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A practical synthesis of a new series of isoflavanones

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Abstract

A practical six-step synthesis of 12 methylated and hydroxylated isoflavanones was accomplished starting from readily available *m*-xylene. A significant improvement of this procedure included application of the simple and commercially available reagents, avoidance of expensive reagents and catalysts, simple operations and excellent yields.

Keywords: Deoxybenzoins; Isoflavanones; Synthesis

Isoflavanones as a group of natural products existing in plant are extensively studied for their immunosuppressive [1], cytotoxic [2], anti-microbial [3], anti-HIV [4], estrogenic and anti-tumor activities [5]. The isoflavanone moiety is the key structural feature of many synthetic intermediates to other phytoalexines such as pterocarpans and isoflavones. Although some isoflavanone have been isolated from the *leguminaceae* family, the limited distribution in the plant kingdom restricts further study on their bioactivities. This situation has prompted exploration toward chemical synthesis of isoflavanones. There are several methods reported for the preparation of isoflavanones [6]. However, these methods are unsatisfactory for many deficiencies such as expensive reagents and metallic catalysts, harsh reaction conditions, complicated products, and toxic reagents. In this paper we presented a practical total synthetic route to prepare a new series of isoflavanone.

Three classical methods for synthesizing isoflavanones were reported in literatures: (1) reduction of readily available alkoxyisoflavones using a noble metal catalyst or complex metal hydrides [7]; (2) Heck arylation of 4-acyloxy-2*H*-chromenes with aryl mercury (II) compounds in the presence of catalytic amounts of palladium acetate [8]; (3) addition of a single carbon at the benzylic position of deoxybenzoins followed by cyclization [9]. Our strategy reported here involved annulation of deoxybenzoins to form isoflavanones. And the protection for hydroxyl group and cyclization are the most critical two synthetic steps in this route. Although various conditions were attempted in our work, the protection for hydroxyl group of deoxybenzoins by chloromethyl ethyl ether (CMEE) or chloromethyl methyl ether (CMME) was complicated and very low yields of the desired compounds were obtained. Fortunately immediate success was achieved by using dimethyl sulfate. In order to cyclize deoxybenzoins [10], commercially available CMEE was examined firstly, but the produced olefine ketone hardly converted to isoflavanones by treatment with DBU (Scheme 1) [11]. To our delight, however, the further synthesis proceeded favorably in one step with paraformaldehyde as the reactant (Scheme 2).

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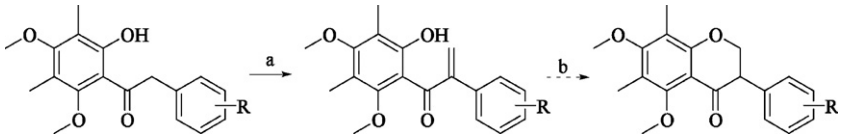
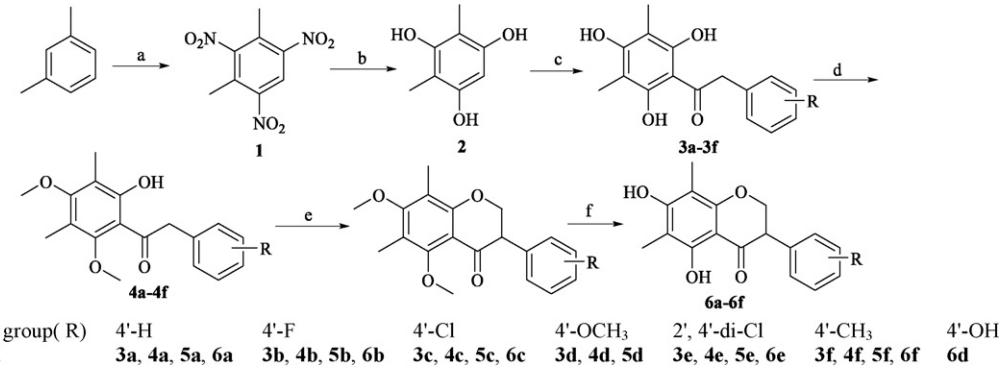


Scheme 1. Preliminary attempts to cyclize deoxybenzoins with CMEE and DBU. (a) $ClCH_2OC_2H_5$, K_2CO_3, acetone and (b) DBU, THF.



Scheme 2. Reagents and conditions: (a) H_2SO_4, HNO_3, 110 °C, 3 h; (b) hydrochloric acid, Sn, 100 °C, 3–5 h, then, pH 3–4, 100 °C, 24 h; (c) HCl, $ZnCl_2$, nitrile, Et_2O, 0 °C, 2.5 h, then, 4 °C, 12 h; (d) Me_2SO_4, K_2CO_3, Me_2CO; (e) $(CH_2O)_n$, Et_2NH, EtOH; (f) BBr_3, CH_2Cl_2.

Deoxybenzoins **4** were key intermediates which were obtained conveniently by the Houben-Hoesch condensation of **2** with different substituted benzacetonitril followed by partial methylation of the resulting **3**. Then deoxybenzoins **4** were condensated with paraformaldehyde in the presence of diethylamine and anhydrous ethanol to afford the corresponding methylated isoflavanones **5**. Final removal of the methyl groups was accomplished with BBr_3, which afforded the hydroxylated isoflavanones **6** in high yields.

1. Experimental

^1H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance-400 FT nuclear magnetic resonance spectrometer with TMS as the internal standard. MS spectra were taken on a high resolution ESI-FTICR mass spectrometer (Varian 7.0T). The melting points were determined on an XT4 melting point apparatus. All the reagents were of analytical grade.

Compound **1**: *m*-Xylene (2.4 mL, 19 mmol) was subjected to a mixture of sulfuric acid (6 mL) and nitric acid (3 mL) below 40 °C. Then, nitrosonitric acid (3 mL) was added to the above solution. The mixture was heated at 110 °C for 3 h, and then followed by filtration to yield compound **1** as a white solid 4.3 g (96.0%) [12].

Compound **2**: A mixture of compound **1** (9.0 g, 37 mmol) and Sn powder (36 g, 200 mmol) was added to hydrochloric acid (95 mL). The mixed solution was stirred at 60 °C until the solid was completely dissolved. And then the solution was heated at 100 °C for 3–5 h. On cooling, the mixture was adjusted to pH 3–4. Then, the solution was refluxed for 24 h. The solution was extracted with diethyl ether, and the organic phase was dried with anhydrous sodium sulfate, evaporated at a reduced pressure to form compound **2** as a yellow solid 3.7 g (64.6%) [13].

Compound **3**: Dry hydrogen chloride was bubbled through the cold solution of compound **2** (3.1 g, 20 mmol) and the corresponding cyanide (20 mmol) in the anhydrous ether containing dry zinc chloride (1.4 g, 10 mmol) with vigorous stirring for 2.5 h. The ketimine hydrochloride could separate out as a yellow solid for fully placed at 4 °C. After decanting off the solvent, the solid was dissolved in water and refluxed for 1 h, and the yellow solid emerged was collected to give compound **3**.

Compound **4**: To a solution of **3** (3 mmol) in dry acetone were added anhydrous potassium carbonate (6 mmol) and dimethyl sulfate (6 mmol), the mixture was refluxed at 70 °C for 45 min with TLC monitoring. After the reaction was complete the reaction mixture was filtered hot, washed with acetone and the filtrate was concentrated to prepare compound **4**.

Compound **5**: Compound **4** (1 mmol) was dissolved in ethanol and refluxed with paraformaldehyde (2 mmol) and diethylamine (2 mmol) for 1–1.5 h. The progress of the reaction was monitored by TLC. Ethanol was removed and the mixture was acidified with diluted acid. The desired isoflavanone **5** was purified by chromatography column.

Compound **6**: The removal of the methyl groups of compound **5** (1 mmol) was accomplished by using boron tribromide (5 mL, 1 mol/L) in DCM to generate isoflavanone **6**.

5a: Oil (78.2% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (m, 5H), 4.68 (d, 2H, J = 7.01 Hz), 3.92 (t, 1H, J = 7.12 Hz), 3.80 (s, 3H), 3.77 (s, 3H), 2.18 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.54, 163.31, 159.66, 158.03, 135.57, 128.79, 128.56, 127.60, 118.81, 115.35, 111.937, 70.82, 61.07, 60.13, 52.94, 8.89, 8.65; ESI-MS (m/z): 310.9 ([M−H]$^-$); HR-MS 335.1257 ([M+Na]$^+$; Calcd. for $C_{19}H_{20}NaO_4$ 335.1254).

5b: White solid (74.3% yield), mp 66.0–66.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27(d, 2H, J = 8.57 Hz), 7.06 (d, 2H, J = 8.70 Hz), 4.67 (dd, 1H, J = 5.38, 11.38 Hz), 4.62 (dd, 1H, J = 8.50, 11.42 Hz), 3.90 (dd, 1H, J = 5.40, 8.43 Hz), 3.79 (s, 3H), 3.78 (s, 3H), 2.17 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.33, 163.44, 161.02, 159.56, 158.04, 131.27, 130.18, 130.11, 118.97, 115.82, 115.60, 115.42, 111.76, 70.73, 61.06, 60.15, 52.12, 8.89, 8.65; ESI-MS (m/z): 329.1([M−H]$^-$); HR-MS 353.1162 ([M+Na]$^+$; Calcd. for $C_{19}H_{19}FNaO_4$ 353.1160).

5c: White solid (77.6% yield), mp 84.6–86.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (d, 2H, J = 8.54 Hz), 7.24 (d, 2H, J = 8.41 Hz), 4.67 (dd, 1H, J = 5.46, 11.40 Hz), 4.63 (dd, 1H, J = 8.20, 11.42 Hz), 3.89 (dd, 1H, J = 5.50, 8.23 Hz), 3.79 (s, 3H), 3.77 (s, 3H), 2.17 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.01, 163.50, 159.53, 158.05, 133.97, 133.56, 129.89, 128.96, 119.01, 115.43, 111.72, 70.51, 61.07, 60.15, 52.21, 8.884, 8.65; ESI-MS (m/z): 347.1 ([M+H]$^+$); HR-MS 369.0866 ([M+Na]$^+$; Calcd. for $C_{19}H_{19}ClNaO_4$ 369.0864).

5d: White solid (75.5% yield), mp 63.6–65.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (d, 2H, J = 8.65 Hz), 6.90 (d, 2H, J = 8.75 Hz), 4.66 (dd, 1H, J = 5.73, 11.39 Hz), 4.63 (dd, 1H, J = 8.29, 11.37 Hz), 3.87 (dd, 1H, J = 5.72, 8.24 Hz), 3.91 (s, 3H), 3.80 (s, 3H), 3.76 (s, 3H), 2.17 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.87, 163.24, 159.63, 159.00, 158.00, 129.58, 127.50, 118.75, 115.32, 114.25, 111.89, 70.89, 61.06, 60.13, 55.27, 52.11, 8.90, 8.64; ESI-MS (m/z): 343.2 ([M+H]$^+$); HR-MS 365.1357 ([M+Na]$^+$; Calcd. for $C_{20}H_{22}NaO_5$ 365.1359).

5e: White solid (73.6% yield), mp 102.4–103.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (d, 1H, J = 2.13 Hz), 7.26 (dd, 1H, J = 2.14, 8.51 Hz), 7.11 (d, 1H, J = 8.35 Hz), 4.53 (m, 3H), 3.82 (s, 3H), 3.78 (s, 3H), 2.19 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.32, 163.60, 159.81, 158.09, 135.40, 134.14, 132.12, 131.04, 129.78, 127.49, 119.14, 115.55, 112.26, 69.84, 61.07, 60.17, 50.24, 8.87, 8.69; ESI-MS (m/z): 381.2 ([M+H]$^+$); HR-MS 403.0476 ([M+Na]$^+$; Calcd. for $C_{19}H_{18}Cl_2NaO_4$ 403.0473).

5f: Viscous oil (69.4% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18 (s, 4H), 4.65 (m, 2H), 3.89 (m, 1H), 3.80 (s, 3H), 3.76 (s, 3H), 2.35 (s, 3H), 2.17 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.77, 163.24, 159.67, 158.01, 137.27, 132.43, 129.50, 128.40, 118.74, 115.31, 111.94, 70.85, 61.07, 60.12, 52.57, 21.11, 8.89, 8.64; ESI-MS (m/z): 327.6 ([M+H]$^+$); HR-MS 349.1415 ([M+Na]$^+$; Calcd. for $C_{20}H_{22}NaO_4$ 349.1411).

6a: Yellow solid (90.1% yield), mp 136.6–138.4 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.39 (s, 1H), 7.35 (m, 5H), 4.65 (dd, 1H, J = 5.24, 11.34 Hz), 4.59 (dd, 1H, J = 8.33, 11.29 Hz), 3.97 (dd, 1H, J = 5.22, 8.23 Hz), 2.09 (s, 3H), 2.09 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 196.87, 160.98, 159.75, 157.77, 135.26, 128.94, 127.90, 103.11, 102.82, 101.83, 71.23, 51.29, 7.47, 6.94; ESI-MS (m/z): 285.5 ([M+H]$^+$); HR-MS 283.0974 ([M−H]$^-$; Calcd. for $C_{17}H_{15}O_4$ 283.0976).

6b: Yellow solid (93.4% yield), mp 184.0–186.0 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.37 (s, 1H), 9.82 (s, 1H), 7.34 (m, 2H), 7.18 (m, 2H), 4.60 (d, 2H, J = 6.96 Hz), 4.21 (t, 1H, J = 6.89 Hz), 1.98 (s, 3H), 1.97 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 197.35, 163.05, 160.46, 159.26, 157.84, 131.50, 131.30, 131.22, 115.91, 115.69, 103.91, 102.83, 102.17, 71.01, 49.80, 8.61, 8.11; ESI-MS (m/z): 300.9 ([M−H]$^-$); HR-MS 301.0880 ([M−H]$^-$; Calcd. for $C_{17}H_{14}FO_4$ 301.0882).

6c: Yellow solid (95.5% yield), mp 157.5–158.6 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.34 (s, 1H), 9.77 (s, 1H), 7.42 (d, 2H, J = 8.47 Hz), 7.32 (d, 2H, J = 8.47 Hz), 4.60 (d, 2H, J = 6.89 Hz), 4.22 (t, 1H, J = 6.88 Hz), 1.98 (s, 3H), 1.97 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 197.07, 163.11, 159.27, 157.82, 135.23, 132.64, 131.17, 128.98, 103.95, 102.87, 102.18, 70.86, 49.91, 8.61, 8.11; ESI-MS (m/z): 316.8 ([M−H]$^-$); HR-MS 317.0584 ([M−H]$^-$; Calcd. for $C_{17}H_{14}ClO_4$ 317.0586).

6d: Yellow solid (94.1% yield), mp above 300 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.46 (s, 1H), 9.73 (s, 1H), 7.07 (d, 2H, J = 8.57 Hz), 6.73 (d, 2H, J = 8.59 Hz), 4.54 (d, 2H, J = 7.52 Hz), 3.99 (t, 1H, J = 7.28 Hz), 1.97 (s, 3H), 1.96 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 198.02, 162.90, 159.28, 157.86, 157.14, 130.13, 126.41, 115.79,

103.80, 102.72, 102.18, 71.32, 49.78, 8.63, 8.12; ESI-MS (*m*/*z*): 301.4 ([M+H]$^+$); HR-MS 299.0922 ([M−H]$^-$; Calcd. for $C_{17}H_{15}O_5$ 300.0998).

6e: Yellow solid (94.4% yield), mp 204.6–206.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.24 (s, 1H), 9.81 (s, 1H), 7.70 (d, 1H, J = 2.16 Hz), 7.45 (dd, 1H, J = 2.17, 8.41 Hz), 7.37 (d, 1H, J = 8.41 Hz), 4.62 (m, 3H), 1.99 (s, 3H), 1.98 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 195.87, 163.19, 159.23, 157.81, 135.27, 133.63, 132.71, 132.67, 129.58, 128.12, 104.14, 103.11, 102.37, 69.58, 43.36, 8.61, 8.12; ESI-MS (*m*/*z*): 350.8 ([M−H]$^-$); HR-MS 351.0197([M−H]$^-$; Calcd. for $C_{17}H_{13}Cl_2O_4$ 351.0196).

6f: Yellow solid (89.7% yield), mp 149.3–151.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.43 (s, 1H), 9.74 (s, 1H), 7.16 (s, 4H), 4.58 (d, 2H, J = 6.62 Hz), 4.09 (t, 1H, J = 6.63 Hz), 2.28 (s, 3H), 1.96 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 197.69, 162.98, 159.29, 157.87, 137.03, 133.30, 129.57, 129.02, 103.84, 102.77, 102.25, 71.19, 50.19, 21.12, 8.62, 8.11; ESI-MS (*m*/*z*): 299.4 ([M+H]$^+$); HR-MS 297.1134 ([M−H]$^-$; Calcd. for $C_{18}H_{17}O_4$ 297.1132).

In conclusion, we developed a convenient six-step synthetic approach for isoflavanones from *m*-xylene, and 12 new desired products were obtained. Comparing with the classical methods [7–9], this practical synthetic strategy could produce various methylated and hydroxylated isoflavanones by using commercially available cheap reagents with simple operations and excellent yields. The pharmacological study of the new isoflavanones is ongoing.

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