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Facile synthesis of 8-Hydroxymethyl-8,9-Dihydro-2h-Furo[2,3-H] Chromene-3-Carbaldehyde

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ABSTRACT

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

Introduction

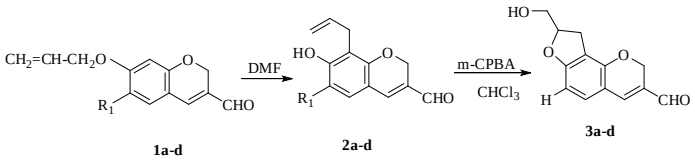
Chromones and isoflavones constitute an important class of oxygen heterocyclics. Substituted as well as heterocyclic ring fused chromones and isoflavones have a wide range of pharmacological activity. Chromones and isoflavones with medicinal use are Khellin a coronary vasodilator. Chromones-2-carboxylate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

With a view synthesize new heterocyclic ring fused chromones and isoflavones we studied the knoevenagel condensation of 8-formyl-7-hydroxychromones and isoflavones. Literature shows that knoevenagel condensation reaction of 2-Hydroxy benzaldehyde proceeds via acrylo intermediate to gives rise to either three substituted 2-H chromones. Selective formation of 2-hydroxy benzaldehyde depends on solvent and structural features of substrate.

Result and discussions:

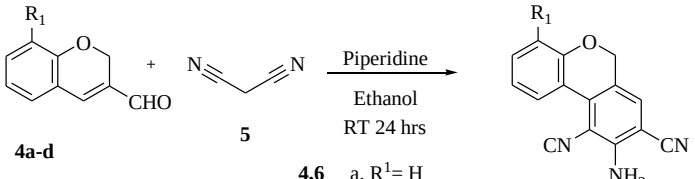
Synthesis of 8-hydroxymethyl-8, 9-dihydro-2H-furo[2,3-h] chromene-3-carbaldehyde (3a-d): Equimolar amounts of 7-hydroxy-8-allyl-2H-3-chromene carbaldehyde (2a) and m-CPBA in chloroform on heating for 6 hrs. Chloroform was removed by distillation and the product column chromatography and elution with Pet. ether to give quantitatively 8-hydroxymethyl-8,9-dihydro-2H-furo[2,3-h] chromene-3-carbaldehyde (3a) . In its IR (3a) C=C of chromone appeared at 1624 cm^{-1}. C-O appeared at 1014 cm^{-1} the aldehyde C=O appeared at 1664 cm^{-1}.UV (MeOH) spectrum showed bands at 241 nm, (log ε 3.7) 263 nm (log ε 3.6), 348 nm (log ε 3.7). In the ^{1}H NMR (200 MHz $CDCl_3$), spectrum recorded the benzylic 9-CH_2 protons which are diastereotopic in nature appeared ABq x 2. One of these methylene appeared as double doublet at δ 3.20 (J=1.0 Hz).

Scheme-1



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

Scheme-2



4,6 a. R^1= H
b. R^1 = Cl
c. R^1 =Br
d. R^1 = CH_3

Meterial 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-hydroxymethyl-8,9-dihydro-2H-furo[2,3-h]chromene-3-carbaldehydes(3a-d)

i. 8-hydroxymethyl-8,9-dihydro-2H-furo[2,3-h]chromene-3-carbaldehydes(3a)

7-Hydroxy-8-allyl-2H-3-chromenecarbaldehyde (2a) (2.16g, 10mmol), m-CPBA (1.62g) (10mmols) were dissolved in dry $CHCl_3$ (25 ml) and refluxed for 6 hrs. After cooling to room temperature, the separated m-chlorobenzoic acid was filtered. The filtrate was washed with aq $NaHCO_3$ (2%, 3 X 100 ml) to remove traces of m-chlorobenzoic acid and then with

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water (2 X 100 ml) dried and concentrated. The residue on chromatography over silica gel by eluting with pet.ether:ethylacetate (8:2) gave 8-hydroxymethyl-8,9-dihydro-2H-furo[2,3-h]chromene-3-carbaldehyde (3a) (1.2g) (51% yield), which was recrystallised from chloroform as colorless needles, m.p 150 ºC

IR (KBr): 1014 cm^{-1} (C-O), 1624 cm^{-1} (C=C) and 1664 cm^{-1} (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, 8.0Hz, CH_2-9, H_A), 3.20 (dd, J=16.0, 10.0Hz, 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=10.0Hz, H-5), 7.18(s, H-4), 9.50(s,CHO).

FABMS: m/z 233 (M+1), m/z 231 (M-1).

Employing a similar procedure as mentioned for 3a, compounds 3b-d was obtained from 2b-d as solids 50-60% yield.

ii. 6-Chloro-8-hydroxymethyl-8,9-dihydro-2H-furo[2,3-h]chromene-3-carbaldehydes(3b)

Recrystallised from chloroform as colorless needles, m.p 155 ºC

IR (KBr): 1014 cm^{-1} (C-O), 1624 cm^{-1} (C=C) and 1664 cm^{-1} (C=O).

UV (MeOH): 241 nm (log ε 3.7), 263nm (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, 8.0Hz, CH_2-9, H_A), 3.20 (dd, J=16.0, 10.0Hz, 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=10.0Hz, H-5), 7.18(s, H-4), 9.50(s,CHO).

FABMS: m/z 268 (M+1), m/z 266 (M-1).

iii. 6-Bromo-8-hydroxymethyl-8,9-dihydro-2H-furo[2,3-h]chromene-3-carbaldehydes(3c)

Recrystallised from chloroform as colorless needles, m.p 160 ºC

IR(KBr): 1014 cm^{-1} (C-O), 1624 cm^{-1} (C=C) and 1664 cm^{-1} (C=O).

UV (MeOH): 241 nm (log ε 3.7), 263nm (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, 8.0Hz, CH_2-9, H_A), 3.20 (dd, J=16.0, 10.0Hz, 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=10.0Hz, H-5), 7.18(s, H-4), 9.50(s,CHO).

FABMS: m/z 311 (M+1), m/z 309 (M-1).

iv. 8-hydroxymethyl-8,9-dihydro-6-methyl-2H-furo[2,3-h]chromene-3-carbaldehydes(3d)

Recrystallised from chloroform as colorless needles, m.p 158 ºC

IR (KBr): 1014 cm^{-1} (C-O), 1624 cm^{-1} (C=C) and 1664 cm^{-1} (C=O).

UV (MeOH): 241 nm (log ε 3.7), 263nm (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, 8.0Hz, CH_2-9, H_A), 3.20 (dd, J=16.0, 10.0Hz, 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=10.0Hz, 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-6H-benzochromene-8,10-dicarbonitriles (6a-d)

i. 9-amino-6H-benzochromene-8, 10-dicarbonitrile (6a)

2H-3-Chromene carbaldehyde (3.2g, 20mmol) (4a) is dissolved in ethanol (20ml) and piperidine (3ml) is added and the reaction mixture was stirred for 5 hrs and then 2.64g (40 mmol) of malononitrile is added and stirring is continued for 24 hrs 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-6H-benzochromene-8,10-dicarbonitrile (6a) (2.6g yield) which was recrystallised from chloroform as pale yellow needles m.p 172 ºC.IR (KBr): 1027 cm^{-1} (C-O), 1203 cm^{-1} (C=O), 2360 cm^{-1} (CN), 3358 cm^{-1} (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, 10Hz, 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).

Employing a similar procedure as mentioned for 6a, compounds 6b-d was obtained from 4b-e as solids in 50-60% yield.

ii. 9-amino-4-chloro-6H-benzochromene-8,10-dicarbonitrile (6b)

Recrystallised from chloroform as pale yellow needles m.p 167 ºC.

IR (KBr): 2215 cm^{-1} (C-N), 2335 cm^{-1} (C=O), 3354 cm^{-1} (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, 10Hz, 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.

iii. 9-amino-4-Bromo-6H-benzochromene-8,10-dicarbonitrile (6c)

Recrystallised from chloroform as pale yellow needles m.p 164 ºC.

IR (KBr): 1018 cm^{-1} (C-O), 1210 cm^{-1} (C=O), 1322 cm^{-1} (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, 10Hz, 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.

iv. 9-amino-4-Methyl-6H-benzochromene-8,10-dicarbonitrile (6d)

Recrystallised from chloroform as pale yellow needles m.p 152 ºC.

IR (KBr): 2211 cm^{-1} (C≡N), 23444 cm^{-1} (CN), 3367 cm^{-1} (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, 10Hz, 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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