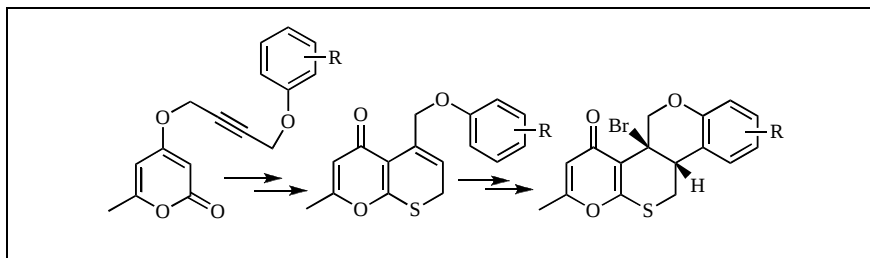


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A number of tetracyclic polyhetero scaffolds have been regioselectively synthesised in 70-75% yield from 4-[(3-aryloxy-2-propynyl)oxy]-6-methyl-pyran-2-ones *via* thionation of the lactone carbonyl, sequential Claisen rearrangements and pyridine hydrotribromide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

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INTRODUCTION

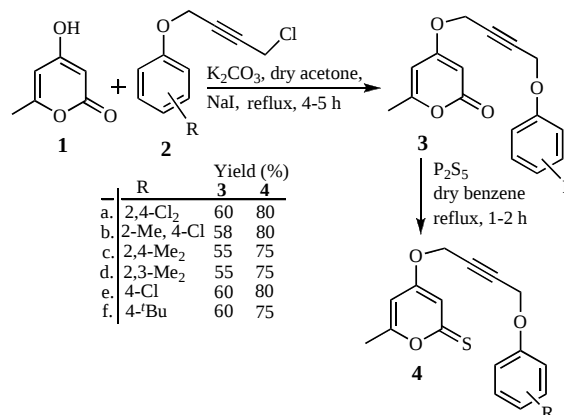
The 4-hydroxy-6-methyl-2-pyrone moiety is important because of its occurrence in a number of naturally occurring compounds [1]. Some of these naturally occurring compounds possess biogenetically active groups [2] at C-3 or C-5 or both. As a logical extension, many more structurally analogous pyrones 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-2-butyne **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

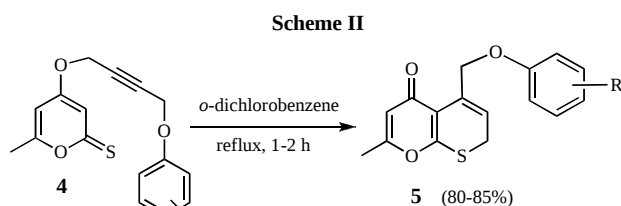
rearrangements. Usually sigmatropic rearrangements of 4-[(4'-aryloxy-2'-propynyl)-oxy, thio or amino]-pyran-2-ones are known to provide access to angularly fused heterocycles [15,16]. Here we have changed the strategy by thionation of the pyrone carbonyl. We felt that this may change the mode of cyclization 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

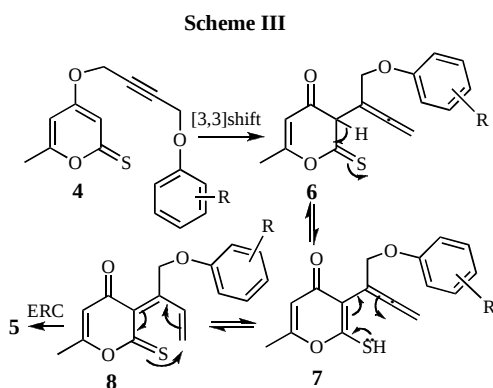


The products **4a-h** were characterized from their elemental analyses and spectroscopic data. Disappearance of carbonyl stretching frequency in the ir spectra of compounds **4a-h** clearly indicates the formation of $-C=S$

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

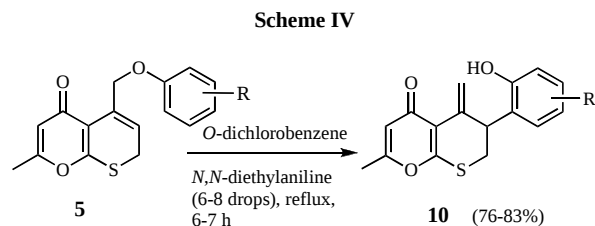


The compounds **5a-f** were characterized from their elemental analyses and spectroscopic data. The ^1H NMR spectrum of **5a** showed signals at δ 3.50 (d, $J = 5.6$ Hz, 2H), 5.17 (d, $J = 1.3$ Hz, 2H) and a one proton double triplet at δ 6.03 ($J = 5.6$ Hz, $J = 1.3$ Hz) indicating the formation of 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**.



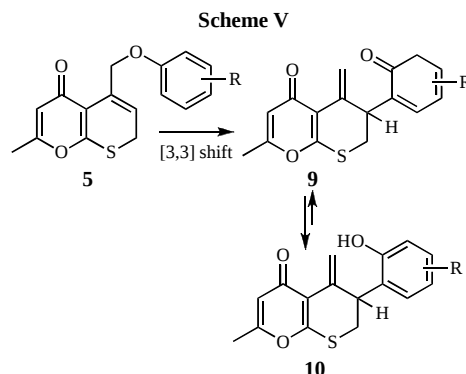
As the products still possess the allyl aryl ether moiety, these were subjected to heating in refluxing *o*-dichlorobenzene in the presence of *N,N*-diethyl aniline for 6-7 h to give the phenolic products **10a-f** in 76-83% yield (Scheme IV).

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

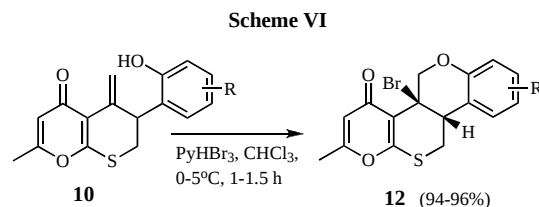


presence of phenolic OH group in the compound **10a**. ^1H NMR spectrum of the compound **10a** showed signal at δ 5.26 (s, 1H) and 5.78 (s, 1H) indicating the presence of an exocyclic double bond in the compound **10a**.

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).



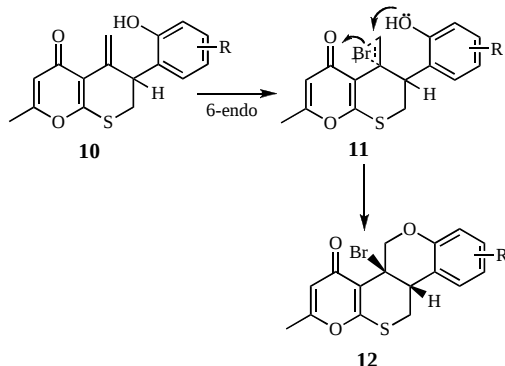
Our target was to synthesize polyheterocyclic compounds. We have earlier used pyridine hydrotribromide [20], hexamine hydrotribromide [21] and *N*-iodosuccinimide [22] for regioselective cyclization of *o*-cyclohex-2-ynyl phenols. We therefore treated products **10a-f** with one equivalent of pyridine hydrotribromide at $0-5^\circ\text{C}$ for 1-1.5 h to give the products **12a-f** in almost quantitative yield (94-96% yield) (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 ^1H 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 ($\nu_{\max}$ in cm^{-1}) on KBr disks. UV absorption spectra were recorded in EtOH on a Shimadzu UV-2401PC spectrophotometer ($\lambda_{\max}$ 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 were 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-yne (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) $\nu_{\max}$ = 1720, 1580, 1250, 1130 cm^{-1} ; uv (EtOH): $\lambda_{\max}$ = 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 $\text{C}_{16}\text{H}_{12}\text{O}_4\text{Cl}_2$: C, 56.64; H, 3.54; Found C, 56.71; H, 3.64%.

Compound 3b. Yield: 58%; sticky liquid; ir (neat) $\nu_{\max}$ = 1720, 1580, 1250, 1140 cm^{-1} ; uv (EtOH): $\lambda_{\max}$ = 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 $\text{C}_{17}\text{H}_{15}\text{O}_4\text{Cl}$: C, 64.05; H, 4.71; Found C, 64.25; H, 4.89%.

Compound 3c. Yield: 55%; sticky liquid; ir (neat) $\nu_{\max}$ = 1720, 1580, 1250, 1130 cm^{-1} ; uv (EtOH): $\lambda_{\max}$ = 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 $\text{C}_{18}\text{H}_{18}\text{O}_4$: C, 72.48; H, 6.04; Found C, 72.56; H, 6.25%.

Compound 3d. Yield: 55%; sticky liquid; ir (neat) $\nu_{\max}$ = 1720, 1580, 1250, 1130 cm^{-1} ; uv (EtOH): $\lambda_{\max}$ = 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 $\text{C}_{18}\text{H}_{18}\text{O}_4$: C, 72.48; H, 6.04; Found C, 72.61; H, 6.18%.

Compound 3f. Yield: 60%; sticky liquid; ir (neat) $\nu_{\max}$ = 1720, 1580, 1250, 1130 cm^{-1} ; uv (EtOH): $\lambda_{\max}$ = 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 $\text{C}_{20}\text{H}_{22}\text{O}_4$: 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) $\nu_{\max}$ = 1651, 1542, 1457, 1090 cm^{-1} ; uv (EtOH): $\lambda_{\max}$ = 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 $\text{C}_{16}\text{H}_{12}\text{O}_3\text{SCl}_2$: C, 54.08; H, 3.38; Found C, 54.28; H, 3.59%.

Compound 4b. Yield: 80%, sticky liquid; ir (neat) $\nu_{\max}$ = 1650, 1540, 1459, 1085 cm^{-1} ; uv (EtOH): $\lambda_{\max}$ = 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 $\text{C}_{17}\text{H}_{15}\text{O}_3\text{SCl}$: C, 60.99; H, 4.48; Found C, 61.15; H, 4.69%.

Compound 4c. Yield: 75%, sticky liquid; ir (neat) $\nu_{\max}$ = 1651, 1537, 1452, 1088 cm^{-1} ; uv (EtOH): $\lambda_{\max}$ = 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) $\nu_{\max}$ = 1650, 1537, 1450, 1090 cm^{-1} ; uv (EtOH): $\lambda_{\max}$ = 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) $\nu_{\max}$ = 1651, 1537, 1452, 1088 cm^{-1} ; uv (EtOH): $\lambda_{\max}$ = 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) $\nu_{\max}$ = 1650, 1540, 1451, 1090 cm^{-1} ; uv (EtOH): $\lambda_{\max}$ = 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) $\nu_{\max}$ = 1728, 1659, 1609, 1481, 1290 cm^{-1} ; uv (EtOH): $\lambda_{\max}$ = 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) δ_c = 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) $\nu_{\max}$ = 1726, 1657, 1480, 1292 cm^{-1} ; uv (EtOH): $\lambda_{\max}$ = 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) $\nu_{\max}$ = 1662, 1617, 1504, 1255 cm^{-1} ; uv (EtOH): $\lambda_{\max}$ = 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) $\nu_{\max}$ = 1726, 1655, 1500, 1250 cm^{-1} ; uv (EtOH): $\lambda_{\max}$ = 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) $\nu_{\max}$ = 1726, 1658, 1480, 1288 cm^{-1} ; uv (EtOH): $\lambda_{\max}$ = 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) $\nu_{\max}$ = 1726, 1652, 1485, 1290 cm^{-1} ; uv (EtOH): $\lambda_{\max}$ = 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) $\nu_{\max}$ = 3290, 1660, 1403, 1159 cm^{-1} ; uv (EtOH): $\lambda_{\max}$ = 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) $\nu_{\max}$ = 3300, 1665, 1405, 1160 cm^{-1} ; uv (EtOH): $\lambda_{\max}$ = 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) $\nu_{\max}$ = 3290, 1655, 1591, 1395 cm^{-1} ; uv (EtOH): $\lambda_{\max}$ = 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) $\nu_{\max}$ = 3310, 1650, 1590, 1395 cm^{-1} ; uv (EtOH): $\lambda_{\max}$ = 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, SCH₂), 3.57 (dd, $J = 12.4$ Hz, 7.9 Hz, 1H, SCH₂), 4.14 (dd, $J = 7.9$ Hz, 3 Hz, 1H), 4.88 (s, 1H, =CH₂), 5.23 (s, 1H, =CH₂), 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 C₁₈H₁₈O₃S: 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) $\nu_{\max} = 3290, 1657, 1591, 1407$ cm⁻¹; uv (EtOH): $\lambda_{\max} = 284, 236, 221$ nm; ¹H NMR (CDCl₃, 500 MHz) $\delta = 2.22$ (s, 3H), 3.33 (dd, $J = 12.7$ Hz, 3.2 Hz, 1H, SCH₂), 3.58 (dd, $J = 12.7$ Hz, 5.8 Hz, 1H, SCH₂), 4.29 (dd, $J = 5.8$ Hz, 3.2 Hz, 1H), 5.28 (s, 1H, =CH₂), 5.81 (s, 1H, =CH₂), 6.11 (s, 1H), 6.76–6.89 (m, 4H, ArH & -OH); ms: $m/z = 320, 322$ (M⁺). *Anal. Calcd.* for C₁₆H₁₃O₃SCl: 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) $\nu_{\max} = 3289, 1655, 1591, 1508, 1395$ cm⁻¹; uv (EtOH): $\lambda_{\max} = 287, 227$ nm; ¹H NMR (CDCl₃, 500 MHz) $\delta = 1.21$ (s, 9H), 2.21 (s, 3H), 3.25 (dd, $J = 12.1$ Hz, 3.3 Hz, 1H, SCH₂), 3.65 (dd, $J = 12.1$ Hz, 8.2 Hz, 1H, SCH₂), 4.16 (dd, $J = 8.2$ Hz, 3.3 Hz, 1H), 5.13 (s, 1H, =CH₂), 5.22 (s, 1H, =CH₂), 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 C₂₀H₂₂O₃S: 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-4H,5H,11H-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(5H)-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 Na₂SO₄. 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) $\nu_{\max} = 1664, 1618, 1460, 1388$ cm⁻¹; uv (EtOH): $\lambda_{\max} = 276, 232, 216$ nm; ¹H NMR (CDCl₃, 500 MHz) $\delta = 2.24$ (s, 3H), 2.92 (dd, $J = 13.2$ Hz, 10.8 Hz, 1H), 3.17 (dd, $J = 4.0$ Hz, 13.2 Hz, 1H, SCH₂), 3.56 (d, $J = 9.8$ Hz, 1H, OCH₂), 3.99 (dd, $J = 4.0$ Hz, 10.8 Hz, 1H, SCH₂), 4.87 (d, $J = 9.8$ Hz, 1H, OCH₂), 6.08 (s, 1H), 7.2 (s, 1H, ArH), 7.23 (s, 1H, ArH); ¹³C NMR (CDCl₃, 125 MHz) $\delta_c = 19.5, 30.9$ (C₁₁), 49.85 (C_{10b}), 60.2 (C_{12c}), 76.57 (C₅), 110.5 (C₃), 117.5 (C_{10a}), 119.2 (C_{12b}), 127.0 (C₇), 127.2 (C₁₀), 129.0 (C₉), 129.5 (C₈), 154.7 (C_{6a}), 166.7 (C₂), 173.9 (C_{12a}), 183.06 (-C=O); ms: $m/z = 432, 434, 436, 438$ (M⁺). *Anal. Calcd.* for C₁₆H₁₁O₃SBrCl₂: 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) $\nu_{\max} = 1670, 1620, 1460, 1390$ cm⁻¹; uv (EtOH): $\lambda_{\max} = 275, 230, 220$ nm; ¹H NMR (CDCl₃, 500 MHz) $\delta = 2.19$ (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, SCH₂), 3.52 (d, $J = 9.6$ Hz, 1H, OCH₂), 3.89 (dd, $J = 3.1$ Hz, 10.3 Hz, 1H, SCH₂), 4.80 (d, $J = 9.6$ Hz, 1H, OCH₂), 6.07 (s, 1H), 7.01 (s, 1H, ArH), 7.03 (s, 1H, ArH); ms: $m/z = 412, 414, 416$ (M⁺). *Anal. Calcd.* for C₁₇H₁₄O₃SBrCl: 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) $\nu_{\max} = 1660, 1480, 1390$ cm⁻¹; uv (EtOH): $\lambda_{\max} = 276, 260, 218$ nm; ¹H NMR (CDCl₃, 500 MHz) $\delta = 2.19$ (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, SCH₂), 3.52 (d, $J = 9.2$ Hz, 1H, OCH₂), 3.84 (dd, $J = 3.0$ Hz, 12.2 Hz, 1H, SCH₂), 4.81 (d, $J = 9.2$ Hz,

1H, OCH₂), 6.07 (s, 1H), 6.83 (s, 1H, ArH), 6.86 (s, 1H, ArH); ms: $m/z = 392, 394$ (M⁺). *Anal. Calcd.* for C₁₈H₁₇O₃SBr: 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) $\nu_{\max} = 1665, 1480, 1388$ cm⁻¹; uv (EtOH): $\lambda_{\max} = 280, 262, 220$ nm; ¹H NMR (CDCl₃, 500 MHz) $\delta = 2.19$ (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, SCH₂), 3.52 (d, $J = 9.6$ Hz, 1H, OCH₂), 3.88 (dd, $J = 3.8$ Hz, 10.9 Hz, 1H, SCH₂), 4.79 (d, $J = 9.6$ Hz, 1H, OCH₂), 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 C₁₈H₁₇O₃SBr: 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) $\nu_{\max} = 1663, 1614, 1391$ cm⁻¹; uv (EtOH): $\lambda_{\max} = 351, 277, 218$ nm; ¹H NMR (CDCl₃, 500 MHz) $\delta_H = 2.24$ (s, 3H), 2.92 (dd, $J = 13.2$ Hz, 11.2 Hz, 1H), 3.15 (dd, $J = 4.1$ Hz, 13.2 Hz, 1H, SCH₂), 3.55 (d, $J = 9.7$ Hz, 1H, OCH₂), 3.98 (dd, $J = 4.1$ Hz, 11.2 Hz, 1H, SCH₂), 4.89 (d, $J = 9.7$ Hz, 1H, OCH₂), 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 C₁₆H₁₂O₃SBrCl: 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) $\nu_{\max} = 1661, 1619, 1487, 1392$ cm⁻¹; uv (EtOH): $\lambda_{\max} = 278, 230, 218$ nm; ¹H NMR (CDCl₃, 500 MHz) $\delta = 1.30$ (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, SCH₂), 3.52 (d, $J = 9.5$ Hz, 1H, OCH₂), 3.88 (dd, $J = 4.1$ Hz, 12.2 Hz, 1H, SCH₂), 4.78 (d, $J = 9.5$ Hz, 1H, OCH₂), 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 C₂₀H₂₁O₃SBr: C, 57.01; H, 4.99; Found C, 57.22; H, 5.06%.

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