Malaysian Journal of Science (**24**): 173-176 (2005)

Synthesis of C-Methyl Flavones

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ABSTRACT Flavonoids possesss interesting biological actions. Some C-alkylated favonoids have been isolated from natural sources. In the present investigation, we have synthesised C-methyl flavones from *m*-cresol. Acetylationof *m*-cresol has afforded *m*-cresyl acetate. Fries rearrangement of *m*-cresyl acetate with $AlCl_3$ at 185°C afforded only monoacetyl cresol, which was identified as 2-hydroxy-4-methylacetophenone. Condensation of 2-hydroxy-4-methylacetophenone with anisaldehyde gave 2-hydroxy-4'-methoxy-4-methylchalcone which on oxidative cyclisation with SeO_2 gave 4'-methoxy-7-methylflavone. The structures of the pure compounds were identified by spectroscopic techniques.

ABSTRAK Flavonoid mempunyai pelbagai kegunaan biologi. Terdapat beberapa jenis flavonoid teralkil-C telah diasingkan daripada sumber semula jadi. Dalam kajian ini, sebatian flavon termetil-C telah disintesis. Pengasetilan *m*-kresol menghasilkan *m*-kresil asetat. Penyusunan semula Fries ke atas *m*-kresil asetat dengan $AlCl_3$ pada 185°C menghasilkan kresol monoasetat yang telah dikenal pasti sebagai 2-hidroksi-4-metilasetofenon. Kondensasi 2-hidroksi-4-metilasetofenon dengan anisaldehid menghasilkan 2-hidroksi-4'-metoksi-4-metilkalkon dan dengan pensiklikan oksidatif menggunakan SeO_2 memberikan 4'-metoksi-7-metilflavon. Semua struktur sebatian tulen dikenal pasti dengan teknik spektroskopi.

(flavonoid, acetylation, Fries migration, oxidative cyclisation)

INTRODUCTION

Some novel C-alkylated flavonoids have been isolated from natural sources [1-3]. In this paper, we wish to report the synthesis of 4'-methoxy-7-methylflavone, a C-alkylated flavone by convenient methods [4].

4'-Methoxy-7-methylflavone was synthesized using *m*-cresol as starting material. *m*-cresol **1** underwent acetylation to form *m*-cresyl acetate **2**. Fries migration of *m*-cresyl acetate with a Lewis acid at 185°C afforded only monoacetyl cresol, which was identified as 2-hydroxy-4-methylacetophenone **3**. Aldol condensation of compound **3** with anisaldehyde gave 2-hydroxy-4'-methoxy-4-methylchalcone **4** which on oxidative cyclisation with SeO_2 gave 4'-methoxy-7-methylflavone **5** [4].

EXPERIMENTAL

Instrument

Mps (uncorr.) were determined on a Leica Galen III apparatus. The IR spectra were run on a FTIR Shimadzu 8300 Model. The ^1H and ^{13}C NMR spectra were obtained from Bruker Avance spectrometer which were recorded at 300 and 75 MHz respectively.

Chemicals

Triethylamine (Et_3N), acetic anhydride (Ac_2O), dimethylaminopyridine (DMAP) were purchased from Merck. Aluminium chloride ($AlCl_3$) was purchased from Riedel-de Haen. Anisaldehyde and selenium oxide (SeO_2) were obtained from Fluka and Merck-Schuchardt.

Synthesis of m-cresyl acetate 2

A mixture of *m*-cresol **1** (2.16 g, 20 mmol), triethylamine (3.03 g, 30 mmol), acetic anhydride (3.06 g, 50 mmol) and DMAP (185 mg) in dichloromethane (20 mL) was stirred for 2 hours at room temperature. The mixture was washed

with 2 M HCl followed by saturated $NaHCO_3$ solution. The organic extracts were washed with water, dried ($MgSO_4$), and evaporated to give *m*-cresyl acetate **2** as brownish liquid (3.00 g, 66.6%); IR $\nu_{max}cm^{-1}$: 3031.9 (=CH sp^2), 2922.0 (-CH sp^3), 1766.7 (C=O ester), 1589.2 and 1488.9 (C=C aromatic), 1207.4 (C-O); NMR δ_H ($CDCl_3$): 2.27 (3H, s, $MeCO_2$), 2.34 (3H, s, $-CH_3$), 6.86 (1H, m, H-6), 6.89 (1H, s, H-2), 7.01-7.04 (1H, m, H-4), 7.24 (1H, dd, J = 7.8 Hz and 6.9 Hz, H-5); NMR δ_C ($CDCl_3$): 21.11 (CH_3 aromatic), 21.26 (CH_3 acyl), 118.46 (C-4), 122.12 (C-5), 126.61 (C-2), 129.10 (C-6), 139.58 (C-3), 150.58 (C-1) and 169.60 (C=O).

Synthesis of 2-hydroxy-4-methylacetophenone 3

m-Cresyl acetate **2** (1.64 g, 11 mmol) was heated in oil-bath and anhydrous $AlCl_3$ (1.57 g, 11.8 mmol) was added to it. The mixture was stirred with a glass rod and heated at 185°C for 2.5 hours. After cooling to room temperature, the reaction mixture was decomposed with HCl (5 %, 15 mL) and heated on a boiling water bath for 45 minutes before the reaction was left overnight at room temperature until a green layer separated out, which was extracted with Et_2O (5 × 10 mL). The ethereal layer was washed with distilled water, dried with anhydrous $MgSO_4$ and evaporated to dryness. Purification by preparative TLC with PE:Et_2O (4:1) as the eluent has afforded 2-hydroxy-4-methylacetophenone **3** (0.63 g, 38.36%) as yellowish liquid; IR ν_{max} cm^{-1}: 3400.0-2500.0 (-OH), 3033.3 (=CH sp^2), 2922.6 (-CH sp^3), 1639.5 (C=O, conjugated ketone), 1574.9 and 1507.3 (C=C aromatic) and 1247.1 (C-O); NMR δ_H ($CDCl_3$): 2.17 (3H, s, $MeCO_2$), 2.34 (3H, s, $-CH_3$), 6.72 (1H, d, J = 8.0 Hz, H-5), 7.59 (1H, d, J = 8.0 Hz, H-6), 6.78 (1H, s, H-3), 12.28 (1H, s, -OH); NMR δ_C ($CDCl_3$): 21.91 (CH_3 acyl), 26.43 (CH_3 aromatic), 117.52 (C-1), 118.36 (C-5), 120.17 (C-6), 130.56 (C-3), 148.05 (C-2), and 162.44 (C=O).

Synthesis of 2-hydroxy-4'-methoxy-4-methylchalcone 4

To a solution of 2-hydroxy-4-methylacetophenone **3** (53.7 mg, 3.58 mmol) in oxygen free ethanol (6 mL) was added anisaldehyde (0.6 mL, 4.95 mmol) followed by dropwise addition of a solution of KOH (1.5 g) in distilled water (1.5 mL). The reaction mixture was covered with petroleum ether (10 mL) and left at room temperature for 48 hours. The reaction mixture was poured into cold water (5 mL). The solid obtained upon acidification with HCl was filtered, washed with 10% $NaHCO_3$ solution followed by water and crystallised from petroleum ether to afford 2-hydroxy-4'-methoxy-4-methylchalcone **4** (0.96 g, 92 %) as yellow needles, m.p 108-110°C (lit. [4] 108°C); UV λ_{max}(nm) EtOH : 258.0 and 385.4; IR ν_{max} cm^{-1}: 3462.0 (-OH), 3004.9 (=CH sp^2), 2912.3 (-CH sp^3), 1639.4 (C=O conjugated ketone), 1604.7 (C=C alkene), 1569.9 and 1512.1 (C=C aromatic), 1259.4 (C-O); NMR δ_H ($CDCl_3$): 2.37 (3H, s, $-CH_3$), 3.87 (3H, s, $-OCH_3$), 6.75 (1H, d, J = 8.0 Hz, H-5), 6.83 (1H, s, H-3), 6.95 (2H, d, J = 8.4 Hz, H-3' and H-5'), 7.63 (2H, d, J = 8.4 Hz, H-2' and H-6'), 7.52 (1H, d, J = 15.2 Hz, H-α), 7.80 (1H, d, J = 8.0 Hz, H-6), 7.89 (1H, d, J = 15.2 Hz, H-β), 13.00 (1H, s, -OH); MS: *m/z* 268 [M^+, $C_{17}H_{16}O_3$] (10), 267 (63), 251 (10), 161 (17), 135 (13), 133 (4), 121 (29).

Synthesis of 4'-methoxy-7-methylflavone 5

2-Hydroxy-4'-methoxy-4-methylchalcone **4** (0.4 g, 1.49 mmol) was added to an isoamyl alcohol (10 mL). The mixture was heated in a water bath. This was followed by the addition of freshly sublimed SeO_2 (0.5 g, 4.51 mmol). The reaction mixture was refluxed for 24 hours under anhydrous condition. The mixture was then filtered and the filtrate was evaporated with methanol to dryness. The residue is washed with boiling petroleum ether. Purification of the product with column chromatography afforded 4'-methoxy-7-methylflavone (5) (0.07 g, 18%) as yellow crystals, m.p 135°C (lit. [4] 148°C); UV λ_{max}(nm) EtOH : 256.2 and 323.6; IR ν_{max} cm^{-1}: 3004.9 (=CH sp^2), 2912.3 (-CH sp^3), 1653.8 (C=O conjugated ketone), 1629.7 (C=C alkene), 1606.6 and 1512.1 (C=C aromatic), 1266.2 (C-O); NMR δ_H ($CDCl_3$): 2.51 (3H, s, $-CH_3$), 3.89 (3H, s, $-OCH_3$), 6.72 (1H, s, H-3), 7.02 (2H, d, J = 8.8 Hz, H-3' and H-5'), 7.22 (1H, d, J = 8.0 Hz, H-5), 7.36 (1H, s, H-8), 7.87 (2H, d, J = 8.8 Hz, H-2' and H-6'), 8.10 (1H, d, J = 8.0 Hz, H-6), NMR δ_C ($CDCl_3$): 21.82 ($-CH_3$), 55.48 ($-OCH_3$), 106.08 (C-3), 114.39 (C-2' and C-6'), 117.73 (C-8), 121.61 (C-4a), 124.12 (C-1'), 125.36 (C-5), 126.55 (C-6), 127.91 (C-3' and C-5'), 144.85 (C-7), 156.29 (C-8a), 162.26 (C-4'), 163.13 (C-2') and 178.39 (C=O); MS: *m/z* 266 [M^+, $C_{17}H_{14}O_3$] (18), 265 (100), 283 (13), 236 (5), 235 (5), 223 (20), 134 (45), 132 (46) and 107 (5).

RESULTS AND DISCUSSION

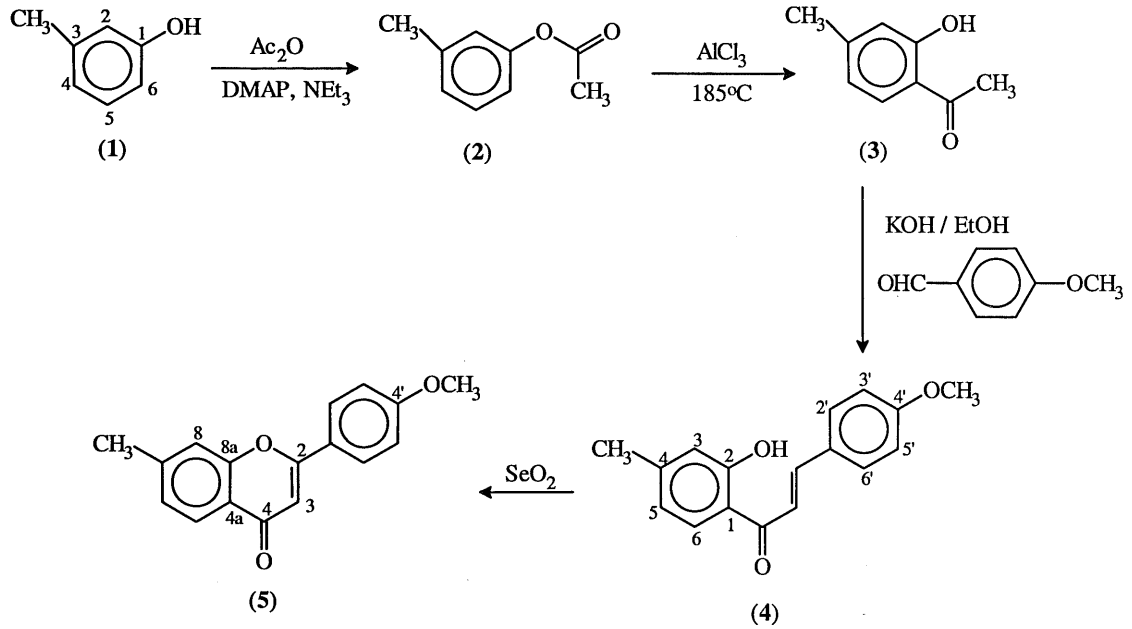
Acetylation of *m*-cresol **1** using Ac_2O and DMAP with the presence of triethylamine has afforded *m*-cresyl acetate **2** as brown liquid. The IR spectrum displayed the absorption band at 1766.7 cm^{-1} indicated the presence of an ester carbonyl group (C=O). Moreover, C=C aromatic stretchings were observed at 1589.2 cm^{-1} and 1488.9 cm^{-1}, meanwhile a strong absorption band at 1207.4 cm^{-1} was due to C-O group. The ^1H NMR spectrum of **2** exhibited a singlet at δ 2.27 attributed to the methyl protons of the acetate group. A singlet at δ 2.34 was assigned to protons of a methyl group at C-3. A multiplet resonated at δ 6.86 was attributed to H-6, while a signal at δ 6.89 was assigned to H-2. The aromatic proton, H-4 was presented by a multiplet resonated at δ 7.01-7.04. The aromatic proton, H-5 was indicated by a double of doublet signal (J= 7.8 Hz and 6.9 Hz) which appeared at δ 7.24. The ^{13}C NMR spectrum of **2** showed the presence of nine peaks. Signals for CH_3 acyl and CH_3 aromatic were observed at δ 21.26 and 21.11 respectively. Signals resonated at δ 118.46, 122.12, 126.61 and 129.10 were assigned to C-4, C-5, C-6 and C-2. The quaternary carbon signals were observed at δ 139.58 (C-3) and δ 150.58 (C-1) while the C=O was resonated at δ 169.60.

Fries rearrangement of compound **2** with $AlCl_3$ at 185°C afforded 2-hydroxy-4-methylacetophenone **3** as yellowish liquid. The IR spectrum of **3** showed the existing of a hydroxyl group at 3400.0-2500.0 cm^{-1}. In addition, the C=O stretching for a conjugated ketone was observed at 1639.5 cm^{-1}. The ^1H NMR spectrum of **3** displayed two singlets at δ 2.17 and δ 2.34 which were attributed to the acetyl and methyl protons in the molecule. A singlet appeared at δ 6.78 was assigned to the aromatic proton, H-3 while another downfield singlet resonated at δ 12.28 represented a hydroxyl proton. A doublet resonated at δ 6.72 (J = 8.0 Hz) was attributed to the aromatic proton, H-5 while another doublet at δ 7.59 (J = 8.0 Hz) was assigned to the aromatic proton, H-6. Fries migration of compound **2** has moved the ^{13}C NMR signal from δ 150.58 to upfield region, δ 117.52 for compound **3**.

Aldol condensation of compound **3** with anisaldehyde in the presence of ethanolic base gave 2-hydroxy-4'-methoxy-4-methylchalcone **4** as yellow needles, m.p 108-110°C (lit.[4] 108°C). The IR spectrum exhibited a band for a hydroxyl group at 3462.0 cm^{-1}. The presence of an absorption band at 1639.4 cm^{-1} was attributed to the carbonyl group of a conjugated ketone. Moreover, C=C alkene stretching was displayed at 1604.7 cm^{-1}, and the C=C aromatic stretchings were observed at 1569.9 cm^{-1} and 1512.1 cm^{-1}. A strong absorption band at 1259.4 cm^{-1} indicated the presence of a C-O group. The ^1H NMR spectrum displayed signals for a methoxyl (δ 3.87) and a methyl (δ 2.37) protons at C-4' and C-4 respectively. In additions, three signals attributed to three aromatic protons resonated at δ 6.75 (1H, d, J = 8.0 Hz), δ 7.80 (1H, d, J = 8.0 Hz) and δ 6.83 (1H, s). These signals were attributed to H-5, H-6 and H-3 for ring A respectively. The J values of 8.0 Hz suggested that both H-5 and H-6 were *ortho* to each other. Two doublet signals at δ 6.95 (2H, J = 8.4 Hz) and δ 7.63 (2H, J = 8.4 Hz) assigned to H-3'/H-5' and H-2'/H-6' respectively, hence indicated that ring B was symmetrically substituted with a methoxyl group at C-4'. The signals at δ 7.52 (1H, d, J = 15.2 Hz) and δ 7.89 (1H, d, J = 15.2 Hz) were assigned to olefinic protons, H-α and H-β respectively. The J values suggested that both protons were in *trans*-relationship and thus coupled to each other. The UV spectrum of **4** showed two absorption maxima at 258.0 and 385.4 nm, which were characteristics for chalcone moieties [5]. The mass spectrum of **4** exhibited the molecular ion peak at *m/z* 268 which was in agreement with the molecular formula $C_{17}H_{16}O_3$.

Oxidative cyclisation of compound **4** with SeO_2 gave 4'-methoxy-7-methylflavone **5** as yellow crystals and melted at 135°C (lit. [4] 148°C). The IR spectrum of compound **5** showed the same pattern with the IR spectrum of compound **4** except an absorption band for the hydroxyl group has disappeared. The ^1H NMR spectrum exhibited a singlet at δ2.51 (3H) attributed to the methyl group. A singlet at δ 3.89 (3H) was assigned to the methoxyl group at C-4' whereas a singlet resonated at δ 6.72 (1H) was assigned to H-3. Signals for A_2B_2 protons were observed at δ 7.02 (2H, J = 8.8 Hz, H-3' and H-5') and δ 7.87 (2H, J = 8.8 Hz, H-2' and H-6'). A set of doublets at δ 7.22 (1H, J = 8.8 Hz) and δ 8.10 (1H, d, J = 8.8 Hz) were assigned to H-5 and H-6 which were *ortho* to each other. A singlet at δ 7.36 was assigned to H-8. The ^{13}C NMR

spectrum of compound **5** showed the presence of 15 peaks correspond to 17 carbons in the molecule. Signals at δ 21.82, 55.48, 106.8, 114.39, 117.73, 121.61, 124.12, 125.36, 126.55, 127.91, 144.85, 156.29, 162.26, 163.13 and 178.39 were assigned to $-CH_3$, $-OCH_3$, C-3, C-2'/C-6', C-8, C-4a, C-1', C-5, C-6, C-3'/C-5', C-7, C-8a, C-4', C-2' and C=O respectively. The mass spectrum of **5** exhibited a molecular ion peak at *m/z* 266 which was in agreement with the molecular formula $C_{17}H_{14}O_3$. The radical cations at *m/z* 132 and *m/z* 134 resulted from a *retro* Diels-Alder reaction in the molecule. These ions are important for the determination of a flavone compound [6]. The UV spectrum of **5** displayed two absorption maxima at 256.2 and 323.6 nm, characteristics for a flavone compound [6].



(1) (2) (3) (4) (5)

CONCLUSION

Acetylation of *m*-cresol **1** with Ac_2O and DMAP in triethylamine has yielded *m*-cresyl acetate **2**. This was followed by Fries rearrangement of *m*-cresyl acetae **2** with $AlCl_3$ at 185°C to afford monoacetyl cresol, which was identified spectroscopically as 2-hydroxy-4-methylacetophenone **3**. On Aldol condensation of **3** with anisaldehyde under basic condition gave the corresponding chalcone namely, 2-hydroxy-4'-methoxy-4-methylchalcone **4** which, on oxidative cyclisation with SeO_2 gave 4'-methoxy-7-methylflavone **5**.

Acknowledgement This research work was supported by a grant from IRPA Malaysia vote 74044.

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