Synthesis of 7,8-methylenedioxy-4′-methoxyisoflavone from *Indigofera linnaei* and two new related flavonoids

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The synthesis of naturally occurring 7,8-methylenedioxy-4′-methoxyisoflavone and 7,8-methylenedioxy-4′-methoxyflavone from 2′-hydroxy-3′,4′-methylenedioxy-4-methoxychalcone via the intermediacy of 7,8-methylenedioxy-4′-methoxyflavanone using thallium(III) acetate and catalytic amount of perchloric acid is reported. The products flavanone and the flavone are new flavonoids characterised by spectral analysis.

Keywords: isoflavone, flavanone, flavone, thallium(III)acetate, *Indigofera linnaei*

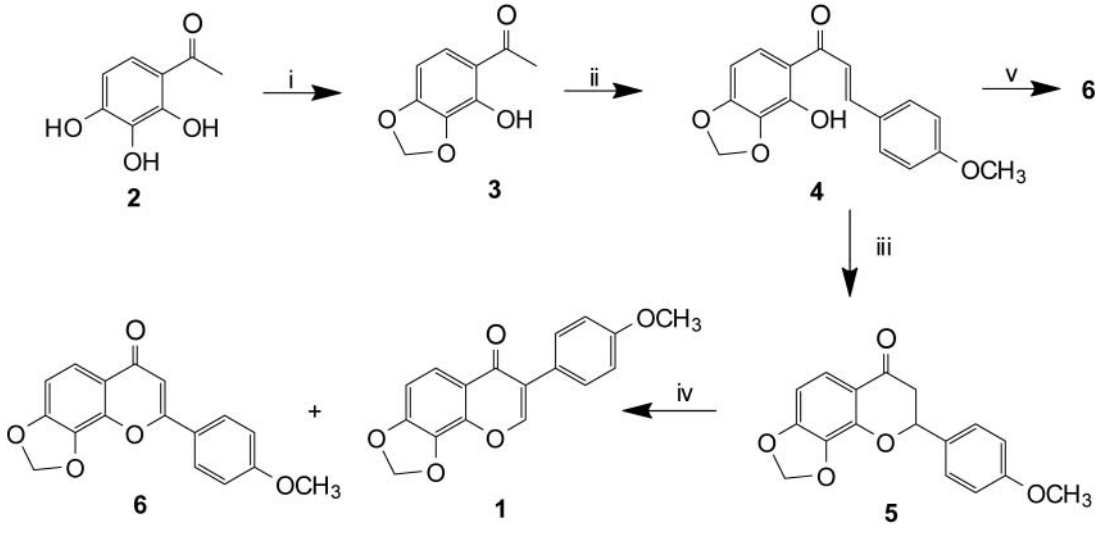
Prasad and Chakradhar reported in 2004[1] the isolation of a new isoflavone from *Indigofera linnaei* and assigned to it the structure 7,8-methylenedioxy-4′-methoxyisoflavone **1** on the basis of its IR, ^{1}H NMR and MS data. A literature search revealed that this isoflavone **1** had also been isolated previously[2] by Rao and Murthy from *Tephrosia maxima*. Subsequently, its synthesis was reported by Parmar *et al*.[3] Dagne *et al*.[4] reported the isolation of **1** from *Millettia dura*. In view of these additional reports,[2–4] the claim made by Prasad and Chakradhar[1] that **1** is a new isoflavone is incorrect.

Although the ^{1}H NMR and MS data[1] can account for the structure **1** assigned, the carbonyl band at 1685 cm^{-1} in its IR data appeared untenable for the isoflavone structure because the carbonyl of isoflavones,[5–8] having substitution pattern similar to that of **1,** shows absorption in the region 1630–1660 cm^{-1}. Thus the discrepancy observed[1–4] in the data including the melting point[1] reported for the same isoflavone **1** prompted us to synthesise this isoflavone **1** again.

Our synthetic route was based on the formation of isoflavones by 1,2-aryl migration of flavanones which, in turn, are formed in nature from the corresponding chalcones (Scheme 1).

Thus the required 2′,3′,4′-trihydroxyacetophenone (gallacetophenone) **2** and 2′-hydroxy-3′,4′-methylenedioxyacetophenone **3** were prepared using known literature procedures.[9,10] Base-catalysed condensation[11] of **3** with *p*-methoxybenzaldehyde gave 2′-hydroxy-3′,4′-methylenedioxy-4-methoxychalcone **4** whose spectral data (IR and NMR) matched well with those reported.[3] Heating **4** in trifluoroacetic acid (TFA) under reflux[12] for 1 h, gave pale yellow needles, m.p. 118°C whose IR spectrum showed a strong carbonyl band at 1682 cm^{-1} as expected for a flavanone. The presence of three signals (doublet of doublets) at δ 2.86 (H-3*eq*), 3.10 (H-3*ax*) and 5.47 (H-2) in its ^{1}H NMR spectrum and the signals at δ 190.3 (CO) and 44.5 (C-3) in its ^{13}C NMR spectrum coupled with DEPT experiments established the presence of the flavanone moiety and hence structure 7,8-methylenedioxy-4′-methoxyflavanone **5**. Literature survey indicated that **5** is a new flavanone and its structure was further corroborated by its HRESIMS data.

Heating **5** in acetonitrile with thallium(III) acetate (TTA)[13] and catalytic amount of perchloric acid[14] for 1 h, followed by silica gel column chromatography gave colourless crystals of **1**, m.p. 198 °C, (reported 248 °C for the natural[1] and 192–193 °C for the synthetic[3] **1**) which showed a strong band in the IR at 1657 cm^{-1} (reported[1] 1685 cm^{-1}) as expected and reported[4–8] for the carbonyl of isoflavones. The ^{1}H NMR chemical shifts (in $CDCl_3$) for the various protons of our synthetic **1** agreed well with those reported for the natural[2,4] and synthetic[3] **1**. However, the ^{1}H NMR chemical shifts (in DMSO-d_6) of our synthetic **1** varied significantly from those reported[1] (in DMSO-d_6) for the natural **1** by Prasad and Chakradhar. The rearrangement of flavanone **5** to isoflavone **1** under the conditions employed, is well precedented.[14] Further elution of the column gave a white solid, m.p. 220 °C, whose IR spectrum displayed a strong carbonyl band at 1655 cm^{-1}. Its ^{1}H and ^{13}C NMR data showed signals characteristic of a flavone moiety[15] and indicated it to be 7,8-methylenedioxy-4′-methoxyflavone **6**. Literature survey revealed **6** to be a new flavone. Its structure was further supported by its HRESIMS data. Finally, the flavone **6** was also prepared in 95% yield by simply heating



Scheme 1 Reagents: (i) CH_2I_2, Cs_2CO_3, DMF; (ii) *p*-anisaldehyde, NaOH, EtOH; (iii) TFA; (iv) TTA, $HClO_4$; (v) I_2, DMSO.

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chalcone **4** under reflux in DMSO[16] containing a crystal of I_2.

In conclusion, our simple synthetic route has furnished the natural isoflavone **1** along with the new flavanone **5** and the new flavone **6**. Our definitive synthesis of the structure **1** and the discrepancies (in the melting point, IR and ^{1}H NMR data) observed are so significant that the natural product in ref. 1 needs further investigation.

Experimental

Melting points were determined in open capillary tubes and are uncorrected. UV spectra were recorded in methanol using matched quartz cells on a Shimadzu (UV-2450) spectrophotometer. IR spectra were recorded as KBr diluted pellets on a Shimadzu (IR Prestige-21) FTIR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz respectively on a Bruker WT 300 FT-NMR instrument with TMS as internal standard and chemical shifts are recorded in δ values. The multiplicities of carbon signals were obtained from distortionless enhancement by polarisation transfer (DEPT). HRESITOFMS was recorded on QSTARXL MS/MS, Applied Biosystems, Switzerland. All yields refer to isolated products unless stated otherwise. Petroleum ether refers to hydrocarbon fraction boiling in the range 60–80 °C.

2′-Hydroxy-3′,4′-(methylenedioxy)acetophenone (**3**):[10] To a stirred suspension of 2′,3′,4′-trihydroxyacetophenone **2** (1.0 g, 5.95 mmol) and Cs_2CO_3 (1.94 g, 5.95 mmol) in dry DMF (15 mL) was added CH_2I_2 (0.48 mL, 1.595 g, 5.95 mmol) and the resulting mixture was boiled under reflux. After 8 h, the mixture was allowed to cool to room temperature, filtered through a pad of celite and washed with EtOAc. The filtrate and washings were concentrated almost to dryness, residue diluted with water and extracted with Et_2O. The combined ether extracts were washed with water, brine and dried over Na_2SO_4. Evaporation of the solvent gave a dark-tan solid, which was purified by silica gel column chromatography using 5% Et_2O in petroleum ether to afford pure 2′-hydroxy-3′,4′-(methylenedioxy)acetophenone **3** as a pale yellow solid (0.54 g, 50.5%). Recrystallisation from petroleum ether gave colourless flakes, m.p. 96–98 °C as reported.[10]

2′-Hydroxy-3′,4′-methylenedioxy-4-methoxychalcone (**4**): To a mixture of **3** (0.24 g, 1.3 mmol), *p*-methoxybenzaldehyde (0.199 g, 1.46 mmol) in EtOH (1 mL) was added aq. NaOH (2.5 g in 5 mL H_2O) dropwise and the reaction mixture was stirred for 1 h at 45 °C. Stirring was further continued overnight at room temperature. The yellow orange mixture obtained was diluted with water and acidified with conc. HCl. The yellow solid separated was filtered, washed with water and dried to give **4** (0.34 g, 86%). Recrystallisation from hot ethanol gave fine yellow needles, m.p. 176 °C (lit.[3] 143 °C from benzene). UV (nm): 363, 244, 212. IR (cm^{-1}): 1657 (CO), 1605 (C=C). ^{1}H NMR ($CDCl_3$) δ: 3.87 (s, 3H, OCH_3), 6.09 (s, 2H, OCH_2O), 6.52 (d, 1H, H-5′, J = 8.4 Hz), 6.95 (d, 2H, H-3 & H-5, J = 8.7 Hz), 7.44 (d, 1H, H-α, J = 15.3 Hz), 7.58 (d, 1H, H-6′, J = 8.4 Hz), 7.61 (d, 2H, H-2 & H-6, J = 9 Hz), 7.86 (d, 1H, H-β, J = 15.3 Hz), 13.05 (s, 1H, OH). ^{13}C NMR ($CDCl_3$) δ: 55.4 (OCH_3), 100.6 (OCH_2O), 102.6 (C-5′), 114.5 (C-3, C-5), 117.3 (C-1′), 117.8 (C-α), 125.5 (C-6′), 127.4 (C-1), 130.4 (C-2, C-6), 134.5 (C-3′), 144.8 (C-β), 148.1 (C-2′), 153.9 (C-4), 161.9 (C-4′), 192.7 (CO).

7,8-Methylenedioxy-4′-methoxyflavanone (**5**): A mixture of chalcone **4** (0.28 g, 0.94 mmol) and trifluoroacetic acid (8 mL) was heated to reflux. After 1 h (monitored by TLC) the reaction mixture was diluted with water and extracted with $CHCl_3$. The combined extracts were washed with saturated $NaHCO_3$ solution, brine and dried over Na_2SO_4.Filtration followed by concentration gave a residue (0.33 g) which was purified by silica gel column chromatography using hexane:EtOAc (95:5) to give unreacted **4** (0.074 g) followed by elution with hexane:EtOAc (9:1) to give **5** (0.187 g, 66%). Recrystallisation from hexane:chloroform mixture gave fine pale yellow needles m.p. 118 °C. UV (nm): 292, 242, 216. IR (cm^{-1}): 1682 (CO). ^{1}H NMR ($CDCl_3$) δ: 2.86 (dd, 1H, H-3*eq*, J = 16.8, 2.7 Hz), 3.10 (dd, 1H, H-3*ax*, J = 16.8, 12.9 Hz), 3.82 (s, 3H, OCH_3), 5.47 (dd, 1H, H-2, J = 12.6, 2.7 Hz), 6.07 (s, 2H, OCH_2O), 6.60 (d, 1H, H-6, J = 8.4 Hz), 6.94 (d, 2H, H-3′ & H-5′, J = 8.7 Hz), 7.40 (d, 2H, H-2′ & H-6′, J = 8.7 Hz), 7.59 (d, 1H, H-5, J = 8.4 Hz). ^{13}C NMR ($CDCl_3$) δ: 44.5 (C-3), 55.3 (OCH_3), 80.1 (C-2), 102.6 (OCH_2O), 103.4 (C-6), 114.2 (C-3′, C-5′), 117.7 (C-4a), 122.6 (C-5), 127.8 (C-2′, C-6′), 130.4 (C-1′), 134.6 (C-8), 145.6 (C-8a), 154.2 (C-4′), 160.0 (C-7), 190.3 (C-4). HRESIMS: *m/z* 321.0738 [M + Na]$^+$; Calcd for $C_{17}H_{14}O_5Na^+$: 321.0733.

7,8-Methylenedioxy-4′-methoxyisoflavone (**1**) *and 7,8-methylenedioxy-4′-methoxyflavone* (**6**): To a solution of thallium(III) acetate (0.168 g, 0.4 mmol) and 70% perchloric acid (0.168 g, 1.17 mmol) in acetonitrile (7 mL) was added **5** (0.1 g, 0.33 mmol) and the reaction mixture was heated in a boiling water bath for 30 min. The reaction mixture was then cooled to room temperature, CH_2Cl_2 (15 mL) was added and kept at 0 °C for 15 min. The solid so obtained was filtered to remove thallium (I) salt and washed with CH_2Cl_2. The combined filtrate was washed successively with water, saturated $NaHCO_3$ solution, water and dried over Na_2SO_4. Evaporation of the solvent gave a crude residue (0.102 g) which was purified by silica gel column chromatography using petroleum ether:ethyl acetate (9:1) to give **1** as a white solid (0.025 g, 25%). Recrystallisation from petroleum ether-chloroform mixture gave crystals, m.p. 198 °C in agreement with literature values.[2–4] UV (nm): 294, 241, 217. IR (cm^{-1}): 1657 (CO). ^{1}H NMR ($CDCl_3$) δ: 3.86 (s, 3H, OCH_3), 6.23 (s, 2H, OCH_2O), 6.99 (d, 1H, H-6, J = 8.7 Hz), 6.99 (d, 2H, H-3′ & H-5′, J = 8.7 Hz), 7.49 (d, 2H, H-2′ & H-6′, J = 8.7 Hz), 7.91 (d, 1H, H-5, J = 8.7 Hz), 7.92 (s, 1H, H-2). ^{1}H NMR (DMSO-d_6) δ: 3.78 (s, 3H, OCH_3), 6.12 (s, 2H, OCH_2O), 6.75 (d, 1H, H-6, J = 8.4 Hz), 6.75 (d, 2H, H-3′ & H-5′, J = 8.4 Hz), 6.99 (d, 2H, H-2′ & H-6′, J = 8.4 Hz), 7.44 (d, 1H, H-5, J = 8.4 Hz), 7.48 (s, 1H, H-2).

Continued elution with petroleum ether:ethyl acetate (6:4) gave **6** (0.014 g, 14%) which on recrystallisation from hot ethanol gave fine cotton like clusters, m.p. 220 °C. UV (nm): 312, 267, 222. IR (cm^{-1}): 1655 (CO). ^{1}H NMR ($CDCl_3$) δ: 3.87 (s, 3H, OCH_3), 6.19 (s, 2H, OCH_2O), 6.64 (s, 1H, H-3), 6.92 (d, 1H, H-6, J = 8.4 Hz), 6.99 (d, 2H, H-3′ & H-5′, J = 9 Hz), 7.78 (d, 1H, H-5, J = 8.4 Hz), 7.85 (d, 2H, H-2′ & H-6′, J = 8.7 Hz). ^{13}C NMR ($CDCl_3$) δ: 55.5 (OCH_3), 103.1 (OCH_2O), 105.5 (C-3), 106.9 (C-6), 114.5 (C-3′, C-5′), 119.9 (C-4a), 120.0 (C-5), 123.7 (C-1′), 127.9 (C-2′, C-6′), 134.7 (C-8), 141.1 (C-8a), 152.3 (C-2), 162.4 (C-4′), 162.6 (C-7), 177.3 (C-4). HRESIMS: *m/z* 319.0571 [M + Na]$^+$; Calcd for $C_{17}H_{12}O_5Na^+$: 319.0577.

7,8-Methylenedioxy-4′-methoxyflavone (**6**): To 2′-hydroxy-3′,4′-methylenedioxy-4-methoxychalcone **4** (0.11 g, 0.36 mmol) suspended in DMSO (5 mL), a crystal of I_2 was added. The mixture was heated to reflux for 45 min, cooled to room temperature, diluted with water and extracted with ethyl acetate. The organic extracts were washed with aq. sodium thiosulfate, water and dried over Na_2SO_4. Evaporation of the solvent afforded **6** as white solid (0.104 g, 95%) which on recrystallisation from hot ethanol gave fine cotton like clusters m.p. 220 °C.

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