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Research Article

FACILE SYNTHESIS OF 8-(1H BENZO [D] IMIDAZOL-2-YL)-7-METHOXY FLAVONES

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Abstract

8-Formyl-7-methoxyflavones **(1a-d)** with o-phenylene diamine **(2)** to give 8-(1H-benzo[d]imidazol-2-y1)-7-methoxyflavones **(3a-d)** and 8-formy1-2-(2'- fury1)-7-methoxy-3-methylchromone **(4a)** with. 2-aminothiophenol **(5**) to give 8-(1, 3-benzothiazo1-2-y1)-2-(2'-fury1)-7- methoxy-3-methylchromone **(6a-d).**

Keywords: 8-Formyl-7-methoxyflavones, 2-aminothiophenol, Staudingerreaction, benzothiazoles, benzoimiazoles, o-phenylene diamine.

Introduction

Natural and synthetic heterocyclic compounds play an important role in both drug discovery and chemical biology. The heterocycles are mainly of the classes of alkaloids, chromones, flavones, isoflavones etc. The natural heterocyclics are plant secondary metabolites, which protect the plant from attack by pathogens, fungi, bacteria and insects. Several synthetic analogs of these heterocyclics show different bioactivity[1-5]. More than 50% of the drug used in the modern medicine is either derived from synthetic or natural heterocyclic systems.

With a view synthesize new heterocyclic ring fused chromones and flavones pendent aromatic / aliphatic aldehyde or acid or acid chloride with 2-aminothiophenol. This reaction proceeds via the dihydro intermediate that arise from the cyclisation, on aerial oxidation or in the presence of oxidation reagent[6-10].

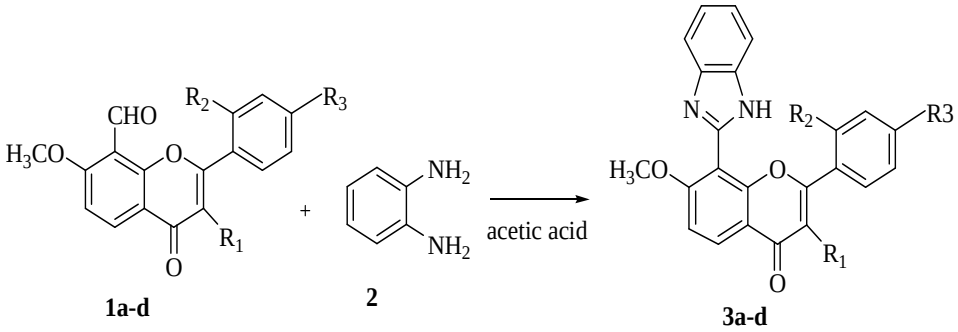
Results and Discussion

Synthesis of 8-(1H-benzo[d] imidazo1-2-y1)-7-methoxyflavones (3a-d):[11-15]

Equimolar quantities of 8-formy1-7-methoxyflavone **(1a)** and o-phenylenediamine **(2)** taken in acetic acid on heating gave 8-(1H-benzo[d]imidazol-2-y1)-7-methoxyflavone **(3a).** In the IR spectrum of 8-(1H-benzo[d]imidazol-2-yl)-7-methoxy-3-methylflavone **(3a),** the absorption due to the NH was observed at 3475 cm^{-1}, the C=N at 1596 cm^{-1} and the flavone CO at 1628 cm^{-1}. Its UV (MeOH) spectrum showed absorption maxima at 320 nm (log ε 4.2), 278 nm (log ε 4.6) and 224 nm (log ε 4.8). In the ^{1}H NMR ($CDCl_3$) spectrum of (**3a)** the signals due to the imidazol-2-yl ring system protons H-4",7" appeared at δ 7.31-7.39 as a multiplet and the H-5", H-6" appeared as a multiplet overlapping with H-3',4',5' at δ 7.10-7.28. The 7-OCH_3 appeared at δ 3.79 as a singlet and the 3-CH_3 appeared as a singlet at δ 2.01.

In the ^{13}C NMR ($CDCl_3$) spectrum of 8-(lH-benzo [dimidazol-2-yl)-7-methoxy-3-methylflavone **(3a)** the carbon signals due to the benzimidazole moiety are as follows: 6 161.7(C-2"), 137.6(C-3"a, C-7"a), 114.0(C-4", C-7") and 123.8(C-5", C-6't). The signal assignments to the flavone ring carbons are as follows: δ 155.3(C-2), 116.7(C-3), 177.6(CO at C-4), 117.9(C-4a), 130.3(C-5), 109.2(C-6), 159.2(C-7),106.3(C-8), 144.0(C-8a), 132.2(C-l'), 128.5(C-2',6'), 129.1(C-3',5'), 1 33.4(C-4'), 56.6 (C-7-OCH_3) and 11 .4(C-3-CH_3).

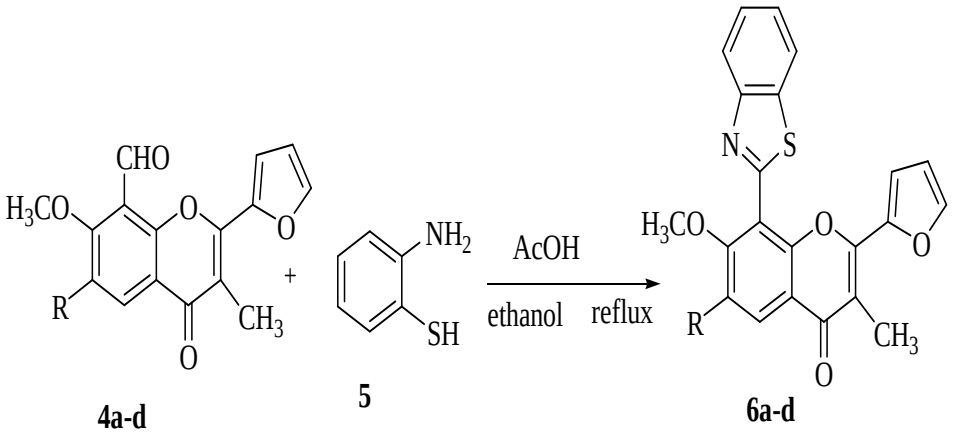
Scheme-1



1a-d **2** **3a-d**

1, 3 **a** = R_1 = CH_3 R_2 = R_3 = H
b = R_1 = CH_3 R_2 = Cl R_3 = H
c = R_1 = CH_3 R_2 = H R_3 = Cl
d = R_1 = CH_3 R_2 =H R_3 = =OCH_3

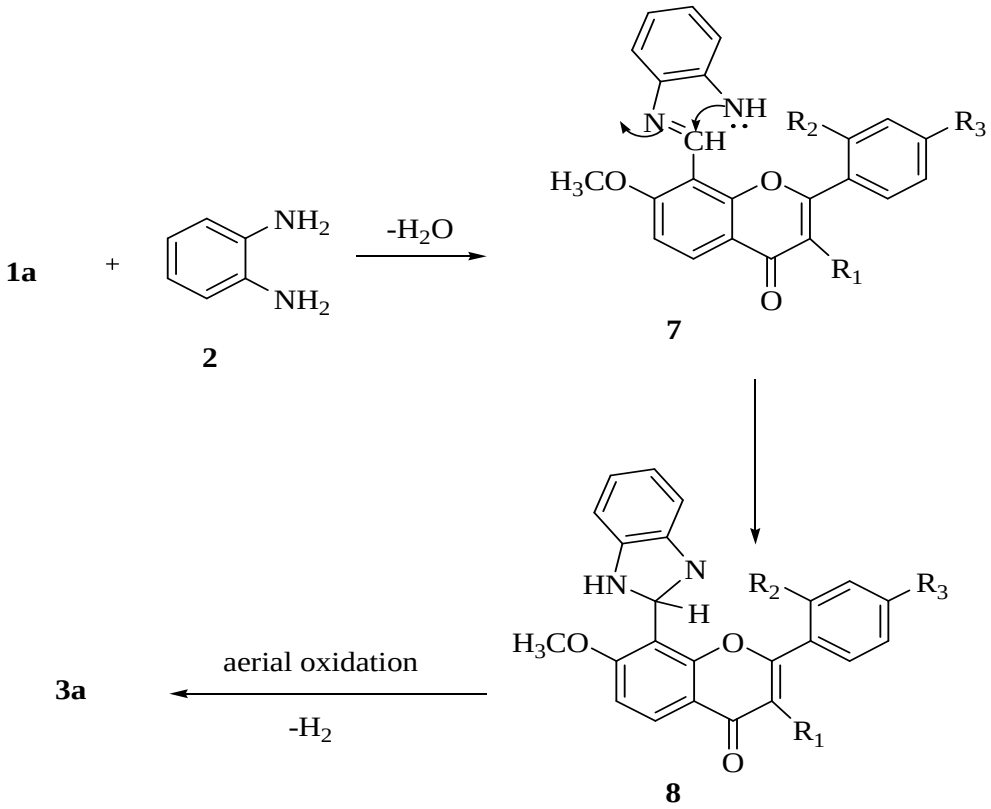
Scheme-2



4a-d **5** **6a-d**

4, 6 **a** = R = H **b** = R = Cl
c = R =Br **d** = R = CH_3

Scheme-3



2 **7** **8** **3a**

Experimental Section

General: - Melting points were determined in a sulfuric acid-bath and are uncorrected. IR spectra were recorded in KBr on a Shimadzu 435 spectrometer, ^{1}H NMR spectra on a Varian Gemini 200 MHz spectrometer with TMS as an internal standard and mass spectra on a Perkin Elmer Hitachi RDO-62 and MS-30 instrument.

General procedure for the synthesis of 8-(1H-benzo[d] imidazol-2-yl)-7-methoxy-3-methylflavones (3a-d):

i.8-(1H-benzoi[d] imidazol-2-y1)-7-methoxy-3-methylflavone (3a):

To a solution of 8-formy1-3-methyl-7-methoxyflavone **(1a)** (2.94g) (10 mmol) in glacial acetic acid (20mL) and o-phenylenediamine **(2)** (1.08g, 10 mmol) were added and stirred at room temperature for 30 min. Then the mixture was refluxed on oil bath for 6 h. Acetic acid was removed by distillation under reduced pressure, the residue obtained was treated with crushed ice (100g). The solid obtained was filtered and subjected to column chromatography with 60-120 mesh silica gel and eluted with petroleum ether: ethyl acetate (1:1) to give 8-(1,3-benzo[d]imidazol-2-y1)-7-methoxy-3- methylflavone **(3a)** (2.21g, 58% yield). It was recrystallised from methanol as white coloured needles. mp 151 °C

IR (KBr): 3475 cm^{-1} (NH), 1596 cm^{-1}(C=N), 1628 cm^{-1}(flavone C=O)

UV (MeOH): 320 nm (log ε 42), 278 nm (log ε 4.6), 224 nm (log ε 4.8)

^{1}H NMR (CDC1$_3$) (300MHz): δ 7.89(d, .1-9.0Hz, H-5), 7.52-7.60(m, H-2', 6'), 7.31-7.39(m, H-4", 7"), 7.10-7.28(m, H-3', 4', 5'; H-5", 6"), 6.74(d, J=9.0Hz, H-6), 3.79(s, 7-OCH_3), 2.01(s, 3-CH_3).

^{13}C NMR(CDC1$_3$)(100.6MHz): δ 177.6(C-4, C=O), 161.7(C-2"), 159.2(C-7), 155.3(C-4"2), 144.0(C-8a), 137.6(C-3a,7"a), 133 .4(C-4'), 132.2(C-1'), 130.3(C-5), 129.1(C-3',5'),3-128.5(C-2',6'), 123.8(C-5",6"),117.9(C-4a), 116.7(C-3),114.0(C-4,7"),109.2(C-6),13(106.3(C-8), 56.6(C-7-OCH_3), 11.4(C-3-CH_3).

MS: m/z 383[M+H]$^+$.

Employing the similar procedure as mentioned for **3a,** compounds **3b-e** were obtained from **1b-d** and **6a-d** were

obtained from **4a-d** as solids in 55-65% yield.

ii) 8-(1H-Benzo[d] imidazol-2-y1)-2'-chloro-7-methoxy-3-methylflavone (3b):

Column chromatography and recrystallisation from methanol gave, light brown coloured needles, mp 167 °C

IR (KBr): 3489 cm^{-1}(NH), 1604 cm^{-1}(C=N), 1634 cm^{-1} (flavone C=O)

UV (MeOH): 304 nm (log ε 4.5), 280 nm (log ε 4.7), 246 nm (log ε 4.8)

^{l}H NMR ($CDCl_3$)(300 MHz): δ 8.05(d, J=9.0Hz, H-5), 7.54(m, H-6'), 7.13-7.35(m,H-5'; H-4,5",6",7"), 6.82-6.97(m, H-6; H-3',4'), 3.83(s, 7-OCH_3), 1.84(s, 3-CH_3).

^{13}C NMR ($CDC1_3$)(100.6 MHz): δ 177.3(C-4, C=O), 161.6(C-2"), 159.1(C-7), 154.8(C-8a), 143.5(C-2), 38.7(C-3"a,7"a), 132.6(C-2'), 131.1(C-4'), 130.9(C-3'), 130.5(C.-5), 129.5(C-5'), 128.9(C-l'), 126.6(C-6'), 122.3(C-5't,6"), 118.8(C-4a), 116.3(C-3), 115.2(C4",7"), I 09.0(C-6),

1 07.3(C-8), 56.3(C-7-OCH_3), 11 .0(C-3-CH_3).

MS: m/z 417$[M+H]^+$ and 418$[M+2]^+$

iii) 8-(IH-Benzo[d]imidazol-2-yl)-4'-chloro-7-methoxy-3-methylflavone (3c) :

Column chromatography and recrystallisation from methanol gave light brown coloured crystals, mp 192 °C

IR (KBr): 3476 cm^{-1}(NH), 1605 cm^{-1}(C=N), 1639 cm^{-1} (flavone C=O)

UV (MeOH): 309 nm (log ε 4.6), 274 nm (log ε 4.7), 221 nm (log ε 4.9)

^{1}H NMR ($CDC1_3$)(300 MHz): δ 8.04(d, J=9.0Hz, H-5), 7.22-7.50(m, H-2',6'; H-4",5",'6",7") 7.03(d, J=8.7Hz, H-3',5'), 6.57(d, J=9.0Hz, H-6), 3.87(s, 7-OCH_3), 2.02(s, 3-CH_3).

^{13}C NMR ($CDCl_3$)(75. 5 MHz): δ 177.4(C-4, C=O), 161.6(C-2"), 159-3)(C-7), 155.7(C-2), 144.5(C-8a), 138 0(C-3"a,7"a), 136.2(C-4'), 133.1(C-5), 131 3(C-1'),130 8(C-2',6'),

128.5(C-3', 5'), 122.2(C-5",6"), 117.9(C-4a), 116.7(C-3), 114.3(C-4",7"), 109.4(C-6), 106.0(C-8), 56.7(C-7-OCH_3), H-.6(C-3-CH_3).

MS: m/z 417$[M+H]^+$.

iv) 8-(IH-Benzo[d] imidazol-2-yl)- 7,4 '-dimelhoxy-3-methylfiavone (3*d*):

Column chromatography and recrystallisation from methanol gave white solid, mp 183 °C.

IR (KBr): 3481 cm^{-1} (NH), 1605 cm^{-1} (CN), 1629 cm^{-1}(flavone C=O)

UV (MeOH): 314 nm (log ε 4.4), 278 nm (log ε 4.6), 248 nm (log ε 4.8), 224 nm (log ε4.7).

^{1}H NMR ($CDCl_3$+DMSO-d_6)(200MHz): δ 8.20(d, J=9.0Hz, H-5), 7.53-7.71(m, H-2',6'; H-4",7"), 7.10-7.28(rn, H-6; H-5",6"), 6.80(d, J=8.6Hz, H-3t,5'), 3.97(s, 7-OCH_3), 2.14(s, 3-CH_3).

^{13}C NMR ($CDCl_3$+DMSO-d_6)(100.6 MHz): δ 176.6(C-4, C=O), 160.5(C-4'), 159.7(C2"), 159.5(C-7), 153.7(C-2), 142.8(C-8a), 1 37.4(C-3"a,7"a), 129.5(C-2,6'), 127.7(C-5),

123.9(C-1'), 121.2(C-5", 6"), 115.2(C-4a), 114.5(C-3), 114.0(C-4", 7"), 112.4(C-3', 5'), 108.0(C-6), 106.7(C-8), 55.5(C-7-OCH_3), 54.2(C-4'-OCH_3), 10.7(C-3-CH_3).

MS: m/z 413$[M+H]^+$ and 435 $[M+Na]^+$

vi. ***8-(1, 3-Benzothiazol-2-yl) (2'-furyl)- 7-methoxy-3-methylchromone (6a):***

Column chromatography and recrystallisation from methanol gave light brown coloured solid, mp 199 °C

IR (KBr): 1597 cm^{-1}(CN), 1633 cm^{-1}(chromone C=O).

UV (MeOH): 324 nm (log ε 4. 3), 227 nm (log ε 4.6), 208 nm (log ε 4.9).

^{1}H NMR ($CDCl_3$)(300MHz): δ 6 8.34(d, J=9.0Hz, H-5), 8.17(dd, J=8.lHz, $J_{4,6}$1.5Hz, H-4'), 7.99(dd, $J_{7,6}$7.5Hz,$J_{7,5}$ l .5Hz, H-7"), 7.40-7.61(m, H-5',5",6"), 7.10(d, J=9.0Hz, H-6), 6.90(dd, J=3.7Hz, 0.8Hz, H-3'), 6.48(dd, J=3.7Hz, 1.5Hz, H-4'),4.01(s, 7-OCH_3), 2.39(s, 3-CH_3).

^{13}C NMR ($CDCl_3$) (50.3MHz): δ 177.6(C-4, C=O), 161.2(C-2"), 158.6(C-7), 154, 0(C- 3"a), 152.8(C-8a), 150.9(C-2), 147.9(C-2'), 145.0(C-5'), 136.0(C-7"a), 129.4(C-5),125.9(C-5"), 125.2(C-6"), 12-12(C-4"), 121.3(C-7"), 116.7(C-4a), 115.0(C-3'), 114.8(C- 3), 111.9(C-4'), 1 10.6(C-8), 108.8(C-6), 56.5(C-7-OCH_3), 9.3(C-3-CH_3).

MS: m/z 390$[M+H]^+$.

vi. 8-(1, 3-Benzothiazol-2-yl) -6-chloro-(2'-furyl)-7-methoxy-3-methylchromone (6b):

Column chromatography and recrystallisation from methanol gave light brown coloured solid, mp 195 °C

IR (KBr): 1592 cm^{-1}(CN), 1633 cm^{-1}(chromone C=O).

UV (MeOH): 324 nm (log ε 4. 3), 227 nm (log ε 4.6), 208 nm (log ε 4.9).

^{1}H NMR ($CDCl_3$)(300MHz): δ 8.34(d, J=9.0Hz, H-5), 8.17(dd, J=8.lHz, $J_{4,}$=1.5Hz, H-4'), 7.99(dd, J_7=7.5Hz,$J_{7,5}$=l.5Hz, H-7''), 7.40-7.61(m, H-5',5'',6''), 7.10(d, J=9.0Hz,), 6.90(dd, J=3.7Hz, 0.8Hz, H-3'), 6.48(dd, J=3.7Hz, 1.5Hz, H-4'),4.01(s, 7-OCH_3), 2.39(s, 3-CH_3).

^{13}C NMR ($CDCl_3$) (50.3MHz): δ 177.6(C-4, C=O), 161.2(C-2''), 158.6(C-7), 154, 0(C- 3''a), 152.8(C-8a), 150.9(C-2), 129.4(C-5),125.9(C-5''), 125.2(C-6''), 12-12(C-4''), 121.3(C-7''), 116.7(C-4a), 115.0(C-3'), 114.8(C- 3), 111.9(C-4'), 1 10.6(C-8), 108.8(C-6), 56.5(C-7-OCH_3), 9.3(C-3-CH_3).

MS: m/z 423$[M+H]^+$.

8-(1, 3-Benzothiazol-2-yI) -6-bromo-('2 '-fury!)- 7-methoxy-3-methylchromone (6c):

Column chromatography and recrystallisation from methanol gave light brown coloured solid, mp 198 °C

IR (KBr): 1595 cm^{-1}(CN), 1630 cm^{-1}(chromone C=O).

UV (MeOH): 324 nm (log ε 4. 3), 227 nm (log ε 4.6), 208 nm (log ε 4.9).

^{1}H NMR ($CDCl_3$)(300MHz): δ 6 8.34(d, J=9.0Hz, H-5), 8.17(dd, J=8.lHz, $J_{4,}$1.5Hz, H-4'), 7.99(dd, $J_{7,}$=7.5Hz,$J_{7,5}$=l .5Hz, H-7''), 7.40-7.61(m, H-5',5'',6''), 7.10(d, J=9.0Hz, H-6), 6.90(dd, J=3.7Hz, 0.8Hz, H-3'), 6.48(dd, J=3.7Hz, 1.5Hz, H-4'),4.01(s, 7-OCH_3), 2.39(s, 3-CH_3).

^{13}C NMR ($CDCl_3$) (50.3MHz): δ 177.6(C-4, C=O), 161.2(C-2''), 158.6(C-7), 154, 0(C- 3''a), 152.8(C-8a), 150.9(C-2), 147.9(C-2'), 129.4(C-5),125.9(C-5''), 125.2(C-6''), 12-12(C-4''), 121.3(C-7''), 116.7(C-4a), 115.0(C-3'), 114.8(C- 3), 111.9(C-4'), 1 10.6(C-8), 108.8(C-6), 56.5(C-7-OCH_3), 9.3(C-3-CH_3).

MS: m/z 468$[M+H]^+$.

8-(1, 3-Benzothiazol-2-yl)-6-methyl-('2 '-fury!)- 7-methoxy-3-methylchromone (6d):

Column chromatography and recrystallisation from methanol gave light brown coloured solid, mp 189 °C

IR (KBr): 1590 cm^{-1}(CN), 1635 cm^{-1}(chromone C=O).UV (MeOH): 324 nm (log ε 4. 3), 227 nm (log ε 4.6), 208 nm (log ε 4.9).^{1}H NMR ($CDCl_3$)(300MHz): δ 6 8.34(d, J=9.0Hz, H-5), 8.17(dd, J=8.lHz, J_4=1.5Hz, H-4'), 7.99(dd, J_7=7.5Hz,$J_{7'5}$=l .5Hz, H-7''), 7.40-7.61(m, H-5',5'',6''), 7.10(d, J=9.0Hz, H-5), 6.90(dd, J=3.7Hz, 0.8Hz, H-3'), 6.48(dd, J=3.7Hz, 1.5Hz, H-4'),4.01(s, 7-OCH_3), 2.39(s, 3-CH_3).^{13}C NMR ($CDCl_3$) (50.3MHz): δ 177.6(C-4, C=O), 161.2(C-2''), 158.6(C-7), 154, 0(C- 3''a), 152.8(C-8a), 150.9(C-2), 147.9(C-2'), 145.0(C-5'), 136.0(C-7''a), 129.4(C-5),125.9(C-5''), 125.2(C-6''), 114.8(C- 3), 111.9(C-4'), 1 10.6(C-8), 108.8(C-6), 56.5(C-7-OCH_3), 9.3(C-3-CH_3).MS: m/z 403$[M+H]^+$.

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