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Facile synthesis of 2-(2-furyl)-3,6-di-substituted-4-oxo-4h,8h-pyrano[2,3-f] chromene-9-carbonitrilies

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ABSTRACT

The Baylis-Hillmann reaction of 8-formyl-7-hydroxy furyl chromones on react with Acrylonitrile in DABCO/$CHCl_3$ medium under nitrogen atmosphere at room temperature gives of 2-(2-furyl)-3-methyl-4oxo-4H,8H-pyrano[2,3-f]chromene-9-carbonitrilies (4a-h) in good yields.

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Introduction

Oxygen containing natural and synthetic hetero cycles are widely found in nature.[1] The chromones (i.e., 4-Oxo-4H-chromenes) constitute one of the major classes of naturally occurring compounds. These compounds exhibits various biological activities include anticancer, neuroprotective, HIV-inhibitory, antimicrobial, antifungal, and antioxidant activity.[2] Also, chromones with pyridyl, furyl, and quinoyl substitutents at 2-position have been tested for antitumor activity.[3] In addition, hetroannulated chromones exhibited significant biological activity including pharmacological, anti-inflammatory, and antiplatelet activities.[4] On the other hand, flavones also constitute one of the major classes of oxygen containing natural products as well known to posses several biological activities.[5] In addition, many flavonoids contains the basic skeleton of chromone motif have been found to posses diverse interesting biological activities.[6]

Experimental Section

General Methods. 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 (100.6 MHz) were recorded on 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 2-(2-furyl)-3-methyl-4oxo-4H,8H-pyrano[2,3-f]chromene-9-carbonitrilies (4a-h):

To a solution containing 8-formyl-7-hydroxy-2-(2-furyl)-3-methylchromone (**2a**) (3 g, 0.011 mol, 1.0 equiv), acrylonitrile (0.588 g, 0.011 mol, 1.0 equiv) in chloroform (20 mL) was added DABCO (0.62 g, 0.005 mol, 0.5 equiv). After the reaction mixture was stirred under nitrogen atmosphere at room temperature for 60 h. Then solvent was removed concentrated under reduced pressure to afford a residue. Purification of the residue by chromatography with a silica gel column chromatography (100-200 mesh), eluted with petroleum ether and ethyl acetate (9:1) and further recrystallised with chloroform to give 2-(2-furyl)-3-methyl-4oxo-4H,8H-pyrano[2,3-f]chromene-9-carbonitrilies (**4a**) (2.3 g, 68%), mp (recrystallized from $CHCl_3$) 195-196 °C. By following the aforementioned procedures, we have synthesized rest of the analogues (i.e., **4b-h**).

i). 9′ cyano-2-(furan-2-yl)-3-methyl-4-oxo-4H-8H-pyrano[2,3-f]chromene (4a):

After recrystallised with chloroform yield 68%, mp 195-197 ºC.
IR: (KBr**);** C=O chromone 1614 cm^{-1}, CN 2212 cm^{-1}
UV :(MeOH); 342 nm (log ε 3.9), 260 nm (log ε 4.3), 240 nm (log ε 4.2).
^{1}H NMR: (200 MHz): δ 7.40 (d, 1 H, J = 9.0 Hz, H-5), 6.93 (d, 1 H, J = 1.5 Hz, H-6), 7.49 (s, 1 H, H-10), 4.97 (d, 2 H, J =1.5Hz, 8-OCH_2), 1.95 (s, 3 H, 3-CH_3), 7.80 (d, 1 H, H-2,4′), 6.65 (dd, 1 H, H-2, 2’), 7.05 (d, 1 H, H-2,2’).
^{13}C NMR (100.6 MHz): δ 178.1 (C-4, C=O); 161.4 (C-6a); 157.8 (C-10b); 153.2 (C-2); 149.4 (C-5'); 144.7 (C-2'); 131.1 (C-10); 129.1 (C-5)117.5 (C-4a), 116.3 (9-CN), 115.2 (C-3'), 114.4 (C-6), 113.4 (C-3), 111.5 (C4') 110.3 (C-9), 102.6 (C-10a), 63.8 (C-8-OCH_2), 9.0 (C-3-CH_3).
MS: m/z 307 $[M+H]^+$ and 328 $[M+Na]^{+.}$

ii) 9′ cyano-6-Chloro-2-(furan-2-yl)-3-methyl-4-oxo-4H-8H-pyrano[2,3-f]chromene (4b):

After recrystallised with chloroform yield 72%, mp 196-198 ºC.
IR: (KBr**);** C=O chromone 1625cm^{-1}, CN 2214 cm^{-1}.
UV :(MeOH); 345 nm (log ε 3.9), 265 nm (log ε 4.3), 245 nm (log ε 4.2).
^{1}H NMR: (200 MHz): δ 8.27 (s, 1H ,J=9.0Hz, H-5); 7.66 (s, 1H, H-10), 4.98 (d, 2H J=1.5Hz, 8-OCH_2), 1.95 (s, 3H, 3-CH_3), 7.80 (d, 1H, H-2,4’), 6.65 (dd, 1H, H-2, 2’), 7.05 (d, 1H, H-2,2’).
^{13}C NMR (100.6 MHz)**:** δ 178.1 (C-4, C=O), 161.4 (C-6a), 157.8 (C-10b), 153.2 (C-2), 149.4 (C-5'), 144.7(C-2'), 131.1 (C-10), 129.1 (C-5), 121.3 (C-Cl), 117.5 (C-4a), 116.3 (9-CN), 115.2 (C-3'), 113.4 (C-3), 111.5 (C-4'), 110.3 (C-9), 102.6 (C-

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10a), 63.8 (C-8-OCH_2), 9.0 (C-3-CH_3).
MS: m/z 341 $[M+H]^+$ and 362 $[M+Na]^+$.

iii)* 9′ cyano-*6-Bromo-2-(furan-2-yl)-3-methyl-4-oxo-4H-8H-pyrano[2,3-f]chromene (4c):

After recrystallised with chloroform yield 74%, mp 194-196 ºC.
IR: (KBr**);** C=O chromone 1622cm^{-1}, CN 2220 cm^{-1}.
UV: (MeOH); 340 nm (log ε 3.9), 265 nm (log ε 4.3), 245 nm (log ε 4.3).
^{1}H NMR: (200 MHz): δ8.31 (s, 1H, J=9.0Hz, H-5),7.68 (s, 1H, H-10), 4.98 (d, 1H, J=1.5Hz, 8-OCH_2), 7.80 (d, 1H, H-2,4′), 6.65 (dd, 1H, H-2,3′), 7.05 (d, 1H, H-2,2') , 1.95 (s, 3-CH_3),
^{13}C NMR (100.6 MHz)**:** δ 178.1 (C-4, C=O), 161.4 (C-6a), 157.8 (C-10b), 153.2 (C-2); 149.4 (C-5'); 144.7 (C-2'), 131.1(C-10), 129.1(C-5), 117.5 (C-4a), 116.3 (9-CN), 115.2 (C-3'), 113.4 (C-3), 147.5 (C-4'), 110.3 (C-9), 110.6 (C-10a), 108.8 (C-Br), 63.8 (C-8-OCH_2), 9.0 (C-3-CH_3).
MS: m/z 384 & 386$[M+H]^+$ and 406 $[M+Na]^+$.

iv)* 9′ cyano-*2-(furan-2-yl)-3,6-dimethyl-4-oxo-4H-8H-pyrano[2,3-f]chromene (4d).

After recrystallised with chloroform yield 70%, mp 189-190 ºC.
IR: (KBr**);** C=O chromone 1625cm^{-1}, CN 2225 cm^{-1}.
UV :(MeOH); 342 nm, (log ε 3.9), 260 nm (log ε 4.3), 265 nm (log ε 4.3).
^{1}H NMR: (200 MHz): δ 7.55 (s, 1H, J=9.0Hz, H-5), 7.68 (s, 1H, H-10), 4.98 (d, 2H, J=1.5Hz, 8-OCH_2), 2.32 (s, 3H, 3-CH_3), 2.35 (s, 3H, -6-CH_3). 7.80 (d, 1H, H-2,4′), 6.65 (dd, 1H, H-2,3′), 7.07 (d, 1H, H-2,2′).
^{13}C NMR (100.6 MHz)**:** δ 178.1 (C-4, C=O), 161.4 (C-6a), 157.8 (C-10b), 153.2 (C-2),149.4 (C-5'), 144.7 (C-2'), 131.1 (C-10), 129.1(C-5), 117.5 (C-4a), 116.3 (9-CN), 115.2 (C-3'), 114.4 (C-6), 113.4 (C-3), 111.5 (C-4'),110.3 (C-9), 102.6 (C-10a), 65.8 (C-8-OCH_2), 9.0 (C-3-CH_3), 14.5 (C-6-CH_3).
MS: m/z 320 $[M+H]^+$ and 342 $[M+Na]^+$.

v)* 9′ cyano-*2-(furan-2-yl)-4-oxo-3-phenyl-4H-8H-pyrano[2,3-f]chromene (4e):

After recrystallised with chloroform yield 75%, mp 94-96 ºC.
IR: (KBr**);** C=O chromone 1820cm^{-1}, CN 2217 cm^{-1}.
UV :(MeOH); 350 nm (log ε 3.9), 265 nm (log ε 4.3).
^{1}H NMR: (200 MHz): δ 7.39 (d, 1H, J=9.0Hz, H-5), 7.66 (s, 1H, H-10), 6.51 (s, 1H, H-6), 4.98 (d, 2H, J=1.5Hz, 8-OCH_2), 7.41 (m, 2H, H-2′,6′), 7.28 (m, 3H, H-3′4′5′), 7.80 (d, 1H, H-2,4′), 6.65 (dd, 1H, H-2,3′), 7.07 (d, 1H, H-2,2').
^{13}C NMR (100.6 MHz)**:** δ 178.1 (C-4, C=O), 161.4 (C-6a), 157.8 (C-10b), 153.2 (C-2), 149.4 (C-5'), 144.7 (C-2'), 143.4 (C-10), 131.1 (C-10), 117.5 (C-4a), 116.3 (9-CN), 115.2 (C-3'), 114.4 (C-6), 113.4 (C-3), 111.5 (C-4'), 110.3(C-9), 102.6 (C-10a), 63.8 (C-8-OCH_2), 126-138 (6C,C-3-Ph).
MS: m/z 368 $[M+H]^+$ and 390$[M+Na]^+$.

vi)* 9′ cyano-*6-Chloro-2-(furan-2-yl)-4-oxo-3-phenyl-4H-8H-pyrano[2,3-f]chromene (4f):

After recrystallised with chloroform yield 70%, mp 110-112 ºC.
IR: (KBr**);** C=O chromone 1825cm^{-1}, CN 2252 cm^{-1}.
UV :(MeOH); 355 nm, (log ε 3.9), 265 nm (log ε 4.3).
^{1}H NMR: (200 MHz): δ 8.34 (d, 1H, J=9.0Hz, H-5), 7.66 (s, 1H, H-10), 4.97 (d, 2H, J=1.5Hz, 8-OCH_2), 7.41(m, 2H, H-2′,6′), 7.28 (m, 3H, H-3′4′5′), 7.80 (d, 1H, H-2,4′), 6.65 (dd, 1H, H-2,3′), 7.07 (d, 1H, H-2,2′).
^{13}C NMR (100.6 MHz)**:** δ 178.1 (C-4, C=O), 161.4 (C-6a), 157.8 (C-10b), 153.2 (C-2), 149.4 (C-5'), 144.7 (C-2'), 131.1 (C-10), 129.1 (C-5), 117.5 (C-4a), 116.3 (9-CN), 115.2 (C-3'), 114.4 (C-6), 113.4 (C-3), 111.5 (C-4′), 110.3 (C-9), 102.6 (C-10a), 63.8 (C-8-OCH_2), 111.4 (C-2,2′), 1112.5 (C-2,3′), 145.5 (C-2-4′), 68.8 (C-8-OCH_2).
MS: m/z 402 and 404 $[M+H]^+$.

vii)* 9′ cyano-*6-Bromo-2-(furan-2-yl)-4-oxo-3-phenyl-4H-8H-pyrano[2,3-f]chromene (4g):

After recrystallised with chloroform yield 75%, mp 96-98 ºC.
IR: (KBr**);** C=O chromone 1830cm^{-1}, CN 2255 cm^{-1}.
UV :(MeOH); 350 nm (log ε 3.9), 265 nm (log ε 4.3).
^{1}H NMR: (200 MHz): δ 8.41 (d, 1H, J=9.0Hz, H-5), 7.67 (s, 1H, H-10), 4.98 (d, 2H, J=1.5Hz, 8-OCH_2), 7.41 (m, 2H, H-2′,6′), 7.28 (m, 3H, H-3′4’5′), 7.80(d, 1H, H-2,4′), 6.65 (dd, 1H, H-2,3′), 7.07 (d, 1H, H-2,2′).
^{13}C NMR (100.6 MHz)**:** δ 178.1 (C-4, C=O); 161.4 (C-6a); 157.8 (C-10b); 157.2 (C-2); 128.4 (C-5'); 126.7 (C-2'); 131.1 (C-10); 129.1 (C-5), 117.5 (C-4a), 116.3 (9-CN), 128.2 (C-3'), 114.4 (C-6), 113.4 (C-3), 111.5 (C-4'), 110.3 (C-9), 102.6 (C-10a), 63.8 (C-8-OCH_2), 111.4 (C-2,2′), 1112.5 (C-2,3′), 145.5 (C-2,4′).
MS: m/z 446 and 448 $[M+H]^+$.

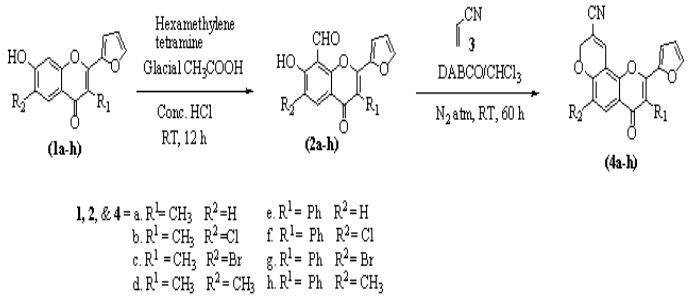
viii)* 9′ cyano-*2-(furan-2-yl)-6-methyl-4-oxo-3-phenyl-4H-8H-pyrano[2,3-f]chromene (4h):

After recrystallised with chloroform 70%, mp 95-97 ºC.
IR: (KBr**);** C=O chromone 1624cm^{-1}, CN 2219 cm^{-1}.
UV :(MeOH); 365 nm (log ε 3.9), 275 nm (log ε 4.3).
^{1}H NMR: (200 MHz): δ 7.20 (s, 1H, J=9.0Hz, H-5), 7.66 (s, 1H, H-10), 4.65 (d, 2H, J=1.5Hz, 8-OCH_2), 2.15 (s, 1H, 6-CH_3), 7.41 (m, 2H, H-2′,6′), 7.28 (m, 3H, H-3′4′5′), 7.80 (d, 1H, H-2,4′), 6.65 (dd, 1H, H-2,3′), 7.07 (d, 1H, H-2,2′).
^{13}C NMR (100.6 MHz)**:** δ 178.1 (C-4, C=O), 161.4 (C-6a), 157.8 (C-10b), 153.2 (C-2), 128.7 (C-5'), 126.7 (C-2'), 141.5 (C-10), 129.1 (C-5), 113.5 (C-4a), 116.3 (9-CN), 128.7(C-3'), 131.4 (C-6), 157.4 (C-3), 128.5 (C4'), 110.3 (C-9), 122.6 (C-10a), 63.8 (C-8-OCH_2).
MS: m/z 382 $[M+H]^+$ and 404 $[M+Na]^+$.

Results And Discussion:

The present work describes the design and synthesis of some new hetroannulated chromone derivatives *via* Baylis-Hillmann reaction[7] as key step. With synthesis of 8-formyl-7-hydroxychromones and isoflavones as potential starting materials (i.e., **2a-h**), those can be synthesized by Duff's formylation of suitably substituted hydroxyl chromones (**1a-h**).[8] Accordingly, treatment of hydroxy chromones (**1a-h**) with hexamine in the presence of glacial acetic acid yielded the desired intermediates (i.e., **2a-h**) in good yields.[8] The compounds were well characterized with all the spectral data. The regioselectivity of Duff's formylation depends on solvent and structural features of substrate. Then, condensation of 8-formyl-7-hydroxy-2-furylchromones (**2a**) with acrylonitrile (**3**) in the presence of 1, 4-diazobicyclo [2, 2, 2]-Octane (i.e., DABCO) afforded titled compound (**4a**) as white solid in 68% yield. This compound exhibited doublet corresponds the 8-OCH_2 group of the newly formed pyran ring with J = 1.5 Hz at 4.97 ppm due to allylic coupling with proton of C_{10}-H. Also exhibited singlet corresponds to the proton of C_{10}-H. In addition, in its ^{13}C NMR spectrum, resonance occurred at 116.3 and 178.1 ppm for the C=O and CN functional groups respectively. Furthermore, in the IR spectrum of compound exhibited one strong stretching absorption band appeared at 1614 cm^{-1} for the (C=O) group of chromone moiety and at 2212 cm^{-1} for the CN group.

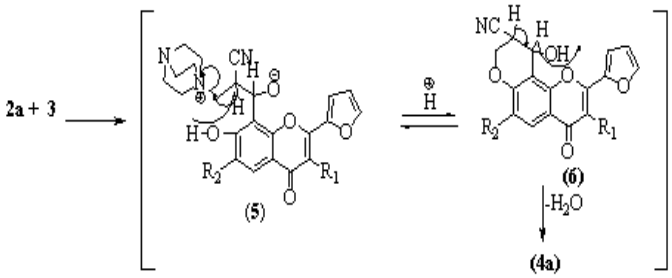
Scheme-1



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

The mechanistic pathway for the conversion of **2a** to **4a** is depicted in Scheme 2. The Michael reaction of DABCO with acrylonitrile (**3a**) generates the anion □-position to the cyano group, which reacts with formyl moiety of chromone (**2a**) to give an intermediate (**5**). Then intramolecular nucleophilic substitution involving the 7-OH of 2-furyl-3-methyl chromone (**2a**) leads to the removal of the DABCO and Pyran ring formation. Then subsequent loss of H_2O form intermediate (**6**) in the presence of DABCO gives rise to desired hetroannulated chromene-9-carbonitrile (**4a**).

Scheme-2



Conclusion:

We have developed a mild method for the synthesis of eight new 2-(2-furyl)-3-methyl-4oxo-4H,8H-pyrano[2,3-f]chromene-9-carbonitrilies from readily available 8-formyl-7-hydroxy-2-furylchromones *via* DABCO catalyzed Baylis-Hillmann reaction. Also, the required key starting materials (i.e., 8-formyl-7-hydroxy-2-furylchromones) have been synthesized by use of Duff's formylation. This newly established method useful for the preparation of biologically active 2-(2-furyl)-3-methyl-4oxo-4H,8H-pyrano[2,3-f]chromene-9-carbonitrilies.

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