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SYNTHESIS OF 1,2,3,5-TETRAHYDRO-4,1-BENZOTHIAZEPINE-2-THIONE DERIVATIVES *VIA* CYCLIZATION OF 2-[(2-ISOTHIOCYANATOPHENYL)METHYLSULFANYL]ACETATES WITH SODIUM HYDRIDE

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Abstract – A convenient method for the preparation of the title derivatives, 2-thioxo-1,2,3,5-tetrahydro-4,1-benzothiazepine-3-carboxylates and 2-alkylsulfanyl-3,5-dihydro-4,1-benzothiazepine-3-carboxylates, has been developed. It is depends on cyclization of 2-[(2-isothiocyanatophenyl)methylsulfanyl]acetates, generated in situ from the corresponding isocyanides on treatment with sulfur in the presence of a catalytic amount of selenium, using sodium hydride as a base. These isocyanides can be easily prepared from *N*-[(2-chloromethyl)phenyl]-formamides *via* an easy two-step sequence.

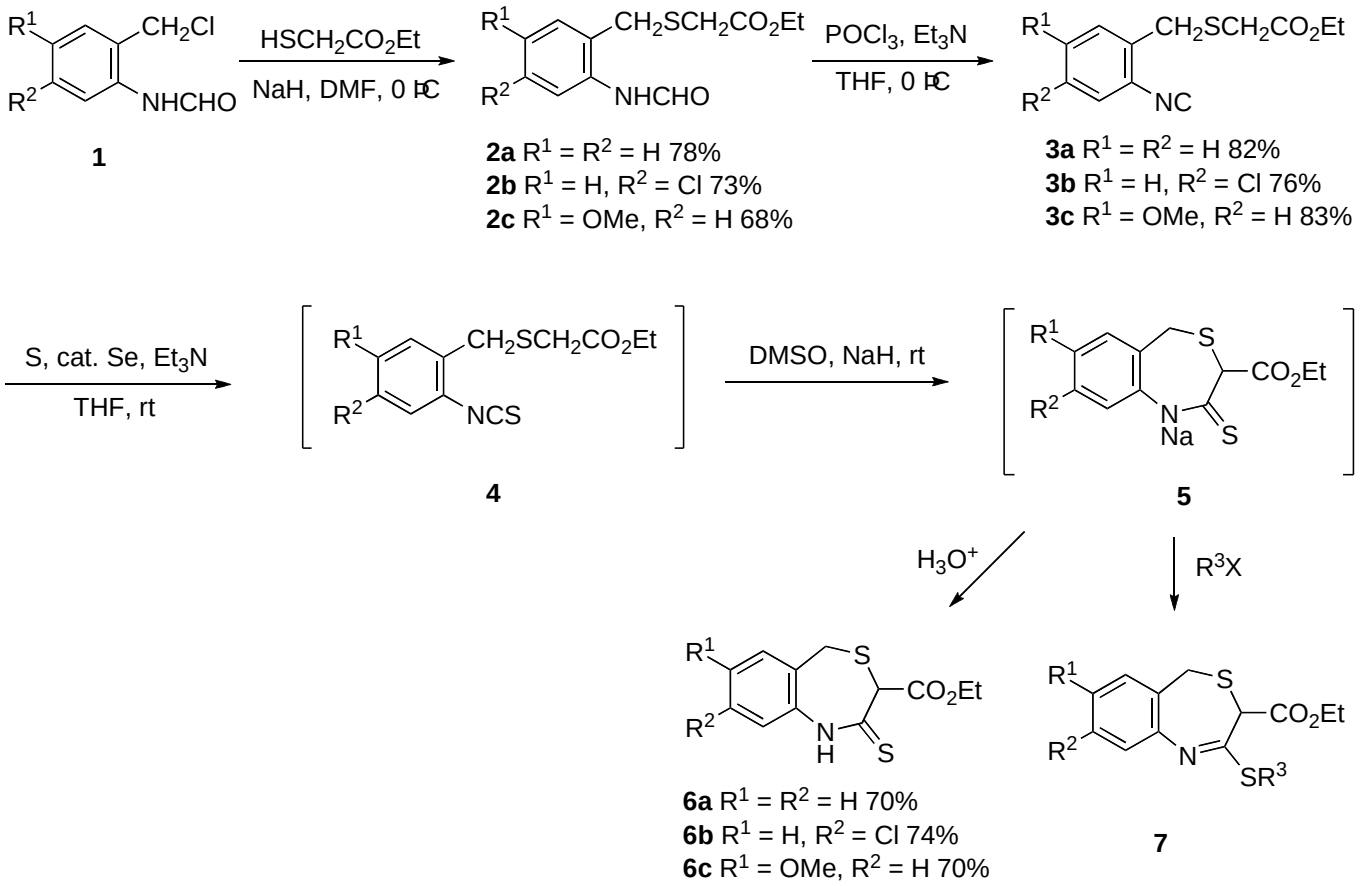
INTRODUCTION

The 4,1-benzothiazepine structure is found in some biological active compounds.[1] For example, 7-chloro-5-(2-chlorophenyl)-1,2,3,5-tetrahydro-4,1-benzothiazepin-2-one (CGP-37157) is known as a mitochondrial Na^+–Ca^{2+} exchange inhibitor.[1d] A number of 1,2,3,5-tetrahydro-4,1-benzothiazepine-2-thione derivatives have been prepared and most of them also have been reported to exhibit variety of biological activities.[2] Several methods exist for the preparation of 4,1-benzothiazepine derivatives.[1a,b,3] However, there have been few reports on the practical preparation of 1,2,3,5-tetrahydro-4,1-benzothiazepine-2-thione derivatives.[4] In this paper we report a simple one-pot procedure for the preparation of 1,2,3,5-tetrahydro-4,1-benzothiazepine-2-thione derivatives, ethyl 2-thioxo-1,2,3,5-tetrahydro-4,1-benzothiazepine-3-carboxylates (**6**) and ethyl 2-alkylsulfanyl-3,5-dihydro-4,1-benzothiazepine-3-carboxylates (**7**), using cyclization of ethyl 2-[(2-isothiocyanatophenyl)methylsulfanyl]acetates (**4**), generated in situ from ethyl 2-[(2-

isocyanophenyl)methylsulfanyl]acetates (**3**).

RESULTS AND DISCUSSION

The isocyano compounds (**3**) could be prepared by an easy four-step sequence starting with readily available *N*-[2-(chloromethyl)phenyl]formamides (**1**) as illustrated in Scheme 1. Thus, compounds **1** were transformed into ethyl 2-[(2-formylaminophenyl)methyl]acetates (**2**) on treatment with ethyl sulfanylacetate in DMF in the presence of sodium hydride as a base at 0 ˚C in relatively good yields. Formamides (**2**) were then converted into the corresponding isocyanides (**3**) by dehydration with phosphoryl chloride in THF in the presence of triethylamine at 0 ˚C[5] in good yields.



Scheme 1

The preparations of 1,2,3,5-tetrahydro-4,1-benzothiazepine-2-thione derivatives (**6**) and (**7**) from isocyanides (**3**) was shown in Scheme 1 as well. First, the synthesis of **6** was achieved as follows. Reaction of **3** with sulfur in THF in the presence of a catalytic amount of selenium and excess triethylamine at room temperature according to the procedure reported by Fujiwara *et al*.[6] generated the corresponding isothiocyanates (**4**). To these solutions of **4** was added to a half volume of DMSO relative to THF and the mixture was treated with an equimolar amount of sodium hydride at the same temperature.

Deprotonation of α-hydrogen of the ester moiety and subsequent cyclization by the addition of the resulting carbanion to the isothiocyanate carbon proceeded rapidly and cleanly to generate the sodio thioamide intermediates (**5**). In the absence of DMSO cyclization proceeded very sluggishly even at elevated temperatures. Quenching with saturated aqueous ammonium chloride afforded, after purification by preparative TLC on silica gel, ethyl 2-thioxo-1,2,3,5-tetrahydro-4,1-benzothiazepine-3-carboxylates (**6**) in fair yields, as shown in Scheme 1.

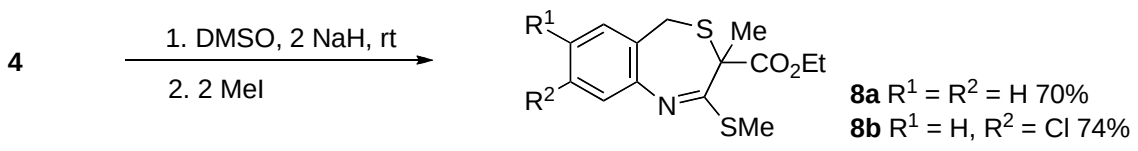
Table 1. Preparation of 2-alkylsulfanyl-3,5-dihydro-4,1-benzothiazepine-3-carboxylates **7**

Entry	**1**	R^3X	**7**	Yield/%[a]
1	**1a** ($R^1 = R^2 = H$)	MeI	**7a**	70
2	**1a**	EtI	**7b**	62
3	**1a**	CH_2=$CHCH_2Br$	**7c**	67
4	**1a**	BnBr	**7d**	72
5	**1b** ($R^1 = H$, $R^2 = Cl$)	EtI	**7e**	73
6	**1b**	CH_2=$CHCH_2Br$	**7f**	69
7	**1c** ($R^1 = OMe$, $R^2 = H$)	BnBr	**7g**	66

[a] Yields of isolated products.

The synthesis of ethyl 2-alkylsulfanyl-3,5-dihydro-4,1-benzothiazepine-3-carboxylates (**7**) were accomplished by alkylation of the anionic intermediates (**5**) with reactive alkyl halides at the same temperature, followed by aqueous workup and subsequent purification by preparative TLC on silica gel. The yields based on **3** were relatively good as summarized in Table 1. Alkylation with a less reactive alkyl halide, such as bromoethane, under the same conditions was examined. However, the intermediates (**5**) did not ethylated at all (data not shown).

When ethyl 2-[(2-isothiocyanatophenyl)methylsulfanyl]acetates (**4**) were treated with two equivalents of sodium hydride under the same conditions as described for the preparation of **7** and were allowed to react with two equivalents of iodomethane, ethyl 3-methyl-2-methylsulfanyl-3,5-dihydrobenzothiazepine-3-carboxylates (**8**) were obtained in moderate yields, as shown in Scheme 2. Subsequently, we tried to prepare ethyl 3-ethyl-2-ethylsulfanyl-3,5-dihydro-4,1-benzothiazepine-3-carboxylate by using two equivalents of ethyl iodide under the same conditions as for the preparation of **8**. Unfortunately, however, no trace of the desired product could be produced and only ethyl 2-ethylsulfanyl-3,5-dihydro-4,1-benzothiazepine-3-carboxylate (**7b**) was obtained in 60% yield. This result indicates that only methyl group can be introduced at the 3-position of the 4,1-benzothiazepine-3-carboxylate structure.



Scheme 2

In conclusion, we have synthesized ethyl 2-thioxo-1,2,3,5-tetrahydro-4,1-benzothiazepine-3-carboxylates (**6**) and ethyl 2-alkylsulfanyl-3,5-dihydro-4,1-benzothiazepine-3-carboxylates (**7**) and (**8**). The method developed here for the construction of 1,2,3,5-tetrahydro-4,1-benzothiazine-2-thione derivatives is convenient and of use in organic synthesis because of the ready availability of the starting materials and the easiness of operations.

EXPERIMENTAL

The melting points were obtained on a Laboratory Devices MEL-TEMP II melting apparatus and are uncorrected. IR spectra were recorded with a Perkin-Elmer Spectrum65 FTIR spectrophotometer. The ^{1}H NMR spectra were recorded in $CDCl_3$ using TMS as an internal reference with a Bruker Biospin AVANCE II 600 spectrometer operating at 600 MHz, a JEOL ECP500 FT NMR spectrometer operating at 500 MHz, or JEOL LA400FT NMR spectrometer operating at 400 MHz. The ^{13}C NMR spectra were recorded in $CDCl_3$ using TMS as an internal reference with a Bruker Biospin AVANCE II 600 spectrometer operating at 150 MHz, a JEOL ECP500 FT NMR spectrometer operating at 125 MHz, or JEOL LA400FT NMR spectrometer operating at 100 MHz. Low- and high-resolution MS spectra (EI, 70 eV) were measured by a JEOL JMS AX505 HA spectrometer. TLC was carried out on a Merck Kieselgel 60 PF_{254}. Column chromatography was performed using WAKO GEL C-200E. All of the organic solvents used in this study were dried over appropriate drying agents and distilled prior to use.

Starting Materials. (2-Amino-5-methoxyphenyl)methanol,[7] *N*-[2-(chloromethyl)phenyl]formamide (**1a**)[8] and *N*-[5-chloro-2-(chloromethyl)phenyl]formamide (**1b**)[9] were prepared by the appropriate reported methods. All other chemicals used in this study were commercially available.

***N*-[2-(Hydroxymethyl)-4-methoxyphenyl]formamide.** This compound was prepared by the *N*-formylation of (2-amino-5-methoxyphenyl)methanol[7] with HCO_2Et under the previously reported conditions;[9] 53% yield; a pale-yellow solid; mp 93–95 ˚C (hexane–CH_2Cl_2); IR (KBr) 3248, 1657, 1613 cm^{-1}; ^{1}H NMR (500 MHz) δ 2.1–2.4 (br, 1H), 3.80 and 3.81 (2s, combined 3H), 4.68 and 4.69 (2s, combined 2H), 6.79–8.45 (m, 5H). Anal. Calcd for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.63; H, 6.13; N, 7.49.

***N*-[2-(Chloromethyl)-4-methoxyphenyl]formamide (1c).** This compound was prepared by the treatment of *N*-[2-(hydroxymethyl)-4-methoxyphenyl]formamide with $SOCl_2$/pyridine under the previously reported conditions;[8] 71% yield; a pale-yellow solid; mp 110–111 ˚C (hexane–Et_2O); IR (KBr) 3221, 1653, 1620 cm^{-1}; ^{1}H NMR (500 MHz) δ 3.81 and 3.82 (2s, combined 3H), 4.56 and 4.57 (2s, combined 2H), 6.89–8.45 (m, 5H). Anal. Calcd for $C_9H_{10}ClNO_2$: C, 54.15; H, 5.05; N, 7.02. Found: C, 54.02; H, 5.25; N, 6.74.

General Procedure for the Preparation of Ethyl 2-[(2-Formylaminophenyl)methylsulfanyl]acetates

(2). These compounds were prepared by the treatment *N*-[2-(chloromethyl)phenyl]formamides (**1**) (5.0 mmol) with $NaSCH_2CO_2Et$ (5.5 mmol), generated in situ from $HSCH_2CO_2Et$ (5.5 mmol) and NaH (60% in mineral oil; 5.5 mmol) in DMF (15 mL) at 0 ˚C for 1 h, followed by usual aqueous workup (aq. NH_4Cl/AcOEt) and subsequent purification using column chromatography on silica gel.

Ethyl 2-[(2-Formylaminophenyl)methylsulfanyl]acetate (2a): a pale-yellow oil; R_f 0.45 (THF–hexane, 2:5); IR (neat) 3254, 1726, 1647 cm^{-1}; ^1H NMR (500 MHz) δ 1.31 and 1.33 (2t, J = 7.3 Hz each, combined 3H), 3.08 and 3.20 (2s, combined 2H), 3.86 and 3.88 (2s, combined 2H), 4.22 and 4.24 (2q, J = 7.3 Hz, combined 2H), 7.09–7.34 (m, 4H), 8.08–8.86 (m, 2H). Anal. Calcd for $C_{12}H_{15}NO_3S$: C, 56.90; H, 5.97; N, 5.53. Found: C, 56.74; H, 5.90; N, 5.46.

Ethyl 2-[(4-Chloro-2-formylaminophenyl)methylsulfanyl]acetate (2b): a white solid; mp 49–51 ˚C (hexane–Et_2O); IR (KBr) 3302, 1736, 1690 cm^{-1}; ^1H NMR (500 MHz) δ 1.30 and 1.32 (2t, J = 7.3 Hz, each, combined 3H), 3.08 and 3.23 (2s, combined 2H), 3.82 and 3.84 (2s, combined 2H), 4.22 and 4.24 (2q, J = 7.3 Hz each, combined 2H), 7.06–9.08 (m, 5H). Anal. Calcd for $C_{12}H_{14}ClNO_3S$: C, 50.09; H, 4.90; N, 4.87. Found: C, 50.04; H, 5.17; N, 4.72.

Ethyl 2-[(2-Formylamino-5-methoxyphenyl)methylsulfanyl]acetate (2c): a pale-yellow solid; mp 77–79 ˚C (hexane–Et_2O); IR (KBr) 3270, 1726, 1655, 1614 cm^{-1}; ^1H NMR (500 MHz) δ 1.29 and 1.31 (2t, J = 7.3 Hz each, combined 3H), 3.06 and 3.16 (2s, combined 2H), 3.58, 3.79, 3.81, and 3.82 (4s, combined 5H), 4.23 and 4.24 (2q, J = 7.3 Hz each, combined 2H), 6.81–8.56 (m, 5H). Anal. Calcd for $C_{13}H_{17}NO_4S$: C, 55.11; H, 6.05; N, 4.94. Found: C, 55.03; H, 6.15; N, 4.87.

Ethyl 2-[(2-Isocyanophenyl)methylsulfanyl]acetates (3). These compounds were prepared by dehydration of ethyl 2-[(2-formylaminophenyl)methylsulfanyl]acetates with $POCl_3/Et_3N$ under the previously reported conditions.[5]

Ethyl 2-[(2-Isocyanophenyl)methylsulfanyl]acetate (3a): a pale-green oil; R_f 0.47 (C_6H_6); IR (neat) 2122, 1732 cm^{-1}; ^1H NMR (500 MHz) δ 1.30 (t, J = 7.3 Hz, 3H), 3.13 (s, 2H), 3.98 (s, 2H), 4.20 (q, J = 7.3 Hz, 2H), 7.31 (dd, J = 7.8, 7.3 Hz, 1H), 7.38 (dd, J = 7.8, 7.3 Hz, 1H), 7.41 (d, J = 7.8 Hz, 1H), 7.46 (d, J = 7.8 Hz, 1H). HR-MS. Calcd for $C_{12}H_{13}NO_2S$: M, 235.0667. Found: *m/z* 235.0684.

Ethyl 2-[(4-Chloro-2-isocyanophenyl)methylsulfanyl]acetate (3b): a yellow oil; R_f 0.47 (C_6H_6); IR (neat) 2126, 1716 cm^{-1}; ^1H NMR (400 MHz) δ 1.30 (t, J = 7.3 Hz, 3H), 3.11 (s, 2H), 3.94 (s, 2H), 4.20 (q, J = 7.3 Hz, 2H), 7.36 (d, J = 8.3 Hz, 1H), 7.41–7.43 (m, 2H). HR-MS. Calcd for $C_{12}H_{12}ClNO_2S$: M, 269.0277. Found: *m/z* 269.0301.

Ethyl 2-[(2-Isocyano-5-methoxyphenyl)methylsulfanyl]acetate (3c): a yellow oil; R_f 0.47 (AcOEt–hexane, 1:2); IR (neat) 2119, 1731, 1607 cm^{-1}; ^1H NMR (400 MHz) δ 1.30 (t, J = 6.9 Hz, 3H), 3.15 (s, 2H), 3.83 (s, 3H), 3.93 (s, 2H), 4.20 (q, J = 6.9 Hz, 2H), 6.79 (dd, J = 8.8, 2.9 Hz, 1H), 6.97 (d, J = 2.9 Hz, 1H), 7.33 (d, J = 8.8 Hz, 1H). HR-MS. Calcd for $C_{13}H_{15}NO_3S$: M, 265.0773. Found: *m/z* 265.0793.

Typical Procedure for the Preparation of 2-Thioxo-1,2,3,5-tetrahydro-4,1-benzothiazepine-3-carboxylates (6). Ethyl 2-Thioxo-1,2,3,5-tetrahydro-4,1-benzothiazepine-3-carboxylate (6a). A solution of **3a** (0.15 g, 0.64 mmol) and Et_3N (0.16 g, 1.6 mmol) in THF (5 mL) containing sulfur (25 mg, 0.77 mmol) and selenium (1.5 mg, 0.019 mmol) was stirred at rt for 3 h. The mixture was cooled to 0 ˚C, and DMSO (2.5 mL) and then NaH (60% in oil; 51 mg, 1.3 mmol) was added. After 15 min saturated aqueous NH_4Cl (10 mL) was added. The organic materials were extracted with Et_2O twice (10 mL each), and the combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated by evaporation. The residue was purified by preparative TLC on silica gel (THF–hexane, 1:6) to afford **6a** (0.10 g, 60%); a beige solid; mp 96–97 ˚C (hexane–CH_2Cl_2); IR (KBr) 3179, 1730, 1487 cm^{-1}; ^1H NMR (600 MHz) δ 1.20 (t, *J* = 6.9 Hz, 3H), 3.80 (d, *J* = 13.0 Hz, 1H), 3.93 (d, *J* = 13.0 Hz, 1H), 4.01–4.11 (m. 2H), 4.59 (s, 1H), 7.09 (dd, *J* = 7.3, 1.5 Hz, 1H), 7.04–7.36 (m, 3H), 9.43 (br s, 1H); ^{13}C NMR (150 MHz) δ 13.89, 30.33, 54.91, 62.56, 123.44, 128.96, 129.04, 129.95, 132.10, 137.19, 166.30, 198.60; MS *m/z* 267 (M^+, 100). Anal. Calcd for $C_{12}H_{13}NO_2S_2$: C, 53.91; H, 4.90; N, 5.24. Found: C, 53.93; H, 4.93; N, 5.04.

Ethyl 8-Chloro-2-thioxo-1,2,3,5-tetrahydro-4,1-benzothiazepine-3-carboxylate (6b): an orange solid; mp 92–94 ˚C (hexane–CH_2Cl_2); IR (KBr) 3229, 1730, 1490 cm^{-1}; ^1H NMR (400 MHz) δ 1.22 (t, *J* = 6.9 Hz, 3H), 3.80 (d, *J* = 13.7 Hz, 1H), 3.90 (d, *J* = 13.6 Hz, 1H), 4.11 (q, *J* = 6.9 Hz, 2H), 4.59 (s, 1H), 7.10 (s, 1H), 7.27–7.30 (m, 2H), 9.53 (br s, 1H); ^{13}C NMR (150 MHz) δ 13.94, 29.85, 55.09, 62.84, 123.74, 129.14, 130.62, 130.97, 134.50, 138.09, 166.23, 198.71; MS *m/z* 301 (M^+, 100). Anal. Calcd for $C_{12}H_{12}ClNO_2S_2$: C, 47.75; H, 4.01; N, 4.64. Found: C, 47.73; H, 4.02; N, 4.55.

Ethyl 8-Methoxy-2-thioxo-1,2,3,5-tetrahydro-4,1-benzothiazepine-3-carboxylate (6c): a beige solid; mp 90–92 ˚C (hexane–CH_2Cl_2); IR (KBr) 3121, 1726, 1604, 1497 cm^{-1}; ^1H NMR (400 MHz) δ 1.22 (t, *J* = 6.9 Hz, 3H), 3.75 (d, *J* = 12.7 Hz, 1H), 3.83 (s, 3H), 3.89 (d, *J* = 12.7 Hz, 1H), 4.05–4.14 (m, 2H), 4.59 (s, 1H), 6.84–6.86 (m, 2H), 7.01 (dd, *J* = 6.8 and 2.0 Hz, 1H), 9.18 (br s, 1H); ^{13}C NMR (100 MHz) δ 13.92, 30.57, 54.88, 55.62, 62.59, 114.37, 114.44, 124.83, 129.88, 133.50, 159.70, 166.34, 198.28; MS *m/z* 297 (M^+, 100). Anal. Calcd for $C_{13}H_{15}NO_3S_2$: C, 52.50; H, 5.08; N, 4.71. Found: C, 52.39; H, 5.12; N, 4.70.

Typical Procedure for the Preparation of 2-Alkylsulfanyl-3,5-dihydro-4,1-benzothiazepine-3-carboxylates (7). Ethyl 2-Methylsulfanyl-3,5-dihydro-4,1-benzothiazepine-3-carboxylate (7a). Compound (**3a**) (0.15 g, 0.64 mmol) was converted into the corresponding isothiocyanate (**4a**) and treated with an equimolar amount of NaH as described for the preparation of **6a**. After 15 min MeI (91 mg, 0.64 mmol) was added and the resulting mixture was stirred for 1 h at the same temperature. A workup similar to that for the preparation of **6a** gave a residue, which was purified by preparative TLC on silica gel (THF–hexane, 1:10) to afford **7a** (0.11 g, 60%); a yellow solid; mp 100–101 ˚C (hexane–Et_2O); IR (KBr) 1738, 1604 cm^{-1}; ^1H NMR (500 MHz) δ 1.15 (t, *J* = 7.3 Hz, 3H), 2.58 (s, 3H), 3.42 (d, *J* = 12.4 Hz, 1H),

3.71 (d, *J* = 12.4 Hz, 1H), 3.90–4.01 (m, 2H), 4.07 (s, 1H), 6.88 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.05 (td, *J* = 7.3, 1.0 Hz, 1H), 7.19 (dd, *J* = 7.3, 1.4 Hz, 1H), 7.26 (ddd, *J* = 7.8, 7.3, 1.4 Hz, 1H); ^{13}C NMR (100 MHz) δ 13.72, 13.92, 30.69, 49.82, 62.50, 122.80, 125.16, 126.45, 128.64, 128.92, 148.92, 165.03, 167.08; MS *m/z* 281 (M^+, 100). Anal. Calcd for $C_{13}H_{15}NO_2S_2$: C, 55.49; H, 5.37; N, 4.98. Found: C, 55.30; H, 5.38; N, 4.97.

Ethyl 2-Ethylsulfanyl-3,5-dihydro-4,1-benzothiazepine-3-carboxylate (7b): a yellow oil; R_f 0.48 (AcOEt–hexane, 1: 6); IR (neat) 1738, 1605 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.16 (t, *J* = 7.3 Hz, 3H), 1.44 (t, *J* = 7.3 Hz, 3H), 3.19 (q, *J* = 7.3 Hz, 1H), 3.44 (d, *J* = 12.7 Hz, 1H), 3.70 (d, *J* = 12.7 Hz, 1H), 3.90–4.01 (m, 2H), 4.05 (s, 1H), 6.87 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.05 (ddd, *J* = 7.8, 7.3, 1.0 Hz, 1H), 7.19 (dd, *J* = 7.3, 1.0 Hz, 1H), 7.26 (td, *J* = 7.3, 1.0 Hz, 1H); ^{13}C NMR (100 MHz) δ 13.85, 13.88, 24.99, 30.64, 49.88, 62.45, 122.71, 125.08, 126.40, 128.58, 128.87, 148.94, 164.34, 167.08; MS *m/z* 329 (M^+, 100). Anal. Calcd for $C_{14}H_{16}ClNO_2S_2$: C, 50.98; H, 4.89; N, 4.25. Found: C, 50.93; H, 5.03; N, 4.28.

Ethyl 2-(Prop-2-enylsulfanyl)-3,5-dihydro-4,1-benzothiazepine-3-carboxylate (7c): a yellow oil; R_f 0.26 (AcOEt–hexane, 1: 20); IR (neat) 1740, 1605 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.16 (t, *J* = 7.3 Hz, 3H), 3.42 (d, *J* = 12.7 Hz, 1H), 3.70 (d, *J* = 12.7 Hz, 1H), 3.85 (d, *J* = 6.8 Hz, 2H), 3.90–4.01 (m, 2H), 4.06 (s, 1H), 5.19 (d, *J* = 10.7 Hz, 1H), 5.37 (dd, *J* = 18.6 Hz, 1H), 5.99–6.05 (m, 1H), 6.87 (d, *J* = 7.8 Hz, 1H), 7.05 (dd, *J* = 7.8, 6.9 Hz, 1H), 7.19 (d, *J* = 7.8 Hz, 1H), 7.26 (dd, *J* = 7.8, 6.8 Hz, 1H); ^{13}C NMR (125 MHz) δ 13.88, 30.63, 33.29, 49.77, 62.49, 118.35, 122.70, 125.15, 126.37, 128.59, 128.89, 132.53, 148.78, 163.57, 166.97. MS *m/z* 307 (M^+, 100). Anal. Calcd for $C_{15}H_{17}NO_2S_2$: C, 58.60; H, 5.57; N, 4.56. Found: C, 58.54; H, 5.65; N, 4.46.

Ethyl 2-Phenylmethylsulfanyl-3,5-dihydro-4,1-benzothiazepine-3-carboxylate (7d): a yellow oil; R_f 0.32 (AcOEt–hexane, 1:20); IR (neat) 1738, 1604 cm^{-1}; ^{1}H NMR (500 MHz) δ 1.14 (t, *J* = 7.3 Hz, 3H), 3.31 (d, *J* = 12.8 Hz, 1H), 3.59 (d, *J* = 12.8 Hz, 1H), 3.90–3.99 (m, 2H), 4.05 (s, 1H), 4.41 (d, *J* = 13.7 Hz, 1H), 4.44 (d, *J* = 13.7 Hz, 1H), 6.88 (d, *J* = 7.8 Hz, 1H), 7.06 (ddd, *J* = 7.8, 7.3, 1.4 Hz, 1H), 7.18 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.25–7.28 (m, 2H), 7.32 (dd, *J* = 7.8, 7.3 Hz, 2H), 7.46 (d, *J* = 7.8 Hz, 2H); ^{13}C NMR (150 MHz) δ 13.91, 30.55, 34.90, 49.73, 62.51, 122.73, 125.21, 126.52, 127.32, 128.47, 128.63, 128.95, 129.24, 137.02, 148.82, 163.79, 167.00; MS *m/z* 357 (M^+, 100). Anal. Calcd for $C_{19}H_{19}NO_2S_2$: C, 63.83; H, 5.36; N, 3.92. Found: C, 63.90; H, 5.48; N, 3.84.

Ethyl 8-Chloro-2-ethylsulfanyl-3,5-dihydro-4,1-benzothiazepine-3-carboxylate (7e): a yellow oil; R_f 0.30 (AcOEt–hexane, 1:3); IR (neat) 1741, 1605 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.18 (t, *J* = 6.8 Hz, 3H), 1.43 (t, *J* = 7.8 Hz, 3H), 3.17 (q, *J* = 6.8 Hz, 2H), 3.38 (d, *J* = 12.7 Hz, 1H), 3.69 (d, *J* = 12.7 Hz, 1H), 3.93–4.40 (m, 2H), 4.06 (s, 1H), 6.88 (d, *J* = 2.0 Hz, 1H), 7.02 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.12 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR (150 MHz) δ 13.83, 13.91, 25.18, 30.11, 50.07, 62.75, 122.86, 125.06 (two overlapped Cs), 129.88, 134.17, 150.03, 165.86, 166.96; MS *m/z* 329 (M^+, 100). Anal. Calcd for $C_{14}H_{16}ClNO_2S_2$: C, 50.98; H, 4.89; N, 4.25. Found: C, 50.72; H, 5.03; N, 4.21.

Ethyl 8-Chloro-2-(prop-2-enylsulfanyl)-3,5-dihydro-4,1-benzothiazepine-3-carboxylate (7f): a yellow oil; R_f 0.68 (AcOEt–hexane, 1:3); IR (neat) 1740, 1636 cm^{-1}; ^1H NMR (400 MHz) δ 1.18 (t, J = 7.3 Hz, 3H), 3.37 (d, J = 12.7 Hz, 1H), 3.68 (d, J = 12.7 Hz, 1H), 3.81–3.83 (m, 2H), 4.00 (q, J = 7.3 Hz, 2H), 4.03 (a, 1H), 5.20 (d, J = 9.8 Hz, 1H), 5.38 (d, J = 17.1 Hz, 1H), 5.95–6.05 (m, 1H), 6.88 (s, 1H), 7.03 (d, J = 7.8 Hz, 1H), 7.12 (d, J = 7.8 Hz, 1H); ^{13}C NMR (150 MHz) δ 13.91, 30.10, 33.43, 49.96, 62.80, 118.62, 122.85, 125.03, 125.14, 129.90, 132.30, 134.19, 149.88, 165.08, 166.86; MS *m/z* 341 (M^+, 100). Anal. Calcd for $C_{15}H_{16}ClNO_2S_2$: C, 52.70; H, 4.72; N, 4.10. Found: C, 52.52; H, 4.54; N, 4.24.

Ethyl 7-Methoxy-2-phenylmethylsulfanyl-3,5-dihydro-4,1-benzothiazepine-3-carboxylate (7g): a yellow oil; R_f 0.52 (AcOEt–hexane, 1:3); IR (neat) 1739, 1609 cm^{-1}; ^1H NMR (400 MHz) δ 1.15 (t, J = 6.9 Hz, 3H), 3.27 (d, J = 12.7 Hz, 1H), 3.57 (d, J = 12.7 Hz, 1H), 3.79 (s, 3H), 3.90–4.02 (m, 2H), 4.04 (s, 1H), 4.39 (d, J = 13.7 Hz, 1H), 4.43 (d, J = 13.7 Hz, 1H), 6.72 (s, 1H), 6.80–6.83 (m, 2H), 7.26 (t, J = 6.9 Hz, 1H), 7.32 (dd, J = 7.8, 6.9 Hz, 2H), 7.46 (d, J = 7.8 Hz, 2H); ^{13}C NMR (125 MHz) δ 13.88, 30.67, 34.79, 49.54, 55.44, 62.46, 113.49, 114.53, 123.86, 127.24, 127.57, 128.40, 129.18, 137.00, 141.86, 156.89, 163.31, 167.07; MS *m/z* 387 (M^+, 100). Anal. Calcd for $C_{20}H_{21}NO_3S_2$: C, 61.99; H, 5.46; N, 3.61. Found: C, 61.92; H, 5.68; N, 3.70.

3-Methyl-2-methylsulfanyl-3,5-dihydro-4,1-benzothiazepine-3-carboxylates (8). Ethyl 3-Methyl-2-methylsulfanyl-3,5-dihydro-4,1-benzothiazepine-3-carboxylate (8a). Compound (**3a**) (0.15 g, 0.64 mmol) was converted into the corresponding isothiocyanate (**4a**) and treated with 2 equiv. of NaH as described above. After 15 min, MeI (0.18 g, 1.3 mmol) was added and the resulting mixture was stirred for 1 h at the same temperature. A workup similar to that for the preparation of **6a** gave a residue, which was purified by preparative TLC on silica gel (THF–hexane, 1:10) to afford **8a** (70 mg, 46%); a yellow oil; R_f 0.23; IR (neat) 1746, 1586 cm^{-1}; ^1H NMR (400 MHz) δ 1.07 (t, J = 6.8 Hz, 3H), 1.64 (s, 3H), 2.54 (s, 3H), 3.15 (d, J = 12.7 Hz, 1H), 3.57–3.61 (m, 1H), 3.73–3.76 (m, 1H), 3.96 (d, J = 12.7 Hz, 1H), 6.79 (d, J = 7.8 Hz, 1H), 7.01 (dd, J = 7.8, 7.3 Hz, 1H), 7.14 (d, J = 7.8 Hz, 1H), 7.22 (dd, J = 7.8, 7.3 Hz, 1H); ^{13}C NMR (125 MHz) δ 13.71, 13.77, 22.66, 31.50, 56.43, 62.31, 122.97, 124.67, 126.61, 128.20, 128.36, 148.72, 168.98, 171.48; MS *m/z* 295 (M^+, 100). Anal. Calcd for $C_{14}H_{17}NO_2S_2$: C, 56.92; H, 5.80; N, 4.74. Found: C, 56.92; H, 5.90; N, 4.71.

Ethyl 8-Chloro-3-methyl-2-methylsulfanyl-3,5-dihydro-4,1-benzothiazepine-3-carboxylate (8b): a yellow oil; R_f 0.34 (AcOEt–hexane, 1:3); IR (neat) 1739, 1580 cm^{-1}; ^1H NMR (400 MHz) δ 1.12 (t, J = 6.9 Hz, 3H), 1.64 (s, 3H), 2.52 (s, 3H), 3.14 (d, J = 12.7 Hz, 1H), 3.64–3.72 (m, 1H), 3.81–3.88 (m, 1H), 3.90 (d, J = 12.7 Hz, 1H), 6.80 (d, J = 2.0 Hz, 1H), 6.98 (dd, J = 8.7, 2.0 Hz, 1H), 7.09 (d, J = 8.7 Hz, 1H); ^{13}C NMR (150 MHz) δ 13.79, 13.90, 22.70, 30.98, 56.69, 62.70, 123.02, 124.70, 125.30, 129.39, 133.78, 149.87, 170.50, 171.37; MS *m/z* 329 (M^+, 100). Anal. Calcd for $C_{14}H_{16}ClNO_2S_2$: C, 50.98; H, 4.89; N, 4.25. Found: C, 50.94; H, 4.99; N, 4.07.

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