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Synthesis of 3-benzo[d] [1, 3[thiazo-yl-2h-chromones and 3-(1h-benzo[d] imidazol-2-yl)-2h-6-bromochromones

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ABSTRACT

2H-3-chromenecarbaldehydes (**5a-e)** on reaction with o-amino thiophenol **(6)** gave 3- benzo [d][1,3]thaizol-2yl-2H-chromenes **(7a-e)** and 6-bromo-2H-3-chromenecarbaldehyde **(5c)** on reaction with different ary1 or hetery1 1,2 diamines gave 3-(1H-benzo[d]imidazol-2-yl)-2H-6-bromo chromenes **(9a-d)** in good yields.

Keywords: bromochromones, synthesis

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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[1-5]. Chromones -2-carboxylate spasnolitic agent and disodium chromo glycate and anti elergitic drug[5-7]. Genstein having estrogen hormonal activity, and 7- isopropoxy flavones for treatment of postmenopausal and senile osteoporosis.

Substituted chromanones and chromenes show a variety of biological activity, such as dopamine antihypertensive, ATP sensitive potassium channel openers antitumor and gastro protective agent[9-10]. In the present study new 2-aminothiophenol to give a Schiff base which cyclises to give Aerial oxidation gives rise to 3-benzo[d] [1, 3] thiazol-2-yl-2H-chromenes.

EXPERIMENTAL

General: -

Melting points were determined in a sulfuric acid-bath and are uncorrected. IR spectra were recorded in KBr on a Shimadzu 435 spectrometer, ^{1}H NMR spectra on a Varian Gemini 200 MHz spectrometer with TMS as an internal standard and mass spectra on a Perkin Elmer Hitachi RDO-62 and MS-30 instrument.

Section-A:

General procedure for the synthesis of benzo[d][1,3] thiazol-2-yl-2H-chromones(7a-e) To a solution of 2H-3-chromene carbaldehyde **(5a) (**3.2g) (20 mmol) in 10 mL of absolute ethanol, 4-5 drops of glacial acetic acid and o-aminothiophenol **(6)** (2.5g, 20mmol) were added. The mixture was refluxed for 8 hrs. Then the excess of ethanol was removed by distillation under reduced pressure and the residue was treated with crushed ice (100g) and extracted three times with ethyl acetate (40mL) and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure affording a solid. This was subjected to column chromatography with silica gel and elution with petroleum ether. Ethy1acetate (9:1) gave 3-benzo[d] [1, 3] thiazol-2-yl-2H-chromene **(7a)** (2.5g) (47% yield). It was recrystallised from chloroform as pale yellow needles mp.156 ºC, similarly **(7b-e)** prepared.

i) 3- Benzo[d] [1, 3] thiazol-2-yl-chromene **(7a):**

IR (KBr): 1600 cm^{-1} (C=N).
UV: 245 nm (log ε 3.9), 314 nm (log ε 3.8) and 369 nm (log ε 4.0)
^{1}H NMR (200 MHz) ($CDC1_3$): δ5.42 (s, OCH_2), 6.88 (m, H-6, 8), 7.10-7.50 (m, H-5, 7, 5, 6, 4), 7.85 (dd, J=10.0, 2.0 Hz, H-7) and 7.98 (dd, J=10.0, 2.0 Hz, H-4).

^{13}C NMR (50.3MHz) ($CDC1_3$): δ 65.4 (C-2), 115.8 (C-3), 121.0 (C-8). 121.2(C-7), 122.6 (C-6), 125.4 (C-4), 126.0 (C-5), 128.8(C-4a, 7a), 128.9 (C-7), 129.0(C-5, 6), 130.4 (C-4), 134.0(C-3a), 153.4(C-8a) and 154.5 (C-2a).
MS: m/z 265 (M^+) (35), 236 (35)160 (15%) and 149 (100).

ii) 3-Benzo[d] [1, 3] thiazol-2-yl-2H-6-chlorochromene **(7b):**

Recrystallised from chloroform as colourless needles, mp. 121 °C

IR (KBr): 1612 cm^{-1} (C=N).
UV (MeOH): 250 nm (log ε 4.03), 315 nm (log ε 4.01) and 374 nm (log ε 4.07).
^{1}H NMR (200 MHz) ($CDC1_3$): δ 5.40(s, OCH_2), 6.80 (d, J=10.0 Hz, H-8), 7.12 (s, H-4) 7.15 (m, H-5, 7), 7.85 (dd, J=10.0, 2.0 Hz, H-7), 7.40 (m, H-5, 6) and 7.98 (dd, J=10.0, 2.0Hz, H-4).
^{13}C NMR (50.3 MHz) ($CDC1_3$): δ 64.2 (C-2), 116.2 (C-4a,7a), 119.2 (C-4), 120.0 (C-8), 124.6 (C-7), 129.4 (C-5,6), 130.2 (C-6), 131.2(C-4), 132.4 (C-5), 134.4 (C-7), 135.2 (C-3), 138.2 (C-3a), 144.2 (C-8a) and 149.8 (C-2a).
MS: m/z 299 (M^+), 270 and 236.

iii) 3-Benzo [d] [1, 3] thiazol-2-yl-2H-6-bromochromene **(7c):**

Recrystallised from chloroform as pale yellow needles, mp.112 °C.

I.R (KBr): 1608 cm^{-1} (C=N)
UV (MeOH): 284 (log ε 4.1), 306 nm (log ε 4.2) and 370 (log ε 4.0).
^{1}H NMR (200 MHz) ($CDC1_3$): δ 5.38(s, OCH_2), 6.75 (d, J=10.0Hz, H-8), 7.10 (s, H-4), 7.22 (m, H-5, 7), 7.35 (m, H-5, 6) 7.82 (dd, J=10.0, 2.0 Hz, H-7), 7.95 (dd, J=10.0, 2.0 Hz, H-4).
^{13}C NMR (50.3 MHz) ($CDC1_3$): δ 64.0 (C-2), 121.4 (C-8), 122.0 (C-7(, 124.2(C-4a,7a), 126.4 (C-4), 128.2 (C-4), 129.8 (C-5,6), 130.0 (C-6), 132.0 (C-5), 133.6 (C-7), 135.2 (C-3), 138.4(C-3a), 146.2 (C-8a) and 151.2(C-2a).
MS: m/z 343 (M^+).

iv) 3-Benxo[d] [1, 3] thiazol-2-yl-2H-8-chlorochromene **(7d):**

Recrystallised from chloroform as colourless needles, mp 126 °C
IR (KBr): 1614 cm^{-1} (C=N).
UV (MeOH): 242 nm (log ε 4.1), 289 nm (log ε 4.1) and 356 nm (log ε 4.0)
^{1}H NMR (200 MHz) ($CDC1_3$): δ 5.45 (s, OCH_2), 6.80-7.15(m, H-5, 6, 7), 7.15 (s, H-4) 7.40(m, H-5, 6), 7.80 (dd, J=10.0, 2.0Hz) and 7.94(dd, J=10.0, 2.0Hz, H-4).
^{13}C NMR (50.3 MHz) ($CDC1_3$): δ 63.4 (C-2), 121.6 (C-8), 122.4 (C-4a,7a), 124.0 (C-7), 126.2 (C-4), 126.4 (C-5), 128.2(C-6), 129.6 (C-5,6), 131.8(C-4),132.2 (C-7), 134.0(C-3), 136.2(C-3a), 142.2 (C-8a) and (148.2(C-2a).
MS: m/z 299 (M+).

v) 3-Benzo[d] [1, 3] thiazol-2-yl-2H-5-ethoxychromene **(7e):**

Recrystallised from chloroform as colourless needles, mp116 °C
IR (KBr): 1608 cm^{-1} (C=N).
UV (MeOH): 248 nm (log ε 4.0), 274nm (log ε 4.1) and 367 nm (log ε 4.2).
^{1}H NMR (200 MHz) ($CDC1_3$) δ 1.45 (t,J=7.0 Hz, CH_3), 4.05 (q, J=7.0 Hz, OCH_2), 5.4 (s,OCH_2), 6.78 (m,H-6,7,8), 7.12(s,H-4), 7.35(m,2H,H-5',6), 7.78 (dd, J=10.0,2.0Hz,H-7), 7.94 (dd, J=10.0,2.0 Hz,H-4).
^{13}C NMR (50.3MHz($CDC1_3$); δ 14.6(CH_3), 63.0(OCH_2CH_3), 65.0 (C-2), 117.2 (C-3), 119.2 (C-8), 120.2 (C-6), 123.4(C-7), 124.4 (C-7), 127.2 (C-4), 128.2 (C-5), 130.2 (C-6), 130.4 (C-4a,7a), 132.6 (C-3a), 138.2 (C-4), 140.2 (C-5), 140.2 (C-5), 145.2 (c-8a) and 151.2 (C-2a).
MS: m/z 309 (M^+).

Section-B: General Procedure for the synthesis of 3-(4, 7-Dimethy1-benzo[d]imidazol-2-yl)-2H-6-bromochromenes (9a-d):

i) 3-(4, 7-Dimethy1-1H-benzo[d]imidazol-2-yl)-2H-6-bromochromene **(9a):**

To a solution of 6-bromo-2H-3-chromenecarbaldehyde **(5c)** (4.76g)(20 mmol) in glacial acetic acid (20mL) and 3,6-dimethy1,2-benzenediamine **(8a**) (2.27g) (20 mmol) were added and stirred at room temperature for 30 minutes and then refluxed on oil bath for 6 hrs. Then the excess of acetic acid was removed by distillation under reduced pressure and the residue obtained was treated with of crushed ice (50g), the solid obtained was filtered and subjected to column chromatography with 60-120 mesh silica gel and this on elution with petroleum ether: ethy1acetate (7:3) gave 3- (4,7-dimethy1-1H-benzo[d]imidazol-2-yl)-2H-6-bromochromene **(9a**) (3.8g) (yield 55%). It was recrystallised from methanol as pale yellow needles, mp 152 ºC, similarly **(9b-d)** prepared.

IR (KBr): 1654 cm^{-1} (C=N) and 3421 cm^{-1} (N-H).
UV (MeOH) 254 nm (log ε 4.0) 260 nm (log ε 3.8) and 323 nm (log ε 4.1)
^{1}H NMR (200 MHz) ($CDC1_3$+DMSO-d_6): δ 2.35 (s, CH_3), 5.30 (s, OCH_2), 6.80 (d, J=10.0 Hz, H-8), 7.25 (s, H-4), 7.20-7.40 (m, H-7, 5'6), 12.4 (BS, NH).
^{13}C NMR (50.3 MHz) ($CDCl_3$ + DMSO-d_6): δ 19.9 (CH_3-4,5)64.8(OCH_2-2), 84.8 (C-3), 112.8(C-6)117.2 (C-7,8), 121.4 (C-4), 123.9(C-6) 124.0(C-5)129.4(C-4,5), 131.6 (C-7a), 131.9(C-7),147.4(C-3a), 152.4 (C-8a) and 167.9 (C-2).
MS: m/z 354 (M^+) (100), 327 (77), 247(21), 231 (10) and 171(29).

ii) 3-(1H-Benzo[d]imidazol-2yl)-2H-6-bromochromene **(9b):**

Recrystallised from methanol as pale yellow needles, mp154 °C
IR (KBr) 1636 cm^{-1} (C=N) and 3483 cm^{-1} (N-H).
UV (MeOH) 246 nm (log ε 4.2) 272 nm (log ε 4.3) and 326 nm (log ε 4.4)
^{1}H NMR (200 MHz) ($CDC1_3$ + DMSO-d_6) δ 5.30 (s, OCH_2) 6.75 (d, J=10.0 Hz, H-8), 7.20 (m, H-7, 5, 6), 7.30 (s, H-4) 7.35 (s, H-), 7.45 (dd, J=10.0, 2.0 Hz, H-7), 12.62 (bs, NH).

^{13}C NMR ($CDC1_3$ + DMSO-d_6): δ 63.5 (OCH_2-2), 101.5 (C-6), 116.0 (C-7, 8), 119.4 (C-4), 122.4 (C-5, 6), 127.9 (C-4, 5), 130.4 (C-7,7a0, 146.4 (C-3a), 151.4 (C-8a) and 168.0 (C-2).
MS: m/z 326 (M^+) 225, 144 and 115.

iii) 3-(6-Bromo-1H-pyridyl[d]imidazol-2-yl) -2H-6-bromochromene **(9c):**

Recrystallised from methanol as pale yellow needles, mp132 °C
IR (KBr): 1654 cm^{-1} (C=N) and 3567 cm^{-1} (N-H).
UV (MeOH):254 nm (log ε 3.8), 264 nm (log ε 3.7) and 303 nm (log ε 3.7) and 303nm (log ε 3.6)
^{1}H NMR (200 MHz) ($CDC1_3$ + DMSO-d_6) δ 5.20 (s, OCH_2) 6.75 (dd, J=10.0, 2.0 Hz, H-8), 7.00 (m,H-6), 7.30 (H-4), 7.40 (M, H-7), 7.70 (m, H-5), 7.90 (d, J=2.0Hz, H-7) 8.32 (bs, H-5), 12.40 (bs, NH).
^{13}C NMR (50.3 MHz) ($CDC1_3$ + DMSO-d_6): δ 64.0 (OCH_2), 106.2 (C-3), 117.2 (C-6), 124.4 (C-8), 129.8 (C-4), 131.0(C-6), 131.2 (C-5), 132.0(C-4,5), 133.0 (C-7), 134.0 (C-7a), 146.0 (C-3a), 156 .4 (C-8a) and 167.2 (C-2).
MS: m/z 409 (M^+) (100), 392,238,209 and 198.

iv) 3-(6-Nitro-1H-benzo[d]imidazol-2-yl)-2H-6-bromochromene **(9d):**

Recrystallised from methanol as pale yellow needles, mp 132 °C.
IR (KBr): 1626 cm^{-1} (C=N) and 3324 cm^{-1} (N-H).
UV (MeOH) 248 nm (log ε 4.0), 259 nm (log ε 4.1) and 301nm (log ε 3.9)
^{1}H NMR (200 MHz) ($CDC1_3$ + DMSO-d_6): δ 5.32 (s, OCH_2), 6.78 (d, J=10.0Hz, H-8), 7.30 (m, H-7), 7.35 (H-4), 7.40 (H-5), 7.60 (m, H-4), 8.10 (m, H-5), 8.50 (bs, H-7), 12.50 (bs, NH).
^{13}C NMR (50.3 MHz) ($CDC1_3$ + DMSO-d_6): δ 64.8 (OCH_2), 80.8 (C-3), 105.0 (C-6), 123.5 (C-8), 124.4 (C-4), 127.5 (C-6), 128.0 (C-5), 130.2 (C-4,5), 133.8 (C-7,7a), 143.6 (C-3a), 153.5 (c-8a) and 164.4 (c-2).
MS: m/z 372 (M^+) (100), 355, 218, 200 and 137.

RESULTS AND DISCUSSIONS

Synthesis of 3-benzo[d] [1, 3] thiazol-2yl-2H-chromones (7a-e)

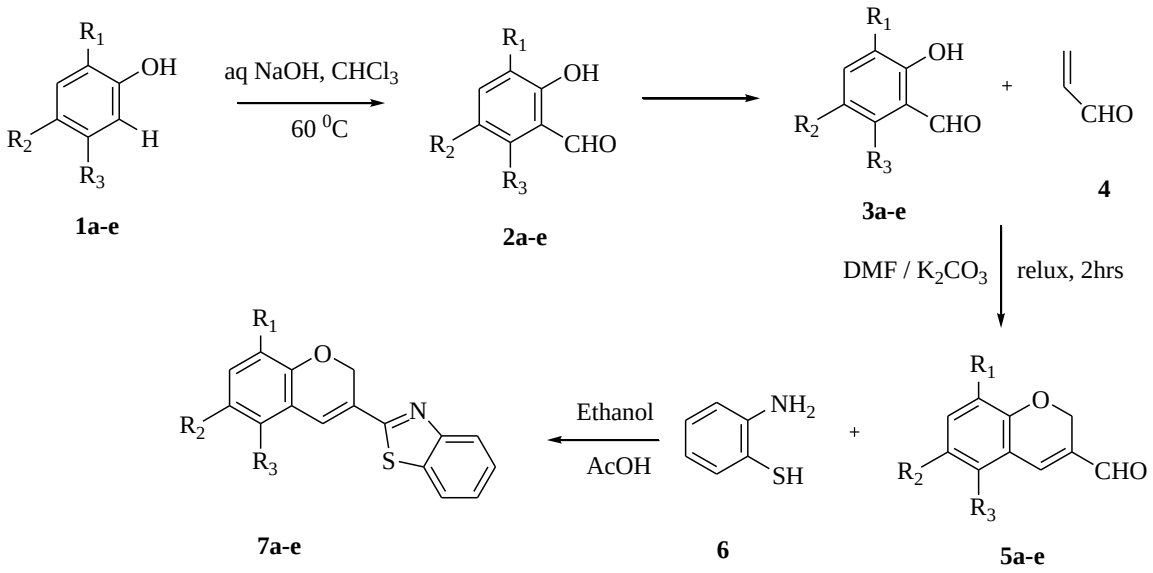
Equimolar quantities of 2H-3-chromene carbaldehyde **(5a**) and o-aminothiophenol **(6)** taken in ethanol containing a few drops of acetic acid on heating gave 3-benzo[d][1,3] thiazol -2-yl-2H-chromene **(7a).** It is characterized from its analytical and spectral data In the IR spectrum of 3-benzo[d] [1,3] thiazol -2-yl-2H-chromene **(7a),** C=N absorption is observed at 1600 cm^{-1}. Its UV spectrum showed bands at 245nm (log ε3.9) 314 nm (log ε 3.8) and 369 nm (log ε 4.0) indication an extended conjugation between the two heterocyclic systems. In its ^{1}H NMR the signals due to the thiazol-2-yl ring system appeared as follows H-4 appeared at δ 7.98 as a double doublet, J=10.0, 2.0 Hz while H-7 appeared at 7.85 as a multiplet. The two other aromatic protons H-5' and 6' appeared in the region 7.10-7.50 as a multiplet. The chromene ring protons showed the signals at expected positions, H-4 appeared as a singlet at 7.20. The

methylene protons at C-2 appeared as a singlet at δ 5.42 H-6,8 appeared at δ 6.88 as multiplet and H-5, 7 appeared as multiplet in the region δ 7.10-7.50.

In its ^{13}C NMR spectrum showed the signals due to the benzothiazole moiety at δ154.5 (C-2a), 134.0 (C-3a), 129.0 (C-5, 6), 128.8 (C-7a), 125.4 (C-4) and 121.2 (c-7). The signals due to the chromene ring system are assigned as follows: δ153.4 (C-8a), 130.4 (C-4), 128.9(C-7), 128.8 (C-4a), 126.0 (C-5), 122.6 (C-6), 121.0 (C-8), 115.8 (C-3) and 65.4 (C-2).
The MS of **7a** showed the M^+ at m/z 265 (35%). The base peak in the spectrum appeared at 149 (100). Other prominent ions in the spectrum are a t 236 (35%), 160 (15%).

The mechanic pathway of 2H-3-chromene carbaldehyde **5c** reacts with the 2-aminothiophenol **1** to give a Schiff base **10** which cyclises to give **11.** Aerial oxidation of **11** gives rise to 3-benzo[d] [1,3]thiazol-2-yl-2H-chromene **(7a)** (**Scheme-3**).

Section-A: Scheme-1



1,2,3,5,7, a = $R_1 = R_2 = R_3 = H$
b = $R_1 = H$, $R_2 = Cl$, $R_3 = H$
c = $R_1 = H$, $R_2 = Br$, $R_3 = H$
d = $R_1 = Cl$, $R_2 = H$, $R_3 = H$
e = $R_1 = H$, $R_2 = H$, $R_3 = OEt\ H$

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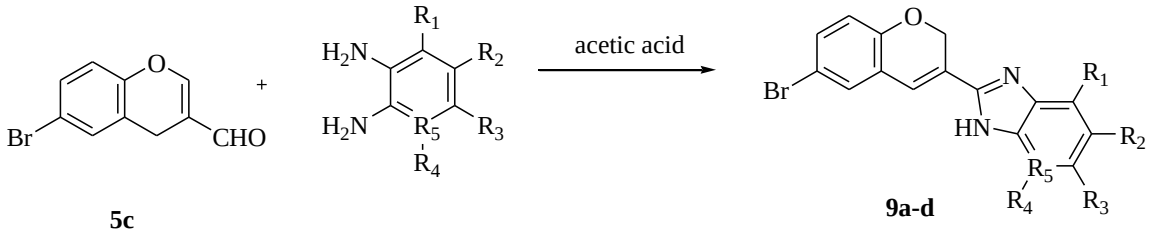
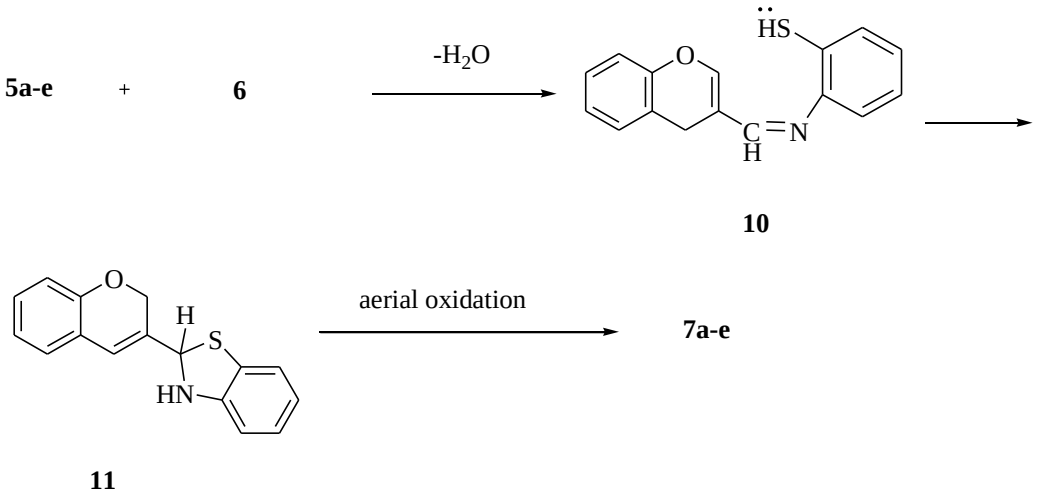
Section-B: Scheme-2



5c **8a-d** **9a-d**

8,9 **a** = $R_{1=}$ CH_3, R_2 =H R_3= H, R_4 = CH_3, R_5 = C
b = $R_{1=}$ H, R_2 =H R_3= H, R_4 = H, R_5 = C
c = $R_{1=}$ H, R_2 =Br, R_3= H, R_4 = H, R5 =N
d = $R_{1=}$ H, R_2 =H R_3=NO_2, R_4 = H, R_5 = C

Scheme-3



10 **11**

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