SYNTHESIS OF 7-HYDROXY/METHOXY-8-[2' (4,6-DIMETHYL-3-CARBOXY-5-CARBETHOXY-2,3-DIHYDROPYRIDYL)]ISOFLAVONES

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ABSTRACT

7-Hydroxy/methoxy-8-formylisoflavones (2a-e & 6a-c) react with ethyl-3-amino-crotonate (3) by a modified Hantzsch reaction gave 7-hydroxy/methoxy-8-[2'(4,6-dimethyl-3-carboxy-5-carbethoxy-2,3-dihydropyridyl)]isoflavones (4a-e & 7a-c)

Keywords: 7-Hydroxy-8-formylisoflavones, 7-methoxy-8-formylisoflavones, ethyl-3-amino-crotonate, Hantzsch reaction, Pyridines.

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 Kellin a coronary vasodilator, Chromenes-2-carboxylate spasmolitic agent and disodium chromoglycate and anti-ergic drug. Genstein having estrogen hormonal activity, and 7-isopropoxy agent and disodium chromoglycate and anti-ergic drug.

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.

RESULTS AND DISCUSSION

Synthesis of 7-hydroxy-8-[2'(4,6-dimethyl-3-carboxy-5-carbethoxy-2,3-dihydropyridyl)]isoflavones (4a-e)

7-Hydroxy-8-formylisoflavones (2a-e) and ethyl-3-amino-crotonate (3) in methanol on stirring at room temperature to gave 7-hydroxy-8-[2'(4,6-dimethyl-3-carboxy-5-carbethoxy-2,3-dihydropyridyl)]isoflavones (4a-e). In the IR spectrum, ester carbonyl peak appeared at 1742 cm⁻¹ and isoflavon C=O at 1651 cm⁻¹. In the UV spectrum absorption maxima appeared at 238 nm (log ε 4.6) and 272 nm (log ε 4.8). In the 1H NMR spectrum of 4a recorded in (300 MHz) (CDCl₃), signals due to the newly formed 2,3-dihydropyridyl moiety at 8-position are as follows. The H-2 appeared as a doublet at δ 3.05 (J=3.9 Hz) and the H-3 appeared as a doublet at δ 4.62 (J=3.9 Hz). The protons of the 4-CH₃ and 6-CH₃ groups appeared at δ 1.88 and δ 1.25. Signals due to one COOEt appeared at δ 1.30(CH₃) as triplet with (J=7.0 Hz) and the OCH₃ protons appeared at δ 4.15 as quartet (J=7.0 Hz). A COOH proton appeared as a broad singlet at δ 8.90 and the 7-hydroxyl proton appeared as a broad singlet at δ 7.80. The other signals are due to the isoflavone moiety. The H-2 appeared as singlet at δ 8.0. The H-5 appeared as doublet at δ 7.95 (J=9.0 Hz). In the 13C NMR (75.5 MHz) (CDCl₃) spectrum of the product 4a there is evidence for the pyridyl ring carbons. The signal assignments are as follows: δ 45.83 (C-2'), 60.13 (C-3'), 168.69 (C-3'-COOH), 152.81 (C-4'), 19.81 (C-4'-CH₃), 133.01 (C-5'), 154.31 (C-5'-COO), 61.13 (C-5'-OCH₃), 14.21 (C-5'-CH₃), 169.0 (C-6'), 25.07 (C-6'-CH₃). The carbon signal assignment due to isoflavone moiety are as follows: δ 174.72 (C-4'), 155.73 (C-7), 155.33 (C-8a), 152.81 (C-2), 135.25 (C-2'), 135.12 (C-4'), 127.10 (C-6'), 129.69 (C-5'), 129.32 (C-1'), 125.97 (C-5), 125.97 (C-3), 123.35 (C-3'), 118.36 (C-4a), 116.27 (C-6), 114.32 (C-8). The MS of (4a) showed the [M+H]^+ ion at m/z 531, M-at m/z 529. The other ions at m/z 483, 223.

![Scheme 1](image-url)
EXPERIMENTAL SECTION (4a-e)

**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 1H NMR (300 MHz) and 13C NMR (75.5 MHz) were recorded on a VarianGemini 200 spectrometer using TMS as internal standard (chemical shifts and ppm). UV spectra were recorded 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 7-hydroxy-8-[2'-(4,6-dimethyl-3-carboxy-5-carboethoxy-2,3-dihydropyridyl)]isoflavone (4a-e)**

i) **7-Hydroxy-8-[2'-(4,6-dimethyl-3-carboxy-5-carboethoxy-2,3-dihydropyridyl)]-2',4'-dichloroisoflavone (4a)**

A mixture of 7-hydroxy-8-formyl-2',4'-dichloroisoflavone (2a) (26g,10.0mmol), ethyl-3-aminocrotanate (3) (20 mmol) in methanol (20ml) stirred at room temperature for 48 hrs. The reaction mixture was poured on to crushed ice. Pale yellow solid separated out. It was filtered washed with water and the reaction mixture was poured on to crushed ice. Pale yellow solid was obtained. It was filtered and washed with water and dried to give 7-hydroxy-8-[2'-(4,6-dimethyl-3-carboxy-5-carboethoxy-2,3-dihydropyridyl)]-2',4'-dichloroisoflavone (4a).

**UV (MeOH):** 238 nm (log ε 4.8), 272 nm (log ε 4.6).

**1H NMR (300 MHz) (CDCl3):** δ 8.90 (bs,COOH), 8.01 (s,H-2), 7.95 (d,J=9.0Hz,H-5), 7.20-7.60 (m,H-3',5',6'), 6.85 (d,J=9.0Hz,H-6), 5.80 (bs,OH-7), 1.30 (t,J=7.0Hz,CH3(COOH)), 3.05 (d,J=3.9Hz,H-2'), 4.62 (d,J=3.9Hz,H-3'), 4.15 (q,J=7.0Hz,CH3(COOH)), 1.88 (s,CH3-4'), 1.25(s,CH3-6').

**13C NMR (75.5 MHz) (CDCl3):** δ 174.72 (C-4), 169.0 (C-6'), 168.69 (C-3'COOH), 155.73 (C-7), 154.31 (C-5'COO), 153.33 (C-8a), 152.81 (C-4'), 152.81 (C-2), 135.25 (C-2'), 135.12 (C-4'), 133.01 (C-5'), 129.69 (C-5), 129.32 (Cf), 127.10 (C-6'), 125.97 (C-5'), 125.97 (C-3), 123.35 (C-3'), 118.36 (C-4a), 116.27(C-6'), 114.32 (C-8), 60.13 (C-3'), 61.13 (C-5'COOH), 45.83 (C-2'), 25.07 (C-6'-CH3), 19.81 (C-4'-CH3), 14.21 (C-5'-CH3).

**MS: [M+H]+/m/z 462.**

**ii) **7-Hydroxy-8-[2'-(4,6-dimethyl-3-carboxy-5-carboethoxy-2,3-dihydropyridyl)]isoflavone (4b)**

Recrystallized from methanol gave pale yellow needles mp 162 °C.

**IR (KBr):** 1651cm⁻¹, isoflavone (C=O), 1742 cm⁻¹ (=C-O, ester).

**UV (MeOH):** 238 nm (log ε 4.8), 272 nm (log ε 4.6).

**1H NMR (300 MHz) (CDCl3):** δ 8.90 (bs,COOH), 8.05 (d,J=9.0Hz,H-5), 7.90 (s,H-2), 7.45 (d,J=9.0Hz,H-6'), 6.90 (d,J=9.0Hz,H-3',5'), 6.85 (d,J=9.0Hz,H-6'), 5.70 (bs,OH-7), 4.60 (d,J=3.9Hz,H-3'), 4.20 (q,J=7.0Hz,CH3(COOH)), 3.80 (s,4'-OCH3), 3.05 (d,J=3.9Hz,H-2'), 2.25 (s,CH3-6'), 1.90 (s,CH3-4'), 1.30 (t,J=7.0Hz,CH3(COOH)).

**13C NMR (75.5 MHz) (CDCl3):** δ 175.8 (C-4), 168.78 (C-3'COOH), 168.78 (C-6'), 159.6 (C-4'), 155.3 (C-8a), 154.1 (C-5'COO), 150.82 (C-2), 151.51 (C-2'), 150.12 (C-4'), 130.13 (C-5'), 129.55 (C-5), 124.0 (C-3), 118.5 (C-4a), 114.02 (C-6'), 112.9 (C-1'), 111.98 (C-5'-OH), 45.56 (C-2'), 31.12 (C-3'), 55.33 (C-4'-OCH3), 25.15 (C-6'-CH3), 19.81 (C-4'-CH3), 14.22 (C-5'-CH3).

**MS: [M+H]+/m/z 492.**

**iv) **7-Hydroxy-8-[2'-(4,6-dimethyl-3-carboxy-5-carboethoxy-2,3-dihydropyridyl)]-4'-methoxyisoflavone (4c)**

Recrystallized from methanol pale yellow needles mp 150 °C.

**IR (KBr):** 1635 cm⁻¹, isoflavone (C=O), 1740 cm⁻¹ (=C-O, ester).

**UV (MeOH):** 257 nm (log ε 5.2).
[M+] m/z 496.

v) 7-Hydroxy-8-[2-(4,6-dimethyl-3-carboxy-5-carboethoxy-2,3-dihydropyridyl)]-2'-chloroisoflavone (7c)

Recrystallized from chloroform as pale yellow needles mp. 195 °C.

IR (KBr): 3638 (C=O), 1724 cm

UV (MeOH): 255 nm (log ε 4.4).

vi) 7-Methoxy-8-[2'-(3",5"-dimethyl-4',6'-dicarbethoxypyridyl)]-2', 4'-dichloroisoflavone (7b)

Recrystallized from chloroform as pale yellow needles mp. 195 °C.

IR (KBr): 1763 cm (C=O of COOEt); 1545 (C=O); 1349 (C=O).

UV (MeOH): 380 nm (log ε 3.7).

REFERENCES


Employing the similar procedure as mentioned for 7a, compounds 7b-c were obtained from 6b-c solids in 40-60% yield.

i) 7-Methoxy-8-[2'-(3",5"-dimethyl-4',6'-dicarbethoxypyridyl)]-2', 4'-dichloroisoflavone (7b)

Recrystallized from chloroform as pale yellow needles mp. 195 °C.

IR (KBr): 1763 cm (C=O of COOEt); 1545 (C=O); 1349 (C=O).

UV (MeOH): 1634 nm (log ε 4.4).

ii) 7-Methoxy-8-[2'-(3",5"-dimethyl-4',6'-dicarbethoxypyridyl)]-2', 4'-dichloroisoflavone (7b)

Recrystallized from chloroform as pale yellow needles mp. 195 °C.

IR (KBr): 1763 cm (C=O of COOEt); 1545 (C=O); 1349 (C=O).

UV (MeOH): 380 nm (log ε 3.7).

iii) 7-Methoxy-8-[2'-(3",5"-dimethyl-4',6'-dicarbethoxypyridyl)]-2'-chloroisoflavone (7c)

Recrystallized from chloroform as pale yellow needles mp. 195 °C.

IR (KBr): 1631 cm (C=O) 1724 cm (C=O, ester).

UV (MeOH): 368 nm (log ε 4.4).

MS: [M+H]+ m/z 538.

Synthesis of 7-methoxy-8-[2-(3",5"-dimethyl-4',6'-dicarbethoxypyridyl)] isoflavones (7a-c)

i) 7-Methoxy-8-[2'-(3", 4', 5'-trimethyl-4',6'-dicarbethoxypyridyl)] isoflavone (7a)

7-Methoxy-8-formylisoflavone (6a) (2.7g, 10.0mmol), ethyl-3-acetoacetate (3) (20mmol) in methanol (20ml), stirred at room temperature for 48 hrs. The reaction mixture was poured on to crushed ice. Pale yellow solid separated out which was chromatographed over silica gel by eluting with pet ether; ethyl acetate to give 7-methoxy-8-[2"-(3",5"-dimethyl-4',6'-dicarbethoxypyridyl)] isoflavone (7a).

MS: [M+H]+ m/z 496.

Employing the similar procedure as mentioned for 7a, compounds 7b-c were obtained from 6b-c solids in 40-60% yield.

ii) 7-Methoxy-8-[2'-(3",5"-dimethyl-4',6'-dicarbethoxypyridyl)]-2', 4'-dichloroisoflavone (7b)

Recrystallized from chloroform as pale yellow needles mp. 195 °C.

IR (KBr): 1763 cm (C=O of COOEt); 1545 (C=O); 1349 (C=O).

UV (MeOH): 380 nm (log ε 4.4).

iii) 7-Methoxy-8-[2'-(3",5"-dimethyl-4',6'-dicarbethoxypyridyl)]-2'-chloroisoflavone (7c)

Recrystallized from chloroform as pale yellow needles mp. 195 °C.

IR (KBr): 1631 cm (C=O) 1724 cm (C=O, ester).

UV (MeOH): 368 nm (log ε 4.4).

MS: [M+H]+ m/z 538.

REFERENCES


