REGIOSELECTIVE SYNTHESIS OF THIOPYRANO[2,3-*b*][1]-BENZOPYRAN-5(2*H*)-ONES[#]

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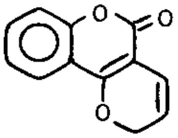
Abstract - A number of thiopyrano[2,3-*b*][1]benzopyran-5(2*H*)-ones (5a-g) have been regioselectively synthesised in 65-82% yields from 4-propynyloxycoumarins (8a-g) through thionation followed by sigmatropic rearrangement.

Recently the regioselective synthesis of a number of 3,4-fused 2*H*-pyranocoumarins[1] (1) and thiocoumarins[2] (2), 2,3-fused 2*H*-thiopyrano- and 4*H*-thiopyranothiochromones[3] (3,4) have been reported. However, to our knowledge the synthesis of 2,3-fused 2*H*-thiopyranochromones (5) remain unreported. We devised a simple strategy to synthesise this heterocyclic ring system through thionation of the lactone carbonyl of easily available propynyloxy derivatives of 4-hydroxycoumarin followed by thermal sigmatropic rearrangement and <u>*in situ*</u> cyclisation to the 2*H*-thiopyrano[2,3-*b*][1]chromone instead of 2*H*-pyrano[3,2-*c*]coumarin[1] due to incorporation of sulphur in the substrate. Here we report the results of this investigation. The starting materials (8a-g) for this study were synthesised



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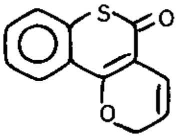

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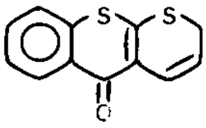

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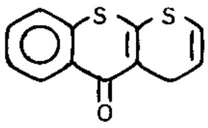

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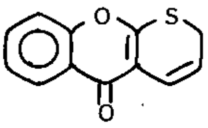

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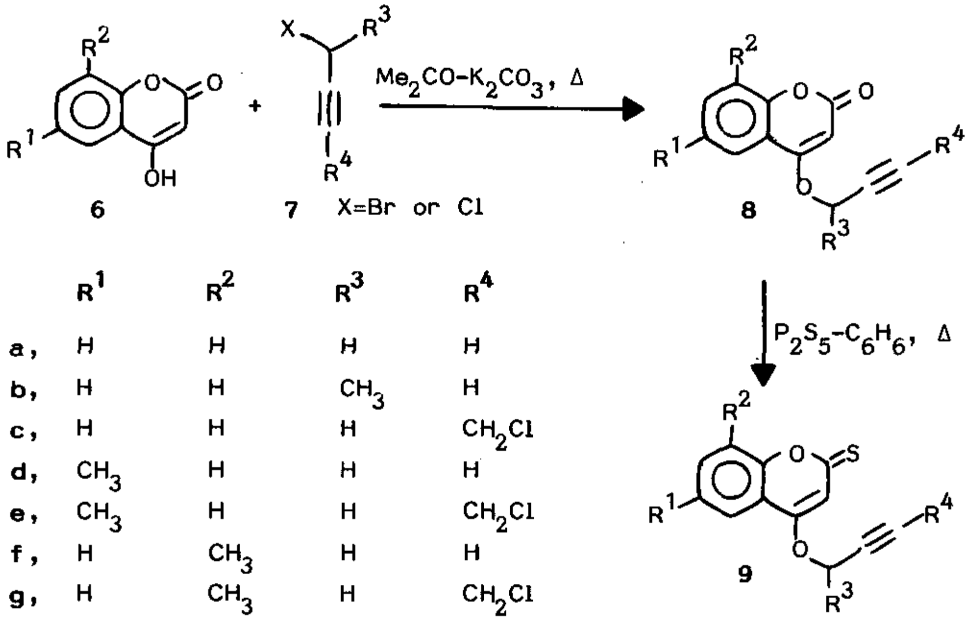
[#] This paper is dedicated to Professor B.S.Thyagarajan of the University of Texas at San Antonio, Texas on the occasion of his 65th birth anniversity.

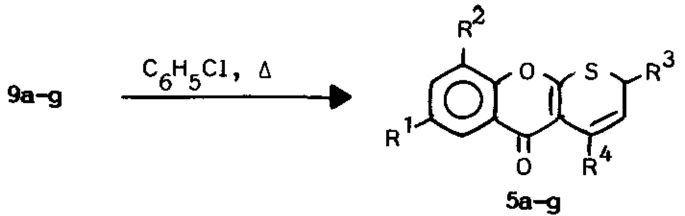
according to our earlier published procedure.[1] When compound (**8a**) was refluxed with phosphorus pentasulphide in dry benzene for 5 h, a yellow crystalline solid mp 174°C was isolated from the reaction mixture in 83% yield. This was characterised as product (**9a**) from its elemental analysis and spectral data. Formation of a single product from this reaction encouraged us to synthesise other derivatives (**9b-g**) from **8b-g** in 75-85% yield (Scheme 1).



	R^1	R^2	R^3	R^4
a,	H	H	H	H
b,	H	H	CH_3	H
c,	H	H	H	CH_2Cl
d,	CH_3	H	H	H
e,	CH_3	H	H	CH_2Cl
f,	H	CH_3	H	H
g,	H	CH_3	H	CH_2Cl

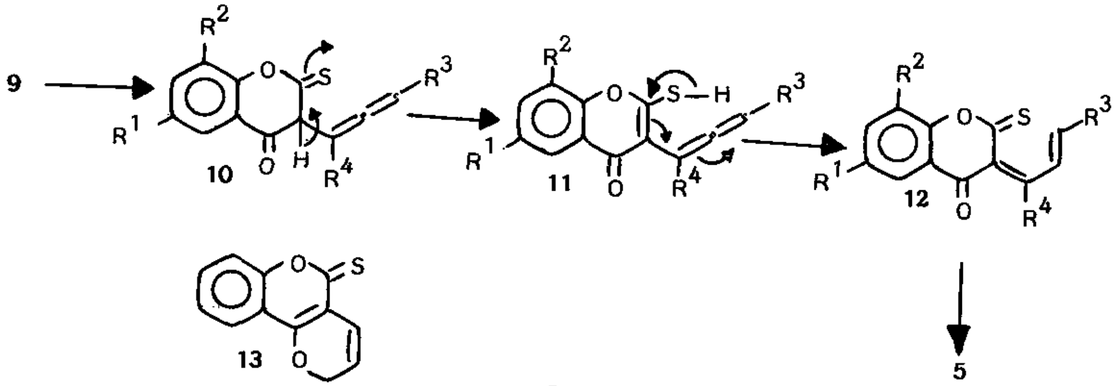
Scheme 1

When **9a** was refluxed in chlorobenzene for 10 h, a white crystalline product mp 144°C in 75% yield was obtained. This was characterised to be thiopyrano-[2,3-*b*][1]benzopyran-5(2*H*)-one (**5a**) from its elemental analysis and spectral data. Nmr spectrum of **5a** showed two proton doublet of a doublet at δ 3.74 (J=5 Hz, 1.2 Hz) due to $-S-CH_2$, one proton doublet of a triplete at δ 5.68 (J=9.9 Hz, 5 Hz) due to $-S-CH_2-CH=CH$, one proton doublet at δ 6.90 (J=9.9 Hz) due to $-S-CH_2-CH=CH$ and one proton doublet of doublet at δ 8.21 (J=5.7 Hz, 2 Hz) due to aromatic H_6. The mass spectrum of **5a** showed signal at m/z 216 (base peak, M^+). To generalise the regioselectivity of this reaction other substrates (**9b-g**) were similarly refluxed in chlorobenzene and products (**5b-g**) were isolated in 65-82% yields (Scheme 2).



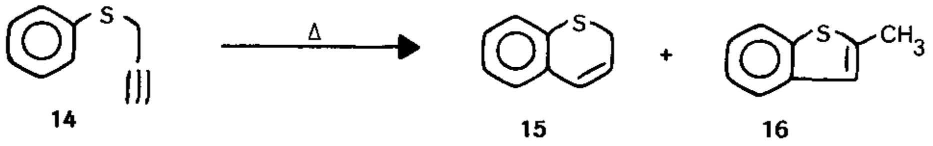
Scheme 2

The formation of 5 from 9 can easily be explained[4] by the [3,3] sigmatropic rearrangement of 9 to form the intermediate (10) followed by enolisation, [1,5] hydrogen shift and electrocyclic ring closer to give the cyclic product (5) (Scheme 3). The exclusive formation of 2*H*-thiopyrano[2,3-*b*][1]chromone (5) instead of 2*H*-pyrano[3,2-*c*][1]benzopyran-5(2*H*)-thione (13) is explicable by the presence of sulphur for this cyclisation.



Scheme 3

It is interesting to note that there is no indication for the formation of isomeric methylthienochromones during this rearrangement although it is reported[5] that phenyl propynyl sulphide (14) on thermal rearrangement gave a mixture of 2*H*-benzothiopyran (15) and 2-methylbenzo[*b*]thiophene (16) (Scheme 4).



Scheme 4

The reaction is found to be regioselective with the seven substrates (**9a–g**) studied so far. This provides a simple and efficient method for the synthesis of thiopyrano[2,3-*b*][1]benzopyran-5(2*H*)-ones (**5**).

EXPERIMENTAL

The melting points were recorded on a sulphric acid bath and are uncorrected. Uv spectra were recorded on a Hitachi 200-20 spectrophotometer using ethanol as a solvent. Ir spectra were recorded in KBr discs on a Perkin Elmer 1330 ir spectrophotometer. Nmr spectra were ditermined in deuteriochloroform using tetramethylsilane as an internal standard on a Jeol FX-100 instrument at IICB, Calcutta and on a Bruker 400 AC (250 MHz) spectrometer at the University of Konstanz, Konstanz, Germany. Mass spectra and elemental analyses were carried out at RSIC, CDRI, Lucknow. Pet. ether indicates petroleum ether of boiling range 60-80°C and silica gel (60-120 mesh) is obtained from Qualigen, India.

General procedure for alkylation of 4-hydroxy coumarins :

Compound (**8a–g**) are prepared according to our earlier published procedure.[1] Compound (**8a–c**) were reported earlier.[1]

Compound (**8d**) : Yield 55%; mp 146°C; uv (λ, nm) : 222 (log ε 3.71), 261 (log ε 4.02), 309 (log ε 3.23); ir (ν, cm^{-1}): 3200, 3080, 2110, 1700, 1615, 1245, 1205, 1100; nmr (δ, ppm) (250 MHz) : 2.41 (3H, s), 2.67 (1H, t, J=2.4 Hz), 4.85 (2H, d, J=2.4 Hz), 5.80 (1H, s), 7.20-7.38 (2H, m) 7.61(1H, s); ms(m/z) 214(M^+). Anal. Calcd for $C_{13}H_{10}O_3$ C, 72.90; H, 4.67. Found C, 72.62; H, 4.93.

Compound (**8e**) : Yield 52%; mp 140°C; uv (λ , nm) : 216 (log ε 3.71), 310 (log ε 3.23); ir (ν, cm^{-1}) : 3050, 1700, 1600, 1540, 1315, 1240, 1100; nmr (δ, ppm) (250 MHz) : 2.43 (3H, s), 4.20 (2H, t, J=2 Hz), 4.93 (2H, t, J=2 Hz), 6.85 (1H, s), 7.39-7.44 (2H, m), 7.64 (1H, s); ms(m/z) 262, 264; Anal. Calcd for $C_{14}H_{11}O_3Cl$ C, 64.00; H, 4.86. Found C, 64.20; H, 4.58.

Compound (**8f**) : Yield 50%; mp 138°C; uv (λ, nm) : 223 (log ε 3.81), 261 (log ε 4.09), 309 (log ε 3.34); ir (ν, cm^{-1}) : 3220, 3100, 2110, 1700, 1620, 1575, 1250, 1205, 1100; nmr (δ, ppm) (250 MHz) : 2.43 (3H, s), 2.70 (1H, t, J=2.4 Hz), 4.88 (2H, d, J=2.4 Hz), 6.89 (1H, s), 7.27-7.64 (3H, m); ms(m/z) 214. Anal.

Calcd for $C_{13}H_{10}O_3$ C, 70.90; H, 4.67. Found C, 70.70; H, 4.43.

Compound (**8g**) : Yield 58%; mp 156°C; uv (λ, nm) : 216 (log ε 3.77), 310 (log ε 3.33); ir (ν, cm^{-1}) : 3040, 1690, 1595, 1540, 1360, 1320, 1240, 1110; nmr (δ, ppm) (100 MHz) : 2.40 (3H, s), 4.20 (2H, t, J=2 Hz), 4.92 (2H, t, J=2 Hz), 6.84 (1H, s), 7.40-7.62 (3H, m); ms(*m/z*) 262, 264. Anal. Calcd for $C_{14}H_{11}O_3Cl$ C, 64.00; H, 4.86. Found C, 64.25; H, 4.61.

General procedure for synthesis of 9a-g :

A mixture of compound (**8a-g**) (0.002 mol) and phosphorus pentasulphide (0.670 g, 0.003 mol) was refluxed in dry benzene (50 ml) on water bath for 5 h. The reaction mixture was cooled and extracted with benzene (3x25 ml) and the extract was dried over Na_2SO_4. Removal of solvent gave a solid mass which was then chromatographed over silica gel. The solid product (**9a-g**) were obtained when the column was eluted with benzene:pet. ether (1:3).

Compound (**9a**) : Yield 83%; mp 174°C; uv (λ , nm) : 215 (log ε 3.05), 275 (log ε 2.76), 362 (log ε 2.78); ir (ν, cm^{-1}) : 3240, 2110, 1600, 1545, 1370, 1335, 1115; nmr (δ, ppm) (250 MHz) : 2.70 (1H, t, J=2.4 Hz), 2.89 (2H, d, J=2.4 Hz), 6.91 (1H, s), 7.35-7.85 (4H, m); ms(m/z) 216. Anal. Calcd for $C_{12}H_8O_2S$ C, 66.66; H, 3.70. Found C, 66.32; H, 3.96.

Compound (**9b**) : Yield 84%; mp 168°C; uv (λ , nm) : 219 (log ε 3.04), 278 (log ε 2.86), 376 (log ε 2.94); ir (ν, cm^{-1}) : 2980, 1640, 1460, 1355, 1215, 1150; nmr (δ , ppm) (250 MHz) : 1.80 (3H, d, J=6.6 Hz), 2.67 (1H, d, J=2.1 Hz), 5.05 (1H, q, J=2.1 Hz), 6.99 (1H, s), 7.34-7.88 (4H, m); ms(m/z) 230. Anal. Calcd for $C_{13}H_{10}O_2S$ C, 67.83; H, 4.35. Found C, 68.00; H, 4.00.

Compound (**9c**) : Yield 85%; mp 130°C; uv (λ, nm) : 216 (log ε 3.25), 276 (log ε 3.06), 363 (log ε 3.12); ir (ν, cm^{-1}) : 3000, 1460, 1415, 1345, 1215, 1165; nmr (δ , ppm) (100 MHz) : 4.16 (2H, s), 4.92 (2H, s), 6.84 (1H, s), 7.20-7.92 (4H, m); ms(m/z) 264, 266. Anal. Calcd for $C_{13}H_9O_2ClS$ C, 58.98; H, 3.40. Found C, 59.22; H, 3.15.

Compound (**9d**) : Yield 80%; mp 172°C; uv (λ, nm) : 215 (log ε 3.10), 275 (log ε 2.80), 362 (log ε 2.82); ir (ν, cm^{-1}) : 2980, 1645, 1460, 1350, 1235, nmr (δ, ppm) (250 MHz) : 2.43 (3H, s), 2.70 (1H, t, J=2.4 Hz), 4.87 (2H, d, J=2.4 Hz), 6.89 (1H, s), 7.35-7.45 (2H, m), 7.64 (1H, s); ms(m/z) 230. Anal. Calcd for $C_{13}H_{10}O_2S$ C, 67.83; H,4.35. Found C, 76.60; H, 4.05.

Compound (**9e**) : Yield 82%; mp 146°C; uv (λ, nm) : 216 (log ε 2.90), 275 (log ε 2.70), 363 (log ε 2.87); ir (ν, cm^{-1}) : 3005, 1605, 1365, 1330, 1110; nmr (δ, ppm) (250 MHz) : 2.43 (3H, s), 4.20 (2H, t, J=1.9 Hz), 4.93 (2H, t, J=1.9 Hz), 6.85 (1H, s), 7.36-7.42 (2H, m), 7.64 (1H, s); ms(m/z) 278, 280. Anal. Calcd for $C_{14}H_{11}O_2ClS$ C, 60.32; H, 3.95. Found C, 60.00; H, 3.75.

Compound (**9f**) : Yield 75%; mp 138°C; uv (λ, nm) : 215 (log ε 2.98), 275 (log ε 2.70); ir (ν, cm^{-1}) : 3240, 2120, 1600, 1360, 1330, 1110; nmr (δ, ppm) (250 MHz) : 2.43 (3H, s), 2.70 (1H, t, J=2.4 Hz), 4.78 (2H, d, J=2.4 Hz), 6.89 (1H, s), 7.35-7.64 (3H, m); ms(m/z) 230. Anal. Calcd for $C_{13}H_{10}O_2S$ C, 67.83; H, 4.35. Found C, 67.50; H, 4.02.

Compound (**9g**) : Yield 78%; mp 142°C; uv (λ, nm) : 216 (log ε 3.20), 275 (log ε 3.03); 363 (log ε 3.09); ir (ν, cm^{-1}) : 3245, 2120, 1600, 1555, 1370, 1335, 1110; nmr (δ, ppm) (100 MHz) : 2.40 (3H, s), 4.18 (2H, t, J=1.9 Hz), 4.92 (2H, t, J=1.9 Hz), 6.82 (1H, s), 7.42-7.64 (3H, m); ms(m/z) 278, 280. Anal. Calcd for $C_{14}H_{11}O_2ClS$ C, 60.32; H, 3.95. Found C, 60.02; H, 3.70.

Rearrangement of (9a-g) in chlorobenzene :

Compound (**9a-g**) (2 mmol) was refluxed in chlorobenzene (5 ml) for 8-10 h. The reaction was monitored by tlc. Solvent was removed by column chromatography over silica gel when column was eluted with pet. ether. Compound (**5a-g**) were obtained when the column was eluted with pet. ether : benzene (3:1).

Compound (**5a**) : Yield 75%; mp 144°C; uv (λ, nm) : 255 (log ε 3.25), 283 (log ε 2.99); ir (ν, cm^{-1}) : 3250, 3060, 1600, 1550, 1375, 1335, 1110; nmr (δ, ppm) (250 MHz) : 3.74 (2H, dd, J=5 Hz, 1.2 Hz), 5.68 (1H, dt, J=9.9 Hz, 4.9 Hz), 6.90 (1H, d, J=9.9 Hz), 7.35-7.65 (3H, m), 8.21 (1H, dd, J=5.7 Hz, 2 Hz); ms(m/z) 216. Anal. Calcd for $C_{12}H_8O_2S$ C, 66.66; H, 3.70. Found C, 67.00; H, 3.96.

Compound (**5b**) : Yield 70%; mp 122°C; uv (λ, nm) : 258 (log ε 3.06), 283 (log ε

2.82); ir (ν, cm^{-1}) : 3240, 2980, 1600, 1545, 1350, 1100; nmr (δ, ppm) (250 MHz) : 1.48 (3H, d, J=7 Hz), 3.90-4.01 (1H, m), 5.70 (1H, dd, J=5.6 Hz, 5.6 Hz), 6.88 (1H, d, J=9.9 Hz), 7.35-7.65 (3H, m), 8.21 (1H, dd, J=8.1 Hz, 1.4 Hz); ms(m/z) 230. Anal. Calcd for $C_{13}H_{10}O_2S$ C, 67.83; H, 4.35. Found C, 67.60; H, 4.70.

Compound (**5c**) : Yield 75%; mp 130°C; uv (λ, nm) : 216 (log ε 2.58), 278 (log ε 2.59), 371 (log ε 2.69); ir (ν, cm^{-1}) : 2975, 1605, 1455, 1385, 1220, 1100; nmr (δ , ppm) (100 MHz) : 3.48 (2H, d, J=6 Hz), 4.84 (2H, s), 5.90 (1H, t, J=5 Hz), 7.24-7.80 (3H, m), 8.20 (1H, d, J=8 Hz); ms(m/z) 264, 266. Anal. Calcd for $C_{13}H_9O_2ClS$ C, 58.98; H, 3.40. Found C, 58.80; H, 3.10.

Compound (**5d**) : Yield 65%; mp 166°C; uv (λ, nm) : 225 (log ε 3.23), 283 (log ε 2.98); ir (ν, cm^{-1}) : 2940, 1635, 1605, 1450, 1345, 1210; nmr (δ, ppm) (100 MHz) : 2.42 (3H, s), 3.78 (2H, d, J=6 Hz), 5.68 (1H, dt, J=10 Hz, 5 Hz), 6.92 (1H, d, J=10 Hz), 7.20-7.60 (2H, m), 8.00 (1H, s); ms(m/z) 230. Anal. Calcd for $C_{13}H_{10}O_2S$ C, 67.83; H, 4.35. Found C, 67.08; H, 4.60.

Compound (**5e**) : Yield 82%; mp 146°C; uv (λ, nm) : 222 (log ε 2.14), 261 (log ε 2.77), 371 (log ε 2.42); ir (ν, cm^{-1}) : 1600, 1455, 1385, 1330, 1220, 1100; nmr (δ , ppm) (100 MHz) : 2.44 (3H, s), 3.52 (2H, d, J=6 Hz), 4.90 (2H, s), 5.94 (1H, t, J=6 Hz), 7.20-7.60 (2H, m), 8.00 (1H, s); ms(m/z) 278, 280. Anal. Calcd for $C_{14}H_{11}O_2ClS$ C, 60.32; H, 3.95. Found C, 60.92; H, 3.60.

Compound (**5f**) : Yield 79%; mp 122°C; uv (λ, nm) : 255 (log ε 3.11), 283 (log ε 2.86); ir (ν, cm^{-1}) : 2960, 1635, 1610, 1455, 1400, 1345, 1215; nmr (δ, ppm) (250 MHz) : 2.44 (3H, s), 3.72 (2H, d, J=5 Hz), 5.68 (1H, dt, J=10 Hz, 5 Hz), 6.90 (1H, d, J=10 Hz), 7.25-7.44 (2H, m), 7.98 (1H, s); ms(m/z) 230. Anal. Calcd for $C_{13}H_{10}O_2S$ C, 67.83; H, 4.35. Found C, 68.10; H, 4.02.

Compound (**5g**) : Yield 68%; mp 140°C; uv (λ, nm) : 222 (log ε 2.22), 262 (log ε 2.88), 372 (log ε 2.51); ir (ν, cm^{-1}) : 2980, 1605, 1465, 1410, 1305; nmr (δ , ppm) (100 MHz) : 2.44 (3H, s), 3.52 (2H, d, J=6 Hz), 4.90 (2H, s), 5.94 (1H, t, J=6 Hz), 7.20-7.80 (2H, m), 8.00 (1H, s); ms(m/z) 278, 280. Anal. Calcd for $C_{14}H_{11}O_2ClS$ C, 60.32; H, 3.95. Found C, 60.10; H, 3.70.

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