. We also performed the reaction under solvent-free condition, *i.e.* 2 mmol **1a** and 3 mmol triethyl orthoformate was heated

Table 1 Cyclisation of α-phenyl-*o*-hydroxyacetophenone under different conditions[a]

Entry	Formyl	Catalyst (equiv.)[b]	Temperature/°C	Time/h	Yield/%[c]
1	DMF	Et_3N (0.1)	80	6	71
2	DMF	DMAP (0.1)	100	4	92
3	DMF	–	80	6	38
4	$HC(OEt)_3$	–	80	6	<5
5	$HC(OEt)_3$	Et_3N (0.1)	80	6	74
6	$HC(OEt)_3$	Pyridine (0.1)	100	6	82
7	$HC(OEt)_3$	3-Methyl pyridine (0.1)	100	6	85
8	$HC(OEt)_3$	NaOAc (1.0)	100	6	36
9	$HC(OEt)_3$	NaOH (1.0)	100	6	41
10	$HC(OEt)_3$	K_2CO_3 (1.0)	100	6	44
11	$HC(OEt)_3$	Morpholine (0.1)	100	6	76
12	$HC(OEt)_3$	DABCO (0.1)	100	6	86
13	$HC(OEt)_3$	DMAP (0.1)	100	4	96
14	$HC(OEt)_3$	DMAP (0.02)	100	4	95
15	HCOOEt	DMAP (0.02)	50	10	81
16	$HCONH_2$	DMAP (0.02)	100	4	90

[a]2.0 mmol **1a** and 1 ml formyl reagent were used.
[b]Based on **1a**, DABCO: 1,4-diazabicyclo[2.2.2]octane; DMAP: 4-dimethylaminopyridine.
[c]Based on **1a**.

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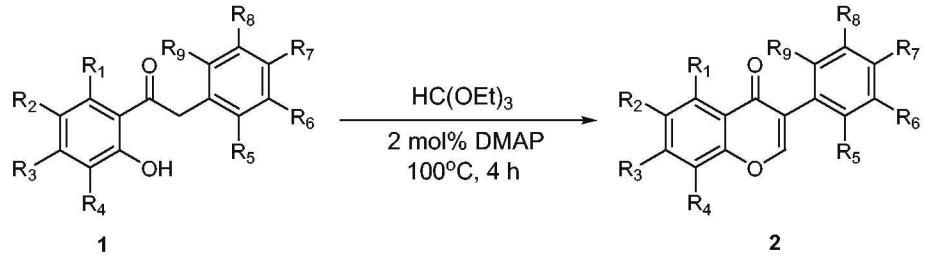


Scheme 2 Preparation of isoflavones.

at 100 °C for 4 h in the presence of catalytic amount of DMAP (2 mol%), but the yield of **2a** was only about 50%. Due to the poor mixing under the given condition, the substrates did not react well. If excess triethyl orthoformate was added to improve mixing, the yield was increased obviously.

With these results in hand, the reaction was extended to many o-hydroxyl-α-phenylacetophenone derivatives. The condensation reaction was carried out using 0.02 equiv. of DMAP as the catalyst in 1 ml of triethyl orthoformate (Scheme 2). The results were shown in Table 2.

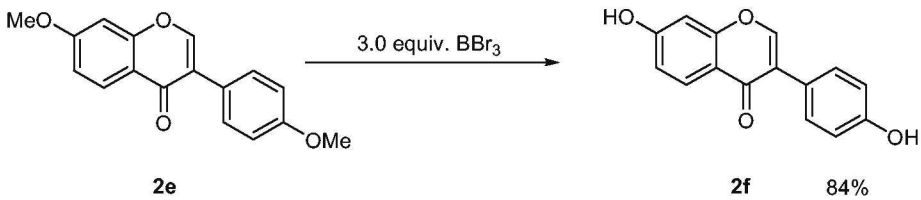
All the substrates were satisfactorily converted to the desired product in high yield. The aromatic substituents did not obviously affect the yield. In addition, methylated product could be easily transformed to hydroxy product in good yield using demethylation reagent such us BBr_3 (Scheme 3).

In order to investigate the reaction mechanism, a test reaction (Scheme 4) was carried out. To our surprise, no reaction occurred when *o*-hydroxylbenzophenone was treated with triethyl orthoformate using DMAP. But high yield the acetal **4** was obtained when the reaction was carried out with triethyl orthoformate in the presence of gaseous HCl or para-toluene sulfonic acid (p-TSA). A plausible mechanism was postulated in Scheme 5. The Knoevenagel reaction proceeded firstly in the presence of DMAP to form the unsaturated ketone **B**, followed by a Michael addition and elimination of ethanol to obtain the desired product **2a**.

In summary, DMAP is an effective catalyst for the synthesis of isoflavones from o-hydroxyl-α-phenylacetophenone derivatives via a condensation reaction with triethyl orthoformate. The advantages of above method include good selectivity, high yields, catalytic reaction, short reaction time and simple process. Isoflavones are useful compounds for its potential bioactivity and pharmacological activity.

Experimental

Melting points were uncorrected. IR spectra were recorded using KBr pellets on a Nicolet NEXUS-470-FT-IR instrument. The NMR spectra were measured with a Bruker-400 instrument using $CDCl_3$

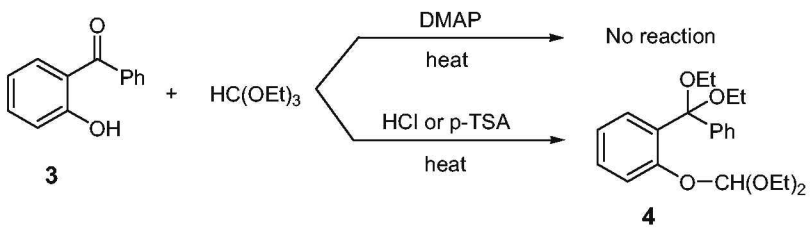


Scheme 3 Demethylation of **2e**.

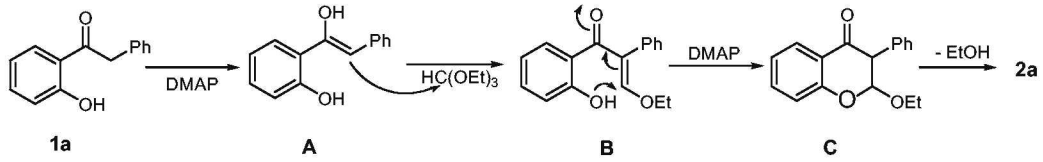
Table 2 Preparation of isoflavones in the presence of DMAP[a]

Entry	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	R_9	Product	Yield/%[b]
1	H	H	H	H	H	H	H	H	H	**2a**	95
2	H	H	OMe	H	H	H	H	H	H	**2b**	94
3	OH	H	OH	H	H	H	H	H	H	**2c**	92
4	H	H	H	H	H	H	Cl	H	H	**2d**	95
5	H	H	OMe	H	H	H	OMe	H	H	**2e**	94
6	H	H	OH	H	H	H	OH	H	H	**2f**	90
7	H	OH	OMe	H	H	H	OMe	H	H	**2g**	93
8	OH	H	OH	H	H	Cl	Cl	H	H	**2h**	95
9	OH	H	OH	H	H	OMe	H	H	H	**2i**	91
10	OH	H	OH	H	H	H	OMe	H	H	**2j**	90

[a]2 mmol **1** and 1 ml triethyl orthoformate were used.
[b]isolated yield based on **1**.



Scheme 4 Reaction of *o*-hydroxylbenzophenone with triethyl orthoformate.



Scheme 5 Possible route to the formation of **2a**.

or DMSO-d_6 as the solvent with TMS as internal standard. Chemical shifts (δ) are reported in ppm and coupling constants J is given in Hz. Mass spectra were measured with Bruker Esquire-3000-plus spectrometer. All spectral data of the products were identical to authentic samples.

General procedure

To a solution of **1** (2 mmol) in 1 ml triethyl orthoformate, DMAP (0.04 mmol, 4.9 mg) were added. The reaction mixture was heated to 100 °C and stired for 4 h. After completion (monitored by TLC) the reaction mixture was quenched with water (10 ml) and extracted with CH_2Cl_2 (10 ml × 3). The organic phase was washed with brine and dried over $MgSO_4$. After concentration in vacuum, the residue was purified by column chromatography using petroleum ether–ethyl acetate (8 : 1) as eluent to afford **2** (generally up to 90% yield).

Spectra data for products:

Isoflavone **(2a)**: White solid; m.p. 128.5–129.5 °C. [lit.(18): 131–132 °C]. IR (KBr) ν_{max}: 3045, 1641, 1611 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.35–7.48 (m, 5H), 7.57–7.60 (m, 2H), 7.68–7.74 (m, 1H), 8.01 (s, 1H) 8.28–8.31 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 118.1, 124.5, 125.1, 125.4, 126.4, 128.3, 128.5, 128.8, 131.7, 133.6, 153.2, 156.2, 176.3. MS (*m/z*) 223.

7-Methoxyisoflavone **(2b)**: White solid; m.p. 157.5–159.0 °C. [lit.[19]: 156–158 °C]. IR (KBr) ν_{max}: 3041, 1651, 1608 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ = 3.93 (s, 3H), 7.07 (dd, 1H, J = 8.8 Hz, 2.0 Hz), 7.16 (d, 1H, J = 1.6 Hz), 7.39 (m, 1H) 7.45 (t, 2H, J = 6.8 Hz, 7.2 Hz), 7.59 (d, 2H, J = 6.8 Hz), 8.05 (d, 1H, J = 8.4 Hz), 8.48 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 55.1, 100.2, 109.7. 118.5, 125.3, 128.5, 128.7, 128.9, 129.1, 131.5, 152.3, 157.6, 164.1, 175.8. MS (*m/z*) 253.

5,7-Dihydroxyisoflavone **(2c)**: White solid; m.p. 195.5–197.0 °C. [lit.[20]: 198–201 °C]. IR (KBr) ν_{max}: 3440, 3380, 1651, 1614 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ = 6.31 (d, 1H, J = 1.6 Hz), 6.45 (d, 1H, J = 1.6 Hz, 2.0 Hz), 7.46–7.54 (m, 5H), 8.25 (s, 1H), 9.77 (s, 1H), 13.05 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 93.6, 99.0, 105.4, 123.1, 128.4, 129.2, 131.1, 154.3, 158.2, 163.1, 164.1, 180.6. MS (*m/z*) 255.

4'-Chloroisoflavone **(2d)**: White solid; m.p. 185.0–186.0 °C. [lit.[21]: 186–188 °C]. IR (KBr) ν_{max}: 1639, 1618 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ = 8.23 (m, 1H), 7.95 (s, 1 Hz), 7.58 (m, 2H), 7.40 (m, 4H) 7.32 (m, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 117.9, 124.4, 125.0, 125.5, 126.3, 128.5, 128.9, 131.6, 133.6, 153.1, 156.3, 177.1. MS (*m/z*) 259(M + 2), 258.

7,4'-Dimethoxyisoflavone **(2e)**: White solid; m.p. 158.3–159.7 °C. [lit.(22): 159 °C]. IR (KBr) ν_{max}: 1639, 1610 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ = 8.20 (d, 1H, J = 7.6 Hz), 7.90 (s, 1H), 7.48–7.52 (m, 2H), 6.99–7.02 (m, 1H), 6.94–6.98 (m, 2H), 6.85 (d, 1H, J = 1.6 Hz), 3.93 (s, 3H), 3.85 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 53.1, 56.0, 100.2, 113.5, 114.6, 117.8, 123.9, 124.1, 127.0, 130.1, 153.0, 157.7, 159.1, 163.8, 175.0. MS (*m/z*) 283.

7,4'-Dihydroxyisoflavone **(2f)**: White solid; m.p. 309.3–314.7 °C. [lit.[23]: 322 °C]. IR (KBr) ν_{max}: 3448, 1630, 1608 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ = 8.25 (s, 1H), 7.98 (d, 1H, J = 7.6 Hz), 7.36–7.39 (m, 2H), 6.92 (dd, 1H, J = 1.6, 7.6 Hz), 6.85 (d, 1H, J = 1.6 Hz), 6.15–6.19 (m, 2H), 12.13 (s, 1H), 13.05 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 102.1, 115.0, 117.0, 122.6, 123.8, 127.1, 130.0, 152.2, 157.2, 157.6, 162.6, 178.8. MS (*m/z*) 255.

6-Hydroxy-7,4'-dimethoxyisoflavone **(2g)**: Yellow oil. [lit.[24]] IR (KBr) ν_{max}: 3428, 1660, 1618 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ = 12.78 (s, 1H), 7.96 (s, 1H), 7.65 (s, 1H), 7.40–7.44 (m, 2H), 6.88–6.91 (m, 3H), 4.02 (s, 3H), 3.98 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 54.8, 57.2, 100.1, 108.2, 113.7, 117.8, 122.9, 124.6, 130.1, 145.4, 151.1, 152.4, 153.8, 159.0, 174.7. MS (*m/z*) 299.

5,7-Dihydroxy-3',4'-dichloroisoflavone **(2h)**: White solid; m.p. 295–299 °C (decomposed). [lit.[25]]. IR (KBr) ν_{max}: 3538, 3480, 1650, 1605 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ = 12.78 (s, 1H), 9.80 (s, 1H), 8.39 (s, 1H), 7.86 (d, 1H, J = 1.6 Hz), 7.62–7.65 (m, 2H), 6.44 (d, 1H, J = 1.6 Hz), 6.31 (d, 1H, J = 1.6 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 94.0, 99.4, 105.3, 121.0, 129.0, 130.3, 130.9, 131.5, 131.6, 131.9, 155.2, 158.2, 163.0, 164.4, 179.8. MS (*m/z*) 325, 324, 323.

5,7-Dihydroxy-3'-methoxyisoflavone **(2i)**: White solid; m.p. 301–305 °C (decomposed). [lit.[25]]. IR (KBr) ν_{max}: 3448, 3400, 1659, 1613 cm^{-1}; 1H NMR (DMSO-d_6, 400 MHz): δ = 13.08 (s, 1H), 8.23 (s, 1H), 7.34 (t, 1H, J = 7.2 Hz), 7.18–7.21 (m, 2H), 6.95–6.97 (m, 1H,), 6.45 (d, 1H, J = 1.6 Hz), 6.32 (d, 1H, J = 1.6 Hz), 3.88 (s, 3H); ^{13}C NMR (DMSO-d6, 100 MHz): δ = 54.5, 93.8, 99.1, 105.3, 113.4, 114.9, 121.1, 123.1, 129.3, 132.4, 154.5, 158.2, 159.7, 163.0, 164.3, 180.3. MS (*m/z*) 285.

5,7-Dihydroxy-4'-methoxyisoflavone **(2j)**: White solid; m.p. 207–209 °C. [lit.[20]: 211–213 °C]. IR (KBr) ν_{max}: 3438, 3406, 1655, 1616 cm^{-1}; 1H NMR (DMSO-d_6, 400 MHz): δ = 12.88 (s, 1H), 10.86 (s, 1H), 8.38 (s, 1H), 7.52 (d, 2H, J = 8.0 Hz), 7.00 (d, 2H, J = 8.0 Hz), 6.41 (d, 1H, J = 1.6 Hz), 6.24 (d, 1H, J = 1.6 Hz), 3.82 (s, 3H); ^{13}C NMR (DMSO-d6, 100 MHz): δ = 55.4, 94.3, 99.3, 105.3, 114.1, 123.1, 123.5, 130.2, 152.9, 158.1, 159.8, 162.2, 164.0, 180.6. MS (*m/z*) 285.

We thank Hangzhou Normal University for financial support.

Received 10 September 2008; accepted 13 October 2008
Paper 08/0164 *doi: 10.3184/030823408X382135*
Published online: 10 December 2008

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