Regioselective Synthesis of Polyheterocyclic Scaffolds by Sequential [3,3] Sigmatropic Rearrangements and Pyridine Hydrotribromide Mediated Heterocyclization

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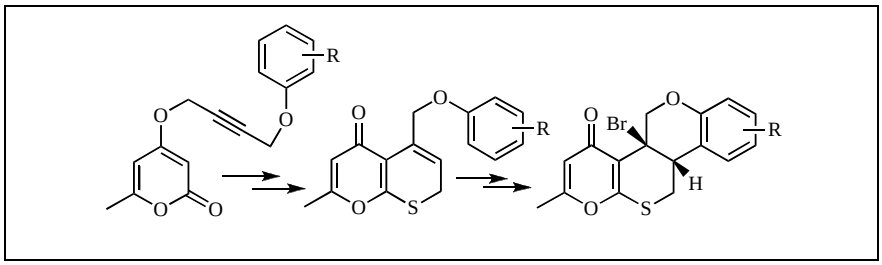

A number of tetracyclic polyhetero scaffolds have been regioselectively synthesised in 70-75% yield from 4-[(3-aryloxy-2-propynyl)oxy]-6-methyl-pyran-2-ones *via* thionation of the lactone carbonyl, sequential Claisen rearrangements and pyridine hydrotribromide mediated heterocyclization.

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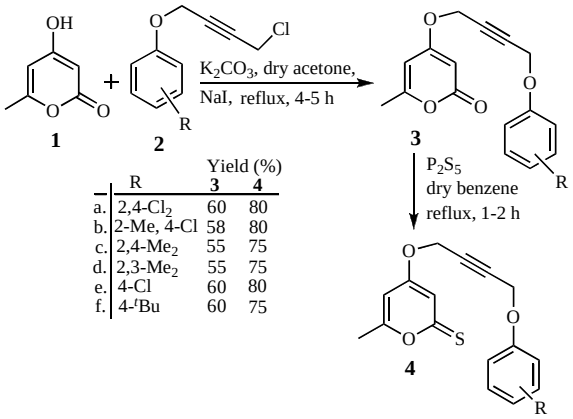
INTRODUCTION

The 4-hydroxy-6-methyl-2-pyrone moiety is important because of its occurrence in a number of naturally occurring compounds [1]. Some of these naturally occurring compounds possess biogenetically active groups [2] at C-3 or C-5 or both. As a logical extension, many more structurally analogous pyrones have been synthesized [3] and their bioactivity has been evaluated. Some 4-hydroxy-2-pyrones have also been tested as anticoagulant agents [4]. Our continued interest in the synthesis of bioactive heterocycles by the application of the sigmatropic rearrangements has directed us to synthesize a number of heterocyclic compounds *viz.* pyrrolopyrimidines [5], thiopyrano[3,2-*c*]quinolones [6], thiopyrano[3,2-*c*]-coumarins [7], pyrrolo[3,2-*c*]coumarins [8], 2,3-dihydrothieno[3,2-*c*]coumarins [9] and also 4-hydroxy-6-methyl-2-pyrones [10-12] annulated heterocycles. Our success in the sequential Claisen rearrangements of coumarin [13] and dithiocoumarin systems [14] prompted us to undertake a study on the thermal rearrangement of 4-[(3-aryloxy-2-propynyl)oxy]-6-methyl-pyran-2-thiones. Herein we report the results. The substrates **3a-f** for this purpose have been synthesized [15] in 55-60% yield from 4-hydroxy-6-methyl-2-pyrones 1 and 1-aryloxy-4-chloro-but-2-ynes **2** by refluxing in dry acetone, anhydrous K_2CO_3 and a catalytic amount of sodium iodide (Finkelstein condition).

RESULTS AND DISCUSSION

We have reported the synthesis of pyrano- [15], pyrido- [16] and thiopyranopyrones [10] fused at 3,4 position of the pyrone nucleus by the application of the sigmatropic rearrangements. Usually sigmatropic rearrangements of 4-[(4'-aryloxy-2'-propynyl)-oxy, thio or amino]-pyran-2-ones are known to provide access to angularly fused heterocycles [15,16]. Here we have changed the strategy by thionation of the pyrone carbonyl. We felt that this may change the mode of cyclization for the formation of a new heterocyclic ring since sulfur is more nucleophilic than oxygen. With this in view, the 4-[(3-aryloxy-2-propynyl)oxy]-6-methyl-pyran-2-ones were subjected to thionation [17] with P_2S_5 in refluxing benzene for 1-2 h to give 4-[(3-aryloxy-2-propynyl)oxy]-6-methyl-pyran-2-thiones **4a-f** in 75-80% yield (Scheme I).

Scheme I

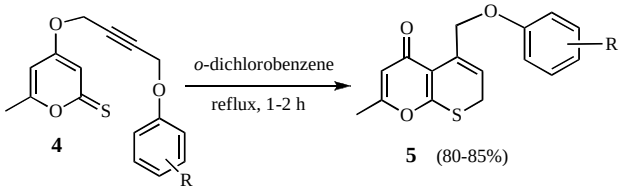


	R	Yield (%) 3	4
a.	2,4-Cl_2	60	80
b.	2-Me, 4-Cl	58	80
c.	2,4-Me_2	55	75
d.	2,3-Me_2	55	75
e.	4-Cl	60	80
f.	4-^{t}Bu	60	75

The products **4a-h** were characterized from their elemental analyses and spectroscopic data. Disappearance of carbonyl stretching frequency in the ir spectra of compounds **4a-h** clearly indicates the formation of –C=S

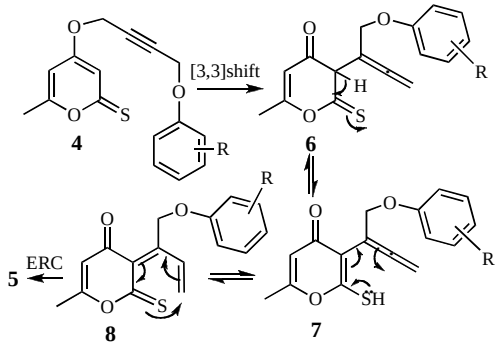
from –C=O. The substrates **4a-f** were then refluxed in *o*-dichlorobenzene for 1-2 h to give **5a-f** in 80-85% yield (Scheme II).

Scheme II



The compounds **5a-f** were characterized from their elemental analyses and spectroscopic data. The ^{1}H NMR spectrum of **5a** showed signals at δ 3.50 (d, J = 5.6 Hz, 2H), 5.17 (d, J = 1.3 Hz, 2H) and a one proton double triplet at δ 6.03 (J = 5.6 Hz, J = 1.3 Hz) indicating the formation of a six-membered thiopyran ring fused at the 2,3 position of the pyrone nucleus. Although substrates **4a-f** possess two potential sites for [3,3] sigmatropic rearrangement – aryl propargyl ether moiety and a vinyl propargyl sulfide moiety. All the substrates underwent a [3,3] sigmatropic rearrangement at the vinyl propargyl sulfide moiety to give the products **5a-f**. The formation of products **5a-f** may be explained by considering an initial [3,3] sigmatropic rearrangement in **4a-f** to give allenyl intermediates **6a-f**. Enolisation followed by cyclisation *via* 1,5-H shift and subsequent 6π-electrocyclic ring closure may afford products **5a-f** (Scheme III). It is remarkable to note that all the substrates **4a-f** studied at this instance regioselectively afforded exclusively products **5a-f**.

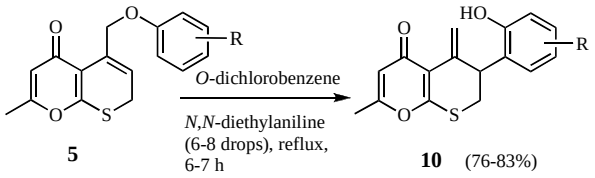
Scheme III



As the products still possess the allyl aryl ether moiety, these were subjected to heating in refluxing *o*-dichlorobenzene in the presence of *N,N*-diethyl aniline for 6-7 h to give the phenolic products **10a-f** in 76-83% yield (Scheme IV).

The compounds **10a-f** were characterized from their elemental analyses and spectroscopic data. A peak in the region 3290 cm^{-1} in the IR spectrum appeared due to the

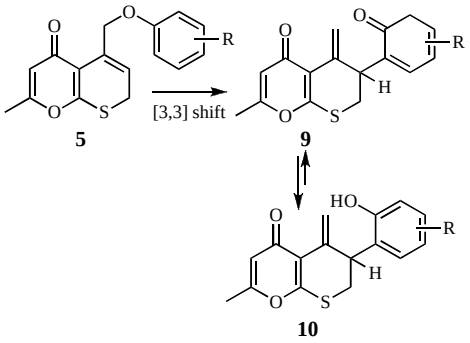
Scheme IV



presence of phenolic –OH group in the compound **10a**. ^{1}H NMR spectrum of the compound **10a** showed signal at δ 5.26 (s, 1H) and 5.78 (s, 1H) indicating the presence of an exocyclic double bond in the compound **10a**.

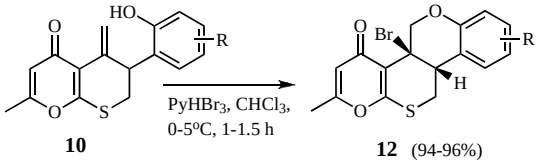
Here also the isolation of the phenolic products is quite unusual. In most of the previous instances either the formation of cyclic product or rearranged phenolic products were reported [18,19]. The formation of **10a-f** from **5a-f** is easily explained by a [3,3] sigmatropic rearrangement followed by enolisation (Scheme V).

Scheme V



Our target was to synthesize polyheterocyclic compounds. We have earlier used pyridine hydrotribromide [20], hexamine hydrotribromide [21] and *N*-iodosuccinimide [22] for regioselective cyclization of *o*-cyclohex-2-ynyl phenols. We therefore treated products **10a-f** with one equivalent of pyridine hydrotribromide at 0-5°C for 1-1.5 h to give the products **12a-f** in almost quantitative yield (94-96% yield) (Scheme VI).

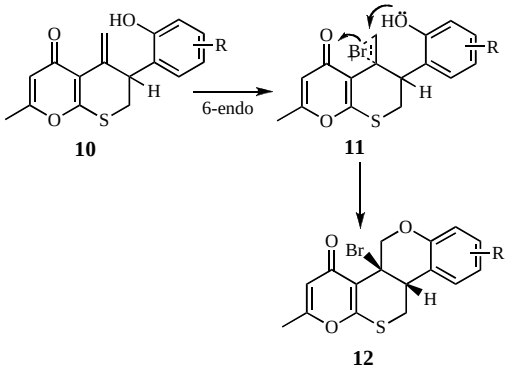
Scheme VI



The products **12a-f** were characterized from their elemental analyses and spectroscopic data. Disappearance of phenolic –OH group in the IR spectrum and two one-proton singlets (due to exocyclic double bond) in the ^{1}H NMR spectrum confirmed the formation of compound

12a. The formation of the products can easily be explained by the formation of a cyclic bromonium ion followed by a *"6-endo"* cyclisation to give angularly fused [6,6] pyranothiopyrans (Scheme VII).

Scheme VII



The Stereochemistry of the ring fusion of the cyclic system can only be surmised from the molecular models (Dreiding Model), which showed a strain free *cis*-arrangement.

Summing up we have developed new, simple and practical synthesis of potentially bioactive polyheterocycles, 12c-Bromo-2-methyl-10b,12c-dihydro-4*H*,5*H*,11*H*-trihydropyrano[3′,4′:5,6]thiopyrano[3,2-*c*]benzopyran-4-ones by the conversion of carbonyl to thiocarbonyl in the substrate and application of two consecutive [3,3] sigmatropic rearrangements.

EXPERIMENTAL

Melting points were determined in an open capillary and are uncorrected. IR spectra were recorded on a Perkin-Elmer L120-000A spectrometer (ν_{max} in cm^{-1}) on KBr disks. UV absorption spectra were recorded in EtOH on a Shimadzu UV-2401PC spectrophotometer (λ_{max} in nm). ^1H NMR (300 MHz, 500 MHz) and ^{13}C NMR (75.5 MHz, 125 MHz) spectra were recorded on a Bruker DPX-300 and Bruker DPX-500 spectrometer in $CDCl_3$ (chemical shift in δ) with TMS as internal standard. Mass spectra was recorded on a JEOL JMS-600 instrument. ^1H NMR and ^{13}C NMR spectra were recorded at the Indian Institute of Chemical Biology, Kolkata and Bose Institute, Kolkata. Silica gel [(60-120 mesh), Spectrochem, India] was used for chromatographic separation. Silica gel G [E-Merck (India)] was used for TLC. Petroleum ether refers to the fraction boiling between 60°C and 80°C.

General procedure for the synthesis of 4-[(3-aryloxy-2-propynyl)oxy]-6-methyl-2*H*-pyran-2-ones (3a-f). A mixture of 1-aryloxy-4-chlorobut-2-ynes (10 mmol) (**2**), 4-hydroxy-6-methyl-2-pyrone (1.26 g, 10 mmol) (**1**), anhydrous K_2CO_3 (3 g) and NaI (0.06 g) were refluxed in dry acetone for 4-5 h. The reaction mixture was cooled; removal of the solvent from the filtrate gave a gummy mass. The gummy mass was subjected to column chromatography over silica gel. Elution of the column with 1:9 ethylacetate-petroleum ether gave the compounds **3a-f**.

Compound 3a. Yield: 60%, sticky liquid; ir (neat) ν_{max} = 1720, 1580, 1250, 1130 cm^{-1}; uv (EtOH): λ_{max} = 220, 280 nm; ^1H NMR ($CDCl_3$, 300MHz) δ = 2.23 (s, 3H), 4.69 (t, *J* = 1.6 Hz, 2H), 4.81 (t, *J* = 1.6 Hz, 2H), 5.47 (s, 1H), 5.78 (s, 1H), 6.93-7.40 (m, 3H); ms: *m/z* = 338, 340, 342 (M^+). *Anal* Calcd. for $C_{16}H_{12}O_4Cl_2$: C, 56.64; H, 3.54; Found C, 56.71; H, 3.64%.

Compound 3b. Yield: 58%; sticky liquid; ir (neat) ν_{max} = 1720, 1580, 1250, 1140 cm^{-1}; uv (EtOH): λ_{max} = 216, 277 nm; ^1H NMR ($CDCl_3$, 300MHz): δ = 2.21 (s, 3H), 2.30 (s, 3H), 4.68 (t, *J* = 1.6 Hz, 2H), 4.79 (t, *J* = 1.6 Hz, 2H), 5.46 (s, 1H), 5.77 (s, 1H), 6.87-7.34 (m, 3H); ms: *m/z* = 318, 320 (M^+). *Anal* Calcd. for $C_{17}H_{15}O_4Cl$: C, 64.05; H, 4.71; Found C, 64.25; H, 4.89%.

Compound 3c. Yield: 55%; sticky liquid; ir (neat) ν_{max} = 1720, 1580, 1250, 1130 cm^{-1}; uv (EtOH): λ_{max} = 216, 277 nm; ^1H NMR ($CDCl_3$, 500MHz) δ = 2.19 (s, 3H), 2.20 (s, 3H), 2.26 (s, 3H), 4.67 (t, J = 1.6 Hz, 2H), 4.71 (t, J = 1.6 Hz, 2H), 5.48 (s, 1H), 5.78 (s, 1H), 6.76-6.96 (m, 3H); ms: m/z = 298(M^+). Anal Calcd. for $C_{18}H_{18}O_4$: C, 72.48; H, 6.04; Found C, 72.56; H, 6.25%.

Compound 3d. Yield: 55%; sticky liquid; ir (neat) ν_{max} = 1720, 1580, 1250, 1130 cm^{-1}; uv (EtOH): λ_{max} = 214, 278 nm; ^1H NMR ($CDCl_3$, 500MHz) δ = 2.15 (s, 3H), 2.20 (s, 3H), 2.26 (s, 3H), 4.68 (t, J = 1.6 Hz, 2H), 4.73 (t, J = 1.6 Hz, 2H), 5.48 (s, 1H), 5.78 (s, 1H), 6.75-7.06 (m, 3H); ms: m/z = 298(M^+). Anal Calcd. for $C_{18}H_{18}O_4$: C, 72.48; H, 6.04; Found C, 72.61; H, 6.18%.

Compound 3f. Yield: 60%; sticky liquid; ir (neat) ν_{max} = 1720, 1580, 1250, 1130 cm^{-1}; uv (EtOH): λ_{max} = 216, 280 nm; ^1H NMR ($CDCl_3$, 500MHz) δ = 1.29 (s, 9H), 2.20 (s, 3H), 4.68 (t, *J* = 1.6 Hz, 2H), 4.70 (t, *J* = 1.6 Hz, 2H), 5.48 (s, 1H), 5.78 (s, 1H), 6.83-7.31 (m, 4H); ms: *m/z* = 326(M^+). *Anal* Calcd. for $C_{20}H_{22}O_4$: C, 73.62; H, 6.75; Found C, 73.85; H, 6.94%.

Compound 3e was prepared according to the published procedure [15].

General Procedure for the Synthesis of 4-[(3-Aryloxy-propynyl)oxy)]-6-methyl-2*H*-pyran-2-thiones (4a-f). A mixture of 4-[(3-aryloxy-2-propynyl)oxy]-6-methyl-2*H*-pyran-2-ones **3a-f** (2 mmol) and P_2S_5 (3 mmol) were refluxed in anhydrous benzene (50 ml) on a water bath for 1-2 h. The reaction mixture was then cooled, solid residue was extracted with benzene (3 x 25 ml) and the combined benzene layer was washed with water, and then dried over Na_2SO_4. Removal of solvent gave a gummy mass, which was then chromatographed over silica gel. Sticky liquids were obtained when all the columns were eluted with 1: 9.5 ethyl acetate-petroleum ether.

Compound 4a. Yield: 80%, sticky liquid; ir (neat) ν_{max} = 1651, 1542, 1457, 1090 cm^{-1}; uv (EtOH): λ_{max} = 358, 281, 229 nm; ^1H NMR ($CDCl_3$, 300 MHz) δ = 2.36 (s, 3H), 4.73 (t, *J* = 1.7 Hz, 2H), 4.82 (t, *J* = 1.7 Hz, 2H), 6.06 (s, 1H), 6.72 (s, 1H), 6.93-7.39 (m, 3H); ms: *m/z* = 354, 356, 358(M^+). *Anal* Calcd. for $C_{16}H_{12}O_3SCl_2$: C, 54.08; H, 3.38; Found C, 54.28; H, 3.59%.

Compound 4b. Yield: 80%, sticky liquid; ir (neat) ν_{max} = 1650, 1540, 1459, 1085 cm^{-1}; uv (EtOH): λ_{max} = 355, 281, 229 nm; ^1H NMR ($CDCl_3$, 500 MHz) δ = 2.19 (s, 3H), 2.33 (s, 3H), 4.70 (t, *J* = 1.7 Hz, 2H), 4.73 (t, *J* = 1.7 Hz, 2H), 6.03 (s, 1H), 6.71 (s, 1H), 6.76-7.11 (m, 3H); ms: *m/z* = 334, 336(M^+). *Anal* Calcd. for $C_{17}H_{15}O_3SCl$: C, 60.99; H, 4.48; Found C, 61.15; H, 4.69%.

Compound 4c. Yield: 75%, sticky liquid; ir (neat) ν_{max} = 1651, 1537, 1452, 1088 cm^{-1}; uv (EtOH): λ_{max}= 358, 280, 227 nm; ^1H NMR ($CDCl_3$, 500 MHz) δ = 2.19 (s, 3H), 2.26 (s, 3H), 2.33 (s, 3H), 4.73 (s, 4H, OCH_2), 6.05 (s, 1H), 6.72 (s, 1H),

6.75-6.96 (m, 3H, ArH); ms: *m/z* = 314(M^+). *Anal* Calcd. for $C_{18}H_{18}O_3S$: C, 68.79; H, 5.73; Found C, 68.95; H, 5.65%.

Compound 4d. Yield: 75%, sticky liquid; ir (neat) ν_{max} = 1650, 1537, 1450, 1090 cm^{-1}; uv (EtOH): λ_{max} = 358, 280, 227 nm; ^1H NMR ($CDCl_3$, 500 MHz) δ = 2.15 (s, 3H), 2.27 (s, 3H), 2.34 (s, 3H), 4.72 (t, *J* =1.7 Hz, 2H), 4.73(t, *J* =1.7 Hz, 2H), 6.05 (s, 1H), 6.73 (s, 1H), 6.74-7.09 (m, 3H, ArH); ms: *m/z* = 314(M^+). *Anal* Calcd. for $C_{18}H_{18}O_3S$: C, 68.79; H, 5.73; Found C, 68.87; H, 5.97%.

Compound 4e. Yield: 80%, sticky liquid; ir (neat) ν_{max} = 1651, 1537, 1452, 1088 cm^{-1}; uv (EtOH): λ_{max} = 358, 280, 227 nm; ^1H NMR ($CDCl_3$, 500 MHz) δ = 2.34 (s, 3H), 4.72 (t, *J* =1.7 Hz, 2H), 4.83 (t, *J* =1.7 Hz, 2H), 6.05 (s, 1H), 6.72 (s, 1H), 6.96-7.38 (m, 4H, ArH); ms: *m/z* = 320, 322(M^+). *Anal* Calcd. for $C_{16}H_{13}O_3SCl$: C, 59.91; H, 4.06; Found C, 60.15; H, 4.26%.

Compound 4f. Yield: 75%, sticky liquid; ir (neat) ν_{max} = 1650, 1540, 1451, 1090 cm^{-1}; uv (EtOH): λ_{max} = 358, 281, 229 nm; ^1H NMR ($CDCl_3$, 500 MHz) δ = 1.30 (s, 9H), 2.34 (s, 3H), 4.66 (t, *J* =1.7 Hz, 2H), 4.72 (t, *J* =1.7 Hz, 2H), 6.05 (s, 1H), 6.74 (s, 1H), 6.86-7.33 (m, 4H, ArH); ms: *m/z* = 342(M^+). *Anal* Calcd. for $C_{20}H_{22}O_3S$: C, 70.18; H, 6.43; Found C, 70.35; H, 6.56%.

General Procedure for the Synthesis of 5-[(Aryloxy)methyl]-2-methyl-4*H*,7*H*-thiopyrano[2,3-*b*]pyran-4-ones (5a-f). 4-[(3-Aryloxy-propynyl)oxy)]-6-methyl-2*H*-pyran-2-thiones **4a-f** (500 mg) were refluxed in *o*-dichlorobenzene (5 ml) for 1-2 h. The reaction mixture was then cooled and directly subjected to column chromatography over silica gel. *o*-Dichlorobenzene was eluted out with petroleum ether. All the compounds **5a-f** were obtained as white solid when the columns were eluted with 1:6.5 ethyl acetate-petroleum ether.

Compound 5a. Yield: 85%, white solid, mp 140-142°C; ir (KBr) ν_{max} = 1728, 1659, 1609, 1481, 1290 cm^{-1}; uv (EtOH): λ_{max} = 284, 259, 246, 221 nm; ^1H NMR ($CDCl_3$, 300 MHz) δ = 2.26 (s, 3H), 3.50 (d, *J* = 5.6 Hz, 2H, SCH_2), 5.17 (d, *J* =1.3 Hz, 2H, OCH_2), 6.05 (s, 1H), 6.03 (tt, *J* = 1.3 Hz, 5.6 Hz, 1H), 6.90 (d, *J* = 8.8 Hz, 1H,ArH), 7.13-7.17 (dd, *J* = 8.8 Hz, 2.4 Hz, 1H, ArH), 7.34 (d, *J* = 2.4 Hz, 1H, ArH); 13_C NMR ($CDCl_3$, 125 MHz) δc =19.07, 21.35, 69.7, 108.4, 118.2, 123.1, 123.2, 125.7, 124.49, 127.32, 139.08, 152.99, 155.0, 161.5, 183.4 (-C=O); ms: *m/z* = 354, 356, 358(M^+). *Anal* Calcd. for $C_{16}H_{12}O_3SCl_2$: C, 54.08; H, 3.38; Found C, 54.32; H, 3.42%.

Compound 5b. Yield: 80%, white solid, mp 150-152°C; ir (KBr) ν_{max} = 1726, 1657, 1480, 1292 cm^{-1}; uv (EtOH): λ_{max} = 281, 258, 246, 220 nm; ^1H NMR ($CDCl_3$, 300 MHz) δ = 2.20 (s, 3H), 2.26 (s, 3H), 3.49 (d, *J* = 5.7 Hz, 2H, SCH_2), 5.09 (d, *J* =1.5 Hz, 2H, OCH_2), 6.05 (s, 1H), 5.92-5.96 (tt, *J* = 1.5 Hz, 5.7 Hz, 1H), 6.76 (d, *J* = 8.2 Hz, 1H, ArH), 7.05 (dd, *J* = 8.2 Hz, 2.4 Hz, 1H, ArH), 7.08 (d, *J* = 2.4 Hz, 1H, ArH); ms: *m/z* = 334, 336(M^+). *Anal* Calcd. for $C_{17}H_{15}O_3SCl$: C, 60.99; H, 4.84; Found C, 61.20; H, 4.76%.

Compound 5c. Yield: 80%, white solid, mp 130-132°C; ir (KBr) ν_{max} = 1662, 1617, 1504, 1255 cm^{-1}; uv (EtOH): λ_{max} = 279, 257, 246, 220 nm; ^1H NMR ($CDCl_3$, 300 MHz) δ = 2.21 (s, 3H), 2.24 (s, 3H), 2.25 (s, 3H), 3.48 (d, *J* = 5.7 Hz, 2H, SCH_2), 5.09 (d, *J* =1.6 Hz, 2H, OCH_2), 6.05 (s, 1H), 5.98 (tt, *J* = 1.6 Hz, 5.7 Hz, 1H), 6.74-6.93 (m, 3H, ArH); ms: *m/z* = 314(M^+). *Anal* Calcd. for $C_{18}H_{18}O_3S$: C, 68.79; H, 5.73; Found C, 68.89; H, 5.82%.

Compound 5d. Yield: 82%, white solid, mp 127-129°C; ir (KBr) ν_{max} = 1726, 1655, 1500, 1250 cm^{-1}; uv (EtOH): λ_{max} = 278, 255, 247, 222 nm; ^1H NMR ($CDCl_3$, 300 MHz) δ = 2.26 (s, 3H), 2.25 (s, 3H), 2.26 (s, 3H), 3.49 (d, *J* = 5.7 Hz, 2H, SCH_2), 5.10 (d, *J* = 1.5 Hz, 2H, OCH_2), 5.97 (tt, *J* = 1.5 Hz, 5.7 Hz, 1H), 6.05 (s, 1H), 6.74-7.04 (m, 3H, ArH); ms: *m/z* = 314(M^+). *Anal* Calcd. for $C_{18}H_{18}O_3S$: C, 68.79; H, 5.73; Found C, 68.84; H, 5.87%.

Compound 5e. Yield: 80%, white solid, mp 125-127°C; ir (KBr) ν_{max} = 1726, 1658, 1480, 1288 cm^{-1}; uv (EtOH): λ_{max} = 282, 259, 247, 221 nm; ^1H NMR ($CDCl_3$, 500 MHz) δ = 2.26 (s, 3H), 3.51 (d, *J* = 5.7 Hz, 2H, SCH_2), 5.19 (d, *J* = 1.5 Hz, 2H, OCH_2), 6.09 (tt, J = 1.5 Hz, 5.7 Hz, 1H), 6.07 (s, 1H), 6.86 (ddd, *J* = 1.3 Hz, 7.8 Hz, 8.2 Hz, 1H, ArH), 6.99 (dd, *J* = 1.3 Hz, 8.2 Hz, 1H,ArH), 7.17 (ddd, *J* = 1.5 Hz, 8.2 Hz, 7.8 Hz, 1H, ArH), 7.33 (dd, *J* = 1.5 Hz, 7.8 Hz, 1H, ArH), ms: *m/z* = 320, 322(M^+). *Anal* Calcd. for $C_{16}H_{13}O_3SCl$: C, 59.91; H, 4.06; Found C, 60.21; H, 4.12%.

Compound 5f. Yield: 78%, sticky liquid; ir (neat) ν_{max} = 1726, 1652, 1485, 1290 cm^{-1}; uv (EtOH): λ_{max} = 282, 258, 246, 223 nm; ^1H NMR ($CDCl_3$, 500 MHz) δ = 1.28 (s, 9H), 2.25 (s, 3H), 3.48 (d, *J* = 5.75 Hz, 2H, SCH_2), 5.10 (d, *J* = 1.25 Hz, 2H, OCH_2), 5.95 (tt, *J* = 1.25 Hz, 5.75 Hz, 1H), 6.07 (s, 1H), 6.85 (d, *J* = 8.7 Hz, 2H, ArH), 7.25 (d, *J* = 8.7 Hz, 2H, ArH); ms: *m/z* = 342(M^+). *Anal* Calcd. for $C_{20}H_{22}O_3S$: C, 70.18; H, 6.43; Found C, 70.27; H, 6.55%.

General Procedure for the Synthesis of 6-(2-Hydroxyaryl)-2-methyl-5-methylene-6,7-dihydrothiopyrano[2,3-*b*]pyran-4(5*H*)-ones (10a-f). 5-[(Aryloxy)methyl]-2-methyl-4*H*,7*H*-thiopyrano[2,3-*b*]pyran-4-ones **5a-f** (300 mg) were refluxed in *o*-dichlorobenzene (5 ml) in the presence of *N*,*N*-diethylaniline (7-8 drops) for about 6-7 h. Then the reaction mixture was allowed to cool and directly subjected to column chromatography over silica gel. All the compounds **10a-f** were obtained as white solid when the columns were eluted with 1:5 ethyl acetate-petroleum ether.

Compound 10a. Yield: 82%, white solid, mp 190-192°C; ir (KBr) ν_{max} = 3290, 1660, 1403, 1159 cm^{-1}; uv (EtOH): λ_{max} = 293, 235, 217 nm; ^1H NMR ($CDCl_3$, 500 MHz) δ = 2.23 (s, 3H), 3.31 (dd, *J* = 12.3 Hz, 7.1 Hz, 1H, SCH_2), 3.51 (dd, *J* = 12.3 Hz, 3.0 Hz, 1H, SCH_2), 4.28 (dd, *J* = 7.1 Hz, 3.0 Hz, 1H), 5.26 (s, 1H, $=CH_2$), 5.78 (s, 1H, $=CH_2$), 6.10 (s, 1H), 6.84 (s, 1H), 6.96 (brs, 2H, ArH); ms: *m/z* = 354, 356, 358(M^+). *Anal* Calcd. for $C_{16}H_{12}O_3SCl_2$: C, 54.08; H, 3.38; Found C, 54.27; H, 3.51%.

Compound 10b. Yield: 80%, white solid, mp 180-182°C; ir (KBr) ν_{max} = 3300, 1665, 1405, 1160 cm^{-1}; uv (EtOH): λ_{max} = 290, 225, 215 nm; ^1H NMR ($CDCl_3$, 300 MHz) δ = 2.23 (s, 6H), 3.22 (dd, *J* = 12.6 Hz, 3.38 Hz, 1H, SCH_2), 3.50 (dd, *J* = 12.6 Hz, 7.8 Hz, 1H, SCH_2), 4.15 (dd, *J* = 7.8 Hz, 3.38 Hz, 1H), 5.02 (s, 1H, $=CH_2$), 5.21 (s, 1H, $=CH_2$), 6.09 (s, 1H), 6.80 (s, 1H), 6.84 (d, *J* = 2.18 Hz, 1H, ArH), 7.04 (d, *J* = 2.18 Hz, 1H, ArH); ms: *m/z* = 334, 336(M^+). *Anal* Calcd. for $C_{17}H_{15}O_3SCl$: C, 60.99; H, 4.84; Found C, 61.16; H, 4.90%.

Compound 10c. Yield: 83%, white solid, mp 175-177°C; ir (KBr) ν_{max} = 3290, 1655, 1591, 1395 cm^{-1}; uv (EtOH): λ_{max} = 282, 218, 205 nm; ^1H NMR ($CDCl_3$, 300 MHz) δ = 2.20 (s, 3H), 2.22 (s, 6H), 3.21 (dd, *J* = 12.1 Hz, 6.8 Hz, 1H, SCH_2), 3.57 (dd, *J* = 12.1 Hz, 2.9 Hz, 1H, SCH_2), 4.14 (dd, *J* = 6.8 Hz, 2.9 Hz, 1H), 5.02 (s, 1H, $=CH_2$), 5.20 (s, 1H, $=CH_2$), 6.10 (s, 1H), 6.66 (s, 1H), 6.79 (s, 1H, ArH), 6.87 (brs, 1H, ArH); ms: *m/z* =314(M^+). *Anal* Calcd. for $C_{18}H_{18}O_3S$: C, 68.79; H, 5.73; Found C, 68.91; H, 5.84%.

Compound 10d. Yield: 76%, White solid, mp 170-172°C; ir (KBr) ν_{max} = 3310, 1650, 1590, 1395 cm^{-1}; uv (EtOH): λ_{max} = 280, 219, 205 nm; ^1H NMR ($CDCl_3$, 500 MHz) δ = 2.16 (s, 3H),

2.21 (s, 3H), 2.26 (s, 3H), 3.25 (dd, *J* = 12.4 Hz, 3 Hz, 1H, SCH_2), 3.57 (dd, *J* = 12.4 Hz, 7.9 Hz, 1H, SCH_2), 4.14 (dd, *J* = 7.9 Hz, 3 Hz, 1H), 4.88 (s, 1H, $=CH_2$), 5.23 (s, 1H, $=CH_2$), 6.08 (s, 1H), 6.70 (d, *J* = 7.6 Hz, 1H, ArH), 6.76 (d, *J* = 7.6 Hz, 1H, ArH), 6.80 (s, 1H); ms: *m/z* = 314 (M^+). *Anal* Calcd. for $C_{18}H_{18}O_3S$: C, 68.79; H, 5.73; Found C, 68.94; H, 5.77%.

Compound 10e. Yield: 80%, white solid, mp 160-162°C; ir (KBr) ν_{max} = 3290, 1657, 1591, 1407 cm^{-1}; uv (EtOH): λ_{max} = 284, 236, 221 nm; ^1H NMR ($CDCl_3$, 500 MHz) δ = 2.22 (s, 3H), 3.33 (dd, *J* = 12.7 Hz, 3.2 Hz, 1H, SCH_2), 3.58 (dd, *J* = 12.7 Hz, 5.8 Hz, 1H, SCH_2), 4.29 (dd, *J* = 5.8 Hz, 3.2 Hz, 1H), 5.28 (s, 1H, $=CH_2$), 5.81 (s, 1H, $=CH_2$), 6.11 (s, 1H), 6.76-6.89 (m, 4H, ArH & -OH); ms: *m/z* = 320, 322(M^+). *Anal* Calcd. for $C_{16}H_{13}O_3SCl$: C, 59.91; H, 4.06; Found C, 60.17; H, 4.19%.

Compound 10f. Yield: 78%, white solid, mp 155-157°C; ir (KBr) ν_{max} = 3289, 1655, 1591, 1508, 1395 cm^{-1}; uv (EtOH): λ_{max} = 287, 227 nm; ^1H NMR ($CDCl_3$, 500 MHz) δ = 1.21 (s, 9H), 2.21 (s, 3H), 3.25 (dd, *J* = 12.1 Hz, 3.3 Hz, 1H, SCH_2), 3.65 (dd, *J* = 12.1 Hz, 8.2 Hz, 1H, SCH_2), 4.16 (dd, *J* = 8.2 Hz, 3.3 Hz, 1H), 5.13 (s, 1H, $=CH_2$), 5.22 (s, 1H, $=CH_2$), 6.09 (s, 1H), 6.72 (d, *J* = 7.7 Hz, 1H, ArH), 6.76 (s, 1H), 7.02 (s, 1H, ArH), 7.14 (d, *J* = 7.7 Hz, 1H, ArH); ms: *m/z* = 342(M^+). *Anal* Calcd. for $C_{20}H_{22}O_3S$: C, 70.18; H, 6.43; Found C, 70.29; H, 6.58%.

General Procedure for the Synthesis of 12c-Bromo-2-methyl-10b,12c-dihydro-4*H*,5*H*,11*H*-trihydropyrano[3′,4′:5,6]thiopyrano[3,2-*c*]benzopyran-4-ones (12a-f). 6-(2-Hydroxyaryl)-2-methyl-5-methylene-6,7-dihydrothiopyrano[2,3-*b*]pyran-4(5*H*)-ones **10a-f** (100 mg) were treated with one equivalent of pyridine hydrotribromide in chloroform at 0-5°C for about 1-1.5 h. The reaction mixture was washed with 10% sodium bisulfite, water and brine. Finally it was dried over anhydrous Na_2SO_4. Column chromatography was performed and all the compounds **12a-f** were eluted with 1:9 ethyl acetate-petroleum ether to give white crystalline solids.

Compound 12a. Yield: 95%, white solid, mp 205-207°C; ir (KBr) ν_{max} = 1664, 1618, 1460, 1388 cm^{-1}; uv (EtOH): λ_{max} = 276, 232, 216 nm; ^1H NMR ($CDCl_3$, 500 MHz) δ = 2.24 (s, 3H), 2.92 (dd, *J* = 13.2 Hz, 10.8 Hz, 1H), 3.17 (dd, *J* = 4.0 Hz, 13.2 Hz, 1H, SCH_2), 3.56 (d, *J* = 9.8 Hz, 1H, OCH_2), 3.99 (dd, *J* = 4.0 Hz, 10.8 Hz, 1H, SCH_2), 4.87 (d, *J* = 9.8 Hz, 1H, OCH_2), 6.08 (s, 1H), 7.2 (s, 1H, ArH), 7.23 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ_c = 19.5, 30.9(C_{11}), 49.85(C_{10b}), 60.2(C_{12c}), 76.57(C_5), 110.5(C_3), 117.5(C_{10a}), 119.2(C_{12b}), 127.0(C_7), 127.2(C_{10}), 129.0(C_9), 129.5(C_8), 154.7(C_{6a}), 166.7(C_2), 173.9(C_{12a}), 183.06 (-C=O); ms: *m/z* = 432, 434, 436, 438(M^+). *Anal* Calcd. for $C_{16}H_{11}O_3SBrCl_2$: C, 44.24; H, 2.53; Found C, 44.36; H, 2.67%.

Compound 12b. Yield: 94%, white solid, mp 200-202°C; ir (KBr) ν_{max} = 1670, 1620, 1460, 1390 cm^{-1}; uv (EtOH): λ_{max} = 275, 230, 220 nm; ^1H NMR ($CDCl_3$, 500 MHz) δ = 2.19 (s, 3H), 2.24 (s, 3H), 2.89 (dd, *J* = 12.6 Hz, 10.3 Hz, 1H), 3.13 (dd, *J* = 3.1 Hz, 12.6 Hz, 1H, SCH_2), 3.52 (d, *J* = 9.6 Hz, 1H, OCH_2), 3.89 (dd, *J* = 3.1 Hz, 10.3 Hz, 1H, SCH_2), 4.80 (d, *J* = 9.6 Hz, 1H, OCH_2), 6.07 (s, 1H), 7.01 (s, 1H, ArH), 7.03 (s, 1H, ArH); ms: *m/z* = 412, 414, 416(M^+). *Anal* Calcd. for $C_{17}H_{14}O_3SBrCl$: C, 49.34; H, 3.38; Found C, 49.52; H, 3.49%.

Compound 12c. Yield: 95%, white solid, mp 190-192°C; ir (KBr) ν_{max} = 1660, 1480, 1390 cm^{-1}; uv (EtOH): λ_{max} = 276, 260, 218 nm; ^1H NMR ($CDCl_3$, 500 MHz) δ = 2.19 (s, 3H), 2.23 (s, 3H), 2.27 (s, 3H), 2.88 (dd, *J* = 12.2 Hz, 10.6 Hz, 1H), 3.11 (dd, *J* = 3.0 Hz, 10.6 Hz, 1H, SCH_2), 3.52 (d, *J* = 9.2 Hz, 1H, OCH_2), 3.84 (dd, *J* = 3.0 Hz, 12.2 Hz, 1H, SCH_2), 4.81 (d, *J* = 9.2 Hz, 1H, OCH_2), 6.07 (s, 1H), 6.83 (s, 1H, ArH), 6.86 (s, 1H, ArH); ms: *m/z* = 392, 394(M^+). *Anal* Calcd. for $C_{18}H_{17}O_3SBr$: C, 54.96; H, 4.32; Found C, 55.12; H, 4.51%.

Compound 12d. Yield: 96%, white solid, mp 185-187°C; ir (KBr) ν_{max} = 1665, 1480, 1388 cm^{-1}; uv (EtOH): λ_{max} = 280, 262, 220 nm; ^1H NMR ($CDCl_3$, 500 MHz) δ = 2.19 (s, 3H), 2.23 (s, 3H), 2.32 (s, 3H), 2.87 (dd, *J* = 13.1 Hz, 10.9 Hz, 1H), 3.11 (dd, *J* = 3.8 Hz, 13.1 Hz, 1H, SCH_2), 3.52 (d, *J* = 9.6 Hz, 1H, OCH_2), 3.88 (dd, *J* = 3.8 Hz, 10.9 Hz, 1H, SCH_2), 4.79 (d, *J* = 9.6 Hz, 1H, OCH_2), 6.07 (s, 1H), 6.84 (d, *J* = 7.6 Hz, 1H, ArH), 6.86 (d, *J* = 7.6 Hz, 1H, ArH); ms: *m/z* = 392, 394(M^+). *Anal* Calcd. for $C_{18}H_{17}O_3SBr$: C, 54.96; H, 4.32; Found C, 55.16; H, 4.41%.

Compound 12e. Yield: 96%, white solid, mp 175-177°C; ir (KBr) ν_{max} = 1663, 1614, 1391 cm^{-1}; uv (EtOH): λ_{max} = 351, 277, 218 nm; ^1H NMR ($CDCl_3$, 500 MHz) δ_H = 2.24 (s, 3H), 2.92 (dd, *J* =13.2 Hz, 11.2 Hz, 1H), 3.15 (dd, *J* = 4.1 Hz, 13.2 Hz, 1H, SCH_2), 3.55 (d, *J* = 9.7 Hz, 1H, OCH_2), 3.98 (dd, *J* = 4.1 Hz, 11.2 Hz, 1H, SCH_2), 4.89 (d, *J* = 9.7 Hz, 1H, OCH_2), 6.10 (s, 1H), 6.88 (t, *J* = 7.7 Hz, 1H, ArH), 7.13 (d, *J* = 7.7 Hz, 1H, ArH), 7.21 (d, *J* = 7.7 Hz, 1H, ArH); ms: *m/z* =398, 400, 402(M^+). *Anal* Calcd. for $C_{16}H_{12}O_3SBrCl$: C, 48.06; H, 3.0; Found C, 48.21; H, 3.13%.

Compound 12f. Yield: 94%, white solid, mp 170-172°C; ir (KBr) ν_{max} = 1661, 1619, 1487, 1392 cm^{-1}; uv (EtOH): λ_{max} = 278, 230, 218 nm; ^1H NMR ($CDCl_3$, 500 MHz) δ = 1.30 (s, 9H), 2.24 (s, 3H), 2.88 (dd, *J* = 14.1 Hz, 12.2 Hz, 1H), 3.12 (dd, *J* = 4.1 Hz, 14.1 Hz, 1H, SCH_2), 3.52 (d, *J* = 9.5 Hz, 1H, OCH_2), 3.88 (dd, *J* = 4.1 Hz, 12.2 Hz, 1H, SCH_2), 4.78 (d, *J* = 9.5 Hz, 1H, OCH_2), 6.10 (s, 1H), 6.86 (d, *J* = 8.9 Hz, 1H, ArH), 7.22 (d, *J* = 8.9 Hz, 1H, ArH), 7.24 (s, 1H, ArH); ms: *m/z* = 420, 422(M^+). *Anal* Calcd. for $C_{20}H_{21}O_3SBr$: C, 57.01; H, 4.99; Found C, 57.22; H, 5.06%.

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