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Regioselective Synthesis of 4-(Aryloxymethyl)Thiopyrano [2,3-B] [1]Benzothiopyran-5(2H)-Ones

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REGIOSELECTIVE SYNTHESIS OF 4-(ARYLOXYMETHYL)THIOPYRANO [2,3-**b**][1]BENZOTHIOPYRAN-5(2H)-ONES

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Abstract : Phase transfer catalysed alkylation of 4-hydroxy dithiocoumarin (3) with a number of 1-aryloxy-4-chloro-but-2-ynes (4) furnished several 2-(4'-aryloxy-but-2'-ynyl thio)-[1]-benzothiopyran-4-ones (5) which when heated in chlorobenzene gave hitherto unreported 4-(aryloxymethyl)thiopyrano[2,3-**b**] benzothiopyran-5(2H)-ones (2) in excellent yields.

Thieno[2,3-**b**]benzothiopyran-4-one skeleton (1) has been used as an intermediate for the synthesis of a series of drugs[1] which are useful for the treatment of psychotic disturbances. Literature search revealed that the synthesis[2] of this important intermediate was achieved by a long route. Very recently a simple synthesis[3] of thieno[2,3-**b**]benzothiopyran-4-one skeleton and thiopyrano[2,3-**b**]benzothiopyran-5(2H)-one skeleton has been reported by us. We have also reported a simple method for the regioselective formation of the fused pyran ring[4] in the bioactive coumarins. We expected to synthesise 4-(aryloxymethyl)thiopyrano[2,3-b]benzothiopyran-5(2H)-ones(2) using this

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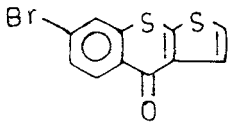
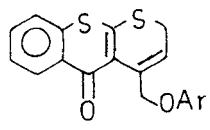
simple methodology. Herein we report the results of our investigation.



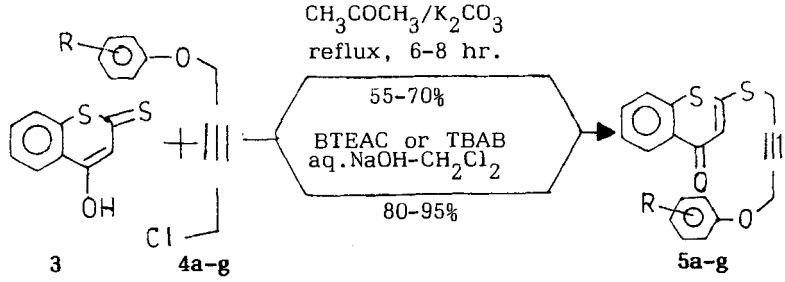
1



2

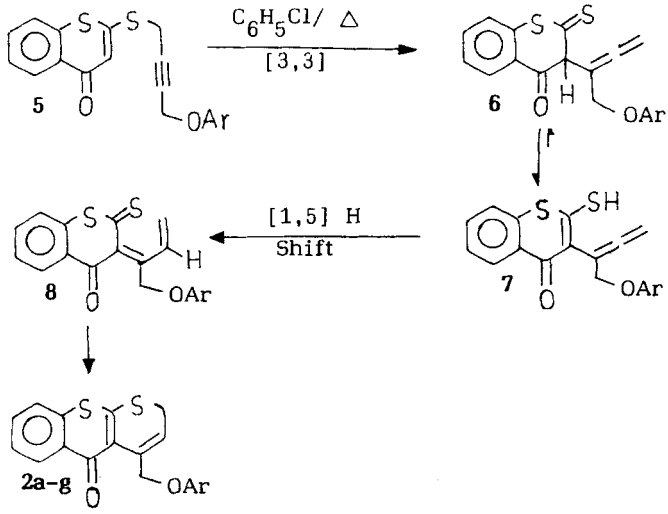
The starting materials 2-[4'-aryloxy-but-2'-ynylthio]-1-benzothiopyran-4-ones (**5**) for this study were prepared by the alkylation[5,6] of 4-hydroxy-[1]-benzothiopyran-2-thione.This can be achieved by either classical alkylation of **3** with a number of 1-aryloxy-4-chlorobut-2-ynes (**4**) in acetone-K_2CO_3 or, PTC alkylation using BTEAC or, TBAB as catalyst in aq. NaOH-CH_2Cl_2. The PTC alkylation is faster and gave a higher yield of S-alkylated products (**5**) 80-95%, whereas classical alkylation needed longer reaction time and the yield of **5** was also relatively lower,55-70%. (Scheme 1). Compounds **5** are crystalline solids except **5g** which is a viscous liquid. The formation of **5** was indicated in the i.r. spectrum by absence of -OH band of **3** in the product and the appearance of a new C=O band at 1610-1640 cm^{-1}. The ^{1}H-NMR spectrum also showed the disappearance of -OH signal and the appearance of two new triplets each for 2H at δ 3.82-3.84 and δ 4.64-4.87.

The aryloxybutynyl sulphides **5** were then refluxed in chlorobenzene for 1-1.5 hr and then removal of chlorobenzene by column chromatography furnished the desired thiopyrano [2,3-b]benzothiopyran-5-ones in 80-95% yield (Scheme 2).Appa-



a, R = 2-CH_3
b, R = 4-Cl
c, R = 4-Br
d, R = 2-Cl
e, R = 2,4-Cl_2
f, R = 4-OCH_3
g, R = H

Scheme 1



Scheme 2

rently there is scope for prototropic shift involving C=O or C=S and in this case prototropic shift takes place in the desired direction finally to give exclusively the linear thiopyranothiochromones, **2**. Compounds **2**, are all crystalline solids and are characterised from their m.p's, elemental analyses and spectral data. The formation of **2** is indicated by the absence of two triplets at δ 3.82-3.84 and δ 4.64-4.87 and the appearance of two doublets each for 2H at δ 3.30-3.64 and δ 5.06-5.20 and a new triplet for 1H at δ 6.04-6.20.

The formation of **2** from **5** may easily be explained by the [3,3]sigmatropic rearrangement of **5** to form the intermediate allenyl en-thiol **7** followed by [1,5] hydrogen shift and electrocyclic ring closure to give the 2H-thiopyrano [2,3-**b**]thiochromone **2**. It may be mentioned here that usually the Claisen rearrangement of arylpropynyl sulphide is reported[7] to give a mixture of 2-methyl benzo(b) thiophene and 2H-benzothiopyran. It is interesting to note here that the thermal rearrangements of seven butynyl sulphides were studied and regioselectivity for the ring closure was observed in all the cases. Therefore, this gives a general regioselective method for the synthesis of linear thiopyrano thiochromones (**2**) in excellent yields.

EXPERIMENTAL

Melting points were determined in capillary on a sulphuric acid bath and are uncorrected. Ultra-violet absorption spectra were recorded on a Hitachi 200-20 spectrometer for solutions

in ethanol. Infrared spectra were run on a Perkin-Elmer Model 1330 infrared spectrometer. Proton NMR and C-13 NMR were recorded on Zeol Fx-100 spectrometer. Microanalyses and recording of mass spectra were carried out at the Indian Institute of Chemical Technology, Hyderabad.

General procedure for the preparation of 1-aryloxy-4-chlorobut-2-ynes (4a-g) :

These compounds were prepared according to published *procedure*[8].

Preparation of 2-(4'-aryloxy-but-2'-ynylthio)-[1]-benzothiopyran-4-ones (5a-g) :

Phase transfer catalysis technique : To a mixture of 4-hydroxy dithiocoumarin (1.16g, 6m mol) and 1-aryloxy-4-chloro-but-2-yne (9 m mol) in dichloromethane (50 ml) was added a solution of BTEAC (0.25g, 0.9 m mol) in 1% aq. NaOH (50 ml) and the mixture was stirred for a period of 3-4 hr. It was then diluted with water (125 ml) and extracted with CH_2Cl_2 (2 x 50 ml). The combined extract was washed with successively with 2(N) HCl (2 x 50 ml), brine (2 x 50 ml) and water (2 x 50 ml) and dried (Na_2SO_4). The solvent was removed and the residual mass was chromatographed over silicagel (BDH, 60-120 mesh). All the compounds were eluted in benzene. The starting ether were recrystallised from chloroform hexane mixture.

Compound **5a**, yield 80%; m.p. 94°C; UV (95% ethanol) : 338(log ε 4.75), 273(log ε 3.92), and 244(log ε 4.25) nm; IR(KBr)

: 1610(C=O), 1595 and 1500 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 100 MHz): δ 2.18 (s, 3H), 3.82 (t, 2H, J=1.5 Hz), 4.80(t,2H, J=1.5 Hz), 6.72-7.72 (m,8H), 8.42-8.64(m, 1H). Anal. calculated for $C_{20}H_{16}O_2S_2$; C, 68.18, H, 4.54. Found C, 68.42, H, 4.64.

Compound **5b**, yield 90%; m.p. 124°C; UV (95% ethanol) : 337(log ε 4.74), 272(log ε 3.88) and 242 (log ε 4.27) nm; IR(KBr) : 1620 (C=O), 1600 and 1520 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 100 MHz): δ 3.84(t, 2H, J=1.5 Hz), 4.66(t,2H, J=1.5 Hz), 6.72-7.80 (m, 8H) and 8.40-8.68(m, 1H). Anal. calculated for $C_{19}H_{13}O_2S_2Cl$; C, 61.20, H, 3.49. Found C, 61.04, H, 3.73.

Compound **5c**, yield 94%; m.p. 126°C; UV (95% ethanol) : 338(log ε 4.80), 274 (log ε 3.90) and 242 (log ε 4.29) nm; IR (KBr) : 1615 (C=O), 1530 and 1500 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 100 MHz) : δ 3.84(t,2H,J=1.5 Hz), 4.68 (t,2H,J=1.5 Hz) 6.68-7.80 (m,8H), 8.40-8.60 (m,1H). Anal. calculated for $C_{19}H_{13}O_2S_2Br$; C, 54.67, H,3.12 Found C, 54.42, H, 3.18.

Compound **5d**, Yield 85%; m.p. 114°C; UV (95% ethanol) : 337(log ε 4.82), 273 (log ε 3.99) and 242 (log ε 4.20) nm; IR (KBr); 1640 (C=O), 1608 and 1500 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 100 MHz) : δ 3.84(t, 2H, J=1.5 Hz), 4.78 (t, 2H, J=1.5 Hz), 6.72-7.80 (m, 8H) and 8.40-8.64 (m, 1H). Anal. calculated for $C_{19}H_{13}O_2S_2Cl$; C, 61.20, H, 3.49. Found C, 61.06, H, 3.64.

Compound **5e**, yield 95%; m.p. 125°C; UV (95% ethanol) : 335 (log ε 4.90), 272 (log ε 3.94) and 243 (log ε 4.21) nm; IR (KBr) : 1620 (C=O), 1600 and 1520, cm^{-1}; ^{1}H-NMR ($CDCl_3$, 100

MHz) : δ 3.84 (t, 2H, J=1.5 Hz), 4.87 (t, 2H, J=1.5 Hz) 6.84-7.76 (m,7H) and 8.40-8.64 (m, 1H). Anal. calculated for $C_{19}H_{12}O_2S_2Cl_2$; C, 56.01, H, 2.95. Found C, 55.88, H, 3.18.

Compound **5f**, yield 85%; m.p. 66°C; UV (95% ethanol) : 338 (log ε 4.78), 273 (log ε 3.87) and 240 (log ε 4.22) nm; IR (KBr) : 1625 (C=O), 1605 and 1520 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 100 MHz) : δ 3.72 (s, 3H), 3.84 (t, 2H, J=1.5 Hz), 4.64 (t, 2H, J=1.5 Hz), 6.76-7.70 (m, 8H) and 8.40-8.60 (m, 1H). Anal. calculated for $C_{20}H_{16}O_3S_2$; C, 65.21, H, 4.35. Found C, 65.47, H, 4.48.

Compound **5g**, yield 90%; viscous liquid; UV (95% ethanol) : 338 (log ε 4.86), 270 (log ε 3.95) and 245 (log ε 4.29) nm; IR (Film) 1640 (C=O), 1610 and 1510 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 100 MHz) : δ 3.84 (t, 2H, J=1.5 Hz), 4.80(t, 2H, J=1.5 Hz), 6.74-7.80 (m, 9H) and 8.40-8.61 (m, 1H). Anal. calculated for $C_{19}H_{14}O_2S_2$; C, 67.45, H, 4.14. Found C, 67.40, H, 4.29.

2-[4'-aryloxy-but-2'ynylthio]-1-benzothiopyran-4-ones (**5a-g**) were also synthesized by classical alkylation procedure i.e., by refluxing a mixture of 4-hydroxy dithiocoumarin (1.16g, 6m mol), 1-aryloxy-4-chloro-but-2-yne (9 m mol) and K_2CO_3 (2.0g) in dry acetone (75 ml) for a period of 6-8 hr. Compound **5a**, yield 60%; Compound **5b**, yield 62%; Compound **5c**, yield 65%; Compound **5d**, yield 57%; Compound **5e**; yield 70%; Compound **5f**, yield 55%, Compound **5g**, yield 58%.

Rearrangement of compound (5a-g) in chlorobenzene

The starting ether (0.2g) was refluxed in chlorobenzene (3 ml) in an oil bath for 1 hr. Chlorobenzene was removed *in vacuo* and the residual mass was chromatographed over silica gel (60-120 mesh, BDH). Elution of the column with pet.ether (60-80°C) removed the residual chlorobenzene and then a white solid was obtained by eluting the column with benzene : pet. ether (60-80°C) 1:1.

Compound **2a**, yield 80%; m.p. 102°C; UV (95% ethanol) : 335 (log ε 4.10), 294(log ε 4.63) and 242 (log ε 4.36) nm; IR (KBr) : 1620 (C=O), 1590 and 1385 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 100 MHz) : δ 2.08 (s, 3H), 3.36-3.60 (d, 2H, J=6Hz), 5.12 (d, 2H, J=1.2 Hz), 6.12-6.36 (dt, 1H, J=6 Hz), 6.72-7.72 (m, 7H) and 8.32-8.52 (m, 1H); ^{13}C-NMR ($CDCl_3$) : δ 16.17, 26.53, 68.24, 111.94, 116.71, 120.48, 124.88, 126.83, 127.71, 128.30, 129.36, 130.53, 131.36, 133.42, 135.83, 136.30, 149.65, 156.71, 177.01; m/e 352(M^+), 246(base), 184; Anal. calculated for $C_{20}H_{16}O_2S_2$; C, 68.18, H, 4.54. Found C, 68.10, H, 4.70.

Compound **2b**, yield 90%; m.p. 130°C; UV (95% ethanol) : 355 (log ε 3.96), 298 (log ε 4.42) and 242 (log ε 4.25) nm; IR (KBr): 1620 (C=O), 1600 and 1490 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 100 MHz) : δ 3.30-3.56 (d, 2H, J=6Hz), 5.09 (d,2H, J=1.2Hz), 6.04-6.28 (dt,1H, J=6Hz), 6.72-7.72 (m, 7H) and 8.28-8.32 (m,1H); ^{13}C-NMR ($CDCl_3$) : δ 26.41, 68.65, 116.36, 117.38, 124.83, 125.59, 127.71, 129.18, 131.36, 133.18, 135.59, 135.71,149.89, 157.24, 176.83; m/e 373 (M^+), 246(base), 184, 171, 109; Anal.

calculated for $C_{19}H_{13}O_2S_2Cl$; C, 61.20, H, 3.49. Found C, 61.12, H, 3.57.

Compound **2c**, yield 90%; m.p 125°C; UV (90% ethanol) : 353 (log ε 3.99), 292 (log ε 4.52) and 242 (log ε 4.30) nm; IR (KBr) : 1615 (C=O), 1600 and 1500 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 100 MHz) : δ3.36-3.60 (d,2H, J=6Hz), 5.08(d, 2H, J=1.2 Hz), 6.04-6.32 (dt,1H, J=6Hz), 6.66-7.80 (m,7H) and 8.28-8.52 (m,1H); ^{13}C-NMR ($CDCl_3$) : δ 26.47, 68.65, 113.00, 117.00, 117.35, 124.88, 127.77, 129.24, 131.42, 132.18, 133.30, 135.65, 135.83, 149.84, 157.77, 176.95; m/e 417 (M^+), 246 (base), 216, 184, 171, 136, 109; Anal. calculated for $C_{19}H_{13}O_2S_2Br$; C, 54.67, H, 3.12. Found C, 54.59, H, 3.22.

Compound **2d**, yield 85%; m.p 155°C; UV (95% ethanol) : 355 (log ε 4.05), 295 (log ε 4.51) and 245 (log ε 4.30) nm; IR (KBr) : 1615 (C=O), 1595 and 1350 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 100 MHz) : δ 3.38-3.60 (d, 2H, J=6Hz), 5.20 (d, 2H, J=1.2 Hz), 6.20-6.44 (dt, 1H, J=6Hz), 6.76-7.68 (m, 7H) and 8.28-8.52 (m, 1H); ^{13}C-NMR ($CDCl_3$) : δ 26.47, 69.06, 111.36, 117.46, 121.47, 122.95, 124.88, 127.71, 128.06, 129.36, 130.12, 131.42, 132.24, 135.30, 135.83, 150.18, 154.01 and 176.95. Anal. calculated for $C_{19}H_{13}O_2S_2Cl$; C, 61.20, H, 3.49. Found C, 61.15, H. 3.56.

Compound **2e**, yield 95%; m.p. 125°C; UV (95% ethanol) : 352 (log ε 3.94), 295 (log ε 4.50) and 242 (log ε 4.29) nm; IR (KBr) : 1630(C=O), 1605 and 1500 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 100

MHz) : δ 3.40-3.64 (d, 2H, J=6Hz), 5.19 (d, 2H, J=1.2Hz), 6.18-6.40 (dt, 1H, J=6Hz), 6.84-7.76(m, 6H) and 8.28-8.52 (m, 1H) Anal. calculated for $C_{19}H_{12}O_2S_2Cl_2$; C, 56.01, H, 2.95. Found C, 55.95, H, 2.99.

Compound **2f**, yield 85%; m.p. 82°C, UV (95% ethanol) : 350 (log ε 4.02), 292 (log ε 4.57) and 240 (log ε 4.28) nm; IR (KBr) : 1600 (C=O), 1585 and 1480 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 100 MHz) : δ 3.36-3.48 (d, 2H, J=6Hz), 3.74 (s, 3H), 5.06 (d, 2H, J=1.2 Hz), 6.06-6.28 (dt, 1H, J=6Hz), 6.78-7.76 (m, 7H) and 8.32-8.54 (m, 1H) Anal. calculated for $C_{20}H_{16}O_3S_2$; C, 65.21. H, 4.35. Found C, 65.12, H, 4.42.

Compound **2g**, yield 90%; m.p. 121°C : UV (95% ethanol) : 355 (log ε 4.12), 295 (log ε 4.48) and 244 (log ε 4.32) nm; IR (KBr) : 1620 (C=O), 1595 and 1485 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 100 MHz) : δ 3.36-3.64 (d, 2H, J=6Hz), 5.20 (d, 2H, J=1.2 Hz), 6.16-6.40 (dt, 1H, J=6Hz), 6.84-7.80 (m, 8H) and 8.30-8.50 (m, 1H). Anal. calculated for $C_{19}H_{14}O_2S_2$; C, 67.45%, H, 4.14%. Found C, 67.29, H, 4.23.

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