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RESEARCH ARTICLE

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SYNTHESIS AND CHARACTERIZATION OF C(8)-METHYL FLAVONES

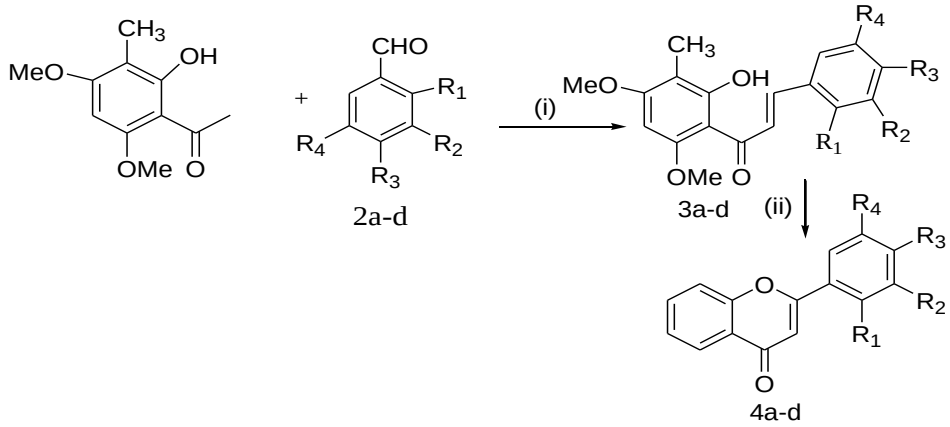
ABSTRACT:

A series of four C(8)-methylated flavones were synthesized from their corresponding C-methyl chalcone intermediates. In the cyclisation of chalcones catalytic amount of Iodine was used in presence of DMSO. The yields of all the compounds obtained were good (62-75%). The compound with methoxy group at (*m*-) and (*p*-) positions had obtained with maximum yield (75%) and the compound with methoxy at *m*-position was obtained with low yield (62%).

Key words: C-methylated flavones, synthesis, characterization.

INTRODUCTION:

Flavones belongs to one of the important class of flavonoids and are potential towards several pharmacological activities like anticancer[1], antioxidant[2-5], antiviral[6] and anti-inflammatory[7,8]. In addition, several researchers[9-12] have reported various flavone derivatives as biologically potent molecules. Recently sayed Alam synthesized variously substituted flavones and reported their cytotoxic and antimicrobial activities[13]. However, according to our knowledge very few reports were available with methyl substitution on flavone skeleton[6,13,14]. So in continuation to our research towards biologically active alkyl flavonoids in the present work we wish to report the synthesis of four methyl flavones with proper characterization. A series of four C-8-methylated flavones with following substitutions (**a-d**) on the ring ′B′ were synthesized by following the scheme 1.



3a-d

a: R_1=OMe, R_2=R_3=R_4=H **b:** R_2 =OMe, R_1=R_3=R_4=H

c: R_1= R_2=H, R_3=R_4= OMe **d:** R_3=Cl, R_1=R_2=R_4=H

Scheme 1: Synthesis of C(8)-methyl flavones(**4a-d**).

Reagents and conditions: (i) KOH, EtOH, rt, 24hr. Yield-70-88% , (ii) DMSO/I_2 , 130-140^{o}C, 1-2h, yield.62-75%.

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MATERIALS AND METHODS:

Phloroglucinol and all other compounds were obtained from Merck Specialties Private Limited, Mumbai, INDIA. Reactions were monitored by TLC using silica gel-G (Merck grade) as the adsorbent and the solvent systems are indicated at appropriate places. Silica gel (100-200 mesh, Merck grade) has been used for column chromatography. The column was subjected to gradient elution using n-hexane, mixtures of hexane and ethyl acetate. All the melting points were determined in open capillaries, using Elico digital melting point apparatus, expressed in °C and are uncorrected.

The ^{1}H NMR spectra of the compounds were recorded on Bruker AMX 400 MHz NMR spectrophotometer and the ^{13}C NMR spectra of the compounds were recorded on Bruker AMX 100 MHz NMR spectrophotometer using TMS as an internal standard and the values are expressed in δ ppm. The Mass spectra of the compounds were recorded on API-ES Mass Spectrometer.

Synthesis of C(8)-methyl flavones

The general and traditional synthetic strategies of flavones have been followed by Baker Venkatraman rearrangement and Claisen-Schmidt condensation. Which involves the conversion of 2-hydroxyacetophenone to corresponding benzoyl ester, followed by rearrangement into 1,3-diphenylpropane-1,3-diones in presence of base; further the cyclization in acidic conditions provides the flavones. The other approach involves formation hydroxychalcone from 2-hydroxy acetophenone and benzaldehyde under Claisen-Schmidt conditions can undergo oxidative cyclization to furnish the flavones ring.

In the present study the required chalcones (**3a-d**) for target flavones (**4a-d**) were synthesized *via* Claisen-Schmidt condensation under the influence of strong base (KOH) in presence of ethanol from methylated acetophenone and aryl aldehydes; the methyl substituted acetophenone in turn was obtained by known methods from phloroglucinol starting material[15,16]. All the intermediates were confirmed by their physical constants and spectral data. Later, the chalcones were cyclised to flavoves using iodine as catalyst to get more yields. All the flavones were synthesized from the C-methylated chalcones by following the scheme 1.

Geneal procedure for synthesis of C(8)-methyl flavones: The methylated chalcone (0.01mole) was suspended in 10mL DMSO in 100mL round bottam flask and crystals of Iodine was added to it[17]. The mixture was refluxed for 30-45 min and diluted with water. The solid was filtered off, washed with 20% $Na_2S_2O_4$ and crystallized with ethanol to give the final compound and were further purified by column chromatography.

Characterization of flavone (4a-d)

Synthesis of 5,7-dimethoxy-2'-methoxy-8-methylflavone (4a): Mol. Form.**:** $C_{19}H_{18}O_5$, Mp. 172-175 ^{o}C; Brick red solid; Yield. 67%; ^{1}HNMR (400MHz, δ in ppm, $CDCl_3$)**:** 7.4 (1H, m, H-4′), 7.9 (1H, d, *J* = 8.2 Hz, H-6′), 7.4 (1H, m, H-3′), 7.1(1H, m, H-5′), 6.4 (1H, s, H-6), 7.0 (1H, s, H-3), 3.9 (3H, s, O$\underline{C}H_3$ at C-5, 7 & 2′), 2.2 (3H, s, $\underline{C}H_3$ at C-8). ^{13}CNMR (100MHz, δ in ppm, $CDCl_3$): 178.7 (C-4), 161.1 (C-7), 158.1 (C-9), 159.1 (C-5), 156.8 (C-2′), 121.1 (C-1′), 131.9 (C-6′), 129.1 (C-4′), 120.7 (C-5′), 113.4 (C-3′), 106.1 (C-8), 108.9 (C-10), 91.5 (C-6), 156.9 (C-2), 56.5, 55.8, 55.6 (O$\underline{C}$H3 at C-7, 5, 2′), 111.7 (C-3), 8.1 ($\underline{C}H_3$ at C-8), LC-MS**:** m/z at 349.3 $(M+Na)^{+}$, +ve ion mode.

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Synthesis of 5,7-dimethoxy-3'-methoxy-8-methylflavone (4b): Mol. Form.: $C_{19}H_{18}O_5$; Mp. : 166-169 ^oC.; Red solid; Yield: 62%; ^1H NMR (400MHz, δ in ppm, $CDCl_3$): 7.5 (1H, d, *J* =1.6Hz, H-4′), 7.4 (1H, m, H-6′), 7.4 (1H, m, H-2′), 7.1(1H, m, H-5′), 6.6 (1H, s, H-6), 6.4 (1H, s, H-3), 4.0, 3.9 & 3.8 (3H, s, OCH_3 at C-5,7,3′), 2.3 (3H, s, CH_3 at C-8). ^{13}C NMR (100MHz, δ in ppm, $CDCl_3$): 178.2 (C-4), 160.3 (C-7), 161.4 (C-9), 160.0 (C-5), 159.1 (C-3′), 130.1 (C-1′), 116.9 (C-5′), 118.4 (C-6′), 118.4 (C-2′), 111.4 (C-4′), 106.2 (C-8), 108.6 (C-10), 91.7 (C-6), 156.7 (C-2), 56.4, 55.8, 55.4 (OCH_3 at C-7,5,3′), 133.4 (C-3), 8.0 (CH_3 at C-8); LC-MS: m/z at 327.3 $(M+H)^+$, +ve ion mode.

Synthesis of 5,7-dimethoxy-3',4'-dimethoxy-8-methylflavone (4c): Molecular formula: $C_{20}H_{20}O_6$; Mp. : 176-179ºC; Brick red solid; Yield: 75%; ^1H NMR (400MHz, δ in ppm, CDCl3): 7.54 (1H, d, J = 8.4Hz, H-6′), 7.38 (1H, s, H-2′), 6.98 (1H, d, J = 8.4Hz), 6.60 (1H, s, H-3), 6.42 (1H, s, H-6), 4.00 (3H, s, OCH3 at C-3′,4′), 3.96 (6H, s, OCH3 J = 14.4, 17.7 Hz, H-3), 3.95(3H, s, OCH3 J = 8.4, 14.4 Hz, H-3), 2.06 (3H, s, CH3 at C-8). 13CNMR(100MHz, δ in ppm, CDCl3): 178.3 (C-4), 161.30 (C-7), 160.4 (C-1), 159.0 (C-9), 156.6 (C-2), 151.7 (C-4′), 149.3 (C-3′), 124.5 (C-1′), 119.45 (C-3), 111.2 (C-2′), 108.7 (C-6′), 107.19 (C-5′), 106.2 (C-10), 91.6 (C-6), 8.0 (CH3 at C-8). LC-MS: m/z at 357.3 (M+Na); 379.3(M+Na)+,+ve ion mode.

Synthesis of 5,7-dimethoxy -4'-chloro--8-methylflavone (4d): Molecular formula: $C_{18}H_{15}O_4Cl$; Mp. : 177-180 ^oC; Brick red solid; Yield: 66%; ^1HNMR (400MHz, δ in ppm, $CDCl_3$): 7.8 (2H, s, H-2′, 6′), 7.8 (2H, s, H-3′, 5′), 6.4 (1H, s, H-6), 6.6 (1H, s, H-3), 3.9 (3H, s, OCH_3 at C-5, 7), 2.3 (3H, s, CH_3 at C-8), ^{13}CNMR (100MHz, δ in ppm, $CDCl_3$): 177.9 (C-4), 163.6 (C-7), 160.8 (C-9), 160.5 (C-5), 156.6 (C-4′), 108.5 (C-1′), 129.2 (C-2′, 6′), 127.1 (C-3′, 5′), 106.1 (C-8), 108.8 (C-10), 91.8 (C-6), 137.3 (C-2), 56.4, 55.8 (OCH_3 at C-7, 5), 130.5 (C-3), 106.1 (CH_3 at C-8), LC-MS: m/z at 331.3 $(M+H)^+$, +ve ion mode.

RESULTS AND DISCUSSINS:

The synthesis of methylated chalcone key intermediates was obtained by a series of conventional methods involving methylation, formylation, reduction, acetylation and condensation[15,16]. All the chalcones synthesized were confirmed by comparing with reported literature data. Further the chalcones were cyclised to 8-methylflavones in presence of catalytic amount of iodine and DMSO. Total four C-methylated flovones were synthesised with good yields (**62-75%**). The compound with methoxy groups at (*m*-) and (*p*-) positions on ring B had obtained with maximum yield (75%) (**3c**) and the compound with methoxy at *m*-position (**3b**) has given lowest yield (62%). The compound **3a** with *o*-methoxy was obtained in 67% and chlorinated flavone (**3d**) was obtained 66%.

CONCLUSION:

A total of four C(8)-methylated flavones were synthesized in good yields by using regular conventional approaches. The compound with methoxy group at (*m*-) and (*p*-) positions had obtained with maximum yield (75%) and the compound with methoxy at *m*-position was obtained with low yield (62%).

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