A FACILE SYNTHESIS OF ANGULAR AND LINEAR 8/2-METHYL FURO[2,3-h]/[3,2-g] CHROMONES AND ANGULAR PYRANO[2,3-f] ISOFLAVONES FROM 7-PROPARGYLOXY CHROMONES AND ISOFLAVONES

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Abstract: The Claisen rearrangement of 7-propargyloxy chromones **(2a-d)** and 7-propargyloxy isoflavones **(8a-f)** in N,N-Diethylaniline at 195°C gave 8/2-methylfuro[2,3-h]/[3,2-g] chromones **(3a-d)** and pyrano [2,3-f] isoflavones **(9a-f)** respectively.

Introduction:

Chromones and isoflavones constitute an important class of oxygen heterocyclics. Substituted as well as heterocycle ring fused chromones and isoflavones have a wide range of pharmacological activity. Chromones and isoflavones with medicinal use are khellin, a coronary vasodialator[1,2] , chromone-2-carboxylate a spasmolytic agent and disodium chromoglycate, an antiallergy drug[3], genstein having estrogen harmonal activity[4,5] and 7-isopropoxy isoflavone for treatment of postmenopausal and senile osteoporosis[6]

Earlier we reported a facile route to linear and angular 2-methyl furano chromones by the oxidative cyclization of 7-hydroxy –6/8-allyl chromones with $PdCl_2/(PhCN)_2$[7]. We also reported the synthesis of 2-methyl furano-2-methyl dihydro furano-pyrano fused flavones and coumarins starting from 7-propargyloxy and 7-hydroxy-8-allyl flavones and coumarins[8-10].

With a view to synthesize new heterocyclic ring fused chromones and isoflavones we studied the Claisen rearrangement of 7-propargyloxy chromones and isoflavones. Literature shows that Claisen rearrangement of aryl propargyl ethers proceed via an allenyl intermediate to give rise to either benzopyran or 2-methyl benzofurans. Selective formation of benzopyrans or 2-methyl benzofurans depends on solvent and structural features of substrate[11-14].

Results and Discussions

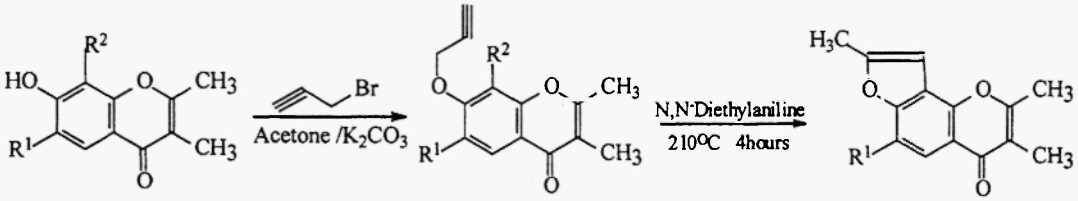
1) **Synthesis of 8/2-methylfuro[2,3-h]/[3,2-g] chromones (3a-d):** Claisen rearrangement of 7-Propargyloxy chromones **(2a-d)** Equimolar amounts of 7-hydroxy-2,3-dimethylchromone **(1a)** and propargyl bromide on refluxing in acetone-K_2CO_3 medium gave quantitatively 7-propargyloxy-2,3-dimethyl chromone **(2a)** . Similarly **2b-d** were prepared. In its IR **2a** shows the C≡C peak at 2130cm^{-1} and C≡C-H at 3260cm^{-1}. In its ^{1}H-NMR the OCH_2 group of the propargyl moiety appeared at δ 4.72 as a doublet (J=2.5Hz) and the acetylinic proton appeared at δ 2.60 as a triplet (J=2.5Hz). The analytical and spectral data of **2a-d** given in **Table-1.** 7-Propargyloxy-2,3-dimethylchromone **(2a)** was dissolved in N,N-diethylaniline and refluxed at 195^{0}C for 4 hours. The reaction mixture was poured in HCl-ice mixture and the product extracted into ether. Ether evaporated and the crude product on column

chromatography on silicagel by eluting with benzene gave 2,3,8-trimethyl furo[2,3-h] chromone ' 2,3,8-trimethyl-4H-furo[2,3-h] chromen-4-one **(3a)**, as a colourless solid, mp 231^{0}C. In its H^1-NMR, **3a** showed peaks characteristics of a methyl substituted furan fused to the chromone angularly. The furan methyl group resonated as a singlet at δ 2.55 and the remaining furan proton resonated as a singlet at δ 6.70. Ortho coupled H-5 and H-6 of the chromone ring appeared as AB doublets at δ 8.05 and δ 7.43 with J=10 Hz indicating that the furan ring is fused to chromone angularly. The other two chromone methyls at C-2 and C-3 appeared as a singlets at δ 2.45 and δ 2.01, In its MS **3a** showed M+ at m/z 228 and m/z 200 (M-CO), 199(M-HCO) and the ion m/z 185 arises due to ring expanded chromenyl cation.

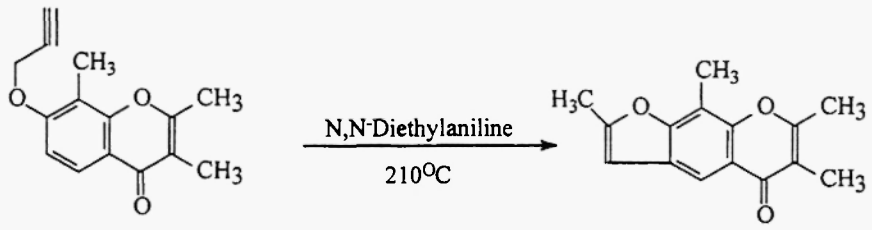
Similarly **2b** and **2c** which have halogen located at 6-position on the chromone gave angularly fused 8-methyl furo[2,3-h] chromones **3b,3c** while **2d** which has an a methyl group at 8-position gave linearly fused 2-methylfuro [3,2-g] chromone/2,6,7,9-tetramethyl-5H-furo [3,2-g] chromene-5-one **3d**. Analytical and spectral data of **3a-d** given in **Table-2**

The mechanistic pathway from **2a** to **3a** is shown in scheme (**2**). **2a** under the thermal conditions of the reaction, undergoes [3,3] sigmatropic shift to give 7-hydroxy-8-allenyl chromone **(5a)**. The chromone carbonyl which is para to the hydroxyl ionizes the hydroxyl group, thereby generating a stable polar intermediate (**6a**). Kinetically controlled nucleophilic attack by the hydroxyl at the allene C-2 give rise to five membered methyl furan ring (**3a**).

Scheme-1



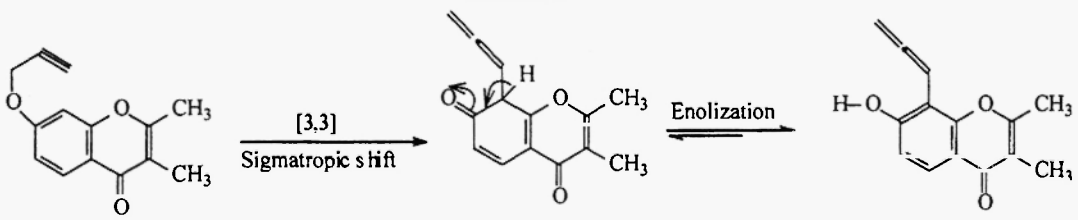
(1a-d) **(2a-d)** **(3a-c)**



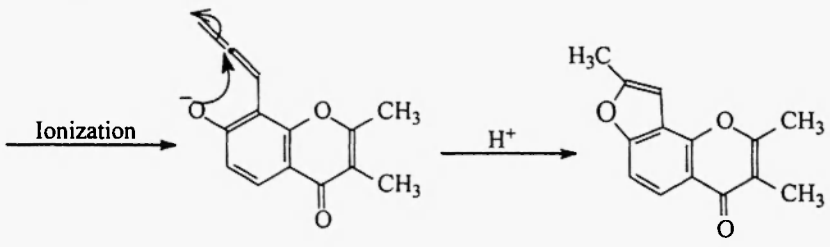
(2d) **(3d)**

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

Scheme-2



(2a) **(4a)** **(5a)**



(3a)

Physical constants and spectral data of 7-Propogyloxy-chromones.**(2a-d): Table-1**

Compound	Mp/°C	IR ν_{max}(cm^{-1}) C=O,C=C,C≡C-H	^{1}H NMR ($CDCl_3$) (δ/ppm, J in Hz) (200MHz), Mass M^+
2a	99	1640, 2130, 3260	2.42(s,CH_3-2),2.05(s,CH_3-3),8.12(d,J=10Hz,H-5),7.00 (dd,J=10Hz,2.5Hz,H-6), 6.88(d,J=2.5Hz, H-8),2.60 (t,J= 2.5Hz,=C-H),4.72(d,J=2.5Hz,-OCH_2), M^+ 228
2b	105	1645, 2125, 3240	2.58(s,CH_3-2),2.03(s,CH_3-3), 8.00(s,H5), 6.91 (s,H-8),2.57(t, J=2.5Hz,=C-H),4.71(d,J=2.5Hz,-OCH_2), M^+262
2c	109	1645, 2130, 3240	2.56 (s,CH_3-2),2.01(s,CH_3-3),8.01(s,H-5),6.98 (s,H-8),2.47(t,J=2.5Hz =C-H),4.71 (d,J=2.5Hz,-OCH_2), M^+ 306
2d	101	1640, 2130, 3260	2.54(s,CH_3-2),2.00(s,CH_3-3),2.38(s,CH_3-8), 7.9 (d,J=10Hz,H-5),6.96(d, J=10Hz,H-6),2.48(t, J=2.5Hz, ≡C-H),4.72(d,J=2.5Hz,-OCH_2), M^+242

Physical constants and spectral data of angular and linear 8/2-methyl furo [2,3-h]/[3,2-g] chromones.**(3a-d): Table-2**

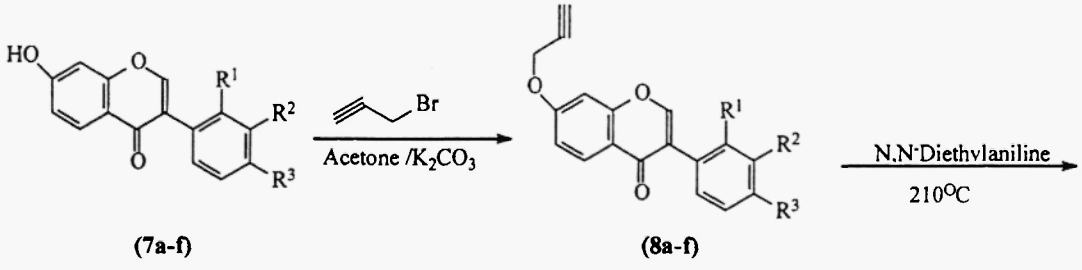
Compound	Mp/°C	IR ν_{max}(cm^{-1}) C=O	^{1}H NMR ($CDCl_3$) (δ/ppm, J in Hz) (200MHz), Mass M^+
3a	231	1640	2.55(s,CH_3-8),2.45(s,CH_3-2),2.01(s,CH_3-3),6.70 (s,H-9),8.05(d,J=10Hz,H-5),7.43(d, J=10Hz,H-6), M^+ 228
3b	253	1640	2.52(s,CH_3-8),2.43(s,CH_3-2),2.06(s,CH_3-3),6.68 (s,H-9),7.98(s,H-5), M^+ 262
3c	261	1645	2.51(s,CH_3-8),2.42(s,CH_3-2),2.04(s,CH_3-3),6.68 (s,H-9),7.97(s,H-5), M^+306
3d	239	1645	2.56(s,CH_3-2),2.48(s,CH_3-7),2.08(s,CH_3-6), 2.49 (s,CH_3-9),6.46(s,H-3),8.15(s,H-5), M^+ 242

2) **Synthesis of pyrano[2,3-f] isoflavones (9a-f):** Claisen rearrangement of 7-Propargyloxy isoflavones **(8a-f)** Reaction of equimolar amounts of 7-hydroxyisoflavone (**7a**) and propargyl bromide in acetone/K_2CO_3 medium gave 7-Propargyloxy isoflavone (**8a**) in high yield. In IR spectrum of **8a** C≡C appeared at 2122cm^{-1}, C≡C-H at 3285cm^{-1} and carbonyl at 1635cm^{-1}. UV spectrum showed the bands at 208nm (logε 4.4) and 220nm (logε 4.3). In its ^{1}H-NMR , the C≡C-H appeared at δ 2.55 triplet (J=2Hz) and the –OCH_2 at δ 4.80 as doublet (J=2Hz), H-5 proton resonated at δ 8.24 as doublet (J=10Hz), H-6 appeared at δ 7.05 as a double doublet (J=10.Hz, 2.5Hz) and the H-8 appeared at δ 6.95 as doublet (J= 2.5Hz), aromatic protons H-2' and H-6' appeared as multiplet at δ 7.52 and H-3',4',5' as multiplet at δ 7.52. In the MS of **8a,** M^+ appeared at m/z 276 (100%) and other peaks at m/z 275 (75%) and at m/z 247 (20%). Analytical and spectral data of **8a-f** is given in **Table-3.**

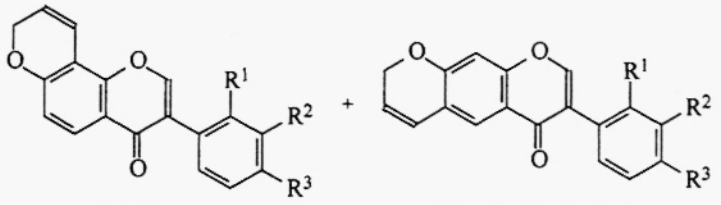
7-Propargyloxy isoflavone (**8a**) dissolved in N,N-diethylaniline and refluxed at 220^{0}C for 6 hours gave pyrano [2,3-f] isoflavone/3-phenyl-4H,8H[2,3-f] chromen-4-one (**9a**) by Claisen rearrangement. In its IR carbonyl peak appeared at 1630cm^{-1}, its UV-showed bands at 205nm (log ε 4.4) and 220nm (log ε 4.3). In the ^{1}H-NMR of **9a** the signal pattern indicates the presence of -OCH_2-CH=CH- group as a part of ring system. The OCH_2 group of new ring system appears as doublet at δ 4.95 (J=1.5Hz). the olefinic proton H-10 appeared as doublet at δ 6.85 (J=10Hz), H-9 appeared at δ5.85 as a double triplet (J=10, 3Hz) indicating pyran ring fused to isoflavone moiety. Other signals are from isoflavone, the H-2 appeared at δ 7.95 as singlet, H-5 and H-6 at δ 8.05 as doublet (J=9Hz), δ 6.80 as doublet (J=9Hz), The phenyl protons H-2',6' appeared as multiplet at δ7.55 and H-3',4',5' at δ7.40 as multiplet.

In this reaction there is a possibility for the formation linearly fused pyrano isoflavone (**10a**), however the ^{1}H-NMR spectrum of the reaction product, H-5,H-6 appeared as AB doublet with coupling constants J=9Hz indicating angularly fused pyranoisoflavone (**9a**). In the MS of **9a** M^+ appeared at m/z 276(100%), Similarly **8b-f** on Claisen rearrangement produced angularly fused isoflavones (**9b-f**). Analytical and spectral characteristics of **9a-f** are given in **Table-4.** The mechanistic pathway from **8a to 9a** shown in scheme(**4**). It is considered that the pyran fused isoflavones are formed by [3,3] sigmatropic shift followed by enolization to give 7-hydroxy-8-allenyl isoflavone **(12a),** which by a [1,5] sigmatropic H-shift followed by electrocyclization gave **9a**.

Scheme-3



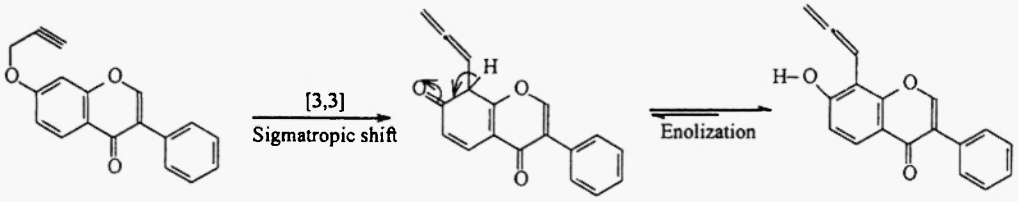
(7a-f) **(8a-f)**

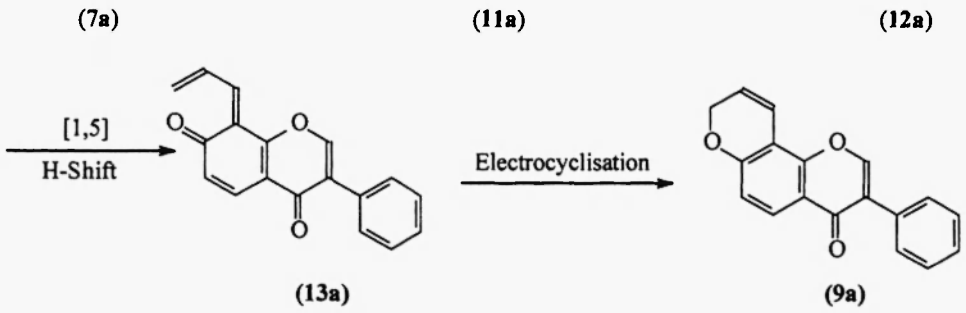


(9a-f) **(10a-f)** not formed.

7,8,9,10. a)R^1,R^2,R^3=H b)R^1,R^2=H, R^3=OCH_3 c)R^1,R^3=Cl, R^2=H
d)R^1,R^2=H, R^3=Cl e)R^1=Cl, R^2,R^3=H f)R^1,R^3=OCH_3, R^2=H

Scheme-4





Physical constants and spectral data of 7-Propogyloxy isoflavones.(**8a-f**): **Table-3**

Compd	Mp/°C	IR $\nu_{max}(cm^{-1})$ C=O,C=C,C≡C-H	UV(MeOH)	^{1}H NMR ($CDCl_3$) (δ/ppm, J in Hz) (200MHz), Mass M^+
8a	156	1635,2122,3285	208nm (logε 4.4) 220nm (log ε 4.3)	7.93(s,H-2),8.24(d,J=10Hz,H-5),7.05(dd,J=10Hz, 2.5Hz,H-6),6.95(d,J=2.5Hz,H8),7.40(m,H-3',4',5')7.52(m,H-2',6'), 4.80(d,J=2Hz,-OCH2),2.55(t, J=2Hz,=C-H), M$^+$ 276
8b	158	1636,2130,3290	244nm (logε 3.9) 264nm (log ε 3.8)	8.0(s,H-2),8.30(d,J=10Hz,H-5),7.10(dd,J=10Hz,2.5Hz,H6), 6.95(d,J=2.5Hz,H-8),7.05(d,J=9Hz,H-3',5'),7.55(d,J=9Hz, H-2',6'),3.92(s,4'-OCH3),4.85(d,J=2Hz,OCH_2),2.62 (t,J=2Hz,≡C-H), M$^+$ 306
8c	193	1630,2125,3289	242nm (logε 3.8) 261nm (log ε 3.4)	7.88(s,H-2),8.23(d,J=10Hz,H-5),7.10(dd,J=9Hz, 2.5Hz,H-6),7.00(d,J=2.5Hz,H-8),7.55(m,H-3',5', ,6'),4.80(d,J=2Hz,-OCH_2),2.55(t, J=2Hz,≡C-H), M$^+$ 345
8d	159	1637, 2128, 3280	210nm (logε 4.9) 225nm (log ε 4.9)	7.95(s,H-2),8.25(d,J=10Hz,H-5),7.08(dd,J=10Hz, 2.5Hz,H-6),6.98(d,J=2.5Hz,H-8),7.43(d,J=10Hz,H-3',5');7.53(d,J=10Hz,H-2',6'),4.80(d,J=2Hz,OCH_2), 2.55(t,J=2Hz, =C-H), M$^+$ 310
8e	143	1624,2128,3290	207nm (logε 5.0) 213nm (log ε 4.9)	7.90(s,H-2),8.25(d,J=10Hz,H-5),7.05(dd,J=10Hz, 2.5Hz,H-6),7.35(m,H-3',4',5'),7.50(m,H-6'), 7.00 (d,J=2.5Hz,H-8),4.80(d,J=2Hz,-OCH_2): 2.55 (t,J= 2Hz, ≡C-H), M$^+$ 310
8f	160	1637,2135,3299	211nm (logε 5.0) 255nm (log ε 4.3)	7.93(s,H-2),8.21(d,J=10Hz,H-5),7.05(dd,J=10Hz, 2.5Hz,H-6),7.18(d,J=2.5Hz,H 8),6.95(d,J=2Hz,H-3'),7.00(dd,J=9Hz,H-5'),7.50(d,J=9Hz,H-6'), 4.80 (d, J= 2Hz,OCH_2),3.94(s,4'-OCH3), 3.92 (s,2 - OCH_3), 2.53(t,J=2Hz, =C-H), M$^+$ 336

Physical constants and spectral data of pyrano[2,3,f] isoflavones (9a-f):**Table-4**

Compound	Mp/°C	IR ν_{max}(cm^{-} C=O	UV(MeOH)	^{1}H NMR ($CDCl_3$) (δ/ppm, J in Hz) (200MHz), Mass $M^{+\bullet}$
9a	120	1630	205nm (logε 4.4) 220nm (log ε 4.3)	7.95(s,H-2),8.05(d,J=9Hz,H-5),6.80(dd,J=9Hz, H-6),5.85(dt,J=3Hz,10Hz,H-9),6.85(d,J=10Hz, H-10),7.55(m,H-2 ,6),7.40(m,H-3 ,4 ,5),4.95 (d,J=1.5Hz,OCH_2-8), $M^{+\bullet}$ 276
9b	158	1631	206nm (logε 5.0) 244nm (log ε 3.9)	7.90(s,H-2),8.05(d,J=9Hz,H-5),6.90(d,J=10Hz, H-6),5.85(dt,J=3Hz,10Hz,H-9),6.85(d,J=10Hz, H-10),7.50(d,J=9Hz,H-2 ,6),6.95(d,J=9Hz,H-3 ,4),4.95(d,J=1.5Hz,OCH_2-8),3.82(s,OCH_3), $M^{+\bullet}$ 306
9c	182	1635	208nm (logε 5.1) 266nm (log ε 4.8)	7.85(s,H-2),8.00(d,J=9Hz,H-5),6.82(d,J=10Hz, H-6),5.83(dt,J=10Hz,H-9),6.86 (d,J=10Hz,H-10),7.20-7.50(m,H-3 ,5 ,6),4.95(d,J= 1.5Hz, OCH_2-8), $M^{+\bullet}$ 345
9d	186	1651	204nm (logε 5.1) 226nm (log ε 4.4)	7.92(s,H-2),8.00(d,J=9Hz,H-5),5.85(dt,J=10Hz, 3.0Hz,H-9),6.82(m,H-6,10),7.50(d,J=9Hz,H-2 ,6), 7.40(d,J=9Hz,H-3 ,5),4.99(bs,OCH_2-8),$M^{+\bullet}$ 310
9e	149	1636	209nm (logε 5.1) 241nm (log ε 4.7)	7.88(s,H-2),8.05(d,J=10Hz,H-5),6.85(d,J=9Hz, H-6)5.86(dt,J=3Hz,10Hz,H-9),6.95(d,J=10Hz,H-10),7.30(m,H-3 ,4 ,5),7.50(m,H-6),4.95(OCH_2-8), $M^{+\bullet}$ 310
9f	140	1632	239nm (logε 5.1) 255nm (log ε 5.4)	7.92(s,H-2),8.04(d,J=9Hz,H-5);5.85(dt,J=10Hz, 3Hz,H-9),6.80-7.40(m,H-6,3 ,5 ,6 ,10), 4.95 (m, OCH_2-8),3.90(s,2OCH_3), $M^{+\bullet}$ 336

Conclusions

The Claisen rearrangement of 7-propargyloxy chromones **(2a-d)** and 7-propargyloxy isoflavones **(7a-f)** afford a new and facile route to 8/2 methylfuro[2,3-h]/[3,2-g] chromones **(3a-d)** and pyrano [2,3,f] isoflavones **(9a-f)** respectively.

Experimental

Melting points were determined in a sulphuric acid bath and are uncorrected. IR spectra are recorded in KBr on a Shimadzu-435 spectrometer, H^1-NMR spectra were obtained on Varian Gemini-200MHz spectrometer with TMS as an internal standard. Mass spectra were recorded on Perkin-Elmer Hitichi RDO-62 instrument.

7-Hydroxychromones **(1a-d)** were prepared by reported methods [15].

General procedure for the synthesis of 7-propargyloxy chromones (2a-d):

7-Hydroxy-2,3-dimethyl chromone **(1a)** (20mmol), propargyl bromide (20mmol) and K_2CO_3 (20g) in acetone (200ml) was refluxed for 4 hours, acetone removed under reduced pressure and the product treated with ice-cold water (100ml). The solid

product that separated out was recrystallised from benzene as light brown crystals of 7-propargyloxy-2,3- dimethyl chromone **(2a),** recrystallised from benzene, yield 95%.**2b**: recrystallised from benzene, yield 96%. **2c**: recrystallised from benzene, yield 96%.**2d**: recrystallised from benzene , yield 96%.

General procedure for the synthesis of 8/2-methyl furo[2,3-h]/ [2,3-g] chromones (3a-d):

7-Propargyloxy-2,3-dimethylchromone **(2a)** (10mmol) was dissolved in N,N-diethylaniline (20ml) and refluxed in an oil bath for 4 hours. After cooling to RT, the reaction mixture was poured into the HCl-ice mixture and stirred well and the resulting oily product was extracted into ether, dried and evaporated. The crude product 2,3,8-trimethyl furo[2,3-h] chromone**(3a)** was chromatographed on silicagel eluting with benzene.**3a:** recrystallised from benzene,Yield 96%.**3b:** recrystallised from benzene, Yield 95% **3c:** recrystallised from benzene, Yield 95%.**3d**: recrystallised from benzene, Yield 95%

7-Hydroxyisoflavones **(7a-f)** were prepared by reported methods [16].

General procedure for the synthesis of 7-Propargyloxy isoflavones (8a-f):

7-Hydroxyisoflavone**(7a)**,(10mmol) dissolved in acetone (40ml), propargyl bromide (40mmol)and potassium carbonate (40mmol) is added and refluxed for 6 hours, product **8a** is purified by column chromatography and recrystallised from chloroform as pale yellow needles 70-80% yields. **8b-f:** recrystallised from chloroform, Yield 70-80%.

General procedure for the synthesis of pyrano [2,3-f] isoflavones (9a-f):

7-Propargyloxy isoflavone **(8a)**,(10mmol) was dissolved in N,N-diethylaniline (20ml) and refluxed for 6 hours. The reaction mixture cooled and poured in cold dil-HCl (100ml) and extracted with ethylacetate (200ml) to give pyrano [2,3-f] isoflavone **(9a)** which was recrystallised from chloroform to give white needles 75-80% yields.**9b-f**: recrystallised from chloroform, Yield 65-75%.

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