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Journal of Chemical and Pharmaceutical Research

ISSN No: 0975-7384
CODEN(USA): JCPRC5

J. Chem. Pharm. Res., 2011, 3(2):617-622

Synthesis of Ethylfuro[2,3-h] Chromone-8-Carboxylates

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ABSTRACT

*A mixture of 8-Formyl-7-hydroxy chromones (**5a-h**) react with ethyl bromo acetate in as K_2CO_3 phase transfer catalyst under Nitrogen atmosphere gives ethylfuro[2,3-h] chromone-8-carboxylates (**7a-h**) in good yields.*

Keywords: Ethyl bromoacetate, nitrogen gas, K_2CO_3, 8-formyl-7-hydroxy chromones.

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[5-10] Genstein having estrogen hormonal activity, and 7-isopropoxy flavones for treatment of postmenopausal and senile osteoporosis.

With a view synthesize new heterocyclic ring fused chromones and isoflavones we studied the Rossing method by 7-hydroxy chromones and isoflavones. Literature shows that Rossing method 2-Acylphenoxyacetic acids 2, 4-Diacetyl resorcinol via or Phase transfer catalyst under nitrogen atmosphere to gives rise to either Benzofuran or 2-Acetyl benzofurans. Selective formation of benzofurans and 2-Acetyl benzofurans depends on solvent and structural features of substrates.

EXPERIMENTAL SECTION

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 ethy1furo [2,3-h] chromone -8-carboxylates (7a-h): 7-Hydroxy and 8-Formyl-7-hydroxychromones (**4a-h & 5a-h**) were synthesized by following literature[11-15] methods.

A stirred mixture of 8-Formy1-7-hydroxy-3-methyl-2-phenylchromone **(5a)** (2.8g, 10mmol), ethy1 bromoacetate **(6)** (2.04ml, 12mmol), powdered K_2CO_3 (2.76g, 20mmol) for refluxed under dry nitrogen atmosphere with a Dean-Stark trap (to remove water) for 6 h. The reaction mixture was allowed cool to room temperature and the reaction mass poured into the crushed ice and left overnight. The crude solid was column chromatographed with silica gel (60-120mesh) and elution with chloroform to obtain ethy1-3-methy1-2-phenyl-furo [2,3-h] chromone-8–carboxylates **(7a)** (2.71g, 78% yield) and recrystallisation from chloroform as a white coloured crystals. mp 184^{0}C. Similarly **(7b-h)** were prepared.

i) Synthesis of ethy1 3-methyl-2-phenyl-furo [2,3-h] chromone-8-carboxylate (7a): Mp 184ºC IR (KBr): 1715 cm^{-1} (ester C=O); 1634 cm^{-1} (chromone C=O), UV (MeOH): 304nm (log ε 4.1), 264 nm (log ε 4.3), 227nm (log ε 4.0) ^{1}H NMR ($CDCl_3$) (200MHz): δ 8.32 (, J=9.0HZ, H-5), 7.81(s, H-9), 7.67 (m,H-2',6'),7.59 (d,J=9.0Hz,H-6),7.55 (m,H-3',4',5') 2.18 (s,3CH_3),1.46 (t,J=6.7Hz,$COOCH_2CH_3$).^{13}C NMR ($CDCl_3$) (100.6 MHz): δ 177.9 (C-4, C=O), 160.2(C-6a), 1.58.7($COOCH_2CH_3$), 158.4(C-2), 151.2(C-9b), 146.4 (C-8), 133.1(C-1'), 130.3(C-4'), 128.9(C-3', 5') 128.5 (C-2', 6), 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 349 $[M+H]^+$ and 371 $[M+Na]^+$.

ii) Ethyl-6-chloro-3-methy1-2-phenyl-furo [2,3-h] chromone-8-carboxylate (7b):Mp153 ^{0}C IR (KBr): 1718 cm^{-1} (ester C=O); 1645 cm^{-1} (chromone C=O), UV (MeOH): 316 nm (log ε 4.1), 258 nm (log ε 4.4), 230 nm (log ε 3.9).^{1}H NMR (CDC1$_3$) (200MHz): δ 8.26(d, J=9.0Hz, H-5), 7.72(s, H-9), 7.54 (m,H-6,6), 7.41 (m, H-3, 4, 5,), 1.92 (s, 3-CH_3), 1.37 (t, J=6.7Hz, $COOCH_2CH_3$).^{13}C NMR (CDC1$_3$) (100.6 MHz): δ 177.4 (C-4, C=O), 158.5 (C-6a), 158.4 ($COOCH_2CH_3$), 158.3 (C-2), 151.4 (C-9b), 146.4 (C-8), 133.5 (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), 110.3(C-611.0 (C-3-CH_3).MS: m/z 383 $[M+H]^+$, 384 [M+2] and 405 $[M+Na]^+$.

iii) Ethy1 6-bromo-3-methy1-2-phenyl- furo[2,3-h] chromone-8-carboxylate (7c): Mp 178 ºC 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 (CDC1$_3$) (200MHz): δ 8.31 (d, J=9.0Hz, H-5), 7.78 (s, H-9), 7.60 (m, H-6,2,6), 7.53 (d, J=8.7Hz, H-3, 5), 2.19 (s,3-CH_3), 1.42(t, J=6.7Hz, $COOCH_2CH_3$).^{13}C NMR (CDC1$_3$) (100.6MHz): δ 177.7 (C-4, C=O), 159.0 (C-6a), 158.6 ($COOCH_2CH_3$).158.4(C-2), 151.1(C-9b), 136.6(C-4'), 131.4(C-1'), 130.3(C-3'5'), 128.9(C-2,6,)

125.3(C-5), 118.7(C-4a) 118.3(C-3), 116.8(C-9a), 110.7(C-9).MS: m/z 420 $[M+H]^+$ and 421 [M+2].

iv) Ethy1 6,3-dimethy1-2-phenyl-furo [2,3-h] chromone -8-carboxylate (7d): 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 ($CDC1_3$) (200 MHz): δ 8.29 (d, J=9.0Hz,H-5), 7.79 (s, H-9), 7.57 (m, H-6, H-2,6) 7.03 (d, J=8.6Hz, H-3,5), 4.44 (q, J=6.7Hz, $COOCH_2CH_3$).^{13}C NMR ($CDC1_3$)(100.6 MHz): δ177.9(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), 61.7 ($COOCH_2CH_3$), 55.4 (C-4-OCH_3), 11.8 (C-3-CH_3).MS: m/z 365 $[M+H]^+$ and 278.

v) Ethyl-2-phenyl furo [2,3-h] chromone -8-carboxylate (7e): 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) ^{1}H NMR ($CDC1_3$)(200 MHz): δ 8.27 (d, J=9.0Hz, H-5), 7.95 (m, H-2',6'), 7.88(s,H-9),7.60(d,J=6.7Hz,H-6),7.55(m,H-3',4',5'),6.87(s,H-4.48(q,J=6.7Hz,$COOCH_2CH_3$),^{13}C NMR ($CDC1_3$) (100.6 MHz): δ 177.4(C-4, C=O), 162.7 (C-6a), 158.6 (C-2), 158.5 ($COOCH_2CH_3$), 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) 61.9 ($COOCH_2CH_3$), MS: m/z 335 $[M+H]^+$ and 357 $[M+Na]^+$.

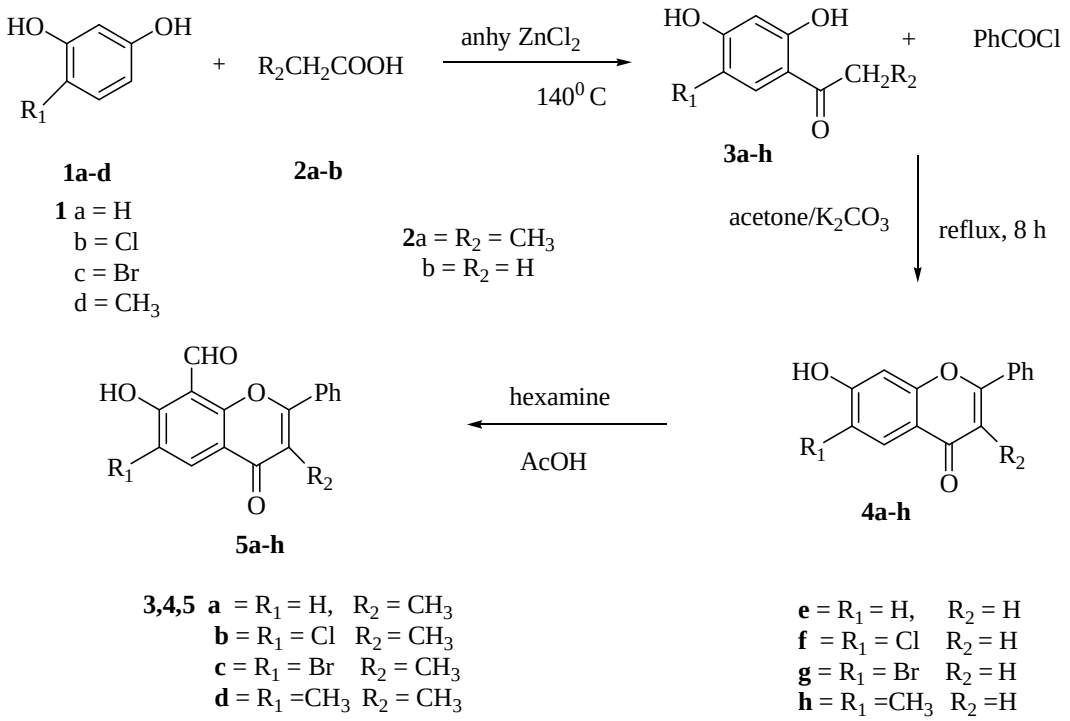
vi) Ethy1 6-chloro –2-phenyl- furo [2, 3-h] chromone– 8 –carboxlate (7f): Mp 158 ^{0}C, IR (KBr): 1717cm^{-1} (ester C=O); 1653 cm^{-1} (chromone C=O), UV (MeOH): 307 nm (log ε 4.2), 264 nm (log ε 4.1), 239nm (log ε 3.8)^{1}H NMR ($CDC1_3$)(200 MHz): δ 8.27 (d, J=9.0Hz, H-5), 7.73 (s, H-9), 7.52(m,H-6, H-6), 7.40(m,H-3,4,5),6.81(s,C-3),4.35(q,J=6.7Hz,$COOCH_2CH_3$),^{13}C NMR ($CDC1_3$)(100.6 MHz): 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),61.9$COOCH_2CH_3$), MS: m/z 369 $[M+1]^+$ and 370.

vii) Ethyl 6-bromo2-phenyl-furo [2,3-h] chromone -8-carboxylate (7g): 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 ($CDC1_3$) (400MHz): δ 8.30 (d, J=9.0 Hz, H-5), 7.91 (m, H-9, H-2,6), 7.63 (d, J=9.0Hz,H-6), 7.55 (d, J=8.7Hz, H-3,5), 6.84(s,H-3), 4.48 (q, J=6.7Hz, $COOCH_2CH_3$), ^{13} C NMR ($CDC1_3$)(100.6 MHz): 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), 61.9($COOCH_2CH_3$), MS: m/z 406 $[M+H]^+$ and 407 [M+2].

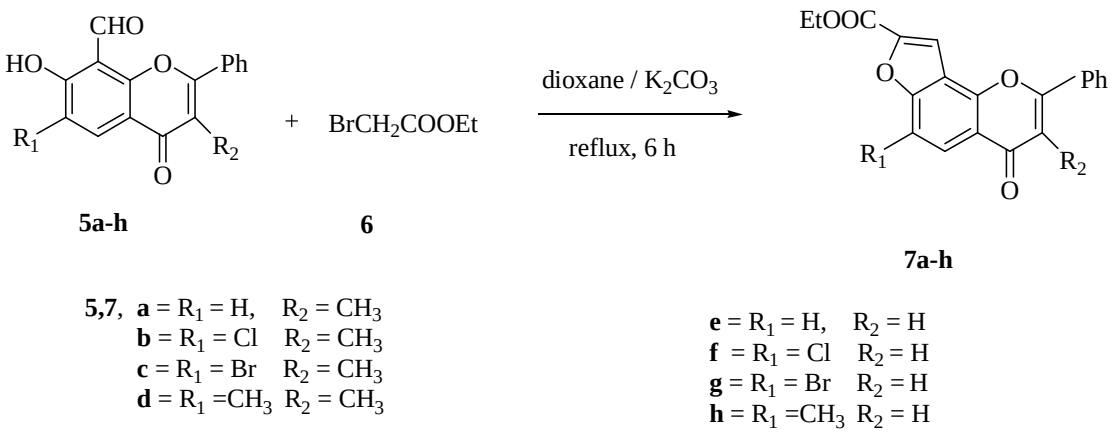
viii) Ethy1 6-methyl-2-phenyl-furo [2,3-h] chromone -8-carboxylate (7h): Mp 178 ^{0}C, IR (KBr): 1739 cm^{-1} (ester C=O), 1654 cm^{-1} (chromone C=O), UV (MeOH): 318 nm (log ε 4.3), 288 nm (log ε 4.2), 229 nm (log ε 3.9) ^{1}H NMR ($CDC1_3$)(200 MHz): δ 8.27 (d, J=9.0Hz,H-5), 7.89(m, H-9, H-2,6), 7.60(d, J=9.0Hz, H-6), 7.02 (d,J=8.6Hz, H-3,5), 6.75 (s,3-H), 4.48 (q, J=6.7Hz, $COOCH_2CH_3$),^{13}C NMR ($CDC1_3$)(100.6 MHz):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), 1103.(C-6), 106.8(C-3), 61.8($COOCH_2CH_3$), MS: m/z 351 $[M+H]^+$.

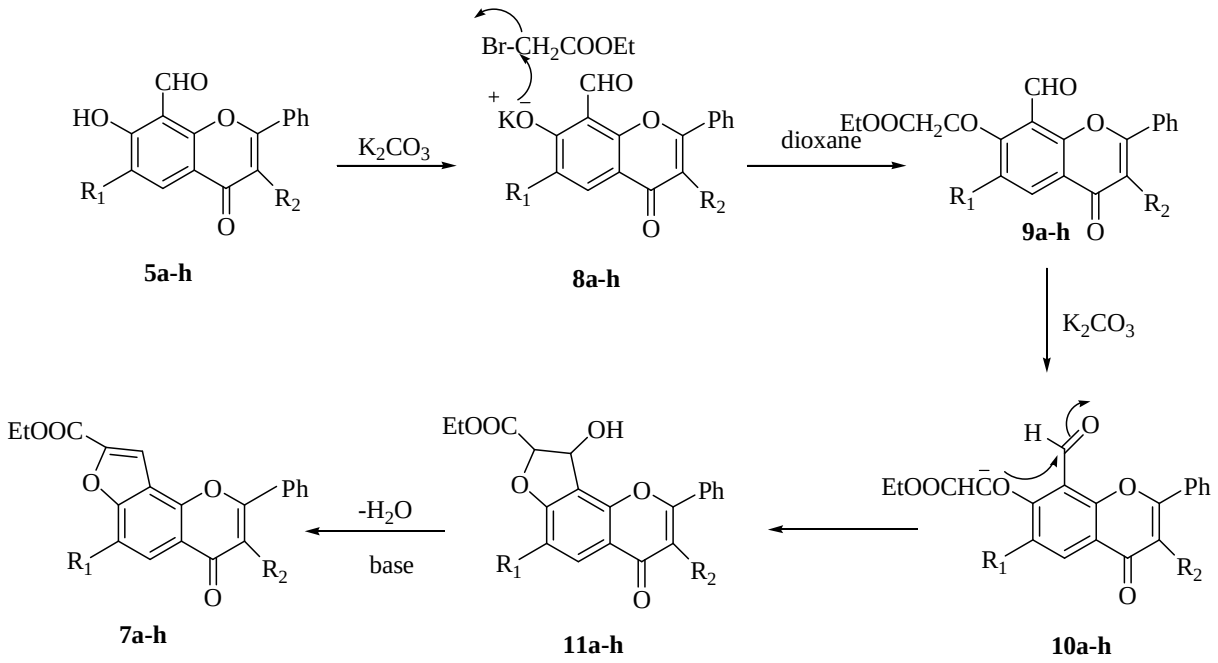
Scheme-1



Scheme-2



Scheme-3



RESULTS AND DISCUSSION

Synthesisofethylfuro[2,3-h]chromone-8-carboxylates(7a-h).[15-20]
8-formyl-7-hydroxy-chromones are synthesized by the following literature methods[11-15] **(Scheme-1).**

Equimolar amount of 8-formyl-7-hydroxy-chromones **(5a),** ethyl bromoacetate **(6)** and anhydrous K_2CO_3 on reflux under dry nitrogen atmosphere with a Dean-Stark trap for 6 hours to give ethyl furo [2,3-h] chromone-8-carboxylates **(7a-h**) (**scheme-2**). 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 (**7a**) showed bands at 304 nm (log ε 4.1), 264 nm (log ε 4.3) and 227 nm (log ε 4.0). The ^1H NMR ($CDCl_3$) (300MHz) spectrum of (7**a**) shows a peak pattern, which indicates furan ring fused at 7,8-position of the chromone and the ester group is at 8-position. The furan ring H-9 appeared at δ 7.81 as a singlet, the CH_3 group of 8-COOEt appeared as a triplet at δ 1.46 (J=6.7 Hz), the OCH_2 of 8-COOEt appeared at δ 4.45 as a quartet (J=6.7 Hz). 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-phenyl chromones. Other signals are from the original 3-methyl-2-phenyl chromones moiety of the 3-CH_3 appeared as a singlet at δ 2.18. The phenyl H-2', 6' appeared at δ 7.67 as a multiplet and H-3', 4', 5' appeared as a multiplet at δ 7.55.

The mechanic pathway of **(5a-7a)** is shown in (**scheme-3**). The base catalyzed reaction of O-hydroxybenzaldehyde **(5a)** moiety with ethyl bromoacetate **(6)** gives ethyl benzofuran-2-carboxylates. First step is the nucleophilic attack of phenoxide ion **(8a)** on ethyl bromoacetate **(6)** to give the ethyl ester of 8-formyl-7-hydroxychromones **(9a**) the base K_2CO_3 generates a

carbanion **(10a)** of the reactive CH_2 group, which reacts intramolecular nucleophilic substitution with CHO to give a dihydro furano alcohol **(11a).** The base catalyzed dehydration of dihydro furano alcohol leads to the formation of ethyl-2-phenyl-3-methyl furo [2,3-h] chromene-8-corboxylates **(7a),** similarly **(7b-h).**

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