# C—C Bond Formation by Radical Cyclization: Facile Syntheses of [6,6]Pyranothiopyrans and [6,6]Pyridothiopyrans



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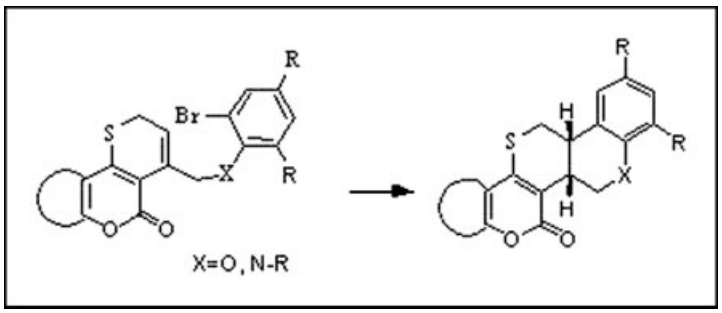


4-Chloromethylthiopyrano[3,2-*c*][1]benzopyran-5-(2*H*)-ones were refluxed with *o*-bromophenols in acetone in the presence of anhydrous potassium carbonate and sodium iodide to afford a number of 4-aryloxymethylthiopyrano[3,2-*c*][1]benzopyan-5-(2*H*)-ones in 72–79% yields. These compounds were refluxed with tri-*n*-butyltin hydride and azobisisobutyronitrile in dry benzene for 7–8 h to give [6,6]pyranothiopyrans in 76–84% yields with good diastereoselectivity. Similarly, [6,6]pyridothiopyrans were also synthesized in 70–75% yields with excellent diastereoselectivity.

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## INTRODUCTION

In recent years, radical cyclization has emerged as a valuable tool for the construction of carbo- and heterocyclic compounds, including natural products [1]. An understanding of the kinetic and the structural information of these reactive intermediates paved the way for the development of modern synthetic radical chemistry [2]. There has been continuing enhanced interest in recent years in the synthesis of coumarin derivatives largely on account of their occurrence in nature [3,4] and biological activity [5] *viz*., anthelmintic, hypnotic, insecticidal, antifungal activities, anticoagulant effect on blood, and diuretic properties. During our work on the synthesis of heterocycles by the application of sigmatropic rearrangements [6], we recently observed the unusual formation of [6,6]pyranopyrans in case of substrates containing 5-hydroxypyrimidines [7] and 3-hydroxycoumarin [8], in the second Claisen rearrangement step. The generation and subsequent reactions of radicals formed from aryl halides using tri-*n*-butyltin hydride and azobisisobutyronitrile (AIBN) are now well established [9]. However, literature reveals only a few examples of heteroaryl radicals [10–13]. Aryl radical cyclization normally has a high 5-*exo*:6-*endo* ratio indicating stronger preference for *exo* cyclization compared to the alkyl radicals. However, this preference is found to be reversed in cyclizations involving stabilized radicals [14]. Recently, we have reported [15] the synthesis of [6,6]pyranothiopyrans by the application of sequential Claisen rearrangement followed by pyridine hydrotribromide-mediated regioselective 6-endo cyclization. We have also reported some successful 6-*endo* aryl radical cyclizations by tri-*n*-butyltin hydride-mediated radical reaction [16]. In continuation of our studies, we became interested to examine the viability of synthesizing the [6,6]pyranothiopyran ring system by tri-*n*-butyltin hydride-induced radical cyclization of appropriate substrates (**3a–f**).

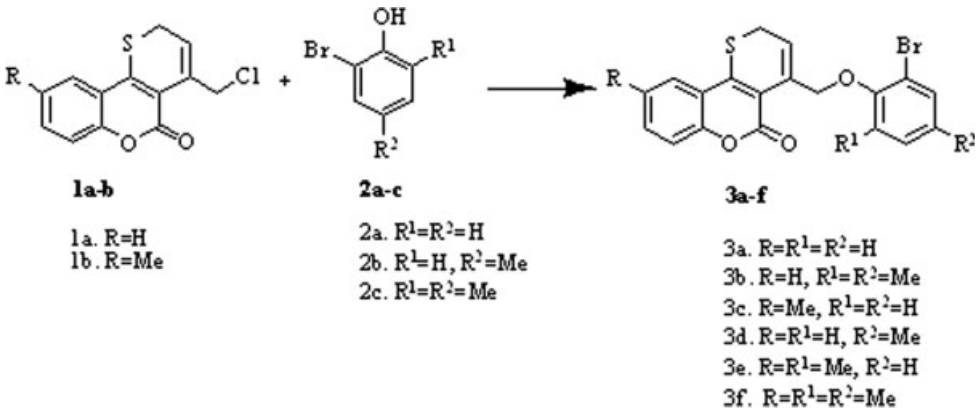
## RESULTS AND DISCUSSION

4-Chloromethylthiopyrano[3,2-*c*][1]benzopyran-5-(2*H*)-ones (**1a–b**) were refluxed with *o*-bromophenol in acetone in the presence of anhydrous potassium carbonate and sodium iodide to afford a number of 4-aryloxymethylthiopyrano[3,2-*c*][1]benzopyran-5-(2*H*)-ones (**3a–f**) (Scheme 1).

Compounds (**3a–f**) were characterized from their elemental analyses and spectral data. IR spectrum of compound **3a** showed carbonyl absorption at 1690 $cm^{-1}$. The high-field (300 MHz) $^1H$ NMR spectrum of compound **3a** exhibited two proton doublet at δ 3.48 for —SC**H**$_2$, two proton doublet at δ 5.18 for —OC**H**$_2$, one proton triplet at δ 6.35 for the vinylic proton among other signals for aromatic protons.

The substrate **3a** was refluxed in dry benzene under nitrogen atmosphere with tri-*n*-butyl tin hydride and

**Scheme 1.** Reagents and condition: $K_2CO_3$, NaI, dry acetone, reflux 3–5 h.




AIBN for 7 h to afford cyclic product **4a** in 80% yield as an inseparable diastereoisomeric mixture (3:1), which was determined by $^1$H, $^{13}$C, COSY, and NOESY experiments. $^1$H NMR spectrum of the product **4a** displayed peaks for two —SC**H**$_2$ protons at δ 3.23 and 3.33, two —OC**H**$_2$ protons at δ 3.88 and 4.70, and two ring juncture protons at δ 3.25 and 3.75 along with eight aromatic protons (δ 6.91–7.76) for the major diastereoisomer, whereas minor diastereoisomer displayed peaks at δ 3.05 and 3.74 for two —SC**H**$_2$ protons, δ 3.93 and 5.67 for two —OC**H**$_2$ protons, and δ 3.17 and 3.42 for two ring juncture protons. IR spectrum of compound **4a** also showed carbonyl absorption at 1700 cm$^{-1}$. The generality of the reaction was tested by subjecting five other substrates **3b–f** under the same reaction condition to give products **4b–f** in 76–84% yields (Scheme 2).

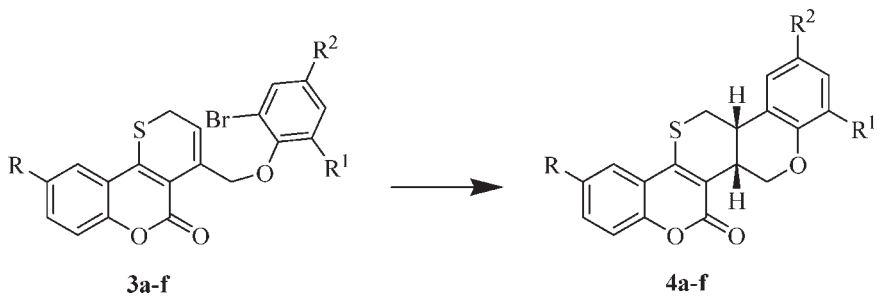
In the course of our studies on the application of sigmatropic rearrangements for the synthesis of heterocyclic compounds, we have already noted the formation of several [6,6]pyranopyran and [6,6]pyranothiopyran ring systems [17] using sequential Claisen rearrangements. However, we failed to synthesize [6,6]pyridothiopyran ring system using the Claisen rearrangement. The aforesaid results motivated us to investigate the synthesis of [6,6]pyridothiopyran ring system by tributyl tin hydride-mediated aryl radical cyclization.

The starting materials for our study 4-arylaminomethyl-7-methyl thioyrano[3,2-*c*]pyran-5-ones **7a–e** were synthesized from 4-chloromethyl-7-methyl-thiopyrano[3,2-*c*]pyran-5-ones **5** and various substituted *o*-bromoanilines **6a–e** in refluxing acetone in the presence of anhydrous $K_2CO_3$ and catalytic amount of NaI (Scheme 3).

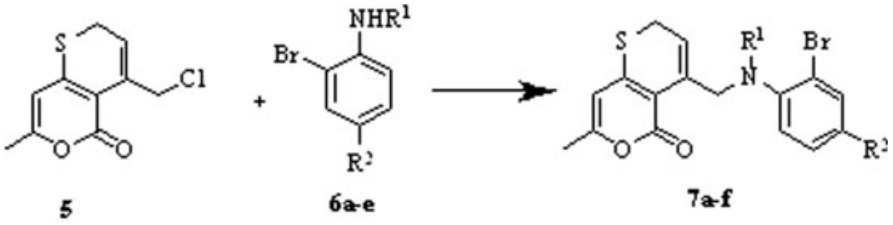
Substrate **7a** was refluxed in benzene with tributyl tin (IV) hydride in the presence of azoisobutyronitrile (AIBN) for 5 h to give compound **8a** (70%), which was characterized from its elemental analysis and spectroscopic data. The IR spectrum of the compound **8a** showed peaks at 3387 and 1682 cm$^{-1}$ for secondary N—H group and carbonyl group, respectively. The high-field $^1$H NMR (500 MHz) spectrum of the product **8a** displayed peaks for two —SC**H**$_2$ protons at δ 2.90 and δ 3.02, two ring juncture protons at δ 3.09 and δ 3.65, and two —NC**H**$_2$ protons at δ 3.19 and 3.33. The mass spectrum of the compound **8a** also displayed a molecular ion peak at *m*/*z* 286 ($M^+ + 1$). Encouraged by this result, other substrates **7b–e** were also similarly treated to give tetracyclic heterocycles **8b–e** in 70–75% yields (Scheme 4).

Substrates **3b** and **3c** also gave diastereomeric mixtures [18] (2.5:1 and 2:1, respectively) under similar reaction conditions, whereas substrates **3d–f** and **7a–e** with $Bu_3SnH$ and AIBN in refluxing benzene gave the

**Scheme 2.** Reagents and condition: $Bu_3SnH$, AIBN, dry benzene, under $N_2$, reflux 7–8 h.



**Scheme 3.** Reagents and reaction condition: $K_2CO_3$, NaI, dry acetone, reflux 4–5 h.




6a. $R^1 = R^2 = H$
6b. $R^1 = H$, $R^2 = Me$
6c. $R^1 = H$, $R^2 = Et$
6d. $R^1 = R^2 = Me$
6e. $R^1 = Me$, $R^2 = Et$

7a. $R^1 = R^2 = H$
7b. $R^1 = H$, $R^2 = Me$
7c. $R^1 = H$, $R^2 = Et$
7d. $R^1 = R^2 = Me$
7e. $R^1 = Me$, $R^2 = Et$

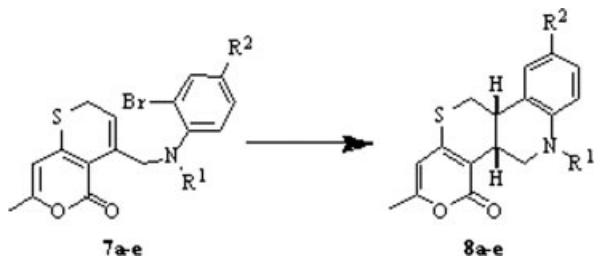
cyclized products **4d–f** and **8a–e**, respectively, with 100% diastereoselectivity. The high-field $^1$H NMR (500 MHz) of the compound **8a** showed the two ring juncture protons at δ 3.09–3.12 (dt, 1H, $J$ = 12.1, 3.5 Hz) and δ 3.65–3.69 (dt, 1H, $J$ = 11.5, 3.6 Hz). The low coupling constants ($J$ = 3.5 and 3.6 Hz) for the ring juncture protons indicate *cis*-stereochemistry of the ring juncture. The *cis*-stereochemistry of the ring juncture is also supported by the comparison of the $^1$H NMR data of similar compounds published earlier [17]. The stereochemistry at the ring juncture can also be surmised from the molecular models (Dreiding model), which shows a strain free *cis*-arrangement.

It was already established [19] that very high level of diastereoselectivity (>50:1) could be obtained when the concentration of the reactants is reduced from 0.1 to 0.01 M. This observation has been attributed to the reversibility of the cyclization and decreased availability of the $Bu_3SnH$. However, no significant change in diastereoselectivity was observed when the substrates **3a–c** were treated with $^nBu_3SnH$ and AIBN in refluxing benzene under a very dilute condition. Therefore, the reason behind the reduced diastereoselectivity in case of **3a–c** over the other is not clear.

The formation of products **4a–f** and **8a–e** from the substrates **3a–f** and **7a–e**, respectively, may easily be explained by the generation of an aryl radical **9** in the tri-*n*-butyltin hydride and azobisisobutyronitrile-mediated reaction. The aryl radical **9** may undergo cyclization by two different modes, a 6-*endo* trig cyclization to afford the heterocyclic radical **11** (pathway a) or a 5-*exo* trig cyclization to give the spiroheterocyclic radical [20] **10** (not isolated, pathway b). The possibility of the formation of heterocyclic radical **11** *via* spirocyclic radical **10** by a neophyl rearrangement [21] cannot be ruled out (Scheme 5).

It is known that radical cyclizations leading to six-membered rings are usually less general than cyclization leading to five-membered rings. The six-membered ring forming reactions are also slower than five-membered ring forming reactions and are subject to competitive formation of reduced uncyclized by-products. However, appropriately substituted 5-hexenyl radicals are known to undergo 6-*endo* cyclization to give six-membered rings. Our noteworthy observation is that the usual oxidation [13] does not occur at the present instance, and the dihydro compounds are isolated in excellent yield with good diastereoselectivity. It is also interesting to note that six-membered heterocyclic rings are regioselectively formed in all the cases. This is an attractive and simple methodology for the synthesis of [6,6]pyranothiopyran and [6,6]pyridothiopyran ring systems.

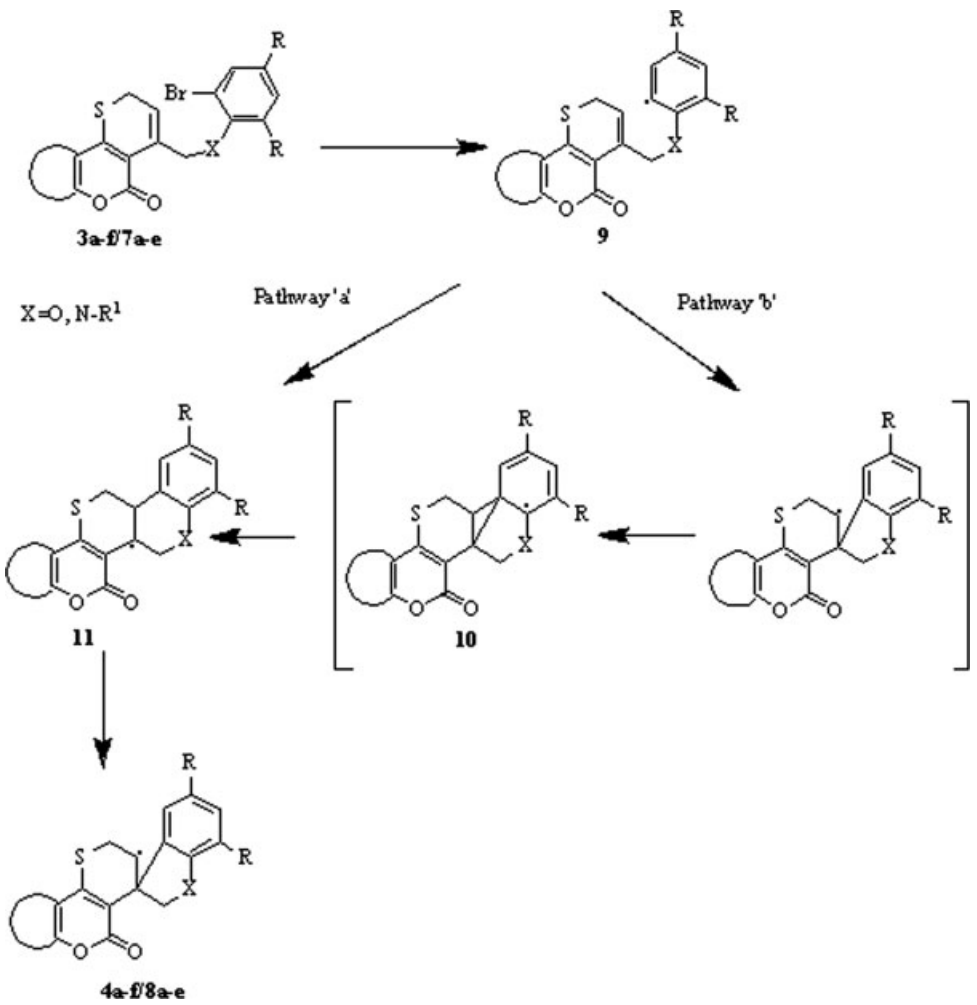
**Scheme 4.** Reagents and reaction condition: $Bu_3SnH$, AIBN, dry acetone, under $N_2$, reflux 5–8 h.




## 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). $^1$H NMR (300 MHz, 500 MHz) and $^{13}$C NMR (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 an internal standard. $^1$H NMR and $^{13}$C NMR spectra were recorded at the Indian Institute of Chemical Biology, Kolkata and Bose Institute,

**Scheme 5**




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 and 80°C.

The starting materials (**1a**,**b**) and **5** for this study were prepared according to our earlier published procedure [22,23].

**General procedure for the preparation of compound 3a–f.** Compound (**1a, b**) (1 mmol) was refluxed with several *o*-bromophenols (**2a**–**c**) (1 mmol) in acetone (100 mL) in the presence of anhydrous potassium carbonate (1g) and catalytic amount of NaI for 3–5 h. The reaction mixture was then cooled, filtered, and the solvent was removed. The residual mass was subjected to column chromatography over silica gel using petroleum ether–ethylacetate (19:1) as eluant to give compounds **3a**–**f**, which were then recrystallized from chloroform.

***Compound 3a.*** Yield 75%; yellow solid; m.p. 90°C; UV(EtOH)$\lambda_{max}$: 214, 243, 371 nm; IR(KBr) $\nu_{max}$: 1690, 1600, 1260 $cm^{-1}$; $^1H$ NMR (500 MHz): δ 3.48 (d, 2H, $J$ = 6 Hz, —$SCH_2$), 4.99 (d, 2H, $J$ = 1 Hz, —$OCH_2$), 6.38–6.42 (tt, 1H, $J$ = 1, 6 Hz, =CH), 7.17–7.23 (m, 3H, ArH), 7.29–7.37 (m, 4H, ArH), 7.50–7.61 (m, 1H, ArH); Anal. Calcd. for $C_{19}H_{13}BrO_3S$: C, 56.85%; H, 3.24%; Found C, 56.91%; H, 3.57%.

***Compound 3b.*** Yield 79%; yellow solid; m.p. 138°C; UV(EtOH) $\lambda_{max}$: 209, 246, 355 nm; IR(KBr) $\nu_{max}$: 1690, 1600, 1270 $cm^{-1}$; $^1H$ NMR (500 MHz): δ 2.34 (s, 3H, —$CH_3$), 2.38 (s, 3H, —$CH_3$), 3.49 (d, 2H, $J$ = 6 Hz, —$SCH_2$), 4.97 (d, 2H, $J$ = 1 Hz, —$OCH_2$), 6.39–6.41 (tt, 1H, $J$ = 1, 6 Hz, =CH), 7.29–7.32 (m, 4H, ArH), 7.51–7.55 (m, 1H, ArH), 7.83–7.85 (m, 1H, ArH); Anal. Calcd. for $C_{21}H_{17}BrO_3S$: C, 58.74%; H, 3.96%; Found C, 59.05%; H, 3.61%.

***Compound 3c.*** Yield 74%; yellow solid; m.p. 136°C; UV(EtOH)$\lambda_{max}$: 218, 240, 336 nm; IR(KBr) $\nu_{max}$: 1700, 1600, 1240 $cm^{-1}$; $^1H$ NMR (500 $MH_Z$): δ 2.43 (s, 3H, —$CH_3$), 3.46 (d, 2H, $J$ = 6 Hz, —$SCH_2$), 5.20 (d, 2H, $J$ = 1 Hz, —$OCH_2$), 6.34–6.35 (tt, 1H, $J$ = 1,6 Hz, =CH), 6.83–7.61 (m, 7H, ArH); Anal. Calcd. for $C_{20}H_{15}BrO_3S$: C, 57.83%; H, 3.61%; Found C, 58.04%; H, 3.73%.

***Compound 3d.*** Yield 72%; yellow solid; m.p. 94°C; UV(EtOH)$\lambda_{max}$: 221, 243, 375 nm; IR(KBr) $\nu_{max}$: 1700, 1590, 1290 $cm^{-1}$; $^1H$ NMR (300 MHz): δ 2.26 (s, 3H, —$CH_3$), 3.46 (d, 2H, $J$ = 6 Hz, —$SCH_2$), 5.16 (d, 2H, $J$ = 1 Hz, —$OCH_2$), 6.31–6.35 (tt, 1H, $J$ = 1, 6 Hz, =CH), 6.84–6.87 (m, 1H,

ArH), 7.02–7.05 (m, 1H, ArH), 7.29–7.35 (m, 3H, ArH), 7.51–7.57 (m, 1H, ArH), 7.82–7.85 (m, 1H, ArH); Anal. Calcd. for $C_{20}H_{15}BrO_3S$: C, 57.83%; H, 3.61%; Found C, 57.98%; H, 3.47%.

***Compound 3e.*** Yield 75%; yellow solid; m.p. 122°C; UV(EtOH)$\lambda_{max}$: 216, 245, 359 nm; IR(KBr) $\nu_{max}$: 3300, 1680, 1590, 1250 $cm^{-1}$; $^1H$ NMR (500 MHz): δ 2.26 (s, 3H, —C**H**$_3$), 2.43 (s, 3H, —C**H**$_3$), 3.45 (d, 2H, $J$ = 6 Hz, —SC**H**$_2$), 5.16 (d, 2H, $J$ = 1 Hz, —OC**H**$_2$), 6.30–6.33 (tt, 1H, $J$ = 1, 6 Hz, =C**H**), 6.84–6.86 (d, $J$ = 9 Hz, 1H, Ar**H**), 7.01–7.03 (dd, 1H, $J$ = 2.5, 9 Hz, Ar**H**), 7.21–7.26 (m, 1H, Ar**H**), 7.32–7.34 (m, 2H, Ar**H**), 7.60 (s, 1H, Ar**H**); Anal. Calcd. for $C_{21}H_{17}BrO_3S$: C, 58.74%; H, 3.96%; Found C, 58.60%; H, 4.19%.

***Compound 3f.*** Yield 73%; yellow solid; m.p. 168°C; UV(EtOH)$\lambda_{max}$: 212, 240, 326 nm; IR(KBr) $\nu_{max}$: 1720, 1700, 1230 $cm^{-1}$; $^1H$ NMR (500 MHz): δ 2.24 (s, 3H, —C**H**$_3$), 2.26 (s, 3H, —C**H**$_3$), 2.43 (s, 3H, —C**H**$_3$), 3.48 (d, 2H, $J$ = 6 Hz, —SC**H**$_2$), 5.00 (d, 2H, $J$ = 1 Hz, —OC**H**$_2$), 6.38–6.42 (t, 1H, $J$ = 6 Hz, =C**H**), 7.19–7.61 (m, 5H, Ar**H**); Anal. Calcd. for $C_{22}H_{19}BrO_3S$: C, 59.59%; H, 4.29%; Found C, 59.70%; H, 4.06%.

**General procedure for the synthesis of compounds 7a–e.** Compound 5 (1 mmol) was refluxed with several *o*-bromoanilines (**6a–e**) (1 mmol) in dry acetone (100 mL) in the presence of anhydrous potassium carbonate (1 g) and catalytic amount of NaI for 4–5 h. The reaction mixture was cooled, filtered, and the solvent was removed. The residual mass was subjected to column chromatography over silica gel using petroleum ether–ethylacetate (19:1) as eluant to give compounds **7a–e**.

***Compound 7a.*** Yield: 80%; Solid, m.p. 170°C; IR (KBr)$\nu_{max}$: 3410, 1698, 1596, 1497 $cm^{-11}$ H NMR ($CDCl_3$, 400 MHz) $\delta_H$ 2.21 (s, 3H), 3.27–3.28 (d, 2H, $J$ = 5.8 Hz), 4.38 (s, 2H), 5.76–5.79 (t, 1H, $J$ = 5.8 Hz), 5.99 (s, 1H), 6.49–6.53 (t, 1H, $J$ = 7.42 Hz), 6.59–6.61 (d, 1H, $J$ = 8 Hz), 7.09–7.12 (t, 1H, $J$ = 7.5 Hz), 7.35–7.37 (d, 1H, $J$ = 8.04 Hz). UV (EtOH) $\lambda_{max}$= 361, 302, 245, 209 nm. Anal. Calcd. for $C_{16}H_{14}NO_2SBr$: C, 52.75%; H, 3.85%; N, 3.85%; Found C, 52.45%; H, 3.55%; N, 3.65%.

***Compound 7b.*** Yield: 80%; Gummy mass. IR (KBr)$\nu_{max}$: 3399, 1698, 1492 $cm^{-1}$ $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta_H$ 2.18 (s, 3H), 2.21 (s, 1H), 3.26–3.28 (d, 2H, $J$ = 5.8 Hz), 4.36 (s, 2H), 5.75–5.78 (t, 1H, $J$ = 5.86 Hz), 5.99 (s, 1H), 6.50–6.52 (d, 1H, $J$ = 8.2 Hz), 6.90–6.92 (dd, 1H, $J$ = 8.24, 1.32 Hz), 7.20–7.21 (d, 1H, $J$ = 1.16 Hz). UV (EtOH) $\lambda_{max}$= 302, 243, 208 nm. Anal. Calcd. for $C_{17}H_{16}NO_2SBr$: C, 53.96%; H, 4.23%; N, 3.70%; Found C, 53.66%; H, 4.53%; N, 3.40%.

***Compound 7c.*** Yield: 75%; Solid, m.p. 125–130°C; IR (KBr)$\nu_{max}$: 3391, 1699, 1594 $cm^{-1}$ $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta_H$ 1.15–1.18 (t, 3H, $J$ = 7.58 Hz), 2.22 (s, 3H), 2.47–2.52 (q, 2H, $J$ = 7.58 Hz), 3.28–3.29 (d, 2H, $J$ = 5.88 Hz), 4.36–4.37 (d, 2H, $J$ = 1.09 Hz), 5.77–5.79 (t, 1H, $J$ = 5.87 Hz), 5.99 (s, 1H), 6.56–6.58 (d, 1H, $J$ = 8.26 Hz), 6.94–6.96 (dd, 1H, $J$ = 8.26, 1.98 Hz), 7.23–7.24 (d, 1H, $J$ = 1.99 Hz). UV (EtOH) $\lambda_{max}$= 303, 246, 209 nm. Anal. Calcd. for $C_{18}H_{18}NO_2SBr$: C, 55.10%; H, 4.59%; N, 3.57%; Found C, 55.40%; H, 4.49%; N, 3.27%.

***Compound 7d.*** Yield: 80%; Solid, m.p. 120°C; IR (KBr)$\nu_{max}$: 1711, 1493 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta_H$ 2.17 (s, 3H), 2.24 (s, 3H), 2.61 (s, 3H, —NMe), 3.23–3.25 (d, 2H, $J$ = 6.04 Hz), 4.15 (s, 2H), 5.92–5.95 (m, 2H), 6.89–6.91 (d, 1H, $J$ = 8.12 Hz), 6.96–6.98 (dd, 1H, $J$ = 8, 1.68 Hz), 7.33 (d, 1H, $J$ = 1.68 Hz). UV (EtOH) $\lambda_{max}$ = 356, 248, 205 nm. Anal. Calcd. for $C_{18}H_{18}NO_2SBr$: C, 55.10%; H, 4.59%; N, 3.57%; Found C, 54.80%; H, 4.89%; N, 3.28%.

***Compound 7e.*** Yield: 75%; Solid, m.p. 110°C; IR (KBr)$\nu_{max}$: 1711, 1495 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta_H$ 1.17–1.20 (t, 3H, $J$ = 7.59 Hz), 2.18 (s, 3H), 2.52–2.57 (q, 2H, $J$ = 7.57 Hz), 2.62 (s, 3H, —NMe), 3.25–3.26 (d, 2H, $J$ = 5.99 Hz), 4.16 (s, 2H), 5.96–5.99 (m, 2H), 6.94–6.96 (d, 1H, $J$ = 8.12 Hz), 7.0–7.02 (dd, 1H, $J$ = 8.15, 1.9 Hz), 7.35 (d, 1H, $J$ = 1.9 Hz). UV (EtOH) $\lambda_{max}$= 359, 299, 249, 215 nm. Anal. Calcd. for $C_{19}H_{20}NO_2SBr$: C, 56.16%; H, 4.93%; N, 3.45%; Found C, 56.36%; H, 4.63%; N, 3.15%.

**General procedure for the preparation of compounds 4a–f and 8a–e by radical cyclization.** A suspension of the compound 3a (0.5 mmol), $^nBu_3SnH$ (0.075 mL), and AIBN (0.5–0.6 mol equiv) in dry benzene (7–10 mL) were refluxed for 7–8 h under $N_2$ atmosphere. The solvent was evaporated under reduced pressure. The residue was dissolved in 10 mL of ether and stirred with 10 mL of 10% aqueous potassium fluoride for 45 min. The white precipitate separated by filtration and the aqueous phase was extracted with $CHCl_3$ (3 × 10 mL). The combined organic extract was washed with brine and dried ($Na_2SO_4$). The residual mass after removal of the solvent was subjected to column chromatography over silica gel using pet-ether–ethyl acetate (19:1) as eluant to give cyclized products **4a**, which were then recrystallized from chloroform–petroleum ether. Similarly, other compounds **4b–f** and **8a–e** were also synthesized.

***Compound 4a.*** Yield 80%; white solid; m.p. 140°C; UV (EtOH) $\lambda_{max}$: 219, 279 nm; IR (KBr) $\nu_{max}$: 2900, 1700, 1195 $cm^{-1}$, $^1H$ NMR ($CDCl_3$, 500 MHz): Major diastereomer: δ 3.23 (t, 1H, $J$ = 11.4 Hz, —SC**H**$_2$), 3.25 (dt, 1H, $J$ = 3.6, 10.5 Hz, ring juncture), 3.33 (dd, 1H, $J$ = 2.4 Hz, 12.6 Hz, SC**H**$_2$), 3.75 (dt, 1H, $J$ = 3.1, 11.4 Hz, ring juncture), 3.88 (t, 1H, $J$ = 10.5 Hz, OC**H**$_2$), 4.70 (dd, 1H, $J$ = 3.08, 10.8 Hz, OC**H**$_2$), 6.88–6.97 (m, 2H, Ar**H**), 7.28–7.35 (m, 2H, Ar**H**), 7.51–7.57 (m, 3H, Ar**H**), 7.74–7.76 (m, 1H, Ar**H**); $^{13}C$ NMR (125 MHz, $CDCl_3$): at 29.6, 31.7, 32.4, 64.5, 114.9, 117.7, 120.7, 121.2, 124.0, 124.5, 129.3, 130.1, 130.2, 130.6, 132.2, 149.9, 151.3, 154.7, and 159.5; MS *m/z* 322 ($M^+$); Anal. Calcd. for $C_{19}H_{14}O_3S$: C, 70.81%; H, 4.35%; Found C, 71.02%; H, 4.43%. Minor diastereomer: $^1H$ NMR ($CDCl_3$, 500 MHz): δ 3.05–3.07 (m, 1H), 3.17–3.20 (m, 1H), 3.42–3.45 (m, 1H), 3.74–3.76 (m, 1H), 3.93–3.96 (m, 1H), 5.66 (dd, 1H, $J$ = 3.4 Hz, 10.46 Hz); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 28.7, 37.5, 38.8, and 69.

***Compound 4b.*** Yield 76%; white solid; m.p. 198°C; UV (EtOH) $\lambda_{max}$: 215, 279 nm; IR (KBr) $\nu_{max}$: 2910, 1700, 1190 $cm^{-1}$, $^1H$ NMR ($CDCl_3$, 500 MHz): Major diastereomer: δ 2.19 (s, 3H, —C**H**$_3$), 2.28 (s, 3H, —C**H**$_3$), 3.20 (t, 1H, $J$ = 11.2 Hz, —SC**H**$_2$), 3.24 (dt, 1H, $J$ = 3.4, 10.8 Hz, ring juncture proton), 3.34 (dd, 1H, $J$ = 2.6, 12.4 Hz, —SC**H**$_2$), 3.72 (dt, 1H, $J$ = 3.2, 11.2 Hz, ring juncture proton), 3.90 (t, 1H, $J$ = 10.8 Hz, —OC**H**$_2$), 4.68 (dd, 1H, $J$ = 2.6, 11.8 Hz, —OC**H**$_2$), 6.84–6.89(s, 2H, Ar**H**), 7.32–7.61 (m, 2H, Ar**H**), 7.73–7.76 (m, 2H, Ar**H**); MS *m/z* 350 ($M^+$); Anal. Calcd. for $C_{21}H_{18}O_3S$: C, 72.0%; H, 5.14%; Found C, 72.25%; H, 5.43%. *Minor diastereomer:* $^1H$ NMR ($CDCl_3$, 500 MHz): δ 2.99–3.22 (m, 3H), 3.73–3.87 (m, 2H), 5.64 (dd, 1H, $J$ = 3.5, 10.7 Hz).

***Compound 4c.*** Yield 82%; white solid; m.p. 182°C; UV (EtOH) $\lambda_{max}$: 219, 280 nm; IR (KBr) $\nu_{max}$ : 2915, 1710, 1190 $cm^{-1}$, $^1H$ NMR ($CDCl_3$, 300 MHz): Major diastereomer: δ 2.43

(s, 3H, —C**H**$_3$), 3.26 (t, 1H, $J$ = 11.4 Hz, —SC**H**$_2$), 3.27 (dt, 1H, $J$ = 3.4, 10.7 Hz, ring juncture proton), 3.35 (dd, 1H, $J$ = 2.5, 12.2 Hz, —SC**H**$_2$), 3.74 (dt, 1H, $J$ = 3.5, 11.4 Hz, ring juncture proton), 3.87 (t, 1H, $J$ = 10.7 Hz, —OC**H**$_2$), 4.64 (dd, 1H, $J$ = 2.6, 10.2 Hz, —OC**H**$_2$), 6.88–6.97 (m, 3H, Ar**H**), 7.14–7.35 (m, 3H, Ar**H**), 7.51(s, 1H, Ar**H**); MS $m/z$ 336 ($M^+$); Anal. Calcd. for $C_{20}H_{16}O_3S$: C, 71.43%; H, 4.76%; Found C, 71.62%; H, 4.83%. Minor diastereomer: $^1$H NMR ($CDCl_3$, 300 MHz): δ 3.00–3.22 (m, 3H), 3.88–3.93 (m, 2H), 5.62 (dd, 1H, $J$ = 3.4, 10.4 Hz).

***Compound 4d.*** Yield 82%; white solid; m.p. 182°C; UV (EtOH) $\lambda_{max}$: 220, 279 nm; IR (KBr) $\nu_{max}$ : 2900, 1700, 1196 cm$^{-1}$, $^1$H NMR ($CDCl_3$, 300 MHz): δ 2.29 (s, 3H, —C**H$_3$**), 3.19 (dd, 1H, $J$ = 2.4, 11.2 Hz, —SC**H**$_2$), 3.26–3.34 (m, 2H), 3.69 (dt, 1H, $J$ = 3.5, 11.0 Hz, ring juncture proton), 3.78 (t, 1H, $J$ = 10.5 Hz, —OC**H**$_2$), 4.61 (dd, 1H, $J$ = 2.1, 10.0 Hz, —OC**H**$_2$), 6.78–7.00 (m, 3H, Ar**H**), 7.27–7.34 (m, 2H, Ar**H**), 7.51–7.56 (m, 1H, Ar**H**), 7.73 (d, $J$ = 7.8 Hz, 1H, Ar**H**); MS $m/z$ 336 ($M^+$); Anal. Calcd. for $C_{20}H_{16}O_3S$: C, 71.43%; H, 4.76%; Found C, 71.59%; H, 4.62%.

***Compound 4e.*** Yield 84%; white solid; m.p. 208°C; UV (EtOH) $\lambda_{max}$: 219, 280 nm; IR (KBr) $\nu_{max}$: 2900, 1690, 1220 cm$^{-1}$, $^1$H NMR ($CDCl_3$, 300 MHz): δ 2.29 (s, 3H, —C**H**$_3$), 2.43 (s, 3H, —C**H**$_3$), 3.18–3.29 (m, 3H), 3.72 (dt, 1H, $J$ = 3.4, 10.7 Hz, ring juncture proton), 3.77 (t, 1H, $J$ = 10.5 Hz, —OC**H**$_2$), 4.60 (dd, 1H, $J$ = 3.2, 10.4 Hz, —OC**H**$_2$), 6.77–7.01 (m, 3H, Ar**H**), 7.20–7.24 (m, 1H, Ar**H**), 7.32 (dd, 1H, $J$ = 1.6, 8.3 Hz, Ar**H**), 7.51 (s, 1H, Ar**H**); MS $m/z$ 350 ($M^+$); Anal. Calcd. for $C_{21}H_{18}O_3S$: C, 72.0%; H, 5.14%; Found C, 72.17%; H, 5.25%.

***Compound 4f.*** Yield 77%; white solid; m.p. 214°C; UV (EtOH) $\lambda_{max}$: 219, 278 nm; IR (KBr) $\nu_{max}$ : 2910, 1690, 1210 cm$^{-1}$, $^1$H NMR ($CDCl_3$, 300 MHz): δ 2.18 (s, 3H, —$CH_3$), 2.26 (s, 3H, —$CH_3$), 2.43 (s, 3H, —$CH_3$), 3.13–3.30 (m, 3H), 3.66–3.71 (dt, 2H, $J$ = 3.6, 10.7 Hz, ring juncture proton), 3.76 (t, 1H, $J$ = 10.6 Hz, —$OCH_2$), 4.66 (dd, 1H, $J$ = 2.1, 10.3 Hz, —$OCH_2$), 6.84–6.87 (d, 2H, $J$ = 9 Hz, ArH), 7.20–7.23 (m, 1H, ArH), 7.32–7.34 (m, 1H, ArH), 7.52 (s, 1H, ArH); MS $m/z$ 364 ($M^+$); Anal. Calcd. for $C_{22}H_{20}O_3S$: C, 72.53%; H, 5.49%; Found C, 72.71%; H, 5.25%.

***Compound 8a.*** Yield: 70%; Solid, m.p. 218°C; IR (KBr)$\nu_{max}$: 3387, 1682, 1539 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta_H$ 2.18 (s, 3H), 2.90–2.94 (ddd, 1H, $J$ = 12.9, 3.2, 2.1 Hz), 3.02–3.06 (t, 1H, $J$ = 11.4 Hz), 3.09–3.12 (dt, 1H, $J$ = 12.1, 3.5 Hz), 3.19–3.24 (t, 1H, $J$ = 12.6 Hz), 3.33–3.37 (dt, 1H, $J$ = 11.02, 4.1 Hz), 3.65–3.69 (dt, 1H, $J$ = 11.5, 3.6 Hz), 4.02 (brs, 1H, N—H), 5.81 (s, 1H), 6.51–6.53 (dd, 1H, $J$ = 8.04, 0.76 Hz), 6.64–6.67 (dt, 1H, $J$ = 7.32, 1.12 Hz), 7.02–7.06 (m, 2H). MS: $m/z$ = 286 (M + 1); UV (EtOH) $\lambda_{max}$= 306, 255, 232, 209 nm. Anal. Calcd. for $C_{16}H_{15}NO_2S$: C, 67.37%; H, 5.26%; N, 4.91%; Found C, 67.67%; H, 4.96%; N, 5.21%.

***Compound 8b.*** Yield: 75%; Solid, m.p. 210°C; IR (KBr)$\nu_{max}$: 3392, 1684, 1539 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta_H$ 2.18 (s, 3H), 2.23 (s, 3H), 2.90–2.97 (m, 1H), 3.00–3.08 (m, 2H), 3.17–3.25 (t, 1H, $J$ = 12.35 Hz), 3.30–3.34 (m, 1H), 3.62–3.66 (d, 1H, $J$ = 11.17 Hz), 3.90 (brs, 1H, N—H), 5.81 (s, 1H), 6.45–6.47 (d, 1H, $J$ = 7.77 Hz), 6.85–6.87 (d, 1H, $J$ = 7.63 Hz), 6.87 (s, 1H). $^{13}$C NMR (125 MHz, $CDCl_3$): 19.8, 20.7, 30.8, 31.0, 35.2, 42.0, 104.3, 112.9, 115.0, 121.9, 126.8, 129.3, 130.5, 141.7, 151.7, 158.0, 161.7. MS: $m/z$ = 300 (M + 1); UV (EtOH) $\lambda_{max}$ = 308, 257, 232, 208 nm. Anal. Calcd. for $C_{17}H_{17}NO_2S$: C, 68.23%; H, 5.69%; N, 4.68%; Found C, 68.53%; H, 5.39%; N, 4.98%.

***Compound 8c.*** Yield: 75%; Solid, m.p. 200°C; IR (KBr)$\nu_{max}$: 3386, 1693, 1545 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta_H$ 1.17–1.20 (t, 3H, $J$ = 7.58 Hz), 2.19 (s, 3H), 2.50–2.55 (q, 2H, $J$ = 7.57 Hz), 2.92–2.95 (dd, 1H, $J$ = 13.11, 2.49 Hz), 2.99–3.03 (t, 1H, $J$ = 11.4 Hz), 3.06–3.09 (dt, 1H, $J$ = 12.14, 3.5 Hz), 3.19–3.24 (t, 1H, $J$ = 12.63 Hz), 3.31–3.34 (dt, 1H, $J$ = 10.98, 4.0 Hz), 3.64–3.66 (dt, 1H, $J$ = 11.44, 3.68 Hz), 3.91 (brs, 1H, N—H), 5.80 (s, 1H), 6.47–6.49 (d, 1H, $J$ = 8.63 Hz), 6.88–6.89 (m, 2H). MS: $m/z$ = 314 (M + 1); UV (EtOH) $\lambda_{max}$= 309, 257, 232, 210 nm. Anal. Calcd. For $C_{18}H_{19}NO_2S$: C, 69.01%; H, 6.07%; N, 4.47%; Found C, 69.31%; H, 5.87%; N, 4.19%.

***Compound 8d.*** Yield: 70%; Solid, m.p. 162°C; IR (KBr)$\nu_{max}$: 1694, 1463 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta_H$ 2.19 (s, 3H), 2.23 (s, 3H), 2.97–3.01 (t, 1H, $J$ = 11.09 Hz), 3.03–3.07 (m, 1H), 3.14–3.19 (t, 1H, $J$ = 12.54 Hz), 3.43–3.47 (dt, 1H, $J$ = 10.83, 4.19 Hz), 3.48–3.51 (ddd, 1H, $J$ = 11.25, 3.9, 1.3 Hz), 5.80 (s, 1H), 6.53–6.55 (d, 1H, $J$ = 8.37 Hz), 6.88–6.89 (d, 1H, $J$ = 1.78 Hz), 6.95–6.97 (dd, 1H, $J$ = 8.31, 1.84 Hz). $^{13}$C NMR (125 MHz, $CDCl_3$): 19.8, 20.6, 30.9, 31.0, 35.8, 39.3, 50.7, 104.3, 111.8, 112.9, 123.2, 125.9, 129.5, 130.4, 143.8, 151.9, 158.0, 161.7. MS: $m/z$ = 314 (M + 1); UV (EtOH) $\lambda_{max}$ = 309, 260, 208 nm. Anal, Calcd. for $C_{18}H_{19}NO_2S$: C, 69.01%; H, 6.07%; N, 4.47%; Found C, 69.29%; H, 6.28%; N, 4.25%.

***Compound 8e.*** Yield: 70%; Solid, m.p. 140°C; IR (KBr)$\nu_{max}$: 1700, 1463 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta_H$ 1.18–1.21 (t, 3H, $J$ = 7.59 Hz), 2.19 (s, 3H), 2.51–2.56 (q, 2H, $J$ = 7.59 Hz), 2.88–2.90 (ddd, 1H, $J$ = 12.8, 3.16, 2.0 Hz), 2.91 (s, 3H), 2.98–3.02 (t, 1H, $J$ = 11.08 Hz), 3.05–3.08 (dt, 1H, $J$ = 12.08, 3.4 Hz), 3.15–3.20 (t, 1H, $J$ = 12.53 Hz), 3.43–3.47 (dt, 1H, $J$ = 10.87, 4.2 Hz), 3.49–3.52 (ddd, 1H, $J$ = 11.2, 2.76, 1.2 Hz), 5.81 (s, 1H), 6.56–6.58 (d, 1H, $J$ = 8.34 Hz), 6.90–6.91 (d, 1H, $J$ = 1.87 Hz), 6.98–7.00 (dd, 1H, $J$ = 8.4, 1.99 Hz). MS: $m/z$ = 328 (M + 1); UV (EtOH) $\lambda_{max}$ = 308, 262, 231, 208 nm. Anal. Calcd. For $C_{19}H_{21}NO_2S$: C, 69.72%; H, 6.42%; N, 4.28%; Found C, 69.45%; H, 6.22%; N, 4.50%.

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