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Der Pharma Chemica, 2012, 4 (1): 442-447
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X
CODEN (USA): PCHHAX

Facile synthesis of 8-methyl-4*H*-furo [2,3-*h*] isoflavones

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ABSTRACT

7-Hydroxyisoflavones ***(1a-e)*** *with allylbromide refluxed for 6 hrs to give7-alloxyisoflavones* ***(2a-e)*** *and their Claisen rearrangement to 8-allyl-7-hydroxyisoflavones* ***(3a-e)*** *with react dichlorobis palladium in benzene for 30 min at room temperature to give 8-methyl-4H-furo [2,3-h] isoflavones****(5a-e)***

Keywords: 7-Hydroxy isoflavones, 8-allyl-7-hydroxy isoflavones, dichlorobis (benzonitrile) palladium, NND, o-allylphenol, Claisen rearrangement.

INTRODUCTION

Flavones and isoflavones constitute an important class of oxygen heterocyclics. Substituted as well as heterocyclic ring fused flavones and isoflavones have a wide range of pharmacological activity. Flavones and isoflavones with medicinal use are Khellin a coronary vasodilator. Chromenes-2-carboxylate spasnolitic agent and disodium chromo glycate and anti elergitic drug. Genstein having estrogen hormonal activity, and 7-isopropoxy isoflavones for treatment of postmenopausal and senile osteoporosis.

In view of the substituted isoflavones show a variety of biological activity, such as dopamine antihypertensive, ATP sensitive potassium channel openers antitumor and gastro protective agent. In the present study 7-aalyloxyisoflavones and substituted isoflavones are synthesized by the Hantzsch reaction involves the reaction of a dichlorobis(benzonitrile) palladium in benzene at room temperature to give 8-methyl-4H-furo[2,3-h] isoflavones.

MATERIALS AND METHODS

General: - Melting points were determined on a Polmon instrument (model no. MP 96).IR spectra were recorded on FT-IR Perkin-Elmer 1605 spectrometer, and^{1}H NMR (200 MHz) and ^{13}C NMR (50.3 MHz) were recorded on a Varian Gemini 200 spectrometer using TMS as internal standard (chemical shifts and ppm). UV spectra were obtained on a Shimadzu UV-visible spectrophotometer (model UV-1601). Mass spectra were recorded on a VG micromass70-70H instrument.

I.General procedure for the synthesis of 8-allyl-7-hydroxyisoflavones (3a-e)

i. *8-Allyl-7-hydroxy-4'-methoxyisoflavone* (3a)

7-Allyloxy-4'-methoxyisoflavone **(2a)** (2.7g, 10.0mmol) was taken in N, N-diethylaniline (20 ml) and refluxed for 6 hrs at 220 °C. The reaction mixture was cooled and poured into dilute hydrochloric acid and extracted with ethyl acetate (200ml) and then washed with water (100ml) and dried over anhydrous Na$_2$SO$_4$. The solvent was removed under reduced pressure. The resulting product, 8-allyl-7-hydroxy-4'-methoxyisoflavone **(3a)** was recrystallized from chloroform as pale yellow crystals, 2.0g in 50-75% yield, and mp.196 °C.

IR (KBr): 1631 cm^{-1} (C=O).; UV (MeOH): 224 nm (log ε 3.7), 210 nm (log ε 3.6); ^{1}H NMR (200 MHz) (CDC1$_3$): δ10.35 (s, 7-OH), 8.10 (s, H-2), 7.48 (d, J= 9.0Hz, H-2', 6'), 6.95 (d, J= 9.0 Hz, H-3', 5'); 7.85 (d, J=9.0 Hz, H-5), 7.0 (d, J= 9.0 Hz, H-6), 5.00 (m, H-3''), 6.00 (m, H-2''), 3.85 (s, 4;-OCH$_3$), 3.58 (d, J= 7.0 Hz, H-l'').

^{13}C NMR (75.5 MHz)(DMSO-D$_6$): δ174.89 (C-4),159.85 (C-7), 158.88 (C-4'), 155.28 (C-2), 153.01 (C-8a), 135.28 (C-2''), 129.99 (C-2',6'), 124.57 (C-1'), 124.22 (C-3), 122.77 (C-5), 116.68 (C-4a), 115.14 (C-3''), 112.79 (C-6), 114.18 (C-8), 113.59 (C-3',51), 55.07; (C-4'-OCH$_3$), 26.48 (C-1''). ; MS: M$^+$ m/z 308(10), 208(100), 279(5), 147(8%).

Employing the similar procedure as mentioned for **3a** compounds **3b-e** were obtained from **2b-e** as solids in 50-75% yield.

ii. 8-Allyl-7-hydroxyisoflavone (3b)

Recrystallized from chloroform as pale yellow crystals, mp. 198 ^{o}C.
IR (KBr): 1632cm^{-1} (C=O).; UV (MeOH): 251 nm (log ε 4.8), 282 nm (log ε 4.2).; ^{1}H NMR (200 MHz) (CDCl$_3$): δ10.0 (7-OH), 8.0 (s, H-2), 7.95 (d, J=9.0 Hz, H-5), 7.55(m, 2H, H-2',6'),7.40 (m,H-3',4',5'),7.0 (d,J=9.0 Hz, H-6), 6.0(m,H-2''), 5.0 (m,H-3''), 3.58(d,J=6.0Hz,H-l'').; ^{13}C NMR (75.5 MHz) (DMSO-D$_6$): δ174.69 (C-4), 159.95 (C-7), 155.30 (C-2), 153.77 (C-8a), 135.25 (C-2''), 132.11 (C-1'),128.87 (C-3',5'), 128.04 (C-2',6'), 127.61 (C-4'),124.60 (C-3),123.18 (C-5), 116.71 (C-4a), 115.18 (C-3''),112.87 (C-6),114.26(C-8), 26.48 (C-l'').

iii. 8-Allyl-7-hydroxy-2',4'-dichloroisoflavone (3c)

Recrystallized from chloroform as pale yellow crystals, mp. 156 °C.
IR (KBr): 1624cm^{-1} (C=O).; UV (MeOH): 205 nm (log ε 4.9), 220 nm (log ε 4.8).; ^{1}H NMR (200 MHz) (CDCl$_3$): δ10.0 (s, 7-OH). 8.20 (d, J= 9.0 Hz, H-5, 7.85 (s, H-2), 7.0 (d,J=9.0 Hz,H-6),7.03-7.60 (m, H-6',5'), 6.85 (d,J=2.0 Hz, H-3'), 5.0 (m, H-3''), 6.0 (m,H-2''), 3.60(d,J=6.0Hz,H-I'').; ^{13}C NMR (75.5 MHz) (DMSO-D$_6$): δ173.74 (C-4), 160.21 (C-7), 155.50

(C-2), 154.73 (C-8a), 135.19 (C-2"), 135.02 (C-2'), 133.66 (C-6'), 133.74 (C-4'), 130.61 (C-5'), 128.63 (C-3'), 127.11 (C-1'), 124.49 (C-3), 121.82 (C-5), 116.34 (C-4a), 115.25 (C-3"), 113.11 (C-6), 114.43 (C-8), 26.53 (C-l").

iv. 8-Allyl-7-hydroxy-4'-bromoisoflavone (3d)
Recrystallized from chloroform as pale yellow crystals, mp. 158 °C.
IR (KBr): 1638 cm^{-1} (C=O).; UV (MeOH): 213 nm (log ε 4.7), 220 nm (log ε 4.8).; ^{1}H NMR (200MHz) ($CDC1_3$): δ 10.4 (s, 7-OH), 8.02 (d, J= 9.0 Hz, H-5), 7.82 (s,H-2), 7.59-7.72(m, 4H,H-2',6',3'5'), 6.99 (d, J=9.0 Hz,H-6), 5.0 (m,H-3"), 6.0 (m.H-2"). 3.6 (d,J=6.0 Hz, H-1").; ^{13}C NMR (75.5 MHz) (DMSO-D_6): δ 174.43 (C-4), 159.30 (C-7). 155.29 (C-2), 154.02 (C-8a). 135.21 (C-2"), 128.77 (C-l'). 130.89 (C-3', 5’), 124.60 (C-2', 6’), 124.60 (C-4'), 124.60 (C-3), 122.55 (C-5), 116.56 (C-4a). 115.13 (C-3"), 112.91 (C-6), 114.37 (C-8), 26.47 (C-l").

v) 8-Allyl-7-hydroxy -2 ',4'-dimethoxyisoflavone (3e)
Recrystallized from chloroform as pale yellow crystals, mp. 160 °C.
IR (KBr): 1633 cm^{-1} (C=O); UV (MeOH): 221 nm (log ε 4.7), 206 nm (log ε 7.4).; ^{1}H NMR (200 MHz)($CDCl_3$) :δ10.5 (s,7-OH), 8.02 (d,J= 9.0 Hz, H-5), 8.0 (s,H-2), 6.99 (d,J=9.0 Hz, H-6), 6.08-7.04 (m, 3H,H-6'-3',5'), 6.0(m, H-2"), 5.0 (m,H-3"), 3.90 (OCH_3 x2), 3.64(d,J=6.0Hz,H-1"). ^{13}C NMR (75.5 MHz)(DMSO-D_6) : δ 174.52 (C-4), 162.47 (0-7), 157.22 (C-2), 153.56 (C-8a), 148.64 (C-4'), 148.28 (C-2'), 132.75 (C-2"), 126.93 (C-6'), 124.33 (C-3), 123.40 (0-3'), 121.19(C-5), 101.36(C-5'), 1 17.65 (C-4a), 118.16(C-8), 112.78(C-6), 111.55 (C-1'), 115.03 (C-3"), 30.59 (C-l "), 55.5 1 (OCH_3x2).

II.General Procedure for the synthesis of 8-methyl-4H-furo [2,3-h] isoflavones (5a-e)
***vi. 8-Methyl-4H-furo [2,3-h]-4'-methoxyisoflavone* (5a)**
A suspension of sodium salt of 8-allyl-7-hydroxy-4'-methoxyisoflavone (2.0g, 10.0 mmols) in benzene (200ml) containing [$PdCl_2(PhCN)_2$] (2.25g,10mmols) of was stirred at room temperature for 30 minutes. The suspension became clear and developed intense red colour during stirring. The clear solution was refluxed for 2 hrs when black metallic palladium separated out and the solution turned colorless. Palladium was filtered and the filtrate concentrated to yield the crude product. The product was purified by column chromatography using silica gel. Elution with benzene gave benzonitrile and subsequent elution with chloroform gave 8-methyl-4H-furo [2,3-h]-4'-methoxyisoflavone **(5a).** It was recrystallized from chloroform as yellow crystals, 2.2g in (70-80% yield).

Recrystallized from chloroform as yellow crystals, mp. 166°C.
IR (KBr): 1634 cm^{-1}(C=O).; UV (MeOH): 257 nm (log ε 4.8), 303 nm (log ε 4.1).; ^{1}H NMR (200 MHz) ($CDCl_3$): δ 8.10 (d, J=9.0 Hz, H-5), 8.00 (s,H-2), 7.50 (d,J=9.0 Hz,H-2',6'), 7.45 (d, J=9.0 Hz, H-6), 6.90 (d, J= 9.0 Hz, 3',5'), 6.70 (s,H-9), 2.55 (s, CH_3-8), 3.82(s,4'-OCH_3).; ^{13}C NMR (75.5 MHz) ($CDCl_3$) : δ 176.21(C-4), 159.48(C-6a), 157.62 (C-4'), 156.49 (C-8), 151.50 (C-2), 149.83 (C-9b), 130.08 (C-2',6'), 124.99 (C-1'), 124.17(C-3), 120.97 (C-5), 119.63 (C-9a), 118.25 (C-4a), 113.83 (C-3',5'), 109.42 (C-6), 99.77 (C-9), 55.20 (4'-OCH_3), 13.97(CH_3-8).; MS: M^+ m/z 306 (99), 291 (10), 174 (40%).

Employing the similar procedure as mentioned for **5a**, compounds **5b-e** were obtained from **4b-e** as solids in 70-80% yield.

vii. 8-Methyl-4H-furo [2,3-h]isoflavone (5b)

Recrystallized from chloroform as yellow crystals, mp. 153 °C.

IR (KBr): 1683 cm^{-1}(C=O); UV (MeOH): 249 nm (log ε 4.0), 290 nm (log ε 4.4); ^1H NMR (200 MHz) ($CDCl_3$): δ 8.10 (d, J=9.0 Hz, H-5), 8.05 (s,H-2),7.30-7.60 (H-6.2',4'6',3',5'), 6.70 (s.H-9), 2.58 (s,CH_3-8).; ^{13}C NMR (75.5 MHz) ($CDCl_3$): δ 176.02(C-4), 161.42 (C-6a), 156.61 (C-8). 152.08 (C-2), 149.88 (C-9b), 131.75 (C-1'), 128.05 (C-2',6'), 127.80 (C-4'), 125.21 (C-3), 125.49 (C-5), 114.94 (C-9a), 118.32 (C-4a), 109.57 (C-6), 128.86 (C-3',5'), 102.79 (C-9), 12.18 (CH_3-8).

MS: M^+m/z 276(2%).

viii. 8-Methyl-4H-furo [2,3-h]-2',4'-dichloroisoflavone (5c)

Recrystallized from chloroform as yellow crystals, mp. 150°C

IR (KBr): 1635 cm^{-1}(C=O); UV (MeOH): 241 nm (log ε 4.8), 270 nm (log ε 4.2) ^1H NMR (200 MMz) ($CDCl_3$): δ 7.65 (d, J=9.0 Hz, H-5), 7.45 (s, H-2), 7.30 (d, J=9.0 Hz, H-6), 6.90-7.30 (m, 3H, H-3', 5', 6'), 6.60 (s, H-9), 2.50 (s, CH_3-8).; ^{13}C NMR (75.5 MHz) ($CDC1_3$) : δ 174.54 (C-4), 159.76 (C-6a), 155.43 (C-8), 155.45 (C-2), 149.80 (C-9b), 135.31 (C-2'), 133.99 (C-4'), 132.52 (C-l') 131.40 (C-3'), 129.48 (C-6'), 125.19 (C-5'), 125.20 (C-3), 122.97 (C-5), 119.16 (C-4a), 113.58 (C-9a), 100.85 (C-6), 100.33 (C-9), 14.04 (CH_3-8).; MS: M^+ m/z 345(10%).

ix. 8-Methyl-4H-furo [2,3-h]-4'-bromoisoflavone (5d)

Recrystallized from chloroform as yellow crystals, mp. 164 °C.

IR (KBr): 1684 cm^{-1} (C=O).; UV (MeOH): 210 nm (log ε 4.7), 221 nm (log ε 4.0).; ^1H NMR (200 MHz) ($CDCl_3$) : δ 8.20 (d, J= 9.0 Hz, H-5), 8.0 (s, H-2), 7.60 (d, J= 9.0 Hz, 2H, H-2',6'), 7.30 (d, J= 9.0 Hz, H-6), 6.90 (d, J=9.0 Hz,2H, H-3',5'), 6.70 (s,H-9), 2.56 (s,CH_3-8).; ^{13}C NMR (75,5 MHz) ($CDCl_3$) : δ 175.54 (C-4), 157.60 (C-6a), 156.67 (C-8),151.78 (C-2), 149.69 (C-9b), 131.28 (C-2',6'), 130.73 (C-1'), 130.39 (C-3',5'), 124.20 (C-3), 121.99 (C-4'), 120.64 (C-5), 119.36 (C-9a), 118.21 (C-4a), 109.58 (C-6), 99.82 (C-9), 13.85 (CH_3-8).; MS: M^+ m/z 355(45%).

x. 8-Methyl-4H-furo [2,3-h]-2',4'-dimethoxyisoflavone (5e)

Recrystallized from chloroform as yellow crystals, mp. 160 °C.

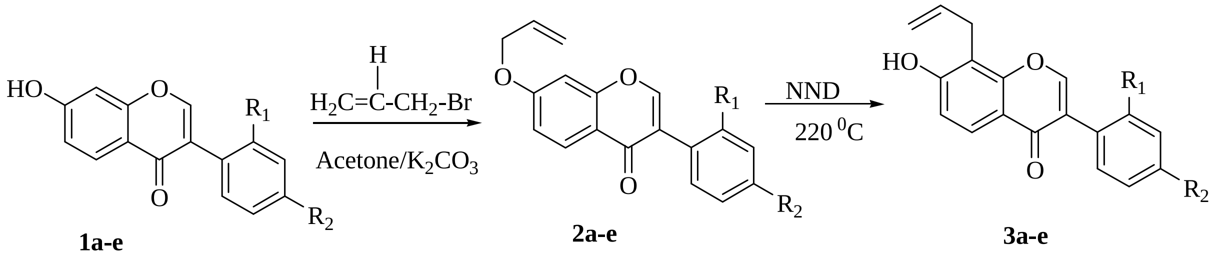
IR (KBr): 1635 cm^{-1}(C=O).; UV (MeOH): 214 nm (log ε 4.9), 220 nm (log ε δ 4.7).; ^1H NMR (200 MHz) ($CDC1_3$) : δ 8.15 (d.J=9.0 Hz, H-5), 8.02 (s,H-2), 7.45 (d,J=9.0 Hz, H-6), 7.25 (d,J=9.0 Hz, H-6'), 7.05 (dd, J=9.0 Hz, H-5'), 6.70 (s,H-9), 6.90 (d,J=9.0 Hz, H-3'), 3.95 (OCH_3x2), 2.58 (s,CH_3-8).; ^{13}C NMR (75.5MHz) ($CDC1_3$) : δ 176.42 (C-4), 157.82 (C-6a), 156.07 (C-4'), 151.78 (C-2), 149.72 (C-8), 149.14 (C-9b), 148.79 (C-2'), 121.09 (C-1'), 112.62 (C-6'), 124.71 (C-3), 121.12 (C-5), 119.76 (C-9a), 118.40 (C-4a), 111.18 (C-3'), 111.18 (C-5'), 109.67 (C-6), 100.08 (C-9), 14.12 (CH_3-8), 55.95 and 55.98 (OCH_3x2).; MS:M^+ m/z 336(100%).

RESULTS AND DISCUSSION

Synthesis of 8-methyl-4H-furo [2, 3-h] isoflavones (5a-e)

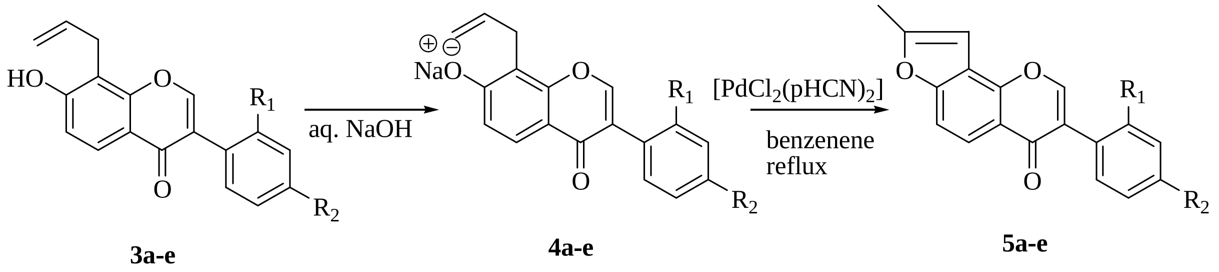
A suspension of sodium salt of 8-allyl-7-hydroxyisoflavones **(3a-e)** and dichlorobis (benzonilrile) palladium [$PdCl_2(PhCN)_2$] in benzene was stirred for 30 min at room temperature gave 8-melhyl-4H-furo[2,3-h]isoflavones **(5a-e).**In its IR spectrum of 8-methyl-4H-furo[2,3-h]-4'-methoxyisoflavone **(5a)** showed the carbonyl peak at 1634 cm^{-1}. Its UV spectrum showed the bands at 257 (log ε 4.8), 303 nm (log ε 4.1). The ^{1}H NMR recorded in CDC1$_3$ at 200MHz, showed a signal pattern due to CH_3-C=C-H as part of a new ring system fused to 7,8-positions of isoflavone. The furan proton H-9 and methyl proton CH_3-8 appeared as singlets at δ 6.70 and 2.55 respectively. H-5 and H-6 appeared as doublets with (J=9.0 Hz) at δ 8.10 and δ 7.45 respectively. The H-2 appeared as a singlet at δ 8.00. The aromatic protons H-3', 5' resonated as doublet with (J=9.0Hz) at δ 6.90, while H-2', 6' resonated as doublet with (J=9.0 Hz) at δ 7.50 and 4'-OCH_3 appeared as singlet at δ 3.82.

Scheme-1



1,2 ,3 a = R$_1$ = H R$_2$ = OCH3
b = R$_1$ = H R$_2$ = H
c = R$_1$ = Cl R$_2$ = Cl
d = R$_1$ = H R$_2$ =Br
e = R$_1$= OCH_3 R$_2$= OCH_3

Scheme-2



3,4 ,5 a = R$_1$ = H R$_2$ = OCH3
b = R$_1$ = H R$_2$ = H
c = R$_1$ = Cl R$_2$ = Cl
d = R$_1$ = H R$_2$ =Br
e = R$_1$= OCH_3 R$_2$= OCH_3

In its ^{13}C NMR spectrum of **(5a)** (75.5 MHz $CDCl_3$) the furan ring carbons resonated at δ 156.49 (C-8), 99.77 (C-9) and 13.97 (CH_3-8), 119.63 (C-9a). The other carbons appeared at 176.21 (C-

4), 159.48 (C-6a), 157.62 (C-4'), 151.50 (C-2), 149.83(C-9b), 130.08 (C-2' 6'), 124.99(C-1'), 124.17(C-3), 120.97 (C-5), 118.25 (C-4a), 109.42 (C-6), 113.83 (C-3', 5'), 55.20 (4'-OCH_3).

In the MS of 8-methyl-4H-furo [2,3-h]-4'-methoxyisoflavone **(5a)** the molecular ion peak was observed at m/z 306 (99), other major ions in the EI mass are m/z 291 (10) and 174(40%).

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