Synthesis of 2-alkylisoflavones under phase-transfer catalysis conditions

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2-alkyl isoflavones were synthesised with the aliphatic acid chloride and 2-hydroxydeoxybenzoins under phase-transfer catalysis in acetone–K_2CO_3 medium involves the modified Baker–VenKataraman transformation

Keywords: tetrabutylammonium hydrogen sulfate, aliphatic acid chloride, 2-hydroxydeoxybenzoins, 2-alkyl isoflavone

Isoflavones are widely found in a number of natural products. These natural products have demonstrated numerous biological activities such as antioxidant,[1] anti-inflammatory,[2] anticardiovascular and anticarcinogenic activities.[3]

Previously the synthesis of 2-alkyl isoflavones can be achieved by adopting the Kostanecki–Robinson reaction,[4,5] the method got the 2-alkyl isoflavone through the reaction of aliphatic acid anhydrides and 2-hydroxydeoxybenzoins in the presence of the sodium or potassium salt of the corresponding acid under the refluxing condition, but the reaction needed high-temperature and long reaction time. Recently the Kostanecki–Robinson reaction was modified, and the sodium salt of the aliphatic acid was replaced with triethylamine,[6–8] the modification lowered the reaction temperature, but the yield is not very good.

The modified Baker–VenKataraman transformation were extensively used to synthesise the flavone compounds,[9] and the 2-phenylisoflavones[10] and 2-furylisoflavones[11] also were synthesised. The method use 2-hydroxydeoxybenzoins and aromatic acid chloride to react and get isoflavones in acetone-K_2CO_3 medium with refluxing, the procedure was very simple. Recentyl 2-arylisoflavones were also acquired with high yield under phase transfer catalysis conditions using tetrabutylammonium hydrogen sulfate as phase transfer catalyst, benzene as a solvent and 20% aq. potassium carbonate as a basic catalyst.[12]

Initial attempts to synthesise 7-hydroxyl-2-methylisoflavone with acetyl chloride and 2,4-dihydroxydeoxybenzoin in acetone–K_2CO_3 medium involve the modified Baker–VenKataraman transformation, but did not give the 7-hydroxyl-2-methylisoflavone. When we added tetrabutyl-ammonium hydrogen sulfate, we obtained the 7-hydroxyl-2-methylisoflavone. When the acetyl chloride was 3 equivalents and tetrabutylammonium hydrogen sulfate was 0.4 equivalents, the yield reached 85% (Table 1).

This success led us to study a variety of 2-hydroxy-deoxybenzoins and aliphatic acid chlorides. Two new isoflavones: 7-hydroxyl-2-propylisoflavone and 7-hydroxy-2-butylisoflavone were obtained (Table 2).

In summary, we have described a practical, efficient and inexpensive pathway for the synthesis of 2-alkylisoflavones in excellent yields using tetrabutylammonium hydrogen sulfate as phase transfer catalyst in acetone–K_2CO_3 medium involves the modified Baker–VenKataraman transformation. The availability of tetrabutylammonium hydrogen sulfate and the mild reaction condition should find a widespread use as the method of choice to synthesise 2-alkylisoflavones.

Table 1 Synthesis of 7-hydroxyl-2-methylisoflavone with the change of amount of acetyl chloride and tetrabutylammonium hydrogen sulfate

No.	Acetyl chloride/ equiv	$TBAHSO_4$/ equiv	Reaction time/h	Yield/%
1	0.2	0	10	0
2	0.2	0.01	10	8
3	0.2	0.05	10	15
4	0.2	0.10	10	24
5	0.2	0.20	10	50
6	0.2	0.40	10	65
7	0.2	0.50	10	71
8	0.3	0.40	10	85

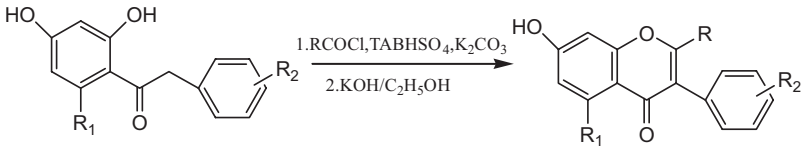
General procedure for synthesising 2-alkyl isoflavones

^{1}H NMR spectra were measured at 400 MHz on a Varian-Inova 400 spectrometer, ^{13}C NMR were measured at 200 MHz on a Bruker–ACE200 spectrometer, and chemical shifts are reported in parts per million (ppm) (δ) relative to TMS as internal standard. Mass spectra (ESI) were determined on API3000 spectrometer and reported as *m/z*. Microanalyses were measured using a Carbo-Erba110G microelemental analyser.

2-hydroxydeoxybenzoins (10 mmol) in acetone (45 ml), tetrabutylammonium hydrogen sulfate ($TBAHSO_4$, 4 mmol) and anhydrous potassium carbonate (4.5 g) were placed in a flask and aliphatic acid chloride (30 mmol) was added dropwise with stirring during 15–20 min.The mixture was stirred for 2 h at room temperature, then was refluxed for 10 h at 75˚C with stirring. The mixture was cooled down and filtered, and solvent of the filter was removed under reduced pressure to give a semi-solid which was refluxed with 5% ethanolic potassium hydroxide(15 ml) for 20 min. The crude semi-solid after removal of ethanol from solution was diluted with water (5 ml) and acidified with dilute hydrochloric acid (15 ml). The resulting solid was filtered, washed with 5% aq. Sodium bicarbonate solution, dried and recrystallised. from the ethanol to give the corresponding isoflavones.

Data for 7-hydroxy-2-propylisoflavone, m.p. 174–176˚C, ^{1}H NMR, d_6-DMSO, δ 0.81–0.84(t, 3H), 1.59–1.69(m, 2H), 2.44–2.52(m, 2H), 6.86–6.864(d, 1H), 6.91–6.93(dd, 1H), 7.23–7.45(m, 5H arom), 7.88–7.90(d, 1H) 10.79(s, 1H, -OH). ^{13}C NMR δ: 175.24, 165.17, 162.75, 157.36, 133.63, 130.67, 128.23, 127.25, 127.57, 122.65, 115.78, 115.00, 102.14, 33.66, 20.34, 13.84. *m/z* 280.1 *Anal*. Calcd. for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75. Found C, 77.18, H, 5.71

Data for 7-hydroxy-2-butylisoflavone, m.p. 162–164˚C, ^{1}H NMR, d_6-DMSO, δ 0.74–0.77(t, 3H), 1.16–1.26(m, 2H), 1.55–1.63(m, 2H), 2.44–2.53(m, 2H), 6.85–6.86(d, 1H), 6.90–6.93(dd, 1H), 7.22–7.45(m, 5H arom), 7.88–7.90(d, 1H), 10.78(s, 1H, –OH). ^{13}C NMR



Scheme 1

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Table 2 Synthesis of 2-alkylisoflavone with the change of structrure of aliphatic acid chloride and 2-hydroxydeoxybenzoins

Entry no.	R_1	R_2	RCOCl	Yield/%	M.p./°C (lit[ref])
1	H	H	CH_3	85	237–238 (240)[4]
2	H	4-OCH_3	CH_3	82	286–287 (286–287)[13]
3	H	4-OCH_3	CH_3CH_2	80	242–244 (242–243.5)[13]
4	H	2-OCH_3	CH_3	80	225–227 (225–227)[14]
5	H	2-OCH_3	CH_3CH_2	76	191–193 (193–194)[7]
6	OH	H	CH_3	55	226–228 (228)[4]
7	OH	4-OCH_3	CH_3	60	174–176 (175–176)[15]
8	OH	4-OCH_3	CH_3CH_2	61	229–231 (229–230)[13]
9	OH	2-OCH_3	CH_3	52	150–151 (150–151)[15]
10	H	H	$CH(CH_3)_2$	60	271–274 (273–275)[8]
11	H	H	$CH_3CH_2CH_2$	60	174–176
12	H	H	$CH_3CH_2CH_2CH_2$	40	162–164

δ: 175.21, 165.45, 162.75, 157.36, 133.61, 130.88, 128.22, 127.26, 127.57, 122.50, 115.79, 114.99, 102.14, 31.62, 29.01, 21.61, 13.57. *m/z* 294.1. *Anal*. Calcd. for $C_{19}H_{18}O_3$. C, 77.53; H, 6.16. Found C, 77.49; H, 6.17

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