

Facile Synthesis of 9-Acetyl-pyrano[2,3-F]isoflavones

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The Baylis-Hillman reaction of 7-hydroxy-8-formyl isoflavones (**1a-f**) react with methyl ketone in presence of 1,4-diazobicyclo[2.2.2]octane with nitrogen atmosphere to give 9-acetyl-pyrano[2,3-f]isoflavones (**3a-f**) in good yields.

Key Words: 7-Hydroxy-8-formyl isoflavones, 1,4-diazobicyclo[2.2.2]octane, Baylis-Hillman reaction, Methyl vinyl ketone.

INTRODUCTION

Natural and synthetic heterocyclic compounds play an important role in both drug discovery and chemical biology. The heterocyclic compounds 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 insects¹⁻⁵. Several synthetic analogs of these heterocyclics show different bioactivity⁶⁻⁸. More than 50 % of the drug used in the modern medicine is either derived from synthetic or natural heterocyclic systems.

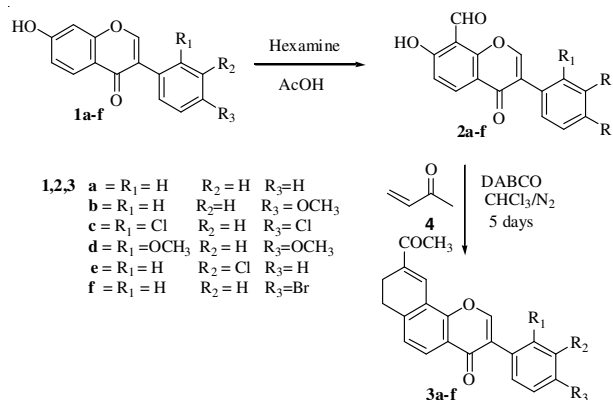
With a view to synthesize new heterocyclic ring fused isoflavones we studied the Duff's reaction of 8-formyl-7-hydroxyisoflavones and isoflavones^{9,10}. Literature shows that Baylis Hillmann reaction of 2-hydroxy benzaldehyde proceed *via* acrylo intermediate to gives rise to either three substituted 2-H isoflavones. Selective formation of 2-hydroxy benzaldehyde depends on solvent and structural features of substrate.

EXPERIMENTAL

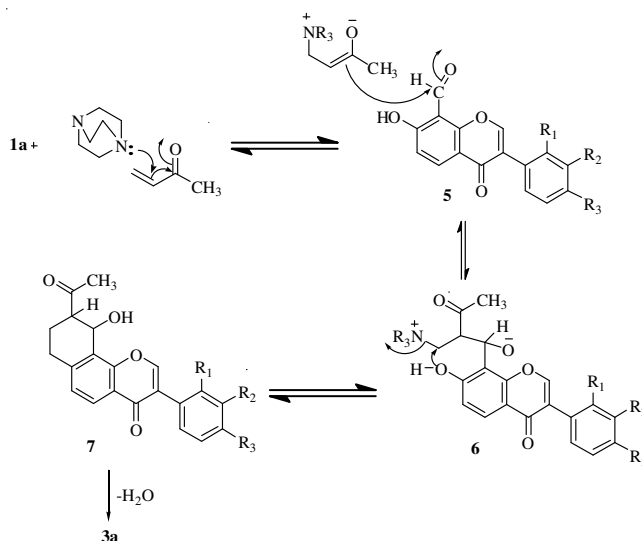
Melting points were determined on a Polmon instrument (model No. MP 96). IR spectra were recorded on FT-IR Perkin-Elmer 1605 spectrometer and ¹H NMR (200 MHz) and ¹³C NMR (50.3 MHz) were recorded on a Varian Gemini 200 spectrometer using TMS as internal standard (chemical shifts are expressed in ppm). UV spectra were obtained on a Shimadzu UV-visible spectrophotometer (model UV-1601). Mass spectra were recorded on a VG micromass 70-70H instrument.

General procedure for the synthesis of 9-acetyl-pyrano[2,3-f]isoflavones (**3a-f**)

9-Acetyl-pyrano[2,3-f]isoflavone (3a**)**^{11,12}: 7-Hydroxy-8-formylisoflavone (3.1 g, 10 mmol), methyl vinyl ketone (**4**)



Scheme-I



Scheme-II

(0.5 mL), 1,4-diazobicyclo[2.2.2]octane (DABCO) (0.5 g, 4.54 mmol) in chloroform (50 mL), was stirred at room temperature under N₂ atmosphere in for 60 h. The chloroform was removed by distillation and the product was purified by column chromatography eluting with petroleum ether:ethylacetate (9:1) to give 9-acetyl-pyrano[2,3-f]isoflavone (**3a**), (2.3 g) 50-75 % yield. **3a** (Scheme-I) was recrystallized from chloroform m.p. 206 °C. IR (KBr, $\nu_{\max}$, cm⁻¹): Isoflavone carbonyl 1626 (C=O), 1654 (COCH₃). UV (MeOH): 219 nm (log ϵ 5.1), 227 nm (log ϵ 4.7). ¹H NMR (300 MHz) (CDCl₃): δ 8.19 (d, J = 9.0 Hz, H-5), 8.0 (s, H-2), 7.77 (bs, 10-H), 7.55 (m, 2H, H-2',6'), 7.42 (m, 3H, H-3', 4', 5'), 6.92 (d, J = 9.0 Hz, H-6), 5.15 (d, J = 1.0 Hz, OCH₂-8), 2.50 (s, 9-COCH₃). ¹³C NMR (75.5 MHz) (CDCl₃): δ 195.38 (9-C=O), 174.97 (C-4), 159.65 (C-6a), 153.32 (C-10b), 151.93 (C-2), 131.30 (C-9), 130.25 (C-1'), 129.62 (C-4'), 128.49 (C-3',5'), 128.35 (C-10), 114.85 (C-10a), 126.21 (C-5), 128.87 (C-2',6'), 125.77 (C-3), 118.8 (C-4a), 109.15 (C-6), 64.97 (C-8), 25.33 (9-CH₃). EI MS: M⁺ m/z 318 (100), 317 (22), 303 (16), 275 (74 %).

Employing the similar procedure as mentioned for **3a**, compounds **3b-f** were obtained from **1b-f** as solids in 50-75 % yield.

9-Acetyl-pyrano[2,3-f]-4'-methoxyisoflavone (3b): Recrystallized from chloroform m.p. 189 °C. IR (KBr, $\nu_{\max}$, cm⁻¹): Isoflavone carbonyl 1628 (C=O), 1654 (COCH₃). UV (MeOH): 227 nm (log ϵ 4.6), 319 nm (log ϵ 4.2). ¹H NMR (300 MHz) (CDCl₃): δ 8.17 (d, J = 9.0 Hz, H-5), 7.95 (s, H-2), 7.75 (bs, 10-H): 7.45 (d, J = 8.7 Hz, 2H, H-2',6'), 6.95 (d, J = 8.7 Hz, 2H, H-3',5'), 6.90 (d, J = 9.0 Hz, H-6), 5.13 (d, J = 1.0 Hz, OCH₂-8), 3.83 (4'-OCH₃), 2.48 (s, 9-COCH₃). ¹³C NMR (75.5 MHz) (CDCl₃): δ 195.34 (9-C=O), 175.52 (C-4), 159.83 (C-6a), 159.52 (C-4'), 153.26 (C-10b), 151.30 (C-2), 130.21 (C-9), 129.99 (C-2',6'), 129.51 (C-10), 126.24 (C-5), 125.30 (C-3), 123.48 (C-1'), 118.78 (C-4a), 114.70 (C-10a), 113.95 (C-3',5'), 109.04 (C-6), 64.89 (C-8), 55.36 (4'-OCH₃), 25.27 (9-CH). EI MS: M⁺ m/z 348 (380 %).

9-Acetyl-pyrano[2,3-f]-2',4'-dichloroisoflavone (3c): Recrystallized from chloroform m.p. 200 °C. IR (KBr, $\nu_{\max}$, cm⁻¹): Isoflavone carbonyl 1629 (C=O), 1633 (COCH₃). UV (MeOH): 223 nm (log ϵ 4.7), 247 nm (log ϵ 4.6). ¹H NMR (300 MHz) (CDCl₃): δ 8.19 (d, J = 9.0 Hz, H-5), 7.95 (s, H-2), 7.78 (bs, 10-H), 7.26-7.33 (m, 2H, H-5',H-6'). 6.95 (d, J = 9.0 Hz, H-6), 7.52 (bs, H-3'), 5.17 (d, J = 1.0 Hz, OCH₂-8), 2.49 (s, 9-C OCH₃). ¹³C NMR (75.5 MHz) (CDCl₃): δ 195.35 (9-C=O), 174.15 (C-4), 159.93 (C-6a), 153.45 (C-10b), 153.45 (C-2), 135.24 (C-2'), 135.12 (C-4'), 132.88 (C-1'), 130.18 (C-9), 129.73 (C-5'), 129.84 (C-10), 128.89 (C-6'), 127.11 (C-3'), 123.50 (C-3), 115.07 (C-10a), 118.65 (C-4a), 125.96 (C-5), 109.26 (C-6), 64.91 (C-8), 25.08 (9-CH₃). EI MS: M⁺ m/z 387 (10 %).

9-Acetyl-pyrano[2,3-f]-2',4'-dimethoxyisoflavone (3d): Recrystallized from chloroform m.p. 188 °C. IR (KBr, $\nu_{\max}$, cm⁻¹): Isoflavone carbonyl 1624 (C=O), 1652 (COCH₃). UV (MeOH): 218 nm (log ϵ 4.4), 230 nm (log ϵ 3.6). ¹H NMR (300 MHz) (CDCl₃): δ 8.21 (d, J = 9.0 Hz, H-5), 8.02 (s, H-2), 7.79 (bs, H-10), 6.92-7.26 (m, 3H, H-3',5',6'), 6.94 (d, J = 9.0 Hz, H-6), 5.16 (d, J = 1.0 Hz, OCH₂-8), 3.94 (2'-OCH₃), 3.92 (4'-OCH₃), 2.50 (s, 9-COCH₃). ¹³C NMR (75.5 MHz) (CDCl₃):

δ 195.58 (9-C=O), 175.40 (C-4), 159.79 (C-2), 159.72 (C-6a), 159.79 (C-4'), 153.45 (C-2), 151.46 (C-10b), 130.13 (C-6'), 129.65 (C-9), 126.37 (C-10), 125.37 (C-5), 114.81 (C-10a), 123.45 (C-3), 118.90 (C-4a), 114.06 (C-6), 114.06 (C-1'), 109.18 (C-3'), 109.17 (C-5'), 64.91 (C-8), 55.36 (OCH₃×2), 25.21 (9-CH₃). EIMS: M⁺ m/z 378 (100 %).

9-Acetyl-pyrano[2,3-f]-3'-chloroisoflavone (3e): Recrystallized from chloroform m.p. 185 °C. IR (KBr, $\nu_{\max}$, cm⁻¹): Isoflavone carbonyl 1636 (C=O), 1654 (COCH₃). UV (MeOH): 210 nm (log ϵ 4.4), 224 nm (log ϵ 4.3). ¹H NMR (300 MHz) (CDCl₃): δ 8.20 (d, J = 9.0 Hz, H-5), 8.01 (s, H-2), 7.78 (bs, 10-H), 7.57 (m, H-2'), 7.40 (m, 3H, H-4',5',6'), 6.95 (d, J = 9.0 Hz, H-6), 5.17 (bs, OCH₂-8), 2.50 (s, 9-COCH₃). ¹³C NMR (75.5 MHz) (CDCl₃): δ 195.30 (9-C=O), 174.20 (C-4), 159.33 (C-6a), 153.54 (C-10b), 153.46 (C-2), 135.24 (C-3'), 135.12 (C-4'), 132.86 (C-1'), 130.19 (C-9), 129.85 (C-10), 129.73 (C-5'), 128.87 (C-2'), 128.87 (C-6'), 125.90 (C-5), 123.49 (C-3), 115.08 (C-10a), 118.66 (C-4a), 109.26 (C-6), 64.91 (C-8), 25.08 (9-CH₃). EI MS: M⁺ m/z 352 (100 %).

9-Acetyl-pyrano[2,3-f]-4-bromoisoflavone (3f): Recrystallized from chloroform m.p. 211 °C. IR (KBr, $\nu_{\max}$, cm⁻¹): Isoflavone carbonyl 1624 (C=O), 1667 (COCH₃). UV (MeOH): 254 nm (log ϵ 4.6), 229 nm (log ϵ 4.4). ¹H NMR (300 MHz) (CDCl₃): δ 8.02 (d, J = 9.0 Hz, H-5), 7.95 (s, H-2), 7.70 (bs, 10-H), 7.55 (d, J = 9.0 Hz, H-2',6'), 7.40 (d, J = 9.0 Hz, H-3',5'), 6.95 (d, J = 9.0 Hz, H-6), 5.15 (d, J = 1.0 Hz, OCH₂-8), 2.45 (s, 9-COCH₃). ¹³C NMR (75.5 MHz) (CDCl₃): δ 195.35 (9-C=O), 174.70 (C-4), 159.82 (C-6a), 153.34 (C-10b), 151.84 (C-2), 131.65 (C-2',6'), 130.40 (C-3',5'), 130.24 (C-9), 130.17 (C-1'), 129.76 (C-10), 114.98 (C-10a), 125.94 (C-5), 124.77 (C-3), 118.73 (C-4a), 109.12 (C-6), 122.62 (C-4'), 64.91 (C-8), 25.09 (9-CH₃). EI MS: M⁺ m/z 397 (100 %).

RESULTS AND DISCUSSION

Synthesis of 9-acetyl-pyrano[2,3-f] isoflavones (3a-f)^{13-15:} 7-Hydroxy-8-formylisoflavones (**2a-f**) on reaction with methyl vinyl ketone (**4**) in the presence catalytic amount of 1,4-diazobicyclo[2.2.2]octane (DABCO), in chloroform under N₂ (Baylis-Hillman reaction) gave 9-acetyl-pyrano[2,3-f] isoflavones, (9-acetyl-4*H*,8*H*-pyrano[2,3-f]chromen-4-ones) (**3a-f**) (Scheme-I).

In its IR spectrum of 9-acetyl-pyrano[2,3-f] isoflavone (**3a**), the C=O appeared at 1626 cm⁻¹ and the acetyl carbonyl at 1654 cm⁻¹. Its UV spectrum (**3a**) showed bands at 219 nm (log ϵ 5.1), 227 nm (log ϵ 4.7). In the ¹H NMR spectrum of **3a** recorded in (300 MHz) (CDCl₃), the 8-OCH₂ group of the new ring system appeared as doublet at δ 5.15 (J = 1.0 Hz) due to allylic coupling with H-10. H-10 appeared as broad singlet at δ 7.77, while the 9-COCH₃ appeared as a singlet at 2.50. These three signals, suggest that a new fused pyran ring is formed at 7,8 position of the isoflavone. Other signals in the ¹H NMR are from the original isoflavone moiety. The H-2 appeared as a singlet at δ 8.00, H-5 appeared as a doublet at 8.19 (J = 9.0 Hz) and H-6 appeared as a doublet at δ 6.92 (J = 9.0 Hz). The other aromatic protons appeared as a multiplets H-2',6' at δ 7.55, H-3',4',5' at δ 7.42. In the ¹³C NMR (75.5 MHz) (CDCl₃) spectrum of 9-acetyl-pyrano[2,3-f]isoflavone

(**3a**), the signals due to the 9-COCH₃ appeared at the δ 195.38 and δ 25.33. The 8-OCH₂ appeared at the 64.97 and the olefine carbons C-9 and C-10 appeared at δ 131.30 and 128.35. The other carbon signals assignments are 174.97 (C-4), 159.65 (C-6a), 153.32 (C-10b), 151.93 (C-2), 130.25 (C-1'), 129.62 (C-4'), 128.87 (C-2',6'), 128.49 (C-3',5'), 125.77 (C-3), 118.88 (C-4a), 126.21 (C-5), 109.15 (C-6), 114.85 (C-10a).

In the EI MS of **3a**. The M⁺ appeared at m/z 318 (100), M-1 317 (22). The other fragment ions are observed at m/z 303 (16) and 275 (74 %).

The mechanistic pathway of **2a-3a** (Scheme-II) methyl vinyl ketone (**4**) with DABCO in a Michael reaction generates an enolate, which reacts with the formyl group of the isoflavone (**5**), to give an intermediate (**6**). The intramolecular nucleophilic substitution involving the 7-OH of isoflavone leads to the removal of the DABCO and pyran ring formation. The loss of H₂O in the presence of DABCO gives rise to pyrano isoflavones (**3a-f**).

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