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SYNTHESIS OF ISOCHROMANES AND ISOTHIOCHROMANES BEARING FLUORINATED ONE-CARBON UNITS VIA INTRAMOLECULAR CYCLIZATIONS OF *ORTHO*-SUBSTITUTED α-(TRIFLUOROMETHYL)STYRENES

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This paper is dedicated to Professor Emeritus, Tohoku University, Keiichiro Fukumoto in celebration of his 75th birthday.

Abstract - *α*-(Trifluoromethyl)styrenes bearing a nucleophilic oxygen or sulfur atom tethered by a methylene or methyne unit at the *ortho* carbon were prepared by the coupling reaction of 2-bromo-3,3,3-trifluoropropene with aryl iodides via (3,3,3-trifluoroprop-1-en-2-yl)boronic acid. The styrenes thus obtained readily undergo an intramolecular nucleophilic addition or substitution (S_N2'-type) of the oxygen and sulfur under basic conditions, leading to 4-trifluoromethyl- or 4-difluoromethylene-substituted isochromanes and isothiochromanes, respectively.

INTRODUCTION

Isochromane (3,4-dihydro-1*H*-2-benzopyran)[1] and isothiochromane (3,4-dihydro-1*H*-2-benzothiopyran)[2] derivatives constitute an important class of natural and synthetic compounds. Because they exhibit a wide variety of biological activities, iso(thio)chromane skeletons are frequently found in the structures of drugs and drug candidates. Moreover, they are structural analogues of tetrahydroisoquinolines, which are widespread in the alkaloid family.[3] Hence, there have been many reports on the use of iso(thio)chromanes as starting materials or intermediates for the synthesis of medicinal and agrochemical agents.[4]

While the synthesis of iso(thio)chromanes has been extensively studied,[1,2,5] a quite limited number of reports have appeared on the synthesis of their partially fluorinated counterparts.[6] The introduction of fluorocarbon substituents into heterocycles has come into wide use as one of the most efficient methods for modification of biological activity, as well as of physical and chemical properties.[7,8] In particular, the incorporation of a trifluoromethyl (CF_3) group into organic molecules increases lipophilicity and affects electron density.[9] An *exo*-difluoromethylene ($=CF_2$) group acts as a reactive site toward nucleophiles,[10,11] and its reduction provides a difluoromethyl (CHF_2) group,[12] which raises lipophilicity and functions as a hydrogen-bond donor without nucleophilicity.[13] Thus, the development of a synthetic method for iso(thio)chromanes with these fluorinated one-carbon units is a highly desirable goal.

α-(Trifluoromethyl)styrenes are susceptible to nucleophilic attack, because of the electron-withdrawing trifluoromethyl group. Utilizing this reactivity, we have recently found that the (trifluoromethyl)styrenes with a nitrogen functionality readily undergo an intramolecular addition or S_N2'-type reaction, depending on conditions with or without a proton source. These reactions provided quinoline and isoquinoline derivatives bearing a fluorinated one-carbon unit such as a CF_3, CHF_2, or $=CF_2$ group.[14]

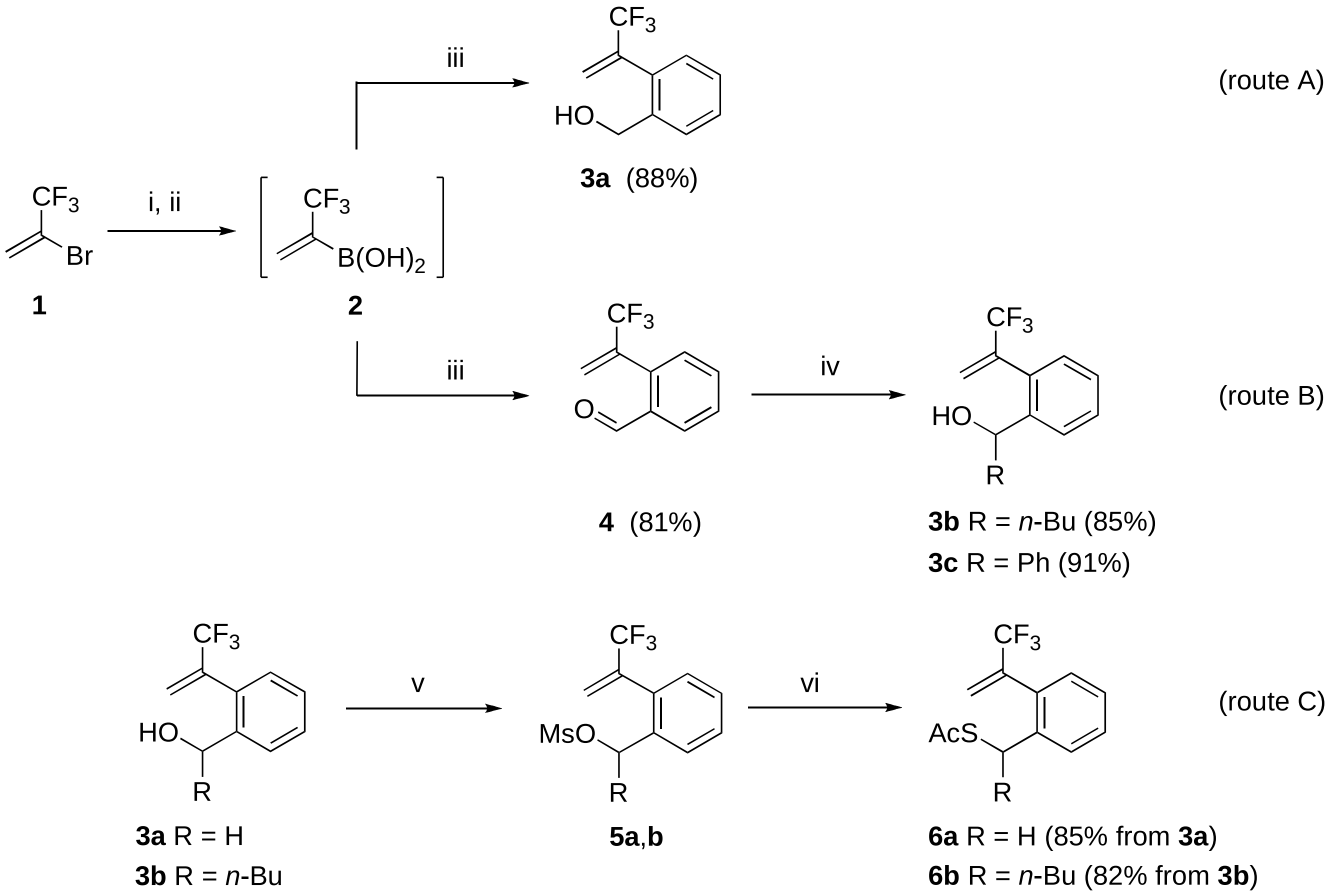
In a continuation of our research on the cyclizations of 2-trifluoromethyl-1-alkenes,[14,15] we sought to apply the intramolecular addition and substitution concept to the construction of 6-membered oxygen- or sulfur-containing heterocycles, isochromane and isothiochromane derivatives. On the basis of these considerations, α-(trifluoromethyl)styrene derivatives were designed to bear a nucleophilic oxygen or a sulfur atom tethered by a methylene or methyne unit at the *ortho* carbon. They were subjected to the ring-forming reactions in a 6-*endo*-trig fashion under basic conditions. Herein we wish to report the results of our studies on the synthesis of 4-trifluoromethyl- or 4-difluoromethylene-substituted isochromanes and isothiochromanes.

RESULTS AND DISCUSSION

Preparation of α-(Trifluoromethyl)styrenes Bearing a Nucleophilic Oxygen or Sulfur Atom

The cyclization precursors, *o*-substituted α-(trifluoromethyl)styrenes, were easily prepared by the Suzuki–Miyaura cross-coupling reaction of aryl iodides with (3,3,3-trifluoroprop-1-en-2-yl)boronic acid **(2)** that was prepared from 2-bromo-3,3,3-trifluoropropene **(1)**, according to a modified literature procedure (Scheme 1).[14a,16] (Trifluoromethyl)styrene **3a** bearing a hydroxymethyl group at the *ortho* position, precursors of isochromanes, was successfully obtained in 88% yield via the coupling of **2** with *o*-iodobenzyl alcohol (Scheme 1, route A). Alcohols **3** were also obtained via another route, which allows the introduction of a substituent (R) on the benzylic carbon (route B). The coupling of **2** with *o*-iodobenzaldehyde afforded (trifluoromethyl)styrene **4** bearing an *o*-formyl group in 81% yield. The addition of nucleophiles such as Grignard reagents to **4** selectively occurred at the formyl carbon to provide **3b** and **3c**.

As sulfur-containing substrates for the synthesis of isothiochromanes, thioacetates **6** were readily prepared from alcohols **3** via the corresponding mesylates **5** by the introduction of an acetylthio (AcS) group at the benzylic position on treatment with the 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) salt of ethanethioic *S*-acid (Scheme 1, route C).



i, Mg (1.2 equiv), $B(OMe)_3$ (3.0 equiv), THF, 0 °C, 3 h; ii, 6 M HCl aq, THF, rt; iii, ArI (**3a**: 0.6 equiv; **4**: 0.3 equiv), $Pd(PPh_3)_4$ (**3a**: 0.01 equiv; **4**: 0.005 equiv), 1 M Na_2CO_3 aq (**3a**: 0.6 equiv; **4**: 0.3 equiv), toluene–MeOH (5:1), 70 °C, **3a**: 16 h; **4**: 32 h; iv, **3b**: *n*-BuMgBr (1.2 equiv), Et_2O, –78 °C, 0.5 h then rt, 3 h; **3c**: PhMgBr (1.2 equiv), Et_2O, –78 °C, 0.5 h then rt, 3 h; v, MsCl (1.2 equiv), Et_3N (1.5 equiv), CH_2Cl_2, 0 °C, 2 h; vi, AcSH (3.0 equiv), DBU (3.0 equiv), DMF, rt, 20 h.

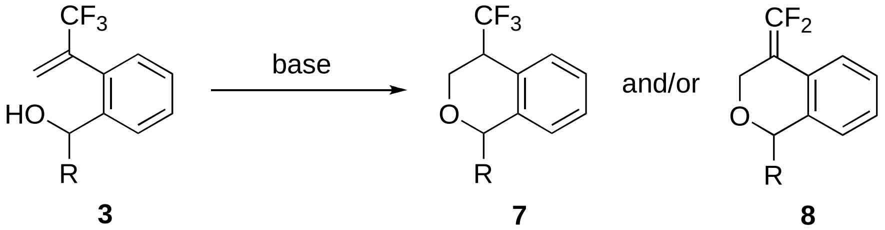
Scheme 1. Preparation of α-(trifluoromethyl)styrenes functionalized at the *ortho* position

Cyclization of α-(Trifluoromethyl)styrenes Bearing a Nucleophilic Oxygen or Sulfur Atom

We first examined the cyclization of (trifluoromethyl)styrenes **3** with a nucleophilic oxygen as precursors of isochromanes. Intramolecular addition of **3a** was attempted under basic conditions with a proton source to trap the intermediary trifluoromethylated carbanion. Treatment of **3a** with KOH (1.5 equiv) in ethylene glycol (ethane-1,2-diol) gave the desired cyclic product **7a** in 37% yield, whereas the addition was more successfully effected by the use of DBU (1.1 equiv) in diglyme [bis(2-methoxyethyl) ether] at 120 °C (Table 1, Entry 1), where the hydroxy group of **3a** and/or $DBU•H^+$ acted as a proton donor. 4-Trifluoromethylated isochromane **7a** was obtained in 82% yield without formation of a substitution product **8a** (*vide infra*). In the case of secondary alcohols **3b**,**c**, ring closure also occurred under similar conditions, leading to 1,4-disubstituted isochromanes **7b**,**c** in 72 and 86% yields with 87:13 and 57:43 diastereomer ratios, respectively (Entries 2 and 3).

Chromane precursors **3** were next subjected to basic conditions in the absence of a proton source to attempt intramolecular substitution, leading to 4-difluoromethylenated isochromanes **8**. Treatment with NaH in dimethylformamide (DMF) mainly caused decomposition of **3a** and afforded the expected S_N2'-type product **8a** only in 10% yield along with **7a** in 20% yield. After screening of basic conditions, we found that treatment with K_3PO_4 (2.0 equiv) in DMF improved the yield of **8a** to 38% with the accompanying formation of **7a** in 11% yield (Entry 4).

Table 1. Synthesis of 4-trifluoromethylated and 4-difluoromethylenated isochromanes

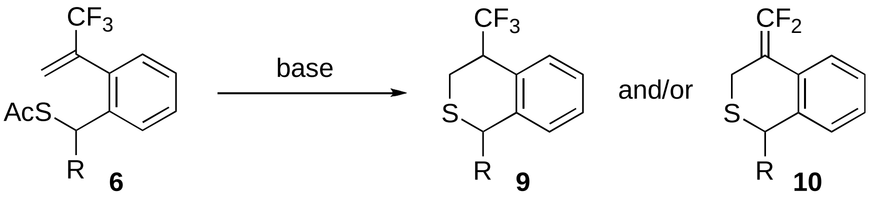


Entry	R (**3**)	Base (equiv)	Solvent	Conditions	Yield (%)[a] **7**	**8**
1	H (**3a**)	DBU (1.1)	diglyme	120 °C, 48 h	82	0
2	*n*-Bu (**3b**)	DBU (1.5)	diglyme	120 °C, 96 h	72 (87 : 13)[b]	0
3	Ph (**3c**)	DBU (1.1)	diglyme	120 °C, 24 h	86 (57 : 43)[b]	0
4	H (**3a**)	K_3PO_4 (2.0)	DMF	120 °C, 3 h	11	38
5	Ph (**3c**)	K_3PO_4 (2.0)	DMF	120 °C, 6 h	8 (69 : 31)[b]	43

[a]Isolated yield. [b]Diastereomer ratio determined by ^{19}F NMR measurement.

We then tried the cyclizations via addition or substitution using sulfur nucleophiles, which would provide isothiochromanes. When thioacetates **6a**,**b** were treated with K_2CO_3 (1.1 equiv) in MeOH, the deacetylation of **6** occurred to generate the corresponding thiolates, whose intramolecular addition readily proceeded in the presence of a proton source. The desired products, 4-trifluoromethylated isothiochromanes **9a**,**b** were obtained in 92% yield and 80% yield with 57:43 diastereomer ratio, respectively (Table 2, Entries 1 and 2). In contrast, treatment of **6a**,**b** with sodium methoxide (2.0–3.0 equiv) in tetrahydrofuran (THF) promoted deacetylation followed by S_N2'-type reaction instead of addition, which is due to the aprotic conditions. The two successive processes provided 4-difluoromethylenated isothiochromanes **10a**,**b** in 76% and 73% yields, respectively (Entries 3 and 4).

Table 2. Synthesis of 4-trifluoromethylated and 4-difluoromethylenated isothiochromanes



Entry	R (**6**)	Base (equiv)	Solvent	Conditions	Yield (%)[a] **9**	Yield (%)[a] **10**
1	H (**6a**)	K_2CO_3 (1.1)	MeOH	0 °C, 4 h	92	4
2	*n*-Bu (**6b**)	K_2CO_3 (1.1)	MeOH	reflux, 2 h	80 (57:43)[b]	3
3	H (**6a**)	NaOMe (2.0)	THF	0 °C, 0.5 h, then rt, 3 h	10	76
4	*n*-Bu (**6b**)	NaOMe (3.0)	THF	reflux, 19 h	0	73

[a]Isolated yield. [b]Diastereomer ratio determined by ^{19}F NMR measurement.

In conclusion, the above results show that our intramolecular addition and substitution concept in 2-trifluoromethyl-1-alkenes can be successfully applied to the construction of 6-membered oxygen- or sulfur-containig heterocycles as well as nitrogen-containing heterocycles. *o*-Substituted α-(trifluoromethyl)styrenes, prepared from 2-bromo-3,3,3-trifluoro-1-propene and aryl iodides, readily undergo 6-*endo* ring closure via addition or substitution, depending on the reaction conditions. These reactions provide a facile method for the construction of selectively trifluoromethylated and difluoromethylenated benzo(thio)pyran frameworks.

EXPERIMENTAL

IR spectra were recorded by ATR (attenuated total reflectance) method. NMR spectra were recorded in $CDCl_3$ at 500 MHz (^{1}H NMR), 126 MHz (^{13}C NMR), and 470 MHz (^{19}F NMR). Chemical shift values were given in ppm relative to internal Me_4Si (for ^{1}H NMR: δ 0.00), $CDCl_3$ (for ^{13}C NMR: δ 77.0), and C_6F_6 (for ^{19}F NMR: δ_F 0.0). Column chromatography and preparative thin-layer chromatography (PTLC) were performed on silica gel. Unless otherwise noted, all reactions were conducted under nitrogen. Toluene, DMF, CH_2Cl_2, THF, and diethyl ether (Et_2O) were dried by passing over a column of activated alumina (A-2, Purity) followed by a column of Q-5 scavenger (Engelhard). MeOH was distilled from Mg, and stored over molecular sieves 3Å. Ethylene glycol and diglyme were distilled from $MgSO_4$ and CaH_2, respectively, and then stored over molecular sieves 4Å.

[2-(3,3,3-Trifluoroprop-1-en-2-yl)phenyl]methanol (3a): To a magnesium turnings (571 mg, 23.4

mmol) and trimethylborate (6.51 mL, 58.5 mmol) in THF (40 mL) was added 2-bromo-3,3,3-trifluoropropene (2.00 mL, 19.5 mmol) in THF (5 mL) over 1 h at 0 °C. The reaction mixture was stirred at 0 °C for 3 h. The reaction mixture was quenched with HCl (20 mL of 6 M aqueous solution), and organic materials were extracted three times each with Et_2O. The combined extracts were washed with brine and then dried over $MgSO_4$. Removal of the solvent under reduced pressure gave the residue, crude 1-(trifluoromethyl)vinylboronic acid (**2**) [^{19}F NMR ($CDCl_3$) δ_F 98.3 (s)], which was immediately used without purification in the following palladium-catalyzed coupling reaction with iodoarenes. The mixture of the crude boronic acid **2**, 2-iodophenylmethanol (2.62 g, 11.2 mmol), sodium carbonate (12 mL of 1.0 M aqueous solution), $Pd(PPh_3)_4$ (259 mg, 0.224 mmol) in toluene–MeOH (140 mL, 5:1) was stirred at 70 °C for 16 h. The reaction was quenched with phosphate buffer (pH 7). The mixture was extracted with ethyl acetate three times. The combined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–AcOEt 3:1) to give **3a** (2.00 g, 88%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 4.67 (s, 2H), 5.60 (q, J_{HF} = 1.2 Hz, 1H), 6.15 (q, J_{HF} = 1.4 Hz, 1H), 7.26 (d, J = 7.6 Hz, 1H), 7.32 (dd, J = 7.6, 7.6 Hz, 1H), 7.43 (dd, J = 7.6, 7.6 Hz, 1H), 7.57 (d, J = 7.6 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$, δ): 62.7, 122.8 (q, J_{CF} = 274 Hz), 123.5 (q, J_{CF} = 5 Hz), 127.5, 128.4, 129.3, 129.8, 132.4, 136.9 (q, J_{CF} = 31 Hz), 139.4. ^{19}F NMR (470 MHz, $CDCl_3$, δ_F): 94.7 (s). IR (neat): 3330, 1342, 1217, 1169, 1115, 1072, 769 cm^{-1}. Anal. Calcd for $C_{10}H_9OF_3$: C, 59.41; H, 4.49. Found: C, 59.2; H, 4.58.

2-(3,3,3-Trifluoroprop-1-en-2-yl)benzaldehyde (4): Compound **4** was prepared by the method described for **3a**. Purification by column chromatography (hexane–AcOEt 5:1) gave **4** (81%) as a colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 5.62 (q, J_{HF} = 1.3 Hz, 1H), 6.29 (q, J_{HF} = 1.3 Hz, 1H), 7.41 (d, J = 7.6 Hz, 1H), 7.56 (dd, J = 7.6, 7.6 Hz, 1H), 7.63 (dd, J = 7.6, 7.6 Hz, 1H), 8.01 (d, J = 7.6 Hz, 1H), 10.1 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$, δ): 122.4 (q, J_{CF} = 274 Hz), 125.1 (q, J_{CF} = 5 Hz), 128.4, 129.5, 130.7, 133.6, 134.8, 135.4 (q, J_{CF} = 32 Hz), 136.6, 190.8. ^{19}F NMR (470 MHz, $CDCl_3$, δ_F): 94.8 (s). IR (neat): 2858, 1701, 1599, 1346, 1173, 1126, 962 cm^{-1}. Anal. Calcd for $C_{10}H_7OF_3$: C, 60.01; H, 3.53. Found: C, 60.03; H, 3.66.

1-[2-(3,3,3-Trifluoroprop-1-en-2-yl)phenyl]pentan-1-ol (3b): To a solution of **4** (1.02 g, 5.09 mmol) in Et_2O (45 ml) was added butylmagnesium bromide (3.06 ml, 2.0 M in Et_2O, 6.12 mmol) at –78 °C. The reaction mixture was stirred at –78 °C for 30 min and at rt for an additional 3 h. Then, phosphate buffer (pH 7) was added to quench the reaction. Organic materials were extracted with Et_2O three times. The combined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–AcOEt 3:1) to give **3b** (1.12 g, 85%) as a colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 0.88 (t, J = 7.2 Hz, 3H), 1.21–1.45 (m, 4H), 1.62–1.69 (m, 1H), 1.76–1.83 (m, 2H), 4.79 (dd, J = 8.3, 5.0 Hz, 1H), 5.52 (q, J_{HF} = 1.2 Hz, 1H), 6.14 (q, J_{HF} = 1.4 Hz, 1H), 7.19 (d, J = 7.6 Hz, 1H), 7.28 (dd, J = 7.6, 7.6 Hz, 1H), 7.43 (dd, J = 7.6, 7.6 Hz, 1H), 7.60 (d, J = 7.6 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$, δ): 13.9, 22.5, 28.2, 38.3, 70.6, 122.8 (q, J_{CF} = 274 Hz), 123.5 (q, J_{CF} = 5 Hz), 126.2, 127.2, 129.5, 129.8, 131.8, 137.5 (q, J_{CF} = 31 Hz), 143.8. ^{19}F NMR (470 MHz, $CDCl_3$, δ_F): 94.5 (s). IR (neat): 2933, 2862, 1340, 1167, 1124, 1095, 953, 762, 631 cm^{-1}. Anal. Calcd for $C_{14}H_{17}OF_3$: C, 65.10; H, 6.63. Found: C, 65.45; H, 7.00.

Phenyl[2-(3,3,3-trifluoroprop-1-en-2-yl)phenyl]methanol (3c): Compound **3c** was prepared by the method described for **3b**. Purification by column chromatography (hexane–AcOEt 5:1) gave **4** (91%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 2.12 (d, J = 3.8 Hz, 1H), 5.42 (q, J_{HF} = 1.1 Hz, 1H), 5.98 (d, J = 3.8 Hz, 1H), 6.12 (q, J_{HF} = 1.4 Hz, 1H), 7.24–7.28 (m, 2H), 7.29–7.35 (m, 5H), 7.40 (dd, J = 7.6, 7.6 Hz, 1H), 7.51 (d, J = 7.6 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$, δ): 72.5, 122.9 (q, J_{CF} = 274 Hz), 124.2 (q, J_{CF} = 5 Hz), 126.6, 127.5, 127.5, 127.9, 128.4, 129.4, 129.9, 132.5, 136.9 (q, J_{CF} = 31 Hz), 142.5, 143.4. ^{19}F NMR (470 MHz, $CDCl_3$, δ_F): 94.7 (s). IR (neat): 3334, 2921, 1342, 1403, 1169, 1122, 1016, 700 cm^{-1}. Anal. Calcd for $C_{16}H_{13}OF_3$: C, 69.06; H, 4.71. Found: C, 68.92; H, 4.78.

***S*-[2-(3,3,3-Trifluoroprop-1-en-2-yl)phenyl]methyl ethanethioate (6a):** Compound **6a** was prepared by the method described for **6b** (*vide infra*). Purification by PTLC (hexane–AcOEt 5:1) gave **6a** (85%) as a colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 2.34 (s, 3H), 4.13 (s, 2H), 5.59 (q, J_{HF} = 1.3 Hz, 1H), 6.17 (q, J_{HF} = 1.4 Hz, 1H), 7.22 (d, J = 7.6 Hz, 1H), 7.27 (dd, J = 7.6, 7.6 Hz, 1H), 7.34 (dd, J = 7.6, 7.6 Hz, 1H), 7.43 (d, J = 7.6 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$, δ): 30.2, 30.8, 122.8 (q, J_{CF} = 274 Hz), 123.9 (q, J_{CF} = 5 Hz), 127.2, 129.4, 130.0, 130.3, 133.3, 136.5, 137.0 (q, J_{CF} = 31 Hz), 194.8. ^{19}F NMR (470 MHz, $CDCl_3$, δ_F): 94.6 (s). IR (neat): 2252, 1684, 1344, 1203, 1132, 903, 721, 650 cm^{-1}. Anal. Calcd for $C_{12}H_{11}OF_3S$: C, 55.38; H, 4.26. Found: C, 55.49; H, 4.43.

***S*-1-[2-(3,3,3-Trifluoroprop-1-en-2-yl)phenyl]pentyl ethanethioate (6b):** To a solution of **3b** (615 mg, 2.38 mmol) and triethylamine (0.50 mL, 3.6 mmol) in CH_2Cl_2 (11 ml) was added methanesulfonyl chloride (0.22 mL, 2.9 mmol) at 0 °C. After the reaction mixture was stirred at 0 °C for 2 h, saturated aqueous NH_4Cl was added to quench the reaction. The organic layer was washed with brine and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave the residue, crude mesylate **5b**, which was used without purification in the following substitution reaction with ethanethioic *S*-acid. To a solution of DBU (1.04 mL, 7.0 mmol) in DMF (3.3 ml) was added ethanethioic *S*-acid (0.50 mL, 7.1 mmol) dropwise at rt. The crude mesylate **5b** in DMF (6.6 ml) was added, and the mixture was stirred at rt for 20 h. The reaction was quenched with saturated aqueous NH_4Cl. After water was added, organic materials were extracted with AcOEt three times. The combined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane–AcOEt 5:1) to give **6b** (600 mg, 82%) as a colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 0.84 (t, J = 7.2 Hz, 3H), 1.16–1.18 (m, 1H), 1.26–1.31 (m, 3 H), 1.87–1.93 (m, 2H), 2.28 (s, 3H), 4.76 (t, J = 7.6 Hz, 1H), 5.59 (q, J_{HF} = 1.1 Hz, 1H), 6.19 (q, J_{HF} = 1.3 Hz, 1H), 7.22–7.27 (m, 2H), 7.36–7.37 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$, δ): 13.8, 22.4, 29.4, 30.3, 37.1, 44.6, 122.9 (q, J_{CF} = 274 Hz), 124.1 (q, J_{CF} = 5 Hz), 126.8, 127.8, 129.3, 130.0, 132.6, 136.6 (q, J_{CF} = 31 Hz), 140.6, 194.2. ^{19}F NMR (470 MHz, $CDCl_3$, δ_F): 95.0 (s). IR (neat): 2931, 2862, 1691, 1402, 1342, 1201, 1167, 1092, 1068, 953, 629 cm^{-1}. Anal. Calcd for $C_{16}H_{19}OF_3S$: C, 60.74; H, 6.05. Found: C, 60.51; H, 6.14.

4-Trifluoromethyl-3,4-dihydro-1*H*-2-benzopyran (7a): To a solution of **3a** (51 mg, 0.25 mmol) in diglyme (2.5 mL) was added DBU (42 μL, 0.28 mmol). After the reaction mixture was heated at 120 °C for 48 h, phosphate buffer (pH 7) was added to quench the reaction. Organic materials were extracted with Et_2O three times. The combined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by PTLC (pentane–Et_2O 5:1) to give **7a** (42 mg, 82%) as a colorless crystal. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 3.42 (qm, J_{HF} = 9.3 Hz, 1H), 3.92 (dm, J = 12.3 Hz, 1H), 4.41 (dd, J = 12.3, 2.3 Hz, 1H), 4.76 (d, J = 15.2 Hz, 1H), 4.87 (d, J = 15.2 Hz, 1H), 7.07 (d, J = 7.6 Hz, 1H), 7.26 (dd, J = 7.6, 7.6 Hz, 1H), 7.32 (dd, J = 7.6, 7.6 Hz, 1H), 7.37 (d, J = 7.6 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$, δ): 41.1 (q, J_{CF} = 26 Hz), 63.8 (q, J_{CF} = 3 Hz), 67.7, 124.7, 126.1 (d, J_{CF} = 1 Hz), 126.2 (q, J_{CF} = 281 Hz), 126.8, 128.3, 130.2, 135.8. ^{19}F NMR (470 MHz, $CDCl_3$, δ_F): 93.7 (d, J_{FH} = 9 Hz). IR (neat): 2871, 1734, 1495, 1456, 1350, 1269, 1230, 1153, 1108, 995, 912, 742 cm^{-1}. Anal. Calcd for $C_{10}H_9OF_3$: C, 59.41; H, 4.49. Found: C, 59.28; H, 4.54.

1-Butyl-4-trifluoromethyl-3,4-dihydro-1*H*-2-benzopyran (7b): Compound **7b** was prepared by the method described for **7a**. Purification by PTLC (pentane–Et_2O 10:1) gave **7b** (72%; 87:13 diastereomer ratio) as a colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$, δ): (major) 0.90 (t, J = 7.2 Hz, 3H), 1.28–1.46 (m, 4H), 1.80–1.88 (m, 1H), 1.94–2.01 (m, 1H), 3.26 (qd, J_{HF} = 9.2, 3.6 Hz, 1H), 3.83 (ddq, J = 12.3, 3.6, 1.8 Hz, 1H), 4.47 (d, J = 12.3 Hz, 1H), 4.74 (dd, J = 7.6, 2.7 Hz, 1H), 7.18 (d, J = 7.6 Hz, 1H), 7.23–7.26 (m, 1H), 7.32–7.35 (m, 2H); (minor) 0.94 (t, J = 7.2 Hz, 3H), 1.32–1.55 (m, 4H), 1.70–1.77 (m, 1H), 1.81–1.89 (m, 1H), 3.38–3.45 (m, 1H), 4.12 (d, J = 4.0 Hz, 2H), 4.79 (dd, J = 10.1, 3.2 Hz, 1H), 7.12 (d, J = 7.6 Hz, 1H), 7.23–7.26 (m, 1H), 7.31 (dd, J = 7.6, 7.6 Hz, 1H), 7.36 (d, J = 7.6 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$, δ): (major) 14.0, 22.8, 26.8, 35.4, 41.8 (q, J_{CF} = 26 Hz), 62.8 (q, J_{CF} = 3 Hz), 76.3, 124.9, 126.2 (q, J_{CF} = 281 Hz), 126.4, 126.9 (q, J_{CF} = 2 Hz), 128.5, 130.5, 139.5; (minor) 14.0, 22.5, 28.1, 34.8, 41.5 (q, J_{CF} = 26 Hz), 58.8 (q, J_{CF} = 3 Hz), 75.0, 125.5, 126.3 (q, J_{CF} = 281 Hz), 126.4 (q, J_{CF} = 2 Hz), 126.6, 128.1, 129.6, 139.8. ^{19}F NMR (470 MHz, $CDCl_3$, δ_F): (major) 93.9 (d, J_{FH} = 9 Hz); (minor) 93.8 (d, J_{FH} = 9 Hz). IR (neat) 2956, 2931, 1250, 1155, 1119, 750, 620 cm^{-1}. Anal. Calcd for $C_{14}H_{17}OF_3$: C, 65.10; H, 6.63. Found: C, 65.02; H, 6.77.

1-Phenyl-4-trifluoromethyl-3,4-dihydro-1*H*-2-benzopyran (7c): Compound **7c** was prepared by the method described for **7a**. Purification by PTLC (pentane–Et_2O 5:1) gave **7b** (86%; 57:43 diastereomer ratio) as a colorless crystal.

^{1}H NMR (500 MHz, CDCl$_3$, δ): (major) 3.40 (qd, J_{HF} = 9.1, 3.6 Hz, 1H), 4.07 (ddq, J = 12.4, 3.6, 1.8 Hz, 1H), 4.59 (d, J = 12.4 Hz, 1H), 5.66 (s, 1H), 6.79 (d, J = 7.5 Hz, 1H), 7.21 (dd, J = 7.5, 7.5 Hz, 1H), 7.25 (dd, J = 7.5, 7.5 Hz, 1H), 7.34–7.37 (m, 5H), 7.39 (d, J = 7.5 Hz, 1H); (minor) 3.52–3.57 (m, 1H), 4.05–4.12 (m, 2H), 5.88 (s, 1H), 6.93 (d, J = 7.4 Hz, 1H), 7.19–7.22 (m, 2H), 7.27–7.38 (m, 5H), 7.47 (d, J = 7.4 Hz, 1H). ^{13}C NMR (126 MHz, CDCl$_3$, δ): (major) 41.5 (q, J_{CF} = 26 Hz), 63.6 (q, J_{CF} = 3 Hz), 80.5, 126.2 (q, J_{CF} = 281 Hz), 126.4 (q, J_{CF} = 2 Hz), 126.9, 127.1, 128.4, 128.5, 128.6, 128.9, 130.2, 138.9, 141.1; (minor) 41.3 (q, J_{CF} = 26 Hz), 59.4 (q, J_{CF} = 3 Hz), 77.8, 126.3 (q, J_{CF} = 281 Hz), 127.2 (q, J_{CF} = 2 Hz), 127.2, 127.5, 127.9, 128.3, 128.4, 129.1, 129.6, 137.1, 140.9. ^{19}F NMR (470 MHz, CDCl$_3$, δ_F): (major) 93.9 (d, J_{FH} = 9 Hz); (minor) 93.8 (d, J_{FH} = 9 Hz). IR (neat): 3064, 3031, 2870, 1455, 1355, 1243, 1155, 999, 747, 700 cm^{-1}. Anal. Calcd for $C_{16}H_{13}OF_3$: C, 69.06; H, 4.71. Found: C, 69.08; H, 4.94.

4-Difluoromethylene-3,4-dihydro-1*H*-2-benzopyran (8a): Compound **8a** was prepared by the method described for **8c** (*vide infra*). Purification by PTLC (pentane–Et$_2$O 5:1) gave **8a** (38%) as a colorless liquid. ^{1}H NMR (500 MHz, CDCl$_3$, δ): 4.50 (dd, J_{HF} = 2.7, 2.7 Hz, 2H), 4.79 (s, 2H), 7.05 (d, J = 7.5 Hz, 1H), 7.21 (dd, J = 7.5, 7.5 Hz, 1H), 7.27 (dd, J = 7.5, 7.5 Hz, 1H), 7.61 (d, J = 7.5 Hz, 1H). ^{13}C NMR (126 MHz, CDCl$_3$, δ): 63.2 (dd, J_{CF} = 4, 4 Hz), 68.9, 85.7 (dd, J_{CF} = 20, 13 Hz), 124.7, 125.7 (d, J_{CF} = 3 Hz), 126.6 (dd, J_{CF} = 10, 5 Hz), 127.0 (dd, J_{CF} = 2, 2 Hz), 127.3, 134.1 (dd, J_{CF} = 5, 3 Hz), 152.3 (dd, J_{CF} = 296, 291 Hz). ^{19}F NMR (470 MHz, CDCl$_3$, δ_F): 75.6 (d, J_{FF} = 41 Hz, 1F), 75.5 (d, J_{FF} = 41 Hz, 1F). IR (neat): 2958, 2846, 1722, 1329, 1261, 1236, 1086, 1053, 760, 737 cm^{-1}. Anal. Calcd for $C_{10}H_8OF_2$: C, 65.93; H, 4.43. Found: C, 66.07; H, 4.59.

4-Difluoromethylene-1-phenyl-3,4-dihydro-1*H*-2-benzopyran (8c): To a solution of **8c** (53 mg, 0.19 mmol) in DMF (2.0 mL) was added K_3PO_4 (81 mg, 0.38 mmol) at rt. After the reaction mixture was stirred at 120 °C for 6 h, phosphate buffer (pH 7) was added to quench the reaction. Organic materials were extracted with Et$_2$O three times. The combined extracts were washed with brine and dried over Na$_2$SO$_4$. After removal of the solvent under reduced pressure, the residue was purified by PTLC (pentane–Et$_2$O 5:1) to give **8c** (21 mg, 43%) as a colorless liquid. ^{1}H NMR (500 MHz, CDCl$_3$, δ): 4.43 (ddd, J = 13.2 Hz, J_{HF} = 3.6, 3.6 Hz, 1H), 4.63 (dd, J = 13.2 Hz, J_{HF} = 2.6 Hz, 1H), 5.76 (s, 1H), 6.81 (d, J = 7.6 Hz, 1H), 7.13 (dd, J = 7.6, 7.6 Hz, 1H), 7.24–7.39 (m, 6H), 7.66 (d, J = 7.6 Hz, 1H). ^{13}C NMR (126 MHz, CDCl$_3$, δ): 61.0 (dd, J_{CF} = 4, 4 Hz), 80.0, 86.0 (dd, J_{CF} = 24, 8 Hz), 126.4 (dd, J_{CF} = 4, 2 Hz), 126.5 (dd, J_{CF} = 14, 2 Hz), 126.9 (dd, J_{CF} = 2, 2 Hz), 127.1, 127.5, 128.4, 128.5, 128.8, 136.5 (dd, J_{CF} = 6, 2 Hz), 140.7, 152.2 (dd, J_{CF} = 300, 287 Hz). ^{19}F NMR (470 MHz, CDCl$_3$, δ_F): 75.5 (d, J_{FF} = 41 Hz, 1F), 75.9 (d, J_{FF} = 41 Hz, 1F). IR (neat): 3066, 3032, 2927, 2854, 1732, 1718, 1238, 760, 700 cm^{-1}. Anal. Calcd for $C_{16}H_{12}OF_2$: C, 74.41; H, 4.68. Found: C, 74.42; H, 4.91.

4-Trifluoromethyl-3,4-dihydro-1*H*-2-benzothiopyran (9a): To a solution of **6a** (44 mg, 0.17 mmol) in

MeOH (1.7 mL) was added K_2CO_3 (26 mg, 0.19 mmol) at 0 °C. After the reaction mixture was stirred at 0 °C for 4 h, phosphate buffer (pH 7) was added to quench the reaction. Organic materials were extracted with Et_2O three times. The combined extracts were washed with brine and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by PTLC (pentane–Et_2O 20:1) to give **7a** (34 mg, 92%) as a colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 3.11 (dd, J = 13.6, 6.4 Hz, 1H), 3.17 (dd, J = 13.6, 5.8 Hz, 1H), 3.73–3.81 (m, 1H), 3.78 (s, 2H), 7.17–7.19 (m, 1H), 7.24–7.29 (m, 2H), 7.37–7.38 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$, δ): 25.6 (q, J_{CF} = 3 Hz), 30.0, 42.9 (q, J_{CF} = 26 Hz), 126.4 (q, J_{CF} = 282 Hz), 127.1, 127.9, 128.6, 129.5 (q, J_{CF} = 1 Hz), 130.4 (q, J_{CF} = 2 Hz), 136.1. ^{19}F NMR (470 MHz, $CDCl_3$, δ_F): 94.6 (d, J_{FH} = 9 Hz). IR (neat): 3064, 2921, 1496, 1448, 1340, 1270, 1241, 1151, 1103, 950, 763, 739 cm^{-1}. Anal. Calcd for $C_{10}H_9F_3S$: C, 55.03; H, 4.16. Found: C, 55.17; H, 4.32.

1-Butyl-4-trifluoromethyl-3,4-dihydro-1*H*-2-benzothiopyran (9b): Compound **9b** was prepared by the method described for **9a**. Purification by PTLC (pentane–Et_2O 30:1) gave **9b** (80%; 57:43 diastereomer ratio) as a colorless liquid.

^{1}H NMR (500 MHz, $CDCl_3$, δ): 0.93 (t, J = 7.2 Hz, 1.8H), 0.94 (t, J = 7.2 Hz, 1.2H), 1.28–1.49 (m, 3H), 1.55–1.66 (m, 1H), 1.78–2.02 (m, 2H), 3.01 (dd, J = 14.1, 4.3 Hz, 0.6H), 3.05–3.14 (m, 0.8H), 3.20 (br dd, J = 14.1, 4.3 Hz, 0.6H), 3.65–3.85 (m, 2H), 7.18–7.31 (m, 3H), 7.34 (d, J = 7.6 Hz, 0.6H), 7.43 (d, J = 7.6 Hz, 0.4H). ^{13}C NMR (126 MHz, $CDCl_3$, δ): 14.0, 14.0, 22.2 (q, J_{CF} = 3 Hz), 22.3 (q, J_{CF} = 3 Hz), 22.3, 22.4, 29.9, 30.2, 35.0, 38.1, 41.9, 42.1, 42.4 (q, J_{CF} = 26 Hz), 43.2 (q, J_{CF} = 26 Hz), 126.3 (q, J_{CF} = 282 Hz), 126.6 (q, J_{CF} = 282 Hz), 126.6, 126.8, 127.5, 127.9, 128.0, 128.7 (q, J_{CF} = 1 Hz), 128.8, 129.2 (q, J_{CF} = 1 Hz), 129.8 (q, J_{CF} = 2 Hz), 130.6 (q, J_{CF} = 2 Hz), 140.2, 140.8. ^{19}F NMR (470 MHz, $CDCl_3$, δ_F): 95.4 (d, J_{FH} = 9 Hz, 1.8F), 94.6 (d, J_{FH} = 9 Hz, 1.2F). IR (neat): 3060, 3025, 2958, 2931, 1493, 1446, 1346, 1273, 1244, 1238, 1151, 1107 cm^{-1}. Anal. Calcd for $C_{14}H_{17}F_3S$: C, 61.29; H, 6.25. Found: C, 61.41; H, 6.43.

4-Difluoromethylene-3,4-dihydro-1*H*-2-benzothiopyran (10a): To a solution of **6a** (56 mg, 0.22 mmol) in THF (2.2 mL) was added NaOMe (24 mg, 0.43 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and at rt for an additional 3 h. Then, phosphate buffer (pH 7) was added to quench the reaction. Organic materials were extracted with Et_2O three times. The combined extracts were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by PTLC (pentane–Et_2O 20:1) to give **10a** (32 mg, 76%) as a colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 3.53 (dd, J_{HF} = 2.3, 2.3 Hz, 2H), 3.79 (s, 2H), 7.16 (d, J = 7.4 Hz, 1H), 7.21 (dd, J = 7.4, 7.4 Hz, 1H), 7.25 (dd, J = 7.4, 7.4 Hz, 1H), 7.50 (d, J = 7.4 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$, δ): 25.1 (dd, J_{CF} = 2, 2 Hz), 30.8, 87.1 (dd, J_{CF} = 23, 12 Hz), 127.0, 127.2, 127.9, 128.5 (dd, J_{CF} = 11, 1 Hz), 129.2 (dd, J_{CF} = 5, 4 Hz), 135.2 (d, J_{CF} = 5 Hz), 152.9 (dd, J_{CF} = 297, 287 Hz). ^{19}F NMR (470 MHz, $CDCl_3$, δ_F): 72.3 (d, J_{FF} = 37 Hz, 1F), 75.1 (d, J_{FF} = 37 Hz, 1F). IR (neat): 3064, 2910, 1712, 1489, 1326, 1228, 1112, 985, 756, 713 cm^{-1}. Anal. Calcd for $C_{10}H_8F_2S$: C, 60.59; H, 4.07. Found: C, 60.38; H, 4.15.

1-Butyl-4-difluoromethylene-3,4-dihydro-1*H*-2-benzothiopyran (10b): Compound **10b** was prepared by the method described for **10a**. Purification by PTLC (pentane–Et_2O 30:1) gave **10b** (73%) as a colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 0.91 (t, J = 7.1 Hz, 3H), 1.28–1.41 (m, 3H), 1.47–1.58 (m, 1H), 1.77–1.88 (m, 2H), 3.46 (ddd, J_{HF} = 14.1, 2.4, 2.4 Hz, 1H), 3.63 (ddd, J_{HF} = 14.1, 2.4, 2.4 Hz, 1H), 3.73 (t, J = 6.8 Hz, 1H), 7.15–7.18 (m, 1H), 7.21–7.27 (m, 2H), 7.43–7.47 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$, δ): 13.9, 22.3, 22.5, 30.1, 36.5, 43.6, 86.9 (dd, J_{CF} = 23, 13 Hz), 126.8, 127.1, 127.3, 128.7, 128.7 (d, J_{CF} = 8 Hz), 140.5 (d, J_{CF} = 5 Hz), 152.9 (dd, J_{CF} = 296, 288 Hz). ^{19}F NMR (470 MHz, $CDCl_3$, δ_F): 71.3 (d, J_{FF} = 37 Hz, 1F), 75.0 (d, J_{FF} = 37 Hz, 1F). IR (neat): 3066, 2956, 2929, 2858, 1716, 1487, 1254, 1232, 1106, 980, 758cm^{-1}. Anal. Calcd for $C_{14}H_{16}F_2S$: C, 66.11; H, 6.34. Found: C, 66.10; H, 6.52.

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