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Research Article

AN EFFICIENT SYNTHESIS OF HETROANNULATED CHROMENE-9-CARBONITRILE DERIVATIVES VIA BAYLIS-HILLMANN REACTION

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ABSTRACT

New series of hetroannulated chromene-9-carbonitrile derivatives have been synthesized from 4-diazobicyclo [2, 2, 2]-octane catalyzed Baylis-Hillmann reaction of diversely substituted 7-hydroxy-8-formyl-2-furylchromones under nitrogen atmosphere at room temperature in good yields. The structures of these newly synthesized were established by IR, NMR, mass spectral analysis.

Keywords: Acrylonitrile, Baylis-Hillmann reaction, Chromones, Chromene-9-carbonitrile, Duff's formylation, 7-hydroxy-8-formyl-2-furylchromone.

INTRODUCTION

Natural products are typically secondary metabolites, produced by organisms in response to externalstimuli such as nutritional changes, infection and competition (COTTON, 1996; STROHL, 2000).Natural products produced by plants, fungi, bacteria, insects and animals have been isolated as biologically active pharmacophores. Approximately one-third of the top- selling drugs in the world is natural products or their derivatives often with ethnoharmacological background. Moreover, natural products are widely recognized in the pharmaceutical industry for their broad structural diversity as well as their wide range of pharmacological activities[1]. Coumarin constitutes one of the major classes of naturally occurring compounds, and interest in its chemistry continues unabated because of its usefulness as biologically active agents. It also represents the core structure of several molecules of pharmaceutical importance. Chromones and isoflavones with medicinal use are Khellin a coronary vasodilator[2-3]. Coumarin has been reported to serve as anti-oxidant [4], antibacterial [5] and antitumour[6] agents. These pharmacological properties of coumarin aroused our interest in synthesizing some coumarin derivatives with the aim of testing their microbiological activity. Coumarins have a variety of bioactivities including anticoagulant, estrogenic, dermal photosensitising, antimicrobial, vasodilator, molluscacidal, antithelmintic, sedative and hypnotic,analgesic and hypothermic activity. The usefulness of coumarins and coumarin derivatives has been shown in various areas of analysis (COOKE *et al*., 1997). The inherent fluorescent properties of many coumarins are a key factor in many applications. Areas where coumarins are widely used include estimation of enzymatic activity (*e.g.* derivatives of 7-hydroxycoumarin as fluorigenic enzyme substrates; EGAN *et al*., 1990). It is used inelectroplating to reduce the porosity and increase the brightness of various deposits, such as nickel.6-methylcoumarin is mainly used as a flavour enhancer, and 7-hydroxycoumarin in sunscreens[7]. This study is based on ethnobotanical knowledge of coumarins and coumarin containing plants Aegopodium podagraria, Anethum graveolens, Angelica archangelica, Levisticum officinalis,Petroselinum crispum, Peucedanum palustre and Ruta graveolens growing in Finland. For the scientific evaluation of traditional use of these plants as drugs, the biological activities of the coumarin containing materials were studied with the biological tests[8]. In conclusion, coumarin compounds can be suggested to be beneficial for the plants themselves as natural biocontrolling antipathogenic compounds, and for human beings as dietary supplements on the basis of their mild antimicrobial and anti-inflammatory effects, and as reference compounds in various bioactivity tests. The use of these compounds as medicinal agents is of importance in the case of hyperproliferative skin diseases like psoriasis[9]. Oxygen containing natural and synthetic hetrocycles are widely found in nature.[10]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.[11] Also, chromones with pyridyl, furyl, and quinoyl substitutents at 2-position have been tested for antitumor activity.[12] In addition, hetroannulated chromones exhibited significant biological activity including pharmacological, anti-inflammatory, and antiplatelet activities.[13] 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.[14]In addition, many flavonoids contains the basic skeleton of chromone motif have been found to posses diverse interesting biological activities.[15]

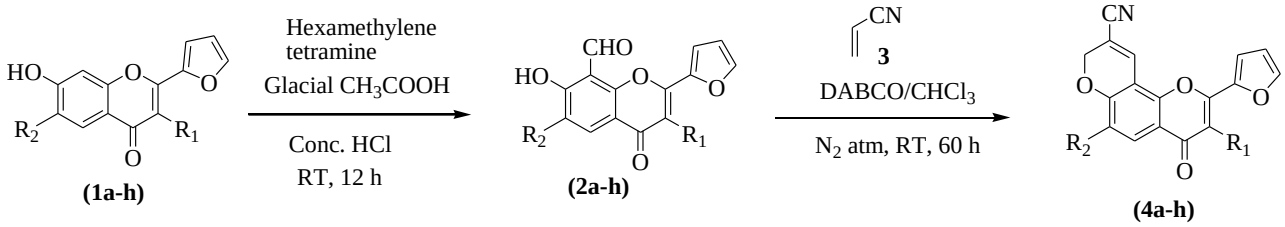
RESULTS AND DISCUSSION

The present work describes the design and synthesis of some new hetroannulated chromone derivatives *via* Baylis-Hillmann reaction[16]as key step. Recently, Baylis-Hillmann reaction[17] has been applied for development of novel synthetic methodologies as well as synthesis of various biologically active hetrocycles. As shown in Scheme 1, our synthesis commenced 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**).[18]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.[18] 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 (50% $CDCl_3$+ 50% DMSO-d_6), resonance occurred at 178.1 and 116.3 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 theCN group. These spectroscopic data clearly indicate the formation of the new chromene-9-carbonitrile (**4a**). By use of similar synthetic strategy, we have synthesized all the chromene-9-carbonitrile derivatives (**4b-h**) with good yields. All the new compounds were well characterized with ^{1}H, [13]C NMR, IR, and MS analysis.

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-

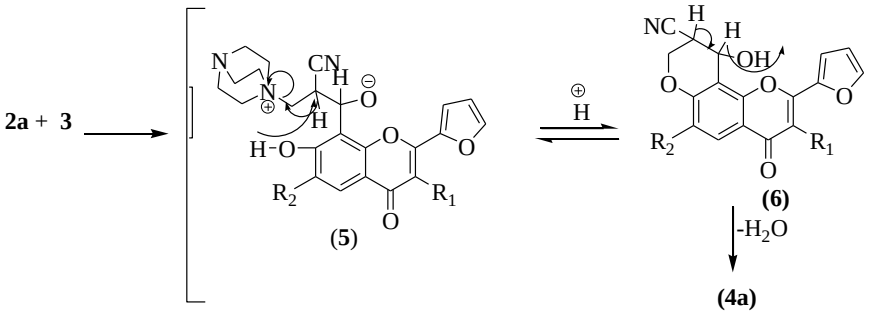
furyl-3-methyl chromone (**2a**) leads to the removal of the DABCO and Pyran ring formation. Then subsequent loss of H_2O form intermediate (**6**) in the presence of DABCO gives rise to desired hetroannulated chromene-9-carbonitrile (**4a**).

Scheme-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

Scheme-2



CONCLUSION

We have developed a mild method for the synthesis of eight new chromene-9-carbonitrile derivatives 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 hetroannulated chromene-9-carbonitrile derivatives.

Experimental Section

General Methods

All reactions were carried out in oven-dried glassware (120 °C) under an atmosphere of nitrogen unless as indicated otherwise. 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 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 2-(furan-2-yl)-7, 8-dihydro-3-methyl-4-oxo-4H-benzo[h] chromene-9-carbonitriles (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-(furan-2-yl)-7, 8-dihydro-3-methyl-4-oxo-4H-benzo[h] chromene-9-carbonitrile (**4a**) (2.3 g, 68%), mp (recrystallized from $CHCl_3$) 195-197 °C. By following the aforementioned procedures, we have synthesized rest of the analogues (i.e., **4b-h**).

i) 2-(furan-2-yl)-7, 8-dihydro-3-methyl-4-oxo-4H-benzo[h] chromene-9-carbonitrile (4a): Yield 68%, **(**recrystallised from chloroform) 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}HNMR: (200 MHz $CDCl_3$): 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; $CDCl_3$+DMSO-d_6): 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 306 $[M+H]^+$ and 328 $[M+Na]^+$.

ii) 6-Chloro-2-(furan-2-yl)-7,8-dihydro-3-methyl-4-oxo-4H-benzo[h]chromene-9-crbonitrile (4b): Yield 72%, **(** recrystallised from chloroform) , 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}HNMR: (200 MHz $CDCl_3$): δ 8.27 (s, 1H , 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 ($CDCl_3$+DMSO-d_6)**&** (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-10a), 63.8(C-8-OCH_2), 9.0 (C-3-CH_3).

MS: m/z 340 $[M+H]^+$ and 362 $[M+Na]^+$.

iii) 6-Bromo-2-(furan-2-yl)-7, 8-dihydro-3-methyl-4-oxo-4H-benzo[h]chromene-9-carbonitrile (4c): Yield 74 %(recrystallised from chloroform), 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}HNMR: (200 MHz $CDCl_3$): 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 ($CDCl_3$+DMSO-d_6)**&** (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) 2-(furan-2-yl)-7,8-dihydro-3,6-dimethyl-4-oxo-4H-benzo[h] chromene-9-carbonitrile (4d): Yield 70%,(recrystalised from chloroform), 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}HNMR: (200 MHz $CDCl_3$): 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 ($CDCl_3$+DMSO-d_6)**&** (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) 2-(furan-2-yl)-7, 8-dihydro-4-oxo-3-phenyl-4H-benzo[h] chromene-9-carbonitrile (4e): Yield 75 %,(recrystalised from chloroform), 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}HNMR: (200 MHz $CDCl_3$): 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 ($CDCl_3$+DMSO-d_6)**&** (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) 6-Chloro-2-(furan-2-yl)-7,8-dihydro-4-oxo-3-phenyl-4H-benzo[h]chromene-9-carbonitrile (4f): Yield 71% (recrystalised with chloroform), 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}HNMR: (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 ($CDCl_3$+DMSO-d_6)**&** (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) 6-Bromo-2-(furan-2-yl)-7,8-dihydro-4-oxo-3-phenyl-4H-benzo[h]chromene-9-carbonitrile (4g): Yield 75% (recrystalised from chloroform), 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}HNMR: (200 MHz $CDCl_3$): 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 ($CDCl_3$+DMSO-d_6)**&** (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) 2-(furan-2-yl)-7,8-dihydro-6-methyl-4-oxo-3-phenyl-4H-benzo[h]chromene-9-carbonitrile (4h): Yield 70% (recrystalised from chloroform), 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}HNMR: (200 MHz $CDCl_3$): 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 ($CDCl_3$+DMSO-d_6)**&** (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 $[M+Na]^+$.

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