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# Reactions of $\alpha$-Lithiatd 4*H*-1-Benzothiopyran-4-one and 1,2-Dihydrocyclopenta[*b*][1]benzothiopyran-9(3*H*)-one Derivatives

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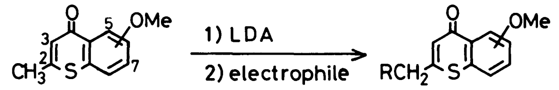
Treatment of 5- and 7-methoxy-2-methyl-4*H*-1-benzothiopyran-4-one with lithium diisopropylamide followed by electrophiles gave 2-substituted 4*H*-1-benzothiopyran-4-ones. Utilizing this reaction, 3-substituted 6- and 8-methoxy-1,2-dihydrocyclopenta[*b*][1]benzothiopyran-9(3*H*)-ones were also synthesized, and several compounds showed potential analgesic and anti-inflammatory activities.

In our previous synthetic studies on heterocyclic compounds directed to the development of biologically active substances, we prepared polycyclic derivatives of 1-alkyl-4-pyridone[1] and 4-pyrone,[2] which have a common 6-membered cyclic structure with nitrogen or oxygen atom at 1-position and a carbonyl group at 4-position. Recently, we found that a sulfur analogue, 1,2-dihydro-8-methoxycyclopenta[*b*][1]benzothiopyran-(3*H*)-one (**8**), possesses analgesic and anti-inflammatory activities. In order to examine the activities of the related compounds, we devised an $\alpha$-lithiation reaction of this heterocyclic system. The present report describes the reaction of the lithiated 4*H*-1-benzothiopyran-4-ones with electrophiles.

The starting materials, 7- and 5-methoxy-2-methyl-4*H*-1-benzothiopyran-4-one (**3** and **4**) or 8- and 6-methoxy-1,2-dihydrocyclopenta[*b*][1]benzothiopyran-9(3*H*)-one (**8** and **9**), are synthesized from *m*-methoxybenzenethiol (**1**) and ethyl acetoacetate (**2**) or ethyl 2-oxo-1-cyclopentanecarboxylate (**7**), respectively, by the condensation in polyphosphoric acid at 80 °C.[3] Each isomer is separable by chromatography on silica gel. The assignment is based on the NMR spectra. Thus, a triplet with 8 Hz of the coupling constant at $\delta$ 7.4 was observed for **4** and **8**, indicating the presence of 1,2,3-trisubstituted aromatic ring, while the other isomers **3** and **9** showed a broad singlet at $\delta$ 6.9.

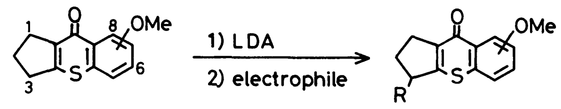
Benzothiopyranones **3**, **4**, **8**, and **9**, thus obtained, were treated with lithium diisopropylamide (LDA) and lithiation ocurred smoothly. The reaction with several alkyl halides and aldehydes gave the corresponding benzothiopyranones **5**, **6**, **10**, and **11** (Scheme 1 and 2). The results are summarized in Tables 1 and



**3** (7-MeO)
**4** (5-MeO)

**5** (7-MeO)
**6** (5-MeO)

Scheme 1.



**8** (8-MeO)
**9** (6-MeO)

**10** (8-MeO)
**11** (6-MeO)

Scheme 2.

Table 1. Synthesis of 2-substituted 7- and 5-methoxy-4*H*-1-benzothiopyran-4-ones

| Substrate | Electrophile | Product | R | Yield/% |
|---|---|---|---|---|
| **3** | MeI | **5a** | Me | 57 |
| | $CH_2{=}CHCH_2Br$ | **5b** | $CH_2{=}CHCH_2$ | 43 |
| | $C_2H_5O_2CCH_2Br$ | **5c** | $C_2H_5O_2CCH_2$ | 70 |
| | PhCHO | **5f** | PhCH(OH) | 67 |
| | $p$-$MeOC_6H_4CHO$ | **5g** | $p$-$MeOC_6H_4CH(OH)$ | 63 |
| | 3,4-$(OCH_2O)C_6H_3CHO$ | **5h** | 3,4-$(OCH_2O)C_6H_3CH(OH)$ | 58 |
| **4** | PhCHO | **6f** | PhCH(OH) | 71 |
| | $p$-$MeOC_6H_4CHO$ | **6g** | $p$-$MeOC_6H_4CH(OH)$ | 21 |

Table 2. Synthesis of 3-substituted 8- and 6-methoxy-1,2-dihydrocyclopenta [*b*][1] benzothiopyran-9(3*H*)-ones

| Substrate | Electrophile | Product | R | Yield/% |
|---|---|---|---|---|
| **8** | MeI | **10a** | Me | 70 |
| | $C_2H_5O_2CCH_2Br$ | **10c** | $C_2H_5O_2CCH_2$ | 69 |
| | EtI | **10d** | Et | 43 |
| | $PhCH_2Br$ | **10e** | $PhCH_2$ | 40 |
| | PhCHO | **10f** | PhCH(OH) | 60 |
| | $O_2$ | **10i** | HO | 17 |
| **9** | $C_2H_5O_2CCH_2Br$ | **11c** | $C_2H_5O_2CCH_2$ | 65 |
| | $O_2$ | **11i** | HO | 15 |

2. In general, the reaction ocurred at C-2 methyl carbon for **3** and **4**, and at 3-position for **8** and **9**. However, a small amount of mixture of other products, presumable compounds formed by alkylation at C-3 carbon, was also detected in methylation and allylation of **3**.

When attentions are paid on $\beta$-sulfur substituted $\alpha,\beta$-unsaturated carbonyl moiety of these benzothiopyranones, the present process can be classified as the $\gamma$-alkylation of enone system. As $\beta$-sulfur substituted enones are reported to give $\alpha,\alpha$-dialkylated products,[4] this synthesis provides a novel example of $\gamma$-alkylation. In contrast, carbon–carbon bond formation at $\gamma$-position of $\alpha,\beta$-unsaturated carbonyl compounds possessing nitrogen[5] or oxygen[6] substituents are well known (Fig. 1).

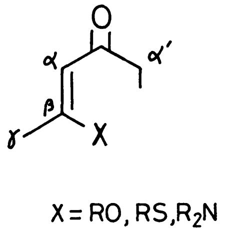
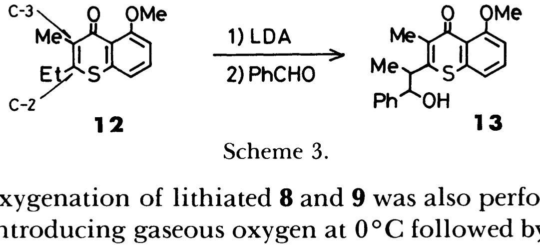


Fig. 1.

Though the lithiation of **3** was performed at −78 °C in THF–HMPA, lithiated **4** was unstable under these reaction conditions. After the examination of the conditions including bases and solvents, the lithiation was achieved in toluene–HMPA at −78 °C, and addition to aldehydes gave the alcohols **6**. The alkylation, however, was ineffective even in this solvent system.

The lithiated **8** and **9** are treated with electrophiles in THF–HMPA at 0 °C to give 3-substituted 1,2-dihydrocyclopenta[*b*][1]benzothiopyran-9(3*H*)-ones **10** and **11** in good yields. The possibility of the lithiation at 1-position could be excluded for **8** and **9** from the following observations. Thus, 2-ethyl-3-methyl-5-methoxy-4*H*-1-benzothiopyran-4-one (**12**), synthesized from ethyl 2-methyl-3-oxopentanoate, was treated with LDA in toluene–HMPA at −78 °C followed by benzaldehyde, and 2-(2-hydroxy-1-methyl-2-phenylethyl)-3-methyl-5-methoxy-4*H*-1-benzothiopyran-4-one (**13**) was isolated as a mixture of diastereomers. The structure was determined by ¹H-NMR. Disappearance of a triplet ($\delta$ 1.26) of **12**, and observation of a couple of doublets at $\delta$ 1.06 and 1.40 in **13** show that the addition ocurred at the methylene carbon of C-2 ethyl group and not at C-3 methyl carbon (Scheme 3.).



Scheme 3.

Oxygenation of lithiated **8** and **9** was also perfomed by introducing gaseous oxygen at 0 °C followed by the reduction of the resulted peroxide with sodium sulfite[7] to give 6- and 8-methoxy-1,2-dihydro-3-hydroxycyclopenta[*b*][1]benzothiopyran-9(3*H*)-one (**10i** and **11i**). Several attempts to improve the yields, however, were unsuccessful.

Esters **10c** and **11c** were further converted to the corresponding carboxylic acids **10j** and **11j** by treating with lithium hydroxide in refluxing THF–$H_2O$ for 2 h.

Compounds **8**, **10a**, and **10d** showed a potent analgesic activities by the acetic acid induced writhing method. $ED_{50}$: **8**; 11.5 mg/Kg. **10a**; 5.8 mg/Kg. **10b**; 12.5 mg/Kg. And **8** showed an anti-inflammatory activities against carragenan-induced rat paw edma. $ED_{50}$: 30 mg/Kg.

## Experimental

The melting points are uncorrected. ¹H-NMR spectra were obtained with JEOL JNM-FX-60. Chemical shift values are given in ppm relative to internal $Me_4Si$. IR spectra were performed with Shimadzu IR-408. High resolution mass spectra were taken with JEOL JMS-DX-300. Elemental analyses were performed with Yanagimoto CHN Corder, MT-2 type. Silica gel chromatographies were conducted on Wako gel B5F or C-200 (Wako Pure Chemical Industries LTD.).

*7-Methoxy-2-methyl-4*H*-1-benzothiopyran-4-one (3) and 5-Methoxy-2-methyl-4*H*-1-benzothiopyran-4-one (4).* These compounds were synthesized from *m*-methoxybenzenethiol (**1**) and ethyl acetoacetate (**2**) according to the reported method[3] in 28 and 26% yield, after the separation by silica gel chromatography with ethyl acetate:hexane=1:1 as the eluent. **3**: mp 121 °C (benzene–hexane), lit,[8] mp 118—119.5 °C. ¹H-NMR ($CDCl_3$) $\delta$=2.40 (3H, d, $J$=1 Hz), 3.88 (3H, s), 6.75 (1H, d, $J$=1Hz), 6.8—7.1 (2H, m), and 8.39 (1H, dd, $J$=1, 8 Hz). IR (KBr) 1630, 1600, 1260, and 850 cm⁻¹. Found: C, 63.78 H, 4.99%. Calcd for $C_{11}H_{10}O_2S$: C, 64.06; H, 4.89%. **4**: mp 83 °C (benzene–hexane). ¹H-NMR ($CDCl_3$) $\delta$=2.34 (3H, d, $J$=1 Hz), 3.96 (3H, s), 6.69 (1H, d, $J$=1 Hz), 6.90 (1H, dd, $J$=1, 8 Hz), 7.08 (1H, dd, $J$=1, 8 Hz), and 7.46 (1H, t, $J$=8 Hz). IR (KBr) 1610, 1260, and 1030 cm⁻¹. Found: C, 64.29; H, 4.99%. Calcd for $C_{11}H_{10}O_2S$: C, 64.06; H, 4.89%.

*1,2-Dihydro-8-methoxycyclopenta[*b*][1]benzothiopyran-9(3*H*)-one (8), 1,2-Dihydro-6-methoxycyclopenta[*b*][1]benzothiopyran-9(3*H*)-one (9).* Synthesized from **1** and ethyl 2-oxo-1-cyclopentanecarboxylate (**7**) as above (20 and 20% yield). **8**: mp 137 °C (benzene–hexane). ¹H-NMR ($CDCl_3$) $\delta$=1.8—2.4 (2H, m), 2.7—3.2 (4H, m), 3.86 (3H, s), 6.93 (1H, brs), 7.00 (1H, dd, $J$=2.5, 9 Hz), and 8.43 (1H, dd, $J$=1, 9 Hz). IR (KBr) 1590, 1240, and 1020 cm⁻¹ Found: C, 66.91; H, 5.12%. Calcd for $C_{13}H_{12}O_2S$: C, 67.22, H, 5.29%. **9**: mp 155 °C (benzene–hexane). ¹H-NMR ($CDCl_3$) $\delta$=1.8—2.4 (2H, m), 2.7—3.1 (4H, m), 3.95 (3H, s), 6.89 (1H, dd, $J$=1.5, 8 Hz), 7.08 (1H, dd, $J$=1.5, 8 Hz), and 7.42 (1H, t, $J$=8 Hz). IR (KBr) 1605, 1460, 1270, 1040, and 800 cm⁻¹. Found: C, 67.30; H, 5.11%. Calcd for $C_{13}H_{12}O_2S$: C, 67.22, H, 5.21%.

*2-Ethyl-3-methyl-7-methoxy-4*H*-1-benzothiopyran-4-one (12).* The compound **12** was synthesized as described above from ethyl 2-methyl-3-oxopentanoate in 16% yield. **12**: mp 110 °C (benzene–hexane). ¹H-NMR ($CDCl_3$) $\delta$=1.26 (3H, t, $J$=7 Hz), 2.17 (3H, s), 2.63 (2H, q, $J$=7 Hz), 3.94 (3H, s), 6.85 (1H, dd, $J$=1.5, 8 Hz), 7.12 (1H, dd, $J$=1.5, 8 Hz), and 7.40 (1H, t, $J$=8 Hz). IR (KBr) 1610, 1270, 1040, and 800 cm⁻¹. Exact mass

Found: *m/z* 234.0715. Calcd for $C_{13}H_{14}O_2S$: M, 234.0715.

*Reaction of Lithiated* **3** *with Alkyl Halides and Aldehydes. General Procedure*: Under a nitrogen atmosphere, to a THF (1 ml) solution of diisopropylamine (50 mg, 0.5 mmol) was added butyllithium in hexane (0.32 ml, 0.5 mmol) at −78 °C. After 5 min, **3** (103 mg, 0.5 mmol) in THF (2 ml) and HMPA (1 ml) were added successively. The mixture was stirred for 5 min and an alkyl halide (1.5 mmol) or an aldehyde (0.6 mmol) in THF (2 ml) was added. After 15—30 min at the temperature, the reaction was quenched with saturated aqueous ammoinum chloride, and the products were two times extracted with ethyl acetate. The combined extracts were washed with water and brine, dried over $Na_2SO_4$. Removal of the solvents *in vacuo*, and chromatography on silica gel (eluent; ethyl acetate:hexane=1:1) gave the product **5**.

*2-Ethyl-7-methoxy-4*H*-1-benzothiopyran-4-one (**5a**)*: mp 61 °C (ether–hexane). $^1H$-NMR ($CDCl_3$) $\delta$=1.28 (3H, t, *J*=7 Hz), 2.61 (2H, q, *J*=7 Hz), 3.83 (3H, s), 6.72 (1H, s), 6.86 (1H, brs), 6.93 (1H, dd, *J*=2, 8 Hz), and 8.31 (1H, dd, *J*=1, 8 Hz). IR (KBr) 1620, 1600, 1260, 1230, 1050, and 1020 cm$^{-1}$. Found: C, 65.17; H, 5.35%. Calcd for $C_{12}H_{12}O_2S$: C, 65.43; H, 5.49%.

*2-(3-Butenyl)-7-methoxy-4*H*-1-benzothiopyran-4-one (**5b**)*: mp 65 °C (ether–hexane). $^1H$-NMR ($CDCl_3$) $\delta$=2.1—2.9 (4H, m), 3.84 (3H, s), 4.8—5.2 (2H, m), 5.5—6.2 (1H, m), 6.74 (1H, s), 6.8—7.1 (2H, m), and 8.35 (1H, dd, *J*=1, 8 Hz). IR (KBr) 1610, 1600, 1250, and 840 cm$^{-1}$. Found: C, 68.21; H, 5.76%. Calcd for $C_{14}H_{14}O_2S$: C, 68.26; H, 5.73%.

*2-(2-Ethoxycarbonylethyl)-7-methoxy-4*H*-1-benzothiopyran-4-one (**5c**)*: mp 126°C (benzene–hexane). $^1H$-NMR ($CDCl_3$) $\delta$=1.26 (3H, t, *J*=7 Hz), 2.3—3.1 (4H, m), 3.87 (3H, s), 4.16 (2H, q, *J*=7 Hz), 6.78 (1H,s), 6.93 (1H, s), 6.99 (1H, dd, *J*=2, 8 Hz), and 8.35 (1H, dd, *J*=2, 8 Hz). IR (KBr) 1725, 1620, 1600, and 1240 cm$^{-1}$. Found: C, 61.42; H, 5.72%. Calcd for $C_{15}H_{16}O_4S$: C, 61.43; H, 5.52%.

*2-(2-Hydroxy-2-phenylethyl)-7-methoxy-4*H*-1-benzothiopyran-4-one (**5f**)*: mp 129 °C (benzene–hexane). $^1H$-NMR ($CDCl_3$) $\delta$=2.94 (2H, d, *J*=6 Hz), 3.81 (3H, s), 4.33 (1H, brs), 5.04 (1H, t, *J*=6 Hz), 6.7—7.0 (3H, m), 7.0—7.5 (5H, m), and 8.18 (1H, dd, *J*=1, 8 Hz). IR (KBr) 3300, 1610, 1600, 1560, 1050, 830, 760, and 710 cm$^{-1}$. Found: C, 68.70; H, 4.87%. Calcd for $C_{18}H_{16}O_3S$: C, 69.21; H, 5.16%.

*2-[2-Hydroxy-2-(*p*-methoxyphenyl)ethyl]-7-methoxy-4*H*-1-benzothiopyran-4-one (**5g**)*: mp 114°C (benzene–hexane). $^1H$-NMR ($CDCl_3$) $\delta$=1.84 (1H, brs), 3.00 (2H, d, *J*=7 Hz), 3.80 (3H, s), 3.88 (3H, s), 5.00 (1H, t, *J*=7 Hz), 6.79 (1H, s), 6.8—7.1 (4H, m), 7.32 (2H, d, *J*=8 Hz), and 8.34 (1H, dd, *J*=1, 8 Hz). IR (KBr) 3400, 1600, 1230, and 835 cm$^{-1}$. Found: C, 66.55; H, 5.32%. Calcd for $C_{19}H_{18}O_4S$: C, 66.65; H, 5.30%.

*2-[2-Hydroxy-2-(3,4-methylenedioxyphenyl)ethyl]-7-methoxy-4*H*-1-benzothiopyran-4-one (**5h**)*: mp 162 °C (ethanol–ether–hexane). $^1H$-NMR ($CDCl_3$) $\delta$=2.97 (2H, d, *J*=7 Hz), 3.88 (3H, s), 4.58 (1H, brs), 4.97 (1H, t, *J*=7 Hz), 6.79 (2H, s), 6.8—7.1 (4H, m), 7.32 (2H, d, *J*=8 Hz), and 8.34 (1H, dd, *J*=1, 8 Hz). IR (KBr) 3400, 1600, 1230, and 835 cm$^{-1}$. Found: C, 66.55; H, 5.32%. Calcd for $C_{19}H_{16}O_5S$; C, 66.65; H, 5.30%.

*Reaction of Lithiated* **4** *with Aldehydes.* The reaction was carried out as described above except that toluene was used as the reaction solvent instead of THF, and ethyl acetate:hexane=3:1 was used for chromatography.

*2-(2-Hydroxy-2-phenylethyl)-5-methoxy-4*H*-1-benzothiopyran-4-one (**6f**)*: mp 84 °C (benzene–hexane). $^1H$-NMR ($CDCl_3$) $\delta$=2.87 (2H, d, *J*=6 Hz), 3.79 (3H, s), 4.55 (1H, brs), 4.98 (1H, t, *J*=6 Hz), 6.5—6.9 (2H, m), and 6.9—7.5 (7H, m). IR (KBr) 3400, 1600, 1270, and 1040 cm$^{-1}$. Found: C, 69.28; H, 5.48%. Calcd for $C_{18}H_{16}O_3S$: C, 69.21; H, 5.16%.

*2-[2-Hydroxy-2-(*p*-methoxyphenyl)ethyl]-5-methoxy-4*H*-1-benzothiopyran-4-one (**6g**)*: mp 138 °C (benzene–hexane). $^1H$-NMR ($CDCl_3$) $\delta$=1.73 (1H, brs), 2.94 (2H, d, *J*=7 Hz), 3.79 (3H, s), 3.93 (3H, s), 4.99 (1H, t, *J*=7 Hz), 6.71 (1H, s), 6.7—7.0 (1H, m), 6.87 (2H, d, *J*=7 Hz), 7.18 (1H, dd, *J*=1.5, 8 Hz), 7.31 (2H, d, *J*=7 Hz), and 7.44 (1H, t, *J*=8 Hz). IR (KBr) 3400, 1610, 1260, and 1040 cm$^{-1}$. Found: C, 66.45; H, 5.41%. Calcd for $C_{19}H_{18}O_3S$: C, 66.65; H, 5.30%.

*Reaction of Lithiated* **8** *with Electrophiles. General Procedure*: Under a nitrogen atmosphere, diisopropylamine (1 mmol) was suspended in THF (1 ml) at 0 °C. A hexane solution (0.64 ml) of butyllithium (1 mmol) was added and the solution was stirred at 0 °C for 5 min. Then, **8** (232 mg, 1 mmol) was added in one portion followed, after 10 min, by HMPA (2 ml). The mixture was stirred for 10 min. An alkyl halide (3 mmol) or aldehyde (1.1 mmol) in THF (2 ml) was added, and stirring was continued for additional 40—60 min. The reaction was quenched by the addition of saturated aqueous ammonium chloride. The products were extracted twice with ethyl acetate, washed with brine, and dried over $Na_2SO_4$. The solvents were evaporated *in vacuo*, and the residue was chromatographed on silica gel using ethyl acetate–hexane (1:1) as the eluent.

*1,2-Dihydro-3-methyl-8-methoxycyclopenta[*b*][1]benzothiopyran-9(3*H*)-one (**10a**)*: mp 103 °C (benzene–hexane). $^1H$-NMR ($CDCl_3$) $\delta$=1.31 (3H, d, *J*=7 Hz), 1.4—2.6 (2H, m), 2.6—3.1 (2H, m), 3.1—3.6 (1H, m), 3.96 (3H, s), 6.90 (1H, dd, *J*=1.5, 8 Hz), 7.13 (1H, dd, *J*=1.5, 8 Hz), and 7.44 (1H, t, *J*=8 Hz). IR (KBr) 1610, 1590, 1450, 1260, and 1040 cm$^{-1}$.

*1,2-Dihydro-3-ethyl-8-methoxycyclopenta[*b*][1]benzothiopyran-9(3*H*)-one (**10d**)*: mp 131 °C (benzene–hexane). $^1H$-NMR ($CDCl_3$) $\delta$=0.98 (3H, t, *J*=7 Hz), 1.4—2.5 (4H, m), 2.6—3.4 (3H, m), 3.94 (3H, s), 6.90 (1H, dd, *J*=1.5, 8 Hz), 7.11 (1H, dd, *J*=1.5, 8 Hz), and 7.42 (1H, t, *J*=8 Hz). IR (KBr) 1610, 1590, 1260, and 1040 cm$^{-1}$. Found: C, 68.92; H, 6.43%. Calcd for $C_{15}H_{16}O_2S$: C, 69.20; H, 6.19%.

*3-Benzyl-1,2-dihydro-8-methoxycyclopenta[*b*][1]benzothiopyran-9(3*H*)-one (**10e**)*: mp 131 °C (benzene–hexane). $^1H$-NMR ($CDCl_3$) $\delta$=1.5—2.3 (2H, m), 2.6—3.1 (5H, m), 3.2—3.8 (1H, m), 3.92 (3H, s), 6.86 (1H, dd, *J*=1.5, 8 Hz), 7.07 (1H, dd, *J*=1.5, 8 Hz), 7.23 (5H, s), and 7.39 (1H, t, *J*=8 Hz). IR (KBr) 1615, 1260, and 1035 cm$^{-1}$. Found: C, 73.86; H, 5.77%. Calcd for $C_{20}H_{18}O_2S$: C, 74.50; H, 5.63%.

*1,2-Dihydro-3-(α-hydroxybenzyl)-8-methoxycyclopenta[*b*][1]benzothiopyran-9(3*H*)-one (**10f**)*: mp 98—105 °C (benzene–hexane). $^1H$-NMR ($CDCl_3$) $\delta$=1.4—2.0 (2H, m), 2.4—3.0 (2H, m), 3.5—4.0 (1H, m), 3.86 (3H, s), 4.4—5.0 (2H, m), and 6.6—7.6 (8H, m). IR (KBr) 3400, 1590, 1260, 1040, 760, and 700 cm$^{-1}$. Found: C, 71.06; H, 5.32%. Calcd for $C_{20}H_{18}O_3S$: C, 70.98; H, 5.36%.

*1,2-Dihydro-3-ethoxycarbonylmethyl-8-methoxycyclopenta[*b*][1]benzothiopyran-9(3*H*)-one (**10c**)*: mp 97 °C (benzene–hexane). $^1H$-NMR ($CDCl_3$) $\delta$=1.28 (3H, t, *J*=7 Hz), 1.4—3.1 (6H, m), 3.3—4.0 (1H, m), 3.94 (3H, s), 4.19 (2H, q, *J*=7 Hz), 6.89 (1H, dd, *J*=1.5, 8 Hz), 7.08 (1H, dd, *J*=1.5, 8 Hz), and 7.41 (1H, t, *J*=8 Hz). IR (KBr) 1720, 1600, 1260, 1170, 1040, 790, 770, and 690 cm$^{-1}$. Found: C, 63.63: H, 6.04%. Calcd for $C_{17}H_{18}O_4S$: C, 64.13; H, 5.70%.

*1,2-Dihydro-3-hydroxy-8-methoxycyclopenta[*b*][1]benzothiopyran-9(3*H*)-one (**10i**)*: The compound was synthesized by introducing gaseous oxygen to the solution of lithiated **8** for 20 min at 0 °C followed by the reductive treatment with aqueous sodium sulfite. Mp 182 °C (dichloromethane–hexane). $^1$H-NMR ($CDCl_3$) $\delta$=1.8—3.2 (4H, m), 3.34 (1H, brs), 5.0—5.4 (1H, m), 6.88 (1H, dd, $J$=1, 8 Hz), 6.97 (1H, dd, $J$=1, 8 Hz), and 7.40 (1H, t, $J$=8 Hz). IR (KBr) 3400, 1605, 1585, 1040, and 795 cm$^{-1}$. Exact mass, Found: m/z 248.0559. Calcd for $C_{13}H_{12}O_3S$: M, 248.0507.

*Reaction of Lithiated **9** with Electrophiles.* The reaction was carried out as described for **8**.

*1,2-Dihydro-3-ethoxycarbonylmethyl-6-methoxycyclopenta[*b*][1]benzothiopyran-9(3*H*)-one (**11c**)*: mp 82 °C (benzene–hexane). $^1$H-NMR ($CDCl_3$) $\delta$=1.29 (3H, t, $J$=7 Hz), 1.4—3.1 (6H, m), 3.3—4.0 (1H, m), 3.86 (3H, s), 4.20 (2H, q, $J$=7 Hz), 6.91 (1H, brs), 6.98 (1H, dd, $J$=1, 9 Hz), and 8.37 (1H, dd, $J$=1, 8 Hz). IR (KBr) 1730, 1600, 1025, and 760 cm$^{-1}$. Found: C, 64.17; H, 5.67%. Calcd for $C_{17}H_{18}O_4S$: C, 64.13; H, 5.70%.

*1,2-Dihydro-3-hydroxy-6-methoxycyclopenta[*b*][1]benzothiopyran-9(3*H*)-one (**11i**)*: mp 184 °C (benzene–hexane). $^1$H-NMR ($CDCl_3$) $\delta$= 1.6—3.0 (4H, m), 3.37 (1H, brs), 3.89 (3H, s), 5.0—5.2 (1H, m), 7.16 (1H, dd, $J$=2.5, 9 Hz), 7.39 (1H, d, $J$=2.5 Hz), and 8.27 (1H, d, $J$=9 Hz). IR (KBr) 3400, 1590, and 1230 cm$^{-1}$. Exact mass, Found: *m/z* 248.0523. Calcd for $C_{13}H_{12}O_3S$: M, 248.0508.

*Reaction of Lithiated **12** with Benzaldehyde.* The reaction was performed as depicted in the synthesis of 5-methoxy-4*H*-1-benzothiopyran-4-one **6**.

*2-(2-Hydroxy-1-methyl-2-phenylethyl)-5-methoxy-3-methyl-4*H*-1-benzothiopyran-4-one (**13**)*: oil. $^1$H-NMR ($CDCl_3$) $\delta$=1.06 (1.5H, d, $J$=7 Hz), 1.40 (1.5H, d, $J$=7 Hz), 1.99 (1.5H, s), 2.23 (1.5H, s), 3.22 (1H, brs), 3.2—3.9 (1H, m), 3.93 (3H, s), 4.81 (0.5H, d, $J$=6 Hz), 4.94 (0.5H, d, $J$=4 Hz), and 6.7—7.8 (8H, m). IR (KBr) 3400, 1600, 1265, 1045, 765, and 700 cm$^{-1}$. Exact mass, Found: *m/z* 339.1113. Calcd for $C_{20}H_{19}O_3S$: M-1, 339.1055.

*Hydrolysis of **10c**.* A solution of **10c** (760 mg, 2.4 mmol) in THF (10 ml) and 4 M† lithium hydroxide (30 ml) was refluxed for 2 h. On cooling, the mixture was acidified with 6 M hydrochloric acid and the products were extracted twice with a mixture of THF and ethyl acetate (1:2). The combined extracts were washed with brine, dried over $Na_2SO_4$, and concentrated *in vacuo*. The residue was chromatographed on silica gel using ethyl acetate as the eluent to give 3-carboxymethyl-1,2-dihydro-8-methoxycyclopenta[*b*][1]benzothiopyran-9(3*H*)-one (**10j**) (420 mg, 60%): mp 202 °C (dichloromethane–hexane). $^1$H-NMR ($d_6$-DMSO) $\delta$=1.4—3.0 (6H, m), 3.4—4.0 (1H, m), 3.85 (3H, s), 5.76 (1H, brs), 6.9—7.3 (2H, m), and 7.50 (1H, t, $J$=8 Hz). IR (KBr) 3700, 2500, 1720, 1270 and 1030 cm$^{-1}$. Found: C, 61.60; H, 5.11%. Calcd for $C_{15}H_{14}O_4S$: C, 62.05; H, 4.86%.

*Hydrolysis of **11c**.* The reaction was carried out as described above except that the products were extracted with ethyl acetate, and chromatographed with ethyl acetate–hexane (1:1) to give 3-carboxymethyl-1,2-dihydro-6-methoxy-cyclopenta[*b*][1]benzothiopyran-9(3*H*)-one (**11j**) (58% yield): mp 200 °C (benzene–hexane). $^1$H-NMR ($CDCl_3$–$d_6$-DMSO) $\delta$=1.4—2.0 (2H, m), 2.0—3.0 (4H, m), 3.91 (3H, s), 3.5—4.0 (1H, m), 5.39 (1H, brs), 7.0—7.1 (2H, m), and 8.37 (1H, d, $J$=9 Hz). IR (KBr) 3700, 2400, 1715, 1570, 1540, and 1240 cm$^{-1}$. Exact mass, Found: 290.0545. Calcd for $C_{15}H_{14}O_4S$: M, 290.0612.

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† 1 M=1 mol dm$^{-3}$.