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SYNTHESIS OF 3-(ALKYLSULFANYL)-1,4-BENZOTHIAZINE DERIVATIVES BASED ON CYCLIZATION OF 2-[(CYANOMETHYL)SULFANYL]PHENYL ISOTHIOCYANATE

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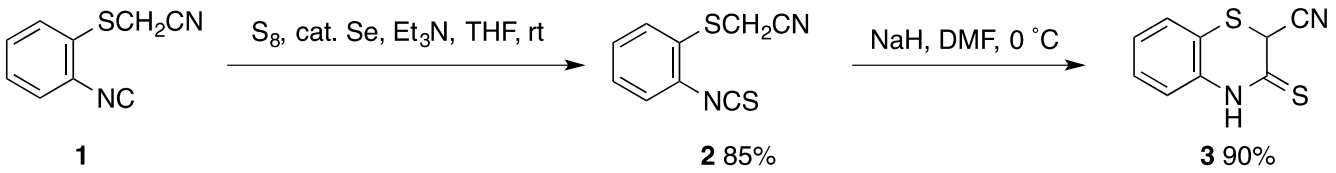
Abstract – Efficient procedures for the preparation of 1,4-benzothiazine-based bicyclic and tricyclic heterocycles have been developed. The reaction of 2-[(cyanomethyl)sulfanyl]phenyl isothiocyanate, readily prepared from commercially available 2-aminobenzenethiol, with sodium hydride was found to give, after aqueous workup, 3-thioxo-3,4-dihydro-2*H*-1,4-benzothiazine-2-carbonitrile. Treatment with alkyl halides prior to workup yielded 3-(alkylsulfanyl)-4*H*-1,4-benzothiazine-2-carbonitriles. Successive treatment of these compounds with sodium hydride and alkyl halides afforded 4-alkyl-3-(alkylsulfanyl)-2*H*-1,4-benzothiazine-2-carbonitriles. These procedures can be applied to the synthesis of some 1,4-benzothiazine-based tricyclic heterocycles.

A number of 4*H*-1,4-benzothiazine derivatives have recently been synthesized and some of these compounds have been reported to exhibit biological activities.[1] 2*H*-1,4-Benzothiazine derivatives have also attracted respectable attention in recent years due to their potential use as biologically active compounds.[2] Some 2*H*-[3] and 4*H*-1,4-benzothiazine[4] derivatives have been used for the preparation of more structurally complex organic compounds. The literature procedures to prepare 2*H*-1,4-benzothiazines usually involve the reactions of 2-aminobenzenethiol with α-halo ketones,[5] though a few new syntheses of 2*H*-1,4-benzothiazine derivative have recently been reported.[6] However, there have been no methods, which can allow preparation of 2*H*- or 4*H*-1,4-benzothiazine derivatives carrying an alkylsulfanyl group at the 3-position, while a few method for the preparation of 3,4-dihydro-2*H*-1,4-benzothiazine-3-thiones have been reported.[7] In this manuscript, we wish to report a convenient and direct method for the preparation of 2-(alkylsulfanyl)-4*H*-1,4-benzothiazine (**4**) and 2-(alkylsulfanyl)-2*H*-

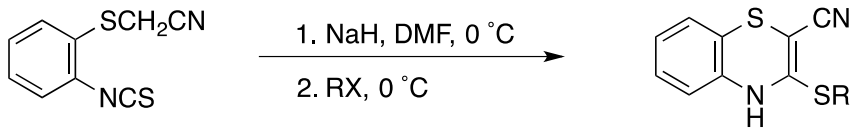
1,4-benzothiazine derivatives (**5**) and (**6**) from 2-[(cyanomethyl)sulfanyl]phenyl isothiocyanate (**2**).

The starting isothiocyanate (**2**) was prepared in a good yield by the treatment of 2-[(cyanomethyl)sulfanyl]phenyl isocyanide (**1**),[8] easily accessible from commercially available 2-aminobenzenethiol, with sulfur in the presence of triethylamine and a catalytic amount of selenium[9] as shown in Scheme 1. First, compound (**2**) was allowed to react with sodium hydride in DMF at 0 ˚C. After aqueous workup, 3-thioxo-3,4-dihydro-2*H*-1,4-benzothiazine-2-carbonitrile (**3**) was obtained in an excellent yield as shown in Scheme 1 as well. Addition of haloalkanes prior to aqueous workup resulted in the formation of 3-(alkylsulfanyl)-4*H*-1,4-benzothiazine-2-carbonitriles (**4**), as shown in Scheme 2. We have prepared a range of these derivatives using this methodology and the results are compiled in Table 1, which indicates that not only reactive haloalkanes but also a normal haloalkane, such as *n*-butyl bromide can be used, though the yields of the products **4b** is somewhat lower (Entry 2) than the others.



1 **2** 85% **3** 90%

Scheme 1



2 **4**

Scheme 2

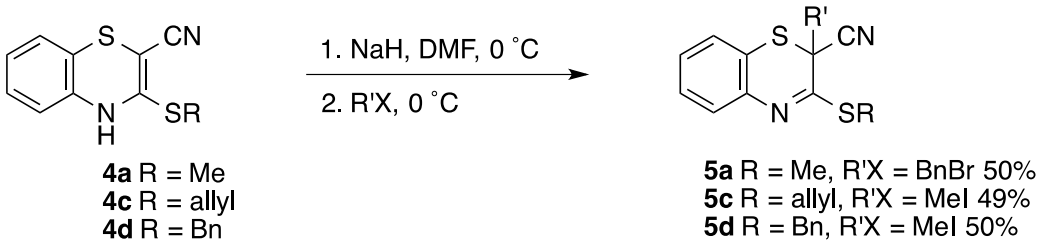
Table 1. Preparation of 2-(alkylsulfanyl)-4*H*-1,4-benzothiazines (**4**)

Entry	RX	**4**	Yield/%[a]
1	MeI	**4a**	68
2	*n*-BuBr	**4b**	47
3	CH_2=$CHCH_2Br$	**4c**	78
4	BnBr	**4d**	86
5	$PhCOCH_2Br$	**4e**	80
6	$4\text{-}ClC_6H_4COCH_2Br$	**4f**	80
7	*t*-$BuOCOCH_2Br$	**4g**	68
8	$NCCH_2Br$	**4h**	62

[a] Yields of isolated products.

The deprotonation of some of compounds (**4**) with sodium hydride in DMF at 0 ˚C followed by treatment with haloalkanes afforded 2-alkyl-3-(alkylsulfanyl)-2*H*-1,4-benzothiazines (**5**) in fair yields, as depicted

in Scheme 3. The 2*H*-1,4-benzothiazine structure was determined by their IR and NMR spectral data. The IR spectra uniformly exhibit very weak bands due to nitrile triple bonds around 2230 cm^{-1}. Signals around δ 156 assignable to C(3) were observed in their ^{13}C NMR spectra. The ^{1}H NMR spectra were good agreement with their structures.

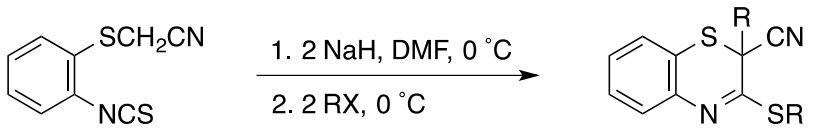


4a R = Me
4c R = allyl
4d R = Bn

5a R = Me, R'X = BnBr 50%
5c R = allyl, R'X = MeI 49%
5d R = Bn, R'X = MeI 50%

Scheme 3

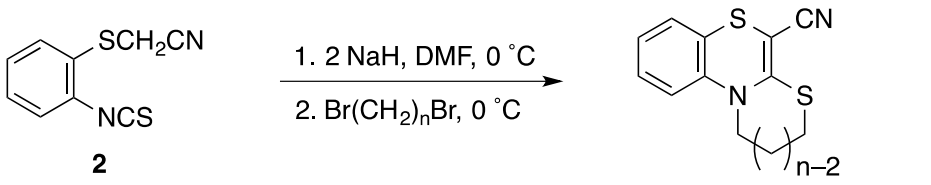
Compound (**2**) was treated with two equivalents of sodium hydride in DMF at 0 ˚C, and subsequent addition of two equivalents of alkyl halides to achieve simultaneous 2,*S*-dialkylation provided 2-alkyl-3-(alkylsulfanyl)-2*H*-1,4-benzothiazines (**6**) directly in moderate yields, as shown in Scheme 4.



2

6a RX = MeI 52%
6b RX = CH_2=$CHCH_2$Br 65%
6c RX = BnBr 61%

Scheme 4



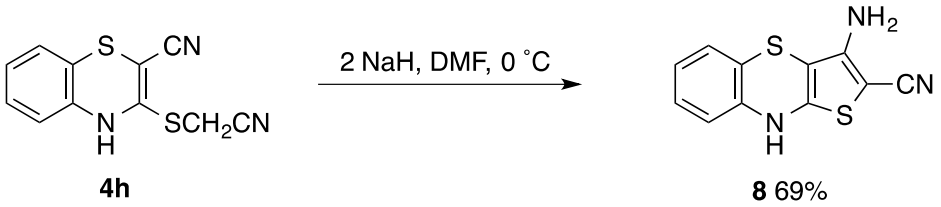
2

7a n = 2 48%
7b n = 3 62%
7c n = 4 43%

Scheme 5

Compound **2** was then subjected to the treatment with two equivalents of sodium hydride in DMF at 0 ˚C, and an equimolar amount of 1,ω-dibromoalkanes in place of two equivalents of alkyl halides were added. Surprisingly, however, it was found that the products obtained were 4,*S*-dialkylated tricyclic compounds (**7**), as depicted in Scheme 5. The production of these compounds is presumably due to the avoidance of the structural strain of the 2,*S*-dilakylated products. Synthesis and biological activities of

thiazolo[2,3-*c*][1,4]benzothiazine derivatives (n = 2) have been reported.[10]



4h **8** 69%

Scheme 6

The preparation of a 9*H*-thieno[3,2-*b*][1,4]benzothiazine derivative was also achieved. When compound (**4h**) was treated with two equivalents of sodium hydride in DMF at 0 ˚C, immediate cyclization occurred to give 3-amino-9*H*-thieno[3,2-*b*][1,4]benzothiazine-2-carbonitrile (**8**) in relatively good yield, as illustrated in Scheme 6. Some compounds with 9*H*-thieno[3,2-*b*][1,4]benzothiazine structure have been prepared and reported to exhibit biological activities.[11]

In conclusion, we have demonstrated that 4*H*- and 2*H*-1,4-benzothiazine derivatives carrying an alkylsulfanyl substituent at the 3-position can be produced *via* easily operated reaction sequences starting from 2-[(cyanomethyl)sulfanyl]phenyl isothiocyanate, which is readily prepared from a commercially available starting material, 2-aminobenzenthiol. The present methods proved to be applicable to the construction of some 1,4-benzothiazine-based tricyclic heterocyclic compounds.

EXPERIMENTAL

All melting points were obtained on a Laboratory Devices MEL-TEMP II melting apparatus and are uncorrected. IR spectra were recorded with a Perkin–Elmer Spectrum 65 FTIR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 500 and 125 MHz, respectively. High-resolution MS spectra were measured by a JEOL JMS-T100GCV (EI, TOF; 70 eV) or a Thermo Scientific Exactive (DART or ESI, positive) spectrometer. Elemental analyses were performed with an Elementar Vario EL II instrument. TLC was carried out on 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-[(2-Isocyanophenyl)sulfanyl]acetonitrile (**1**) was prepared according to the reported method.[8] Butyllithium was supplied by Asia Lithium Corporation. All other chemicals used in this study were commercially available.

2-[(2-Isothiocyanatophenyl)sulfanyl]acetonitrile (2). This compound was prepared by a slight modification of Fujiwara's method.[9] A mixture of **1** (0.93 g, 5.3 mmol), S_8 (0.17 g, 5.3 mmol), Se (25 mg,

0.32 mmol), and Et_3N (1.3 g, 13 mmol) in THF (5 mL) was stirred at rt for 1 h. The precipitate was filtered off through a Celite 545 pad under reduced pressure and filtrate was concentrated by evaporation. The residue was purified by column chromatography on SiO_2 to give **2** (0.94 g, 85%); a yellow oil; R_f 0.32 (CH_2Cl_2/hexane 1:1); IR (neat) 2249, 2064 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.63 (s, 2H), 7.326 (t, J = 7.4 Hz, 1H), 7.333 (d, J = 7.4 Hz, 1H), 7.40 (td, J = 7.4, 1.7 Hz, 1H), 7.64 (dd, J = 7.4, 1.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 20.4, 115.6, 127.1, 128.0, 128.8, 130.6, 134.2, 134.6 (2 overlapped Cs). HR-MS (EI). Calcd for $C_9H_6N_2S_2$ (M): 205.9972. Found: *m*/*z* 205.9960.

3-Thioxo-3,4-dihydro-2*H*-1,4-benzothiazine-2-carbonitrile (3). To a stirred suspension of NaH (60% in mineral oil; 40 mg, 1.0 mmol) in DMF (2 mL) at 0 ˚C was added a solution of **2** (0.21 g, 1.0 mmol) in DMF (2 mL) dropwise. After 10 min, saturated aqueous NH_4Cl (15 mL) was added and the mixture was extracted with AcOEt (3 × 10 mL). The combined extracts were washed with H_2O (3 × 15 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated by evaporation. The residual solid was recrystallized from hexane/CH_2Cl_2 to give **3** (0.13 g, 65%); an orange solid; mp 114–116 ˚C; IR (KBr) 3208, 2242, 1601, 1542, 1478, 1443, 1390, 1104, 1067 cm^{-1}; ^1H NMR (DMSO-d_6) δ 5.91 (s, 1H), 7.26 (t, J = 7.6 Hz, 1H), 7.36 (d, J = 7.6 Hz, 1H), 7.41 (t, J = 7.6 Hz, 1H), 7.57 (d, J = 7.6 Hz, 1H), 13.28 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 37.03, 115.31, 117.73, 118.53, 125.71, 128.49, 128.60, 135.67, 182.15. HR-MS (EI). Calcd for $C_9H_6N_2S_2$ (M): 205.9972. Found: *m*/*z* 205.9970. Anal. Calcd for $C_9H_6N_2S_2$: C, 52.40; H, 2.93; N, 13.58. Found: C, 52.17; H, 3.12; N, 13.30.

Typical Procedure for the Preparation of 2-(Alkylsulfanyl)-4*H*-1,4-benzothiazines (4). 3-(Methylsulfanyl)-4*H*-1,4-benzothiazine-2-carbonitrile (4a). After compound **2** (0.21 g, 1.0 mmol) was treated with NaH as described above, MeI (0.14 g, 1.0 mmol) was added dropwise. After 10 min, the mixture was worked up as described for the preparation of **3**. The residual solid was recrystallized from hexane/CH_2Cl_2 to give **4a** (0.15 g, 68%); a yellow solid; mp 153–155 ˚C; IR (KBr) 3332, 2174, 1542, 1469 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.55 (s, 3H), 6.96 (d, J = 7.6 Hz, 1H), 7.05–7.10 (m, 2H), 7.19 (t, J = 7.3 Hz, 1H), 10.01 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 16.22, 65.59, 116.60, 117.20, 118.29, 126.13, 126.89, 128.41, 139.54, 155.86. HR-MS (EI). Calcd for $C_{10}H_8N_2S_2$ (M): 220.0129. Found: *m*/*z* 220.0130. Anal. Calcd for $C_{10}H_8N_2S_2$: C, 54.52; H, 3.66; N, 12.72. Found: C, 54.31; H, 3.70; N, 12.59.

3-(Butylsulfanyl)-4*H*-1,4-benzothiazine-2-carbonitrile (4b): a yellow solid; mp 69–71 ˚C (hexane/CH_2Cl_2); IR (KBr) 3278, 2190, 1550, 1463 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (t, J = 7.4 Hz, 3H), 1.42–1.49 (m, 2H), 1.63–1.69 (m, 2H), 2.99 (t, J = 7.4 Hz, 2H), 6.57 (br s, 1H), 6.63 (dd, J = 8.0, 1.1 Hz, 1H), 6.99 (dd, J = 7.4, 1.7 Hz, 1H), 7.03 (ddd, J = 8.0, 7.4, 1.1 Hz, 1H), 7.10 (td, J = 7.4, 1.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.50, 21.56, 31.64, 34.51, 73.38, 115.62, 116.68, 119.18, 126.30, 127.32, 128.14, 139.23, 152.98. HR-MS (EI). Calcd for $C_{13}H_{14}N_2S_2$ (M): 262.0598. Found: *m*/*z* 262.0595.

3-[(Prop-2-enyl)sulfanyl]-4*H*-1,4-benzothiazine-2-carbonitrile (4c): a yellow solid; mp 151–153 ˚C (hexane/THF); IR (KBr) 3321, 2183, 1635, 1541, 1463 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.58 (d, *J* = 6.9 Hz, 2H), 5.22–5.27 (m, 2H), 5.89–5.97 (m, 1H), 6.59 (d, *J* = 7.4 Hz, 1H), 6.64 (s, 1H), 6.97 (d, *J* = 7.4 Hz, 1H), 7.03 (t, *J* = 7.4 Hz, 1H), 7.09 (t, *J* = 7.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 37.69, 74.63, 115.52, 116.62, 118.83, 119.72, 126.32, 127.34, 128.14, 132.68, 139.09, 151.55. HR-MS (EI). Calcd for $C_{12}H_{10}N_2S_2$ (M): 246.0285. Found: *m*/*z* 246.0280. Anal. Calcd for $C_{12}H_{10}N_2S_2$: C, 58.51; H, 4.09; N, 11.37. Found: C, 58.32; H, 4.05; N, 11.52.

3-[(Phenylmethyl)sulfanyl]-4*H*-1,4-benzothiazine-2-carbonitrile (4d): a yellow solid; mp 100–103 ˚C (hexane/CH_2Cl_2); IR (KBr) 3258, 2191, 1550, 1466 cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.30 (s, 2H), 6.97 (t, *J* = 6.9 Hz, 2H), 7.02 (t, *J* = 6.9 Hz, 1H), 7.15–7.27 (m, 6H), 10.01 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 36.93, 69.05, 116.42, 116.86, 117.66, 125.97, 126.79, 127.44, 128.33, 128.45, 128.72, 136.38, 139.45, 152.21. HR-MS (EI). Calcd for $C_{16}H_{12}N_2S_2$ (M): 296.0442. Found: *m*/*z* 296.0439. Anal. Calcd for $C_{16}H_{12}N_2S_2$: C, 64.83; H, 4.08; N, 9.45. Found: C, 64.82; H, 4.13; N, 9.36.

3-[(2-Oxo-2-phenylethyl)sulfanyl]-4*H*-1,4-benzothiazine-2-carbonitrile (4e): a yellow solid; mp 150–153 ˚C (hexane/CH_2Cl_2); IR (KBr) 3328, 2172, 1682 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.26 (s, 2H), 6.65 (dd, *J* = 7.4, 1.1 Hz, 1H), 6.93 (d, *J* = 7.4 Hz, 1H), 7.00 (td, *J* = 7.4, 1.1 Hz, 1H), 7.06 (td, *J* = 7.4 Hz, 1.1 Hz, 1H), 7.54 (t, *J* = 7.4 Hz, 2H), 7.68 (tt, *J* = 7.4, 1.1 Hz, 1H), 7.98 (dd, *J* = 7.4, 1.1 Hz, 2H), 8.49 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 39.32, 73.11, 115.96, 116.47, 118.27, 126.24, 127.17, 128.21, 128.83, 129.18, 134.75, 134.92, 139.23, 150.30, 196.96. HR-MS (EI). Calcd for $C_{17}H_{12}N_2OS_2$ (M): 324.0391. Found: *m*/*z* 324.0376. Anal. Calcd for $C_{17}H_{12}N_2OS_2$: C, 62.94; H, 3.73; N, 8.63. Found: C, 62.81; H, 3.60; N, 8.61.

3-{[2-(4-Chlorophenyl)-2-oxoethyl]sulfanyl}-4*H*-1,4-benzothiazine-2-carbonitrile (4f): a yellow solid; mp 154–156 ˚C (hexane/CH_2Cl_2); IR (KBr) 3337, 2173, 1678 cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.73 (s, 2H), 6.83 (d, *J* = 8.0 Hz, 1H), 6.99 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.03 (ddd, *J* = 8.0, 7.4, 1.7 Hz, 1H), 7.12 (ddd, *J* = 8.0, 7.4, 1.1 Hz, 1H), 7.57 (d, *J* = 8.6 Hz, 2H), 7.93 (d, *J* = 8.6 Hz, 2H), 10.02 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 39.50, 79.12, 116.48, 116.65, 118.69, 125.98, 126.73, 128.32, 128.87, 130.31, 133.66, 138.69, 139.48, 151.80, 192.39. HR-MS (ESI). Calcd for $C_{17}H_{12}ClN_2OS_2$ (M+H): 359.0079. Found: *m*/*z* 359.0066. Anal. Calcd for $C_{17}H_{11}ClN_2OS_2$: C, 56.90; H, 3.09; N, 7.81. Found: C, 56.71; H, 3.24; N, 7.75.

1,1-Dimethylethyl 2-[(2-Cyano-4*H*-1,4-benzothiazin-2-yl)sulfanyl]acetate (4g): a yellow viscous oil; R_f 0.34 (AcOEt/hexane 1:3); IR (neat) 3281, 2193, 1727 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.54 (s, 9H), 3.43 (s, 2H), 6.64 (d, *J* = 7.4 Hz, 1H), 6.95 (d, *J* = 7.4 Hz, 1H), 7.01 (t, *J* = 7.4 Hz, 1H), 7.06 (t, *J* = 7.4Hz, 1H), 8.93 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 27.86, 36.47, 71.80, 84.61, 115.87, 116.48, 118.55, 126.20, 127.22, 128.14, 139.31, 150.68, 171.57. HR-MS (ESI). Calcd for $C_{15}H_{16}N_2O_2S_2$ (M+H): 321.0731. Found: *m*/*z* 321.0725.

3-[(Cyanomethyl)sulfanyl]-4*H*-1,4-benzothiazine-2-carbonitrile (4h): a brown viscous oil; R_f 0.40 (AcOEt/hexane 1:4); IR (neat) 3288, 2194 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.69 (s, 2H), 6.71 (d, J = 8.0 Hz, 1H), 6.937 (br s, 1H), 6.944 (d, J = 7.4 Hz, 1H), 7.06 (t, J = 7.4 Hz, 1H), 7.11 (dd, J = 8.0, 7.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 19.98, 78.91, 115.56, 115.79, 116.30, 118.02, 127.05, 127.38, 128.62, 138.79, 146.66. HR-MS (EI). Calcd for $C_{11}H_7N_3S_2$ (M): 245.0081. Found: *m*/*z* 245.0073.

Typical Procedure for the Preparation of 2-Alkyl-3-(alkylsulfanyl)-2*H*-1,4-benzothiazine-2-carbonitriles (5). 2-Methyl-3-[(phenylmethyl)sulfanyl]-2*H*-1,4-benzothiazine-2-carbonitrile (5d). To a stirred suspension of NaH (60% in mineral oil; 22 mg, 0.55 mmol) in DMF (2 mL) at 0 ˚C was added a solution of **4d** (0.16 g, 0.55 mmol) in DMF (2 mL) dropwise. Evolution of H_2 gas had ceased, MeI (78 mg, 0.55 mmol) was added. After 15 min, the mixture was worked up as described for the preparation of **3**. The residue was purified by column chromatography on SiO_2 (AcOEt/hexane 1:7) to give **5d** (85 mg, 50%); a white solid; mp 151–153 ˚C (hexane); IR (KBr) 2231, 1594 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.80 (s, 3H), 4.34 (s, 2H), 7.10 (t, J = 7.4 Hz, 1H), 7.18–7.29 (m, 5H), 7.33 (d, J = 7.4 Hz, 2H), 7.38 (d, J = 7.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.61, 35.58, 36.66, 117.39, 118.73, 126.76, 126.85, 127.26, 127.64, 128.07, 128.68, 129.24, 135.92, 141.28, 156.18. HR-MS (EI). Calcd for $C_{17}H_{14}N_2S_2$ (M): 310.0598. Found: *m*/*z* 310.0607. Anal. Calcd for $C_{17}H_{14}N_2S_2$: C, 65.77; H, 4.55; N, 9.02; S, 20.66. Found: C, 65.48; H, 4.49; N, 9.05; S, 20.56.

3-(Methylsulfanyl)-2-(phenylmethyl)-2*H*-1,4-benzothiazine-2-carbonitrile (5a): a white solid; mp 118–120 ˚C (hexane/CH_2Cl_2); IR (KBr) 2227, 1593 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.52 (s, 3H), 2.93 (d, J = 13.7 Hz, 1H), 3.22 (d, J = 13.7 Hz, 1H), 7.20–7.21 (m, 3H), 7.30–7.35 (m, 5H), 7.46 (d, J = 7.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.24, 39.15, 44.23, 116.24, 117.62, 126.63, 126.78, 127.36, 128.05, 128.20, 128.35, 130.45, 132.43, 141.25, 156.58. HR-MS (EI). Calcd for $C_{17}H_{14}N_2S_2$ (M): 310.0598. Found: *m*/*z* 310.0589. Anal. Calcd for $C_{17}H_{14}N_2S_2$: C, 65.77; H, 4.55; N, 9.02. Found: C, 65.53; H, 4.51; N, 9.01.

2-Methyl-3-[(prop-2-enyl)sulfanyl]-2*H*-1,4-benzothiazine-2-carbonitrile (5c): a pale-yellow oil; R_f 0.54 (AcOEt/hexane 1:10); IR (neat) 2232, 1661, 1637, 1594 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.88 (s, 3H), 3.84 (d, J = 6.9 Hz, 2H), 5.20 (d, J = 10.3 Hz, 1H), 5.35 (d, J = 16.6 Hz, 1H), 5.88–5.99 (m, 1H), 7.16 (t, J = 7.4 Hz, 1H), 7.28–7.31 (m, 2H), 7.40 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.6, 33.8, 36.7, 117.4, 118.6, 119.1, 126.7, 126.8, 127.2, 128.0, 131.9, 141.2, 155.8. HR-MS (DART). Calcd for $C_{13}H_{13}N_2S_2$ (M+H): 261.0520. Found: *m*/*z* 261.0508.

Typical Procedure for the Preparation of 2-Alkyl-3-(alkylsulfanyl)-2*H*-1,4-benzothiazine-2-carbonitriles (6). 2-Methyl-3-(methylsulfanyl)-2*H*-1,4-benzothiazine-2-carbonitrile (6a). To a stirred suspension of NaH (60% in mineral oil; 53 mg, 1.3 mmol) in DMF (2 mL) at 0 ˚C was added a solution of **2** (0.15 g, 0.66 mmol) in DMF (2 mL) dropwise. Evolution of H_2 gas had ceased, MeI (0.19 g, 1.3 mmol) was added. After 15 min, the mixture was worked up as described for the preparation of **3**. The

residue was purified by column chromatography on SiO_2 to give **6a** (81 mg, 52%); a pale-yellow oil; R_f 0.56 (AcOEt/hexane 1:7); IR (neat) 2230, 1592 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.89 (s, 3H), 2.56 (s, 3H), 7.16 (ddd, *J* = 8.0, 7.4, 1.1 Hz, 1H), 7.29–7.32 (m, 2H), 7.42 (dd, *J* = 8.0, 1.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.98, 21.69, 36.71, 117.51, 118.50, 126.61, 126.81, 127.20, 128.02, 141.38, 157.18. HR-MS (EI). Calcd for $C_{11}H_{10}N_2S_2$ (M): 234.0285. Found: *m*/*z* 234.0274. Anal. Calcd for $C_{11}H_{10}N_2S_2$: C, 56.38; H, 4.30; N, 11.95; S, 27.37. Found: C, 56.51; H, 4.65; N, 11.83; S, 27.55.

2-(Prop-2-enyl)-3-[(prop-2-enyl)sulfanyl]-2*H*-1,4-benzothiazine-2-carbonitrile (6b): a pale-yellow oil; R_f 0.70 (AcOEt/hexane 1:3); IR (neat) 2239, 1639, 1593 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.53 (dd, *J* = 13.5, 7.4 Hz, 1H), 2.81 (dd, *J* = 13.5, 6.9 Hz, 1H), 3.81–3.90 (m, 2H), 5.19–5.23 (m, 2H), 5.31–5.37 (m, 2H), 5.85–5.98 (m, 2H), 7.16 (t, *J* = 7.4 Hz, 1H), 7.26–7.31 (m, 2H), 7.38 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 33.98, 37.97, 42.51, 116.12, 117.67, 119.09, 122.05, 126.68, 126.78, 127.34, 127.98, 129.16, 131.88, 141.13, 154.91. HR-MS (EI). Calcd for $C_{15}H_{14}N_2S_2$ (M): 286.0598. Found: *m*/*z* 286.0580.

2-(Phenylmethyl)-3-[(phenylmethyl)sulfanyl]-2*H*-1,4-benzothiazine-2-carbonitrile (6c): a pale-yellow solid; mp 100–102 ˚C (hexane); IR (KBr) 2241, 1596 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.93 (d, *J* = 13.2 Hz, 1H), 3.20 (d, *J* = 13.2 Hz, 1H), 4.33 (d, *J* =13.7 Hz, 1H), 4.43 (d, *J* = 13.7 Hz, 1H), 7.14 (d, *J* = 6.9 Hz, 2H), 7.20 (t, *J* = 7.4 Hz, 1H), 7.24–7.37 (m, 10H), 7.48 (d, *J* = 7.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 35.7, 39.3, 44.1, 116.1, 117.9, 126.6, 126.9, 127.4, 127.5, 128.1, 128.2, 128.4, 128.6, 129.3, 130.5, 132.3, 136.0, 141.2, 155.5. Anal. Calcd for $C_{23}H_{18}N_2S_2$: C, 71.47; H, 4.69; N, 7.25; S, 16.59. Found: C, 71.13; H, 4.80; N, 7.22; S, 16.72.

Typical Procedure for the Preparation of Tricyclic Benzothiazine-Fused Compounds (7). 1,2-Dihydrothiazolo[2,3-*c*][1,4]benzothiazine-4-carbonitrile (7a). To a stirred suspension of NaH (60% in mineral oil; 79 mg, 2.0 mmol) in DMF (2 mL) at 0 ˚C was added a solution of **2** (0.20 g, 0.99 mmol) in DMF (2 mL) dropwise. Evolution of H_2 gas had ceased, $Br(CH_2)_2Br$ (0.19 g, 0.99 mmol) was added. After 2.5 h, the mixture was worked up as described for the preparation of **3**. The residue was purified by column chromatography on SiO_2 (AcOEt/hexane 1:2) to give **7a** (81 mg, 48%); a yellow solid; mp 137–139 ˚C (hexane/CH_2Cl_2); IR (KBr) 2184, 1550 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.46 (t, *J* = 6.9 Hz, 2H), 3.95 (t, *J* = 6.9 Hz, 2H), 6.65 (d, *J* = 8.0 Hz, 1H), 6.97–6.99 (m, 2H), 7.08–7.12 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 29.2, 53.0, 64.8, 113.2, 116.8, 119.1, 125.6, 127.2, 128.1, 140.4, 157.2. Anal. Calcd for $C_{11}H_8N_2S_2$: C, 56.87; H, 3.47; N, 12.06; S, 27.60. Found: C, 56.58; H, 3.37; N, 12.25; S, 27.87.

2,3-Dihydro-1*H*-[1,4]benzothiazino[3,4-*b*]thiazine-5-carbonitrile (7b): a yellow solid; mp 117–119 ˚C (hexane/CH_2Cl_2); IR (KBr) 2185, 1534 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.34–2.40 (m, 2H), 3.03 (t, *J* = 7.4 Hz, 2H), 4.00 (t, *J* = 6.3 Hz, 2H), 6.87 (d, *J* = 8.0 Hz, 1H), 7.08–7.12 (m, 2H), 7.19–7.24 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 24.0, 26.9, 45.9, 70.8, 114.4, 116.8, 122.9, 125.9, 128.06, 128.10, 142.7, 158.0. Anal. Calcd for

$C_{12}H_{10}N_2S_2$: C, 58.51; H, 4.09; N, 11.37; S, 26.03. Found: C, 58.24; H, 4.22; N, 11.41; S, 26.20.

8,9,10,11-Tetrahydro[1,4]benzothiazino[3,4-*b*]thiazepine-6-carbonitrile (7c): a yellow solid; mp 135–137 ˚C (hexane/CH_2Cl_2); IR (KBr) 2187, 1527 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.94–1.97 (m, 4H), 2.72–2.75 (m, 2H), 4.06–4.10 (m, 2H), 6.90 (d, J = 8.0 Hz, 1H), 6.93 (dd, J = 7.4, 1.7 Hz, 1H), 7.00 (t, J = 7.4 Hz, 1H), 7.09 (ddd, J = 8.0, 7.4, 1.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 28.5, 29.1, 34.3, 52.0, 71.0, 115.2, 117.6, 123.3, 126.2, 127.6, 127.9, 142.9, 157.7. Anal. Calcd for $C_{13}H_{12}N_2S_2$: C, 59.97; H, 4.65; N, 10.76; S, 24.63. Found: C, 59.73; H, 4.72; N, 10.80; S, 24.93.

3-Amino-9*H*-thieno[3,2-*b*][1,4]benzothiazine-2-carbonitrile (8). To a stirred suspension of NaH (60% in mineral oil; 88 mg, 2.2 mmol) in DMF (7 mL) at 0 ˚C was added a solution of **4g** (0.28 g, 1.1 mmol) in DMF (3 mL) dropwise. After 20 min, the mixture was worked up as described for the preparation of **3**. The residual solid was purified by recrystallization from hexane/$CHCl_3$ to give **8** (0.19 g, 69%); a brown solid; mp 181–184 ˚C; IR (KBr) 3457, 3368, 3269, 2187, 1619 cm^{-1}; ^1H NMR (DMSO-d_6) δ 6.21 (s, 2H), 6.57 (d, J = 7.4 Hz, 1H), 6.83 (td, J = 7.4, 1.1 Hz, 1H), 6.90 (d, J = 8.0 Hz, 1H), 7.00 (ddd, J = 8.0, 7.4, 1.1 Hz, 1H), 9.90 (s, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 64.10, 93.96, 115.22 (2 overlapped Cs), 116.48, 123.68, 127.10, 127.98, 140.38, 145.05, 151.94. HR-MS (EI). Calcd for $C_{11}H_7N_3S_2$ (M): 245.0081. Found: m/z 245.0088. Anal. Calcd for $C_{11}H_7N_3S_2$: C, 53.85; H, 2.88; N, 17.13. Found: C, 53.70; H, 3.16; N, 16.75.

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