ISSN: 0975-766X
Research Article
Available Online through
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SYNTHESIS OF 9' CYANO PYRANO [2, 3-F] 2'3' DI HYDROFURANO CHROMONES.

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Received on 12-02-2011 *Accepted on 24-02-2011*

Abstract:

The Baylis-Hillmann reaction of 8-formyl-7-hydroxychromones and isoflavones on react with acrylonitrile in DABCO/$CHCl_3$ medium under nitrogen atmosphere at room temperature gives 9 cyano pyrano [2, 3-f] chromones (4a-h) in good yields.

Introduction:

Chromones and isoflavones constitute an important class of oxygen heterocyclics. Substituted as well as heterocyclic ringfused 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.[6-8] Genstein having estrogen hormonal activity,[9-10] 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 Duff's reaction of 8-formyl-7-hydroxychromones and isoflavones. Literature shows that Baylis Hillmann reaction of 2-Hydroxy benzaldehyde proceed via acrylo intermediate to gives rise to either three substituted 2-H chromones. Selective formation of 2-hydroxy benzoldehyde depends on solvent and structural features of substrate.

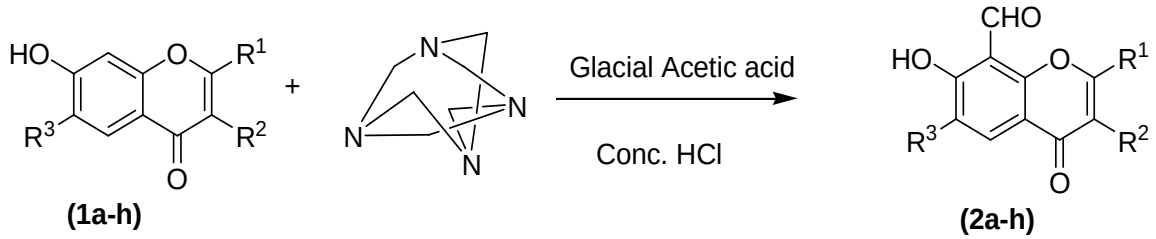
Results and Discussions:

Synthesis of 9-cyano pyrano [2, 3-f] chromones (4a-h): Baylis-Hillmann reaction[11-16] of 8-formyl-7-hydroxychromones (**2a-h**).

Equimolar amounts of 8-Formyl-7-hydroxychromones **(2a)** and acrylonitrile, 1,4-diazobicyclo [2,2,2]-Octane(DABCO) in chloroform stirred at room temperature under nitrogen atmosphere for 60 hrs. Chloroform was removed by distillation and the product column chromatography and elution with Pet. ether to give quantitatively 9-cyano pyrano-[2, 3-f] chromones. Similarly **4b-h** were prepared. In it's IR **(4a)** C=O of chromone appeared at 1620 cm^{-1}**.** CN appeared at 2212.2cm^{-1} .UV (MeOH) spectrum showed bands at 302 nm, (log ε 3.8) 289 nm. (Log ε 4.0), 245nm (log ε 4.2). In the ^{1}H NMR (200 MHz $CDCl_3$), spectrum recorded in the 8-OCH_2 group of the new ring system appeared as doublet at δ 5.15 (J=1.0 Hz) due to allylic coupling with C_{10}-H. C_{10}-H appeared as broad singlet at δ 7.77. These signals suggest that a new pyran ring is formed at 7,8 positions of the 2, 3-dimethyl chromone. Other signals are from the original 2, 3-dimethyl-chromone moiety. The C_2-CH_3, C_3-CH_3 protons appeared as a singlet at δ 2.5, δ 2.1. C_5-H appeared as doublet at δ 8.19. (J= 9.0Hz) and C_6-H appeared as a doublet at δ 6.92 (J=9.0Hz). Analytical and spectral data of **(4a-h),** given experimental section.

The mechanic pathway of (**2a-4a**) is shown in **scheme-3**, **2a** under the room temperature condition of the Michael reaction generates, which reacts with the formyl group of the 2, 3-Dimethyl chromones to give an intermediate. The Intramolecular neucleophilic substitution involving the 7-OH of 2, 3-Dimethyl chromone leads to the removal of the DABCO and Pyrin ring foprmation. The loss of water in presence of DABCO gives rise to Pyrano [2, 3-f] 2,3 di methyl chromones.

Scheme-1

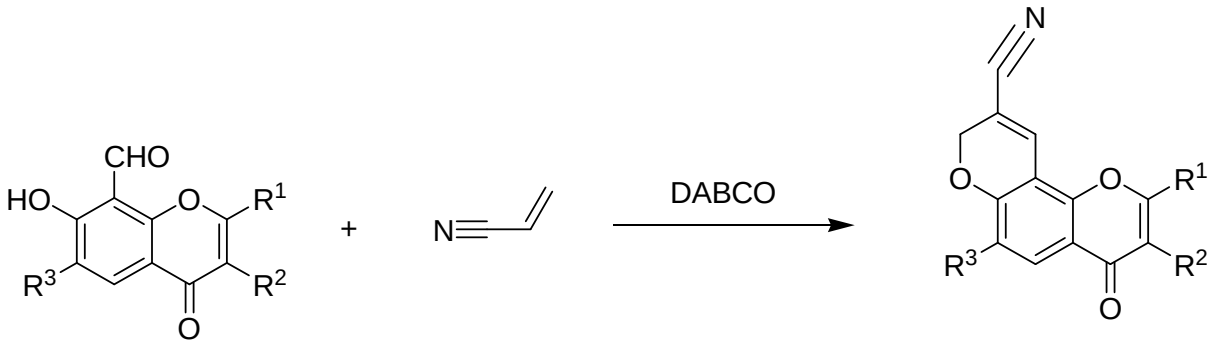


(1a-h) **(2a-h)**

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

e. R^1 = CH_3, R^2 = Ph, R^3 = H
f. R^1 = CH_3, R^2 = Ph, R^3 = Cl
g. R^1 = CH_3, R^2 = Ph, R^3 = Br
h. R^1, R^3 = CH_3, R^2 = Ph

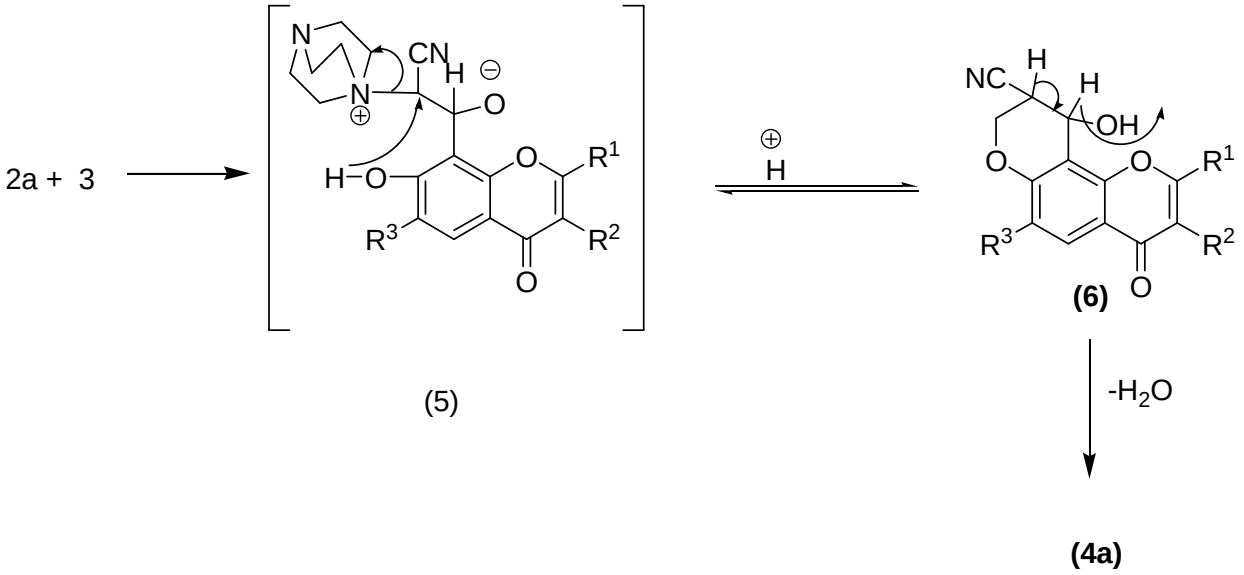
Scheme-2



(2a-h) **(3)** **(4a-h)**

2,4= a. R^1, $R^2 = CH_3$, R^3 = H
b. R^1, $R^2 = CH_3$, R^3 = Cl
c. R^1, $R^2 = CH_3$, R^3 = Br
d. R^1, R^2, $R^3 = CH_3$
e. $R^1 = CH_3$, R^2 = Ph, R^3 =H
f. $R^1 = CH_3$, R^2 = Ph, R^3 =Cl
g. $R^1 = CH_3$, R^2 = Ph, R^3 =Br
h. R^1, $R^3 = CH_3$, R^2 = Ph

Scheme-3



(5) **(6)** **(4a)**

Experimental Section (4a-h):

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.

General procedure for the synthesis of 9-cyano pyrano [2, 3- f] chromones (4a-h).

7-hydroxy and 8-formyl-7-hydroxychromones (**1a-h&2a-h**) were synthesized following literature methods[17-20].

8-Formyl-7-hydroxy-2,3-di methyl chromone (**2a**)(3g),acrylonitrile(0.5ml), 1,4-diazobicyclo [2, 2, 2] octane (DABCO), (0.5 g), dissolved in chloroform was stirred at room temperature under nitrogen atmosphere in for 60 hours. After the chloroform was removed by distillation and the product on column chromatography and elution with petroleum ether, ethyl acetate 9:1 to give 9-cyano-pyrano [2, 3-f] 2,3-di methyl chromone (**4a**)(2.3g) 65-75% yield was recrystallised from chloroform. MP 176 ^{0}C. Similarly (**4b-h**) were prepared.

i) 9-cyano pyrano [2,3-f] 2, 3-di methyl chromone (4a): Mp.176 ºC, yield75%.

IR: (KBr**);** C=O chromone 1620cm^{-1}, CN 2212.2cm^{-1} UV :(MeOH); 302 nm, (log ε 3.8) 289 nm. (Log ε 4.0), 245 nm (log ε 4.2).^{1}H NMR: (200 MHz $CDCl_3$): δ 2.5 (H-2, s); δ 2.1 (H-3, s,); δ 8.19 (H-5, d, J = 9Hz); δ 6.92 (H-6, d, J = 9Hz); δ 5.15 (OCH_2, s, J = 1.O Hz); δ 7.77 (H-10, bs, J = 9 Hz).^{13}C NMR**:** δ 117.5 (CN); 65 (OCH_2); 132.31 (C-9); 131.2 (C-10); 174.91 (C-4); 158.55(C-6a); 153.21(C-10b); 151.5(C-2); 125.56(C-3); 118.1(C-4a); 125.66(C-5); 108(C-6); 115.01(C-10a); 21.5 C2-CH_3; 18.3 C-3-CH_3.

Mass (EIMS): M•$^+$ m/z 253, 252(M-1), 238, 224, 210, 200

ii) 9-Cyano pyrano [2,3- f] 6-chloro- 2, 3-di methyl chromone (4b)

Mp.175 ºC, yield 75%. IR: (KBr); (C=O chromone) 1626cm^{-1} ; CN 2212.8cm^{-1}

UV :(MeOH); 298nm, (log ε 5.2) 246nm (log ε 4.7)

^{1}H NMR: (200 MHz $CDCl_3$): δ 2.59 (H-2, s); δ 2.21 (H-3, s); δ 8.27 (H-5, d J = 9Hz); δ 5.05 (OCH_2, s, J = 1.O Hz); δ 7.62 (H-10, bs, J = 9 Hz).

^{13}C NMR: δ 118.7 (CN); 65.55 (OCH_2); 133.7 (C-9); 132.12 (C-10); 175.4 (C-4);

157.5 (C-6a); 154.3 (C-10b); 152.1 (C-2); 126.5(C-3) 119.4 (C-4a); 126.55(C-5); 22.85 C2-CH_3; 18.9 C-3-CH_3.

Mass (EIMS): $M\bullet^+$ m/z 287.5, 288.5 (M+1) 252, 238, 224, 210, 200

iii) 9-Cyano pyrano [2,3- f] 6-bromo-2,3-di methyl chromone (4c).

Mp.179 ºC, yield 76%. IR (KBr): (C=O of chromone) 1625 cm^{-1}; CN 2213.2cm^{-1}

UV :(MeOH); 292nm, (log ε 5.2) 245nm (log ε 4.7)

^{1}H NMR: (200 MHz $CDCl_3$): δ 2.45 (H-2, CH_3,); δ 2.31 (H-3, CH3, s); δ 8.32 (H-5, d); δ 2.22 (H-6, d, J = 9Hz); δ 5.18 (OCH_2, s, J = 1.O Hz); δ 7.69 (H-10, bs, J = 9 Hz).

^{13}C NMR: δ 117.1 (CN); 64.95 (OCH_2); 130.2 (C-9); 129.5 (C-10); 173.91 (C-4); 156.55 (C-6a); 152.1 (C-10b); 151.9 (C-2); 125.9(C-3) 118.6 (C-4a); 124.96(C-5); 107.8(C-6); 114.51(C-10a); 20.1 C2-CH_3; 18.55 C-3-CH_3.

Mass (EIMS): $M\bullet^{++}$ m/z 332, 334 (M+2), 252, 238, 224, 210,200

iv) 9-Cyano pyrano [2,3-f] 2,3,6-tri methyl chromone (4d).

Mp. 180 ºC, yield 75%. IR (KBr); (C=O chromone) 1621.6cm^{-1} ; CN 2211.2cm^{-1}

UV :(MeOH**);** 290nm, (log ε 5.2) 241nm (log ε 4.7)

^{1}H NMR: (200 MHz $CDCl_3$): δ 2.44 (CH_3, H–2 s); δ 2.21 (H-3, s); δ 7.98 (H-5, d J = 9Hz); δ 1.8 (CH_3 H-6, d, J = 9Hz);δ 4.95 (OCH_2, J = 1.O Hz); δ 7.62 (H-10, J = 9 Hz).

^{13}C NMR**:** δ 116.7(CN); 65.02 (OCH_2); 131.25(C-9); 130.19 (C-10); 173.49 (C-4); 157.55(C-6a); 153.41 (C-10b); 151.9 (C-2); 124.33(C-3) 119.7 (C-4a); 124.56(C-5); 107.85(C-6); 114.44(C-10a); 23.55 CH_3-C-6; 22.22 CH_3-C-2; 18.45 CH_3-C-3;

Mass (EIMS): $M\bullet^+$ m/z 267, 266 (M-1), 253, 238, 224, 210, 200

v) 9-Cyano pyrano [2,3-f] 2- methyl-3-phenyl chromone (4e).

Mp.64 ºC, yield 70%. IR: 1633.1 cm^{-1} (C=O chromone); 2213.8 cm^{-1} (CN);

UV: (MeOH): 338 nm, (log ε3.8) 289 nm. (Log ε 4.0), 252 nm (log ε 4.2)

^{1}H NMR: (200 MHz):δ 2.5 (CH_3, H–2 s);δ 8.28 (H-5, d, J = 9Hz);δ 6.95(H-6, d, J = 9Hz); δ 7.85 (H-10, bs);δ 5.00 (OCH_2-8 s);δ 7.41 (H-2', 6', m); δ 7.28 (H-3', 4', 5', m)

^{13}C NMR: δ 118.2 (CN); OCH_2 δ 65.55; 131.90, 129.26 (C-9& C-10); 174 (C-4); 156.85 (C-6a); 151 (C-10b); 153.5 (C-2); 130.2 (C-1'); 129.62 (C-4'); 128.8 (C-2', 6'); 128.49 (C-3', 5'); 126 (C-3); 119 (C-4a); 126.2 (C-5); 112 (C-6); 114.85 (C-10a):

20.25 CH_3-C-2:

Mass (EIMS): $M^{\bullet+}$ m/z-315, 314 (M-1), 300, 272.

vi) 9-Cyano pyrano [2,3-f] 6-chloro-2- methyl-3-phenyl chromone (4f).

Mp.65 ºC yield 70%. IR: 1633.1 cm^{-1} (C=O chromone); 2213.8 cm^{-1} (CN);

UV :(MeOH): 223 nm, (log ε 5.7) 229nm. (Log ε 4.7)

^{1}H NMR: (200 MHz): δ 2.45 (CH_3, H–2, s); δ 8.22 (H-5, d, J = 9Hz); δ 7.45, (H-10, bs); δ 5.21 (OCH_2-8 s). δ 7.52 (H-2', 6', m); δ 7.40 (H-3', 4', 5', m)

^{13}C NMR: δ 117.66 (CN); OCH_2 δ 65.87; 131.99, 129.22 (C-9& C-10); 172.44 (C-4); 157.98 (C-6a); 151.33 (C-10b); 153.19 (C-2); 130.29(C-1'); 129.92 (C-4'); 128.18 (C-2', 6'); 128.99(C-3', 5'); 126.11 (C-3); 119.88 (C-4a); 126.28 (C-5); 112.55 (C-6); 114.18 (C-10a): 20.6 CH_3-C-2;

Mass (EIMS): $M^{\bullet+}$ m/z 349.^{5}, 350.5 (M+1), 314, 300, 223.199.

vii) 9-Cyano pyrano [2,3-f] 6-bromo-2- methyl-3-phenyl chromone (4g).

Mp.69 ºC, yield 68%. IR: 1633.1 cm^{-1} (C=O); 2213.8 cm^{-1} (CN);

UV :(MeOH): 301 nm, (log ε 5.7) 250 nm. (Log ε 4.7)

^{1}H NMR: (200 MHz): δ 2.58 (CH_3 –2 s); δ 8.33 (H-5, d, J = 9Hz); δ 7.22 (H-10, bs); δ 5.27 (OCH_2-8 s); δ 7.47 (H-2', 6', m); δ 7.39 (H-3', 4', 5', m)

^{13}C NMR: δ 119.15 (CN); OCH_2 at δ 65.77; 131.29,128.45 (C-9& C-10); 173.4(C-4); 157.28 (C-6a); 150.81 (C-10b); 152.15 (C-2); 130.29 (C-1'); 129.65 (C-4'); 127.2 (C-2', 6'); 127.89 (C-3', 5'); 126.15 (C-3); 118.9 (C-4a); 126.52 (C-5); 111.2 (C-6); 113.85 (C-10a): 20.95 CH_3-C-2;

Mass (EIMS): $M^{\bullet+}$ m/z 394, 396 (M +2), 314, 300, 223, 199.

viii) 9-Cyano pyrano [2,3-f] 2,6-di methyl-3-phenyl chromone (4h).

Mp.66 ºC, yield 65%. IR: 1634 cm^{-1} (C=O chromone); 2214 cm^{-1} (CN);

UV :(MeOH): 293 nm, (log ε 5.7), 242nm. (Log ε 4.7)

^{1}H NMR: (200 MHz): δ 2.55 (H-2, S); δ 8.34 (H-5, d, J = 9Hz); δ 2.15 (CH_3-6, S); δ 7.65 (H-10, bs); δ 5.18 (OCH_2-8 s). δ 7.59 (H-2', 6', m); δ 7.48 (H-3', 4', 5', m)

^{13}C NMR: δ 118.3 (CN); OCH_2 at δ 65.29; 130.19, 129.77 (C-9& C-10); 172.4 (C-4); 157.1 (C-6a); 150.2 (C-10b); 153.75 (C-2); 131.52 (C-1'); 129.9 (C-4'); 127.2 (C-2', 6'); 128.99 (C-3', 5'); 125.6 (C-3); 119.4 (C-4a); 126.5 (C-5); 112.75 (C-6); 113.85 (C-10a): 21.95 CH_3-C-2;

Mass (EIMS): $M\bullet^{+}$ m/z 328, 329 (M+1), 299, 271.

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