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Diastereoselective Synthesis of Substituted Tetrahydrothiopyrans via (3,5)-Thionium−Ene Cyclization Reaction

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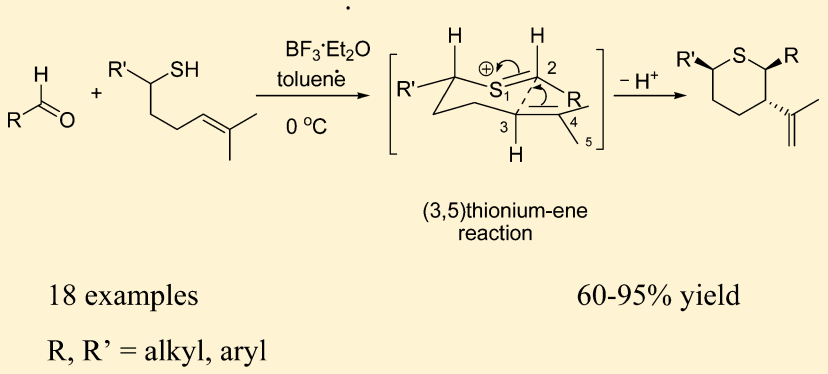
Supporting Information



ABSTRACT: Tetrahydrothiopyrans have been efficiently synthesized in good yields with excellent diastereoselectivity from aldehydes and substituted 5-methylhex-4-ene-1-thiol via (3,5)-thionium−ene cyclization reaction mediated by boron trifluoride etherate.

Tetrahydrothiopyrans, analogues of tetrahydropyrans, are important structural units in biologically active molecules.[1] Some tetrahydrothiopyrans are found in petroleum products.[2] The sulfur analogues of oligosaccharides are found to be potential enzyme inhibitors.[3] Apart from these, the tetrahydrothiopyrans can be transformed into a variety of structures.[4] Although there are many procedures for the synthesis of tetrahydropyrans,[5] the methods for the synthesis of tetrahydrothiopyrans are limited. Tetrahydrothiopyrans are prepared by Prins cyclization,[6] intramolecular ring-opening of epoxides by thiolates,[7] double-conjugate addition of sulfide to divinyl ketone,[8] hydrothiolation of nonactivated olefins,[9] and Pummerer rearrangement,[10] but the existing methods are associated with major drawbacks such as a lack of diastereoselectivity and use of expensive reagents. Therefore, to improve upon these limitations it is important to develop an efficient method for the synthesis of tetrahydrothiopyrans. Herein, we report the synthesis of substituted tetrahydrothiopyrans via thionium−ene cyclization.

Oxonium−ene cyclization reactions have been intensively studied in the recent past. They have been considered as powerful tools for the construction of various cyclic ethers.[11] In continuation of our interest in heterocyclic chemistry,[12] we were in search of an efficient method for the synthesis of tetrahydrothiopyrans. To the best of our knowledge, thionium−ene cyclization reaction has not been used for the synthesis of tetrahydrothiopyrans. We envisioned that reaction of olefinic compounds with a thiol group at the γ-position with aldehyde would generate thionium ion which after the thionium−ene reaction will provide tetrahydrothiopyrans. Thus, the reaction of 6-methylhept-5-ene-2-thiol with benzaldehyde **1a** in the presence of boron trifluoride etherate in toluene afforded 3-isopropenyl-6-methyl-2-phenyltetrahydrothiopyran **3a** in 86% yield with good diastereoselectivity.

To prove the reaction's general applicability, a variety of alkyl and aryl aldehydes were investigated, and the results are summarized in Table 1. It was observed that the reaction holds good for both electron-withdrawing as well as electron-donating groups on the aromatic ring of the aromatic aldehydes. The reaction is diastereoselective as determined from the ^{1}H and ^{13}C NMR spectrum of the crude product, and in all cases, the substituents at 2 and 3 are *trans*, whereas substituents at 2 and 6 are in the *cis* position. The structure of the compounds was determined by ^{1}H NMR and NOE experiments (Figure 1). The strong NOE between H-2 and H-6 protons of **3b** indicates that they are in the *cis* position. The coupling constant between H-2 and H-3 was found to be 11.2 Hz, which indicates that protons H-2 and H-3 are *trans*, and therefore, the propenyl group and aryl groups are in the *trans*-position. Finally, the structure of **3b** was confirmed by X-ray crystallographic analysis. It was observed that the aromatic aldehydes having electron-withdrawing groups gave better yields compared to aromatic aldehydes having electron-donating groups. This might be due to the increase in electrophilicity of the thiocarbenium ion (species **8**, Scheme 1), caused by the electron-withdrawing character of the aryl

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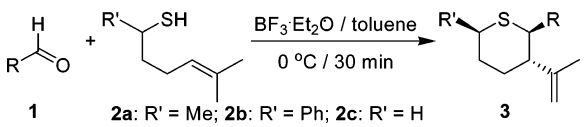
Table 1. Synthesis of Tetrahydrothiopyrans



entry	aldehyde	thiol R' =	product 3	yield (%)[a]
a	1a	Me	3a	86
b	1b	Me	3b	90
c	1c	Me	3c	95
d	1d	Me	3d	94
e	1e	Me	3e	75
f	1f	Me	3f	81
g	1g	Me	3g	60
h	1h	Me	3h	92
i	1i	Me	3i	85
j	1j	Me	3j	65
k	1k	Ph	3k	73
l	1l	Ph	3l	75
m	1m	Ph	3m	64
n	1n	Ph	3n	78
o	1o	Ph	3o	72
p	1p	Ph	3p	78
q	1q	Ph	3q	85
r	1r	H	3r	91

[a]Yields refer to isolated yields. Compounds are characterized by ^{1}H, ^{13}C NMR, IR, and mass spectroscopy.

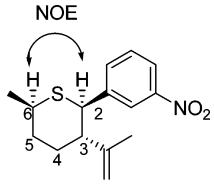
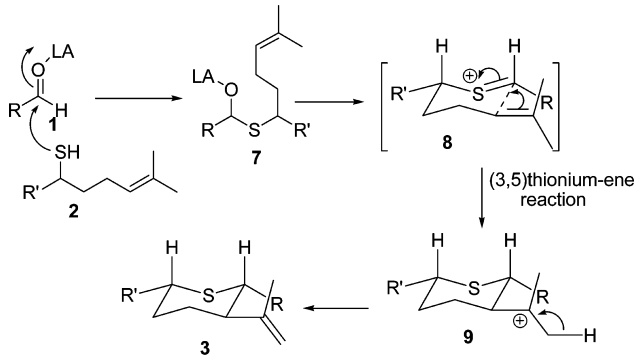


Figure 1. NOE of compound **3b**.

Scheme 1. Mechanism for the Formation of Tetrahydrothiopyrans



ring, which in turn is attacked by the double bond effectively. On the other hand, the electron-donating groups on the aromatic ring decreases the electrophilicity of the thiocarbenium ion. Further, the reaction with aliphatic aldehydes also gave good yields. Electron-rich aromatic aldehyde 3,4,5-trimethoxybenzaldehyde (entry g and p) gave tricyclic compounds **3g** and **3p**, whereas phenylacetaldehyde (entry j and m) resulted benzothiochromenes **3j** and **3m**. It is evident from the above two results that the reaction proceeds through a stepwise manner via carbocation intermediate but not in a concerted fashion. The structure of **3m** was confirmed by X-ray crystallographic analysis.[13] The reaction is very fast and within 30 min all the starting materials are consumed to give the products. This may be attributed to the extra stability imparted by the sulfur d-orbital.

The mechanism of the reaction can be explained as follows. Lewis acid activates the carbonyl group of aldehyde **1** to facilitate the nucleophilic attack by thiol **2** to give the acetal **7**, which after decomposition forms thionium ion **8**. The thionium ion **8** after cyclization provides carbocation **9**, which after elimination of proton gives tetrahydrothiopyrans **3** (Scheme 1).

CONCLUSION

In summary, we have developed a simple and efficient methodology for the synthesis of tetrahydrothiopyrans in good yields. The reaction is diastereoselective and gave only one isomer.

EXPERIMENTAL SECTION

General Information. All reagents are commercially obtained. $BF_3{\cdot}Et_2O$ was distilled over CaH_2 prior to use. ^{1}H NMR spectra were recorded in $CDCl_3$ on 400 MHz NMR spectrometer using TMS as internal standard. The ^{13}C and ^{19}F NMR spectra were recorded at 100 and 376 MHz, respectively. For ^{13}C and ^{19}F NMR $CDCl_3$ and C_6F_6 were used as internal standard. IR spectra were recorded on FT-IR spectrometer. Melting points were measured in open capillary tubes and are uncorrected.

Synthesis of 6-Methylhept-5-ene-2-thiol and 5-Methyl-1-phenylhex-4-ene-1-thiol (2a–c). The thiols **2a–c** were synthesized

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as per literature procedure.[14] The compound **2a** is known, and the analyses were consistent with the literature.[14]

*5-Methyl-1-phenylhex-4-ene-1-thiol (**2b**):* 124 mg, 60%; pale yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.53 (s, 3 H), 1.68 (s, 3 H), 1.90 (d, J = 5.2 Hz, 1 H), 1.93−2.05 (m, 4 H), 3.97 (dt, J = 7.2 and 5.2 Hz, 1 H), 5.07 (t, J = 6.8 Hz, 1 H), 7.20−7.25 (m, 2 H), 7.29−7.35 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.9, 25.9, 26.4, 39.8, 43.6, 123.2, 127.0, 127.2, 128.7, 132.6, 144.8; IR (KBr, neat) 3027, 2929, 1601, 1493, 1453, 1252, 1167, 1072, 758 cm^{-1}; HRMS (APCI) calcd for $C_{13}H_{18}S$ (M + H)$^+$ requires 207.1202, found 207.1202.

*5-Methylhex-4-ene-1-thiol (**2c**):* 90 mg, 68%; pale yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (t, J = 7.2 Hz, 1 H), 1.62 (s, 3 H), 1.64 (t, J = 7.2 Hz, 2 H), 1.69 (s, 3 H), 2.06−2.11 (m, 2 H), 2.52 (q, J = 7.2, 2 H), 5.08 (t, J = 7.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.9, 24.3, 25.9, 26.8, 34.3, 123.4, 132.5; IR (KBr, neat) 2924, 2853, 1646, 1458, 1377, 1267, 1152, 748 cm^{-1}; HRMS (APCI) calcd for $C_7H_{14}S$ (M + H)$^+$ requires 131.0889, found 131.0891.

Typical Procedure for the Synthesis of 3-Isopropenyl-6-methyl-2-phenyltetrahydrothiopyran (3a, Table 1). 6-Methylhept-5-ene-2-thiol (86 mg, 0.6 mmol) in 2 mL of toluene was added dropwise to a stirring mixture of benzaldehyde (53 mg, 0.5 mmol), boron trifluoride etherate (63 μL, 0.5 mmol), and toluene (2 mL) at 0 °C. The stirring was continued at the same temperature for 30 min, and then the mixture was poured into saturated $NaHCO_3$ (5 mL). The reaction mixture was extracted with ethyl acetate and then washed with brine and water. The organic layers were collected, dried over Na_2SO_4, filtered, and concentrated. Then the resultant crude residue was purified by column chromatography over silica gel (petroleum ether/EtOAc 98:2) to give 3-isopropenyl-6-methyl-2-phenyltetrahydrothiopyran **3a** (100 mg, 86%) as a pale yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (d, J = 6.8 Hz, 3 H), 1.49 (s, 3 H), 1.55−1.60 (m, 2 H), 1.91−2.00 (m, 1 H), 2.10 (dt, J = 10.4 and 2.8 Hz, 1 H), 2.63 (dt, J = 14.0 and 2.8 Hz, 1 H), 2.97−3.06 (m, 1 H), 3.90 (d, J = 10.8 Hz, 1 H), 4.56 (t, J = 1.2 Hz, 1 H), 4.59 (s, 1 H), 7.17−7.22 (m, 1 H), 7.23−7.28 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.3, 21.2, 33.8, 37.2, 39.8, 51.0, 51.5, 112.3, 127.3, 128.3, 128.4, 140.8, 147.5; IR (KBr, neat) 2960, 2922, 1644, 1450, 1374, 1159, 1070, 888 cm^{-1}; HRMS (APCI) calcd for $C_{15}H_{20}S$ (M + H)$^+$ requires 233.1358, found 233.1350.

Tetrahydro-6-methyl-2-phenyl-2-(3-nitrophenyl)(prop-1-en-2-yl)-2*H*-thiopyran (3b): pale yellow crystalline solid; mp 100−102 °C (125 mg, 90%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (d, J = 6.8 Hz, 3 H), 1.49 (s, 3 H), 1.52−1.65 (m, 2 H), 1.95−2.05 (m, 1 H), 2.09−2.19 (m, 1 H), 2.63 (dt, J = 10.4 and 2.8 Hz, 1 H), 2.97−3.06 (m, 1 H), 3.99 (d, J = 11.2 Hz, 1 H), 4.57−4.61 (m, 2 H), 7.44 (t, J = 8.0 Hz, 1 H), 7.61 (d, J = 7.6 Hz, 1 H), 8.07 (d, J = 7.2 Hz, 1 H), 8.16 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.3, 21.1, 33.4, 37.0, 40.0, 50.1, 51.5, 113.1, 122.4, 123.4, 129.3, 134.6, 143.1, 146.6, 148.3; IR (KBr, neat) 2963, 2924, 1639, 1529, 1448, 1350, 1267, 1098, 891 cm^{-1}; HRMS (APCI) calcd for $C_{15}H_{19}NO_2S$ (M + H)$^+$ requires 278.1209, found 278.1223.

Methyl 4-(tetrahydro-6-methyl-3-(prop-1-en-2-yl)-2*H*-thiopyran-2-yl)benzoate (3c): pale yellow crystalline solid; mp 58−60 °C (138 mg, 95%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (d, J = 6.4 Hz, 3 H), 1.47 (s, 3 H), 1.53−1.64 (m, 2 H), 1.92−2.00 (m, 1 H), 2.07−2.17 (m, 1 H), 2.63 (dt, J = 14.0 and 2.8 Hz, 1 H), 2.98−3.06 (m, 1 H), 3.89 (s, 3 H), 3.96 (d, J = 10.8 Hz, 1 H), 4.54−4.58 (m, 2 H), 7.34 (d, J = 8.4 Hz, 2 H), 7.94 (d, J = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.3, 21.1, 33.6, 37.1, 39.9, 50.8, 51.5, 52.1, 112.6, 128.4, 129.1, 129.8, 146.1, 147.0, 167.0; IR (KBr, neat) 2954, 2923, 1722, 1610, 1435, 1375, 1279, 1112, 1019, 752 cm^{-1}; HRMS (APCI) calcd for $C_{17}H_{22}O_2S$ (M + H)$^+$ requires 291.1413, found 291.1406.

2-(4-Bromophenyl)tetrahydro-6-methyl-3-(prop-1-en-2-yl)-2*H*-thiopyran (3d): colorless liquid (146 mg, 94%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (d, J = 7.2 Hz, 3 H), 1.48 (s, 3 H), 1.50−1.60 (m, 2 H), 1.90−1.97 (m, 1 H), 2.08−2.12 (m, 1 H), 2.56 (dt, J = 11.2 and 2.8 Hz, 1 H), 2.96−3.05 (m, 1 H), 3.86 (d, J = 10.8 Hz, 1 H), 4.57−4.59 (m, 2 H), 7.15 (d, J = 8.4 Hz, 2 H), 7.38 (d, J = 8.0 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.3, 21.1, 33.7, 37.1, 39.9, 50.3, 51.6, 112.6, 121.0, 130.0, 131.6, 139.9, 147.1; IR (KBr, neat) 2960, 2922, 1644, 1448, 1374, 1074, 1010, 890, 771 cm^{-1}; HRMS (APCI) calcd for $C_{15}H_{19}BrS$ (M + H)$^+$ requires 311.0464, found 311.0464.

4-(Tetrahydro-6-methyl-3-(prop-1-en-2-yl)-2*H*-thiopyran-2-yl)phenol (3e): brownish liquid (93 mg, 75%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (d, J = 6.8 Hz, 3 H), 1.49 (s, 3 H), 1.53−1.59 (m, 2 H), 1.89−1.96 (m, 1 H), 2.06−2.11 (m, 1 H), 2.57 (dt, J = 11.2 and 2.8 Hz, 1 H), 2.97−3.05 (m, 1 H), 3.84 (d, J = 10.8 Hz, 1 H), 4.56−4.60 (m, 2 H), 6.71 (d, J = 8.4 Hz, 2 H), 7.13 (d, J = 8.8 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.3, 21.2, 33.8, 37.2, 40.1, 50.4, 51.7, 112.3, 115.5, 129.5, 132.7, 147.7, 154.9; IR (KBr, neat) 3453, 2956, 2867, 1637, 1467, 1335, 1114, 1028, 738 cm^{-1}; HRMS (APCI) calcd for $C_{15}H_{20}OS$ (M + H)$^+$ requires 249.1308, found 249.1301.

Tetrahydro-2-(4-methoxyphenyl)-6-methyl-3-(prop-1-en-2-yl)-2*H*-thiopyran (3f): colorless oil (106 mg, 81%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (d, J = 6.8 Hz, 3 H), 1.49 (s, 3 H), 1.51−1.59 (m, 2 H), 1.89−1.96 (m, 1 H), 2.04−2.11 (m, 1 H), 2.89 (dt, J = 10.8 and 2.8 Hz, 1 H), 2.97−3.05 (m, 1 H), 3.77 (s, 3 H), 3.87 (d, J = 10.8 Hz, 1 H), 4.57−4.60 (m, 2 H), 6.79 (d, J = 8.4 Hz, 2 H), 7.19 (d, J = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.3, 21.2, 33.9, 37.2, 39.9, 50.2, 51.7, 55.2, 112.2, 113.8, 129.3, 132.9, 147.7, 158.7; IR (KBr, neat) 2922, 2836, 1644, 1450, 1301, 1247, 1176, 1037, 811 cm^{-1}; HRMS (APCI) calcd for $C_{16}H_{22}OS$ (M + H)$^+$ requires 263.1464, found 263.1469.

2,3,4,4a,5,9b-Hexahydro-6,7,8-trimethoxy-2,5,5-trimethylindeno[1,2-*b*]thiopyran (3g): pale yellow liquid (97 mg, 60%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (d, J = 6.8 Hz, 3 H), 1.42 (s, 6 H), 1.45−1.56 (m, 2 H), 1.81−1.92 (m, 2 H), 2.16−2.21 (m, 1 H), 2.97−3.05 (m, 1 H), 3.83 (s, 3 H), 3.84 (s, 3 H), 3.89 (dd, J = 10.8 and 1.2 Hz, 1 H), 3.92 (s, 3 H), 6.51 (d, J = 1.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.1, 21.5, 25.5, 26.4, 37.6, 39.9, 45.3, 50.1, 56.2, 60.4, 60.7, 60.9, 101.9, 135.6, 136.9, 141.7, 150.7, 153.1; IR (KBr, neat) 2960, 2923, 1639, 1448, 1374, 1261, 1172, 1034, 786 cm^{-1}; HRMS (APCI) calcd for $C_{18}H_{26}O_3S$ (M + H)$^+$ requires 323.1675, found 323.1687.

Tetrahydro-6-methyl-3-(prop-1-en-2-yl)-2-styryl-2*H*-thiopyran (3h): colorless liquid (119 mg, 92%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (d, J = 6.4 Hz, 3 H), 1.47 (ddd, J = 11.2, 10.8, and 10.0 Hz, 1 H), 1.55−1.67 (m, 1 H), 1.63 (s, 3 H), 1.83 (dt, J = 10.0 and 2.8 Hz, 1 H), 2.02−2.08 (m, 1 H), 2.27 (dt, J = 11.2 and 2.8 Hz, 1 H), 2.92−2.98 (m, 1 H), 3.57 (t, J = 10.0 Hz, 1 H), 4.70−4.80 (m, 2 H), 6.99 (dd, J = 15.6 and 8.8 Hz, 1 H), 6.51(d, J = 15.6 Hz, 1 H), 7.18−7.22 (m, 2 H), 7.25−7.33 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.7, 21.3, 32.9, 36.9, 38.7, 48.0, 52.2, 112.1, 126.5, 127.6, 128.6, 128.9, 132.0, 137.1, 147.9; IR (KBr, neat) 2960, 2922, 1644, 1448, 1374, 1159, 1028, 890 cm^{-1}; HRMS (APCI) calcd for $C_{17}H_{22}S$ (M + H)$^+$ requires 259.1515, found 259.1518.

2-Cyclohexyltetrahydro-6-methyl-3-(prop-1-en-2-yl)-2*H*-thiopyran (3i): pale yellow liquid (101 mg, 85%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.10−1.26 (m, 2 H), 1.20 (d, J = 6.8 Hz, 3 H), 1.33−1.58 (m, 6 H), 1.63 (s, 3 H), 1.67−1.78 (m, 6 H), 1.94−2.00 (m, 1 H), 2.36 (dt, J = 11.2 and 2.8 Hz, 1 H), 2.75−2.81 (m, 2 H), 4.75 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.9, 21.8, 26.7 (2C), 26.9, 27.1, 32.4, 34.0, 37.3, 38.3, 39.4, 49.6, 52.3, 112.0, 148.3; IR (KBr, neat) 2923, 2852, 1639, 1448, 1371, 1267, 889 cm^{-1}; HRMS (APCI) calcd for $C_{15}H_{26}S$ (M + H)$^+$ requires 239.1828, found 239.1828.

3,4,4a,5,10,10a-Hexahydro-2,5,5-trimethyl-2*H*-benzo[*g*]-thiochromene (3j): light yellow solid; mp 83−85 °C (80 mg, 65%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (s, 3 H), 1.20 (d, J = 6.4 Hz, 3 H), 1.37 (s, 3 H), 1.41−1.51 (m, 1 H), 1.55 (dt, J = 11.2 and 2.4 Hz, 1 H), 2.05−2.15 (m, 3 H), 2.76 (dd, J = 16.0 and 12.0 Hz, 1 H), 2.86−2.94 (m, 2 H), 3.18 (ddd, J = 11.6, 5.2, and 4.8 Hz, 1 H), 7.00 (d, J = 8.0, 1 H), 7.10 (t, J = 7.2, 1 H), 7.18 (t, J = 7.2, 1 H), 7.36 (d, J = 8.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.3, 21.4, 27.5, 27.9, 28.6, 36.9, 37.6, 38.0, 38.7, 48.5, 125.7, 126.5, 127.2, 128.4, 133.5, 146.1; IR (KBr, neat) 2962, 2884, 1633, 1491, 1447, 1364, 1291, 1174, 1034, 764, 730 cm^{-1}; HRMS (APCI) calcd for $C_{16}H_{22}S$ (M + H)$^+$ requires 247.1515, found 247.1526.

2-(2-Chlorophenyl)tetrahydro-6-phenyl-3-(prop-1-en-2-yl)-2-styryl-2*H*-thiopyran (3k): colorless oil (120 mg, 73%); ^{1}H NMR

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(400 MHz, $CDCl_3$): δ 1.59 (s, 3 H), 1.70−1.84 (m, 1 H), 2.10−2.23 (m, 2 H), 2.30−2.37 (m, 1 H), 2.83 (dt, J = 13.6 and 2.8 Hz, 1 H), 4.15 (dd, J = 11.6 and 2.4 Hz, 1 H), 4.60 (s, 1 H), 4.67 (s, 1 H), 4.69 (d, J = 12.0 Hz, 1 H), 7.10−7.15 (m, 1 H), 7.18−7.25 (m, 2 H), 7.28−7.32 (m, 3 H), 7.37−7.40 (m, 2 H), 7.45 (d, J = 8.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.3, 34.1, 35.8, 46.8, 49.5, 51.1, 112.5, 127.0, 127.5, 127.6, 128.4, 128.7, 129.4, 129.7, 133.8, 137.7, 141.5, 147.0; IR (KBr, neat) 2928, 2857, 1645, 1442, 1376, 888 cm^{-1}; HRMS (APCI) calcd for $C_{20}H_{21}ClS$ (M + H)$^+$ requires 329.1125, found 329.1134.

Tetrahydro-6-phenyl-3-(prop-1-en-2-yl)-2-propyl-2*H*-thiopyran (3l): brownish liquid (98 mg, 75%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, J = 7.2 Hz, 3 H), 1.23−1.33 (m, 2 H), 1.54−1.67 (m, 2 H), 1.69 (s, 3 H), 1.88−1.96 (m, 2 H), 1.98−2.05 (m, 1 H), 2.16−2.26 (m, 2 H), 2.97 (dt, J = 10.0 and 2.8 Hz, 1 H), 3.89 (dd, J = 11.6 and 2.0 Hz, 1 H), 4.79 (brs, 2 H), 7.21−7.25 (m, 1 H), 7.28−7.33 (m, 2 H), 7.34−7.37 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 19.5, 19.8, 33.9, 35.4, 35.6, 46.5, 48.1, 52.4, 112.2, 127.5, 127.6, 128.7, 142.5, 148.1; IR (KBr, neat) 2957, 2927, 1634, 1452, 1376, 1186, 1076, 756 cm^{-1}; HRMS (APCI) calcd for $C_{17}H_{24}S$ (M + H)$^+$ requires 261.1671, found 261.1678.

3,4,4a,5,10,10a-Hexahydro-5,5-dimethyl-2-phenyl-2*H*-benzo[*g*]thiochromene (3m): colorless solid; mp 113−115 °C (97 mg, 64%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (s, 3 H), 1.42 (s, 3 H), 1.43−1.51 (m, 1 H), 1.71 (dt, J = 11.6 and 3.2 Hz, 1 H), 2.07 (dq, J = 12.8 and 2.4 Hz, 1 H), 2.20−2.27 (m, 1 H), 2.31−2.37 (m, 1 H), 2.80 (dd, J = 16.0 and 11.6 Hz, 1 H), 2.93 (dd, J = 16.4 and 5.2 Hz, 1 H), 3.35 (ddd, J = 11.6, 5.6, and 5.2 Hz, 1 H), 3.99 (dd, J = 11.6 and 2.4 Hz, 1 H), 7.01 (d, J = 7.6, 1 H), 7.10 (t, J = 7.6, 1 H), 7.19 (t, J = 8.0, 1 H), 7.24−7.28 (m, 1 H), 7.33 (t, J = 7.2 Hz, 2 H), 7.38 (d, J = 7.6, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.6, 28.3, 28.6, 36.1, 36.6, 38.1, 39.9, 47.7, 48.5, 125.8, 126.5, 127.3, 127.6, 127.7, 128.4, 128.8, 133.5, 142.1, 146.1; IR (KBr, neat) 2965, 2926, 1634, 1446, 1365, 1188, 1080, 965 cm^{-1}; HRMS (APCI) calcd for $C_{21}H_{24}S$ (M + H)$^+$ requires 309.1671, found 309.1681.

Tetrahydro-6-phenyl-3-(prop-1-en-2-yl)-2-*p*-tolyl-2*H*-thiopyran (3n): brownish solid; mp 118−120 °C (120 mg, 78%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.54 (s, 3 H), 1.68−1.79 (m, 1 H), 2.00−2.15 (m, 2 H), 2.19 (dd, J = 12.4 and 2.8 Hz, 1 H), 2.29 (s, 3 H), 2.77 (dt, J = 11.2 and 2.8 Hz, 1 H), 4.06 (d, J = 12.4 Hz, 1 H), 4.10 (dd, J = 12.0 and 2.8 Hz, 1 H), 4.61 (s, 1 H), 4.66 (s, 1 H), 7.07 (d, J = 7.6 Hz, 2 H), 7.20 (d, J = 8.0 Hz, 2 H), 7.24 (d, J = 8.4 Hz, 1 H), 7.30 (d, J = 7.2 Hz, 2 H), 7.38 (d, J = 7.2 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.4, 21.3, 34.1, 35.5, 50.3, 51.4, 52.5, 112.5, 127.7 (2C), 128.3, 128.7, 129.2, 136.8, 137.1, 141.4, 147.3; IR (KBr, neat) 2926, 2855, 1643, 1452, 1375, 1282, 1030, 753 cm^{-1}; HRMS (APCI) calcd for $C_{21}H_{24}S$ (M + H)$^+$ requires 309.1671, found 309.1675.

Tetrahydro-2-(2,3-dimethoxyphenyl)-6-phenyl-3-(prop-1-en-2-yl)-2*H*-thiopyran (3o): yellow solid; mp 96−98 °C (133 mg, 72%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.57 (s, 3 H), 1.70−1.80 (m, 2 H), 2.10−2.20 (m, 2 H), 2.28−2.40 (m, 1 H), 2.75 (dt, J = 11.6 and 2.8 Hz, 1 H), 3.83 (s, 3 H), 3.92 (s, 3 H), 4.14 (d, J = 11.6 Hz, 1 H), 4.56 (s, 1 H), 4.65 (s, 1 H), 4.72 (d, J = 11.2 Hz, 1 H), 6.74−6.78 (m, 1 H), 6.98−7.02 (m, 2 H), 7.22 (t, J = 6.8 Hz, 1 H), 7.30 (t, J = 7.2 Hz, 2 H), 7.39 (d, J = 7.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2, 34.3, 36.1, 43.1, 49.6, 51.1, 55.8, 61.6, 111.0, 112.1, 120.6, 124.1, 127.5, 127.7, 128.7, 134.1, 142.0, 146.8, 147.6, 152.6; IR (KBr, neat) 2930, 2853, 1642, 1478, 1376, 1272, 1087, 1060, 1007, 888, 758 cm^{-1}; HRMS (APCI) calcd for $C_{22}H_{26}O_2S$ (M + H)$^+$ requires 355.1726, found 355.1733.

2,3,4,4a,5,9b-Hexahydro-6,7,8-trimethoxy-5,5-dimethy-2-phenylindeno[1,2-*b*]thiopyran (3p): colorless solid; mp 108−110 °C; (150 mg, 78%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (s, 3 H), 1.47 (s, 3 H), 1.99−2.14 (m, 4 H), 2.35−2.40 (m, 1 H), 3.79 (s, 3 H), 3.85 (s, 3 H), 3.93 (s, 3 H), 4.07 (dd, J = 11.6 and 3.6 Hz, 1 H), 4.09 (d, J = 10.6 Hz, 1 H), 6.52 (s, 1 H), 7.24−7.29 (m, 1 H), 7.32−7.36 (m, 2 H), 7.39−7.42 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 25.8, 26.4, 36.3, 45.5, 49.6, 51.0, 56.2, 60.4, 60.8, 61.0, 101.9, 127.5 (2C), 128.7, 135.6, 136.7, 141.9, 142.2, 150.8, 153.2; IR (KBr, neat) 2932, 2866, 1602, 1470, 1410, 1335, 1113, 1096, 1027, 736, 699 cm^{-1}; HRMS (APCI) calcd for $C_{23}H_{28}O_3S$ (M + H)$^+$ requires 385.1832, found 385.1843.

2-(4-Fluorophenyl)tetrahydro-6-phenyl-3-(prop-1-en-2-yl)-2*H*-thiopyran (3q): brownish liquid (128 mg, 85%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.53 (s, 3 H), 1.73 (dq, J = 12.8 and 2.8 Hz, 1 H), 2.08−2.15 (m, 1 H), 2.19 (dd, J = 12.8 and 2.8 Hz, 1 H), 2.30 (dq, J = 13.2 and 2.7 Hz, 1 H), 2.72 (dt, J = 12.0 and 3.2 Hz, 1 H), 4.05 (d, J = 11.2 Hz, 1 H), 4.09 (dd, J = 11.6 and 2.0 Hz, 1 H), 4.62 (s, 1 H), 4.65 (s, 1 H), 6.95 (t, J = 8.8 Hz, 2 H), 7.23−7.33 (m, 5 H), 7.37 (d, J = 7.2 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.4, 34.1, 35.5, 49.7, 51.4, 51.8, 112.7, 115.3 (d, J = 21.3 Hz), 127.6 (2C), 128.8, 129.9 (d, J = 7.6 Hz), 136.2, 141.6, 147.3, 162.0 (d, J = 244.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3/C_6F_6$) δ 46.58−46.63 (m, −F); IR (KBr, neat) 2927, 2851, 1639, 1451, 1375, 1222, 1157, 836, 755, 697 cm^{-1}; HRMS (APCI) calcd for $C_{20}H_{21}FS$ (M + H)$^+$ requires 313.1421, found 313.1434.

Tetrahydro-2-(4-nitrophenyl)-3-(prop-1-en-2-yl)-2*H*-thiopyran (3r): pale yellow liquid (120 mg, 91%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.49 (s, 3 H), 1.56 (ddd, J = 13.2, 12.0, and 3.2 Hz, 1 H), 1.86 (qt, J = 13.2, and 3.2 Hz, 1 H), 1.98 (dd, J = 14.0, and 2.8 Hz, 1 H), 2.18 (dt, J = 14.0 and 2.8 Hz, 1 H), 2.65−2.72 (m, 2 H), 2.89 (ddd, J = 12.8, 10.8, and 2.8 Hz, 1 H), 3.93 (d, J = 10.8 Hz 1 H), 4.56 (s, 1 H), 4.58 (s, 1 H), 7.45 (d, J = 8.4 Hz, 2 H), 8.14 (d, J = 8.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.3, 28.0, 31.2, 33.0, 49.8, 52.1, 113.0, 123.7, 129.3, 146.8, 147.1, 148.7; IR (KBr, neat) 2928, 2852, 1644, 1598, 1520, 1346, 1287, 1110, 1074, 853, 738 cm^{-1}; HRMS (APCI) calcd for $C_{14}H_{17}NO_2S$ (M + H)$^+$ requires 264.1053, found 264.1066.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra of all compounds, ^{19}F NMR spectra of **3e**, **4e**, and **8d**, and crystal parameters and ORTEP diagrams of compounds **3b** and **3i**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Woodward, R. B.; Heusler, K.; Gosteli, J.; Naegeli, P.; Oppolzer, W.; Ramage, R.; Ranganathan, S.; Vorbrüggen, H. *J. Am. Chem. Soc.* **1966**, *88*, 852−853. (b) Casy, G.; Lane, S.; Taylor, R. J. K. *J. Chem. Soc., Perkin. Trans. 1* **1986**, 1397−1404. (c) Ohuchida, S.; Hamanaka, N.; Hayashi, M. *Tetrahedron* **1983**, *39*, 4273−4278.

(2) (a) Gal'pern, G. D. *Int. J. Sulfur Chem., B.* **1971**, *6*, 115−130. (b) Payzant, J. D.; Cyr, T. D.; Montgomery, D. S.; Strausz, O. P. *Tetrahedron Lett.* **1985**, *26*, 4175−4178.

(3) Mehta, S.; Andrews, J. S.; Johnston, B. D.; Svensson, B.; Pinto, B. M. *J. Am. Chem. Soc.* **1995**, *117*, 9783−9790.

(4) (a) Block, E. *Reactions of Organosulfur Compounds*: Academic Press: New York, 1978. (b) Woodward, R. B.; Logusch, E.; Nambiar, K. P.; Sakan, K.; Ward, D. E.; Au-Yeung, B. W.; Balaram, P.; Browne, L. J.; Card, P. J.; Chen, C. H. *J. Am. Chem. Soc.* **1981**, *103*, 3210−3213. (c) Almena, J.; Foubelo, F.; Yus, M. *Tetrahedron* **1997**, *53*, 5563−5572. (d) Agarwal, V. K.; Smith, H. W.; Hynd, G.; Jones, R. V. H.; Fieldhouse, R.; Spey, S. E. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3267−3276.

(5) (a) Boger, D. L.; Weinerb, S. M. *Hetero Diels−-Alder Methodology in Organic Synthesis*; Academic Press: San Diego, 1987. (b) Gademann, K.; Chavez, D. E.; Jacobson, E. N. *Angew. Chem., Int. Ed.* **2002**, *41*, 3059−3061. (c) Gouverneur, V.; Reiter, M. *Chem.—Eur. J.* **2005**, *11*, 58065815. (d) Gademann, K.; Chavez, D. E.; Jacobson, E. N. *Angew. Chem., Int. Ed.* **2005**, *44*, 3485−3488. (e) Desimoni, G.; Faita, G.; Toscanini, M.; Boiocchi, M. *Chem.—Eur. J.* **2007**, *13*, 9478−9485. (f) Paterson, I.; Steven, A.; Luckhurst, C. A. *Org. Biomol. Chem.* **2004**, *2*, 3026−3038. (g) Liu, P.; Jacobson, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 10772−10773. (h) Voight, E. A.; Seradj, H.; Roethle, P. A.; Burke, S. D. *Org. Lett.* **2004**, *6*, 4045−4048. (i) Ruijter, E. R.; Schltingkemper, H.; Wessjohann, L. A. *J. Org. Chem.* **2005**, *70*, 2820−2823. (j) Clarke, P. A.; Santos, S.; Martin, W. H. C. *Green. Chem.* **2007**, *9*, 438−440. (k) Clarke, P. A.; Martin, W. H. C.; Hargreaves, M. J.; Wilson, C.; Blake, A. *J. Org. Biomol. Chem.* **2005**, *3*, 3551−3563. (l) Avery, T. D.; Caiazza, D.; Culbert, J. A.; Taylor, D. K.; Tiekink, R. T. *J. Org. Chem.* **2005**, *70*, 8344−8351. (m) Yadav, J. S.; Reddy, B. V. S.; Maity, T.; Kumar, G. G. K. S. *Tetrahedron Lett.* **2007**, *48*, 7155−7159. (n) Chan, K.-P.; Seow, A.-H.; Loh, T.-P. *Tetrahedron Lett.* **2007**, *48*, 37−41. (o) Yadav, J. S.; Reddy, B. V. S.; Kumar, G. G. K. S. N.; Swamy, T. *Tetrahedron Lett.* **2007**, *48*, 2205−2208.

(6) (a) Yang, X.-F.; Mague, J. T.; Li, C.-J. *J. Org. Chem.* **2001**, *66*, 739−747. (b) Yang, X.-F.; Li, C.-J. *Tetrahedron Lett.* **2000**, *41*, 1321−1325.

(7) Ozaki, S.; Matsui, E.; Yoshinaga, H.; Kitagawa, S. *Tetrahedron Lett.* **2000**, *41*, 2621−2624.

(8) Rosiak, A.; Frey, W.; Christoffers, J. *Eur. J. Org. Chem.* **2006**, 4044−4054.

(9) (a) Weïwer, M.; Coulombel, L.; Duñach, E. *Chem. Commun.* **2006**, 332−334. (b) Weïwer, M.; Chaminade, X.; Bayón, J. C.; Duñach, E. *Eur. J. Org. Chem.* **2007**, 2464−2469.

(10) Tamura, Y.; Choi, H.-D.; Shindo, H.; Uenishi, J.; Ishibashi, H. *Tetrahedron Lett.* **1981**, *22*, 81−84.

(11) (a) Blumenkopf, T. A.; Look, G. C.; Overman, L. E. *J. Am. Chem. Soc.* **1990**, *112*, 4399−4403. (b) Overman, L. E. *Acc. Chem. Res.* **1992**, *25*, 352−359. (c) Overman, L. E.; Thompson, A. S. *J. Am. Chem. Soc.* **1988**, *110*, 2248−2256. (d) Sonawane, H. R.; Maji, D. K.; Jana, G. H.; Pandey, G. *Chem. Commun.* **1998**, 1773−1774. (e) Sasmal, P. K.; Maier, M. E. *J. Org. Chem.* **2003**, *68*, 824−831. (f) Ohmura, H.; Smyth, G. D.; Mikami, K. *J. Org. Chem.* **1999**, *64*, 6056−6059. (g) Mikami, K.; Ohmura, H.; Yamanaka, M. *J. Org. Chem.* **2003**, *68*, 1081−1088. (h) Ohmura, H.; Mikami, K. *Tetrahedron Lett.* **2001**, *42*, 6859−6863. (i) Loh, T.-P.; Hu, Q.-Y.; Tan, K.-T.; Cheng, H.-S. *Org. Lett.* **2001**, *3*, 2669−2672. (j) Saha, P.; Reddy, U. C.; Bondalapati, S.; Saikia, A. K. *Org. Lett.* **2010**, *12*, 1824−1826. (k) Saha, P.; Gogoi, P.; Saikia, A. K. *Org. Biomol. Chem.* **2011**, *9*, 4626−4634. (l) Bondalapati, S.; Reddy, U. C.; Saha, P.; Saikia, A. K. *Org. Biomol. Chem.* **2011**, *9*, 3428−3438.

(12) (a) Reddy, U. C.; Raju, B. R.; Kumar, E. K. P.; Saikia, A. K. *J. Org. Chem.* **2008**, *73*, 1628−1630. (b) Reddy, U. C.; Bondalapati, S.; Saikia, A. K. *Eur. J. Org. Chem.* **2009**, 1625−1629. (c) Reddy, U. C.; Bondalapati, S.; Saikia, A. K. *J. Org. Chem.* **2009**, *74*, 2605−2608. (d) Reddy, U. C.; Saikia, A. K. *Synlett* **2010**, 1027−1032.

(13) The crystallographic data for compounds **3b** and **3m** have been deposited with the Cambridge Crystallographic Data Centre as Supplementary publication nos. CCDC 848785 and 848786.

(14) Stach, D.; Zheng, Y. F.; Perez, A. L.; Oehlschlager, A. C. *J. Med. Chem.* **1997**, *40*, 201−209.