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Facile Synthesis of 8-Hydroxymethyl-8,9-dihydro-2*H*-furo[2,3-h]chromene-3-carbaldehyde

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7-Hydroxy-8-allyl-2*H*-3-chromene carbaldehyde and *m*-chloro benzoic acid in chloroform on heating to gave 8-hydroxymethyl-8,9-dihydro-2*H*-furo[2,3-h]chromene-3-carbaldehydes (**3a-d**) and 2*H*-3-chromene carbaldehyde reaction with malononitrile to gave 9-amino-6*H*-benzochromene-8,10-dicarbonitriles (**6a-d**) in good yields.

Key Words: *m*-Chloro benzoic acid, 7-Hydroxy-8-allyl chromene carbaldehyde, Piperidine, Knoevenagel condensation.

INTRODUCTION

Chromones and isoflavones constitute an important class of oxygen heterocyclics. Substituted as well as heterocyclic ring fused chromones and isoflavones have a wide range of pharmacological activity[1-5]. Chromones and isoflavones with medicinal use are Khellin a coronary vasodilator. Chromones-2-carboxylate spasnolitic agent and disodium chromo glycate and anti elergitic drug. Genstein having estrogen hormonal activity[6-8] and 7-isopropoxy isoflavones for treatment of post-menopausal and senile osteoporosis[9,10].

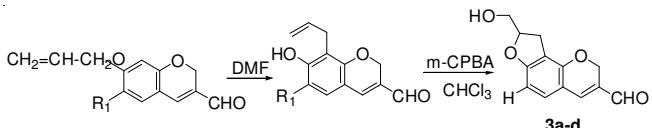
With a view to synthesize a new heterocyclic ring fused chromones and isoflavones, we studied the Knoevenagel condensation of 8-formyl-7-hydroxychromones and isoflavones[11,12]. Literature shows that Knoevenagel condensation reaction of 2-hydroxy benzaldehyde proceeds *via* acrylo intermediate to gives rise to either three substituted 2-H chromones[13-15]. Selective formation of 2-hydroxy benzoldehyde 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 ^{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.

General procedure for the synthesis of 8-hydroxymethyl-8,9-dihydro-2*H*-furo[2,3-h]chromene-3-carbaldehydes (3a-d)

7-Hydroxy-8-allyl-2*H*-3-chromenecarbaldehyde (**2a**) (2.16 g, 10 mmol), *m*-chloro benzoic acid (1.62 g) (10 mmol) were dissolved in dry $CHCl_3$ (25 mL) and refluxed for 6 h. After cooling to room temperature, the separated *m*-chloro benzoic acid was filtered. The filtrate was washed with aqueous $NaHCO_3$ (2 %, 3 × 100 mL) to remove traces of *m*-chloro benzoic acid and then with water (2 × 100 mL) dried and concentrated. The residue on chromatography over silica gel by eluting with petroleum ether:ethylacetate (8:2) gave 8-hydroxymethyl-8,9-dihydro-2*H*-furo[2,3-h]chromene-3-carbaldehyde (**3a**) (1.2 g) (51 % yield), which was recrystallized from chloroform as colourless needles, m.p. 150 ºC (**Scheme-I**).



1,2,3 a. R^1 = H
b. R^1 = Cl
c. R^1 = Br
d. R^1 = CH_3

Scheme-I

Spectral data

8-Hydroxymethyl-8,9-dihydro-2*H*-furo[2,3-h]chromene-3-carbaldehydes (3a): IR (KBr, ν_{max}, cm^{-1}): 1014 (C-O), 1624 (C=C) and 1664 (C=O). UV (MeOH): 241 nm (log ε 3.7), 263 nm (log ε 3.6) and 348 nm (log ε 3.7). ^{1}H NMR (200 MHz) ($CDCl_3$): δ 2.95 (dd, J = 16.0, 8.0 Hz, CH_2-9, H_A), 3.20 (dd, J = 16.0, 10.0 Hz, CH_3, H_B), 3.75 (dd, J = 16.0, 6.0 Hz, 8-

CH_2OH, H_D), 3.90 (dd, *J* = 16.0, 4.0 Hz, 8-CH_2OH, H_E), 5.05 (s, OCH_2-2), 5.36 (m, H-8), 6.42 (d, *J* = 10.0 Hz, H-6), 7.00 (d, *J* = 10.0 Hz, H-5), 7.18 (s, H-4), 9.50 (s, CHO). FABMS: m/z 233 (M+1), m/z 231 (M-1).

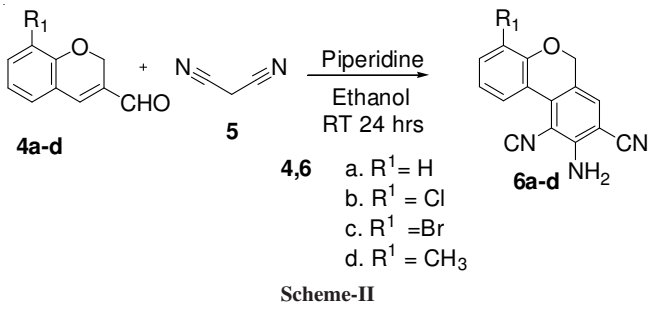
6-Chloro-8-hydroxymethyl-8,9-dihydro-2*H*-furo[2,3-h]-chromene-3-carbaldehydes (3b): Recrystallized from chloroform as colourless needles, m.p. 155 ºC. IR (KBr, ν_{max}, cm^{-1}): 1014 (C-O), 1624 (C=C) and 1664 (C=O). UV (MeOH): 241 nm (log ε 3.7), 263 nm (log ε 3.6) and 348 nm (log ε 3.7). ^{1}H NMR (200 MHz) ($CDCl_3$): δ 2.95 (dd, *J* = 16.0, 8.0 Hz, CH_2-9, H_A), 3.20 (dd, *J* = 16.0, 10.0 Hz, CH_3, H_B), 3.75 (dd, *J* = 16.0, 6.0 Hz, 8-CH_2OH, H_D), 3.90 (dd, *J* = 16.0, 4.0 Hz, 8-CH_2OH, H_E), 5.05 (s, OCH_2-2), 5.36 (m, H-8), 7.00 (d, *J* = 10.0 Hz, H-5), 7.18 (s, H-4), 9.50 (s,CHO). FABMS: m/z 268 (M+1), m/z 266 (M-1).

6-Bromo-8-hydroxymethyl-8,9-dihydro-2*H*-furo[2,3-h]-chromene-3-carbaldehydes (3c): Recrystallized from chloroform as colourless needles, m.p. 160 ºC. IR (KBr, ν_{max}, cm^{-1}): 1014 (C-O), 1624 (C=C) and 1664 (C=O). UV (MeOH): 241 nm (log ε 3.7), 263 nm (log ε 3.6) and 348 nm (log ε 3.7). ^{1}H NMR (200 MHz) ($CDCl_3$): δ 2.95 (dd, *J* = 16.0, 8.0 Hz, CH_2-9, H_A), 3.20 (dd, *J* = 16.0, 10.0 Hz, CH_3, H_B), 3.75 (dd, *J* = 16.0, 6.0 Hz, 8-CH_2OH, H_D), 3.90 (dd, *J* = 16.0, 4.0 Hz, 8-CH_2OH, H_E), 5.05 (s, OCH_2-2), 5.36 (m, H-8), 7.00 (d, *J* = 10.0 Hz, H-5), 7.18 (s, H-4), 9.50 (s,CHO). FABMS: m/z 311 (M+1), m/z 309 (M-1).

8-Hydroxymethyl-8,9-dihydro-6-methyl-2*H*-furo[2,3-h]-chromene-3-carbaldehydes (3d): Recrystallized from chloroform as colourless needles, m.p. 158 ºC. IR (KBr, ν_{max}, cm^{-1}): 1014 (C-O), 1624 (C=C) and 1664 (C=O). UV (MeOH): 241 nm (log ε 3.7), 263 nm (log ε 3.6) and 348 nm (log ε 3.7).^{1}H NMR (200 MHz) ($CDCl_3$): δ 2.95 (dd, *J* = 16.0, 8.0 Hz, CH_2-9, H_A), 3.20 (dd, *J* = 16.0, 10.0 Hz, CH_3, H_B), 3.75 (dd, *J* = 16.0, 6.0 Hz, 8-CH_2OH, H_D), 3.90 (dd, *J* = 16.0, 4.0 Hz, 8-CH_2OH, H_E), 5.05 (s, OCH_2-2), 5.36 (m, H-8), 7.00 (d, *J* = 10.0 Hz, H-5), 7.18 (s, H-4), 9.50 (s,CHO). FABMS: m/z 247 (M+1), m/z 245 (M-1).

General procedure for the synthesis of 9-amino-6*H*-benzochromene-8,10-dicarbonitriles (6a-d)

2*H*-3-Chromene carbaldehyde (3.2 g, 20 mmol) (**4a**) is dissolved in ethanol (20 mL) and piperidine (3 mL) is added and the reaction mixture was stirred for 5 h and then 2.64 g (40 mmol) of malononitrile is added and stirring is continued for 24 h at room temperature. After completion of the reaction, solvent was removed under reduced pressure affording a gum. This on column chromatography over silica gel and elution with petroleum ether:ethylacetate (7:3) gave 9-amino-6*H*-benzochromene-8,10-dicarbonitrile (**6a**) (2.6 g yield) which was recrystallized from chloroform as pale yellow needles m.p. 172 ºC (**Scheme-II**).



Scheme-II

Spectral data

9-Amino-6*H*-benzochromene-8, 10-dicarbonitrile (6a): IR (KBr, ν_{max}, cm^{-1}): 1027 (C-O), 1203 (C=O), 2360 (CN), 3358 (NH_2). UV (MeOH): 255 nm (log ε 4.2), 249 nm (log ε 4.0), 349 nm (log ε 3.7) and 387 nm (log ε 3.9). ^{1}H NMR (200 MHz) ($CDCl_3$ + DMSO): δ 4.86 (s,OCH_2), 6.02 (bs, NH_2), 7.02 (bd, *J* = 10 Hz, H-4), 7.15 (dd, *J* = 10, 10 Hz, H-3), 7.40 (dd, *J* = 10.0, 10.0 Hz, H-2), 7.50 (m, H-2,3,4), 7.45 (s,H-7) 8.38 (dd, *J* = 10.0, 2.0 Hz, H-1). ^{13}C NMR (50.3 MHz) ($CDCl_3$ + DMSO): δ 66.7 (OCH_2-6), 90.5 (C-10), 94.3 (C-8), 116.2 (C≡N, C-10), 116.6 (C=N, C-8), 117.8 (C-4), 120.0 (c-10b), 121.6 (C-6a), 122.2 (C-2), 126.0 (C-3), 132.6 (C-1), 134.3 (C-&), 137.6 (C-10a), 153.8 (C-9) 156.5 (C-4a). MS: m/z 247 (M+) 246 (M-1).

9-Amino-4-chloro-6*H*-benzochromene-8,10-dicarbonitrile (6b): Recrystallized from chloroform as pale yellow needles m.p. 167 ºC. IR (KBr, ν_{max}, cm^{-1}): 2215 (C-N), 2335 (C=O), 3354 (NH_2). UV (MeOH): 241 nm (log ε 4.2), 255 nm (log ε 4.0), 293 nm (log ε 3.7) and 381 nm (log ε 3.9). ^{1}H NMR (200 MHz) ($CDCl_3$ + DMSO): δ 4.90 (s, OCH_2), 6.30 (bs, NH_2), 7.05 (bd, *J* = 10 Hz, H-4), 6.37 (dd, *J* = 10, 10 Hz, H-3), 7.40 (dd, *J* = 10.0, 10.0 Hz, H-1), 7.50 (m, H-2,3,4), 7.55 (s, H-7) 8.38 (dd, *J* = 10.0, 2.0 Hz, H-1). ^{13}C NMR (50.3 MHz) ($CDCl_3$ + DMSO): δ 64.7 (OCH_2-6), 94.5 (C-10), 95.3 (C-8), 116.2 (C=N, C-10), 116.6(C=N, C-8), 119.0 (c-10b), 126.6 (C-6a), 122.2 (C-2), 129.0 (C-3), 132.6 (C-1), 134.3 (C-2), 137.6 (C-10a), 153.4 (C-9) 156.5 (C-4a). MS: m/z 281 (M^+), 217, 189, 164 and 138.

9-Amino-4-bromo-6*H*-benzochromene-8,10-dicarbonitrile (6c): Recrystallized from chloroform as pale yellow needles m.p. 164 ºC. IR (KBr, ν_{max}, cm^{-1}): 1018 (C-O), 1210 (C=O), 1322 (NH_2). UV (MeOH): 249 nm (log ε 4.6), 296 nm (log ε 4.4), 337 nm (log ε 4.2) and 383 nm (log ε 4.5). ^{1}H NMR (200 MHz) ($CDCl_3$ + DMSO): δ 4.90 (s, OCH_2), 5.32 (bs, NH_2), 7.00 (bd, *J* = 10 Hz, H-4), 7.55 (dd, *J* = 10, 10 Hz, H-3), 7.50 (m, H-2,3,4), 7.45 (s,H-7) 8.55 (dd, *J* = 10.0, 2.0 Hz, H-1). ^{13}C NMR (50.3 MHz) ($CDCl_3$ + DMSO): δ 67.2 (OCH_2-6), 95.6 (C-10), 95.8 (C-8), 116.0 (C=N, C-10), 116.2 (C=N, C-8), 119.8 (c-10b), 126.6 (C-6a), 120.2 (C-2), 135.0 (C-3), 132.6 (C-1), 134.3 (C-2), 135.6 (C-10a), 153.8 (C-9) 156.5 (C-4a). MS: m/z 326 (M^+), 218, 189, 164.

9-Amino-4-methyl-6*H*-benzochromene-8,10-dicarbonitrile (6d): Recrystallized from chloroform as pale yellow needles m.p. 152 ºC. IR (KBr, ν_{max}, cm^{-1}): 2211 (C=N), 2344 (CN), 3367 (NH_2). UV (MeOH): 244 nm (log ε 4.1), 302 nm (log ε 3.7), 336 nm (log ε 3.5) and 383 nm (log ε 3.8). ^{1}H NMR (200 MHz) ($CDCl_3$ + DMSO): δ 2.25 (s, 4-CH_3), 4.89 (s, OCH_2), 6.30 (bs, NH_2), 7.05 (bd, *J* = 10 Hz, H-2), 7.25 (dd, *J* = 10, 10 Hz, H-3), 7.58 (s, H-7) 8.18 (dd, *J* = 10.0, 2.0 Hz, H-1). ^{13}C NMR (50.3 MHz) ($CDCl_3$ + DMSO): δ 18.2 (4-CH_3), 67.8 (OCH_2-6), 92.4 (C-10), 95.2 (C-8), 116.0 (C=N, C-8), 120.8 (c-10b), 123.6 (C-6a), 124.2 (C-2), 127.0 (C-3), 132.4 (C-1), 136.6 (C-10a), 153.4 (C-9) 155.8 (C-4a). MS: m/z 261 (M^+), 232, 199, 130.

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