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Facile synthesis of methyl-2-(furyl-2-yl) 3-methyl-4-oxo-4h-furo (2, 3-H) chromene-8-carboxylate

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ABSTRACT

*New series of methyl furo (2,3-h) chromene-8-carboxylate derivatives have been synthesized from 8-formyl-7-hydroxy furylchromones (**2a-h)** react with methylbromo acetate in as anhydrous K_2CO_3 under inert atmosphere give methyl-2-(furyl-2-yl) 3-methyl-4-oxo-4H-furo (2, 3-h) chromene-8-carboxylates **(4a-h)** in good yields.*

Keywords: - 8-formyl-7-hydroxy furylchromones, methylbromo acetate, nitrogen gas, Dean-Stark apparatus.

INTRODUCTION

Natural products are typically secondary metabolites, produced by organisms in response to external stimuli 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[1,2,3,4]. Approximately one-third of the top-selling drugs in the world are 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 [5,6,7].

Furanochromones are abundant subclass of the chromones class of compounds and are widely distributed in nature. They exhibit a variety of biological activities like insecticidal, pesticidal, antihelmintic, anticancer and antitumor etc [9.10]. They also used in traditional medicines for the treatment of tumours, piles, skin diseases, wounds and ulcers etc. Benzofurans and aroylbenzofurans were reported as antifertility agents.

MATERIALS AND METHODS

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 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 methyl furo (2, 3-h) chromene-8-carboxylates (4a-h).
To a stirred solution of 8-Formy1-7-hydroxy-2-furylchromone **(2a)** (2.8g, 10mmol, 1 eq), methy1 bromoacetate **(3)** (2.04ml, 12mmol, 1.2 eq) and powdered K_2CO_3 (2.76g, 20mmol, 2 eq) were refluxed (120 ^{0}C) under inert atmosphere (N_2 gas) with a Dean-Stark apparatus (collectedwater) for 6 h. The reaction mixture was allowed cool to

room temperature and the reaction masspoured into the crushed ice and left overnight. The crude reaction mass was dissolved in hloroform, the organic layer was separated and evaporated with vaccum.The crude was column Chromatographed with silica gel (100-200mesh) and recrystalised with chloroform to obtain methyl 2-(furan-2-yl)-3-methyl-4-oxo-4H-furo [2, 3-h] chromene-8-carboxylate **(4a)** (2.71g,78%) as a white colored crystals. mp 165 ^{0}C. Similarly we synthesized **(4b-h)** analogues.

Employing the similar procedure as mentioned for **4a,** compounds **4b-h** were obtained from **2b-h** as solids.

i).Methyl-2-(furyl-2-yl) 3-methyl-4-oxo-4H-furo (2, 3-h) chromene-8-carboxylate (4a):

IR (KBr): 1650 cm^{-1} (ester C=O); 1625 cm^{-1} (chromone C=O); UV (MeOH): 340 nm (log ε 4.1), 265 nm (log ε 4.3), 200 nm (log ε 4.0); ^{1}H NMR: δ 8.32 (d, J=9.0 Hz, H-5), 7.81 (s, H-9), 7.67 (m, H-2'), 7.59 (d, J=9.0 Hz, H-6), 7.55 (m, H-3',4'), 7.80 (s, H-4') 2.18 (s, 3-CH_3), 3.46 (s, $COOCH_3$). ^{13}C NMR: δ 177.9 (C-4, C=O), 160.2 (C-6a), 158.7 ($COOCH_3$), 158.4 (C-2), 151.2 (C-9b), 146.4 (C-8), 133.1 (C-1'), 130.3 (C-4'), 128.9 (C-3'), 128.5 (C-2'), 125.4 (C-5), 118.6 (C-4a), 118.3 (C-3), 116.9 (C-9a), 110.9 (C-9), 110.2 (C-6), 11.7 (C-3-CH_3); MS: m/z 325 [M+H]$^+$.

ii) Methyl-6-chloro-2-(furyl-2-yl)-3-methyl-4-oxo-4H-furo(2,3-h)chromene-8-carboxylate(4b):

Recrystalised with chloroform to obtained as a white colored crystals 74 % yield mp 153 ^{0}C.

IR (KBr): 1675 cm^{-1} (ester C=O); 1645 cm^{-1} (chromone C=O); UV (MeOH): 320 nm (log ε 4.1), 260 nm (log ε 4.4), 235 nm (log ε 3.9); ^{1}HNMR: δ 8.26 (d, J=9.0 Hz, H-5), 7.72 (s, H-9), 7.41 (m, H-3, 4,), 1.92 (s, 3-CH_3), 1.37 (s, $COOCH_3$). ^{13}C NMR: δ 177.4 (C-4, C=O), 158.4 ($COOCH_3$), 158.3 (C-2), 151.4 (C-9b), 146.4 (C-8), 133.59 (C-1), 131.9 (C-2), 131.5 (C-4), 130.8 (C-3), 130.0 (C-5), 126.9 (C-5), 125.2 (C-6), 120.5 (C-6), 120.5 (C-4a), 118.6 (C-3), 116.9 (C-9a), 110.8 (C-9), 11.0 (C-3-CH_3). MS: m/z 359 [M+H]$^+$.

***iii)Methyl-6-bromo-2-(furyl-2-yl)-3-methyl-4-oxo-4H-furo(2,3-h)chromene-8-carboxylate (4c)*:**

Recrystalised with chloroform to obtained as a white colored crystals 72 % yield mp 178 ^{0}C.

IR (KBr): 1736 cm^{-1} (ester C=O); 1648 cm^{-1} (chromone C=O); UV (MeOH):316 nm (log ε 4.1), 268 nm (log ε 4.2), 232 nm (log ε 4.0); ^{1}H NMR: δ 7.75 (d, J=9.0 Hz, H-5), 7.78 (s, H-9), 7.60 (m, H-2,3,4), 7.53 (d, J=8.7Hz, H-5), 2.19 (s,3-CH_3), 1.42(s, J=6.7Hz, $COOCH_3$).^{13}C NMR: δ 180.7 (C-4, C=O), 127.0 (C-4a), 158.6 ($COOCH_3$).158.4(C-2), 151.1(C-9b), 115.6(C-4'), 131.4(C-1'), 130.3(C-3'), 128.9(C-2') 125.3(C-5), 118.7(C-4a) 118.3(C-3), 116.8(C-9a), 110.7(C-9). MS: m/z 402 [M+H]$^+$.

iv).Methyl-6,3-dimethyl-2-(furyl-2-yl)-4-oxo-4H-furo(2,3-h)chromene-8-carboxylate(4d): Recrystallisation from chloroform as a white colored crystals 70 % yield mp 145 ^{0}C.

IR (KBr): 1736 cm^{-1} (ester C=O), 1645 cm^{-1} (chromone C=O); UV (MeOH): 317 nm (log ε 4.2), 264 nm (log ε 4.1), 225nm (log ε 4.0); ^{1}H NMR: δ 7.35 (d, J=9.0 Hz, H-5), 7.79 (s, H-9), 2.35 (m, H-6-CH_3) 7.03 (d, J=8.6 Hz, H-3, 5), 4.44 (s, COOCH3), 1.95 (s, 3-CH_3). ^{13}C NMR: δ 177.9 (C-4,C=O), 161.1 (C-4), 160.1 (C-6a), 158.3 (C-2), 151.1 (C-9b), 146.3 (C-8), 131.6 (C-1), 130.5 (C-2,6), 125.3 (C-5), 118.2 (C-4a), 117.7 (C-3), 116.8 (C-9a), 113.9 (C-3,5), 110.8 (C-9), 110.0 (C-6), 40.7 ($COOCH_3$), 55.4 (C-4-OCH_3), 11.8 (C-3-CH_3); MS: m/z 339 [M+H]$^+$

***v).Methyl-2-(furyl-2-yl)3-phenyl-4-oxo-4H-furo(2,3-h)chromene-8-carboxylate* (4e):**

Recrystallisation from chloroform as a white colored crystals 72 % yield, mp 166 ^{0}C.

IR (KBr): 1718 cm^{-1} (ester C=O), 1647 cm^{-1} (chromone C=O); UV (MeOH): 310 nm (log ε 4.3), 273 nm (log ε 4.1), 223 nm (log ε 4.0). H^1 NMR: δ 7.55 (d, J=9.0 Hz, H-5), 7.95 (m, H-2', 6'), 7.25 (s, H-9), 7.60 (d, J=6.7 Hz, H-6), 7.55 (m, H-', 4', 5'), 6.87 (s, H-4) 3.89 (s, $COOCH_3$). ^{13}C NMR: δ 177.4 (C-4, C=O), 162.7 (C-6a), 158.6 (C-2), 158.5 ($COOCH_3$), 151.8 (C-9b), 146.7 (C-8), 131.7 (C-4), 129.1 (C-2,6), 128.4 (C-1), 126.1 (C-3,5), 125.0 (C-5), 119.8 (C-4a), 117.1 (C-9a), 110.7 (C-9), 110.6 (C-6), 108.3 (C-3), 40.5 ($COOCH_3$). MS: m/z 386 [M+H]$^+$.

vi). Methyl-6-chloro-2-(furyl-2-yl) 3-phenyl-4-oxo-4H-furo (2, 3-h) chromene-8-carboxylate (4f):

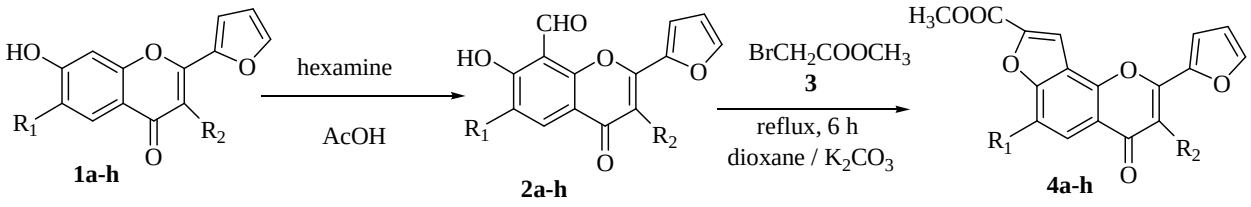
Recrystallisation from chloroform as a white colored crystals 70 % yield, mp 158 ^{0}C.

IR (KBr): 1717cm^{-1} (ester C=O); 1653 cm^{-1} (chromone C=O). UV (MeOH): 307 nm (log ε 4.2), 264 nm (log ε 4.1), 239nm (log ε 3.8). ^{1}H NMR: δ 7.55 (d, J=9.0 Hz, H-5), 7.73 (s, H-9), 7.52(m, H-6), 7.40 (m, H-3, 4, 5), 6.81 (s, C-3), 4.35 (s, $COOCH_3$). ^{13}C NMR: δ 177.2 (C-4, C=O), 162.1 (C-6a), 158.6 (C-2), 151.7 (C-9b), 146.7 (C-8), 132.7 (C-1), 132.0 (C-4), 131.4 (C-2), 130.9 (C-3,), 130.7 (C-5) , 127.2 (C-6'), 125.0 (C-5), 119.8 (C-4a), 117.3 (C-9a) , 113.7 (C-9), 110.8 (C-6), 108.4 (C-3), 40.5 ($COOCH_3$). MS: m/z 420 [M+1]$^+$.

***vii).Methyl-6-bromo-2-(furyl-2-yl)3-phenyl-4-oxo-4H-furo(2,3-h)chromene-8-carboxylate(4g)*:** Recrystallisation from chloroform as a white colored crystals 72 % yield mp 181 ^{0}C.
IR (KBr): 1718 cm^{-1} (ester C=O); 1640 cm^{-1} (chromone C=O). UV (MeOH): 313 nm (log ε 4.4), 285 nm (log ε 4.1), 220 nm (log ε 4.0). ^{1}H NMR: δ 7.57 (d, J=9.0 Hz, H-5), 7.91 (m, H-9, H-2,), 7.55 (d, J=8.7 Hz, H-3, 5), 6.84 (s, H-3), 4.48 (s, $COOCH_3$). ^{13}C NMR: δ 177.5 (C-4, C=O), 161.6 (C-6a), 158.6 (C-2), 151.2 (C-9b), 146.1 (C-8), 138.0 (C-4), 130.1(C-1), 129.4 (C-3,5), 127.3 (C-2,6), 125.0 (C-5), 119.8 (C-4a), 117.5 (C-9a), 110.8 (C-9), 110.6 (C-6), 108.4 (C-3), 40.5 ($COOCH_3$). MS: m/z 465 [M+H] $^+$

viii).Methyl-6-methyl-2-(furyl-2-yl)3-phenyl-4-oxo-4H-furo(2,3-h)chromene-8-carboxylate (4h):
Recrystallisation from chloroform as a white colored crystals 72 % yield, mp 178 ^{0}C.
IR (KBr): 1739 cm^{-1} (ester C=O), 1654 cm^{-1} (chromone C=O). UV (MeOH): 318 nm (log ε 4.3), 288 nm (log ε 4.2), 229 nm (log ε 3.9); ^{1}H NMR: δ 7.57 (d, J=9.0 Hz, H-5), 7.89 (m, H-9, H-2,6), 7.60 (d, J=9.0 Hz, H-6), 7.02 (d, J=8.6 Hz, H-3,5), 6.75 (s,3-H), 4.48 (s, $COOCH_3$). ^{13}C NMR: δ 177.3 (C-4,C=O), 162.7 (C-4), 162.5 (C-6a), 158.6 (C-2), 151.1 (C-9b), 146.7 (C-8), 127.8 (C-2,6), 125.0 (C-5), 123.6 (C-1), 119.8 (C-4a), 117.1 (C-9a), 114.6 (C-3,5), 110.6 (C-9), 110.3 (C-6), 106.8 (C-3), 40.5 ($COOCH_3$). MS: m/z 401 [M+H] $^+$.

Scheme-1



1, 2,4 **a** = R_1 = H, R_2 = CH_3 **e** = R_1 = H, R_2 = H
b = R_1 = Cl R_2 = CH_3 **f** = R_1 = Cl R_2 = H
c = R_1 = Br R_2 = CH_3 **g** = R_1 = Br R_2 = H
d = R_1 =CH_3 R_2 = CH_3 **h** = R_1 =CH_3 R_2 =H

RESULTS AND DISCUSSION

The present work describes the design and synthesis of some new hetroannulated chromone derivatives *via* Baylis-Hillmann reaction as key step. Recently, Baylis-Hillmann reaction 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**). 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. 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 methylbromo acetate (**3**) and K_2CO_3 in the presence inert atmosphere afforded titled compound (**4a**) as white colour crystals in 78% yield. In its IR, the C=O of ester group appeared at 1715 cm^{-1} and the chromone carbonyl observed at 1634 cm^{-1}. The UV (MeOH) spectrum of (**4a**) showed bands at 304 nm (log ε 4.1), 264 nm (log ε 4.3) and 227 nm (log ε 4.0). The ^{1}H NMR ($CDCl_3$) (200MHz) spectrum of (**4a**) shows a peak pattern, which indicates furan ring fused at 7, 8-position of the chromone and the ester group is at 10-position. The furan ring H-9 appeared as a singlet at δ 7.81, the CH_3 group of 8-$COOCH_3$ appeared as a singlet at δ 3.46. The H-6 appeared as a doublet at δ 7.59 (J=9.0 Hz) and the H-5 at δ 8.32 as a doublet (J=9.0 Hz). These signals suggest that a new furan ring is formed at 7, 8 positions of the 3-methyl-2-furyl chromones. Other signals are from the original 3-methyl-2-furyl chromones moiety of the 3-CH_3 appeared as a singlet at δ 2.18. All the new compounds were well characterized with ^{1}H, ^{13}C NMR, IR, and MS analysis.

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