Regioselective Synthesis of Pyrone-Annulated Sulfur Heterocycles by Aryl Radical Cyclization

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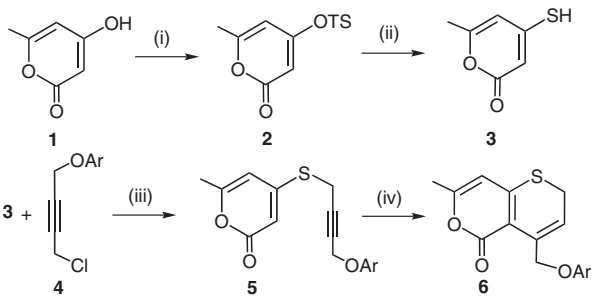
Abstract: The tri-*n*-butyltin hydride mediated cyclization of a number of 4-(2′-bromophenoxymethyl)-7-methylthiopyrano[3,2-*c*]pyran-5-ones have been carried out to afford tetracyclic [6,6]pyranothiopyrans in 70–80% yield and good to excellent diastereoselectivity. The substrate ethers were obtained by a *thio*-Claisen rearrangement of the corresponding 4-(4′-aryloxybut-2′-ynyl)-6-methyl pyran-2-ones. The *cis* stereochemistry of the predominant diastereomer has been corroborated by single crystal X-ray analysis.

Keywords: 4-mercapto-6-methyl pyran-2-one, tri-*n*-butyltin hydride, 6-*endo* cyclization, azobisisobutyronitrile, *thio*-Claisen rearrangement

Aryl radical cyclization has recently emerged as a valuable tool for organic synthesis,[1] mainly for the construction of carbo- and heterocyclic compounds, including natural products. There has been continuing and increasing interest in recent years in the synthesis of pyran-2-one derivatives due to their diverse pharmacological properties.[2] Compounds of these ring system are widely present in naturally occurring physiologically active substances in the form of isolated and fused ring systems.[3] In the course of our studies on the application of sigmatropic rearrangements[4] for the synthesis of heterocyclic compounds we recently noted the formation of furanothiopyrans from the substrate containing 4-thiopyran-2-one[5] moieties in the second Claisen rearrangement step. Though several [6,6]pyranothiopyran[6a] and pyranopyran[6b] ring systems were synthesized using sequential Claisen rearrangements we became interested to investigate whether the synthesis of [6,6]pyranothiopyran ring system could be achieved by tributyl tin hydride mediated aryl radical cyclization. The generation and subsequent reaction of radicals formed from aryl halides using tributyl tin hydride and azobisisobutyronitrile (AIBN) are now well established and the syntheses of a wide range of natural products based on aryl radical cyclization have been reported.[7] Aryl radical cyclization normally gives a high 5-*exo*:6-*endo* ratio indicating a stronger preference for *exo* cyclization compare to alkyl radical cyclization.[8] However this preference is found to be reversed in cyclizations involving stabilized radicals. Herein, we have explored this possibility to synthesize a number of [6,6]pyranothiopyrans by tributyltin hydride mediated radical cyclization.

The starting materials for our study, 4-aryloxymethyl-7-methylthiopyrano[3,2-*c*]pyran-5-ones **6a–f** were synthesized by the thermal rearrangement of 4-(4′-aryloxybut-2′-ynylthio)-6-methyl-pyran-2-ones **5a–f** in 75–85% yields.[5] The compounds **5a–f**, in turn, were prepared by the treatment of 4-marcapto-6-methylpyran-2-one **3** with 1-aryloxy-4-chlorobut-2-ynes **4a–f** at room temperature under phase-transfer catalysis conditions using benzyltriethylammonium chloride (BTEAC). Compound **3** in turn was synthesized by the reaction of 6-methyl-4-tosyloxypyran-2-one **2** with NaSH in anhydrous ethanol at room temperature under nitrogen atmosphere (Scheme 1).



	Ar	Yield (%)
6a	2-BrC_6H_4	80
b	2-Br-3-MeC_6H_3	82
c	2-Br-4-OMeC_6H_3	75
d	1-Br-2-$C_{10}H_6$	85
e	2-Br-4-MeC_6H_3	75
f	2-Br-4,6-$Me_2C_6H_2$	80

Scheme 1 *Reagent and conditions*: (i) TSCl, Py, r.t.; (ii) NaSH, anhyd EtOH, r.t., 2 h, N_2 atm; (iii) $CHCl_3$–H_2O, 10% NaOH, r.t., 4 h; (iv) *o*-chlorobenzene, reflux, 5 h.

Substrate **6a** was refluxed in benzene with tributyltin(IV) hydride in the presence of AIBN for 4 hours to give compound **7a** in 75% yield (Scheme 2), which was characterized from its elemental analysis and spectroscopic data. The IR spectrum of the compound **7a** showed a peak at 1685 cm^{-1} for carbonyl group. The high field ^1H NMR (300 MHz) spectrum of the product **7a** displayed a typical one proton double doublet at δ = 2.99 (SCH_2), one proton double triplet at δ = 3.11 (ring juncture proton), one proton triplet at δ = 3.18 (SCH_2), one proton double triplet at δ = 3.51 (ring juncture proton), one proton triplet at δ =

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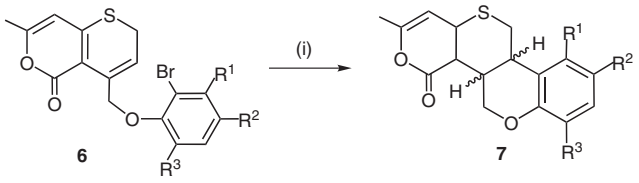
3.72 (OCH_2) and one proton double doublet at δ = 4.55 (OCH_2). The mass spectrum of compound **7a** also displayed a molecular ion peak at *m/z* = 286 [M^+]. Encouraged by this result, other substrates **6b–f** were also treated similarly to give tetracyclic heterocycles **7b–f** in 70–80% yield.



	R^1	R^2	R^3	Yield (%)		R^1	R^2	R^3	Yield (%)
7a	H	H	H	75	**7d**	-C_6H_4[a]-		H	80
b	Me	H	H	78	**e**	H	Me	H	75 (3:1)[b]
c	H	OMe	H	75	**f**	H	Me	Me	70 (2.3:1)[b]

[a] Benzo
[b] Diastereomer ratio determined from the ^{1}H NMR spectrum.

Scheme 2 *Reagent and conditions*: (i) Bu_3SnH, AIBN, anhyd benzene, N_2 atm, reflux, 4–5 h.

The formation of products **7a–f** from **6a–f** may be explained by the generation of an aryl radical **8** which may give the intermediate radical **10** by a direct '6-*endo*' cyclization (Scheme 3). An alternative route via a '5-*exo*' cyclization of radical **8** to the spiroheterocyclic radical[9] **9** (not isolated) followed by a neophyl rearrangement[10] to radical intermediate **10** may also be considered. Abstraction of hydrogen from Bu_3SnH by radical intermediate **10** could have occurred from either side of the radical center, giving rise to a diastereomeric mixture (in the cases of **7e**, **7f** from **6e** and **6f**, respectively).

It was observed that when the substrates **6a–d** were treated with AIBN and Bu_3SnH in refluxing benzene, cyclization proceeded with 100% diastereoselectivity leading to one diastereoisomer; **7a–d** was formed in 75–80% yield in each case. However, treatment of substrates **6e** and **6f** under similar reaction conditions resulted in a diastereomeric mixture of the cyclized product **7e** and **7f** in 75% and 70% yield, respectively. Both the products were isolated as diastereomeric mixture, in the ratios 3:1 and 2.3:1, respectively, which were not separable on column chromatography. It has already been established[11] that very high level of diastereoselectivity (> 50:1) could be obtained when the concentration of the reactant is reduced from 0.1 to 0.01 M. These observations have been attributed to the reversibility of the cyclization and decreased availability of the Bu_3SnH. However the cyclization of **6e** under very dilute conditions also gave the cyclized product **7e** in similar yield (70%) and a diastereoselectivity of 3:1. Therefore the reason behind the reduced diastereoselectivity in the cases of **7e** and **7f** over the others is not clear, though it is perhaps controlled by the abstraction of hydrogen by radical intermediate **10**.

As we were not able to separate and purify the diastereomeric mixture by column chromatography, we tried to purify the crude mixture by repeated recrystallization. After several recrystallizations of the crude mixture of **7e** we were finally able to get a single crystal, the X-ray crystallographic analysis of which showed *cis* stereochemistry at the ring juncture (Figure 1).

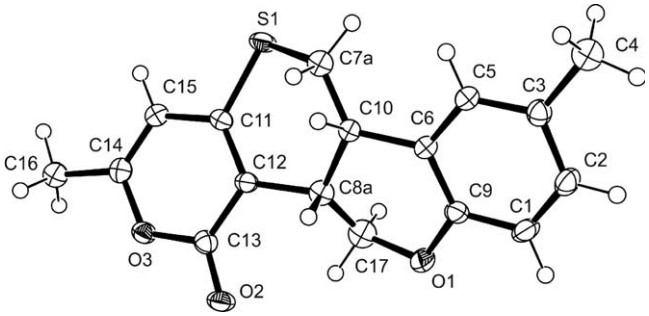
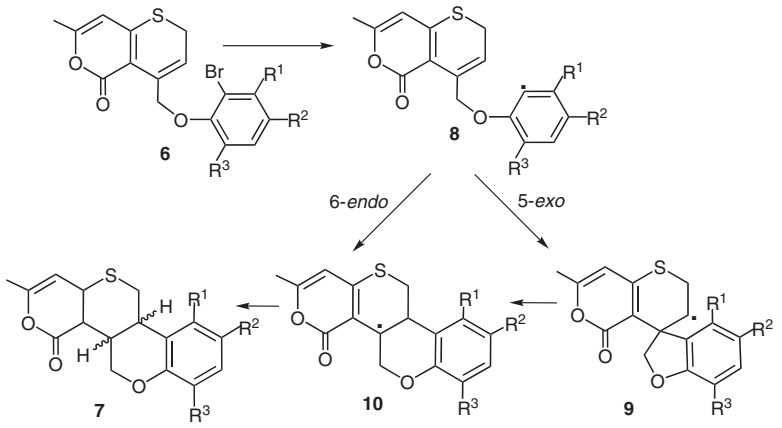


Figure 1 ORTEP diagram of compound **7e**.

It is known that radical cyclization leading to six-membered rings are usually less general than cyclization leading to five-membered rings. However, suitably substituted 5-hexenyl radicals are known to undergo 6-



Scheme 3

endo cyclization to give six-membered rings. It is interesting to note that six-membered rings are formed regioselectively in all the cases we have studied so far. Therefore, this is another instance where the less-common 6-*endo* radical cyclization is preferred over 5-*exo* radical cyclization.

In conclusion, we have developed an attractive and simple strategy using intramolecular aryl radical cyclization for the efficient and regioselective synthesis of [6,6]pyranothiopyran ring system with good to excellent diastereoselectivity, in contrast to the furanothiopyran ring system by sequential Claisen rearrangements in our earlier work.[5]

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, 400 MHz, 500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded on Bruker DPX-300, Varian-400 MHz FT NMR and Bruker DPX-500 spectrometers in $CDCl_3$ (chemical shift in δ) with TMS as internal standard. Elemental analyses and mass spectra were recorded on a Leco 932 CHNS analyzer and on a JEOL JMS-600 instrument, respectively. ^1H NMR and ^{13}C NMR spectra were recorded at the Indian Institute of Chemical Biology, Kolkata and Bose Institute, Kolkata. Single-crystal X-ray analysis of compound **7e** was carried out at the Department of Chemistry of the Indian Institute of Technology, Kanpur. Silica gel [(60–120 mesh), Spectrochem, India] was used for chromatographic separation. Silica gel G (E-Merck, India) was used for TLC analyses. Petroleum ether (PE) refers to the fraction boiling between 60 °C and 80 °C.

Single-crystal X-ray studies were performed on a Bruker APEX CCD diffractometer equipped with an Oxford Instruments low-temperature attachment. Data were collected using monochromated Mo-Kα radiation (λ_α = 0.71069 Å). The frames were integrated in the Bruker SAINT software package,[12] and the data were corrected for absorption using the SADABS program.[13] The structure were solved and refined with SHELX suite of programs.[14] ORTEP-III was used to produce the diagrams.[15]

An off-white crystal of dimensions 0.30 × 0.20 × 0.20 mm^3 was mounted on the tip of a glass fiber with silicone grease and placed in a cold stream of nitrogen at 100 K. The cell constants and orientation matrix for data collection corresponded to a monoclinic cell. A total of 3510 unique reflections were collected to a maximum 2θ value of 56°. During the refinement of the structure it was evident that three of the bridgehead carbon atoms, namely C7, C8 and C10 were disordered. Each of the atoms was modeled over two positions and the final refinement resulted in site occupancies of 80 and 20 percentages. All the non-hydrogen atoms were refined anisotropically except the disordered atoms C7, C8 and C10. Hydrogen atoms of the ligands were included in the final stages of the refinement as riding atoms with values of U_{eq} that were 1.2 times the U_{eq} for the heavy atoms to which they are bonded. Pertinent crystallographic data for compound **7e** are summarized in Table 1.

Table 1 Crystallographic Data for Compound **7e**

Parameters	
Empirical formula	$C_{17}H_{16}O_3S$
Formula weight	300.36
Crystal system	Monoclinic
Space group	$P2_1/c$
a (Å)	8.2785(7)
b (Å)	10.7418(9)
c (Å)	16.3304(14)
α (°)	
β (°)	101.008(2)
γ (°)	
V (Å^3)	1425.5(2)
Z	4
ρ_{calcd} (g cm^{-3})	1.400
u (mm^{-1})	0.234
F(000)	632
Reflections	
Collected	9313
Independent	3510
Observed	2793
[I > 2σ(I)]	
No. of variables	176
Goodness-of-fit	1.049
Final *R* indices	*R*1 = 0.0597
	*wR*2 = 0.1420

Synthesis of 4-(4′-Aryloxybut-2′-ynylthio)-6-methyl-2*H*-pyran-2-ones (5a–f)[5]

To a mixture of 4-mercapto-6-methylpyran-2-one (**3**; obtained from 2.8 g, 10 mmol of **2**) and 1-aryloxy-4-chlorobut-2-ynes **4** (10 mmol) in $CHCl_3$ (50 mL) was added a solution of benzyl triethyl ammonium chloride (BTEAC, 0.5 g, 1.8 mmol) in 1% aq NaOH (50 mL) and the mixture was magnetically stirred at r.t. for 4 h. The reaction mixture was then diluted with H_2O (25 mL). The $CHCl_3$ layer was taken out and washed with 2 N HCl (1 × 20 mL), brine (1 × 20 mL), H_2O (2 × 20 mL) and dried over Na_2SO_4. Evaporation of $CHCl_3$ left a gummy residue that was subjected to column chromatography. Elution of the column with PE–EtOAc (9:1) afforded compounds **5a–f**.

5a

Yield: 75%; solid; mp 100 °C.

IR (KBr): 1725, 1630, 1480, 1280 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 2.20 (s, 3 H), 3.65 (t, *J* = 1.9 Hz, 2 H, SCH_2), 4.71 (t, *J* = 1.85 Hz, 2 H, OCH_2), 5.82 (s, 1 H), 5.91 (s, 1 H), 6.78–6.82 (m, 1 H), 6.93 (dd, *J* = 1.2, 8.2 Hz, 1 H), 7.19–7.24 (m, 1 H), 7.73 (dd, *J* = 1.5, 8.8 Hz, 1 H).

MS: *m*/*z* = 364, 366 [M^+].

UV (EtOH): λ_{max} = 204, 270, 292 nm.

Anal. Calcd for $C_{16}H_{13}O_3SBr$: C, 52.60; H, 3.56. Found: C, 52.85; H, 3.79.

5b
Yield: 72%; solid; mp 90 °C.

IR (KBr): 1732, 1635, 1488 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 2.21 (s, 3 H), 2.23 (s, 1 H), 3.65 (t, *J* = 2.0 Hz, 2 H, SCH_2), 4.72 (t, *J* = 2.0 Hz, 2 H, OCH_2), 5.83 (s, 1 H), 5.91 (s, 1 H), 6.71 (d, *J* = 8.8 Hz, 1 H), 7.46 (d, *J* = 8.8 Hz, 1 H), 7.73 (s, 1 H).

MS: *m*/*z* = 378, 380 [M^+].

UV (EtOH): λ_{max} = 203, 272, 300 nm.

Anal. Calcd for $C_{17}H_{15}O_3SBr$: C, 53.82; H, 3.95. Found: C, 53.97; H, 3.87.

5c
Yield: 70%; solid; mp 80 °C.

IR (KBr): 1718, 1637, 1488, 1279 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 2.20 (s, 3 H), 3.66 (t, *J* = 1.9 Hz, 2 H, SCH_2), 3.77 (s, 3 H), 4.71 (t, *J* = 1.9 Hz, 2 H, OCH_2), 5.82 (s, 1 H), 5.91 (s, 1 H), 6.80 (dd, *J* = 2.9, 8.9 Hz, 1 H), 6.94 (d, *J* = 8.9 Hz, 1 H), 7.10 (d, *J* = 2.9 Hz, 1 H).

MS: *m*/*z* = 394, 396 [M^+].

UV (EtOH): λ_{max} = 204, 272, 292 nm.

Anal. Calcd for $C_{17}H_{15}O_4SBr$: C, 51.64; H, 3.79. Found: C, 51.45; H, 3.86.

5d
Yield: 75%; solid; mp 130 °C.

IR (KBr): 1708, 1635, 1528, 1274 cm^{-1}.

^1H NMR (500 MHz. $CDCl_3$): δ = 2.14 (s, 3 H), 3.65 (t, *J* = 2.0 Hz, 2 H, SCH_2), 4.91 (t, *J* = 2.0 Hz, 2 H, OCH_2), 5.76 (s, 1 H), 5.91 (s, 1 H), 7.31 (d, *J* = 9.0 Hz, 1 H), 7.41–7.44 (m, 1 H), 7.58 (m, 1 H), 7.79–7.82 (m, 1 H), 8.21 (d, *J* = 9.0 Hz, 1 H).

MS: *m*/*z* = 414, 416 [M^+].

UV (EtOH): λ_{max} = 230, 271, 295, 378 nm.

Anal. Calcd for $C_{20}H_{15}O_3SBr$: C, 57.83; H, 3.61. Found: C, 57.98; H, 3.76.

5e
Yield: 70%; solid; mp 100 °C.

IR (KBr): 1734, 1634, 1539, 1488 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 2.22 (s, 3 H), 2.28 (s, 3 H), 3.66 (t, *J* = 1.8 Hz, 2 H, SCH_2), 4.74 (t, *J* = 1.8 Hz, 2 H, OCH_2), 5.83 (s, 1 H), 5.92 (s, 1 H), 6.87 (d, *J* = 8.0 Hz, 1 H), 7.04 (dd, *J* = 1.5, 8.0 Hz, 1 H), 7.35 (d, *J* = 1.5 Hz, 1 H).

MS: *m*/*z* = 378, 380 [M^+].

UV (EtOH): λ_{max} = 204, 220, 272, 300 nm.

Anal. Calcd for $C_{17}H_{15}O_3SBr$: C, 53.82; H, 3.95. Found: C, 53.97; H, 4.12.

5f
Yield: 72%; solid; mp 80 °C.

IR (KBr): 1730, 1632, 1540, 1488 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 2.21 (s, 3 H), 2.24 (s, 3 H), 2.30 (s, 3 H), 3.66 (t, *J* = 1.9 Hz, 2 H, SCH_2), 4.66 (t, *J* = 1.9 Hz, 2 H, OCH_2), 5.84 (s, 1 H), 5.91 (s, 1 H), 6.89 (s, 1 H), 7.17 (s, 1 H).

MS: *m*/*z* = 392, 394 [M^+].

UV (EtOH): λ_{max} = 202, 271, 294 nm.

Anal. Calcd for $C_{18}H_{17}O_3SBr$: C, 54.96; H, 4.32. Found: C, 55.03; H, 4.51.

Synthesis of 4-(2′-Bromophenoxymethyl)-7-methylthiopyrano[3,2-*c*]pyran-5-ones (6a–f);[5] General Procedure
Compounds **5a–f** (500 mg) were refluxed in chlorobenzene (7 mL) for 5 h. The reaction mixture was then cooled and directly subjected to column chromatography over silica gel. Chlorobenzene was eluted out with PE. Compounds **6a–f** were obtained when the column was eluted with PE–EtOAc (12:1).

6a
Yield: 80%; solid; mp 110 °C.

IR (KBr): 1696, 1630, 1504, 1480 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.22 (s, 3 H), 3.37 (d, *J* = 6.00 Hz, 2 H, SCH_2), 5.11 (d, *J* = 1.60 Hz, 2 H, OCH_2), 6.01 (s, 1 H), 6.14 (tt, *J* = 1.60, 6.00 Hz, 1 H), 6.78–6.82 (m, 1 H), 6.93 (dd, *J* = 1.20, 8.40 Hz, 1 H), 7.20–7.23 (m, 1 H), 7.48 (dd, *J* = 1.40, 8.00 Hz, 1 H).

MS: *m*/*z* = 364, 366 [M^+].

UV (EtOH): λ_{max} = 203, 247, 302, 365 nm.

Anal. Calcd for $C_{16}H_{13}O_3SBr$: C, 52.6; H, 3.56. Found: C, 52.87; H, 3.73.

6b
Yield: 82%; solid; mp 140 °C.

IR (KBr): 1692, 1626, 1503, 1287 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 2.21 (s, 3 H), 2.23 (s, 3 H), 3.42 (d, *J* = 5.85 Hz, 2 H, SCH_2), 5.02 (d, *J* = 1.36 Hz, 2 H, OCH_2), 6.01 (s, 1 H), 6.25 (tt, *J* = 1.36, 5.85 Hz, 1 H), 6.69 (d, *J* = 8.80 Hz, 1 H), 7.41 (d, *J* = 8.80 Hz, 1 H), 7.72 (s, 1 H).

MS: *m*/*z* = 378, 380 [M^+].

UV (EtOH): λ_{max} = 206, 247, 293, 359 nm.

Anal. Calcd for $C_{17}H_{15}O_3SBr$: C, 53.82; H, 3.95. Found: C, 53.96; H, 4.12.

6c
Yield: 75%; solid; mp 110 °C.

IR (KBr): 1709, 1694, 1628, 1492, 1274 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.23 (s, 3 H), 3.37 (d, *J* = 6.00 Hz, 2 H, SCH_2), 3.75 (s, 3 H), 5.05 (d, *J* = 1.60 Hz, 2 H, OCH_2), 6.02 (s, 1 H), 6.10 (tt, *J* = 1.60, 6.00 Hz, 1 H), 6.77 (dd, *J* = 2.40, 9.20 Hz, 1 H), 6.89 (d, *J* = 9.20 Hz, 1 H), 7.09 (d, *J* = 2.40 Hz, 1 H).

MS: *m*/*z* = 394, 396 [M^+].

UV (EtOH): λ_{max} = 206, 222, 247, 299 nm.

Anal. Calcd for $C_{17}H_{15}O_4SBr$: C, 51.64; H, 3.79. Found: C, 51.89; H, 3.65.

6d
Yield: 85%; solid; mp 110 °C.

IR (KBr): 1697, 1636, 1625, 1500 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.23 (s, 3 H), 3.38 (d, *J* = 4.80 Hz, 2 H, SCH_2), 5.28 (d, *J* = 1.60 Hz, 2 H, OCH_2), 6.02 (s, 1 H), 6.15 (tt, *J* = 1.60, 4.80 Hz, 1 H), 7.28–7.38 (m, 2 H), 7.51–7.55 (m, 1 H), 7.73–7.79 (m, 2 H), 8.17–8.19 (m, 1 H).

MS: *m*/*z* = 414, 416 [M^+].

UV (EtOH): λ_{max} = 203, 247, 302, 365 nm.

Anal. Calcd for $C_{20}H_{15}O_3SBr$: C, 57.83; H, 3.61. Found: C, 57.97; H, 3.86.

6e
Yield: 75%; solid; mp 120 °C.

IR (KBr): 1690, 1626, 1500, 1285 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.23 (s, 3 H), 2.26 (s, 3 H), 3.38 (d, *J* = 5.89 Hz, 2 H, SCH_2), 5.09 (d, *J* = 1.31 Hz, 2 H, OCH_2), 6.02 (s, 1 H), 6.14 (tt, *J* = 1.31, 5.89 Hz, 1 H), 6.84 (d, *J* = 8.30 Hz, 1 H), 7.01 (dd, *J* = 1.33, 8.30 Hz, 1 H), 7.34 (d, *J* = 1.33 Hz, 1 H).

MS: *m*/*z* = 378, 380 [M^+].

UV (EtOH): λ_{max} = 206, 247, 302, 367 nm.

Anal. Calcd for $C_{17}H_{15}O_3SBr$: C, 53.82; H, 3.95. Found: C, 53.94; H, 3.82.

6f

Yield: 80%; solid; mp 130 °C.

IR (KBr): 1690, 1627, 1500, 1275 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.22 (s, 3 H), 2.25 (s, 3 H), 2.27 (s, 3 H), 3.41 (d, *J* = 5.60 Hz, 2 H, SCH_2), 4.90 (d, *J* = 1.60 Hz, 2 H, OCH_2), 6.01 (s, 1 H), 6.22 (tt, *J* = 1.60, 5.60 Hz, 1 H), 6.89 (s, 1 H), 7.17 (s, 1 H).

MS: *m*/*z* = 392, 394 [M^+].

UV (EtOH): λ_{max} = 206, 247, 302, 362 nm.

Anal. Calcd for $C_{18}H_{17}O_3SBr$: C, 54.96; H, 4.32. Found: C, 54.76; H, 4.53.

Synthesis of Benzopyrano[4,3-*c*]-6a,12a-dihydro-3-methylthiopyranopyran-1-ones (7a–f); General Procedure

To a solution of **6a–f** (0.4 mmol) in degassed benzene (8–10 mL) under a nitrogen atmosphere were added Bu_3SnH (0.9–1.20 mmol) and AIBN (cat) in degassed benzene (0.5–1.0 mL). The mixture was refluxed under nitrogen and the reaction was monitored by TLC (2–3 h). The solvent was removed and the residue was then magnetically stirred with a sat. solution of KF for 24 h. It was then extracted with CH_2Cl_2 (2 × 10 mL), washed several times with H_2O and dried (Na_2SO_4). The residue was purified by flash column chromatography (silica) with PE–EtOAc (9:1) to afford **7a–d** as single diastereoisomer in 75–80% yield and **7e**, **7f** as an inseparable mixture of diastereoisomers in 75% and 70% yields, respectively.

7a

Yield: 75%; solid; mp 180 °C.

IR (KBr): 1685, 1638, 1543, 1489 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.20 (s, 3 H), 2.99 (dd, *J* = 2.2, 12.1 Hz, 1 H), 3.11 (dt, *J* = 3.4, 11.9 Hz, 1 H), 3.18 (t, *J* = 11.9 Hz, 1 H), 3.51 (dt, *J* = 4.1, 11.1 Hz, 1 H), 3.72 (t, *J* = 11.1 Hz, 1 H), 4.55 (dd, *J* = 2.7, 10.4 Hz, 1 H), 5.82 (s, 1 H), 6.85–6.94 (m, 2 H), 7.13–7.20 (m, 2 H).

MS: *m*/*z* = 286 [M^+].

UV (EtOH): λ_{max} = 204, 225, 308 nm.

Anal. Calcd for $C_{16}H_{14}O_3S$: C, 67.13; H, 4.89. Found: C, 67.34; H, 5.01.

7b

Yield: 78%; solid; mp 160 °C.

IR (KBr): 1684, 1638, 1542 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.20 (s, 3 H), 2.33 (s, 3 H), 2.97 (dd, *J* = 3.3, 12.5 Hz, 1 H), 3.12 (t, *J* = 11.9 Hz, 1 H), 3.18 (dt, *J* = 3.8, 11.9 Hz, 1 H), 3.47 (dt, *J* = 4.1, 11.1 Hz, 1 H), 3.81 (t, *J* = 11.1 Hz, 1 H), 4.52 (dd, *J* = 3.3, 10.8 Hz, 1 H), 5.83 (s, 1 H), 6.71 (d, *J* = 8.0 Hz, 1 H), 6.76 (d, *J* = 7.3 Hz, 1 H), 7.08 (t, *J* = 7.8 Hz, 1 H).

MS: *m*/*z* = 300 [M^+].

UV (EtOH): λ_{max} = 205, 226, 302 nm.

Anal. Calcd for $C_{17}H_{16}O_3S$: C, 67.98; H, 5.37. Found: C, 67.89; H, 5.23.

7c

Yield: 75%; solid; mp 158 °C.

IR (KBr): 1685, 1637, 1497 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.19 (s, 3 H), 3.00 (dd, *J* = 2.5, 13.1 Hz, 1 H), 3.06 (dt, *J* = 3.5, 12.4 Hz, 1 H), 3.19 (t, *J* = 12.4 Hz, 1 H), 3.48 (dt, *J* = 4.1, 10.8 Hz, 1 H), 3.69 (t, *J* = 10.8 Hz, 1 H), 3.76 (s, 3 H), 4.51 (dd, *J* = 2.5, 9.8 Hz, 1 H), 5.82 (s, 1 H), 6.66 (d, *J* = 2.7 Hz, 1 H), 6.74–6.82 (m, 2 H).

MS: *m*/*z* = 316 [M^+].

UV (EtOH): λ_{max} = 205, 228, 277, 306, 362 nm.

Anal. Calcd for $C_{17}H_{16}O_4S$: C, 64.55; H, 5.06. Found: C, 64.74; H, 5.21.

7d

Yield: 80%; solid; mp 220 °C.

IR (KBr): 1681, 1644, 1542 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.22 (s, 3 H), 3.24 (t, *J* = 11.8 Hz, 1 H), 3.35 (dd, *J* = 2.4, 13.7 Hz, 1 H), 3.62 (dt, *J* = 4.1, 11.0 Hz, 1 H), 3.72 (dt, *J* = 3.6, 11.8 Hz, 1 H), 3.94 (t, *J* = 11.0 Hz, 1 H), 4.68 (dd, *J* = 3.1, 10.8 Hz, 1 H), 5.88 (s, 1 H), 7.06 (d, *J* = 9.1 Hz, 1 H), 7.36 (t, *J* = 7.4 Hz, 1 H), 7.67 (d, *J* = 9.1 Hz, 1 H), 7.79–7.81 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.9, 29.04, 30.1, 30.85, 64.6, 104.39, 110.89, 113.95, 119.52, 121.14, 123.81, 127.49, 129.54, 129.76, 129.87, 132.41, 152.3, 152.78, 158.61, 161.57.

MS: *m*/*z* = 336 [M^+].

UV (EtOH): λ_{max} = 233, 276, 289, 319 nm.

Anal. Calcd for $C_{20}H_{16}O_3S$: C, 71.42; H, 4.76. Found: C, 71.63; H, 4.84.

7e

Yield: 75%; solid; mp 170 °C.

IR (KBr): 1689, 1639, 1498, 1246 cm^{-1}.

Major Diastereoisomer

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.19 (s, 3 H), 2.27 (s, 3 H), 2.99 (dd, *J* = 2.5, 13.1 Hz, 1 H), 3.05 (dt, *J* = 3.4, 10.8 Hz, 1 H), 3.17 (t, *J* = 12.1 Hz, 1 H), 3.48 (dt, *J* = 3.9, 12.0 Hz, 1 H), 3.70 (t, *J* = 10.9 Hz, 1 H), 4.52 (dd, *J* = 3.1, 10.7 Hz, 1 H), 5.82 (s, 1 H), 6.75 (d, *J* = 8.2 Hz, 1 H), 6.94 (s, 1 H), 6.96 (d, *J* = 8.2 Hz, 1 H).

MS: *m*/*z* = 300 [M^+].

UV (EtOH): λ_{max} = 204, 226, 277, 310 nm.

Anal. Calcd for $C_{17}H_{16}O_3S$: C, 67.98; H, 5.37. Found: C, 68.15; H, 5.23.

Minor Diastereoisomer

This diastereoisomer was observed by ^{1}H NMR spectroscopy.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.18 (s, 3 H), 2.27 (s, 3 H), 2.91–2.96 (m, 2 H), 3.24–3.27 (m, 1 H), 3.77 (t, *J* = 10.6 Hz, 1 H), 5.66 (dd, *J* = 3.4, 10.5 Hz, 1 H), 6.78 (d, *J* = 8.8 Hz, 1 H).

7f

Yield: 70%; solid; mp 145 °C.

IR (KBr): 1691, 1637, 1538, 1486 cm^{-1}.

Major Diastereoisomer

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.15 (s, 3 H), 2.19 (s, 3 H), 2.25 (s, 3 H), 2.99 (dd, *J* = 2.4, 13.6 Hz, 1 H), 3.04 (dt, *J* = 3.3, 12.2 Hz, 1 H), 3.19 (t, *J* = 12.2 Hz, 1 H), 3.48 (dt, *J* = 4.1, 10.8 Hz, 1 H), 3.71 (t, *J* = 10.8 Hz, 1 H), 4.58 (dd, *J* = 3.3, 10.4 Hz, 1 H), 5.82 (s, 1 H), 6.78–6.87 (m, 2 H).

MS: m/z = 314 [M^+].

UV (EtOH): λ_{max} = 206, 224, 278, 308 nm.

Anal. Calcd for $C_{18}H_{18}O_3S$: C, 68.78; H, 5.73. Found: C, 68.55; H, 5.86.

Minor Diastereoisomer

This diastereoisomer was observed by ^{1}H NMR spectroscopy.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.90–2.95 (m, 2 H), 3.77 (t, J = 10.8 Hz, 1 H), 5.70 (d, J = 9.5 Hz, 1 H).

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